JANNY ELIZABETH LOMMERTS

COLORING THE SPOTS

DIAGNOSIS, MEASUREMENT INSTRUMENTS AND TREATMENT IN VITILIGO

COLORING THE SPOTS

DIAGNOSIS, MEASUREMENT INSTRUMENTS AND TREATMENT IN VITILIGO

JANNY ELIZABETH LOMMERTS

Colofon

Layout & cover design:	Design Your Thesis	www.designyourthesis.com
Printing:	Ridderprint B.V.	www.ridderprint.nl
ISBN:	978-94-6299-990-9	

Made possible by: Avita Medical Ltd., BAP Medical B.V., Bureau Promotiezaken, Huidstichting Chanfleury van IJsselsteijn, ConvaTec Nederland B.V., Dalton Medical B.V., Fagron B.V., Galderma Benelux B.V., La Roche Posay, Laservision Instruments B.V., LeoPharma B.V., Vitiligo.nl, Eurocept Homecare B.V., Mylan B.V., Oldekamp Medisch B.V. and Van der Bend B.V..

COLORING THE SPOTS

DIAGNOSIS, MEASUREMENT INSTRUMENTS AND TREATMENT IN VITILIGO

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op dinsdag 5 juni 2018, te 12.00 uur

door Janny Elizabeth Lommerts

geboren te Arnhem

Promotiecommissie

Promotor(es):	Prof. dr. M.A. de Rie	AMC-UvA
	Prof. dr. R.M. Luiten	AMC-UvA
Copromotor(es):	Dr. M.W. Bekkenk	AMC-UvA
	Dr. A. Wolkerstorfer	AMC-UvA
Overige leden:	Prof. dr. P.I. Spuls	AMC-UvA
	Prof. dr. R. Hoekzema	Vrije Universiteit Amsterdam
	Prof. dr. H.J.C. de Vries	AMC-UvA
	Prof. dr. W. Bergman	Universiteit Leiden
	Prof. dr. T. Passeron	University of Nice Sophia Antipolis
	Dr. M.M.G. Leeflang	AMC-UvA

Faculteit der Geneeskunde

CONTENTS

INTRODUCTION

Vitiligo is a common acquired skin disease characterized by depigmentation of the skin. The disease was first described in *De Medicina* a book published by a Roman physician called Celsus during the second century BCE.[1] The name vitiligo is probably derived from the Latin word for defect (*vitium*).[2]

Vitiligo affects approximately 0.5-1% of the world's population with no differences between sexes, ages or skin types.[1] The female peak prevalence is in the first decade of life and male peak prevalence is in the fifth decade of life.[3] Childhood-onset vitiligo, meaning onset before the age of 12 years, occurs in approximately a third of all cases.[4,5]

BURDEN OF THE DISEASE

Vitiligo is a disfiguring asymptomatic disease, although itch has been reported as a rare symptom.[6] Vitiligo is sometimes considered as a cosmetic disease. However, in our society, where physical appearances play an important role, different appearances can evidently lead to psychosocial difficulties. Several studies show that the quality of life is indeed significantly impaired in vitiligo patients[7-16] and lower than in healthy controls.[14,17] Different factors contributing to this impairment in quality of life have been described, such as female gender[18], extent of vitiligo[13,18], darker skin types[8,9] and localization of the depigmented lesions on visible areas[11]. Furthermore, impairment in quality of life in vitiligo patients also appears to be associated with perceived stigmatisation.[15,19] Stigmatization occurs due to lack of common understanding of the cause of the disease. Vitiligo is for example in some countries still confused with leprosy and sexually transmitted diseases. This perceived stigmatization is more common in patients with visible vitiligo lesions.[20,21] Furthermore, patients with vitiligo also face several psychosocial difficulties, such as problems in sexual function[13,22], sleep disturbances[23], anxiety[24] and lowered self-esteem[19,25].[26] Therefore, vitiligo should not be considered as a cosmetic disease, but as a disfiguring and psychologically devastating skin disease that requires medical treatment.[27]

PATHOGENESIS

Vitiligo is caused by selective destruction of melanocytes. Two main subtypes of vitiligo, non-segmental and segmental, can be distinguished and the pathogenesis of both subtypes is considered to be different. Non-segmental vitiligo is considered to be an auto-immune disease. The pathogenesis involves intrinsic defects within melanocytes

and autoimmunity targeting these melanocytes.[28] Cytotoxic CD8+ T-cells are the main effectors of this autoimmunity by recognition of several melanocyte differentiation antigens, such as gp100, MART1, tyrosinase, and tyrosinase related proteins.[29-31] Furthermore, the IFN-γ induced chemokine CXCL10 and its receptor CXCR3, are involved in the T-cell recruitment in vitiligo and therefore play an essential role in driving the autoimmunity.[28,32-34] Recent genome-wide association studies have identified 50 genetic loci that contribute to the risk on developing vitiligo.[35] The majority of loci are involved in immune regulation and others regulate functions of melanocytes, which confirms the critical role of the immune system in vitiligo pathogenesis.[28] The auto-immune hypothesis in non-segmental vitiligo is also supported by the high prevalence of other auto-immune diseases in vitiligo which is the highest for auto-immune thyroid disease.[36,37] Several provoking factors for vitiligo have been identified, such as exposure to chemical products containing phenols and skin trauma.[38,39]

The current pathogenesis hypothesis for segmental vitiligo is a somatic mosaicism.[40] This phenomenon refers to the occurrence of a postzygotic mutation in an embryonic melanocyte. Subsequently, this melanocyte differentiates into functional epidermal melanocytes and this leads to an unilateral distribution of abnormal melanocytes. In case the mutation is responsible for intrinsic defects in melanocytes, this consequently could lead to unilateral depigmentation by local and self-limiting autoimmunity. This is also confirmed by the presence of anti-MART1 and anti-gp100 specific CD8+ T-cells in the perilesional borders of segmental vitiligo.[41] Although a somatic mosaicism is generally seen as the leading hypothesis for the pathogenesis in segmental vitiligo, no genetic studies have been published up to this date that have confirmed this hypothesis.[28,42]

DIAGNOSIS

Vitiligo is characterized by white, well demarcated, uniform patches surrounded by normal skin. The diagnosis of vitiligo is usually made clinically with the use of a Wood's lamp (handheld ultraviolet A irradiation device).[3,43]

Differential diagnosis

The diagnosis of vitiligo is in most cases straightforward.[43] The main differential diagnoses for vitiligo are other depigmentary or hypopigmentary skin disorders such as piebaldism, pityriasis alba and progressive macular hypopigmentation.[42] An overview of the differential diagnosis of vitiligo with the key features for differentiation from vitiligo can be found in Table 1.[28]

The most alarming differential diagnosis of vitiligo is melanoma-associated leukoderma.[44] Melanoma-associated leukoderma is defined as depigmentation occurring in patients with malignant melanoma, which is an aggressive type of skin cancer originating from melanocytes. The leukoderma in melanoma patients is caused by anti-melanoma immunity which also targets healthy melanocytes, as a result of shared expression of melanocyte differentiation antigens.[45] The depigmentation in melanoma-associated leukoderma occurs spontaneously before or after the detection of melanoma and most frequently occurs during treatment with immunotherapy.[44-47] Melanoma-associated leukoderma is a favorable sign in patients receiving immunotherapy as it is associated with a significantly lower risk on disease progression and death.[45] However, in 20.5% of all melanoma-associated leukoderma cases the depigmentation occurs before the diagnosis of melanoma.[48] The prevalence of melanoma-associated leukoderma in patients with lesions suspected for vitiligo is unknown. Similar clinical patterns between vitiligo and melanoma-associated leukoderma, such as a symmetrical bilateral distribution of the depigmentations, have been reported.[47] However, other studies showed a more varied clinical spectrum with mostly hypopigmented irregularly shaped macules and a confetti-like appearance in melanoma-associated leukoderma as opposed to the well-demarcated white macules in typical vitiligo.[3,44,49,50] To date, the differences and similarities in clinical presentation between vitiligo and melanoma-associated leukoderma are not well defined and the literature is contradictory. Hypothetically, in clinical practice it can be difficult to distinguish between vitiligo and melanoma-associated leukoderma which may lead to misdiagnosing the depigmentation as vitiligo and leading to late detection of the melanoma.[44]

Classification

Vitiligo is generally divided into 2 subtypes: non-segmental and segmental vitiligo (Figure 1).[51] Non-segmental vitiligo is the most common type of vitiligo and is characterized by symmetrically distributed widespread depigmentations on the extensor sites and orifices. It is considered as a slow progressive disease with periods of activity and stability. Segmental vitiligo is characterized by unilateral, segmental or band-shaped depigmentations which do not cross the midline.[52,53] This subtype of vitiligo frequently occurs earlier in life than non-segmental vitiligo and is considered as a stable disease with limited depigmentation after the first rapid initial evolution phase.[54] A third subtype, the undetermined/unclassified type, has recently been defined by the Vitiligo Global Issues Consensus Conference.[51] This undetermined subtype includes both mucosal and focal vitiligo. Focal vitiligo is defined as a small acquired depigmented lesion and mucosal vitiligo is characterized by an isolated depigmented patch located on the mucosa.

Table 1 - Differential diagnosis of vitiligo.[28]

Disorder	Clinical presentation	Diagnosis
Congenital conditions		
Piebaldism	Midline depigmentation; present at birth; lesions contain islands of normal pigment	Dominantly inherited; other affected family members
Waardenburg syndrome	White forelock, some with depigmented patches	Other stigmata of the syndrome, including hearing loss
Multiple ash leaf macules of tuberous sclerosis (TS)	Multiple, well-demarcated, hypopigmented macules	Other cutaneous signs of TS, epilepsy, and other organ involvement
Hypomelanosis of Ito	Blaschkoid hypopigmentation present at birth	May or may not have other stigmata
Inflammatory conditions		
Pityriasis alba	Poorly demarcated hypopigmented macules; scale, erythema may be seen; most commonly in children with skin of color	Does not fluoresce with Wood's lamp; evidence of eczema may be noted
Postinflammatory hypopigmentation	Poorly demarcated hypopigmentation in an area of previous inflammation; may see primary dermatosis (eg, seborrheic dermatitis, eczema)	Decreased number of melanocytes with or without other inflammatory patterns
Lichen sclerosus et atrophicus	Typically on genitals; atrophic skin with or without fissures; figure-of-8 pattern surrounding vaginal introitus and anus	Lichenoid inflammation; epidermal atrophy; sparing of melanocytes
Discoid lupus erythematosus	Head, face, and neck erythematous, scaly macules and plaques with scarring, dyspigmentation and alopecia	Interface dermatitis with sparing of melanocytes
Hypopigmented sarcoidosis	Hypopigmented macules or patches; may be other manifestations of sarcoidosis	Histopathology reveals noncaseating granulomas
Cutaneous malignancy		
Mycosis fungoides (hypochromic variant)	Especially seen in skin of color; bathing suit distribution; with/without scale and signs of inflammation	Epidermotropism; atypical lymphocytes
Infections		
Acquired progressive macular hypomelanosis	Young adults; trunk (especially lower back and axillae)	Wood's lamp may reveal *P.acnes* (pink fluorescence)
Tinea versicolor	Hypopigmentation; trunk	Positive skin scraping with potassium hydroxide preparation; green fluorescence of untreated lesions

Table 1 - (continued)

Disorder	Clinical presentation	Diagnosis
Leprosy (tuberculoid or indeterminate)	Hypopigmented, hypoaesthetic white patches	Skin smear and biopsy specimen reveal *Mycobacterium leprae*
Pinta (late-stage)	Depigmented lesions, typically on distal extremities or other exposed part of the body	Rapid plasma reagin–positive; spirochetes on dark-field microscopy or histopathology
Exogenous causes		
Idiopathic guttate hypomelanosis	Exogenous UV-light exposure causing nonprogressive 1-5 mm hypomelanotic macules in older adults; chronically sun-exposed sites; no leukotrichia	
Trauma-induced hypo- or depigmentation	Geometric shapes and history of trauma or surgical intervention	
Segmental disorders		
Nevus depigmentosus	At birth or first few years of life; grows in proportion to child; usually hypopigmented, has a jagged border, and lacks leukotrichia	Normal number of melanocytes histologically but decreased melanin
Nevus anaemicus	Presents at birth; mostly on the upper aspect of the chest; poorly demarcated white macule with surrounding erythema	Merges with surrounding skin with diascopy; no accentuation with Wood's lamp examination

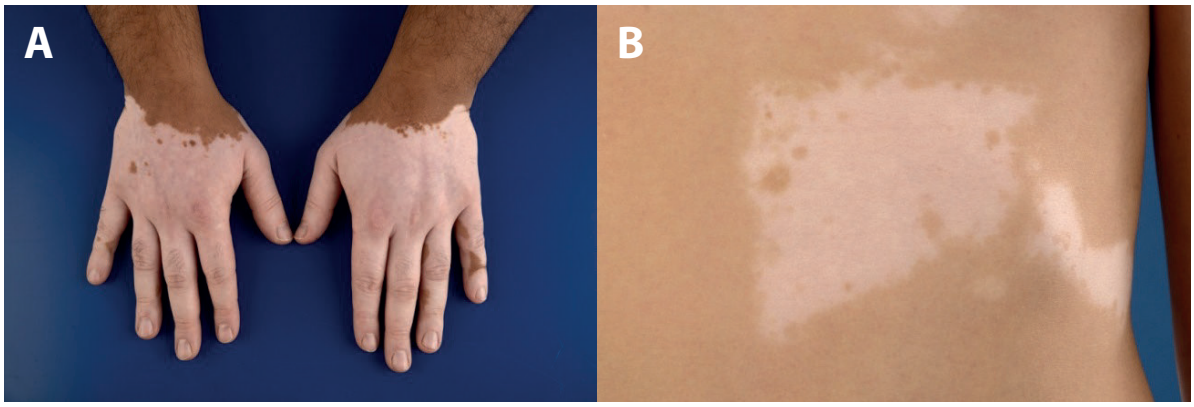


Figure 1 – Non-segmental (A) and segmental (B) vitiligo.[66]

MEASUREMENT INSTRUMENTS

Recently, consensus has been reached on which core set of outcome domains should be measured in vitiligo trials.[55] This core set of outcome domains for vitiligo comprises repigmentation, side-effects and harms, maintenance of gained repigmentation, quality of life, cosmetic acceptability of repigmentation, cessation of spreading and tolerability of treatment. In 2012, Eleftheriadou et al. showed that 48 measurement instruments could be identified that were used in clinical trials for vitiligo up to that date.[56] However, Vrijman et al. showed that most available measurement instruments in vitiligo are non-validated scales and do not meet the COSMIN criteria (Consensus-based Standard for the selection of health Measurement Instruments).[57-59] To date, no consensus is available on which measurement instruments should be used in vitiligo and very little data is available on the measurement properties of the available measurements instruments.

Currently, repigmentation in vitiligo is frequently measured in clinical trials by measuring the change in score of the extent of depigmentation. Measurement of the extent of depigmentation is also helpful in clinical practice as it helps with the assessment of the disease severity and evaluation of progression. Frequently used extent measurement instruments are the Vitiligo Area Scoring Index (VASI)[60] and the Vitiligo European Task Force assessment tool (VETFa)[61]. The VASI and VETFa are reliable and responsive measurement instruments to measure extent of depigmentation in vitiligo.[62] However, caution is needed when interpreting the score changes in individual patients of both tools.[63] The reason for this is that the smallest detectable change (SDC), the minimal difference that can be accurately measured, is relatively large for both tools.[62] This means that these tool are not reliable in measuring small differences in extent of depigmentation in both trials and clinical practice.

Patient reported outcomes are increasingly being recognized as important and also have been recommended by a recent Cochrane review on interventions in vitiligo as important to measure.[64] Most validated patient reported outcome measures in vitiligo are quality of life questionnaires and most evidence on measurement properties is available for the Dermatology Quality of Life Index and Skindex-29.[57] The SA-VASI (Self-Assessment of Vitiligo Area Severity Index) is a recently introduced patient reported outcome measure to assess the extent of depigmentation.[65] However, although the SA-VASI is a valid and fairly reliable patient reported outcome measure it is also a time-consuming measurement instrument.[65]

TREATMENT

The treatment of vitiligo depends mainly on the subtype of vitiligo, extent of depigmentation and disease activity; but also on the location, age and skin type of the patient. The algorithm of treatment in vitiligo, proposed by the Dutch Working Group of Vitiligo of the Dutch Dermatology Association, can be found in Figure 2.[66] The aims of treatment in vitiligo are to stop progression of the disease and to induce repigmentation.

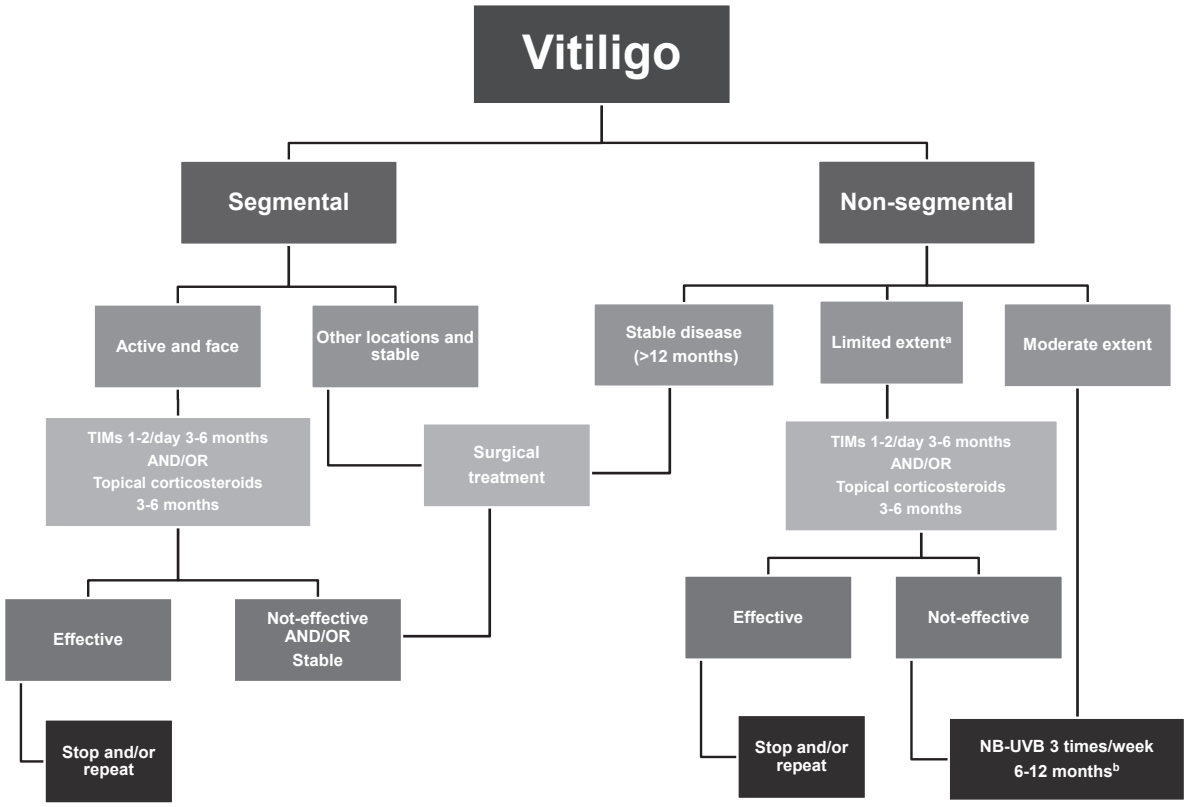


Figure 2 – Treatment algorithm for vitiligo.[66]

TIMS, topical immunomodulators (TIMs); [a] depending on localisation, [b] combined with TIMs and/or topical corticosteroids

Therapies that are available for active vitiligo lesions are topical treatment with corticosteroids or topical immunomodulators (TIMs) which both can be combined with phototherapy two or three times weekly for 6 to 12 months. Oral corticosteroids can also be considered for a short period (3-6 months) in very active and fast progressing vitiligo lesions with the aim to stop the progression of the disease.[67]

The current phototherapy of choice is narrowband ultraviolet B (NBUVB) due to its immunosuppressive qualities and that NBUVB leads to fewer side-effects than for example psoralen combined with ultraviolet A phototherapy (PUVA).[68] The European guidelines on vitiligo state that prolonged maintenance therapy with NBUVB treatment is not recommended, because there is a potential risk on skin photodamage due to the higher susceptibility of vitiligo skin to sunburn.[5,69] Moreover, phototherapy also has side-effects such as increased risk of skin cancer and premature skin aging.[70] However, recent studies show that patients with vitiligo have a decreased risk on both melanoma and non-melanoma skin cancer compared to controls, and that this is also the case for patients treated with phototherapy. [71,72] NBUVB is also an effective treatment option in childhood vitiligo.[73,74] No data are available on the long-term efficacy and safety of NBUVB in childhood vitiligo.[5]

Surgical treatment is performed in stable non-segmental and segmental vitiligo. The main principle of surgical treatment in vitiligo is transplanting melanocytes from normal pigmented skin to a depigmented recipient site. There are several techniques available for melanocyte transplantation. For treatment of large areas, the cell suspension transplantation (CST) is the most appropriate technique. This technique involves the transplantation of autologous non-cultured epidermal cells which are suspended in a fluid medium. Recipient-site preparation before CST is required to allow access to the underlying skin structures necessary for melanocyte adherence.[75,76] There are several recipient site-preparation techniques available, such as full surface ablation and dermabrasion. Most techniques for recipient-site preparation, such as dermabrasion, microneedling and ablation with liquid nitrogen, are difficult to standardize and not suitable for large or concave surfaces.[75-78] Therefore, full surface laser ablation is generally used as recipient-site preparation in CST. However, the optimal ablation depth is not known and full surface laser ablation can lead to persistent side-effects such as scarring and erythema.[75,78] Limited data is available on other less invasive techniques, such as superficial full surface and fractional laser ablation.

Surgical treatment in stable vitiligo lesions is frequently combined with subsequent phototherapy as total repigmentation after melanocyte transplantation is uncommon. International guidelines and a recent Cochrane systematic review on interventions in vitiligo also have recommended combination therapy in the treatment of vitiligo and state that combination therapies are associated with more repigmentation than monotherapies.[64,69,79,80] Phototherapy can enhance the repigmentation after melanocyte transplantation by its anti-inflammatory properties and by inducing melanocyte proliferation and migration. Up to this date, there is no consensus on the role of phototherapy in the surgical treatment of vitiligo.[69]

AIMS AND OUTLINE OF THE THESIS

The overall aim of this thesis was to color the white spots in vitiligo by coloring the blind spots in vitiligo research. The main focus was to answer important questions in the clinical pathway of vitiligo. The clinical pathway of a patient with suspected vitiligo can be divided into the diagnosis, measurement and treatment of vitiligo.

When a patient with depigmentations suspected for vitiligo visits the dermatologist for consultation, the diagnosis of vitiligo firsts needs to be verified or excluded. The most alarming differential diagnosis is melanoma-associated leukoderma. Most dermatologists are not aware of melanoma-associated leukoderma, and may easily diagnose and treat these patients as having non-segmental vitiligo, thereby overlooking the underlying melanoma.[81] *Chapter 2.1* contains a retrospective case series in which the clinical presentation and disease course of patients with melanoma-associated leukoderma who visited the Netherlands Institute for Pigment Disorders is described. Furthermore, the prevalence of melanoma-associated leukoderma in patients with depigmentations suspected for vitiligo is provided. In *Chapter 2.2* we investigated whether a discrimination between the two diagnosis can be made and whether there are discriminative features between vitiligo and melanoma-associated leukoderma.

After the diagnosis of vitiligo is confirmed, it is important to identify the subtype of vitiligo as the prognosis and treatment between subtypes is significantly different. Focal vitiligo is defined as an acquired, small, isolated, depigmented lesion which has not evolved into non-segmental vitiligo or segmental vitiligo after a period of 1-2 years.[51] The chance of progression of focal vitiligo is not known and no prognostic factors have yet been identified.[54] This may lead to treatment-indecision and uncertainty in patients as they want to know their prognosis and chance of further progression. The objective of the survey-study presented in *Chapter 2.3* was to study the characteristics of focal vitiligo and the chance and possible predictors of progression.

Measurement of vitiligo lesions is important for the assessment of both the severity of the disease and the efficacy and safety of treatment. Currently available measurement tools measuring the extent of depigmentation in vitiligo have relatively large smallest detectable changes. Therefore, new measurement tools with lower smallest detectable changes for both physicians and patients should be developed. *Chapter 3.1* comprises a study on the development and validation of a new tool to measure extent of depigmentation in vitiligo: the Vitiligo Extent Score (VES). *Chapter 3.2* comprises a study on the development and validation of a new patient reported outcome measure to measure the extent of depigmentation in vitiligo: the Self-Assessment Vitiligo

Extent Score (SA-VES). Furthermore, in *Chapter 3.3* the prospective assessment of the responsiveness, which is the ability of an instrument to detect real change over time, of both VES and SA-VES is presented.

Cosmetic acceptability of repigmentation is also marked as a core outcome domain for vitiligo and a recent survey showed that patients see cosmetically acceptable repigmentation as the most desirable outcome.[55,56] However, no valid or reliable patient reported outcome measures are yet available to measure this important domain. *Chapter 3.4* presents the validation of a new measurement tool to measure the cosmetic acceptability in vitiligo: the Vitiligo Cosmetic Acceptability Scale (VICAS).

In children, active vitiligo is effectively treated with NBUVB. However, it is not known whether the repigmentation is long-lasting and no data are available on the long-term safety of NBUVB in childhood vitiligo. The study in *Chapter 4.1* is a long-term follow-up survey of a cohort from an uncontrolled clinical trial of 20 years ago in which children with non-segmental vitiligo were treated with NBUVB twice weekly for a maximum period of 1 year. [5,73] The objective of *Chapter 4.1* was to assess the long-term outcome after NBUVB in childhood vitiligo.[5]

In *Chapter 4.2* a randomized, within-subject, controlled trial is presented in which different recipient-site preparations before cell suspension transplantation in segmental vitiligo and piebaldism were compared. The objective of the study was to assess the efficacy and safety of less invasive recipient-site preparations, such as fractional and superficial full surface ablation. In fractional pre-treatment only a "fraction" or column of the tissue is ablated and superficial full surface ablation only gives a superficial ablation of the skin. In each patient, four CO_2-laser recipient-site preparations (i.e. standard, superficial, fractional and control site) were randomly allocated to four depigmented lesions. After six months the repigmentation and side-effects were assessed.

The role of phototherapy as addition to the surgical treatment in vitiligo is unknown. Furthermore, several phototherapy modalities are used in combination with melanocyte transplantation and it is not known which phototherapy improves the outcome of melanocyte transplantation the most. *Chapter 4.3* contains a systematic review in which the benefit of phototherapy as an addition to melanocyte transplantation in vitiligo was investigated. The objective of this systematic review was to improve the surgical treatment strategy in vitiligo by identifying whether phototherapy improves the outcome of melanocyte transplantation.

REFERENCES

1 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *The Lancet* 2015; **386**: 74-84.

2 Panda AK. The medico historical perspective of vitiligo (Switra). *Bull Indian Inst Hist Med Hyderabad* 2005; **35**: 41-6.

3 Alikhan A, Felsten LM, Daly M *et al.* Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *Journal of the American Academy of Dermatology* 2011; **65**: 473-91.

4 Ezzedine K, Diallo A, Leaute-Labreze C *et al.* Pre- vs. post-pubertal onset of vitiligo: multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo. *The British journal of dermatology* 2012; **167**: 490-5.

5 Lommerts JE, Njoo MD, de Rie MA *et al.* Twenty-year follow-up using a postal survey of childhood vitiligo treated with narrowband ultraviolet B phototherapy. *The British journal of dermatology* 2017.

6 Behl PN, Bhatia RK. 400 cases of vitiligo. A clinico-therapeutic analysis. *Indian J Dermatol* 1972; **17**: 51-6.

7 Ongenae K, Beelaert L, van Geel N *et al.* Psychosocial effects of vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2006; **20**: 1-8.

8 Ezzedine K, Grimes PE, Meurant JM *et al.* Living with vitiligo: results from a national survey indicate differences between skin phototypes. *The British journal of dermatology* 2015.

9 Linthorst Homan MW, Spuls PI, de Korte J *et al.* The burden of vitiligo: patient characteristics associated with quality of life. *Journal of the American Academy of Dermatology* 2009; **61**: 411-20.

10 Kostopoulou P, Jouary T, Quintard B *et al.* Objective vs. subjective factors in the psychological impact of vitiligo: the experience from a French referral centre. *The British journal of dermatology* 2009; **161**: 128-33.

11 Ongenae K, Dierckxsens L, Brochez L *et al.* Quality of life and stigmatization profile in a cohort of vitiligo patients and effect of the use of camouflage. *Dermatology* 2005; **210**: 279-85.

12 Radtke MA, Schafer I, Gajur A *et al.* Willingness-to-pay and quality of life in patients with vitiligo. *The British journal of dermatology* 2009; **161**: 134-9.

13 Silverberg JI, Silverberg NB. Association between vitiligo extent and distribution and quality-of-life impairment. *JAMA dermatology* 2013; **149**: 159-64.

14 Kim do Y, Lee JW, Whang SH *et al.* Quality of life for Korean patients with vitiligo: Skindex-29 and its correlation with clinical profiles. *The Journal of dermatology* 2009; **36**: 317-22.

15 Kruger C, Schallreuter KU. Stigmatisation, Avoidance Behaviour and Difficulties in Coping are Common Among Adult Patients with Vitiligo. *Acta dermato-venereologica* 2015; **95**: 553-8.

16 Sampogna F, Johansson V, Axtelius B *et al.* A multilevel analysis of factors affecting the difference in dental patients' and caregivers' evaluation of oral quality of life. *European journal of oral sciences* 2008; **116**: 531-7.

17 Noh S, Kim M, Park CO *et al.* Comparison of the psychological impacts of asymptomatic and symptomatic cutaneous diseases: vitiligo and atopic dermatitis. *Annals of dermatology* 2013; **25**: 454-61.
18 Sampogna F, Raskovic D, Guerra L *et al.* Identification of categories at risk for high quality of life impairment in patients with vitiligo. *The British journal of dermatology* 2008; **159**: 351-9.
19 Kent G, al-Abadie M. Factors affecting responses on Dermatology Life Quality Index items among vitiligo sufferers. *Clinical and experimental dermatology* 1996; **21**: 330-3.
20 Thompson AR, Clarke SA, Newell RJ *et al.* Vitiligo linked to stigmatization in British South Asian women: a qualitative study of the experiences of living with vitiligo. *The British journal of dermatology* 2010; **163**: 481-6.
21 Schmid-Ott G, Kunsebeck HW, Jecht E *et al.* Stigmatization experience, coping and sense of coherence in vitiligo patients. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2007; **21**: 456-61.
22 Sukan M, Maner F. The problems in sexual functions of vitiligo and chronic urticaria patients. *Journal of sex & marital therapy* 2007; **33**: 55-64.
23 Mouzas O, Angelopoulos N, Papaliagka M *et al.* Increased frequency of self-reported parasomnias in patients suffering from vitiligo. *European journal of dermatology : EJD* 2008; **18**: 165-8.
24 Shah R, Hunt J, Webb TL *et al.* Starting to develop self-help for social anxiety associated with vitiligo: using clinical significance to measure the potential effectiveness of enhanced psychological self-help. *The British journal of dermatology* 2014; **171**: 332-7.
25 Porter J, Beuf AH, Nordlund JJ *et al.* Psychological reaction to chronic skin disorders: a study of patients with vitiligo. *General hospital psychiatry* 1979; **1**: 73-7.
26 Morrison B, Burden-Teh E, Batchelor JM *et al.* Quality of life in people with vitiligo: a systematic review and meta-analysis. *The British journal of dermatology* 2017.
27 Ezzedine K, Sheth V, Rodrigues M *et al.* Vitiligo is not a cosmetic disease. *Journal of the American Academy of Dermatology* 2015; **73**: 883-5.
28 Rodrigues M, Ezzedine K, Hamzavi I *et al.* New discoveries in the pathogenesis and classification of vitiligo. *Journal of the American Academy of Dermatology* 2017; **77**: 1-13.
29 Okamoto T, Irie RF, Fujii S *et al.* Anti-tyrosinase-related protein-2 immune response in vitiligo patients and melanoma patients receiving active-specific immunotherapy. *The Journal of investigative dermatology* 1998; **111**: 1034-9.
30 Palermo B, Campanelli R, Garbelli S *et al.* Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. *The Journal of investigative dermatology* 2001; **117**: 326-32.
31 van den Boorn JG, Konijnenberg D, Dellemijn TA *et al.* Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. *The Journal of investigative dermatology* 2009; **129**: 2220-32.
32 Rashighi M, Harris JE. Interfering with the IFN-gamma/CXCL10 pathway to develop new targeted treatments for vitiligo. *Ann Transl Med* 2015; **3**: 343.

33 Wang XX, Wang QQ, Wu JQ *et al.* Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo. *The British journal of dermatology* 2016; **174**: 1318-26.

34 Rashighi M, Agarwal P, Richmond JM *et al.* CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med* 2014; **6**: 223ra23.

35 Spritz RA, Andersen GH. Genetics of Vitiligo. *Dermatologic clinics* 2017; **35**: 245-55.

36 Kroon MW, Vrijman C, Chandeck C *et al.* High prevalence of autoimmune thyroiditis in children and adolescents with vitiligo. *Horm Res Paediatr* 2013; **79**: 137-44.

37 Vrijman C, Kroon MW, Limpens J *et al.* The prevalence of thyroid disease in patients with vitiligo: a systematic review. *The British journal of dermatology* 2012; **167**: 1224-35.

38 van Geel N, Speeckaert R, Mollet I *et al.* In vivo vitiligo induction and therapy model: double-blind, randomized clinical trial. *Pigment cell & melanoma research* 2012; **25**: 57-65.

39 Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. A retrospective study of treatment of 18 vitiligo patients and a review of the literature. *The British journal of dermatology* 1977; **97**: 669-79.

40 van Geel N, Speeckaert R, Melsens E *et al.* The distribution pattern of segmental vitiligo: clues for somatic mosaicism. *The British journal of dermatology* 2013; **168**: 56-64.

41 van Geel NA, Mollet IG, De Schepper S *et al.* First histopathological and immunophenotypic analysis of early dynamic events in a patient with segmental vitiligo associated with halo nevi. *Pigment cell & melanoma research* 2010; **23**: 375-84.

42 Speeckaert R, van Geel N. Vitiligo: An Update on Pathophysiology and Treatment Options. *Am J Clin Dermatol* 2017.

43 Gawkrodger DJ, Ormerod AD, Shaw L *et al.* Guideline for the diagnosis and management of vitiligo. *The British journal of dermatology* 2008; **159**: 1051-76.

44 Lommerts JE, Teulings HE, Ezzedine K *et al.* Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field. *Journal of the American Academy of Dermatology* 2016; **75**: 1198-204.

45 Teulings HE, Limpens J, Jansen SN *et al.* Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**: 773-81.

46 Speeckaert R, Van Geel N, Lambert J *et al.* Immune mediated mechanisms of melanocyte destruction: Paving the way for efficient immunotherapeutic strategies against melanoma. *Oncoimmunology* 2012; **1**: 526-8.

47 Hartmann A, Bedenk C, Keikavoussi P *et al.* Vitiligo and melanoma-associated hypopigmentation (MAH): shared and discriminative features. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* 2008; **6**: 1053-9.

48 Quaglino P, Marenco F, Osella-Abate S *et al.* Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**: 409-14.

49 Nordlund JJ, Kirkwood JM, Forget BM *et al.* Vitiligo in patients with metastatic melanoma: a good prognostic sign. *Journal of the American Academy of Dermatology* 1983; **9**: 689-96.

50 Koh HK, Sober AJ, Nakagawa H *et al.* Malignant melanoma and vitiligo-like leukoderma: an electron microscopic study. *Journal of the American Academy of Dermatology* 1983; **9**: 696-708.

51 Ezzedine K, Lim HW, Suzuki T *et al.* Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment cell & melanoma research* 2012; **25**: E1-13.

52 Gan EY, Eleftheriadou V, Esmat S *et al.* Repigmentation in vitiligo: position paper of the Vitiligo Global Issues Consensus Conference. *Pigment cell & melanoma research* 2017; **30**: 28-40.

53 Ezzedine K, Diallo A, Leaute-Labreze C *et al.* Multivariate analysis of factors associated with early-onset segmental and nonsegmental vitiligo: a prospective observational study of 213 patients. *The British journal of dermatology* 2011; **165**: 44-9.

54 Lommerts JE, Schilder Y, de Rie MA *et al.* Focal vitiligo: long-term follow-up of 52 cases. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2016; **30**: 1550-4.

55 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment cell & melanoma research* 2015; **28**: 363-9.

56 Eleftheriadou V, Thomas KS, Whitton ME *et al.* Which outcomes should we measure in vitiligo? Results of a systematic review and a survey among patients and clinicians on outcomes in vitiligo trials. *The British journal of dermatology* 2012; **167**: 804-14.

57 Vrijman C, Linthorst Homan MW, Limpens J *et al.* Measurement properties of outcome measures for vitiligo. A systematic review. *Archives of dermatology* 2012; **148**: 1302-9.

58 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.

59 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010; **19**: 539-49.

60 Hamzavi I, Jain H, McLean D *et al.* Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Archives of dermatology* 2004; **140**: 677-83.

61 Taieb A, Picardo M, Members V. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. *Pigment Cell Res* 2007; **20**: 27-35.

62 Komen L, da Graca V, Wolkerstorfer A *et al.* Vitiligo Area Scoring Index and Vitiligo European Task Force assessment: reliable and responsive instruments to measure the degree of depigmentation in vitiligo. *The British journal of dermatology* 2015; **172**: 437-43.

63 van Geel N, Lommerts J, Bekkenk M *et al.* Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *The Journal of investigative dermatology* 2016; **136**: 978-84.
64 Whitton ME, Pinart M, Batchelor J *et al.* Interventions for vitiligo. *Cochrane Database Syst Rev* 2015: CD003263.
65 Komen L, van der Kraaij GE, van der Veen JP *et al.* The validity, reliability and acceptability of the SAVASI; a new self-assessment score in vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2145-51.
66 Lommerts A. Vitiligo: een update. *Nederlands Tijdschrift voor Dermatologie en Venereologie* 2016; **26**: 149-54.
67 Singh A, Kanwar AJ, Parsad D *et al.* Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy versus oral minocycline in patients with active vitiligo vulgaris. *Indian journal of dermatology, venereology and leprology* 2014; **80**: 29-35.
68 Bae JM, Jung HM, Hong BY *et al.* Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2017; **153**: 666-74.
69 Taieb A, Alomar A, Bohm M *et al.* Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *The British journal of dermatology* 2013; **168**: 5-19.
70 Valejo Coelho MM, Apetato M. The dark side of the light: Phototherapy adverse effects. *Clin Dermatol* 2016; **34**: 556-62.
71 Paradisi A, Tabolli S, Didona B *et al.* Markedly reduced incidence of melanoma and nonmelanoma skin cancer in a nonconcurrent cohort of 10,040 patients with vitiligo. *Journal of the American Academy of Dermatology* 2014; **71**: 1110-6.
72 Teulings HE, Overkamp M, Ceylan E *et al.* Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *The British journal of dermatology* 2013; **168**: 162-71.
73 Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *Journal of the American Academy of Dermatology* 2000; **42**: 245-53.
74 Sen BB, Rifaioglu EN, Ekiz O *et al.* Narrow-band ultraviolet B phototherapy in childhood. *Cutaneous and ocular toxicology* 2014; **33**: 189-91.
75 Lommerts JE, Meesters AA, Komen L *et al.* Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomised controlled trial comparing full-surface and fractional CO2 laser recipient site preparations. *The British journal of dermatology* 2017.
76 Al-Hadidi N, Griffith JL, Al-Jamal MS *et al.* Role of Recipient-site Preparation Techniques and Post-operative Wound Dressing in the Surgical Management of Vitiligo. *Journal of cutaneous and aesthetic surgery* 2015; **8**: 79-87.
77 Busch KH, Bender R, Walezko N *et al.* Combination of medical needling and non-cultured autologous skin cell transplantation (ReNovaCell) for repigmentation of hypopigmented burn scars. *Burns : journal of the International Society for Burn Injuries* 2016; **42**: 1556-66.

78 Silpa-Archa N, Griffith JL, Williams MS *et al*. Prospective comparison of recipient-site preparation with fractional carbon dioxide laser vs. dermabrasion and recipient-site dressing composition in melanocyte-keratinocyte transplantation procedure in vitiligo: a preliminary study. *The British journal of dermatology* 2016; **174**: 895-7.

79 Oiso N, Suzuki T, Wataya-Kaneda M *et al*. Guidelines for the diagnosis and treatment of vitiligo in Japan. *J Dermatol* 2013; **40**: 344-54.

80 Whitton M, Pinart M, Batchelor JM *et al*. Evidence-based management of vitiligo: summary of a Cochrane systematic review. *The British journal of dermatology* 2016; **174**: 962-9.

81 Teulings HE, Lommerts JE, Wolkerstorfer A *et al*. Vitiligo-like depigmentations as the first sign of melanoma: a retrospective case series from a tertiary vitiligo centre. *The British journal of dermatology* 2017; **176**: 503-6.

DIAGNOSIS

CHAPTER 2.1

VITILIGO-LIKE DEPIGMENTATIONS AS THE FIRST SIGN OF MELANOMA: A RETROSPECTIVE CASE SERIES FROM A TERTIARY VITILIGO CENTER.

H.E. Teulings, J.E. Lommerts, A. Wolkerstorfer, L. Nieuweboer-Krobotova,
R.M. Luiten, M.W. Bekkenk and J.P.W van der Veen

British Journal of Dermatology, 2017 Feb;176(2):503-506

Patients with melanoma may develop vitiligo-like skin depigmentation, referred to as melanoma-associated leukoderma (MAL), melanoma-associated hypopigmentation, melanoma-associated depigmentation or melanoma-associated vitiligo.[1-3] Many dermatologists are not aware of the diagnosis of MAL, and may easily diagnose and treat these patients as having non-segmental vitiligo, thereby overlooking the underlying (metastatic) melanoma. At present, the prevalence of MAL and its clinical characteristics are not well established.

In this case series, we retrospectively analyzed the clinical presentation, type of depigmentation and disease course of patients with MAL who were diagnosed at the Netherlands Institute for Pigment Disorders from 2009 to 2014 (cohort 1). Additionally, we reviewed patients with MAL identified from a questionnaire study that evaluated the lifetime prevalence of melanoma in 1307 patients with vitiligo aged ≥50 years (cohort 2).[4] No clear definitions of MAL currently exist regarding the interval between the start of MAL depigmentation and the detection of melanoma. The largest case series so far reported a mean onset of 4.8 years following the primary diagnosis of melanoma.[3] For this study, we arbitrarily defined MAL as depigmentation that developed within 1 year before the detection of a primary melanoma or within 3 years before the detection of melanoma metastases with an unknown primary tumor.

In the period 2009–2014, 3182 new patients were referred to our clinic by general practitioners and dermatologists for diagnosis and treatment of non-segmental vitiligo. The vitiligo types according to the International Classification of Diseases were acrofacialis (n = 146), focalis (n = 348), inflammatory (n = 1), trichrome (n = 10), vulgaris (n = 2622) and universalis (n = 55). Four white patients were diagnosed with MAL. They either had a primary melanoma at first presentation or developed metastatic melanoma at a later stage with an unknown primary tumor. The clinical characteristics of these patients are summarized in Table 1.

In cohort 2, we identified three other white patients who had been diagnosed with non-segmental vitiligo at our institute between 1982 and 2007. All subsequently developed metastasized melanoma within the following 1–3 years with an unknown primary melanoma (Table 2).

Table 1 – Melanoma and melanoma-associated leukoderma (MAL) characteristics of cohort 1.

Patient	**1**	**2**	**3**	**4**
Sex	Female	Female	Male	Female
Age (years)	72	52	45	59
Melanoma characteristics				
Melanoma diagnosis (year)	2006	2011	2012	2012
Breslow/histology	-	0.52 mm SSM Signs of regression	Unknown primary	2 mm SSM
Site	Back	Abdomen	Unknown	Back
Location of diagnosis	Elsewhere	NIPD, following total-body examination for vitiligo	NA	NIPD, following total-body examination for vitiligo
Year of metastasis	2010	2014	2012/2012	NA
Site	Right axilla	Brain	Brain/left axilla	NA, sentinel node negative
Metastasis stage	III	IV	IV	I
Treatment	LND, radiotherapy	Radiotherapy, dabrafenib	Brain surgery, radiotherapy, LND	Local excision
Follow-up	Alive without melanoma. DFS 5 years	DFS 3 years. 2014 progressed to stage IV, 2015 deceased	Alive without melanoma. DFS 3 years	Alive without melanoma. DFS 3 years
MAL characteristics				
Depigmentation since	2009	2011	2011	2011
First visit to NIPD	2010, referred by dermatologist for vitiligo	2011, referred by dermatologist for vitiligo	2011, referred by dermatologist for vitiligo	2012, referred by dermatologist for vitiligo
MAL site	Right side of face, neck, thorax, upper back	Face (forehead, chin, cheeks, temporal, around eyebrows), neck, axillae, perivulvar	Scattered over the back, chest, axillae, arms, legs, face	Dorsal sides of the hands, wrists and arms
Distribution	First unilateral, later bilateral	Bilateral	Bilateral	Bilateral

Table 1 – (continued)

Patient	**1**	**2**	**3**	**4**
Type of lesions	Multiple small, round, patchy depigmented macules	Multiple small, round, patchy hypopigmented and depigmented macules	Multiple small, round, patchy depigmented macules	Multiple polycyclic lenticular hypopigmented and depigmented macules
MAL course	Very progressive	Progressive, not responsive to therapy	Very progressive with sudden onset, not responsive to therapy	Slowly progressive, not responsive to therapy
Therapy before MAL diagnosis	None	Miconazole, hydrocortisone, tacrolimus ointment, FP, CP	NBUVB three times per week (6 months), FP, tacrolimus ointment	Tacrolimus ointment, pimecrolimus ointment
Follow-up of MAL	Depigmentation progressed for 1 year then stabilized	Depigmentation slowly progressed	Depigmentation stable	Depigmentation stable
Autoimmune disease	-	-	-	Hypothyroid
Family history of vitiligo	-	-	-	-
Clinical characteristics				
Demarcation	Medium to sharp	Medium to sharp	Medium to sharp	Medium to sharp
Confetti-like	+	+	+	+
Poliosis	-	+	+	-
Halo naevus	-	-	-	-
Body surface area	8%	1%	10%	5%

SSM, superficial spreading melanoma; NIPD, Netherlands Institute for Pigment Disorders; NA, not applicable; LND, lymph node dissection; DFS, disease-free survival; FP, fluticasone propionate 0.005% ointment; CP, clobetasol propionate 0.05% ointment; NBUVB, narrowband ultraviolet B.

Table 2 – Melanoma and melanoma-associated leukoderma (MAL) characteristics of cohort 2.

Patient	**Q1**	**Q2**	**Q3**
Sex	Female	Male	Female
Age (years)	71	77	69
Melanoma characteristics			
Melanoma diagnosis (year)	NA	NA	2009
Breslow/histology	Unknown primary	Unknown primary	Melanoma in situ with signs of regression
Site	Unknown	Unknown	Verrucous pigmented lesion on left foot
Location of diagnosis	Elsewhere	Elsewhere	Elsewhere
Year of metastasis	1996/1999	1983	2009
Site	Groin/left abdomen (cutaneous)	Left axilla	Left groin
Metastasis stage	IV	III	III
Treatment	DTIC, LND	LND	LND
Follow-up	Alive without metastasis. DFS 16 years	Alive without metastasis. DFS 22 years	Alive without metastasis. DFS 9 years
MAL characteristics			
Depigmentation since	1993	1982, diagnosed as vitiligo elsewhere	2005
First visit to NIPD	1993, diagnosed with vitiligo	2001, diagnosed with vitiligo	2007, diagnosed with vitiligo
MAL site	Chest, lower extremities	Face, neck, chest, upper arms	Face, abdomen
Distribution	Bilateral	Bilateral	Bilateral
Type of lesions	Depigmented macules	Depigmented macules with monk-hood-like distribution	Depigmented macules starting at the wrists and spreading quickly to the rest of the body
MAL course	Progressive, not responsive to therapy	Progressive, no treatment received because of history of melanoma	Progressive, not responsive to therapy
Therapy before MAL diagnosis	UVA twice weekly, FP, punch grafts, transplantation	Phototherapy	NBUVB for 2 years, FP, tacrolimus ointment
Follow-up of MAL	Depigmentation, stable	Depigmentation, stable	Depigmentation, progressed for 2 years then stabilized

Table 2 – (continued)

Patient	Q1	Q2	Q3
Autoimmune disease	-	-	-
Family history of vitiligo	Brother and mother	-	-
Clinical characteristics			
Demarcation	Sharp	Sharp	Medium to sharp
Confetti-like	-	-	+
Poliosis	-	+	-
Halo naevus	-	-	-
Body surface area	0-10%	11-25%	0-10%

NA, not applicable; DTIC, dacarbazine; LND, lymph node dissection; DFS, disease-free survival; NIPD, Netherlands Institute for Pigment Disorders; UVA, ultraviolet A; FP, fluticasone propionate 0.005% ointment; NBUVB, narrowband ultraviolet B.

Taken together, seven patients initially diagnosed with nonsegmental vitiligo could be identified as having MAL, which gives a rough prevalence of MAL in these cohorts of 0.15%. These cases concerned older white patients, with a sudden onset of highly progressive skin hypo- and depigmentation on nontypical vitiligo predilection sites, with medium-to-sharp demarcations and often consisting of round patchy confetti-like lesions (round depigmented macules of 4–5 mm in diameter). These were mostly symmetrical and scattered over trunk, extremities and/or face, possibly as a sign of rapid progression. This is in contrast to typical vitiligo, which is often bilaterally distributed in an acrofacial pattern, or scattered symmetrically over the entire body with a predilection for extensor surfaces, with a relatively early onset in life and a slowly evolving disease course over time.[5] The lesions were generally refractory to topical steroids and ultraviolet phototherapy.

Six of the seven patients had a bilateral (semisymmetrical) distribution of lesions, but one patient started with a unilateral localization that was restricted to the right side of the body coinciding with the site of the melanoma metastasis. Other authors have also described symmetrical distribution of MAL and MAL lesions near the primary tumor or melanoma metastases, with a frequent localization on the trunk, with centrifugal spread, and with confetti-like appearance of depigmentation.[6,7] Most of our patients with MAL (six out of seven) had a negative vitiligo family history, as described in two other case series.[3,6] Hartmann et al. described MAL lesions as nonprogressive, in most cases with a symmetrical bilateral distribution and with a centripetal spread, corresponding to vitiligo but without an association between the location of lesions and the primary tumor.[3] They found an average age of MAL onset of 56 years, compared with 28 years in their vitiligo control group, which is congruent with our data.

Limitations of our study are its retrospective design, which may underestimate the prevalence of MAL, by missing potential patients with MAL due to melanoma diagnosis and treatment elsewhere. Also, data were collected in a tertiary vitiligo referral center, which may lead to a higher prevalence. Furthermore, it cannot be excluded that in some patients with vitiligo, melanoma might develop to be removed subsequently by an effective immune response, unnoticed by patients and their doctors. Thorough physical investigation and anamnestic information on removed melanocytic lesions in the past is probably the most feasible work-up not to miss MAL. Only in case of lymph node enlargement or other health problems should additional imaging be considered.

The majority of the patients with MAL with metastasized melanoma in this study experienced exceptionally favorable melanoma disease-free survival, as is known for patients with melanoma treated with immunotherapy.[2,8] Unfortunately, one patient died regardless of her progressive MAL lesions. Apparently, in her case her antimelanocyte melanoma immunity was not strong enough to eliminate the tumor. Patients with MAL should be informed about the potentially favorable nature of their depigmentation, and repigmentation treatment of MAL lesions is therefore not advisable.

More studies are needed to study the clinical features and prevalence of MAL in other vitiligo populations. So far, based on clinical characteristics only, it is difficult to distinguish MAL from non-segmental vitiligo. We recently described differences in humoral immunity in patients with MAL and vitiligo. While autoantibodies against gp100 and tyrosinase are found in both patients with MAL and patients with vitiligo, MART-1 antibodies were present only in patients with MAL and undetectable in patients with vitiligo.[9]

In conclusion, although MAL constitutes only a small percentage of patients presenting with vitiligo-like depigmentation, awareness of this phenomenon and correct diagnosis of these patients is crucial to limit further melanoma treatment delay. Thorough physical examination aimed at suspect melanocytic lesions should be performed, and a history on removed melanocytic lesions should be recorded in any patient presenting with atypical vitiligo. Special attention is needed for older white patients presenting with late-onset, very progressive atypical vitiligo-like depigmentations refractory to standard treatment.

REFERENCES

1 Speeckaert R, van Geel N, Vermaelen KV *et al.* Immune reactions in benign and malignant melanocytic lesions: Lessons for immunotherapy. *Pigment Cell and Melanoma Research* 2011; **24**: 334-44.

2 Quaglino P, Marenco F, Osella-Abate S *et al.* Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: Results from a single-institution hospital-based observational cohort study. *Annals of Oncology* 2010; **21**: 409-14.

3 Hartmann A, Bedenk C, Keikavoussi P *et al.* Vitiligo and melanoma-associated hypopigmentation (MAH): shared and discriminative features. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* 2008; **6**: 1053-9.

4 Teulings HE, Overkamp M, Ceylan E *et al.* Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *The British journal of dermatology* 2013; **168**: 162-71.

5 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *The Lancet* 2015; **386**: 74-84.

6 Koh HK, Sober AJ, Nakagawa H *et al.* Malignant melanoma and vitiligo-like leukoderma: an electron microscopic study. *Journal of the American Academy of Dermatology* 1983; **9**: 696-708.

7 Nordlund JJ, Kirkwood JM, Forget BM *et al.* Vitiligo in patients with metastatic melanoma: a good prognostic sign. *Journal of the American Academy of Dermatology* 1983; **9**: 689-96.

8 Teulings HE, Limpens J, Jansen SN *et al.* Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**: 773-81.

9 Teulings HE, Willemsen KJ, Glykofridis I *et al.* The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. *Pigment cell & melanoma research* 2014; **27**: 1086-96.

CHAPTER 2.2

MELANOMA-ASSOCIATED LEUKODERMA AND VITILIGO CANNOT BE DIFFERENTIATED BASED ON BLINDED ASSESSMENT BY EXPERTS IN THE FIELD.

J.E. Lommerts, H.E. Teulings, K. Ezzedine, N. Van Geel, A. Hartmann, R. Speeckaert, P.I. Spuls, A. Wolkerstorfer, R.M. Luiten and M.W. Bekkenk

Journal of the American Academy of Dermatology, 2016 Dec;75(6):1198-1204

ABSTRACT

Background: Melanoma-associated leukoderma (MAL) is a depigmenting disorder that can occur spontaneously in patients with melanoma. The differences in clinical presentation between MAL and vitiligo are not well defined. This may lead to misdiagnosing MAL as vitiligo, resulting in delayed detection of melanoma.

Objective: The objective of this study was to assess whether experts in the field can distinguish between MAL and vitiligo, and to assess if discriminative features can be identified.

Methods: We designed an image comparison study in which 4 experts in the field blindly assessed photographs followed by medical history of 11 patients with MAL and 33 with vitiligo.

Results: The assessors misdiagnosed 72.7% of MAL cases and marked 80.0% of them as typical vitiligo. The median age at onset of the leukoderma was higher (55 years, P = .001) in MAL. No discriminative features were found.

Limitations: Sampling bias because of inclusion in tertiary referral center is a limitation.

Conclusion: The clinical presentation of leukoderma in patients with melanoma resembles that of vitiligo. We propose "melanoma-associated vitiligo" as the more appropriate term for leukoderma in patients with melanoma. Clinicians should be aware that depigmentation in vitiligo can also be caused by melanoma-associated vitiligo and a total body inspection should be performed.

INTRODUCTION

Vitiligo is the most common depigmenting skin disorder affecting approximately 0.5-1% of the world's population.[1] Diagnosis of vitiligo is based on clinical presentation with symmetrical distribution of well-demarcated depigmentations.[2] Probably the most alarming differential diagnosis of vitiligo is melanoma-associated leukoderma (MAL). Depigmentation in MAL can occur spontaneously before or after the detection of melanoma.[3,4] A recent observational study showed that leukoderma occurs in 2.8% of all melanoma patients and before the diagnosis of melanoma in 20.5% of all MAL cases.[5]

The differences and similarities in clinical presentation between MAL and vitiligo are not well defined and the literature is contradictory. A retrospective analysis found in the majority of patients with MAL a symmetrical bilateral distribution in MAL similar to that in vitiligo.[4] However, other studies showed a more varied clinical spectrum between MAL and vitiligo with mostly hypopigmented macules with irregularly shaped borders and confetti-like appearance in MAL as opposed to the well-demarcated white macules in vitiligo.[2,6,7] The clinical presentation of MAL is sometimes described as atypical and not comparable to vitiligo.

To date, in clinical practice it can be difficult to distinguish between MAL and vitiligo. Subsequently, these difficulties may lead to misdiagnosing the leukoderma in MAL as vitiligo resulting in late detection of melanoma. The aim of this study was to identify whether experts in the field can distinguish between MAL and vitiligo, and to assess if discriminative features can be identified.

MATERIALS AND METHODS

We conducted a blinded comparison study of clinical photographs at the Netherlands Institute for Pigment Disorders (NIPD) in Amsterdam. The local ethics committee stated that the Medical Research Involving Human Subjects Act was not applicable. Patients with MAL were retrospectively recruited from July 2010 until February 2015 and prospectively recruited from February 2015 until August 2015. MAL was defined as onset of leukoderma 1 year before the diagnosis of a primary melanoma, 3 years before the detection of melanoma metastases with an unknown primary tumor, onset of leukoderma after diagnosis of melanoma, or after immunotherapy. Patients with MAL were only included when all existing depigmentations were photographed. The medical records were used to extract patient characteristics.

Patients with vitiligo were prospectively and consecutively included until the ratio 1:3 of patients with MAL and vitiligo was reached. The inclusion criteria for vitiligo were as follows: (1) first presentation with vitiligo at the NIPD, (2) diagnosis of vitiligo, (3) Fitzpatrick skin type of I, II, III or IV, (3) age 18 or over. Exclusion criteria were: not willing or able to give written informed consent or patients receiving ultraviolet B treatment in the past 6 months. Eligible vitiligo patients were asked to fill in a questionnaire comprising questions regarding current age, skin type, gender, disease activity (vitiligo disease activity score), age at onset of leukoderma, family history of vitiligo, autoimmune comorbidity and Koebnerization. Subsequently, photographs of all depigmentations were taken by our photography department. From all eligible participants written informed consent was obtained. Furthermore, a total body examination of all patients was performed.

Clinical assessment by experts in the field

All digital photographs and medical history of patients with both MAL and vitiligo were extracted and randomly presented in a digital form. The blinded assessment of patients was performed by four experts in the field (K.E., N.v.G., A.H., R.S.). The ratio of patients with MAL and vitiligo was not known to any of the assessors. The questionnaire was divided into 2 parts: (1) assessment based on photographs; and (2) assessment based on photographs and medical history. In the first part of the questionnaire the assessors were asked to give their diagnosis (MAL or vitiligo), answer the question 'I am certain of my diagnosis' on a Likert-scale, specify in case of vitiligo whether it is typical or atypical vitiligo, evaluate different clinical features, and state on which clinical signs the diagnosis was based. In the second part of the questionnaire, the assessors were asked whether the medical history (excluding potential history of melanoma) changed the diagnosis. If this was the case, they rated the certainty of their changed diagnosis and marked on which features the new diagnosis was based.

Data extraction and analyses

The data were extracted and statistical analyses were performed using software (SPSS, Version 22, IBM Corp, Armonk, NY). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the diagnosis of MAL and vitiligo based on digital photographs with or without medical history assessment were calculated for each assessor with the actual diagnosis as reference. Nonnormal distributed continuous data were presented as medians with their interquartile ranges and categorical data were expressed as percentages. The clinical features for each individual patient assessed by each assessor were pooled. In the case when 3 or more assessors responded similarly, this answer was extracted as the overall clinical feature. The clinical features were marked

with low agreement if 2 or less assessors responded similarly. The data were analyzed using Mann-Whitney U tests for nonnormal distributed numeric data and X^2 test for discrete data. Multiple comparisons (n=45) were made and after Bonferroni correction the significance level was set at *P* less than 0.05/45=0.001. Missing data and clinical features with more than 30% of discrepancy between the assessors were marked as low agreement and excluded from statistical analyses.

RESULTS

In all, 11 patients with MAL and 33 patients with vitiligo were found to be eligible. The median age at onset of the leukoderma was significantly higher in patients with MAL than in patients with vitiligo: 55 versus 34 years respectively (*P*=0.001). Patient characteristics are summarized in Table 1. None of the vitiligo patients had a medical history of melanoma or nevus excision.

Diagnostic accuracy and agreement

The assessors misdiagnosed 72.7% (mean) of patients with MAL after assessment of the photographs only. The mean sensitivity for diagnosing MAL on photographs was 27.3% and the mean specificity was 93.2%. The photographic assessment resulted in a mean PPV and NPV for diagnosing MAL of 56.4% and 79.5%, respectively. The diagnostic accuracy of each assessor is presented in Table 2.

The certainty of the diagnosis was in 3 out of 4 assessors higher ($p<0.05$) in correctly diagnosed vitiligo than in correctly diagnosed MAL. It seems that the diagnosis of MAL gives more uncertainty than diagnosing vitiligo. In the patients with MAL, no significant differences were found between patients with spontaneous leukoderma and those with leukoderma after immunotherapy. In addition, between patients correctly given a diagnosis of MAL and those patients with MAL who were given a misdiagnosis no significant differences were found in the duration between the onset of leukoderma and the diagnosis of MAL.

The patients with misdiagnosed MAL were marked as typical vitiligo in 80.0% (mean; range 70.0-100.0%) versus 66.9% (mean; range 58.0-79.3%) of the correctly diagnosed vitiligo cases. The correct diagnosis of MAL was most frequently based on distribution (66.7%), configuration (50.0%), and localization (50.0%) of the lesions. These diagnostic criteria were similar in patients with vitiligo incorrectly diagnosed as MAL. The

misdiagnosis of MAL was most frequently based on the distribution (78.1%), localization (75.0%), and type of leukoderma (43.8%). These results were comparable with a correct diagnosis of vitiligo.

Table 1 - Patient characteristics.

	MAL	Vitiligo	P value
Patients, N (%)	11 (25)	33 (75)	NA
Male, N (%)	7 (63.6)	18 (54.5)	0.598*
Age, y, median (IQR)	56 (48-62)	39 (29-47)	0.002**
Fitzpatrick skin type, N (%) *I* *II* *III* *IV* *V* *VI*	 0 (0) 8 (72.7) 2 (18.2) 1 (9.1) 0 (0) 0 (0)	 1 (3.0) 12 (36.4) 18 (54.5) 2 (6.1) 0 (0) 0 (0)	0.155*
Age at onset, y, median (IQR)	55 (43-60)	34 (25-44)	0.001**
Disease duration, y, median (IQR)	1 (1-3)	4 (1-7)	0.303**
Onset leukoderma after diagnosis of melanoma, y (IQR)	2.3 (0.9-5.8)	NA	NA
Leukoderma during immunotherapy, N (%)	4 (36.4)	NA	NA
VIDA, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.376**
Koebnerization, N (%) *No* *Unknown*	 3 (27.3) 8 (72.7)	 22 (66.7) 0 (0.0)	 0.230* NA
Auto-immune comorbidity, N (%)	1 (9.1)	7 (21.2)	0.367*
Family history of vitiligo, N (%)	1 (9.1)	10 (30.3)	0.221*

IQR, interquartile range; MAL, melanoma-associated leukoderma; NA, not assessed; VIDA, vitiligo disease activity score.
* Measured with X^2 test.
** Measured with Mann-Whitney U test.

When additional medical history was presented, the diagnosis was changed in a mean number of 4.25 patients. This resulted in a mean 63.6% of patients with misdiagnosed MAL after assessment of the medical history. Mean sensitivity and specificity after evaluation of the medical history was 44.0% and 92.4%, respectively. Mean PPV improved to 68.5% and NPV decreased to 76.6%. In cases with a correct change to MAL, the absence of a positive autoimmune comorbidity (100%) and family history (100%) were the cause of the correct change. In cases with a correct change to vitiligo, positive family history (83.0%) and disease activity (33.3%) were the cause of the diagnosis change. The presence of a positive family history was the most frequent cause for an

incorrect change from MAL to vitiligo. Short disease activity, absence of autoimmune comorbidity, and negative family history of vitiligo were the most common reasons for incorrect changes from vitiligo to MAL. Examples of photographs of correctly and incorrectly diagnosed vitiligo and MAL cases are presented in Figure 1.

Blinded observation

The pooled blinded observation of all assessors is presented in Table 3. No significant differences in clinical presentation between MAL and vitiligo were identified. Generally, no specific morphological pattern was found in patients with either MAL or vitiligo. The extent of the depigmentation was similar with a median affected body surface area of 3.0% (interquartile range 1.4 – 7.1) and 2.3% (interquartile range 0.7 – 7.4) in MAL and vitiligo, respectively. No significant differences were found in the blinded clinical observation between patients with MAL with and without onset of leukoderma during immunotherapy treatment.

Table 2 - Diagnostic accuracy of each assessor.

	A-1	A-2	A-3	A-4
Assessment on photographs				
Missed MAL (%)	72.7%	90.9%	72.7%	54.5%
PPV (%)	60.0%	50.0%	60.0%	55.6%
NPV (%)	79.5%	76.2%	79.5%	82.9%
Sensitivity (%)	27.3%	9.0%	27.3%	45.5%
Specificity (%)	93.9%	97.0%	93.9%	87.9%
Assessment on photographs and medical history				
Change of diagnosis (n) Correct change to MAL (n) Correct change to vitiligo (n) Wrong change to MAL (n) Wrong change to vitiligo (n)	5 2 1 1 1	4 2 1 1 0	5 2 2 0 1	3 0 2 1 0
Misdiagnosed MAL (%)	63.6%	72.7%	63.6%	54.5%
PPV (%)	36.4%	75.0%	100.0%	62.5%
NPV (%)	60.6%	80.0%	82.5%	83.3%
Sensitivity (%)	66.7%	27.3%	36.4%	45.5%
Specificity (%)	81.6%	97.0%	100.0%	90.9%

A-1, Assessor 1; A-2, assessor 2; A-3, assessor 3; A-4, assessor 4; MAL, melanoma-associated leukoderma; NPV, negative predictive value; PPV, positive predictive value.

Table 3 - Clinical features assessed by the assessors.

	MAL (%)	Vitiligo (%)	Low agreement (%)		P value*
			MAL	Vitiligo	
Localization					
Head and neck	90.9	87.9	-	3	0.978
Periorbital	27.3	42.4	27.3	6.1	0.697
Perioral	81.8	48.5	9.1	12.1	0.032
Frontal	63.6	42.4	18.2	3	0.071
Maxillar	18.2	21.2	27.3	6.1	0.885
Mandibular	72.7	39.4	-	6.1	0.079
Neck	45.5	39.4	-	6.1	0.839
Trunk	54.5	42.4	-	-	0.484
Chest / upper body	45.5	24.2	9.1	6.1	0.153
Abdomen	9.1	18.2	-	3	0.454
Upper back	36.4	24.2	-	-	0.434
Lower back	9.1	6.1	-	3	0.750
Limbs	54.5	69.7	-	-	0.359
Axillar	27.3	21.2	-	3.0	0.715
Upper arm	0.0	12.1	-	-	0.226
Elbow, ventral side	0.0	6.1	-	-	0.403
Elbow, dorsal side	9.1	30.3	-	-	0.159
Lower arm	18.2	18.2	-	-	1
Wrist	9.1	33.3	-	3.0	0.107
Hand	27.3	60.6	-	-	0.055
Legs	9.1	21.2	-	3.0	0.347
Knee	0.0	6.1	9.1	6.1	0.410
Foot	0.0	24.2	-	3.0	0.066
Anogenital	0.0	33.3	-	-	0.027
Buttocks	0.0	3.0	-	-	0.559
Symmetric bilateral distribution	**100**	**84.8**	**-**	**6.1**	**0.284**
Confetti-like configuration	**54.5**	**81.8**	**27.3**	**15.2**	**0.053**
Size of lesions					
1-2 mm	36.4	30.3	-	-	0.634
3-10 mm	63.6	69.7	-	-	0.915
1-3 cm	81.8	90.9	-	-	0.418
3-5 cm	63.6	66.7	-	-	0.900
5-15 cm	45.5	33.3	-	-	0.768
> 15 cm	18.2	6.1	-	-	0.476
Shape			**36.4**	**39.4**	**NA**
Polycyclic	18.2	18.2			
Oval	0	15.2			
Irregular and polycyclic	9.1	3			
Irregular	36.4	24.2			
Round	0.0	0.0			
Well demarcated borders	**36.4**	**54.5**	**36.4**	**30.3**	**NA**

Table 3 - (continued)

	MAL (%)	Vitiligo (%)	Low agreement (%)		P value*
			MAL	Vitiligo	
Leukoderma					
Only depigmentation De- and hypopigmentation	54.5 27.3	45.5 24.2	18.2	30.3	NA
Presence of halo nevi	**9,1**	**12.1**	**9.1**	**9.1**	**0.690**
Presence of leukotrichia	**27.3**	**9.1**	**-**	**-**	**0.313**

Pooled assessment of the clinical features of MAL and vitiligo. The percentages represent the number of cases in which the clinical feature was present. The low agreement resembles the percentage of cases in which there was low agreement between the assessors. Multiple comparisons (n = 45) were made, after Bonferroni correction the significance level was set at P< 0.05/45 = 0.001. Bold indicates clinical feature (localization, symmetric bilateral distribution, confetti-like configuration, size of lesions, shape, well-dermarcated borders, leukoderma, presence of halo nevi, presence of leucotrichia). Italic indicates subfeature of the main clinical feature (head and neck, trunk, limbs, anogenital, buttocks). MAL, Melanoma-associated leukoderma; NA, not assessed. *Measured with X^2 test.

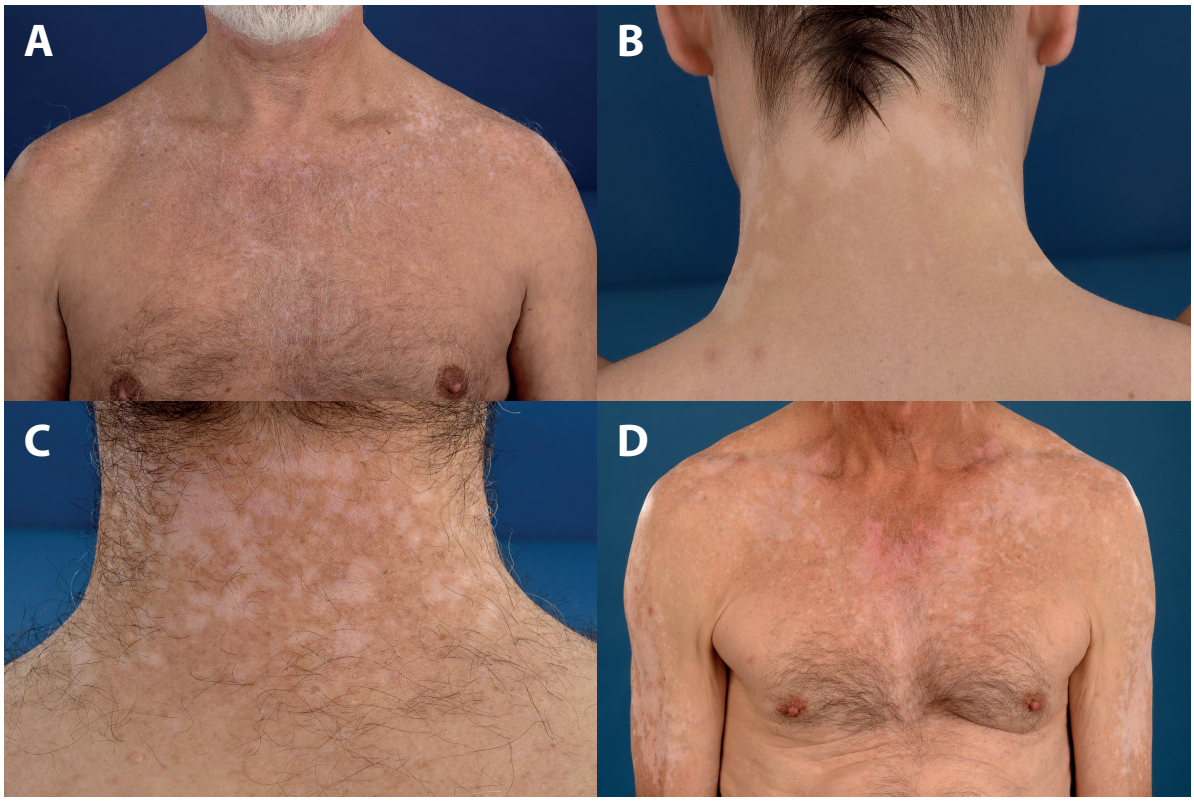


Figure 1 - Melanoma-associated leukoderma (MAL) and vitiligo. Different clinical presentations. Correctly diagnosed MAL (A) and vitiligo (B). Misdiagnosed MAL (C) and vitiligo (D).

DISCUSSION

The results of this study illustrate that even experts in the field cannot clearly differentiate between MAL and vitiligo. Most patients with MAL were given a misdiagnosis based on the assessment of the photographs only. The diagnostic accuracy of MAL was low in all assessors. The assessment of the photographs together with the medical history slightly improved the diagnostic accuracy of MAL. However, incorrect changes to either MAL or vitiligo were made based on medical history. Most importantly, no significant differences in clinical presentation of the leukoderma between MAL and vitiligo were identified.

In previous studies, varying clinical presentations and features of MAL have been described. It seems that patients with MAL have a significantly higher age at onset of depigmentation than patients with vitiligo; this is supported by evidence described in other case series.[4,5] In our study, 9.1% of the patients with MAL had a positive family history of vitiligo. This does not correlate with other case series in which a positive family history of vitiligo was absent in all patients with MAL.[4,7] The distribution of the depigmentation was mostly bilateral and symmetric in MAL, which corresponds with the distribution of vitiligo. We have identified this symmetric distribution pattern in MAL earlier.[4] However, other studies claim a more varying clinical spectrum between MAL and vitiligo with a frequent localization on the trunk and a confetti-like appearance. [6,7] A confetti-like depigmentation may be a sign of rapidly progressing vitiligo.[8] Although the assessors in this study also found a confetti-like figuration in most of the MAL cases (54.5%), this configuration was more frequently identified in vitiligo patients (81.8%).

The strength of this study is that, to our knowledge, it is the first blinded prospective comparison between MAL and vitiligo. Limitations of this study include the fact that the NIPD is a tertiary referral center, which may have led to a sampling bias of vitiligo cases. Furthermore, the inclusion of both patients with MAL and spontaneous leukoderma and those with leukoderma after immunotherapy could also have led to sampling bias of the patients with MAL. However, no differences in clinical presentation were found between the 2 groups. The prevalence of MAL in our center (0.15%) and in this study (25%) are different.[9] Therefore, the PPV and NPV cannot be translated to the diagnostic accuracy in daily practice. Moreover, the assessors were aware that they needed to differentiate between MAL and vitiligo and they showed low agreement on the assessment of possible discriminative features. Therefore, in clinical practice the risk of missing MAL is likely to be higher. Theoretically, patients with spontaneous regression

of a primary melanoma could have been included in the vitiligo group. However, none of the vitiligo patients had suspected melanocytic lesions or a history of previous nevus excision.

MAL cannot be classified as a subtype of vitiligo according to the Vitiligo Global Issues Consensus Conference. [4,10] We previously identified immune responses against melanocyte antigens in both MAL and vitiligo, suggesting a similar pathogenesis.[11] However, the presence of antibody responses against the melanoma-associated antigen recognized by T-cells (MART-1 antigen) in MAL but not in vitiligo indicate that differences in immunity are involved. Vitiligo is triggered by both genetic and environmental factors, whereas MAL is triggered by the presence of melanoma. In a previous comparative study, no histologic differences between MAL and vitiligo could be identified.[4] Clinical, histologic and immunologic data do not support the assumption that MAL and vitiligo are separate entities, making the hypothesis of MAL and vitiligo as subtypes of the same disease with different provoking factors more likely. Therefore, "melanoma-associated vitiligo" seems to be a more appropriate name and we propose that this term be used from now on for leukoderma occurring in patients with melanoma.

Clinical discrimination between MAL and vitiligo is difficult, which results from the lack of specific clinical features. As a consequence, a small percentage of patients could be misdiagnosed as having vitiligo and later develop melanoma metastases. Clinicians should be aware that depigmentation in patients with seemingly typical vitiligo can also be caused by MAL and a total body inspection on suspected melanocytic lesions should be performed, especially in patients with higher age at onset of the leukoderma.

REFERENCES

1 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *Lancet* 2015; **386**: 74-84.

2 Alikhan A, Felsten LM, Daly M *et al.* Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *Journal of the American Academy of Dermatology* 2011; **65**: 473-91.

3 Speeckaert R, Van Geel N, Lambert J *et al.* Immune mediated mechanisms of melanocyte destruction: Paving the way for efficient immunotherapeutic strategies against melanoma. *Oncoimmunology* 2012; **1**: 526-8.

4 Hartmann A, Bedenk C, Keikavoussi P *et al.* Vitiligo and melanoma-associated hypopigmentation (MAH): shared and discriminative features. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* 2008; **6**: 1053-9.

5 Quaglino P, Marenco F, Osella-Abate S *et al.* Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**: 409-14.

6 Nordlund JJ, Kirkwood JM, Forget BM *et al.* Vitiligo in patients with metastatic melanoma: a good prognostic sign. *Journal of the American Academy of Dermatology* 1983; **9**: 689-96.

7 Koh HK, Sober AJ, Nakagawa H *et al.* Malignant melanoma and vitiligo-like leukoderma: an electron microscopic study. *Journal of the American Academy of Dermatology* 1983; **9**: 696-708.

8 Sosa JJ, Currimbhoy SD, Ukoha U *et al.* Confetti-like depigmentation: A potential sign of rapidly progressing vitiligo. *Journal of the American Academy of Dermatology* 2015; **73**: 272-5.

9 Teulings HE, Lommerts JE, Wolkerstorfer A *et al.* Vitiligo-like depigmentations as first sign of melanoma; a retrospective case series from a tertiary vitiligo centre. *The British journal of dermatology* 2016.

10 Ezzedine K, Lim HW, Suzuki T *et al.* Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment cell & melanoma research* 2012; **25**: E1-13.

11 Teulings HE, Willemsen KJ, Glykofridis I *et al.* The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. *Pigment cell & melanoma research* 2014; **27**: 1086-96.

CHAPTER 2.3

FOCAL VITILIGO: LONG-TERM FOLLOW-UP OF 52 CASES.

J.E. Lommerts, Y. Schilder, M.A. de Rie, A. Wolkerstorfer and M.W. Bekkenk

Journal of the European Academy of Dermatology and Venereology, 2016 Sep;30(9):1550-4

ABSTRACT

Background: Focal vitiligo is characterized by depigmented patches located in a small area without a typical segmental distribution. Focal vitiligo is classified as an undetermined type of vitiligo, and a more definitive diagnosis can be made when the lesions have not evolved into non-segmental or segmental vitiligo after a period of 1-2 years. However, the chance of progression is not known and may lead to treatment-indecision.

Objective: The objective was to study the characteristics of patients with focal vitiligo and possible predictors of progression.

Methods: We conducted a survey study in patients with initial diagnosis of focal vitiligo between January 2005 and June 2010. Focal vitiligo was defined as either a small acquired isolated depigmented lesion without typical segmental distribution, or two to three small acquired lesions localized in a non-segmental area with a maximum of 5 cm. The survey comprised of 21 questions concerning the patient's characteristics, the onset of focal vitiligo, progression of depigmentation and treatment history.

Results: We identified 128 eligible patients and the response rate was 40.6% (n = 52 completed questionnaires). Progression to non-segmental vitiligo occurred in 23%. The median follow-up duration was 7 years. In 11.5% of the patients, progression to non-segmental vitiligo occurred within 2 years after onset. Nevertheless, even after a first stable period of more than 2 years, another 11.5% of the patients advanced to non-segmental vitiligo. No associated prognostic factors at baseline of progression to non-segmental or long-lasting focal vitiligo were found.

Conclusion: Focal vitiligo is a rare subtype of vitiligo and most patients have long-lasting focal lesions after onset of the disease. In this study, focal vitiligo progressed to typical non-segmental vitiligo, but not towards typical segmental vitiligo. Progression 2 years after onset of focal vitiligo, occurs in 50% of the patients with eventual progression to non-segmental vitiligo. There seem to be no clinical signs that predict progression in focal vitiligo.

INTRODUCTION

Vitiligo is a common depigmenting skin condition caused by destruction of melanocytes.[1] It affects approximately 0.5 – 1% of the world's population with no differences in skin type or sex.[2] Vitiligo can be a great burden and impair patient's quality of life.[3] Generally, two types of vitiligo can be distinguished by the distribution of the lesions.[4] This differentiation is of prognostic value and has therapeutic consequences. Non-segmental vitiligo is characterized by bilateral white patches with a tendency towards progression and a symmetrical distribution on the extensor sites and orifices. In segmental vitiligo the depigmented lesions are distributed in a limited segmental distribution and usually do not cross the midline.[5] Treatment modalities for non-segmental vitiligo, such as UVB-therapy and topical ointments, are focused on cessation of spread and repigmentation. In contrast, stable segmental vitiligo is mostly treated with surgical techniques.

In focal vitiligo the white patches are located in a small area without a typical segmental distribution. It has been referred to as a precursor of either non-segmental vitiligo or segmental vitiligo. The Vitiligo Global Issues Consensus Conference (VGICC) recently classified focal vitiligo as a subtype of undetermined/unclassified vitiligo and stated that a more definitive classification can be made when the lesions have not evolved into non-segmental vitiligo or segmental vitiligo after a period of 1-2 years of follow-up.[4] To the best of our knowledge, there is only one study available on the long-term follow-up of focal vitiligo. Zaima et al.[6] studied 44 cases with focal vitiligo for 6 years. During the first 2 years of follow-up, 27% developed non-segmental vitiligo and further three of the 44 cases developed non-segmental vitiligo after a period of 5 years.[6] It is not known if further progression of stable disease can occur after this period. Furthermore, the clinical signs predicting progression in initial focal vitiligo are not known.

To date, focal vitiligo is a subtype of undetermined/unclassified vitiligo. However, during onset of the depigmentation it could also be considered as an incompletely evolved non-segmental vitiligo or segmental vitiligo. Little is known about the chance of progression and possible prognostic factors; this may lead to treatment-indecision and uncertainty of prognosis. The objective of this survey was to study the characteristics of patients with focal vitiligo and possible predictors of progression. Furthermore, we hypothesized that focal lesions do not progress to other body regions after 2 years of stability as stated by the VGICC to be an indicative threshold for a more definitive diagnosis of focal vitiligo.

MATERIALS AND METHODS

We retrospectively recruited all patients with the initial diagnosis of focal vitiligo visiting the Netherlands Institute for Pigment Disorders (NIPD) between January 2005 and June 2010. Focal vitiligo was defined as a small acquired isolated depigmented lesion without typical segmental distribution or two to three small acquired lesions localized in a non-segmental area with a maximum of 5 cm (arbitrarily chosen). Initial diagnosis was based upon clinical examination with additional Wood's light examination. Medical records were used to extract data of the first visit to our institute at the onset of the focal vitiligo.

Patients were included when they met the following inclusion criteria: (i) initial diagnosis of focal vitiligo according to criteria mentioned above, (ii) follow-up duration of 5 years or more, and (iii) current age ≥ 12 years. Exclusion criteria were onset of lesions around halo nevi, insufficient mastery of Dutch language or residential outside the Netherlands. All eligible patients were sent a postal survey and were asked to send the questionnaires back in prepaid return envelopes. Non-responsive eligible patients were reminded by telephone and a new questionnaire was sent upon agreement. The parents of patients younger than 16 years were asked to fill in the questionnaire together with their child. The Medical Ethics Committee of the Academic Medical Centre in Amsterdam was notified and stated that the Medical Research Involving Human Subjects Act was not applicable to our study. Written informed consent from all included participants was obtained.

Postal survey

The survey comprised of 21 questions regarding several patient and disease features. These features were similar to those stated as important to assess in vitiligo by the European Dermatology Forum consensus.[2] The questioned patient characteristics included age, gender, skin type, medical and family history of vitiligo, premature hair greying and auto-immune disorders (i.e. thyroid disorders, diabetes mellitus type 1, alopecia areata, psoriasis, systemic lupus erythematosus, rheumatoid arthritis). Questions regarding vitiligo involved the age of onset, presence of leucotrichia and/or halo nevi, triggering factors, treatment history and efficacy. Patients were also asked to give an estimation of the affected body surface area (measured with the 1% hand palm rule) and draw the affected depigmented body areas on a figure. Furthermore, they were asked to fill in other questions concerning the precise location(s) and laterality of the current lesions. The duration of stable focal vitiligo, disease activity and possible triggering factors was extracted from the patients showing progression of depigmentation.

Data analyses

Patients were categorized into 3 groups (i) long-lasting focal vitiligo, (ii) progression to non-segmental vitiligo, and (iii) progression to segmental vitiligo. This categorization was based on the criteria stated by the VGICC. Patient characteristics of the different groups are shown in medians with interquartile ranges or percentages. The photographs of the lesions at first presentation were extracted from the medical file and incidences of the depigmented lesions per group with their corresponding color (from red to yellow) were drawn on a standardized figure (with permission from Wiley, the publisher of the article in which the figure was first used).[7] Possible predicting factors for progression to either non-segmental or segmental vitiligo were assessed using univariate logistic regression.

RESULTS

In the NIPD 3917 patients with vitiligo (all types) were diagnosed between 2005 and 2010. We identified 128 eligible patients with focal vitiligo. The response rate was 40.6% with 52 completed questionnaires. The 76 non-responders were mostly due to an unknown reason (n=45), other reasons for non-responding were invalid contact details (n=28), not willing to participate (n=2) and one eligible patient had died. No evident differences in demographic characteristics were found between the non-responsive and responsive patients.

Patient characteristics

In Table 1 the characteristics of patients with long-lasting focal vitiligo and progression to non-segmental vitiligo are presented. The median age of the responders was 41 years and both genders responded equally to the survey. The median follow-up duration was 7 years. In 12 patients (23%) progression to non-segmental vitiligo occurred while 40 (77%) cases had long-lasting focal vitiligo. No cases of typical segmental vitiligo were identified. Furthermore, no evident differences between long-lasting focal vitiligo and progression to non-segmental vitiligo in baseline and follow-up characteristics were found. The age at onset in both groups was mostly > 18 years. In cases with onset < 12 years the percentage of progression to non-segmental vitiligo (25%) was similar to that of the entire group (23%). No obvious differences in family history of vitiligo and autoimmune diseases, presence of leucotrichia and medical history were found between long-lasting focal vitiligo and progression to non-segmental vitiligo. Furthermore, no prognostic factors at onset for progression were found using univariate regression analyses.

Table 1 - Patient characteristics of long-lasting focal vitiligo and progression to non-segmental vitiligo.

	long-lasting focal vitiligo	progression to non-segmental vitiligo
	n (%)	n (%)
Total (n)	40 (77%)	12 (23%)
Age, median (IQR)	42 (24-52)	34 (20-48)
Age at onset focal vitiligo		
Median (IQR)	34 (17-45)	28 (12-41)
< 12 y	6 (15%)	2 (16.7%)
12 – 18 y	6 (15%)	2 (16.7%)
19-35 y	9 (22.5%)	5 (41.7%)
36-50y	14 (35%)	1 (8.3%)
>50y	5 (12.5%)	2 (16.7%)
Follow-up duration, median (IQR)	7.0 (5.9-8.7)	6.0 (5.8-9.2)
Sex		
Male	20 (50%)	5 (41.7%)
Female	20 (50%)	7 (58.3%)
Skin type		
Fair skin type	21 (52.5%)	10 (83.3%)
Darker skin type	19 (47.5%)	2 (16.7%)
Medical history autoimmune disease		
Thyroid disorder(s)	2 (5%)	1 (8.3%)
Psoriasis	1 (2.5%)	1 (8.3%)
Diabetes mellitus type 1	1 (2.5%)	0 (0%)
Premature hair greying (<40y)	3 (7.5%)	0 (0%)
Family history		
Vitiligo	10 (25%)	4 (33.3%)
Autoimmune disease	17 (42.5%)	6 (50%)
Premature hair greying	10 (25%)	1 (8.3%)
Location of focal vitiligo at onset		
Head and neck	28 (62.5%)	10 (83.4%)
Trunk	1 (2.5%)	1 (8.3%)
Hands	2 (5.0%)	0 (0.0%)
Genitals	9 (22.5%)	1 (8.3%)
Trauma as triggering factor at onset	4 (10%)	0 (0%)
Presence of leucotrichia at onset	18 (45.0%)	4 (33.3%)
Presence of halo nevi at onset	3 (7.5%)	2 (16.7%)
Treatment history		
Topical treatment (cs or TIM)	25 (62.5%)	7 (17.5%)
NBUVB	13 (32.5%)	4 (33.3%)
Mini punch grafting	15 (37.5%)	3 (35%)
Complete response	3 (20%)	0 (0%)
Partial response	10 (66,7%)	2 (66,7%)

Premature hair greying, hair greying with more than 50% of grey hairs before the age of 40 years. n, number of patients; IQR, interquartile range; cs, corticosteroids; y, years; TIM, topical immunomodulators.

Distribution at onset

The distribution of the focal lesions at presentation is shown in Figure 1. The depigmentation was at onset located in the head and neck area in 62.5% and 83.4% of patients with long-lasting focal vitiligo and progression to non-segmental vitiligo, respectively. Most lesions (63.5%) were unilaterally distributed and did not cross the midline. Ten patients were initially diagnosed with focal genital vitiligo and one of these patients progressed to non-segmental vitiligo. No localized depigmentation at onset on the extremities or back was found in both groups.

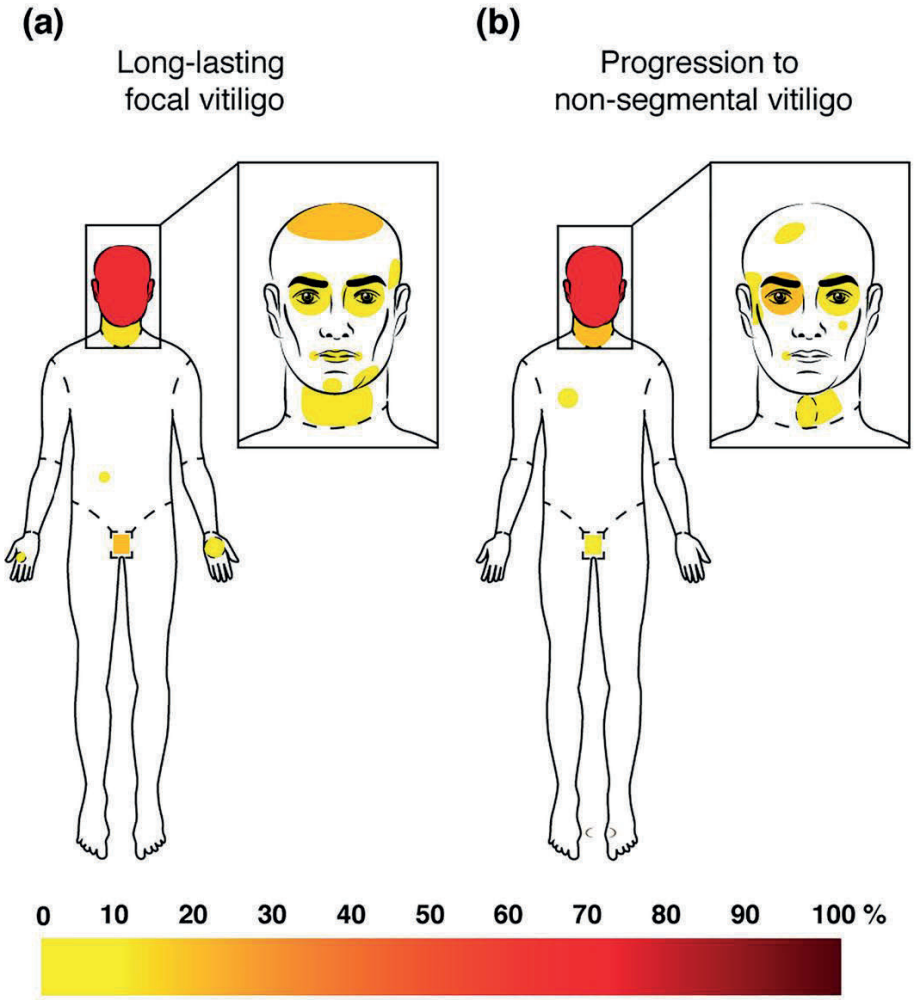


Figure 1 - Incidence of localization of depigmentation at first presentation per body region in (a) long-lasting focal vitiligo and (b) progression to non-segmental vitiligo. Absolute percentages are presented in the colored bar, with bright yellow representing 0% and dark red 100%. Incidences of depigmentation per body region per group are colored in the left figure. The specific incidences within the head and neck-region are colored separately in the right figure for each group.

Progression to non-segmental vitiligo

Figure 2 presents the number of patients with focal vitiligo per time point. Six (11.5%) patients developed non-segmental vitiligo within 2 years after onset of lesions. Another 6 patients advanced to non-segmental vitiligo in a median time of 5 years (range 2-6 years) after onset. From the 12 patients with progression, 10 patients showed typical non-segmental vitiligo with symmetrical depigmentation on predilection sites, for example, friction areas and orifices. All patients with progression to non-segmental vitiligo had limited disease severity with 0-10% affected body surface area after follow-up.

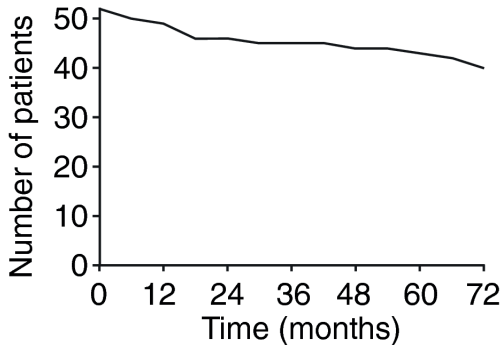


Figure 2 - Number of patients with focal vitiligo during follow-up.

DISCUSSION

Focal vitiligo is characterized by small isolated depigmented macules without a typical segmental distribution.[4] Such localized lesions can also be seen in the initial stages of both non-segmental and segmental vitiligo. Focal vitiligo is a rare subtype of vitiligo; in our institute we identified 3.3% of all vitiligo patients as focal vitiligo. In this study, 77% of all initial focal vitiligo cases demonstrated persistent stability and were classified as long-lasting focal vitiligo.

According to the VGICC, the diagnosis of focal vitiligo is more conclusive when progression to either non-segmental vitiligo or segmental vitiligo did not occur after a period of 1-2 years of follow-up.[4] We included all patients with the initial diagnosis of focal vitiligo, even those patients with fast progression after onset. It can be discussed whether these eventual non-segmental vitiligo patients were given the wrong diagnosis at presentation and may not have been included. However, the objective of

this survey was to study the characteristics of progression in focal vitiligo. This includes also the timeframe in which progression occurred. Therefore, we included all patients with the initial diagnosis of focal vitiligo to study the natural course of small localized depigmented lesions. In this study, 50% of patients with eventual non-segmental vitiligo showed progression within 2 years after onset. Zaima et al showed that 80% of patients with progression to non-segmental vitiligo progressed within 2 years after onset of focal vitiligo.[6] It seems that the 2 years of stability needed for a more definitive diagnosis of focal vitiligo seems rather appropriate. However, even after a long period of stable disease progression of depigmentation can occur and so the unpredictability of focal vitiligo remains.

The prognosis between non-segmental and segmental vitiligo is significantly different – namely, non-segmental vitiligo is generally a progressive disease with widespread depigmentation and periods of activity. Segmental vitiligo is considered as a stable disease after the first rapid initial evolution phase with limited depigmentation. The perpetual stability in long-lasting focal vitiligo similar to that in segmental vitiligo suggests that it is a subtype of segmental vitiligo. However, segmental vitiligo is typically distributed in either a dermatomal or band-shaped pattern and the focal lesions in this study did not fit these typical patterns. Furthermore, no progression to typical segmental vitiligo occurred as opposed to the 7% in a previous case series in focal vitiligo.[6] Nevertheless, recent studies show that segmental vitiligo does not always fit the "typical" patterns and the interpretation of a typical segmental pattern can be very subjective.[8,9] Stable segmental vitiligo normally responds well to surgical treatment.[10] In this study, long-lasting focal lesions showed rather good results after mini punchgrafting. The prolonged disease stability and good results after surgical treatment indicate a more hypothetical local defect in long-lasting focal vitiligo similar to segmental vitiligo as opposed to the generalized auto-immune response seen in non-segmental vitiligo.

Patients with long-lasting focal vitiligo showed high prevalence of halo nevi, and family and personal history of autoimmune disorders similar to patients with non-segmental vitiligo.[5, 11] The long-lasting focal lesions were also mostly located on predilection sites, e.g. friction areas, for non-segmental vitiligo. It seems that relatively more patients with fair skin phototype progressed to non-segmental vitiligo than with dark skin phototype. However, no other evident differences in characteristics between long-lasting focal vitiligo and patients with progression to non-segmental vitiligo were found. These results suggest that focal vitiligo could be more comparable to non-segmental than to segmental vitiligo. In some patients with progression to non-segmental vitiligo the initial focal lesions remained asymmetrically present and could be classified as

mixed type vitiligo. Mixed type vitiligo is a subtype of non-segmental vitiligo and is characterized by coexistence of segmental and non-segmental vitiligo lesions.[12] To date, it remains unclear whether focal vitiligo is a separate entity or a subtype of either non-segmental or segmental vitiligo.

In clinical practice it is important to distinguish between long-lasting focal vitiligo and non-segmental vitiligo. Patients want to know their prognosis and chance of further progression. Moreover, physicians need to know how to treat their patients. In this survey-study, 23% of all patients developed progression to non-segmental vitiligo. Unfortunately, no prognostic factors at baseline for progression were found. Further research in larger populations with focal vitiligo is needed to study probable prognostic factors of progression.

The survey had a fairly good response rate. However, the results may have been biased by the small population size and retrospective study design. Most lesions in long-lasting focal vitiligo and progression to non-segmental vitiligo were located on the head at onset. This could be explained by the fact that patients with depigmentation on visible areas and extensive vitiligo frequently have an impaired quality of life and are more likely to seek help.[3, 13] Moreover, this could have led to selection bias by relatively more patients with progression and lesions located on the head responding. The Netherlands Institute for Pigment Disorders is a tertiary referral center for the diagnosis and treatment of pigment disorders in The Netherlands. This specialized referral function of the institute may also have resulted in further selection bias.

In conclusion, most patients have long-lasting focal lesions after onset of the disease. In the minority of patients, focal vitiligo can progress to typical non-segmental vitiligo, but not towards typical segmental vitiligo. Progression 2 years after onset of focal vitiligo occurs in 50% in patients with eventual progression to non-segmental vitiligo. There seem to be no clinical signs that predict progression in focal vitiligo.

REFERENCES

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015;**386**; 74-84.
2. Taieb A, Alomar A, Bohm M, Dell'anna ML, De Pase A, Eleftheriadou V, et al. Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *Br J Dermatol*. 2013;**168**; 5-19.
3. Ongenae K, Beelaert L, van Geel N, Naeyaert JM. Psychosocial effects of vitiligo. *J Eur Acad Dermatol Venereol*. 2006;**20**; 1-8.
4. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CC, et al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res*. 2012;**25**; E1-13.
5. Ezzedine K, Diallo A, Leaute-Labreze C, Mossalayi D, Gauthier Y, Bouchtnei S, et al. Multivariate analysis of factors associated with early-onset segmental and nonsegmental vitiligo: a prospective observational study of 213 patients. *Br J Dermatol*. 2011;**165**; 44-49.
6. Zaima H, Koga M. Clinical course of 44 cases of localized type vitiligo. *J Dermatol*. 2002;**29**; 15-19.
7. Hettiaratchy S, Papini R. Initial management of a major burn: II--assessment and resuscitation. *BMJ*. 2004;**329**; 101-103.
8. Hann SK, Chang JH, Lee HS, Kim SM. The classification of segmental vitiligo on the face. *Yonsei Med J*. 2000;**41**; 209-212.
9. van Geel N, Speeckaert R, Melsens E, Toelle SP, Speeckaert M, De Schepper S, et al. The distribution pattern of segmental vitiligo: clues for somatic mosaicism. *Br J Dermatol*. 2013;**168**; 56-64.
10. Whitton ME, Pinart M, Batchelor J, Leonardi-Bee J, Gonzalez U, Jiyad Z, et al. Interventions for vitiligo. *Cochrane Database Syst Rev*. 2015;**2**; Cd003263.
11. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol*. 2011;**65**; 473-491.
12. Ezzedine K, Gauthier Y, Leaute-Labreze C, Marquez S, Bouchtnei S, Jouary T, et al. Segmental vitiligo associated with generalized vitiligo (mixed vitiligo): a retrospective case series of 19 patients. *J Am Acad Dermatol*. 2011;**65**; 965-971.
13. Sampogna F, Raskovic D, Guerra L, Pedicelli C, Tabolli S, Leoni L, et al. Identification of categories at risk for high quality of life impairment in patients with vitiligo. *Br J Dermatol*. 2008;**159**; 351-359.

MEASUREMENT INSTRUMENTS

CHAPTER 3.1

DEVELOPMENT AND VALIDATION OF THE VITILIGO EXTENT SCORE (VES): AN INTERNATIONAL COLLABORATIVE INITIATIVE.

N. van Geel, J.E. Lommerts, M.W. Bekkenk, A. Wolkerstorfer, C.A.C. Prinsen,
V. Eleftheriadou, A. Taïeb, M. Picardo, K. Ezzedine and R. Speeckaert

Journal of Investigative Dermatology 2016 May;136(5):978-84

ABSTRACT

The clinical assessment of vitiligo involves an estimation of the affected body surface area. The most commonly used method is the "palm of hand 1% rule" as integrated in the Vitiligo Area Scoring Index. However, this method can be challenging and time consuming. In this study, we introduce a global Vitiligo Extent Score (VES). In the first part of the study, this measurement instrument was developed and subsequently optimized during a pilot scoring session. In a subsequent stage, the inter- and intrarater reliability of the instrument were tested. Live scoring showed an excellent interrater reliability for the VES (intraclass correlation VES: 0.924 vs. Vitiligo Area Scoring Index: 0.846). Subsequent scoring on pictures was comparable with the live evaluation and demonstrated an excellent intrarater reliability. A high intraclass correlation for the VES (intraclass correlation VES: 0.923 vs. Vitiligo Area Scoring Index: 0.757) was also found in an additional subgroup of patients with extensive vitiligo. Moreover, user-friendliness and timing were scored very favorably. In conclusion, this measurement instrument allows us to monitor accurately and easily the affected body surface area in a standardized way. Moreover, our results provide evidence that the VES can be proposed as a promising tool to measure the vitiligo extent in clinical trials and in daily practice.

INTRODUCTION

There is currently a lack of consensus in the standardization of outcome measures in vitiligo, which makes it difficult to compare the outcomes of different studies and therefore hampers evidence based recommendations.[1,2] Previously, two systematic reviews on vitiligo outcome measurements were published in 2012[3,4] and demonstrated that 25 different outcomes were included that were measured by 11 different instruments. A consensus[5] on the core outcome sets for clinical trials in vitiligo has very recently been reached ("what" should be measured)[6]. Three core outcomes were deemed essential (i.e., to be measured in every trial): repigmentation, side effects, and maintenance of gained repigmentation. The next crucial step is to identify appropriate instruments that assess the core outcome domains of vitiligo. The measurement properties (e.g., validity, reliability, and responsiveness) of the available instruments were critically appraised using the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.[7,8] Strong evidence was only found for a positive internal consistency of the Dermatology Life Quality Index.[4]

Currently, evidence for measurement instruments for vitiligo is rather scarce. The Vitiligo European Task Force (VETF) proposed in 2007[9] the Vitiligo European Task Force assessment tool (VETFa) combining analysis of extent, stage of disease, and disease progression. The Vitiligo Area Scoring Index (VASI) is another score system[10] that offers a disease severity index. Recently, the VASI and VETFa were reported[11] to be reliable and responsive instruments to assess the degree of depigmentation in patients with vitiligo. However, authors reported that for use in clinical practice, caution is needed when interpreting score changes in individual patients because of the relatively large smallest detectable change (SDC). The SDC concerns the minimal difference in disease extent that can be accurately measured by the instrument. Nonetheless, even the VASI, which is the most frequently cited tool, is so far not widely used by researchers[3], which might point to limitations in user-friendliness.

A good and validated scoring instrument permits valid measurement of disease extent, a necessary feature that allows the results of clinical trials to be accurately interpreted and compared. It can help in improvement of management, estimation of prognosis, understanding of disease progression, and the development of therapeutic options in vitiligo. Furthermore, it would be possible to categorize disease severity and allocate resources for instance considering reimbursement criteria.

On the basis of this need, we introduce in this study a clinical scoring instrument (i.e., Vitiligo Extent Score (VES)) that fits in the outcome domain requirements. The key principles in the design of this tool were intelligibility, clarity, simplicity, logic, feasibility, and availability for use in both clinical and research settings.

MATERIALS AND METHODS

Study design and ethics

This trial was conducted on behalf of the International Vitiligo Score Working group in close cooperation with the VETF and VGICC group (the International Vitiligo Score Working Group comprises: Nanja van Geel, Reinhart Speeckaert, Janny Lommerts, Marcel Bekkenk, Albert Wolkerstorfer, Viktoria Eleftheriadou, Khaled Ezzedine, Mauro Picardo, and Alain Taïeb). The development and validation of the VES was performed by six scoring sessions as outlined below. This included a face-to-face scoring session (session 2) and a scoring session by using pictures (sessions 1, 3-6).

The results of the VES were compared with the VASI. Clinical disease extent was scored independently by the participating physicians using standardized scoring sheets for both methods. To minimize the bias of subsequent scoring by two methods (VES and VASI), a two-sequence design was randomly adopted (system: GraphPad Software, La Jolla, CA).

The study was approved by the local ethics committees and was performed according to the Declaration of Helsinki. Written informed consents were obtained from all participants. The COSMIN checklist was used as a guidance for designing and reporting our study.

Assessors and participants

Assessors with different levels of experience (dermatology residents, dermatologists, and vitiligo experts) were selected by the principle investigator. Vitiligo experts were defined as dermatologists with at least 3 years of clinical experience in a tertiary vitiligo center. In general, assessors received a short training on how to use both tools (VES and VASI). One day before the face-to-face scoring session (session 2) a second training session was delivered. This training session included mainly the practicalities of the study.

Participants were volunteers of all ages with clinically diagnosed vitiligo (non-segmental). Both patients on or without current treatment were included. Exclusion criteria were unclear diagnosis and patients with segmental vitiligo. In case of mixed vitiligo, only nonsegmental lesions were evaluated. Patients were recruited in a consecutive manner for sessions 1-4. For sessions 5 and 6, patients with vitiligo (non-segmental) and an estimated BSA of more than 5% were selected retrospectively from the existing patients' database. Patients for sessions 1 and 5 were recruited from the Ghent University Hospital (Belgium), whereas patients for session 2 were recruited from the Academic Medical Centre in Amsterdam (the Netherlands). Patients' pictures, which were included in session 2, were used in sessions 3 and 4, whereas pictures from session 5 were reused in session 6.

Design of the model

Session 1

The original concept of the VES was based on clinical pictures of 10 different body locations reflecting the degrees of involvement. Percentage of depigmentation in each picture was calculated by ImageJ analysis (e.g., 1%, 5%, 10%, 25%, 50%, and 75%). Pictures were designed to mimic the natural evolution of vitiligo (nonsegmental). The purpose was to create a template that would allow an easy comparison between the "real life" patients and the scoring sheet. Total and final VES patient's score was the sum of all surface measurements that were calculated from a converting table.

Session 1 was intended to optimize the initial version of the VES template. Based on the experience/results of small-scale testing before conducting session 1, several changes of VES were made to allow a more precise scoring, such as division to left-right and up-down and possibility of selecting 1/2 and 1/4 of the involved area in the first two categories. Complete depigmentation could be chosen as a separate option. After the first scoring session (=session 1), the option of a "plus" or "minus" was added in the other categories, representing 1/4 more or less than the representing picture (=19-item ordinal scale). The >75% depigmentation option represents depigmentation higher than 75% but less than 100% (i.e., complete depigmentation). The final version of the VES included 19 body areas (Figure 1, Supplementary Figures S1 and S2 online). A comparison between the two versions (6-item vs. 19-item ordinal scale) showed that the detailed template resulted in an improved interrater reliability. Therefore, the detailed scale was incorporated in sessions 2-6.

Validation phase

Different scoring sessions were carried out to validate the VES by assessing its inter- and intrarater reliability. Sessions that involved evaluation of the same patients scored previously were separated by 2 weeks to avoid recall bias. If face-to-face evaluation was compared with digital pictures, the pictures were taken during the live evaluation to ensure stability of the lesions during the scoring process.

Session 2

Session 2 was conducted to measure the interrater reliability of face-to-face scoring. At the beginning of the session, each patient was randomized to a room. The assessors were assigned to examination rooms to assess the VASI and VES in a randomized order. Assessors were given 15 minutes per patient evaluation.

Sessions 3 and 4

The aim of session 3 was to investigate the interrater reliability of scoring on pictures. Moreover, the intrarater reliability of face-to-face scoring (session 2) and scoring of pictures was assessed and compared with scoring on pictures at two separate time points (sessions 3 and 4). Standardized digital clinical pictures were taken and scored by the same investigators (session 3), including a retest 2 weeks later (session 4). Again, the VASI and VES were assessed in a randomized order.

Sessions 5 and 6

To evaluate the VES in patients with extensive vitiligo (BSA > 5%), digital clinical pictures of 10 new patients were evaluated in an additional session (session 5). Reassessment on these digital pictures took place 2 weeks later (session 6). One vitiligo expert was not able to participate in this session because of practical reasons. Patients who took part in sessions 5 and 6 were analyzed separately.

Statistics/Data analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Science, Chicago, IL). For data analyses, the interrater and intrarater reliability were assessed and analyzed separately for all different scoring sessions. The interrater and intrarater reliability were determined by their ICCs. The ICC was calculated in a two-way mixed model with absolute agreement and reported as single measures. An ICC of more than 0.8 was found to be acceptable. We also aimed to determine the SDC, that is, change beyond measurement error [12]. Test-retest reliability was investigated using data assessed on the same pictures at different time points. The SDC was calculated by the formula: $SDC95 = 1.96 \times \sqrt{2} \times$ *Standard Error of Measurement (SEM)*; where $SEM = SD \times \sqrt{1}$-*ICC*.

Two types of settings to perform the scoring (face-to-face scoring vs. scoring of digital pictures) were compared by using the ICC and the Wilcoxon signed-rank test to exclude a systematic over- or underestimation of one of the assessment methods. For not normal distributed data, logarithmic transformation was carried out if a normal distribution could be reached.

RESULTS

Interrater reliability

Session 1

The initial version of the VES template was tested by 11 observers including 3 vitiligo experts, 4 dermatologists, and 4 trainees. Pictures of 31 patients with vitiligo (non-segmental) (Table 1) were scored with a mean area of depigmentation of 3.65% (range: 0.02-58.72%). The intraclass correlation (ICC) was 0.960 (95% CI: 0.937-0.978). No marked differences were found between the ICC of the vitiligo experts (ICC: 0.973 [95% CI: 0.952-0.983]), the dermatologists (nonvitiligo experts) (ICC: 0.963 [95% CI: 0.934-0.980]), and the trainees (ICC: 0.956 [95% CI: 0.926-0.977]) (Table 2).

Session 2

Twenty patients with vitiligo (19 nonsegmental and 1 mixed vitiligo) took part in a 1-day face-to-face evaluation session (session 2, Table 1). Assessors included six (four men and two women) clinicians with a wide range of expertise in vitiligo (three vitiligo experts, two dermatologists, and one resident).

Table 1 - Demographic details of the patients.

	Session 1	**Sessions 2 (and 3 and 4)**	**Sessions 5 (and 6)**
Males	11	9	5
Females	20	11	5
Mean age	32.1	42.25	42.8
Age of onset	22.81	33.15	27.5
Photo skin type			
II	4	1	1
III	21	6	7
IV	5	11	-
V	1	1	2
VI	-	1	-

The total scores per patient ranged for the VES (Figure 1) from 0.01% to 34.34%, with a median of 2.17% (interquartile range [IQR]: 0.65-4.72%), and for the VASI from 0.004% to 35.45%, with a median of 2.62% (IQR: 0.85-5.55%). The majority of patients (17 of 20) included in this session had a body surface area (BSA) of less than 10% (Figure 2a). Wilcoxon analysis showed a significant higher estimation of the BSA with the VASI compared with the VES ($P < 0.001$). This was illustrated by a decreased slope of the regression line in the scatter plot (Figure 2a). However, the median difference (0.29% [IQR:0.2 to 1.13%]) in estimated BSA between the two methods was limited. Interrater reliability analysis showed for the VES an ICC of 0.924 (0.862-0.965) and for the VASI an ICC of 0.846 (0.737-0.926). This corresponded to an SDC95 of 4.68% for the VES and 7.79% for the VASI (Table 2).

The Bland-Altman plot (Figure 3a) demonstrated a tendency of increased spread of the data in patients with more extensive vitiligo. This suggests that the accuracy of at least one of the measurement tools is dependent on the magnitude of the measurements.

Session 3

This session involved analysis of digital pictures of 20 patients from session 2. The above-mentioned six assessors (from session 2) independently evaluated these pictures. In this session, the scores of the VES ranged from 0.01% to 34.21%, with a median of 1.97% (IQR: 0.64-5.22), and of the VASI from 0.01% to 29.25%, with a median of 2.40% (IQR: 0.84-6.20%) (Figure 2b). Wilcoxon analysis showed higher values for the VASI compared with the VES ($P = 0.001$). In total, 85 of 120 cases (70.83%) were rated higher with the VASI compared with the VES. However, the median difference between the two score methods was again only 0.32% (IQR: 0.05 to 1.26). In addition, the ICC was 0.922 (95% CI: 0.859-0.965) for the VES and 0.829 (95% CI: 0.701-0.919) for the VASI. This resulted in a very similar SDC_{95} compared with the live scoring (Table 2).

Session 4

During this reassessment session, the ICC of the VASI improved from 0.829 to 0.904 although this was still within the limits of the 95% CI from session 3 and remained slightly inferior to the VES (ICC: 0.943).

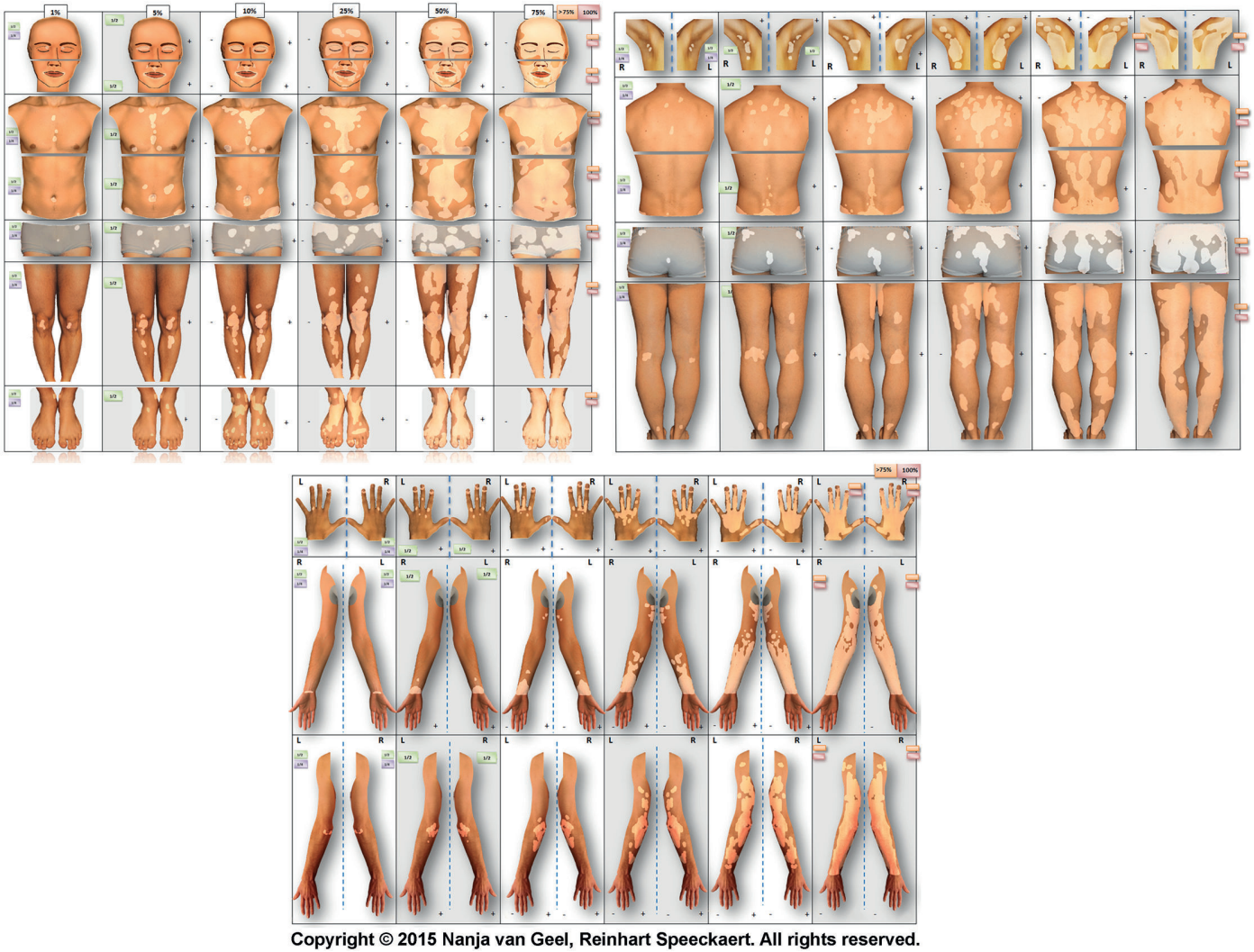


Figure 1 - Scoring sheet Vitiligo Extent Score (VES).

Example of the new scoring system. The 19 different body areas are scored separately depending on the vitiligo extent (online version available at: www.vitiligo-calculator.com)

Table 2 - Interrater reliability.

Scoring session		Number of patients	Evaluation of patients	Number of raters	ICC (95% CI)	SDC_{95}
Pilot						
Sessions to assess optimal tool	1	31	Pictures	11	VES: 0.960 (0.937-0.987)	VES: 5.15
Assessing interrater reliability of VES versus VASI						
Scoring of live patients	2	20	Live patients	6	VES: 0.924 (0.862-0.965) VASI: 0.846 (0.737-0.926)	VES: 4.68 VASI: 7.79
Scoring patients of session 2	3	20	Pictures	6	VES: 0.922 (0.859-0.965) VASI: 0.829 (0.701-0.919)	VES: 4.53 VASI: 7.26
Retest after 2 wk	4	20	Pictures	6	VES: 0.943 (0.897-0.974) VASI: 0.904 (0.802-0.959)	VES: 3.81 VASI: 5.92
Assessing interrater reliability of VES versus VASI in patients with advanced vitiligo						
Scoring of extensive vitiligo patients	5	10	Pictures	5	VES: 0.923 (0.828-0.977) VASI: 0.757 (0.422-0.927)	VES: 11.60 VASI: 20.60
Retest of patients with extensive vitiligo	6	10	Pictures	5	VES: 0.924 (0.817-0.978) VASI: 0.812 (0.539-0.944)	VES: 11.63 VASI: 17.62

CI, confidence interval; ICC, intraclass correlation; SDC, smallest detectable change; VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score.

Sessions 5 and 6

Ten new patients with extensive vitiligo were evaluated by five of the six previously mentioned physicians. For the VES, the scores varied from 4.48% to 63.76%, with a median of 14.27% (IQR: 8.81-21.92%), and for the VASI from 8.60% to 71.00%, with a median of 20.38% (IQR: 12.99-27.05%) (Figure 2c). Similar to previous sessions, paired analysis showed higher values for the VASI as compared with the VES ($P < 0.001$). In total, 38 of 50 cases (76%) were rated higher by the VASI compared with the VES with a median difference of 4.85% (IQR: 0.80-10.22).

The Bland-Altman plot (Figure 3b) displayed an increased dispersion of the differences between the VES and the VASI compared with the face-to-face scoring session (session 2). The data are more spread in patients with extensive vitiligo with higher limits of

agreement: limits of agreement extensive vitiligo (session 5): 17.3 to 7.4 compared with limits of agreement live scoring (session 2): 5.3 to 6.7. The higher scoring of the VASI compared with the VES becomes more pronounced in patients with extensive vitiligo as the mean difference between the VES and VASI is 5.0% BSA in patients with extensive vitiligo compared with 0.7% BSA in the live session. Analysis of these new patients in session 5 demonstrated an ICC of 0.757 (95% CI: 0.422-0.927) for the VASI and 0.923 (95% CI: 0.828-0.977) for the VES. For the VASI the SDC_{95} was 20.60% and for the VES 11.60%. Reassessment of the pictures 2 weeks later showed very similar results that are summarized in Table 2.

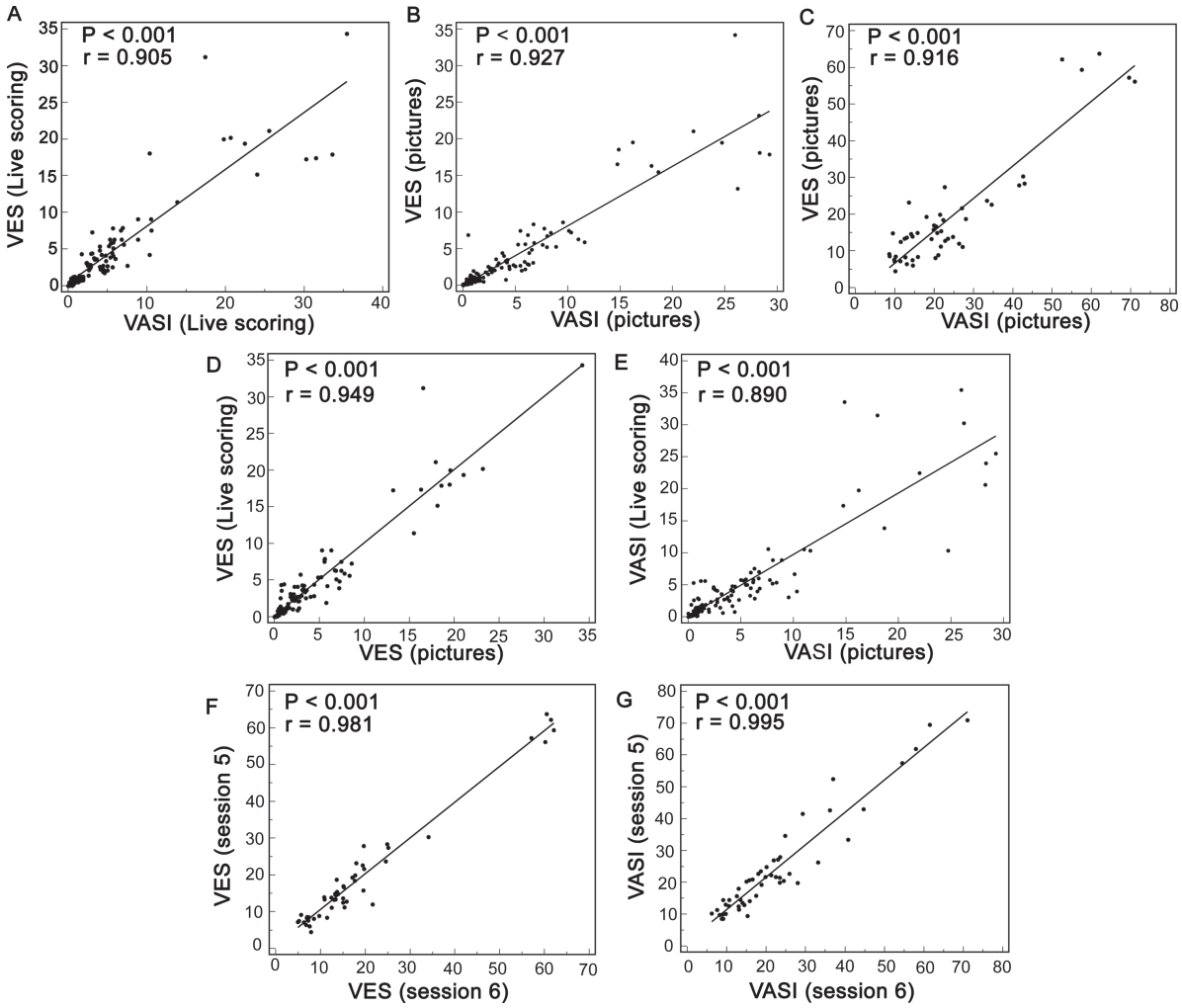


Figure 2 - Correlations between the measured percentages of affected BSA**.**

Correlation analysis between VES and VASI for live scoring of patients (=session 2) (**a**) and scoring on pictures of consecutive patients and patients with extensive vitiligo (session 3 (**b**) and session 5 (**c**)). Correlations between live scoring (=session 2) and picture scoring (=session 3) for (**d**) VES and (**e**) VASI and between scoring of patients with extensive vitiligo at two time points (=sessions 5 and 6) for (**f**) VES and (**g**) VASI. BSA, body surface area; VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score.

Intrarater reliability

The intrarater reliability between the face-to-face scoring (session 2) and scoring of pictures (session 3) was determined to assess the reliability of scoring of digital pictures. The ICC was good for the VASI (ICC = 0.829; 95% CI [0.701-0.919]) and excellent for the VES (ICC = 0.922; 95% CI [0.859-0.965]), which confirms the validity of scoring of digital pictures (Figure 2d and e). In addition, Bland-Altman plots and Wilcoxon analysis showed no significant difference between patients' or pictures scoring. This confirmed the accuracy to validate the developed scoring tool further by picture analysis.

The intrarater reliability between session 3 and session 4 (=test-retest on pictures) was comparable for the VES and the VASI (VES: ICC = 0.943 [95% CI: 0.897-0.974]; VASI: ICC = 0.904 [95% CI: 0.802-0.959]). There was no statistically significant difference between the mean scores obtained in the two different sequences.

In patients with extensive vitiligo (sessions 5 and 6), the intrarater reliability tended to be better for the VES compared with the VASI, illustrated by a closer clustering of the data around the regression line of the scatter plot (Table 3, Figure 2f and g).

Table 3 – Intrarater reliability.

Scoring session	Number of scoring session	Number of patients	Evaluation of patients	Number of raters	ICC (95% CI)	SDC_{95}
Assessing intrarater reliability of VES versus VASI						
Live scoring versus picture scoring	2 versus 3	20	Live patients versus pictures	6	VES: 0.922 (0.859-0.965) VASI: 0.829 (0.701-0.919)	VES: 4.63 VASI: 7.91
Picture scoring versus retest on pictures after 2 wk	3 versus 4	20	Pictures versus pictures	6	VES: 0.943 (0.897-0.974) VASI: 0.904 (0.802-0.959)	VES: 3.83 VASI: 5.81
Assessing intrarater reliability of VES versus VASI in patients with extensive vitiligo						
Test versus retest after 2 wk	5 versus 6	10	Pictures versus pictures	5	VES: 0.924 (0.817-0.978) VASI: 0.812 (0.539-0.944)	VES: 11.52 VASI: 18.16

CI, confidence interval; ICC, intraclass correlation; SDC, smallest detectable change; VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score

Feasibility and subjective evaluation by the raters

The mean time for evaluation of digital pictures by using the VES for all 31 patients (session 1) was 1.39 minutes/patient (range: 1.03-1.7 minutes/patient). No differences between the raters with variable experience could be observed. Both the patients with mild-moderate (session 3) and extensive vitiligo (session 5) were scored faster with the VES compared with the VASI (session 3 = VES: 1 minute and 17 seconds vs. VASI: 1 minute and 42 seconds [P = 0.089]; session 5 = VES: 1 minute and 30 seconds vs. VASI: 2 minutes and 34 seconds [P = 0.015], based on 5 and 4 observers, respectively).

The subjective evaluation (user-friendliness, rapidity, feeling of reliability) scored by the six raters at the end of the live scoring day (session 2) was high for the VES (Table 4) and highlights the user-friendliness of the tool.

Table 4 - Physician's satisfaction of using the VES and VASI.

Question	VES Scale 0-10 (mean)	VASI Scale 0-10 (mean)	P-value	VES Likert 1-5 (mean)	VASI Likert 1-5 (mean)	P-value
User-friendliness of tool	8	4.83	0.002	4.5	2.84	0.026
Rapidity of tool	8	5	0.015	4.3	2.67	0.041
Feeling of reliability of tool	7.5	5.67	0.015	4	3	NS

VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score

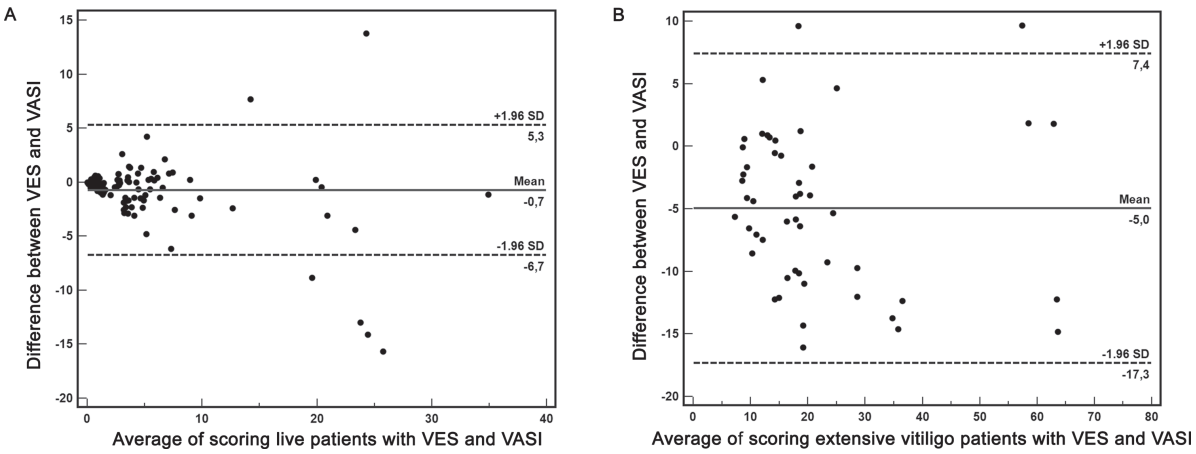


Figure 3 - Bland-Altman plots.

Differences in the measured affected body surface area between the VES and VASI for (**a**) the live scoring session and (**b**) the scoring of patients with extensive vitiligo. VASI, Vitiligo Area Scoring Index; VES, Vitiligo Extent Score.

DISCUSSION

In this study, we developed a practical measurement instrument called the VES. After a careful construction process, we validated this tool. A comparison with a previously developed scale (VASI) was included. In all sessions, the ICCs of the VES were well exceeding the cutoff point of acceptable interrater reliability. The ICCs of the VES remained very high (>0.90) also in patients with extensive vitiligo. Moreover, we could demonstrate the very good intrarater reliability of the VES (test-retest).

As could be expected, the SDC were correlated to the affected BSA. In patients with a BSA less than 5%, which accounts for the majority of patients with vitiligo in daily practice, the SDC_{95} were small (SDC_{95} VES: 1.31% vs. SDC_{95} VASI: 1.85%). Although the VASI performed overall reasonably well for a tool that was essentially constructed to measure repigmentation during UVB treatment, the SDC_{95} of the VES were 36-44% lower (Table 2). Our data with respect to the reliability and SDC of the VASI are in agreement with the results of the study by Komen et al. [11] They reported an SDC of 7.1% for the VASI in a patient population similar to the study group in sessions 2-4 of this study.

The main strengths of the VES lie in the areas of clarity, userfriendliness, and intuitive use. In our opinion, clinical pictures that are used in the VES improve the accessibility of using the tool. Furthermore, the VES can be used to assess the extent of vitiligo for 19 separate areas of the body and therefore improves disease monitoring of the patients. In addition, the possible translation of the VES into categories (Grade 0-6: involved area per region 0%, 1%, 5%, 10%, 25%, 50%, 75%) may be an important advantage compared with currently available tools. This conversion into a certain degree of involvement per area may improve communication between physicians.

The estimated BSA values were higher for the VASI compared with the VES. The problem of the overestimation of the BSA with the 1% hand rule has been described[13] in other skin disorders such as psoriasis. This is probably also due to the fact that the flat closed patient's hand does not exactly account for 1% of the BSA, but in fact represents only 0.70-0.76% of the total BSA[14]. Nonetheless, final statements addressing this issue may only be resolved using exact digital imaging techniques (e.g., 3D imaging) quantifying the affected BSA [15,16]. Digital image instruments are an alternative to measure the vitiligo extent in an objective way, although they are often more time consuming and expensive which limits their worldwide use. Furthermore, many currently available digital tools are often still based on a 2D translation of a 3D reality.

This study assists current international efforts in determination of a core outcome set for vitiligo and assessment of instruments to measure it[5]. The main pitfalls of scoring instruments in cutaneous disorders are the insufficient validation and lack of international consensus. The construction and validation of the VES was initiated by an international "Vitiligo Score Working group" supported by the VETF/Vitiligo Global Issues Consensus Conferences (VGICC) and was discussed at the vitiligo meetings of international congresses (23rd and 24th European Academy of Dermatology and Venereology congress and 23rd World Congress of Dermatology). This may facilitate its widespread implementation. Further validation procedures will also be performed within this international framework. For example, we aim to evaluate the responsiveness of the VES, integration of a disease activity measure as well as a comparison to a digital image analysis tool in the near future.

The comparison between the live scoring and evaluation on clinical pictures demonstrated similar results in this study. This will facilitate future validation processes that can be performed on digital pictures, allowing a larger number of observers to participate in an international setting. In addition, we plan to evaluate the VES as a patient reported outcome measure (self assessment tool). Furthermore, for further implementation and optimization of the feasibility and accessibility of the VES, an internet and smartphone application will be developed (available at: www.vitiligo-calculator.com).

Possible limitations of this study include the fact that the majority of the investigated patient population was of photo skin type 2-4. Moreover, data were collected in two tertiary centers.

Conclusion

This developed and validated VES is a feasible, fast, and userfriendly measurement instrument for clinicians. In this study, we validated this tool, which showed an excellent inter- and intrarater reliability and confirmed its user-friendliness. The possible translation of the VES into clinically relevant categories of extent might be an important advantage compared with currently available tools and can be helpful for inclusion criteria in clinical trials and grading outcomes. It remains however necessary to establish whether the VES is sensitive enough to changes in response to treatment (including follicular repigmentation). We hope that the VES can be incorporated as a preferred instrument in the international consensus on core outcome sets for future vitiligo trials.

REFERENCES

1 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *Lancet* 2015; **386**: 74-84.

2 Ezzedine K, Lim HW, Suzuki T *et al.* Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Res* 2012; **25**: E1-13.

3 Eleftheriadou V, Thomas KS, Whitton ME *et al.* Which outcomes should we measure in vitiligo? Results of a systematic review and a survey among patients and clinicians on outcomes in vitiligo trials. *The British journal of dermatology* 2012; **167**: 804-14.

4 Vrijman C, Linthorst Homan MW, Limpens J *et al.* Measurement properties of outcome measures for vitiligo. A systematic review. *Arch Dermatol* 2012; **148**: 1302-9.

5 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment Cell Melanoma Res* 2015; **28**: 363-9.

6 Williamson PR, Altman DG, Blazeby JM *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; **13**: 132.

7 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.

8 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010; **19**: 539-49.

9 Taieb A, Picardo M, Members V. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. *Pigment Cell Res* 2007; **20**: 27-35.

10 Hamzavi I, Jain H, McLean D *et al.* Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Arch Dermatol* 2004; **140**: 677-83.

11 Komen L, da Graca V, Wolkerstorfer A *et al.* Vitiligo Area Scoring Index and Vitiligo European Task Force assessment: reliable and responsive instruments to measure the degree of depigmentation in vitiligo. *The British journal of dermatology* 2015; **172**: 437-43.

12 de Vet HC, Terwee CB, Ostelo RW *et al.* Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes* 2006; **4**: 54.

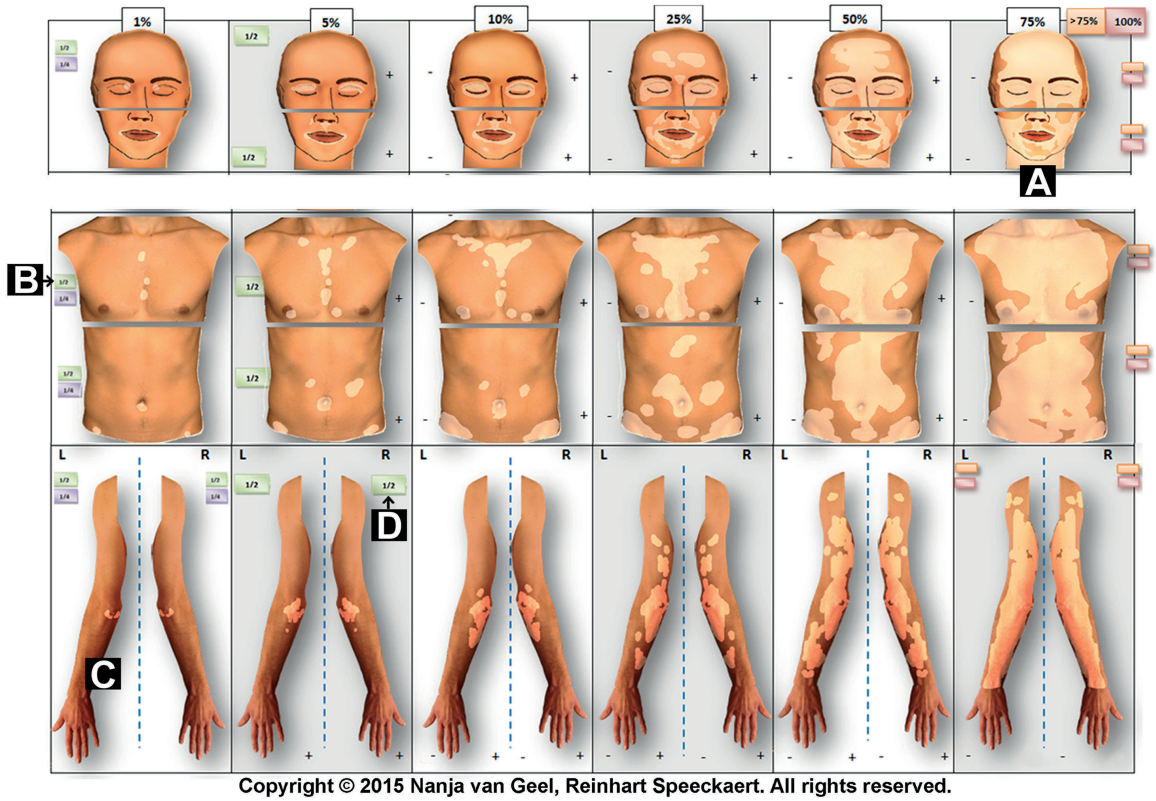
13 Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* 2005; **210**: 194-9.

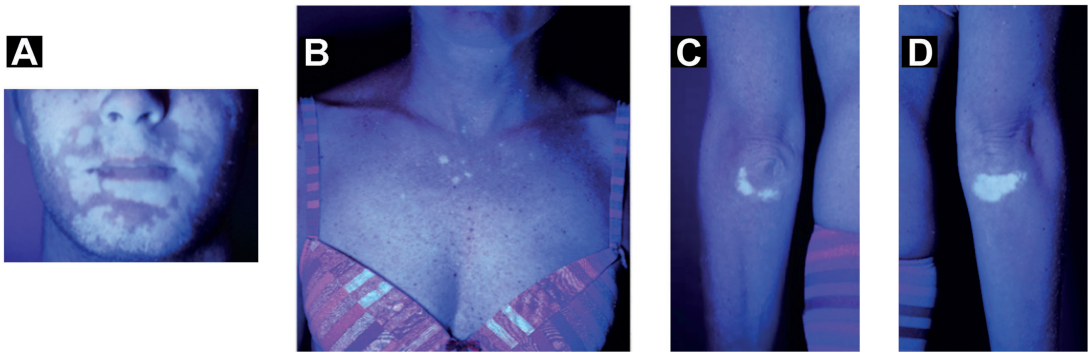
14 Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas = 2 FTU = 1 g. *Arch Dermatol* 1992; **128**: 1129-30.

15 Van Geel N, Vander Haeghen Y, Ongenae K *et al.* A new digital image analysis system useful for surface assessment of vitiligo lesions in transplantation studies. *Eur J Dermatol* 2004; **14**: 150-5.

16 Kohli I, Isedeh P, Al-Jamal M *et al.* Three-dimensional imaging of vitiligo. *Exp Dermatol* 2015; **24**: 879-80.

SUPPLEMENTS



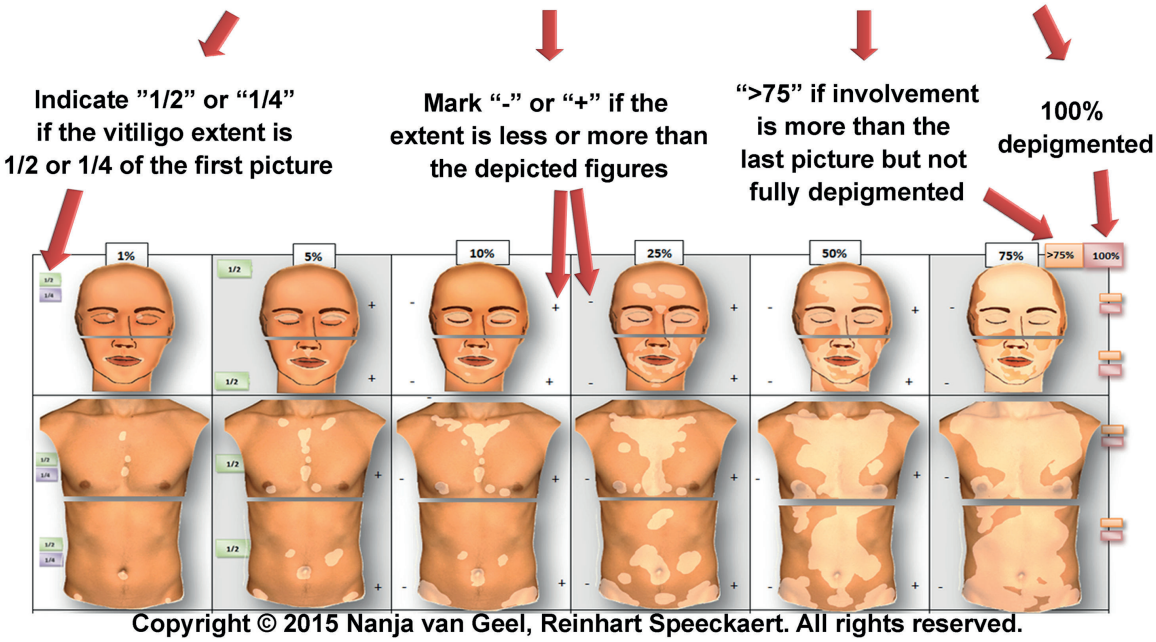


Supplements Figure S1 - Example VES.

User instructions of the VES

1. Choose the pictures which are best representing the vitiligo extent

2. If the pictures are not fully representing the extent



3. Calculate the total BSA: www.vitiligo-calculator.com (available soon)

Supplements Figure S2 - User instructions of the VES.

CHAPTER 3.2

DEVELOPMENT AND VALIDATION OF A PATIENT-REPORTED OUTCOME MEASURE IN VITILIGO: THE SELF ASSESSMENT VITILIGO EXTENT SCORE (SA-VES).

J.E. Lommerts* and N. van Geel*, M.W. Bekkenk, C.A.C. Prinsen, V. Eleftheriadou, A. Taieb, M. Picardo, K. Ezzedine, A. Wolkerstorfer and R. Speeckaert

* Both contributed equally

Journal of the American Academy of Dermatology, 2017 Mar;76(3):464-471

ABSTRACT

Background: The Vitiligo Extent Score (VES) has recently been introduced as a physicians' score for the clinical assessment of the extent of vitiligo, but a good patient self-assessment score is lacking.

Objective: The objective is to develop and validate a simplified version of the VES as a patient-reported outcome measure (PROM).

Methods: After extensive pilot testing, patients were asked to score their vitiligo extent twice with an interval of 2 weeks using the Self Assessment Vitiligo Extent Score (SA-VES). The scores were compared with the physicians' evaluation (VES).

Results: The SA-VES demonstrated very good test-retest reliability (intraclass correlation = 0.948, 95% confidence interval [CI]: 0.911-0.970) that was not affected by age, skin type, or vitiligo distribution pattern. According to patients, this evaluation method was easy to use (22% very easy; 49% easy; 29% normal) and required <5 minutes in the majority of patients (73%, <5 minutes; 24%, 5-10 minutes; 2%, 10-15 minutes). Comparison of the SA-VES and the VES demonstrated excellent correlation (r = 0.986, P <.001).

Limitations: Few patients had a dark skin type.

Conclusion: The results demonstrate excellent reliability of the SA-VES and excellent correlation with its investigator-reported counterpart (VES). This patient-oriented evaluation method provides a useful tool for the assessment of vitiligo extent.

INTRODUCTION

Patient-oriented medicine and patient-empowerment gain increasing attention. It is an emerging concept that is encouraged by the World Health Organization. As recommended by the Cochrane review on interventions in vitiligo[1], it could be valuable if patients could score their vitiligo severity. The determination of the affected body surface area (BSA) is an important part in the assessment of vitiligo severity. However, the assessment of BSA can be difficult even for trained physicians. The most commonly used method is the 1% hand rule. However, this may lead to systematic over- or underestimation due to the wide individual variation in its interpretation.[2]

Recently, we developed the Vitiligo Extent Score (VES) to measure the affected BSA of patients with vitiligo.[3] Initial validation proved that this novel method was superior in terms of reliability and userfriendliness compared to Vitiligo Area Scoring Index (VASI) in which the 1% hand rule is incorporated.[3,4] After extensive validation of the VES, we adapted this version to create a patient-oriented scoring tool. The very intuitive nature of this instrument serves the purpose of a patient-oriented instrument. The aim of this study was to assess the validity and reliability of this new Self Assessment Vitiligo Extent Score (SA-VES). Furthermore, we evaluated the patient-reported acceptability and applicability of this tool.

METHODS

Study design and ethics

This trial was conducted on behalf of the international Vitiligo Score Working Group in close cooperation with the Vitiligo European Task Force and Vitiligo Global Issues Consensus Conference group. The validation study of the SA-VES included 2 scorings by the patient (session 1: day of inclusion and session 2: retest requested after 2-week interval) and 1 additional scoring by physicians (session 3: VES) by using pictures. Validity for the SA-VES was determined by comparing the results of the SA-VES (session 1) and the results of the VES (session 3).

The study was approved by the local ethics committees [reference number Ghent: B670201421409; reference number Amsterdam: W15_117#15.00147] and was performed according to the Declaration of Helsinki. Written informed consents were

obtained from all participants prior to their participation in the study. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was used as a guidance for designing and reporting our study.[5,6]

Participants

Participants were volunteers of all ages (>5 years) with clinically diagnosed vitiligo (non-segmental). Both patients on or without current treatment were included. Patients were enrolled in a consecutive manner at the Ghent University Hospital and the Academic Medical Centre in Amsterdam. The majority (estimation 85%) of this patient population was naive to filling out the scoring template.

Pilot testing, reliability, and validation

During the pilot testing, the SA-VES was evaluated to ensure the comprehensibility and relevance of the tool in different clinical scenarios. To complete the validation a second round of test-retest reliability was performed. Similar to the pilot testing, all patients were asked to score their vitiligo extent again at home (retest) with an interval of 2 weeks to avoid recall bias. Furthermore, in this second round, standardized digital clinical pictures were taken on the day of inclusion for the physicians' evaluation (VES). Only in exceptional situations (e.g. when there was a missing picture) in which the disease was described as stable were pictures taken on previous hospital visits used. VES scores were obtained from 2 independent observers. For comparison, a total VES score was used only when having a complete set of pictures, with the exception of the waist/genital regions. The SA-VES scores for the waist/genital regions were also not taken into account. It was expected that correlations between the SA-VES and the VES were positively related and ≥0.75.

Feasibility

To assess the applicability and acceptability, patients were asked to indicate the time needed to complete the SA-VES (<5 minutes, 5-10 minutes, 10-15 minutes, >15 minutes) and patients were invited to record the difficulty of the questionnaire on a five-point scale (very easy, easy, normal, difficult, very difficult). The correspondence of the distribution pattern of the vitiligo patients with the template was scored on a 6-point grade scale by 2 physicians: no (=0), very limited (=1), moderate (=2), good (=3), very good (=4), and almost perfect resemblance (=5).

Statistics/data analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Science, Chicago, IL, USA). The test-retest reliability was determined by the intraclass correlation coefficient (ICC). The ICC was calculated in a 2-way mixed model with absolute agreement and reported as single measures. Test-retest reliability was found to be adequate if the ICC was ≥0.70.[7] For not normally distributed data, logarithmic transformation was carried out if a normal distribution could be reached. In case normal distribution could not be achieved, Pearson correlation analysis was performed. We also aimed to determine the smallest detectable change (SDC), i.e. change beyond measurement error.[8] The SDC was calculated by the formula $SDC95 = 1.96 \times \sqrt{2} \times STandard\ Error\ of\ Measurement\ (SEM)$, where $SEM = Standard\ Deviation\ (SD)\sqrt{\sigma 2(o) + \sigma 2(e)2}$.

To evaluate the validity of the SA-VES, Pearson correlation coefficients were calculated between the patients' scores and the physicians' scores. Validity was found to be adequate if correlations were >0.50.[7] Bland-Altman plots were used as a parameter for measurement error and to detect systematic differences. Several subanalyses were performed to exclude the influence of possible factors which could affect the reliability of the tool. In all cases, significance level was set at $P < 0.05$.

RESULTS

Development of the scoring template (SA-VES)

In association with the International Vitiligo Score Working Group a simplified version of the validated VES tool was developed as a self-administered tool for the patients (SA-VES). The validated VES instrument is based on clinical pictures that mimic the natural distribution of vitiligo (non-segmental) including 19 different body areas reflecting 6 different degrees of involvement (1%, 5%, 10%, 25%, 50%, 75%).[3] The percentage of depigmentation in each picture was calculated by ImageJ analysis (National Institutes of Health [NIH], Bethesda, MD, USA). The purpose of this tool is to select the most representing pictures from the scoring sheet. In the SA-VES (Figure 1), the number of body areas to score is reduced to 12 and no subscoring options are included, as in the physicians' version (www.vitiligo-calculator.com). The total and final SA-VES score is the sum of measurements from all areas, which can be calculated by using a converting table, which is similar to the VES.

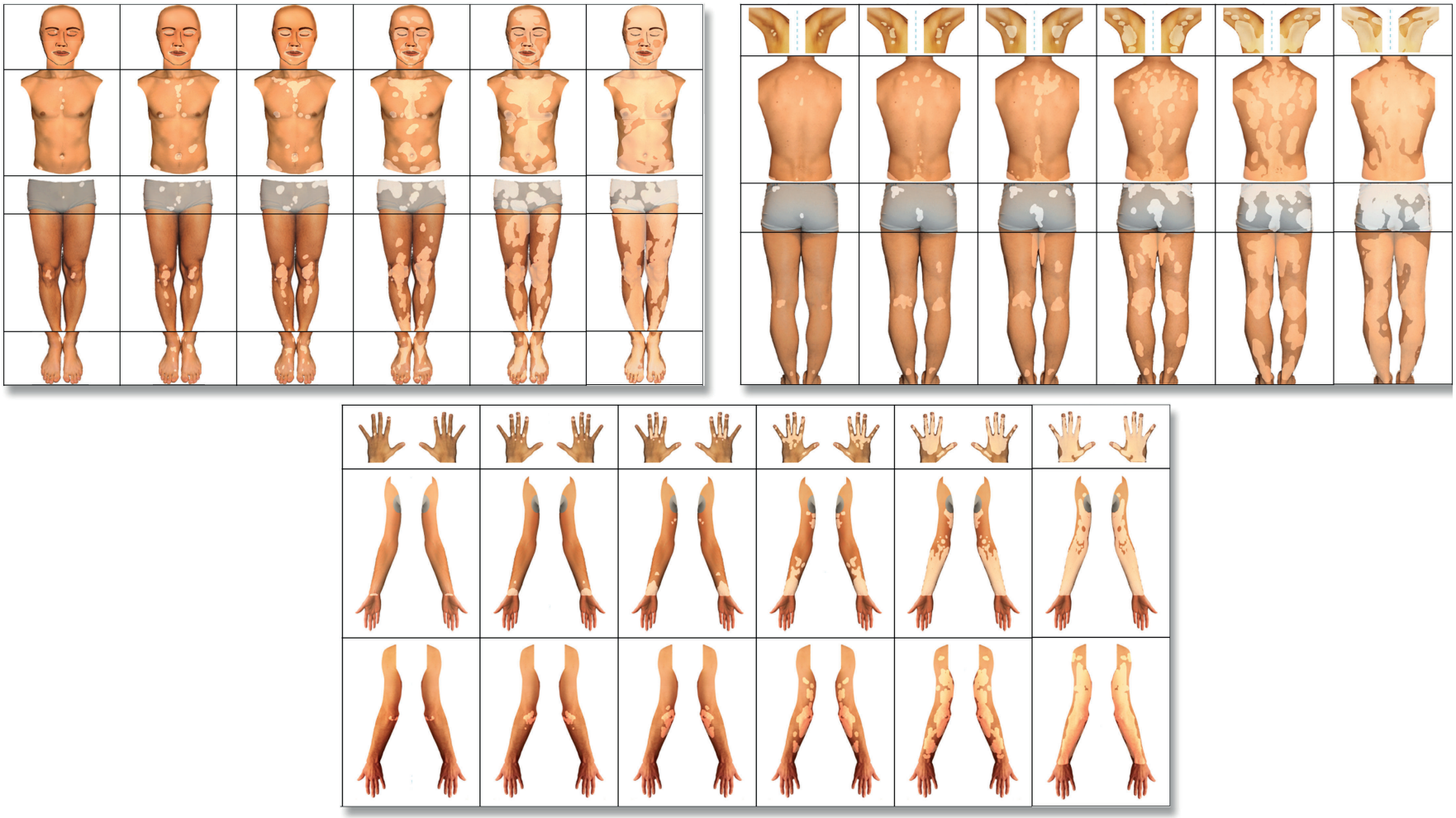


Figure 1 - Scoring sheet of the Self Assessment Vitiligo Extent Score.

Table 1 - Demographics of the vitiligo patients in the pilot test group and validation group.

	Pilot test group	Validation group
Men	47/98 (48%)	23/50 (46%)
Women	51/98 (52%)	27/50 (54%)
Median age (IQR)	40.0 (28.8-47.0)	33.5 (15.8-48.0)
BSA mean (median [IQR])	4.6% (2.57% [1.1-5.14]) (based on SA-VES)	4.79% (1.86% [0.97-4.06]) (based on VES)
Photo skin type		
I	1/98 (1%)	0/50 (0%)
II	14/98 (14%)	10/50 (20%)
III	69/98 (70%)	34/50 (68%)
IV	7/98 (7%)	4/50 (8%)
V	7/98 (7%)	2/50 (4%)
Resemblance with depigmentations of the template		
No	0/98 (0%)	0/50 (0%)
Very limited	0/98 (0%)	0/50 (0%)
Moderate	3/98 (3.1%)	2/50 (4%)
Good	32/98 (32.7%)	13/50 (26%)
Very good	51/98 (52.0%)	28/50 (56%)
Almost perfect	9/98 (9.2%)	7/50 (14%)
Missing pictures	3/98 (3.1%)	0/50 (0%)

BSA, Body surface area; IQR, interquartile range; VES, Vitiligo Extent Score; SA-VES, Self Assessment Vitiligo Extent Score

Pilot testing

The pilot-testing phase was performed in 98 patients (Table 1). All patients were able to fill in the template, which indicates adequate comprehensibility of the instrument. The mean SA-VES score was 4.63% (median: 2.61; interquartile region [IQR]: 1.14-4.92). The ICC between test and retest scores was 0.894 (Table 2). Pearson correlation coefficient between test and retest scores of the pilot testing was high for each body location (face: $r = 0.868$, trunk: $r = 0.961$, extremities: $r = 0.944$, feet: $r = 0.794$, and hands: $r = 0.844$).

Based on the experience during the pilot testing some adjustments were taken into account. As the interval time between test and retest during the pilot testing was less stringently documented this was improved during the validation phase. Additionally, a small correction of the template was performed for the feet area as the depigmented areas on the feet did not correspond exactly with the correct measurement performed by digital image analysis (ImageJ). Furthermore, some patients forgot to fill in the reverse side of the template sheet, which was therefore more clearly emphasized during the validation phase.

Validation phase

Reliability

The SA-VES template was completed by 65 patients (assessment). The reassessment was performed by 54 (83%) of patients above. Four of the re-tests were received after start of the analyses, which comprised finally 50 patients who completed both assessment and reassessment on time. The total scores per patient ranged for the SA-VES from 0.05% to 65.88%, with a mean of 5.51% (median: 2.47%; IQR: 0.91%-5.66%). Most patients (44/50; 88%) included for the analyses had a BSA of <10% (Figure 2). Test-retest reliability analysis for the SA-VES showed an ICC of 0.948 (0.911-0.970). This corresponded to a SDC_{95} of 3.23%. Although the SA-VES values of the retest were similar to the first assessment (SA-VES retest: mean BSA 5.76%, median: 2.46%, IQR: 1.16%-5.89%), paired analysis showed a significant higher estimation of the BSA during the retest session ($P = 0.031$) (Figure 3, A and B). No significant difference in ICC was observed between the pediatric and adult population.

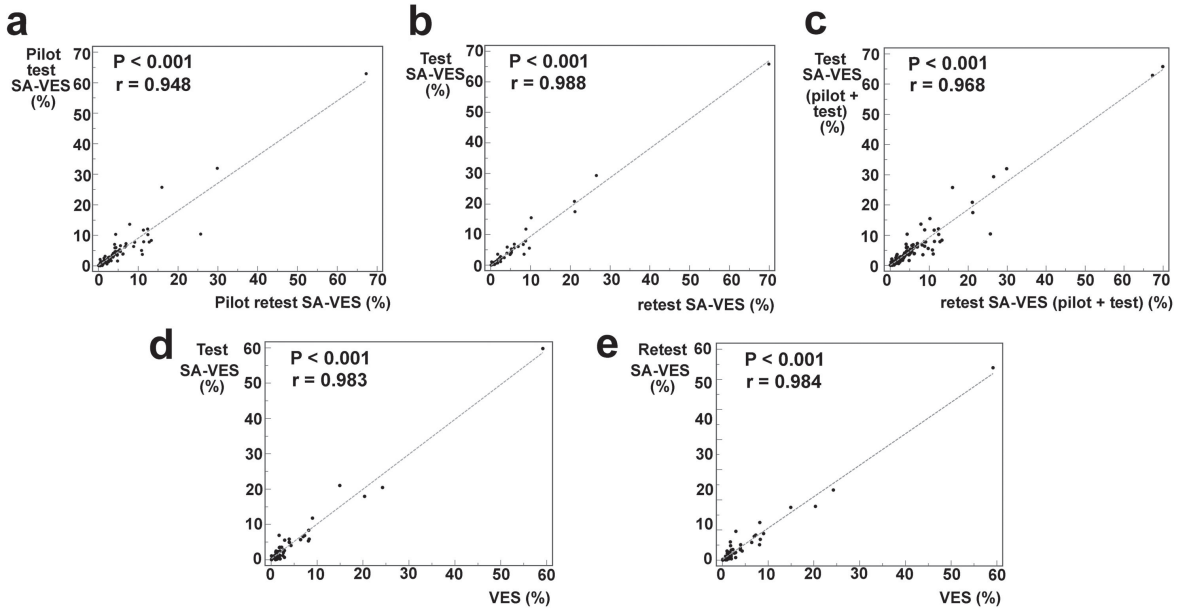


Figure 2 - Correlation analysis between test and retest Self Assessment Vitiligo Extent Score (SA-VES) pilot test group (**A**), validation group (**B**), and combined study group (**C**). Correlation analysis between SA-VES and VES: test SA-VES versus VES (**D**) and retest SA-VES versus VES (**E**).

Validity

We assessed the correlation between SA-VES and VES. The mean area of depigmentation scored by 2 observers using the VES was 4.79% (median: 1.86; range: 0.06%-59.14%). As the ICC between the 2 observers was excellent (0.984 [95% CI 0.972-0.991]; SDC = 2.34%), the mean values of both observers were used for further analyses. The comparison between the patients' and physicians' score demonstrated a correlation coefficient of r = 0.986 (*P* = 0.001). In 28/50 cases (56%) the patients' reported affected BSA was higher compared to physicians'. Wilcoxon analysis showed no significant difference between patients' or physicians' scoring. Bland-Altman plots demonstrated no signs of systematic differences (Figure 3, C and D). Also no obvious floor or ceiling effects were found for the SA-VES compared with the more detailed VES.

Feasibility and subjective evaluation by the patients

User-friendliness and rapidity was evaluated by 41 patients at the day of inclusion. According to the patients this evaluation method was easy in use (very easy: 9/41 [22%], easy: 20/41 [49%], normal 12/41 [29%]). None of the patients rated the SA-VES scoring as difficult or very difficult. Filling out the SA-VES required <5 minutes in most patients (30/41 [73%] <5 minutes, 10/41 [24%] 5-10 minutes, 1/41 [2%] 10-15 minutes). No correlation was found between an increased impact score and a higher assessment of the SA-VES compared to the VES.

Influence of skin type, age and picture resemblance

Skin type had no marked influence on the values of the ICC (test-retest), which ranged for all investigated skin types around 0.9 (Table 2). However, skin types I and VI were not represented in this study population. The age of the patients also did not affect the ICC values, with patients below 16 years of age (n = 21 years; range 6-15 years) having an ICC of 0.937 (0.852-0.974). The resemblance of the patients' vitiligo distribution and the pictures was scored by 2 physicians on a 6-point scale (Table 1). SA-VES scores were not markedly influenced by the grade of resemblance. The ICC scores for moderate resemblance was 0.960 (0.734-0.996), good 0.951 (0.906-0.974), very good 0.881 (0.820-0.922), and almost perfect 0.934 (0.825-0.976).

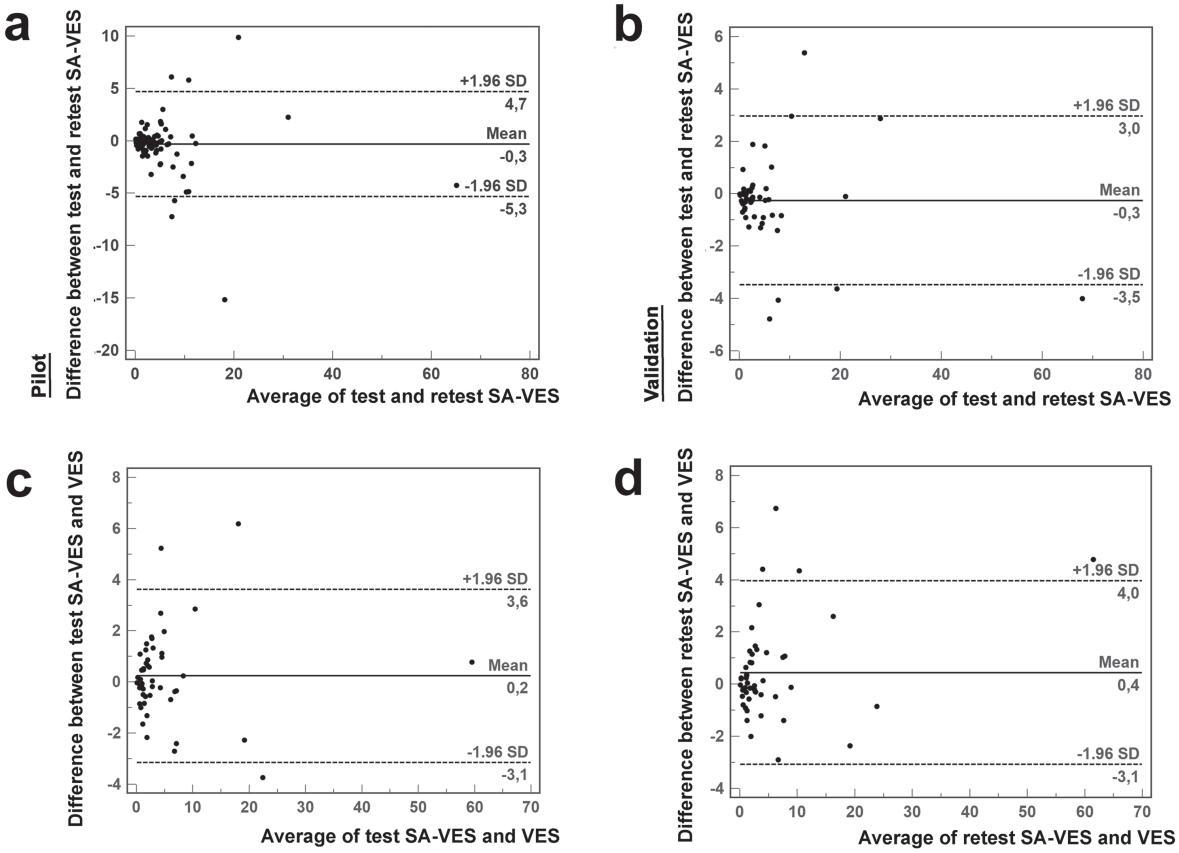


Figure 3 - Bland-Altman plots for the pilot test group, between test and retest Self Assessment Vitiligo Extent Score (SA-VES) (**A**). Bland-Altman plots for the validation group, between test and retest SA-VES (**B**), test SA-VES and VES (**C**), and retest SA-VES and VES (**D**).

Table 2 - Intraclass correlation of the intra-rater agreement and smallest detectable changes.

SA-VES	ICC (95% CI)	SDC_{95}
Pilot test group (n = 98)	0.894 (0.846-0.928)	5.02%
Validation group (n = 50)	0.948 (0.911-0.970)	3.23%
Combined (n = 148)	0.913 (0.881-0.936)	4.49%
Skin type II (combined n = 24)	0.933 (0.849-0.971)	2.03%
Skin type III (combined n = 103)	0.907 (0.865-0.936)	4.24%
Skin type IV (combined n = 11)	0.895 (0.655-0.971)	9.26%
Skin type V (combined n = 9)	0.933 (0.748-0.984)	3.32%

CI, Confidence interval; ICC, intraclass correlation coefficient; SA-VES, Self Assessment Vitiligo Extent Score; SDC, smallest detectable change.

Table 3 - Pearson correlation analysis (validation group).

	Test SA-VES vs retest SA-VES			Test SA-VES vs VES			Retest SA-VES vs VES		
	r	*P* value	Mean Δ BSA%	r	*P* value	Mean Δ BSA%	r	*P* value	Mean Δ BSA%
Face	0.925	<0.001	0.18	0.783	<0.001	0.39	0.772	<0.001	0.36
Trunk	0.972	<0.001	0.49	0.960	<0.001	0.43	0.914	<0.001	0.64
Extremities	0.971	<0.001	0.71	0.984	<0.001	0.60	0.961	<0.001	0.87
Feet	0.922	<0.001	0.09	0.816	<0.001	0.16	0.829	<0.001	0.18
Hands	0.711	<0.001	0.12	0.802	<0.001	0.17	0.817	<0.001	0.17
All locations	0.988	<0.001	0.98	0.987	<0.001	1.17	0.982	<0.001	1.19

BSA, Body surface area; SA-VES, Self Assessment Vitiligo Extent Score; VES, Vitiligo Extent Score

Correlations depending on body locations

High correlations between test and retest scores were found for each body location (Table 3). The Pearson correlation coefficient was lowest for the hands. This was partly due to one patient who had not marked any depigmentations on the hands in the first round while in the retest a depigmentation of 1.5% was marked. Comparing the SA-VES with the VES, the face had the lowest correlation. However, this was due to discrepancy of one patient's self-assessment, where depigmentation of over 50% of the face was indicated; however, this was not confirmed on clinical examination.

DISCUSSION

In this study, we developed and validated an intuitive, patient-reported outcome measurement instrument called the SA-VES. The reliability of the scoring tool was confirmed by an excellent test-retest reliability, which was tested in a large number of patients (n = 148). The patients' characteristics (age, extent, duration of disease, and skin type) had little influence on the reliability of the SA-VES scores. The SDC_{95} was small (1.18%) in patients with a BSA <5%, which is applicable to the majority of patients in daily practice. Moreover, a comparison with the VES for physicians showed an excellent correlation without signs of systematic overestimation or underestimation even in patients with high psychological disease impact.

The SA-VES was given to patients without any information or guidance besides 1 written sentence on top of the scoring template. The tool was comprehensive for most patients, even children (6-15 years). In this study, the same conversion table for estimation of

the total BSA was used for children as well as adults, although a pediatric conversion table could be a valuable addition in the future. A limitation of the SA-VES might be the tendency to increased variation in patients with extensive vitiligo. However, our previous study showed that BSA assessment by using the 1% palm rule introduces more variation in patients with extensive vitiligo.[3] A self-assessment method using the VASI, called the SA-VASI has previously been evaluated by Komen et al.[9] This method was time-consuming with only 35% of patients able to complete the questionnaire in 5 minutes. A poor reliability was observed, which only improved after adding an instruction video (unpublished data). The SA-VASI was considered as easy to use by only 47% of the patients. Another study, by Ukoha et al. investigated whether patient-reported BSA involvement using a questionnaire corresponded with investigator-reported affected BSA using hand units.[10] Agreement using the weighted Kappa statistic was low (0.371) and were rated as fair agreement with Landis' criteria. This method provides, in contrast to the SA-VES, a rather rough estimation of BSA. Another advantage of the SA-VES is the information on the involved body areas. This is known to exert an important influence on the disease impact and response to treatment.[11,12] Moreover, one could assign a degree of involvement for each area. Patient-reported outcome measures (PROMs) are increasingly recognized as valuable and essential information within the current healthcare system.[13] If reliable, self-assessment could allow a better monitoring of the disease status, especially in dedicated internet cohorts. For the implementation of the SA-VES, a web-based application is under construction to improve the feasibility and accessibility of the tool (www.vitiligo-calculator.com). Disease impact and social stigmatization are other key aspects of vitiligo that are not measured by this tool. Methods for quantifying the disease impact are being developed and validated.[14] A combination of an impact measure with the SA-VES would offer a complete assessment of disease severity from the patients' point of view.

Possible limitations of this study include that most of the investigated patient population was of photo skin type II-IV. An additional study, assessing patients of skin type VI will be of interest. Furthermore, the VES is not applicable for segmental vitiligo. Additionally, the patient population had a relatively limited extent of vitiligo and the number of parents that filled in the SA-VES for (or together with) their children was not recorded in a systematic way.

Conclusion

In this study we validated the SA-VES, which proved to be a feasible, fast, and user-friendly instrument according to the patients' feedback. Furthermore, a good correlation to the physicians' score (VES) was demonstrated. The tool is easy to comprehend and may

provide important information about disease extent of a large cohort of patients over time. It represents a valuable tool for everyday clinical practice as well as clinical trials. The overall distribution of SA-VES scores could also be used to establish epidemiological patterns of vitiligo in different institutes, countries, and regions.

REFERENCES

1 Whitton ME, Pinart M, Batchelor J *et al.* Interventions for vitiligo. *Cochrane Database Syst Rev* 2015: CD003263.

2 Rossiter ND, Chapman P, Haywood IA. How big is a hand? *Burns* 1996; **22**: 230-1.

3 van Geel N, Lommerts J, Bekkenk M *et al.* Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *J Invest Dermatol* 2016; **136**: 978-84.

4 Hamzavi I, Jain H, McLean D *et al.* Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Arch Dermatol* 2004; **140**: 677-83.

5 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.

6 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010; **19**: 539-49.

7 Terwee CB, Bot SD, de Boer MR *et al.* Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; **60**: 34-42.

8 de Vet HC, Terwee CB, Knol DL *et al.* When to use agreement versus reliability measures. *J Clin Epidemiol* 2006; **59**: 1033-9.

9 Komen L, van der Kraaij GE, van der Veen JP *et al.* The validity, reliability and acceptability of the SAVASI; a new self-assessment score in vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2145-51.

10 Ukoha UT, Sosa JJ, Hynan LS *et al.* Assessment of vitiligo severity: patient-reported estimates are not accurate. *The British journal of dermatology* 2015; **173**: 1325-6.

11 van Geel N, Desmedt V, De Schepper S *et al.* Cessation of spread as a treatment objective in vitiligo: perception from the patients' point of view. *The British journal of dermatology* 2016; **174**: 922-4.

12 Hofer A, Hassan AS, Legat FJ *et al.* The efficacy of excimer laser (308 nm) for vitiligo at different body sites. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2006; **20**: 558-64.

13 Black N. Patient reported outcome measures could help transform healthcare. *BMJ* 2013; **346**: f167.

14 Salzes C, Abadie S, Seneschal J *et al.* The Vitiligo Impact Patient Scale (VIPs): Development and Validation of a Vitiligo Burden Assessment Tool. *J Invest Dermatol* 2016; **136**: 52-8.

CHAPTER 3.3

PROSPECTIVE EVALUATION OF THE RESPONSIVENESS OF THE VITILIGO EXTENT SCORE (VES) AND SELF ASSESSMENT VITILIGO EXTENT SCORE (SA-VES).

J.E. Lommerts, M.W. Bekkenk, R. Speeckaert, N. van Geel, A. Wolkerstorfer and C.A.C. Prinsen

Submitted

The Vitiligo Extent Score (VES) and Self Assessment Vitiligo Extent Score (SA-VES) are new measurement instruments to measure the degree of depigmentation in vitiligo.[1,2] In our previous studies, the VES and SA-VES were found to be reliable and valid measurement instruments.[1,2] So far, the responsiveness (i.e. ability of an instrument to detect change over time[3]) of the VES was evaluated in a retrospective setting (data submitted). In this study, we assessed the responsiveness of both VES and SA-VES in a prospective setting as this has not yet been investigated. The study was exempted from ethical approval by our Medical Ethics Committee (#W16_036#16.051).

We prospectively and consecutively included 30 patients starting or already receiving narrowband ultraviolet B therapy (NBUVB) at the Netherlands Institute for Pigment Disorders. We included adult patients (≥18 years) with non-segmental vitiligo. Photographs of the lesions (in fair skin types also with Wood's lamp examination) were taken at baseline and 6 months after inclusion by a medical photographer. The degree of depigmentation was assessed by patients (i.e. SA-VES, two time points) and one investigator (i.e. VES, simultaneously by AW) at baseline and after 6 months of NBUVB. In addition, the global degree of repigmentation (scale ranging 0-100%) was assessed after 6 months, and it was also assessed whether the vitiligo was improved (yes/no) by comparing the photographs at baseline and after 6 months by the investigator. Percentage of repigmentation was measured as follows: (1 – degree of depigmentation at 6 months / degree of depigmentation at baseline))*100. Responsiveness was evaluated by testing four hypotheses regarding predefined correlations between the changes in scores of the included instruments. The hypotheses that were used in a responsiveness study of the Vitiligo Area Scoring Index (VASI) by Komen et al. (2015) were adopted in the present study.[4] Responsiveness was found to be acceptable if ≥75% of the hypotheses could be confirmed.[5]

After 6 months of NBUVB, 24 patients were seen for follow-up and included in the data-analysis. Median age was 42 years (interquartile range (IQR): 38-57) and 33% of patients were males. Mostly (88%) fair skin types were included and 67% of patients had active vitiligo in the past 6 months. The degree of depigmentation at inclusion was 2.6% (median, IQR: 1.0-8.6%, VES). After data-analysis, ≥ 75% of hypotheses could be confirmed (Table 1). As expected, percentage of repigmentation after 6 months of NB-UVB was 29.1% (median, IQR: 15.0-43.4%, VES); percentage repigmentation after 6 months was higher on the face (median: 45.5%, IQR: 13.2-71.8%, VES) than on the hands (median: 0.0%, IQR: 0-14.5%, VES); patients marked as improved after 6 months of NBUVB (n=20, median repigmentation: 35.2%; IQR: 18.5-45.5%, VES) showed higher repigmentation than patients marked as not-improved (n=4, median repigmentation: -9.2%; IQR: -77.3-17.7%); and the intra-class correlations between global degree of

repigmentation and percentage repigmentation measured with VES was > 0.5 (ICC: 0.725; 95%CI 0.462-0.871), however with SA-VES it was < 0.5 (ICC: 0.085; 95%CI -0.355-0.452).

Table 1 – Results per hypothesis and measurement tool

Hypotheses	**Measurement tool**	**Result per hypothesis**	**Confirmed**
Percentage repigmentation of VES or SA-VES after 6 months will be ≥ 15%.	*VES*	Repigmentation = 29.1% (median, IQR 15.0 – 43.4%)	Yes
	SA-VES	Repigmentation = 19.0% (median, IQR: -20.0 – 44.7%)	Yes
There will be an ICC ≥ 0.5 between percentage repigmentation of the VES or SA-VES and the global degree of repigmentation assessed by the investigator	*VES*	ICC: 0.725; 95%CI: 0.462-0.871	Yes
	SA-VES	ICC: 0.085; 95%CI: -0.355-0.452	No
Lesions on the face will have ≥ 10% higher repigmentation than lesions on the hands as determined by the VES or SA-VES.	*VES*	Δ repigmentation face and hands = 45.5%*	Yes
	SA-VES	Δ repigmentation face and hands = 55.0%*	Yes
In patients marked as improved after UVB-therapy the percentage repigmentation will be ≥ 10% than in the group with no improvement.	*VES*	Δ repigmentation improved and repigmentation not-improved = 25.2%	Yes
	SA-VES	Δ repigmentation improved and repigmentation not-improved = 24.3%	Yes

VES, Vitiligo Extent Score; SA-VES, Self Assessment Vitiligo Extent Score; IQR, interquartile range; ICC, intra-class correlation; CI, confidence interval; Δ, difference; UVB, ultraviolet-B

* calculated as median repigmentation on the face minus median repigmentation on the hands

This was the first prospective study to assess the responsiveness of both VES and SA-VES. The results of our study show that the responsiveness of the VES and SA-VES is promising. However, because the number of included patients is considered to be low, as less patients were included for data-analysis than expected, the results should be interpreted with some caution. Another limitation of our study is that we included mainly patients with fair skin types. Hypothetically, the responsiveness could be different in darker skin types. We found a 10% difference in repigmentation between the VES and the SA-VES. Hypothetically, our study design could have led to more precise assessment of the VES than SA-VES as patients completed the SA-VES on two different time points, whereas the investigator assessed the VES at baseline and after 6 months of NB-UVB therapy simultaneously. Furthermore, patients assessed SA-VES without Wood's lamp

examination which could have led to less precise assessment of the SA-VES. However, we have chosen this study design because it resembles the use of the VES and SA-VES in reality the most.

In our previous studies we confirmed the validity and reliability of VES and SA-VES.[1,2] In the current study, we prospectively investigated the responsiveness of both instruments. Although the responsiveness of both instruments is promising, further research is needed to confirm our study findings. We recommend to evaluate the responsiveness of the VES and SA-VES in a larger patient sample, with various skin types, in which the VASI could be used as a comparator instrument.

REFERENCES

1 van Geel N, Lommerts J, Bekkenk M *et al.* Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *J Invest Dermatol* 2016; **136**: 978-84.

2 van Geel N, Lommerts JE, Bekkenk MW *et al.* Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES). *J Am Acad Dermatol* 2017; **76**: 464-71.

3 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.

4 Komen L, da Graca V, Wolkerstorfer A *et al.* Vitiligo Area Scoring Index and Vitiligo European Task Force assessment: reliable and responsive instruments to measure the degree of depigmentation in vitiligo. *The British journal of dermatology* 2015; **172**: 437-43.

5 Terwee CB, Bot SD, de Boer MR *et al.* Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; **60**: 34-42.

CHAPTER 3.4

PILOT STUDY ON THE VALIDITY AND RELIABILITY MEASUREMENT OF A NEW PATIENT REPORTED OUTCOME MEASURE IN VITILIGO: THE VITILIGO COSMETIC ACCEPTABILITY SCALE (VICAS).

J.E. Lommerts, M.W. Bekkenk and A. Wolkerstorfer

Submitted

Vitiligo is a common depigmenting skin disorder which can significantly affect the quality of life.[1] Cosmetic acceptability of repigmentation is marked as a core outcome domain for vitiligo.[2] However, no measurement instrument is available to measure this important domain. In this study, we tested the construct validity and reliability of a new patient reported outcome measure (PROM) to assess the cosmetic acceptability of repigmentation: the Vitiligo Cosmetic Acceptability Scale (VICAS). The VICAS is comprised of one question: 'How satisfied are you with the cosmetic aspect of the repigmentation?' answered on a 5-point scale (very dissatisfied to very satisfied).

We included 30 patients with non-segmental vitiligo. After 26 weeks of narrowband ultraviolet B phototherapy (NBUVB), 4 patients were lost to follow-up and 26 patients were included for data-analysis. The median age was 42 years (IQR: 34-54) and 35% of patients were males. Patients had mainly fair skin types II and III (82%). The affected body surface area at inclusion was 6% (median, IQR: 3-12%, SA-VES[3]) and 19% repigmentation (median, IQR: -15 – 46%, SA-VES[3]) was found after 6 months of NBUVB. Measurement of the construct validity was based on hypotheses testing because a gold standard measuring cosmetic acceptability of repigmentation is lacking.[4] The hypotheses were postulated *a priori* and the results per validation hypothesis are presented in Table 1. When ≥ 75% of hypotheses were confirmed, we considered the VICAS as a valid instrument to measure the cosmetic acceptability of repigmentation in vitiligo. However, only 1 of 4 hypotheses was confirmed. The intra-observer reliability was fair (κ=0.391, test at week 26 vs. re-test at week 28) and for 37% of patients the VICAS was easy to very easy in use.[5]

Table 1 – Construct validity of the VICAS (n=26 patients).

Hypothesis	Result
Positive correlation (ρ ≥ 0.4) between VICAS and improvement in quality of life measured with the Skindex-29	ρ = 0.300
Positive correlation (ρ ≥ 0.5) between the VICAS and patient global assessment after treatment	ρ = 0.421
Positive correlation (ρ ≥ 0.5) between the scores of the VICAS of patients and independent physician	ρ = 0.143
Positive correlation (ρ ≥ 0.4) between the scores of the VICAS and VNS[7] scores	ρ = 0.409

Validity testing of the Vitiligo Cosmetic Acceptability Scale. To be valid, three of the four hypotheses need to be confirmed. This table shows that only one hypothesis was confirmed. VICAS, Vitiligo Cosmetic Acceptability Scale;VNS, Vitiligo Noticeability Scale

In conclusion, the VICAS is a fairly reliable PROM to measure the cosmetic acceptability of repigmentation in vitiligo. However, validity of the VICAS was not confirmed. Therefore, it remains unclear whether the VICAS is a useful PROM to measure the cosmetic acceptability of repigmentation. Hypothetically, the pitfall of measuring the validity of the VICAS by hypothesis testing was poor construct definition and potential definition error of the outcome domain. In other words, the outcome domain cosmetic acceptability of repigmentation is poorly defined and the construct is too broad which made validation of the VICAS rather impossible. A recent survey showed that blending with non-lesional skin, noticeability and skin color back to normal are marked by patients themselves to contribute the most to cosmetic acceptability of repigmentation.[6] A validated PROM to measure the noticeability of lesions after treatment (VNS) is already available.[7] However, the correlation in our study between the cosmetic acceptability and the noticeability measured with the VNS was rather low ($\rho = 0.409$) and this suggests that also other factors than noticeability contribute to cosmetic acceptability. Hypothetically, cosmetic acceptability of repigmentation is too different from other outcome domains so that only poor correlation, when comparing the VICAS with other measurement instruments, is detected. In that case, validity testing can be challenging. Main limitation of this study is the small sample size which may have led to not confirming the construct validity. It can also be discussed whether we should measure cosmetic acceptability of repigmentation, because vitiligo is generally not regarded as a cosmetic disease.[8] However, recent consensus is that cosmetic acceptability of repigmentation is an important outcome domain to measure in vitiligo. [2] Further consensus should be reached on whether and how we should measure cosmetic acceptability and which factors contribute to cosmetic acceptability, because it possibly might be more suitable to divide cosmetic acceptability of repigmentation in different subdomains.

REFERENCES

1 Ongenae K, Beelaert L, van Geel N *et al.* Psychosocial effects of vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2006; **20**: 1-8.

2 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment Cell Melanoma Res* 2015; **28**: 363-9.

3 van Geel N, Lommerts JE, Bekkenk MW *et al.* Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES). *Journal of the American Academy of Dermatology* 2017; **76**: 464-71.

4 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.

5 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159-74.

6 Tour SK, Thomas KS, Walker DM *et al.* Survey and online discussion groups to develop a patient-rated outcome measure on acceptability of treatment response in vitiligo. *BMC Dermatol* 2014; **14**: 10.

7 Batchelor JM, Tan W, Tour S *et al.* Validation of the Vitiligo Noticeability Scale: a patient-reported outcome measure of vitiligo treatment success. *The British journal of dermatology* 2016; **174**: 386-94.

8 Ezzedine K, Sheth V, Rodrigues M *et al.* Vitiligo is not a cosmetic disease. *Journal of the American Academy of Dermatology* 2015; **73**: 883-5.

TREATMENT

CHAPTER 4.1

TWENTY-YEAR FOLLOW-UP USING A POSTAL SURVEY OF CHILDHOOD VITILIGO TREATED WITH NARROWBAND ULTRAVIOLET B PHOTOTHERAPY.

J.E. Lommerts, M.D. Njoo, M.A. de Rie, A. Wolkerstorfer and M.W. Bekkenk

British Journal of Dermatology, 2017 Sep;177(3):e60-e61

Vitiligo is a depigmenting skin disorder with an estimated prevalence of 1%.[1] Childhood-onset vitiligo occurs in approximately one-third of all cases.[2] Early-onset childhood vitiligo tends to be a more extensive and progressive type of vitiligo.[3] Narrowband ultraviolet B (NBUVB) phototherapy is an effective treatment option in active vitiligo and leads to >75% repigmentation in 14-75% of childhood cases.[4,5] Unfortunately, no evidence is available whether this repigmentation is long-lasting. To date, no data are available on the long-term efficacy and safety of NBUVB in childhood vitiligo.

This study was designed as a long-term follow-up study after our prospective open uncontrolled clinical trial of 20 years ago in which 51 children with non-segmental vitiligo were treated with NBUVB twice weekly for a maximum period of 1 year.[4] The objective of the current study was to assess the long-term outcome after NBUVB phototherapy in childhood vitiligo. The study was exempted from review by the Ethics Committee of our hospital (#W16_122#16.140). We attempted to retrieve medical files and last known addresses of all 51 patients of our previous study. All patients who participated in the previous study and from which a last known address was available received a questionnaire. Data were collected using a study-specific questionnaire comprised of questions concerning demographics, vitiligo-specific data, occurrence of melanoma or non-melanoma skin cancer and quality of life. Current affected body surface area was measured using the Self Assessment of Vitiligo Extent Score.[6] Descriptive statistics were used to summarize the responses.

Of the 51 patients who participated in the previous study, 36 received the questionnaire, 14 were not reachable due to unknown correct addresses and 1 patient was deceased due to a nondermatological cause. In total 18 patients returned a completed questionnaire, resulting in a response rate of 50%. The reason for nonresponse was unknown in all nonresponders. Median follow-up duration was 20 years and median current age 32 years. Descriptive data are presented in Table 1. Compared to our previous study, more female (72.2% versus 60.7%) and fair skin type patients (66.7% versus 51.0%) responded.[4] Current affected body surface area (mean 7.6%, median 2.7%) was lower than before inclusion in the first study (mean 15.9%).

Four patients received no additional treatment during follow-up. The other 14 patients were treated after the previous study with NBUVB (n=11, median duration 24 months), psoralen combined with ultraviolet A phototherapy (n=1, median duration 24 months) and topical treatment (n=6). Patients treated with additional NBUVB or topical treatment were satisfied with the repigmentation results in 36% and 33%, respectively.

Table 1 - Descriptive data of respondents.

	All patients	Treatment	No treatment
Demographics			
Patients, n (%)	18	14 (77.8%)	4 (22.2%)
Male, n (%)	5 (28%)	3 (21.4%)	2 (50%)
Age (years), median (IQR)	32 (29-33)	31 (29-33)	32 (30-33)
Fitzpatrick skin type, n (%) I II III IV V VI	 0 (0%) 5 (28%) 7 (39%) 1 (6%) 5 (28%) 0 (0%)	 0 (0%) 3 (21%) 5 (36%) 1 (7%) 5 (36%) 0 (0%)	 0 (0%) 2 (50%) 2 (50%) 0 (0%) 0 (0%) 0 (0%)
Vitiligo-specific data			
Age at onset (years), median (IQR)	6 (4-9)	6 (4-9)	6 (2-10)
Age during previous study (years), median (IQR)	12 (9-13)	11 (9-13)	12 (10-14)
Duration in years (Δ onset - first NBUVB), median (IQR)	3.5 (1.0-9.5)	3.5 (2.5-7.5)	6.0 (0.3-11.8)
Localization before first NBUVB, n (%) Head and neck Trunk Limbs Groin	 12 (67%) 11 (61%) 15 (83%) 10 (56%)	 9 (64%) 8 (57%) 11 (79%) 7 (50%)	 3 (75%) 3 (75%) 4 (100%) 3 (75%)
Activity in the past year, n (%)	8 (44%)	7 (50%)	1 (25%)
Koebnerisation, n (%)	6 (33%)	6 (43%)	0 (0%)
Positive family history vitiligo, n (%)	5 (28%)	5 (36%)	0 (0%)
Affected body surface area (%, measured with SA-VES), median (IQR)	2.7 (0.6-9.4)	5.3 (0.8-14.4)	0.6 (0.1-0.6)
Quality of life: DLQI, median (IQR)	1.0 (0.0-7.0)	2.0 (2.0-7.5)	0.0 (0.0-1.5)
Occurrence of NMSC or MSC, (%)	0 (0%)	0 (0%)	0 (0%)
Treatment, n (%)			
NB-UVB	11 (61%)	11 (79%)	-
PUVA	1 (6%)	1 (7%)	-
Topical treatment	6 (33%)	6 (43%)	-

IQR, interquartile range; SA-VES, Self-Assessment of Vitiligo Extent Score; DLQI, Dermatology Life Quality Index (scale 0–30); NMSC, nonmelanoma skin cancer; MSC, melanoma skin cancer; NBUVB, narrowband ultraviolet B phototherapy; PUVA, psoralen combined with ultraviolet A phototherapy.

To our knowledge, this is the first long-term follow-up study after NBUVB phototherapy in childhood vitiligo. We collected data of 18 children with early onset of vitiligo who were treated 20 years ago with NBUVB phototherapy. Hypothetically, treatment of vitiligo in the early phase of the disease could potentially lead to modification of underlying disease processes, which is the case in other autoimmune disorders such as rheumatoid arthritis. This hypothesis is supported by clinical data in which patients with recent onset of vitiligo achieved significantly higher repigmentation than patients with long-standing vitiligo after NBUVB.[7]

In our study, only a small percentage of patients (22%) did not receive any additional treatment after the first study. Patients who received treatment after the first study showed a larger affected body surface area (median 5.3%) than patients who received no additional treatment (median 0.6%). This may suggest that in 22% of cases, the vitiligo was not reactivated or only slowly progressed after the first NBUVB phototherapy treatment. However, the median duration between onset of vitiligo and first treatment with NBUVB was longer in the group without additional treatment. This suggests that also other factors may influence the disease process of vitiligo.

The European guidelines on vitiligo state that prolonged maintenance with NBUVB treatment is not recommended, because there is a potential risk of skin photodamage due to the higher susceptibility of vitiligo skin to sunburn.[8] None of the patients reported occurrence of either melanoma or nonmelanoma skin cancer. However, we cannot draw conclusions concerning the safety of NBUVB phototherapy in childhood vitiligo. On the other hand, a recent study has shown that patients with vitiligo, even those who received phototherapy, have a lower risk on developing melanoma and non-melanoma skin cancer compared to healthy controls.[9] Limitations of this study are the small population size, retrospective uncontrolled design and low response rate. Our data suggest that NBUVB phototherapy may be a safe and effective treatment option in childhood vitiligo which in some cases may change the natural course of the disease. However, more long-term observational and controlled studies are needed to address these important issues.

REFERENCES

1 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *Lancet* 2015; **386**: 74-84.

2 Ezzedine K, Diallo A, Leaute-Labreze C *et al.* Pre- vs. post-pubertal onset of vitiligo: multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo. *The British journal of dermatology* 2012; **167**: 490-5.

3 Mu EW, Cohen BE, Orlow SJ. Early-onset childhood vitiligo is associated with a more extensive and progressive course. *Journal of the American Academy of Dermatology* 2015; **73**: 467-70.

4 Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *Journal of the American Academy of Dermatology* 2000; **42**: 245-53.

5 Sen BB, Rifaioglu EN, Ekiz O *et al.* Narrow-band ultraviolet B phototherapy in childhood. *Cutaneous and ocular toxicology* 2014; **33**: 189-91.

6 van Geel N, Lommerts JE, Bekkenk MW *et al.* Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES). *Journal of the American Academy of Dermatology* 2017; **76**: 464-71.

7 Hallaji Z, Ghiasi M, Eisazadeh A *et al.* Evaluation of the effect of disease duration in generalized vitiligo on its clinical response to narrowband ultraviolet B phototherapy. *Photodermatol Photo* 2012; **28**: 115-9.

8 Taieb A, Alomar A, Bohm M *et al.* Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *The British journal of dermatology* 2013; **168**: 5-19.

9 Teulings HE, Overkamp M, Ceylan E *et al.* Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *The British journal of dermatology* 2013; **168**: 162-71.

CHAPTER 4.2

AUTOLOGOUS CELL SUSPENSION GRAFTING IN SEGMENTAL VITILIGO AND PIEBALDISM: A RANDOMIZED CONTROLLED TRIAL COMPARING FULL SURFACE AND FRACTIONAL CO_2 LASER RECIPIENT-SITE PREPARATIONS.

J.E. Lommerts, A.A. Meesters, L. Komen, M.W. Bekkenk, M.A. de Rie, R.M. Luiten and A. Wolkerstorfer

British Journal of Dermatology, 2017 Nov;177(5):1293-1298

ABSTRACT

Background: Autologous noncultured cell suspension transplantation is an effective treatment for repigmentation in segmental vitiligo and piebaldism. Full surface laser ablation is frequently used to prepare the recipient site before cell suspension transplantation, even though the optimal laser settings and ablation depth are unknown.

Objective: To assess the efficacy and safety of less invasive recipient-site preparations.

Methods: In a randomized, observer-blinded, controlled trial we compared different recipient-site preparations before cell suspension transplantation in segmental vitiligo and piebaldism. In each patient, we randomly allocated three CO_2 laser recipient-site preparations (209 and 144 µm full surface, and fractional) and a control (no treatment) to four depigmentations. After 6 months we assessed repigmentation and side-effects.

Results: We included 10 patients with vitiligo (n = 3) and piebaldism (n = 7). Compared with the control site, we found more repigmentation after full surface ablation at 209 µm (median 68·7%, P = 0·01) and 144 µm (median 58·3%, P = 0·007), but no repigmentation after fractional ablation (median 0·0%, P = 0·14).

Conclusion: Superficial full surface ablation with a depth of 144 µm is an effective recipient-site preparation before cell suspension transplantation, while fractional CO_2 laser is not.

INTRODUCTION

Vitiligo and piebaldism are depigmenting skin disorders that can significantly alter physical appearance and impair quality of life.[1,2] Autologous noncultured cell suspension transplantation (CST) is an effective treatment for repigmentation in segmental vitiligo and piebaldism.[3,4] The CST technique involves the transplantation of autologous epidermal cells, suspended in a fluid medium, from pigmented skin to depigmented recipient sites. Recipient-site preparation before CST is required to allow access to the underlying structures necessary for melanocyte adherence.[5] Full surface ablation is generally used as recipient-site preparation in CST. Unfortunately, this technique can be uncomfortable and may result in persistent side-effects such as scarring and erythema.[6] Furthermore, the optimal depth of full surface ablation for melanocyte adherence is unclear.

In a previous study, we found 78% repigmentation after full surface CO_2 laser ablation to an estimated depth of 209 µm.[7] However, if less invasive recipient-site preparations are at least as effective in repigmentation, patients could be effectively treated more comfortably and with potentially fewer side-effects. Less invasive techniques are for example ablative fractional laser and superficial full surface ablation. In ablative fractional pre-treatment an array of microscopic ablation channels is created.[8] Less invasive techniques may result in minimized side effects, such as persisting erythema and scars, and provide faster healing.[8-10]

The aim of this study was to assess the efficacy and safety of fractional and superficial full surface CO_2-laser ablation of the recipient sites before CST in segmental vitiligo and piebaldism.

MATERIALS AND METHODS

This prospective, randomized, observer-blinded, within-subject, controlled trial was approved by the medical ethical committee of the Academic Medical Centre, Amsterdam (#NL49720.018.14). This study is registered at the U.S. National Institutes of Health (ClinicalTrials.gov) as trial NCT02458417. We recruited and treated the patients at the Netherlands Institute for Pigment Disorders between May 2015 and February 2016. Eligible patients were 18 years or older, diagnosed with either stable segmental vitiligo or piebaldism and able to give written informed consent. Stable segmental vitiligo was defined as the absence of new lesions or enlargement of existing lesions for 12 months

without treatment. Furthermore, eligible patients had at least four depigmented lesions of 3x3 cm or one large lesion of at least 12x3 cm on the trunk or extremities. Patients with Fitzpatrick skin type I, recurrent herpes simplex virus infections, hypertrophic scarring, keloids, cardiac insufficiency, history of ultraviolet hypersensitivity, allergy for local anesthetics and/or clarithromycin, medical history with (non)melanoma skin cancer, atypical nevi and patients who were breastfeeding or pregnant were excluded from participation.

Interventions

Cell suspension preparation

We infiltrated the donor area with lidocaine 2% and harvested a split-thickness skin sample of approximately 4 cm^2 with a depth of 0.2 mm from the hip with an electric dermatome (D42 Dermatome; Humeca, Beverwijk, The Netherlands). The skin sample was then placed in a cell harvesting device (ReCell®; Avita Medical, London, U.K.). Following previous studies[7,11-13] and manufacturer's instructions, the skin sample was placed for approximately 15-20 minutes in a heated well containing an enzyme solution. Subsequently, the sample was rinsed in a sodium lactate solution, and disaggregation of cells from the epidermis and dermis was performed using a scalpel. Lastly, the suspension was drawn up in a syringe.

Recipient-site preparation

For recipient-site preparation, we used a 10,600 nm ablative CO_2 laser (Ultrapulse; Lumenis, Santa Clara, CA, U.S.A.) with a scanner handpiece suitable for full surface ablation (ActiveFx handpiece) and a handpiece for fractional ablation (DeepFx handpiece). In each patient, we randomly allocated four depigmented lesions of 4 cm^2 on the trunk or extremities to one of the following recipient-site preparations: (i) full surface ablation with an estimated depth of 209 µm (ActiveFx, one pass at 200 mJ, 60 W, density 3); (ii) full surface ablation with an estimated depth of 144 µm (ActiveFx, one pass at 150 mJ, 60 W, density 3); (iii) fractional laser ablation with an estimated depth of 225 µm (DeepFx, one pass at 7.5 mJ/microbeam, 20% density, 120 µm diameter) or (iv) untreated control site (no recipient site preparation and no CST).

After infiltration of the treatment sites with lidocaine 2%, the recipient sites were prepared and the necrotic debris on the skin was removed with saline-soaked gauze. The cell suspension was applied on the recipient sites, with exemption of the untreated control site. We used a ratio of one to four or five (donor to recipient site), and the cell suspension was also applied to the donor site. The recipient-site preparations and CST-procedures were performed by the same physicians.

Post-operative care

We covered the recipient and donor sites with a nonadherent, small-pore dressing (Telfa Clear; Covidien, Dublin, Ireland) and a secondary dressing with paraffin gauzes (Jelonet; Smith and Nephew, Hamburg, Germany) for seven days. Furthermore, patients were advised to take clarithromycin 500 mg once daily for 7 days after CST to prevent infections. To make the repigmentation more visible, patients were advised to start with ultraviolet A treatment on all treatment sites twice weekly with a facial tanner (GB9212; Eurosolar, Bonn, Germany) from 4 weeks to 6 months after the CST.

Randomization and allocation concealment

Randomization was based on a digitally generated randomization list not known to any of the involved investigators (Graph Pad Software Inc., La Jolla, CA, U.S.A.). After inclusion, treatment regions were assigned, and numbered, opaque, sealed envelopes containing cards with the allocation were opened in ascending order. The randomization and allocation was concealed for the blinded assessor. The patient and the treating physician were not blinded as this was practically impossible.

Outcomes

Primary outcome

The primary outcome of our study was the percentage of repigmentation per treatment site. This was measured by comparing surface areas of repigmentation copied on transparent sheets (baseline vs. 6 months) using a digital image analysis system (Image J; https://imagej.nih.gov/ij/).

Secondary outcomes

One week after CST, re-epithelialization (0-100%) and pain (on a visual analogue scale) per treatment site were assessed separately by the physician and patient. Six months after CST, a blinded independent physician assessed the repigmentation and side-effects (i.e. erythema, hyperpigmentation, hypopigmentation, scarring) per treatment site. Furthermore, color matching with normal skin was measured using a reflectance meter (DermaSpectrometer; Cortex Technology ApS, Hadsund, Denmark). Patients and physicians were asked to evaluate the global outcome per treatment site measured on a four-point scale (poor, moderate, good or excellent).

Statistical analyses

Statistical analyses were performed using SPSS (version 23; IBM Corp., Armonk, NY, U.S.A.). The Wilcoxon signed-rank test was used to compare the repigmentation percentages between recipient sites and significance level was set at α=0.05. All patients were included in the statistical analyses. Non-normally distributed data are presented as medians with their interquartile ranges (IQRs).

RESULTS

We included 10 patients with either segmental vitiligo (n=3) or piebaldism (n=7). The median age was 22.5 years and the ratio male to female was 4:6. None of the patients was lost to follow-up. The baseline characteristics are presented in Table 1.

Table 1 - Patient characteristics.

Patient	Sex	Age (years)	Diagnosis	Disease duration	Treatment location
1	Female	20	P	> 10 years	Lower leg (proximal)
2	Male	40	P	> 10 years	Knee
3	Female	42	SV	> 10 years	Upper arm (proximal)
4	Female	18	P	> 10 years	Lower leg (proximal)
5	Male	18	P	> 10 years	Lower leg (distal)
6	Male	62	P	> 10 years	Lower abdomen
7	Female	24	P	> 10 years	Knee
8	Male	19	SV	5-10 years	Upper arm (proximal)
9	Female	21	SV	> 10 years	Lower abdomen / side
10	Female	35	P	> 10 years	Lower leg (proximal)

P, piebaldism; SV, segmental vitiligo

Repigmentation

Repigmentation percentages per recipient site are presented in Figure 1. The median repigmentation after 209-µm (68.7%, IQR: 12.7-100.0, p=0.011) and 144-µm (58.3%, IQR 14.3-100.0, p=0.007) full surface ablation were significantly higher than at the control site (0%, IQR: 0-0%). No significant differences between fractional recipient-site preparation (median 0%, IQR: 0-11.9) and the control site were found (p=0.14). Repigmentation was

significantly higher for 209-µm (p=0.012) and 144-µm (p=0.008) full surface ablation than for fractional ablation. Furthermore, no significant difference in repigmentation was found between 209-µm and 144-µm full surface ablation (p=0.89).

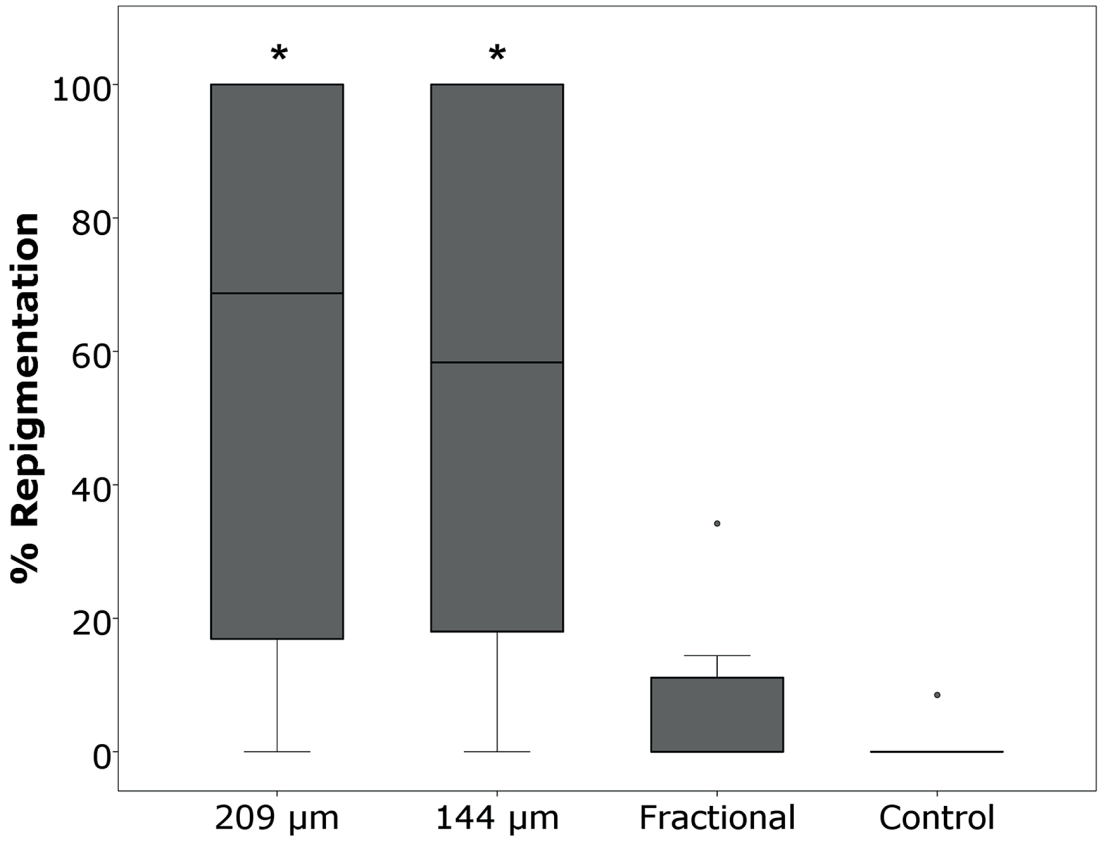


Figure 1 – Box plots with percentage of repigmentation per recipient-site preparation.

* p<0.05 vs. control recipient site evaluated using the Wilcoxon signed-rank test.

More than 75% repigmentation was found in 50% and 40% of the 209-µm and 144-µm full surface ablated recipient sites, respectively. The global assessment of repigmentation corresponded with the repigmentation percentages measured on transparent sheets in 31 of 40 recipient sites. The outcome after 209 µm full surface, 144 µm full surface and fractional ablation was scored by the patients as good to excellent in 60%, 50% and 0% of recipient sites, respectively. The outcomes of all control sites were scored by the patients as poor. The independent physician scored the outcome of the CST as good to excellent in 50% of the full surface ablation and in 10% of the fractional ablated recipient sites. Figure 2 presents a case with excellent responses in the full surface ablation sites.

Side effects

One week after the CST procedure, 100% re-epithelialization was reached in 30% (209 µm), 60% (144 µm), 100% (fractional) and 100% (control) of the lesions. None of the donor sites was 100% re-epithelialized after 1 week (median 5%, IQR: 0-50). Pain 1 week post-treatment was scored as low to absent in all recipient sites.

After 6 months, mild-to-moderate persisting erythema was more frequent in lesions pretreated with full surface ablation with a depth of 209 µm (70%) vs. 144 µm (50%). Mild hyperpigmentation, scored by the blinded physician, was seen in 10% of all full surface ablated lesions and not in fractional or control recipient sites. Objective measurement of the hyperpigmentation with a reflectance meter showed that 10% of the full surface (209 and 144 µm) and 0% of both fractional and control sites was darker (> 10% difference in melanin index) than surrounding healthy skin. No hypopigmentation or scarring of recipient sites was observed. Mild hypertrophic scarring of the donor site occurred in two patients.

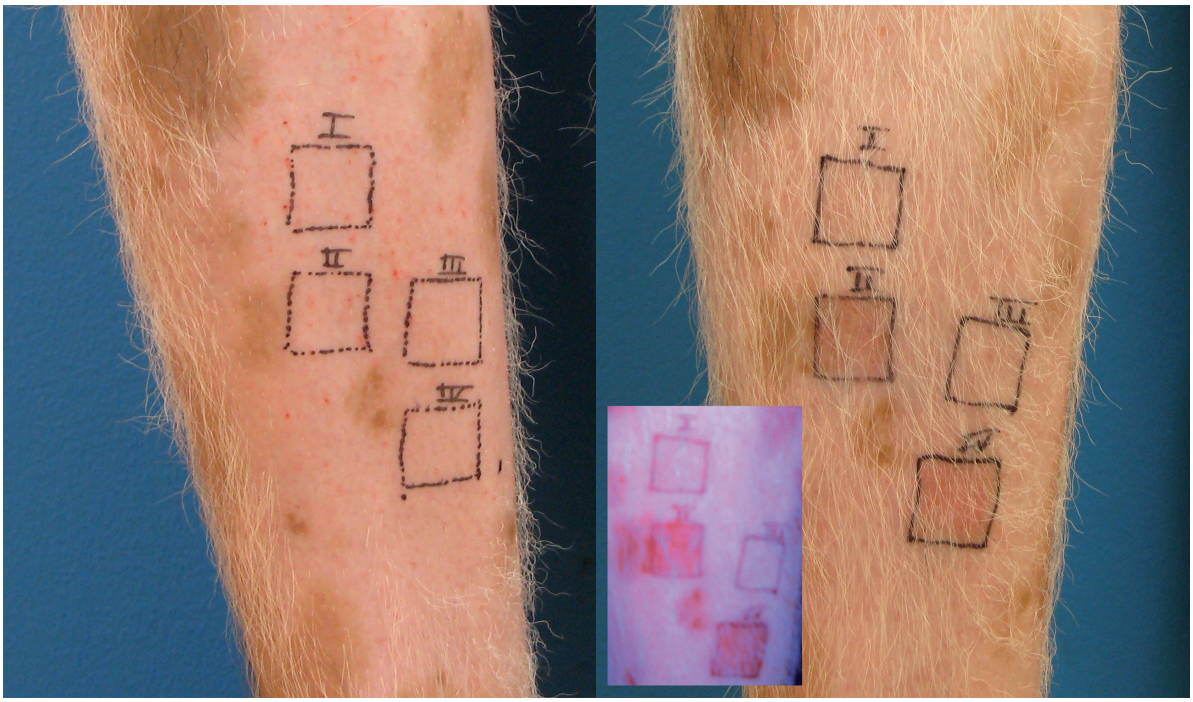


Figure 2 – Images of a patient with excellent responses in the full surface ablation sites. (**a**) before and (**b**) 6 months after treatment.

I, fractional laser; II, 209-µm full surface ablation; III, control site; IV, 144-µm full surface ablation. The full surface ablation sites show 100% repigmentation and persistent erythema. After Wood's lamp examination the excellent (100%) repigmentation was confirmed.

DISCUSSION

We investigated different depths and types of ablation of the recipient site before cell suspension transplantation in segmental vitiligo and piebaldism. The results of our study suggest that more superficial CO_2 laser full surface ablation is effective, while fractional CO_2 laser ablation with the settings used in this study is not.

Previous clinical studies of noncultured CST show varying repigmentation results.[3,14] The reasons for this variation remain unclear, but recipient-site preparation is one potential determinant. The optimal depth of ablation is not known and most studies do not report the depth of ablation. Most techniques for recipient-site preparation, such as dermabrasion, microneedling and ablation with liquid nitrogen, are difficult to standardize and not suitable for large or concave surfaces. [5,6,15] Laser settings are easy to standardize and therefore the use of ablative lasers as recipient-site preparation in CST is preferable.[6]

Repigmentation after full surface CO_2 laser ablation with a depth of approximately 209 µm was similar to that in other studies using the same depth of ablation.[6,7] In our current study, we found comparable repigmentation percentages after superficial and deeper full surface ablation (144 vs. 209 µm ablation). The superficial full surface ablation resulted in faster re-epithelialization and less persistent erythema than deeper full surface ablation. Therefore, superficial ablation seems a better option for recipient-site preparation than deeper full surface ablation. Furthermore, superficial ablation may require only topical rather than infiltration anesthesia, which is much more comfortable for patients.

To our knowledge, this was the first study to assess superficial CO_2 laser and fractional CO_2 laser as recipient-site preparations in CST. A recent prospective study of Silpa-Archa et al. compared dermabrasion and full surface CO_2 laser ablation as recipient site preparations.[6] Silpa-Archa et al. classified their CO_2 laser settings as fractional. However, we consider that their settings are more accurately classified as nonfractional, as the high density (82%) of the ablation channels effectively leads to a full surface ablation.[16] In our study, the recipient sites pretreated with fractional ablation did not show satisfactory repigmentation. This is contradictory to preclinical data suggesting that fractional CO_2 laser results in adequate penetration and adherence of cells.[5,17] On the other hand, fractional CO_2 lasers are known to produce a necrotic eschar that surrounds each ablation channel. Due to this eschar, oozing of exudate is minimized, but it may theoretically also impair permeation and adherence of the cell suspension. As this is the first clinical study investigating ablative fractional laser therapy as recipient-site

preparation for CST, the optimal settings are still unknown. The fractional laser pulse energy settings in the current study were chosen based on expected ablation depth. The optimal depth of ablation is not known. Hypothetically, other CO_2 laser settings (e.g. pulse energy, density, depth and diameter of ablation channels) or the use of a different type of fractional laser may be more effective. Fractional erbium-doped yttrium aluminium garnet lasers usually create less necrotic eschar, and micro-needling creates none, hypothetically leading to better permeation of the cell suspension.[18] However, they are also associated with more exudate and bleeding, which possibly leads to washing out the cell suspension before melanocyte adherence occurs.

Previous studies in non-segmental vitiligo have shown repigmentation after laser ablation alone without cellular grafting. [19,20] However, in piebaldism and segmental vitiligo residual follicular melanocytes are generally lacking. This is the reason why unspecific induction of repigmentation is very unlikely in segmental vitiligo and piebaldism. Furthermore, we previously reported lack of repigmentation after CO_2 laser alone in a similar population.[7] Therefore, we assume that the contribution of laser ablation on the repigmentation is minimal in our study.

A limitation of this study is the small number of patients who were treated. Furthermore, treatment with CST was limited to the trunk and extremities while other body parts may react differently. The study is also limited by including both piebaldism and segmental vitiligo, which are different depigmenting skin disorders. On the other hand, both have the same natural stable course without a persisting auto-immunity against melanocytes, such as in non-segmental vitiligo. Various steps in the cell suspension transplantation process, such as harvesting of the skin sample, disaggregation of the epidermal cells and application of the cell suspension, are performed manually. This might impose another source of variation, possibly explaining the differences in repigmentation between individual patients. Another limitation is that some core outcome domains for vitiligo, such as maintenance of repigmentation and tolerability with treatment, were not measured.[21] No consensus is available on which measurement instruments should be used for target lesion assessment in vitiligo. We used the transparent sheet method that was used in our previous study and that was previously validated by Van Geel et al.[7,22]

In conclusion, we recommend that the recipient site before CST is prepared with full surface ablation with a depth of approximately 144 µm. Fractional CO_2 laser with the settings used in this study is not as effective for recipient-site preparation. Further research on different laser types and optimal settings is needed.

REFERENCES

1 Ongenae K, Beelaert L, van Geel N *et al.* Psychosocial effects of vitiligo. *Journal of the European Academy of Dermatology and Venereology* 2006; **20**: 1-8.

2 Linthorst Homan MW, Spuls PI, de Korte J *et al.* The burden of vitiligo: patient characteristics associated with quality of life. *Journal of the American Academy of Dermatology* 2009; **61**: 411-20.

3 Mulekar SV, Isedeh P. Surgical interventions for vitiligo: an evidence-based review. *The British journal of dermatology* 2013; **169 Suppl 3**: 57-66.

4 van Geel N, Wallaeys E, Goh BK *et al.* Long-term results of noncultured epidermal cellular grafting in vitiligo, halo naevi, piebaldism and naevus depigmentosus. *The British journal of dermatology* 2010; **163**: 1186-93.

5 Al-Hadidi N, Griffith JL, Al-Jamal MS *et al.* Role of Recipient-site Preparation Techniques and Post-operative Wound Dressing in the Surgical Management of Vitiligo. *Journal of cutaneous and aesthetic surgery* 2015; **8**: 79-87.

6 Silpa-Archa N, Griffith JL, Williams MS *et al.* Prospective comparison of recipient-site preparation with fractional carbon dioxide laser vs. dermabrasion and recipient-site dressing composition in melanocyte-keratinocyte transplantation procedure in vitiligo: a preliminary study. *The British journal of dermatology* 2016; **174**: 895-7.

7 Komen L, Vrijman C, Tjin EP *et al.* Autologous cell suspension transplantation using a cell extraction device in segmental vitiligo and piebaldism patients: A randomized controlled pilot study. *Journal of the American Academy of Dermatology* 2015; **73**: 170-2.

8 Manstein D, Herron GS, Sink RK *et al.* Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers in Surgery and Medicine* 2004; **34**: 426-38.

9 Hunzeker CM, Weiss ET, Geronemus RG. Fractionated CO2 laser resurfacing: our experience with more than 2000 treatments. *Aesthetic Surgery Journal* 2009; **29**: 317-22.

10 Brightman LA, Brauer JA, Anolik R *et al.* Ablative and fractional ablative lasers. *Dermatologic clinics* 2009; **27**: 479-89, vi-vii.

11 Mulekar SV, Ghwish B, Al Issa A *et al.* Treatment of vitiligo lesions by ReCell vs. conventional melanocyte-keratinocyte transplantation: a pilot study. *The British journal of dermatology* 2008; **158**: 45-9.

12 Cervelli V, De Angelis B, Balzani A *et al.* Treatment of stable vitiligo by ReCell system. *Acta Dermatovenerol Croat* 2009; **17**: 273-8.

13 Cervelli V, Spallone D, Lucarini L *et al.* Treatment of stable vitiligo hands by ReCell system: a preliminary report. *Eur Rev Med Pharmacol Sci* 2010; **14**: 691-4.

14 Whitton ME, Pinart M, Batchelor J *et al.* Interventions for vitiligo. *The Cochrane database of systematic reviews* 2015; **2**: Cd003263.

15 Busch KH, Bender R, Walezko N *et al.* Combination of medical needling and non-cultured autologous skin cell transplantation (ReNovaCell) for repigmentation of hypopigmented burn scars. *Burns : journal of the International Society for Burn Injuries* 2016; **42**: 1556-66.

16 Farkas JP, Richardson JA, Brown SA *et al.* TUNEL assay to characterize acute histopathological injury following treatment with the active and deep FX fractional short-pulse CO2 devices. *Aesthet Surg J* 2010; **30**: 603-13.
17 Oni G, Lequeux C, Cho MJ *et al.* Transdermal delivery of adipocyte-derived stem cells using a fractional ablative laser. *Aesthet Surg J* 2013; **33**: 109-16.
18 Paasch U, Haedersdal M. Laser systems for ablative fractional resurfacing. *Expert Rev Med Devices* 2011; **8**: 67-83.
19 Shin J, Lee JS, Hann SK *et al.* Combination treatment by 10 600 nm ablative fractional carbon dioxide laser and narrowband ultraviolet B in refractory nonsegmental vitiligo: a prospective, randomized half-body comparative study. *The British journal of dermatology* 2012; **166**: 658-61.
20 Bayoumi W, Fontas E, Sillard L *et al.* Effect of a preceding laser dermabrasion on the outcome of combined therapy with narrowband ultraviolet B and potent topical steroids for treating nonsegmental vitiligo in resistant localizations. *The British journal of dermatology* 2012; **166**: 208-11.
21 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment cell & melanoma research* 2015; **28**: 363-9.
22 Van Geel N, Vander Haeghen Y, Ongenae K *et al.* A new digital image analysis system useful for surface assessment of vitiligo lesions in transplantation studies. *European Journal of Dermatology* 2004; **14**: 150-5.

CHAPTER 4.3

THE ROLE OF PHOTOTHERAPY IN THE SURGICAL TREATMENT OF VITILIGO: A SYSTEMATIC REVIEW.

J.E. Lommerts, S.E. Uitentuis, M.W. Bekkenk, M.A. de Rie and A. Wolkerstorfer

Submitted

ABSTRACT

Vitiligo is frequently treated with the combination of phototherapy and melanocyte transplantation. However, the additional benefit of phototherapy is unclear. Moreover, the optimal type and regimen of phototherapy is unknown. The objective of this systematic review was to identify whether phototherapy improves the outcome of melanocyte transplantation in vitiligo. We searched and screened for eligible studies in the databases of MEDLINE, EMBASE and CENTRAL. We included all clinical studies investigating melanocyte transplantation combined with phototherapy. After screening and selection of abstracts and full-texts, we found 39 eligible clinical studies with 1624 patients. The eligible studies investigated several phototherapy modalities, such as NBUVB (n=9), PUVA (n=19), UVA (n=1), MEL (n=4) and active sunlight exposure (n=9). Four studies directly compared phototherapy versus no phototherapy and two studies confirmed the benefit of phototherapy for melanocyte transplantation. We found no significant differences in repigmentation in studies directly comparing phototherapy modalities. The overall quality of the studies was moderate to poor and high heterogeneity between studies was found. We found limited evidence that phototherapy improves the outcome of melanocyte transplantation in vitiligo. There is insufficient evidence to recommend a specific type or regimen of phototherapy. More studies should be performed investigating the additional benefit of different phototherapies and the preferred moment of phototherapy.

INTRODUCTION

Vitiligo is a common depigmenting skin disorder with a worldwide prevalence of 0.5-1%.[1] Stable vitiligo lesions are treated with various surgical melanocyte transplantation techniques.[2] Melanocyte transplantation in stable vitiligo is frequently combined with subsequent phototherapy. Total repigmentation after melanocyte transplantation is uncommon and phototherapy can potentially have a beneficial effect on the outcome.[3] Phototherapy can enhance the repigmentation after melanocyte transplantation by its anti-inflammatory properties and by inducing melanocyte proliferation and migration. However, phototherapy also has side-effects such as increased risk of skin cancer and premature skin aging.[4] To date, there is no consensus on the role of phototherapy in the surgical treatment of vitiligo.[5]

The objective of our study was to identify whether phototherapy improves the outcome of melanocyte transplantation in vitiligo. Therefore, we designed a systematic review to summarize and review the evidence of the combination therapy of phototherapy and melanocyte transplantation.

MATERIALS AND METHODS

Search strategy and selection

We designed our systematic review with the use of the PRISMA Guideline and registered our study in the PROSPERO database under #53500.[6] Our search strategy comprised main keywords on vitiligo and melanocyte transplantation (Supplements S1). We performed a literature search for relevant studies from inception up to June 2016 of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). Subsequently, screening for other relevant articles in the reference lists of the identified studies was performed. We used Endnote (version X7.7.1) for reference management and duplicate finding. We conducted a first selection based on title and abstract. This was followed by screening for eligibility of the full text copies of selected studies. The selection procedure and the details for exclusion per study were systematically documented in a PRISMA flow diagram.[7]

Eligibility criteria

Studies were found eligible when they met the following pre-specified inclusion criteria: ≥10 vitiligo patients, intervention study with melanocyte transplantation and phototherapy, quantitative repigmentation as outcome measure and English language. Phototherapy was defined as the administration of any type of light before or after melanocyte transplantation. Quantitative repigmentation included mean or median repigmentation, pigment spread and ordinal repigmentation measurement instruments. Furthermore, studies were only included when the results per phototherapy modality were provided separately. Eligible transplantation techniques included punchgrafting (PG), suction blister grafting (SBG), non-cultured autologous melanocyte transplantation (NCAMT), cultured autologous melanocyte transplantation (CAMT), split-thickness grafting (STG) and hair follicle transplantation (HFT).

Quality assessment

We assessed the quality of the clinical trials with the Risk of Bias assessment tool of the Cochrane Collaboration.[8] We evaluated per randomized controlled trial (RCT) or (non-randomized) clinical trial the risk of bias (low, unclear, high) of the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. The quality assessment of the eligible case series was performed with the Quality Appraisal Tool for Case Series. [9] This tool comprises 18 questions on quality appraisal and we added specific assessment criteria to 6 questions in order to adapt the checklist to our specific research question (Supplement S2).

Data extraction and analyses

We included from each study pre-specified data (author, year of publication, study design, patient characteristics, type of surgical treatment, follow-up duration, quantitative repigmentation measures and outcome). Furthermore, from each study we extracted per phototherapy modality the moment of initiation, frequency, duration, initial dose, dose adjustment and cumulative dose of phototherapy. Two assessors (JL and SU) performed the selection, quality assessment and data extraction independently. Disagreements were resolved by discussion with these two assessors and a third assessor (AW).

RESULTS

Literature search

The search strategy generated a total of 1815 unique hits of which 39 articles met the inclusion criteria. The PRISMA flow diagram with the screening and selection procedure with reasons for exclusion is presented in Fig. 1. From these 39 studies, 7 studies compared one phototherapy with another or with no phototherapy as an addition to the surgical treatment in vitiligo; these studies were marked as 'comparative'.[10-16] Furthermore, in the other 32 studies the results of only one phototherapy were presented; these studies were marked as 'non-comparative'.[17-48] In all studies, a total of 1624 patients with vitiligo were evaluated. The study characteristics of the eligible studies are presented in Table 1. In the eligible studies the following phototherapy modalities were studied: narrowband ultraviolet B (NBUVB, n=9), psoralen combined with ultraviolet A (PUVA, n=19), ultraviolet A (UVA, n=1), monochromatic excimer light or laser (MELi and MELa, n=4) and active sunlight exposure (n=9). The specific characteristics of the phototherapy per study can be found in the supplements.

Quality assessment

The risk of bias assessment of the RCTs and quality assessment of the case series are summarized in Table 2. We used the risk of bias tool in 13 RCTs and 1 clinical trial. We identified 25 case series which we critically appraised with the Quality Assessment Checklist of case series (Supplement S3).

Comparative studies

These studies investigated the effect of different phototherapy regimens on the outcome of PG (n=4), SBG (n=1), CAMT (n=1) and NCAMT (n=1). The results of the comparative studies are presented in Table 3.

Comparison between phototherapy and no phototherapy

Ebadi et al. compared repigmentation in 39 lesions within 10 patients after NCAMT with or without MELa treatment. Median repigmentation was higher for the combination NCAMT and MELa than for NCAMT alone (41.9% vs. 15.9%, p=0.01). More than 65% repigmentation in lesions treated with NCAMT and MELa or NCAMT alone was reached in 40% and 11.1% of lesions, respectively.

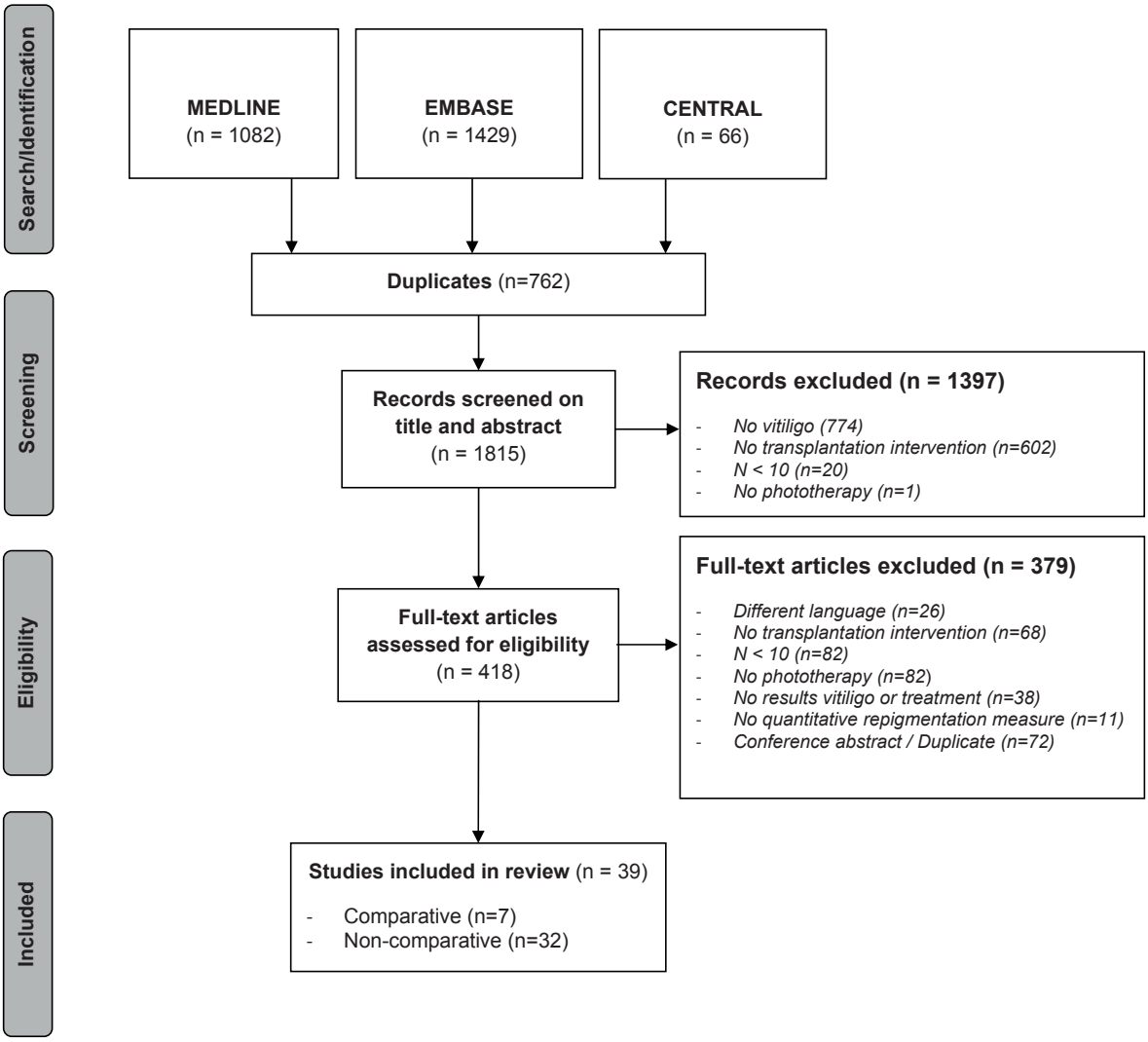


Figure 1 – Screening and selection procedure. This PRISMA flowdiagram shows the screening and selection procedure; n, number of studies.

Barman et al. compared repigmentation in 22 patients treated with PG and systemic PUVA (sPUVA) versus 28 patients treated with PG and topical fluocinolone acetonide 0.1% cream once daily.[16] Six months post grafting, no significant difference in pigmentspread was found between sPUVA and topical corticosteroids groups (6.38mm vs 6.94mm respectively, $p>0.05$).

In the case series of Lim et al., 105 SBG-grafts in 25 patients were treated with either pre- and post-PUVA (n=65 grafts), pre-PUVA (n=26 grafts), post-PUVA (n=4 grafts) or without phototherapy (n=10 grafts). In 50-87.7% of the grafts 100% repigmentation was seen. No differences in percentage of SBG-grafts treated with or without PUVA that reached 100% repigmentation were seen.

Table 1 – Study characteristics.

Author, year	N	Study design	Age in years (range)	Patient characteristics I. Vitiligo type (% of patients) II. Stability duration	Phototherapy	Surgical treatment
Comparative studies						
Barman, 2004	42	RCT	13-60	I. SV (59.5%);NSV (40.5%) II. ≥ 6 mo	sPUVA	PG
Ebadi, 2015	10	CT	21-48	I. NSV (100%) II. ≥ 1 yr	MELa	NCAMT
Lim, 1999	25	CS	14-64	I. NSV (52%), SV (32%), FV (16%) II. > 3 yr	PUVA	SBG
Linthorst Homan, 2012	14	RCT	18-69	I. NSV (100%) II. ≥ 6 mo	MELa NBUVB	PG
Sheth, 2012	10	RCT	21-74	I. Unknown II. ≥ 6mo	MELi NBUVB	PG
Tsuchiyama, 2016	13	CS	7-16	I. SV (100%) II. Unknown	MELa NBUVB	PG
Zhang, 2014	473	RCT	5-55	I. NSV (72%); SV (18%), uk (10%) II. ≥ 6mo	NBUVB	CAMT
Non-comparative studies						
Awad, 2008	20	CS	5-44	I. NSV (60%), SV (20%), halo nevi (20%) II. ≥ 3 months	K-UVA	SBG
Babu, 2008	18	RCT	11-65	I. NSV (5.6%), SV (50%), focal (44.4%) II. ≥ 1yr	PUVASOL	PG SBG
Boersma, 1995	19	CS	15-55	I. NSV (100%) II. ≥ 6 mo	UVA	PG
Budania, 2012	41	RCT	12-40	I. NSV (36.6%), SV (39%), FV (24.4%) II. ≥ 1yr	Sunlight	NCAMT SBG
Chen, 2000	25	CS	13-72	I. SV (100%) II. ≥ 1yr	Sunlight	CAMT
Czajkowski, 2007	40	RCT	14-59	I. Unknown II. ≥ 6 mo	sPUVA	SBG CAMT
De Leeuw, 2011	19	RCT	25-68	I. Unknown II. ≥ 1 yr	K-NBUVB	SBG
El-Zawahry, 2011	25	CS	8-45	I. NSV (84%), SV (8%), FV (8%) II. ≥ 1 yr	PUVA	NCAMT

Table 1 – (continued)

Author, year	N	Study design	Age in years (range)	Patient characteristics I. Vitiligo type (% of patients) II. Stability duration	Phototherapy	Surgical treatment
Ghorpade, 2004	10	CS	18-65	I. Unknown III. ≥ 1 yr	PUVASOL	PG
Gupta, 2002	10	CS	11-19	I. NSV (70%), SV (20%), FV (10%) II. ≥ 1 yr	sPUVA	SBG
Hallaji, 2003	20	CS	13-40	I. NSV (40%), SV (20%), FV (40%) II. ≥ 6 mo	tPUVA	PG
Holla, 2014	31	CS	10-38	I. NSV (38.7%), SV (51.6%), FV (9.7%) II. unknown	Sunlight	NCAMT
Holla, 2013	36	CS	16-47	I. NSV (91.7%), FV (8.3%) II. ≥ 1 yr	Sunlight	NCAMT
Khandpur, 2005	64	RCT	10-42	I. NSV (50%), SV (26.6%), FV (23.4%) II. ≥ 6 mo	PUVASOL	PG STG
Krishnan, 2012	26	CS	15-28	I. Unknown II. ≥ 1 yr	PUVASOL	NCAMT
Lahiri, 2006	66	CS	21-48	I. NSV(39.4%), SV(27.3%), FV(21.2%), other(12.1%) II. ≥ 6 mo	NBUVB	PG
Majid, 2012	40	CS	uk	I. Unknown II. ≥ 1 yr	NBUVB	STG
Malakar, 2004	108	CS	uk	I. NSV (53.7%), other (46.3%) II. ≥ 6 mo	PUVASOL	PG
Mapar, 2014	25	RCT	20-47	I. NSV (100%) II. ≥ 1 yr	NBUVB	PG HFT
Matsuzaki, 2013	27	CS	9-48	I. NSV (25.9%), SV(74.1%) III. unknown	Sunlight	CAMT
Olsson, 1997	19	CS	12-62	I. NSV (94.7%), SV (5.3%) II. unknown	Sunlight	STG
Pai, 2002	29	CS	14-60	I. NSV (10.3%), localized (89.7%) II. Unknown	PUVA	PG SBG
Pianigiani, 2005	93	CS	14-62	I. NSV (19.4%), SV (28.0%), FV (52.7%) II. ≥ 2 yr	NBUVB	CAMT
Sachdev, 2000	13	CS	19-58	I. NSV (23.1%), FV (7.7%), u.k. (69.2%) II. Unknown	PUVA	PG

Table 1 – (continued)

Author, year	N	Study design	Age in years (range)	Patient characteristics I. Vitiligo type (% of patients) II. Stability duration	Phototherapy	Surgical treatment
Sahni, 2011	13	CS	8-17	I. NSV (46.2%), SV (46.2%), FV (7.7%) II. ≥ 1 yr	Sunlight	NCAMT
Sahni, 2011	25	RCT	14-55	I. NSV (72%), SV (12%), FV (16%) II. Mean ± SD: 3.0 ± 3.5 and 3.3 ± 4.2	Sunlight	NCAMT
Sarkar, 2001	15	CS	16-42	I. SV (100%) II. Unknown	PUVASOL	PG
Singh, 1995	32	CS	11-60	I. NSV (6.3%), SV (37.5%), FV (56.3%) II. ≥ 1 yr	PUVASOL	PG
Singh, 1997	55	CS	10-30	I. SV, FV (% percentage unknown) II. Unknown	PUVASOL	PG
Suga, 1996	28	CS	12-60	I. NSV (28.6%), SV (35.7%), FV (35.7%) II. Unknown	tPUVA	SBG
Tegta, 2006	20	RCT	10-54	I. NSV (55%), SV (20%), FV (25%) II. ≥ 1 yr	Sunlight	NCAMT
Verma, 2014	25	RCT	u.k.	I. NSV (72%), SV (8%), FV (12%), other (8%) II. ≥ 1 yr	PUVASOL	NCAMT CAMT

N, number of patients; CS, case series; RCT, randomized controlled trial; CT, clinical trial; NSV, non-segmental vitiligo; SV, segmental vitiligo; FV, focal vitiligo; SBG, suction blister grafting; K-UVA, khelline application with ultraviolet A phototherapy; PUVASOL, psoralen combined with sunlight exposure; sPUVA, systemic psoralen combined with ultraviolet A phototherapy; UVA, ultraviolet A phototherapy; K-NBUVB, khelline application with narrowband ultraviolet B phototherapy; MELa, monochromatic excimer laser; PUVA, psoralen combined with ultraviolet A phototherapy; tPUVA, topical psoralen combined with ultraviolet A phototherapy; NBUVB, narrowband ultraviolet B phototherapy; MELi, monochromatic excimer light; PG, punchgrafting; NCAMT, non-cultured autologous melanocyte transplantation; CAMT, cultured autologous melanocyte transplantation; STG, split-thickness grafting; HFT, hair follicle transplantation

Zhang et al. assessed repigmentation after CAMT in 437 patients randomly allocated to four different study groups. Group 1 received NBUVB before CAMT, group 2 NBUVB after CAMT, group 3 NBUVB before and after CAMT, and group 4 received CAMT only. Six months after transplantation the mean repigmentation was higher in the groups treated with CAMT and NBUVB (79.9-87.7%) than with CAMT only (68.1%). The differences between the four groups were statistically significant ($p < 0.001$).[10]

Table 2 - Risk of bias assessment of clinical trials.

Author, year	Type of bias					
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective outcome reporting
Babu, 2008	Unclear	Unclear	High	Unclear	Low	Unclear
Barman, 2004	Unclear	Unclear	High	Unclear	Low	Unclear
Budania, 2012	Unclear	Unclear	High	Unclear	Low	Unclear
Czajkowski, 2007	Unclear	Unclear	High	Unclear	Unclear	High
De Leeuw, 2011	Unclear	Unclear	High	Low	Unclear	Unclear
Ebadi, 2015	High	High	High	Unclear	Low	High
Khandpur, 2005	Unclear	Unclear	High	Unclear	Low	High
Linthorst, 2012	Low	Unclear	High	Unclear	Low	Low
Mapar, 2014	Low	Unclear	High	Unclear	Low	Unclear
Sahni, 2011	Low	Unclear	High	Unclear	Unclear	Unclear
Sheth, 2012	Low	Unclear	High	Low	Low	Low
Tegta, 2006	Unclear	Unclear	High	Unclear	Low	High
Verma, 2014	Unclear	High	High	High	Low	Unclear
Zhang, 2014	Low	Unclear	High	Unclear	Unclear	Unclear

Comparison between different phototherapies

Linthorst Homan et al. compared repigmentation in 14 patients with non-segmental vitiligo after punchgrafting with subsequent MELa or NBUVB. In this intra-patient comparison, mean repigmentation 4 weeks post punchgrafting was 31% after MELa and 38% after NBUVB. Although >75% repigmentation was more frequently observed in the lesions treated with NBUVB (21%) than with MELa (14%), no significant differences were found ($p>0.05$).

Sheth et al. compared repigmentation in 10 patients treated with punchgrafting combined with either MELi or NBUVB in an intra-patient comparison. Median repigmentation of 13% in the NBUVB-lesions versus 9% in the MELi-lesions were found ($p>0.05$). The mean pigmentspread was higher ($p>0.05$) in the group with NBUVB (4.5 times original size) than in the MELi lesions (2 times original size).

Table 3 – Repigmentation results of comparative studies.

Author, year	FU	Outcomes	N	Intervention	Results
Barman, 2004	6 mo	Mean pigmentspread	17	PG + sPUVA	6.38
			25	PG + topical CS	6.94
Ebadi, 2015	u.k.	I. Median % repigmentation II. 95-100% repigmentation III. 65-94% repigmentation IV. 25-64% repigmentation V. 0-24% repigmentation	9*	NCAMT	I. 15.9% II. 0% III. 11.1% IV. 33.3% V. 55.6%
			10*	NCAMT + MELa	I. 41.9% II. 20% III. 20% IV. 40% V. 20%
			10*	Only MELa	I. 4.7% II. 0% III. 0% IV. 10% V. 90%
			10*	No treatment	I. 0.1% II. 0% III. 0% IV. 0% V. 100%
Lim, 1999	2 mo	I. 100% repigmentation II. 0% repigmentation	65*	Pre-and post PUVA + SBG	I. 87.7%** II. 4.6%**
			26*	Pre PUVA + SBG	I. 53.8%** II. 11.5%**
			4*	Post PUVA + SBG	I. 50%** II. 50%**
			10*	SBG	I. 80%** II. 10%**
Linthorst Homan, 2012	4w	I. >75% repigmentation II. Mean repigmentation	14	PG + MELa	I. 14% II. 31%
				PG + NBUVB	I. 21% II. 38%
Sheth, 2012	12w	I. Median repigmentation II. Mean pigment spread *(times original size)*	10	PG + MELi	I. 9% II. 2 times
				PG + NBUVB	I. 13% II. 4.5 times
Tsuchiyama, 2016	6-32 mo	Mean repigmentation	11	PG + MELa	80.3%
			2	PG + NBUVB	89%

Table 3 – (continued)

Author, year	FU	Outcomes	N	Intervention	Results
Zhang, 2014	6 mo	I. Mean repigmentation II. > 90% repigmentation III. 50-89% repigmentation IV. 20-49% repigmentation V. 0-19% repigmentation	108	CAMT + *pre*NBUVB	I. 83.5% II. 68.5% III. 24.1% IV. 1.8% V. 5.6%
			113	CAMT + *post*NBUVB	I. 79.9% II. 61.9% III. 27.4% IV. 8.0% V. 2.7%
			116	CAMT + *pre*NBUVB + *post*NBUVB	I. 87.7% II. 81.3% III. 13.8% IV. 4.3% V. 0.9%
			110	CAMT + No PT	I. 68.1% II. 43.6% III. 29.1% IV. 19.1% V. 8.2%

FU, follow-up duration after treatment; N, number of patients; mo, months; u.k., unknown; w, weeks; PG, punchgrafting; sPUVA, systemic psoralen combined with ultraviolet A phototherapy; CS, corticosteroids; NCAMT, non-cultured autologous melanocyte transplantation; MELa, monochromatic excimer laser; PUVA, psoralen combined with ultraviolet-A phototherapy; SBG, suction blister grafting; NBUVB, narrowband ultraviolet B phototherapy; MELi, monochromatic excimer light; CAMT, cultured autologous melanocyte transplantation; PT, phototherapy; * number of treated lesions or grafts; ** repigmentation per graft

In the case series of Tsuchiyama et al., 11 patients were treated with MELa after PG and 2 patients with NBUVB after PG. The mean repigmentation between the MELa and NBUVB post grafting was similar (80.3% vs. 89%, respectively).

In the study of Zhang et al., mean repigmentation was not significantly different between patients treated with NBUVB before (83.5%), NBUVB after (79.9%) or NBUVB before and after (87.7%) CAMT. More patients showed >90% repigmentation after grafting in the group treated with pre- and post NBUVB (81.3%) than in the groups treated with pre-NBUVB (68.5%) or post NBUVB (61.9%).

Non-comparative studies

We identified 23 studies investigating only one transplantation technique (PG=9, SBG=3, NCAMT=5, CAMT=3, STG=2) and 10 studies comparing different transplantation techniques within or between patients. In the supplements a table with the results per non-comparative study can be found (Supplement S5). No eligible non-comparative studies investigating MELi or MELa were found.

PUVA

We identified 17 studies assessing the repigmentation after melanocyte transplantation in combination with PUVA (systemic PUVA n=2, topical PUVA n=3, PUVASOL n=9, unknown type n=3). In 3 studies, >75% repigmentation was found in 44-69% of patients treated with PG, in 0-80% of patients treated with SBG, and in 83% of patients treated with STG combined with PUVA.[38,41,43] In 5 studies, 100% repigmentation was found in 25-99% of patients treated with SBG, in 66%-100% of patients treated with PG, and in 50% of patients treated with CAMT combined with PUVA.[33,35,44,46,48] In 6 studies, >90% repigmentation was found in 23%, 39%, 65%, 72%, 80% and 100% of treated patients.[33,36,39,40,42,45] Mean pigmentspread was assessed in 2 studies and ranged from 3.9-5.4 mm.[36,44]

NBUVB

We identified 5 studies which examined NBUVB. One study found a mean repigmentation of 65.3% after SBG combined with NBUVB and khelline application.[31] In 1 case study, 100% repigmentation was found in 60% of patients treated with CAMT and NBUVB.[27] In the case study of Majid et al., >90% repigmentation was found in 83% of patients treated with STG and subsequent NBUVB. Mean pigmentspread was addressed in 2 studies and ranged from 5.0-6.5mm.[28,30]

UVA

We identified only one study that addressed the repigmentation after melanocyte transplantation and UVA.[26] In this case series, >80% repigmentation was found in 38.9% of all lesions treated with PG and UVA.

Sunlight exposure

In 9 studies the repigmentation after melanocyte transplantation and active sunlight exposure was assessed. Most studies (n=8) were performed in sunny areas (India n=6, Taiwan n=1, Japan n=1), whereas one study was performed in Sweden. Six studies found >75% repigmentation in 0-93% of patients and in 45-100% of lesions treated with NCAMT and in 85% of patients treated with SBG combined with sunlight

exposure.[17-19,22,23,25] Olsson et al. found 100% repigmentation in 49% of lesions after STG followed by sunlight exposure. Five studies found >90% repigmentation in 29-79% of lesions and in 44-89% of patients treated with NCAMT, in 52% of patients treated with CAMT, and in 27% of patients treated with SBG combined all combined with sunlight exposure.[18,19,21,22,25]

DISCUSSION

In this study, we reviewed 39 studies investigating 1624 patients with vitiligo. The results of our systematic review suggest that phototherapy improves the outcome of melanocyte transplantation in vitiligo.

We found 2 RCTs, 1 clinical trial and 1 case series comparing phototherapy (MEL, PUVA, UVB) with no phototherapy after melanocyte transplantation.[10,14-16] These studies confirm the benefit of phototherapy for melanocyte transplantation. Recent guidelines and a recent systematic review also have recommended combination therapy in the treatment of vitiligo and state that combination therapies are associated with more repigmentation than monotherapies.[3,5,49,50] Four studies directly compared phototherapy modalities. These studies found no significant differences in repigmentation between phototherapy modalities.

The eligible studies showed high heterogeneity in terms of outcome measures, transplantation techniques, stability of vitiligo, phototherapy regimen, quality and follow-up duration. Most studies (n=25) included different subtypes of vitiligo, such as non-segmental and segmental vitiligo, but in only 14 of 39 studies[13-15,18,21,24,26,28,33,36,37,42,43,45] the results per subtype were provided. Basically, melanocyte transplantation is more effective in patients without a persisting auto-immunity against melanocytes, such as in segmental vitiligo. Due to the high heterogeneity and unavailable data per subtype, we were not able to pool the data, compare the results between modalities and perform a sub-analysis per vitiligo subtype. We also found a high variation in measurement instruments, which further impedes the comparison between studies. Therefore, consensus on a core set of measurement instruments is essential. Only 13 studies reported the duration of the phototherapy (< 6 months = 10 studies, 6 months = 3 studies, unknown = 26 studies). The timing of the phototherapy was mainly post-grafting (n=37 studies), although 2 studies also showed a beneficial effect of NBUVB pre-grafting. Hypothetically, pre-treatment with phototherapy induces more immunosuppression on the acceptor site and melanocyte stimulation on the donor site, leading to more repigmentation after grafting. In the eligible studies, PUVA (n=19

studies) was more frequently used as phototherapy than NBUVB (n=9 studies). In 1997, there was a shift of paradigm in the phototherapy of vitiligo (i.e. from PUVA to NBUVB) as Westerhof et al. were the first to show that NBUVB was as effective as PUVA.[51] Only 3 out of 19 eligible studies investigating PUVA dated before this publication in 1997, although recent international guidelines recommend NBUVB as standard monotherapy in vitiligo due to the favorable safety profile.[5]

A limitation of our review is that we were not able to pool the results per phototherapy modality and/or transplantation technique due to the high heterogeneity between studies. Another limitation is that we included all techniques of melanocytes transplantation even though repigmentation is known to depend on the transplantation technique. We were not able to pool the results per transplantation technique as the procedures of similar transplantation techniques were different between studies. Lastly, we included both prospective and retrospective clinical studies, which led to low quality of the evidence and unknown biases.

We recommend NBUVB as the standard phototherapy after melanocyte transplantation. The immunosuppressive effects and safety profile of NBUVB make this modality the most preferred phototherapy option, especially in non-segmental vitiligo. A recent systematic review and meta-analysis also shows that monotherapy with NBUVB is even as and in some studies more effective than PUVA in vitiligo.[52] The other available phototherapy modalities also have more potential limitations than NBUVB. PUVA for example has more phototoxic effects and a higher potential risk on skin cancer than NBUVB whereas MEL is only appropriate for small areas and only provides immunosuppression locally.[52] The frequency, duration, initial dose, dose adjustments, timing of phototherapy and cumulative dose of the phototherapies varied significantly between studies and no recommendation can be made on which treatment scheme should be used.

In conclusion, the results of our review suggest that phototherapy improves the outcome of melanocyte transplantation in vitiligo. We recommend NBUVB as standard phototherapy after melanocyte transplantation. More prospective randomized controlled studies are needed to investigate the additional benefit of the different phototherapy modalities and the preferred moment of phototherapy for non-segmental and segmental vitiligo separately.

REFERENCES

1 Ezzedine K, Eleftheriadou V, Whitton M *et al.* Vitiligo. *The Lancet* 2015; **386**: 74-84.

2 Mulekar SV, Isedeh P. Surgical interventions for vitiligo: an evidence-based review. *The British journal of dermatology* 2013; **169 Suppl 3**: 57-66.

3 Whitton ME, Pinart M, Batchelor J *et al.* Interventions for vitiligo. *Cochrane Database Syst Rev* 2015: CD003263.

4 Valejo Coelho MM, Apetato M. The dark side of the light: Phototherapy adverse effects. *Clin Dermatol* 2016; **34**: 556-62.

5 Taieb A, Alomar A, Bohm M *et al.* Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *The British journal of dermatology* 2013; **168**: 5-19.

6 Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009; **3**: e123-30.

7 Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.

8 Higgins J. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*: The Cochrane Collaboration. 2011.

9 Guo B, Moga C, Harstall C *et al.* A principal component analysis is conducted for a case series quality appraisal checklist. *J Clin Epidemiol* 2016; **69**: 199-207 e2.

10 Zhang DM, Hong WS, Fu LF *et al.* A randomized controlled study of the effects of different modalities of narrow-band ultraviolet B therapy on the outcome of cultured autologous melanocytes transplantation in treating vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2014; **40**: 420-6.

11 Tsuchiyama K, Watabe A, Sadayasu A *et al.* Successful Treatment of Segmental Vitiligo in Children with the Combination of 1-mm Minigrafts and Phototherapy. *Dermatology* 2016; **232**: 237-41.

12 Sheth VM, Currimbhoy SD, Feetham HJ *et al.* Efficacy of narrowband ultraviolet B versus excimer radiation in repigmenting vitiligo after minigrafting on the distal arms. *Journal of the American Academy of Dermatology* 2012; **67**: 318-20.

13 Linthorst Homan MW, Spuls PI, Nieuweboer-Krobotova L *et al.* A randomized comparison of excimer laser versus narrow-band ultraviolet B phototherapy after punch grafting in stable vitiligo patients. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2012; **26**: 690-5.

14 Lim JT. Repigmentation of vitiligo with autologous blister-induced epidermal grafts. *Annals of the Academy of Medicine, Singapore* 1999; **28**: 824-8.

15 Ebadi A, Rad MM, Nazari S *et al.* The additive effect of excimer laser on non-cultured melanocyte-keratinocyte transplantation for the treatment of vitiligo: A clinical trial in an Iranian population. *Journal of the European Academy of Dermatology and Venereology* 2015; **29**: 745-51.

16 Barman KD, Khaitan BK, Verma KK. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2004; **30**: 49-53.

17 Tegta GR, Parsad D, Majumdar S *et al.* Efficacy of autologous transplantation of noncultured epidermal suspension in two different dilutions in the treatment of vitiligo. *International journal of dermatology* 2006; **45**: 106-10.

18 Sahni K, Parsad D, Kanwar AJ. Noncultured epidermal suspension transplantation for the treatment of stable vitiligo in children and adolescents. *Clinical and Experimental Dermatology* 2011; **36**: 607-12.

19 Sahni K, Parsad D, Kanwar AJ *et al.* Autologous noncultured melanocyte transplantation for stable vitiligo: Can suspending autologous melanocytes in the patients' own serum improve repigmentation and patient satisfaction? *Dermatologic Surgery* 2011; **37**: 176-82.

20 Olsson MJ, Juhlin L. Epidermal sheet grafts for repigmentation of vitiligo and piebaldism, with a review of surgical techniques. *Acta Dermato-Venereologica* 1997; **77**: 463-6.

21 Matsuzaki K, Kumagai N. Treatment of vitiligo with autologous cultured keratinocytes in 27 cases. *European journal of plastic surgery* 2013; **36**: 651-6.

22 Holla AP, Sahni K, Kumar R *et al.* Repigmentation of leukotrichia due to retrograde migration of melanocytes after noncultured epidermal suspension transplantation. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2014; **40**: 169-75.

23 Holla AP, Sahni K, Kumar R *et al.* Acral vitiligo and lesions over joints treated with non-cultured epidermal cell suspension transplantation. *Clinical and experimental dermatology* 2013; **38**: 332-7.

24 Chen YF, Chang JS, Yang PY *et al.* Transplant of cultured autologous pure melanocytes after laser-abrasion for the treatment of segmental vitiligo. *Journal of Dermatology* 2000; **27**: 434-9.

25 Budania A, Parsad D, Kanwar AJ *et al.* Comparison between autologous noncultured epidermal cell suspension and suction blister epidermal grafting in stable vitiligo: a randomized study. *The British journal of dermatology* 2012; **167**: 1295-301.

26 Boersma BR, Westerhof W, Bos JD. Repigmentation in vitiligo vulgaris by autologous minigrafting: results in nineteen patients. *Journal of the American Academy of Dermatology* 1995; **33**: 990-5.

27 Pianigiani E, Risulo M, Andreassi A *et al.* Autologous epidermal cultures and narrow-band ultraviolet B in the surgical treatment of vitiligo. *Dermatologic Surgery* 2005; **31**: 155-9.

28 Mapar MA, Safarpour M, Mapar M *et al.* A comparative study of the mini-punch grafting and hair follicle transplantation in the treatment of refractory and stable vitiligo. *Journal of the American Academy of Dermatology* 2014; **70**: 743-7.

29 Majid I, Imran S. Ultrathin split-thickness skin grafting followed by narrowband UVB therapy for stable vitiligo: An effective and cosmetically satisfying treatment option. *Indian Journal of Dermatology, Venereology and Leprology* 2012; **78**: 159-64.

30 Lahiri K, Malakar S, Sarma N *et al*. Repigmentation of vitiligo with punch grafting and narrow-band UV-B (311 nm)--a prospective study. *International journal of dermatology* 2006; **45**: 649-55.

31 de Leeuw J, Assen YJ, van der Beek N *et al.* Treatment of vitiligo with khellin liposomes, ultraviolet light and blister roof transplantation. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2011; **25**: 74-81.

32 Verma R, Grewal RS, Chatterjee M *et al.* A comparative study of efficacy of cultured versus non cultured melanocyte transfer in the management of stable vitiligo. *Medical journal, Armed Forces India* 2014; **70**: 26-31.

33 Suga Y, Butt KI, Takimoto R *et al.* Successful treatment of vitiligo with PUVA-pigmented autologous epidermal grafting. *International journal of dermatology* 1996; **35**: 518-22.

34 Singh KG, Bajaj AK. Autologous miniature skin punch grafting in vitiligo. *Indian journal of dermatology, venereology and leprology* 1995; **61**: 77-80.

35 Singh SK. Punch grafting in vitiligo : Refinements and case selection. *Indian journal of dermatology, venereology and leprology* 1997; **63**: 296-300.

36 Sarkar R, Mehta SD, Kanwar AJ. Repigmentation after autologous miniature punch grafting in segmental vitiligo in North Indian patients. *Journal of Dermatology* 2001; **28**: 540-6.

37 Sachdev M, Krupa Shankar DS. Pulsed erbium: YAG laser-assisted autologous epidermal punch grafting in vitiligo. *International Journal of Dermatology* 2000; **39**: 868-71.

38 Pai GS, Vinod V, Joshi A. Efficacy of erbium YAG laser-assisted autologous epidermal grafting in vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2002; **16**: 604-6.

39 Malakar S, Lahiri K. Punch grafting for lip leucoderma. *Dermatology* 2004; **208**: 125-8.

40 Krishnan A, Kar S. Smashed skin grafting or smash grafting - a novel method of vitiligo surgery. *International Journal of Dermatology* 2012; **51**: 1242-7.

41 Khandpur S, Sharma VK, Manchanda Y. Comparison of minipunch grafting versus split-skin grafting in chronic stable vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2005; **31**: 436-41.

42 Hallaji Z, Daneshpazhooh M, Rezai-Khiabanloo S. Successful treatment of vitiligo with punch graft followed by outdoor topical psoralen plus ultraviolet a radiation. *Archives of Iranian Medicine* 2003; **6**: 86-90.

43 Gupta S, Kumar B. Epidermal grafting for vitiligo in adolescents. *Pediatric Dermatology* 2002; **19**: 159-62.

44 Ghorpade A. Use of tissue glue for punch grafting in vitiligo--a preliminary report. *Indian journal of dermatology, venereology and leprology* 2004; **70**: 159-61.

45 El-Zawahry BM, Zaki NS, Bassiouny DA *et al.* Autologous melanocyte-keratinocyte suspension in the treatment of vitiligo. *Journal of the European Academy of Dermatology and Venereology* 2011; **25**: 215-20.

46 Czajkowski R, Placek W, Drewa T *et al.* Autologous cultured melanocytes in vitiligo treatment. *Dermatologic Surgery* 2007; **33**: 1027-35.

47 Babu A, Thappa DM, Jaisankar TJ. Punch grafting versus suction blister epidermal grafting in the treatment of stable lip vitiligo. *Dermatologic Surgery* 2008; **34**: 166-78.
48 Awad SS. Chinese cupping: a simple method to obtain epithelial grafts for the management of resistant localized vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2008; **34**: 1186-92; discussion 92-3.
49 Oiso N, Suzuki T, Wataya-Kaneda M *et al.* Guidelines for the diagnosis and treatment of vitiligo in Japan. *J Dermatol* 2013; **40**: 344-54.
50 Whitton M, Pinart M, Batchelor JM *et al.* Evidence-based management of vitiligo: summary of a Cochrane systematic review. *The British journal of dermatology* 2016; **174**: 962-9.
51 Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol* 1997; **133**: 1525-8.
52 Bae JM, Jung HM, Hong BY *et al.* Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2017; **153**: 666-74.

SUPPLEMENTS

Supplements S1 - Search

Search strategy per database

MEDLINE

(vitiligo OR "Vitiligo"[Mesh]) AND (surgical OR surgery OR graft* OR transplantation OR transfer OR "Melanocytes/transplantation"[Mesh] OR "Keratinocytes/transplantation"[Mesh] OR "Skin Transplantation"[Mesh] OR "Transplantation, Autologous"[Mesh])

EMBASE:

(vitiligo) AND (surgical OR surgery OR graft* OR transplantation OR transfer)

CENTRAL:

(vitiligo) AND (surgical OR surgery OR graft* OR transplantation OR transfer)

Terms for search

Terms for vitiligo

Non-MESH: Vitiligo; Depigmentation; Hypopigmentation
MESH: Vitiligo (MESH); Vitiligo/surgery (MESH); Vitiligo/therapy (MESH)

Terms for melanocyte transplantation

Non-MESH: Surgery; Surgical treatment; Surgical therapy; Graft*; Transplantation; Skin transplantation; Cell suspension; Tissue transplantation; Tissue graft*; Cell* transplantation; Cell* graft*; Cultured melanocyte*; Non-cultured melanocyte*; Melanocyte* transplantation; Melanocyte-keratinocyte transplantation; Melanocyte-keratinocyte suspension; Epidermal cell transplantation; Blister roof transplantation; Epidermal blister graft*; Thiersch graft*; Epidermal cellular grafting; Melanocyte* transfer; Melanocyte* keratinocyte* transplantation; Cell suspension transplantation; Epidermal cell suspension transplantation; Keratinocyte-melanocyte graft*; Epidermal graft*; Autologous epidermal graft*; Epithelial graft*; Punchgraft*; Punch graft*; Minigraft*; Mini graft*; Minipunchgraft*; Mini-punchgraft*; Mini-punch graft*; Mini punch graft; Minipunch graft*; Suction blister graft*; Suction blister transplantation; Suction blister epidermal graft*; Suction epidermal graft*; Split-thickness graft*; Miniature punch graft*; Miniature skin punch graft*; Split-thickness skin graft*; Split-skin graft*
MESH: Melanocytes/transplantation (MESH); Keratinocytes/transplantation (MESH); Skin transplantation/methods (MESH); Transplantation, autologous (MESH)

Terms for phototherapy

Non-MESH: Phototherapy; PUVA; PUVASOL; PUVA-SOL; Excimer; UV; UVA; UVB; NB-UVB; NBUVB; Narrowband; Ultraviolet; Ultraviolet-A; Ultraviolet-B; Light; Sunlight; Sun; Helium-Neon

MESH: PUVA Therapy (MESH); Lasers, Excimer/therapeutic use (MESH); Melanocytes/radiation effects (MESH); Ultraviolet Rays (MESH); Phototherapy (MESH); Ultraviolet; Therapy/instrumentation (MESH) ; Ultraviolet Therapy/methods (MESH)

Supplements S2 – Adapted Quality Appraisal tool for Case series

Title: **Author, year:**	
	Yes / no
Study objective	
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	
Study population	
2. Are the characteristics (age, gender, type of vitiligo) of the participants included in the study described?	
3. Were the cases collected in more than one centre?	
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate? (stability, type of vitiligo, treatment before study start)	
5. Were participants recruited consecutively?	
6. Did participants enter the study at a similar point in the disease? (stability)	
Intervention and co-intervention	
7. Was the intervention clearly described in the study? (type of UV treatment (duration, frequency) and transplantation technique)	
8. Were additional interventions (co-interventions) clearly reported in the study? (Prolongation UV, Wound dressing, local immunosuppressants)	
Outcome measure	
9. Are the outcome measures clearly defined in the introduction or methods section? (which outcome measure, blinded/nonblinded, method of measuring)	
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	
11. Were outcomes measured before and after intervention?	
Statistical analysis	
12. Were the statistical tests used to assess the relevant outcomes appropriate?	
Results and conclusions	
13. Was the length of follow-up reported?	
14. Was the loss to follow-up reported?	
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	
16. Are adverse events reported?	
17. Are the conclusions of the study supported by results?	
Competing interests and sources of support	
18. Are both competing interests and sources of support for the study reported?	
Total yes:	

Supplements S3 – Quality Appraisal Case series

Question Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total yes
Awad	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	**11**
Boersma	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	**11**
Chen	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**9**
El-Zawahry	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	**11**
Ghorpade	Yes	Yes	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	Yes	Yes	No	**6**
Gupta	Yes	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**8**
Hallaji	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**9**
Holla	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	**10**
Holla	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	**11**
Krishnan	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	**6**
Lahiri	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	**9**
Lim	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	**6**
Majid	Yes	No	No	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No	**7**
Malakar	Yes	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	No	**6**
Matsuzaki	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes	**8**
Olsson	No	Yes	No	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	**7**
Pai	Yes	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	**4**
Piangiani	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	**11**
Sachdev	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**7**
Sahni	Yes	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**8**
Sarkar	Yes	Yes	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	No	**6**
Singh (1995)	No	Yes	No	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**7**
Singh (1997)	No	Yes	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	**4**
Suga	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	**2**
Tsuchiyama	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	**9**

Supplements S4 – Phototherapy regimen per study.

Author, year	Phototherapy a. Pre/post-surgery b. Frequency/duration c. Initial dose d. Dose adjustment e. Cumulative dose
Awad, 2008	K-UVA a. 1w post; b. 2-3 times/w; c. 2 J/m^2; d. 25%/treatment; e. unknown
Babu, 2008	PUVASOL a. 1w post; b. unknown; c. unknown; d. unknown; e. unknown
Barman, 2004	sPUVA a. 4w post; b. 2 times/w; c. unknown; d. unknown; e. unknown
Boersma, 1995	UVA a. 2w post; b. 2 times/w; c. 10 J/cm2; d. unknown; e. unknown
Budania, 2012	Sunlight a. 8d post; b. Daily (5-30 minutes); c. unknown; d. unknown; e. unknown
Chen, 2000	Sunlight a. 7-10 d post; b. unknown; c. unknown; d. unknown; e. unknown
Czajkowski, 2007	sPUVA a. post; b. 3 times/w, 6 mo; c. 0.5J/cm^2; d. unknown; e. unknown
De Leeuw, 2011	K-NBUVB a. 1w post; b. 3 times/w; c. 1 minute; d. 50%/2 sessions; e. unknown
Ebadi, 2015	MELa a. 2w post; b. 2-3 times/w; c. 200 mJ/cm^2; d. 0-100 mJ/cm^2; e. unknown
El-Zawahry, 2011	PUVA a. 3w post; b. 3 times/w; c. unknown; d. unknown; e. unknown
Ghorpade, 2004	PUVASOL a. 2w post; b. unknown; c. unknown; d. unknown; e. unknown
Gupta, 2002	sPUVA a. 8d post; b. 3-6 mo; c. unknown; d. unknown; e. unknown
Hallaji, 2003	tPUVA a. 3 mo post; b. 3 times/week; 4 mo; c. 15s; d. 10s/session; e. unknown
Holla, 2014	Sunlight a. 6-8 d post; b. Daily; up to 4 mo; c. 20 min; d. unknown; e. unknown
Holla, 2013	Sunlight a. 7-10 d post; b. Min. 4 mo; c. unknown; d. unknown; e. unknown
Khandpur, 2005	PUVASOL a. 2w post; b. 3-4times/week; c. unknown; d. unknown; e. unknown
Krishnan, 2012	PUVASOL a. 2w post; b. unknown; c. unknown; d. unknown; e. unknown
Lahiri, 2006	NBUVB a. post; b. 2 times/w; c. 500mJ/cm^2; d. 10-20%/treatment; e. max: 2270mJ/cm^2

Lim, 1999	Pre-PUVA a. unknown; b. unknown; c. unknown; d. unknown; e. unknown Post PUVA a. unknown; b. 1 mo; c. unknown; d. unknown; e. unknown
Linthorst Homan, 2012	MELa a. 1w post; b. 2 times/w, 12w ; c. 0.05 J/cm^2; d. 0.025-0.10J/cm^2; e. Mean ± SD: 7.3 ± 3.5 J/cm^2 NBUVB a. 1w post; b. 2 times/w, 12w; c. 0.25 J/cm^2; d. 50 mJ/cm^2; e. Mean ± SD: 25.6 ± 11.6 J/cm^2
Majid, 2012	NBUVB a. 10-14 d post; b. 3 times/w, 1-3 mo; c. 200mJ/cm^2; d. 0-20%/treatment; e. unknown
Malakar, 2004	PUVASOL a. post; b. unknown; c. unknown; d. unknown; e. unknown
Mapar, 2014	NBUVB a. 1w post; b. 2 times/w; 6 mo; c. 0.2J/cm^2; d. 20%/treatment; e. unknown
Matsuzaki, 2013	Sunlight a. 3w post; b. Daily; 6 mo; c. 5-10 min; d. unknown; e. 30min-1h
Olsson, 1997	Sunlight a. post; b. unknown; c. unknown; d. unknown; e. unknown
Pai, 2002	Pre-PUVA a. pre; b. unknown; c. unknown; d. unknown; e. unknown Post PUVA a. 15d post; b. unknown; c. unknown; d. unknown; e. unknown
Pianigiani, 2005	NBUVB a. 3w post; b. 2 times/w; 4 mo; c. 200mJ/cm^2; d. unknown; e. max: 1800mJ/cm^2
Sachdev, 2000	PUVA a. 6-8 w pre and 2 w post; b. 3 times/w; c. unknown; d. unknown; e. unknown
Sahni, 2011	Sunlight a. 8d post; b. Daily; c. unknown; d. unknown; e. max: 30 min
Sahni, 2011	Sunlight a. post; b. Daily; c. 30 min; d. unknown; e. unknown
Sarkar, 2001	PUVASOL a. post; b. unknown; c. unknown; d. unknown; e. unknown
Sheth, 2012	MELi a. 1w post; b. 3 times/w, 12w; c. 200mJ/cm^2; d. 50 mJ/treatment; e. unknown NBUVB a. 1w post; b. 3 times/w, 12w; c. 200mJ/cm^2; d. 15%/treatment; e. unknown
Singh, 1995	PUVASOL a. post; b. unknown; c. unknown; d. unknown; e. unknown
Singh, 1997	PUVASOL a. post; b. unknown; . unknown; d. unknown; e. unknown
Suga, 1996	tPUVA a. pre; b. unknown; c. 10-50 J/cm^2; d. unknown; e. unknown

Tegta, 2006	Sunlight a. post; b. Daily; c. 15-20 min. ; d. unknown; e. unknown
Tsuchiyama, 2016	MELa a. 1w post; b. 3 mo; c. unknown; d. unknown; e. unknown NBUVB a. 1w post; b. 3 mo; c. unknown; d. unknown; e. unknown
Verma, 2014	PUVASOL a. post; b. unknown; c. unknown; d. unknown; e. unknown
Zhang, 2014	preNBUVB a. 10w pre; b. 2 times/week; c. 0.40 J/cm^2; d. 0.10J/cm^2 per 2; e. 20 sessions postNBUVB a. 2w postv b. 2 times/week ; c. 0.40 J/cm^2; d. 0.10J/cm^2; e. 30 sessions

Supplements S5 – Results per non-comparative study.

Author, year	Study design	N	Follow-up	Outcomes	Intervention	Results
PUVA						
Awad, 2008	CS	20	2-3 mo	100% repigmentation	SBG + K-UVA	30%
Babu, 2007	RCT	18	1-3 mo	51-100% repigmentation	PG + PUVASOL	75%
					SBG + PUVASOL	60%
Czajkowski, 2007	RCT-IPC	40	6 mo	100% repigmentation	CAMT + sPUVA	50%
					SBG + sPUVA	98.7%
El-Zawahry, 2011	CS	25	6-17mo	I. 90-100% repigmentation II. 50-89% repigmentation III. 20-49% repigmentation IV. <20% repigmentation	NCAMT + PUVA	I. 23% II. 32% III. 27% IV. 18%
Ghorpade, 2004	CS	10	2 yr	I. Median pigment spread II. 100% repigmentation	PG + PUVASOL	I. 4.0 mm II.100%
Gupta, 2002	CS	10	3-6mo	>75% repigmentation	SBG + sPUVA	80%
Hallaji, 2003	CS	20	4 mo	I. 90-100% repigmentation II. 25-50% repigmentation III. 0% repigmentation	PG + tPUVA	I. 65% II. 15% III. 20%

Khandpur, 2005	RCT	64	3 mo	>75% repigmentation	PG + PUVASOL	44.1%
					STG + PUVASOL	83.3%
Krishnan, 2012	CS	26	5 mo	>90% repigmentation	NCAMT + PUVASOL	100%
Malakar, 2004	CS	108	2-5 mo	I. 90-100% repigmentation II. 70-90% repigmentation III. 50-70% repigmentation IV. 30-50% repigmentation V. 0-30% repigmentation VI. 0% repigmentation	PG + PUVASOL	I. 72.2% II. 1.9% III. 7.4% IV. 5.6% V. 1.9% VI. 9.3%
Pai, 2002	CS-IPC	29	n.a.	I. 75-100% repigmentation II. 50-75% repigmentation III. 25-50% repigmentation	PG + PUVA	I. 50% (lesions) II. 50% (lesions) III. 0% (lesions)
					SBG + PUVA	I. 0% (lesions) II. 60% (lesions) III. 40% (lesions)
					laserPG + PUVA	I. 68.8%(lesions) II. 31.3%(lesions) III. 0%(lesions)
					laserSBG + PUVA	I. 0%(lesions) II. 100%(lesions) III. 0%(lesions)
Sachdev, 2000	CS	13	32w	0% repigmentation	PUVA + PG + PUVA	14.4% (lesions)
Sarkar, 2001	CS	15	n.a.	I. 90-100% repigmentation II. 70% repigmentation III. 60% repigmentation IV. Mean pigment spread	PG + PUVASOL	I. 80% II. 13.3% III. 6.7% IV. 5.4 mm
Singh, 1995	CS	32	2-6 mo	I. Pigmentspread 1-4mm II. Pigmentspread 5-8mm III. Pigmentspread 9-12mm IV. Pigmentspread > 13mm	PG + PUVASOL	I. 22.2% (lesions) II. 42.2% (lesions) III. 28.9% (lesions) IV. 6.7% (lesions)
Singh, 1997	CS	55	6mo – 3yr	100% repigmentation	PG + PUVASOL	65.5%

Suga, 1996	CS	28	3 mo	I. 100% repigmentation II. 95-100% repigmentation III. 90-100% repigmentation IV. 85-100% repigmentation V. 80-100% repigmentation VI. 60-80% repigmentation VII. 20-100% repigmentation VIII. >10% repigmentation IX. <5% repigmentation	tPUVA + SBG	I. 25% II. 35.7% III. 39.3% IV. 50% V. 60.7% VI. 71.4% VII. 78.6% VIII. 89.3% IX. 10.7%
Verma, 2013	RCT	25	6 mo	I. > 70% repigmentation II. 31-70% repigmentation III. <31% repigmentation	CAMT + PUVASOL	I. 52% (lesions) II. 1% (lesions) III. 38% (lesions)
					NCAMT + PUVASOL	I. 62% (lesions II. 20% (lesions) III. 18% (lesions)
NBUVB						
De Leeuw, 2011	RCT-IPC	19	3-6mo	Mean repigmentation	SBG + K-NBUVB	65.3%
Lahiri, 2006	CS	66	18 mo	Mean pigment spread	PG + NBUVB	6.5mm
Majid, 2012	CS	40	3-12 mo	> 90% repigmentation	STG + NBUVB	83%
Mapar, 2014	RCT-IPC	25	6 mo	Mean pigment spread	PG + NBUVB	5.3 mm
					HFT + NBUVB	5.0 mm
Pianigiani, 2005	CS	93	18mo	I. 100% repigmentation II. 50-99% repigmentation	CAMT + NBUVB	I. 60% II. 30%
UVA						
Boersma, 1995	CS	19	3-12 mo	I. 80-100% repigmentation II. 50-79% repigmentation III. 0-50% repigmentation	PG + UVA	I. 38.9% (lesions) II. 27.8% (lesions) III. 33.3% (lesions)
Sunlight						
Budania, 2012	RCT	41	16w	I. 90-100% repigmentation II. 75-89% repigmentation III. > 75% repigmentation	NCAMT + Sunlight	I. 71% II. 18% III. 89%
					SBG + Sunlight	I. 27% II. 58% III. 85%

Chen, 2000	CS	25	3-20mo	I. 95-100% repigmentation II. 65-94% repigmentation	CAMT + Sunlight	I. 84% II. 16%
Holla, 2013	CS	36	6-18mo	I. >75% repigmentation II. 50-75% repigmentation III. <50% repigmentation	NCAMT + Sunlight	I. 63.8% (lesions) II. 28.8% (lesions) III. 7.5% (lesions)
Holla, 2014	CS	31	6mo – 1yr	I. >75% repigmentation* II. > 90% repigmentation* III. 74-90% repigmentation* IV. 25-75% repigmentation* V. 0-25% repigmentation* VI. 0% repigmentation* *of leucotrichia	NCAMT + Sunlight	I. 45.2% (lesions) II. 28.6% (lesions) III. 16.7% (lesions) IV. 23.8% (lesions) V. 19% (lesions) VI. 11.9% (lesions)
Matsuzaki, 2013	CS	27	1yr	I. >90% repigmentation II. 50-90% repigmentation III. 0-50% repigmentation	CAMT + Sunlight	I. 51.9% II. 33.3% III. 14.8%
Olsson, 1997	CS	19	4-8mo	I. Mean repigmentation II. 100% repigmentation III. 95% repigmentation IV. 70% repigmentation V. 50% repigmentation VI. 20% repigmentation VII. 10% repigmentation VIII. 0% repigmentation	STG + Sunlight	I.75.1%(lesions) II. 49.0% (lesions) III. 16.3% (lesions) IV. 8.2% (lesions) V. 8.2% (lesions) VI. 2.0% (lesions) VII. 4.1% (lesions) VIII. 12.2% (lesions)
Sahni, 2011	CS	13	1 yr	I. > 90% repigmentation II. 75-90% repigmentation	NCAMT + Sunlight	I. 79% (lesions) II. 21% (lesions)
Sahni, 2011	RCT	25	16w	I. >75% repigmentation II. >90% repigmentation III. 76-90% repigmentation IV. 51-75% repigmentation V. 25-50% repigmentation VI. <25% repigmentation	NCAMT (saline) + sunlight	I. 66.7% (lesions); 64.3% (patients) II. 44.4% (patients) III. 22% (patients) IV. 11% (patients) V. 11% (patients) VI. 11% (patients)
					NCAMT (serum) + sunlight	I. 94.4% (lesions); 92.8% (patients) II. 88.8% (patients) III. 6% (patients) IV. 6% (patients) V. 0% (patients) VI. 0% (patients)

Tegta, 2006	RCT	20	12w	I. >75% repigmentation II. 51-75% repigmentation III. 26-50% repigmentation IV. 1-25% repigmentation V. 0% repigmentation	NCAMT (1:3) + Sunlight	I. 50% II. 20% III. 10% IV. 0% V. 20%
					NCAMT (1:5) + Sunlight	I. 0% II. 10% III. 20% IV. 40% V. 30%

GENERAL DISCUSSION

In the past years, researchers have become increasingly interested in the pathophysiology, disease course and treatment of vitiligo. Although a lot of progress has been made, there are still many blind spots in vitiligo research. In this thesis, the overall aim was to color the white spots in vitiligo by coloring the blind spots in vitiligo research. The main focus was to provide answers to questions regarding the clinical pathway of vitiligo, which can be divided into the diagnosis, measurement and treatment of vitiligo.

DIAGNOSIS

In most cases, the diagnosis of vitiligo is rather straightforward. However, most clinicians are not always aware of melanoma-associated leukoderma (MAL) as a differential diagnosis in vitiligo. In 0.15% (Chapter 2.1) of all patients referred to the Netherlands Institute for Pigment Disorders (NIPD) for vitiligo treatment, MAL was diagnosed instead of vitiligo. In Chapter 2.1, 7 patients with MAL are described who were initially referred to our institute for vitiligo treatment. These were mainly older patients with sudden onset of highly progressive skin depigmentations, which were refractory to treatment. The depigmentations were marked as atypical lesions on non-typical predilection sites for vitiligo. Previous studies have also reported atypical clinical presentations of MAL, such as hypopigmented macules with irregularly shaped borders and a confetti-like appearance.[1-3] Hypothetically, the atypical presentation may suggest that MAL and vitiligo are differentiable from each other. However, the results of Chapter 2.2 illustrate that even experts in the field cannot differentiate between MAL and vitiligo. In this study, 73% of MAL cases were misdiagnosed as vitiligo. The diagnostic accuracy of MAL was low and no significant differences in clinical presentation of the leukoderma between MAL and vitiligo were identified. Patients with MAL had a significantly higher age at onset of depigmentation than the included patients with vitiligo; this is supported by evidence described in other case series.[4,5] In Chapter 2.2, it is described that the confetti-like depigmentation was found in 55% of patients with MAL. However, the confetti-like depigmentation can also be a sign of rapidly progressing vitiligo and was also seen in 82% of patients with vitiligo in our study.[6] Furthermore, the distribution of the depigmentation in MAL cases corresponded merely with the symmetrical distribution of vitiligo cases. A limitation of Chapter 2.2 is that it was performed in a tertiary referral center for vitiligo (NIPD), which may have led to a sampling bias of vitiligo cases. In other words, the clinical presentation of vitiligo in our institute may be different than the clinical presentation of vitiligo in the general clinical practice. Furthermore, the prevalence of MAL in the comparison study (25%, Chapter 2.2) and the estimated prevalence in our institute (0.15%, Chapter 2.1) were different. Therefore, the diagnostic

accuracy found in Chapter 2.2 cannot be translated to daily practice and the risk of missing MAL in clinical practice is likely to be higher. Subsequently, a small percentage of patients with MAL could be misdiagnosed as having vitiligo leading to late detection and treatment of melanoma. Chapter 2.1 and 2.2 emphasize the fact that, although melanoma-associated leukoderma is a rare disease, clinicians should be aware of the diagnosis MAL. Furthermore, based on this thesis we recommend to perform a total body inspection on suspected melanocytic lesions, especially in older patients with progressive depigmentations. Furthermore, we propose the term melanoma-associated vitiligo as a more appropriate term based on the similar assumed pathogenesis between MAL and vitiligo in clinical, histologic and immunologic data.[5,7] However, the presence of antibody responses against the melanoma-associated antigen recognized by T cells (MART-1 antigen) in MAL is not present in vitiligo and this indicates that differences in immunity are involved.[7] We suggest that further research should focus on possible differentiating factors between MAL and vitiligo.

After the diagnosis of vitiligo is confirmed, the subtype of vitiligo must be identified as this is important for treatment and prognosis. A small isolated depigmentation without a typical segmental distribution is defined as focal vitiligo.[8] Focal vitiligo is a rare subtype of vitiligo; we found in our institute that 3.3% of all vitiligo patients have focal vitiligo (Chapter 2.3). However, this number is the prevalence of focal vitiligo in a tertiary referral center and the exact prevalence in the general population is still unknown. Focal vitiligo is classified as an undetermined type of vitiligo and a more definitive diagnosis can be made when the depigmentations have not evolved to other subtypes (i.e. non-segmental and segmental vitiligo) after a period of 2 years.[8] However, patients want to know their prognosis after onset of the disease and little is known about the probability of progression. In Chapter 2.3, we found that 77% of patients with initial focal vitiligo had persisting localized depigmentation(s) after a median follow-up of 7 years and therefore can be classified as 'true' focal vitiligo. The other 23% of patients all evolved to non-segmental vitiligo and 50% of those patients showed noticeable progression within 2 years after onset. In other words, after 2 years of follow-up, 88% of all patients with localized depigmentations had a definitive diagnosis with either non-segmental or focal vitiligo. A previous case series also showed that 80% of patients with initial focal vitiligo show progression to non-segmental vitiligo within 2 years after onset of the disease.[9] Patients with long-lasting focal vitiligo showed similar characteristics as non-segmental vitiligo and were mainly located on predilections sites for non-segmental vitiligo, suggesting that focal vitiligo might be a limited type of non-segmental vitiligo. Notwithstanding these findings, recent studies show that segmental vitiligo often does not fit the “typical” patterns and the interpretation of a typical segmental pattern can be very subjective.[10,11] Stable segmental vitiligo normally responds well to surgical

treatment and patients with long-lasting vitiligo also responded well to surgical treatment.[12] The prolonged disease stability and good results after surgical treatment indicate a more local defect in long-lasting focal vitiligo, similar to segmental vitiligo, as opposed to the generalized auto-immune response seen in non-segmental vitiligo. It remains unclear whether focal vitiligo is a separate entity or a subtype of either non-segmental or segmental vitiligo. Although a somatic mosaicism is generally seen as the leading hypothesis for the pathogenesis in segmental vitiligo, no genetic studies have been published up to this date that have confirmed this hypothesis.[13,14] If, however, we would know the hypothetical genetic alterations of segmental vitiligo, a better understanding of this subtype of vitiligo is within reach, which could ultimately lead to better treatment of segmental vitiligo. Furthermore, when these possible genetic alterations of segmental vitiligo are present in focal vitiligo lesions, we would also get a better understanding of this undetermined subtype of vitiligo. The survey-study of Chapter 2.3 had a fairly good response rate (41%). Limitations of this study were the small population and retrospective setting in a tertiary referral center (NIPD), which is not fully representative for all diagnostic settings. Our findings corroborate that the previously assumed 2 years of observation of stability is sufficient and also required in order to draw a more conclusive and reliable diagnosis for focal vitiligo. However, the unpredictability of focal vitiligo remains as we could not find any prognostic factors at baseline in Chapter 2.3 to predict progression or stable disease.

MEASUREMENT INSTRUMENTS

Measuring is the cornerstone of medical research and also of clinical practice.[15] Measurements form the basics of diagnosis, prognosis and evaluation of the results of medical interventions.[15] However, in vitiligo there is currently no consensus on which measurement instruments should be used. In a recent study, consensus has been reached on which core set of outcome domains ("what should be measured") must be applied in clinical trials in vitiligo.[16,17] However, most available measurement instruments in vitiligo are based on non-validated scales and do not meet the COSMIN criteria (Consensus-based Standard for the selection of health Measurement Instruments).[18-20]

Extent of depigmentation

In Chapters 3.1, 3.2 and 3.3, we evaluated different measurement properties of two new measurement instruments assessing the extent of depigmentation: the Vitiligo Extent Score (VES) and the Self Assessment Vitiligo Extent Score (SA-VES).

In Chapter 3.1, the criterion validity and the reliability of the VES were assessed. Criterion validity is defined as 'the degree to which the scores of a measurement instrument are an adequate reflection of a gold standard'.[15,19] Up to this date, the Vitiligo Area Severity Index (VASI)[21] can be considered as the gold standard for measuring the extent of depigmentation in vitiligo. The correlations between the VES and VASI were strong ($r \geq 0.9$, in the different measurement sessions). In all sessions, the intra- and inter-observer reliability of the VES were excellent (intra-class correlation (ICC) ≥ 0.9). Picture scoring was comparable with live scoring (ICC = 0.922), which facilitates the future validation processes on digital pictures, allowing a larger number of observers to participate in an international setting. Furthermore, reliability was also excellent in patients with extensive vitiligo. In all sessions, the ICCs of the VES were higher compared to the ICCs of the VASI. Furthermore, the smallest detectable change (SDC; minimal difference that can accurately be measured) of the VES was overall smaller (4.7%) than the SDC of the VASI (7.8%). The high SDC of the VASI in Chapter 3.1 was comparable to the SDC found in the study of Komen et al. (7.1%).[22] Hence, the VES method has the ability to assess smaller reliable differences than the VASI and that caution is required when interpreting score changes of the VASI in individual patients because of the relatively large smallest detectable change.[16] Furthermore, extent of depigmentation was higher for the VASI compared with the VES. The VASI uses the 1% hand rule for the assessment of the extent of depigmentation and problems with the overestimation with this 1% hand rule have previously been described in other skin disorders.[23] However, based on our findings no final statements can be made whether the VASI gives an overestimation or whether the VES gives an underestimation of the extent of depigmentation. The findings of Chapter 3.1 verify that the VES is a valid measurement instrument to measure degree of depigmentation and that the VES has excellent inter- and intra-observer reliability. Digital image techniques could probably more accurately quantify the extent of depigmentation, however these techniques are generally time consuming and expensive which at present limits their worldwide use.[16] Limitations of this study were the large number of patients with skin type 2 to 4 that was included and that the data was collected in two tertiary national referral centers for vitiligo. The main strengths of the VES method lie in the areas of clarity, user-friendliness and its intuitive use. Furthermore, the VES can be used to assess the extent of vitiligo for 19 separate areas of the body and therefore improves disease monitoring of the patients.

In Chapter 3.2, the validity, reliability and acceptability of the SA-VES was assessed. The SA-VES is a new patient reported outcome measure to assess the extent of depigmentation. An excellent correlation ($r = 0.986$) between the VES and SA-VES was found, and no significant differences between patient and physician scoring was found. Previously, a self-assessment VASI (SAVASI) was introduced and validated by Komen et al.[24] The

SAVASI was only fairly reliable (ICC=0.75) and was rather time-consuming. Oppositely, the results in Chapter 3.2 describe an excellent intra-observer reliability of the SA-VES (ICC = 0.948) and that the patient characteristics (age, extent, duration of disease, and skin type) had little influence on the reliability of the SA-VES. Furthermore, the SA-VES was evaluated as very easy to easy in use by most patients (71%) and most patients (73%) filled out the SA-VES within 5 minutes. A limitation of the SA-VES might be the tendency to increased outcome variation for patients with extensive vitiligo.[16] However, this has not yet been investigated for the SAVASI and in Chapter 3.1 we showed that the VASI showed more variation in patients with extensive vitiligo. Furthermore, the SDC of the SAVASI (5.4%) is larger than the SDC of the SA-VES (3.2%).[24] Advantages of the SA-VES are the user-friendliness and rapidity. Limitations of this study are that mainly fair skinned patients and patients with limited extent of depigmentation were included. However, we expect that these limitations had only minor influence on the outcome of the current study.

Chapter 3.3 contains the first prospective study to assess the responsiveness (i.e. the ability of an instrument to detect change over time[19]) of the VES and SA-VES. The study is a first important step towards implementation of the VES and SA-VES in daily practice and clinical trials, as determination of their responsiveness can create a solid foundation for the assessment of treatment outcome by the VES and SA-VES. The responsiveness was evaluated by testing four hypotheses regarding predefined correlations between the changes in scores of the included instruments. Of both VES and SA-VES, ≥ 75% of hypotheses were confirmed and, therefore, we stated that the VES and SA-VES are responsive measurement instruments.[25] However, the number of included patients was low and therefore we should interpret these findings with some caution. Other limitations of this study are that mainly patients with fair skin types were included and that the study design could have led to more precise assessment of the VES than SA-VES. On the other hand, this specific study design was chosen because the use of both VES and SA-VES in the design resembles the use of the instruments in daily practice the most.

In conclusion, the VES and SA-VES are valid and reliable measurement instruments to measure the extent of depigmentation in vitiligo (Chapter 3.1 and 3.2). The responsiveness of both tools could be confirmed (Chapter 3.3), although it has only been assessed in a relatively small population. Further research is necessary to assess the responsiveness of the VES and SA-VES in a larger population, with a broader variation in skin types and also in combination with the VASI as a comparator instrument. The repigmentation during narrowband ultraviolet B phototherapy (NBUVB) has a perifollicular pattern which is already incorporated in the VASI as a repigmentation scale, but not in the VES. It

remains unclear whether the VES can pick up this perifollicular repigmentation pattern. Hypothetically, adding an optional perifollicular repigmentation pattern to the VES could lead to better reliability, acceptance and feasibility of the tool. On the other hand, in this thesis the VES already showed lower SDC's and better reliability than the VASI. Therefore, the beneficial value of an optional perifollicular repigmentation remains unclear and further research is needed. Although several measurement instruments are available for vitiligo research, no consensus has yet been reached on which core set of outcome measures should be used in vitiligo research. It might be more suitable to have different core sets of outcome measures for the different treatments in vitiligo. Potentially, repigmentation in surgical treatment is optimally assessed with a target lesion assessment, whereas in topical or systemic treatments for widespread vitiligo it could be best to measure repigmentation with a difference in change score of extent of depigmentation. International consensus should be reached on which measurement instruments should be used for each outcome domain in each setting.

Cosmetic acceptability of repigmentation

Cosmetic acceptability of repigmentation is marked as a core outcome domain for vitiligo.[26] In Chapter 3.4, the validity and reliability of a new measurement instrument, the Vitiligo Cosmetic Acceptability Scale (VICAS), was assessed. This measurement instrument is a patient reported outcome measure to assess the cosmetic acceptability of repigmentation. In this pilot study, the construct validity was assessed with hypothesis testing, because no measurement instrument is yet available to measure cosmetic acceptability of repigmentation. However, only 1 of 4 hypotheses was confirmed and the construct validity of the VICAS could not be confirmed. The intra-observer reliability was fair (κ=0.391) and for 37% of patients the VICAS was easy to very easy in use.[27] It remains unclear whether the VICAS is a useful patient reported outcome measure to assess the cosmetic acceptability of repigmentation. Hypothetical reasons for the inability to validate the VICAS are the low number of included patients and poor construct definition. The outcome domain cosmetic acceptability of repigmentation is poorly defined and the construct is probably too broad, which made validation of the VICAS rather impossible. Hypothetically, cosmetic acceptability of repigmentation is too different from other outcome domains so that only poor correlation, when comparing the VICAS with other measurement instruments, is detected. It can also be discussed whether we should measure cosmetic acceptability of repigmentation, because vitiligo is generally not regarded as a cosmetic disease.[28] Nevertheless, the current consensus is still that cosmetic acceptability of repigmentation should be measured in vitiligo.[26] We conclude tentatively that the VICAS is a fairly reliable measurement instrument, however the validity of the VICAS still remains unclear. Further consensus should be

reached on whether and how we should measure cosmetic acceptability. The construct cosmetic acceptability should be further explored and it is important to know which factors contribute to cosmetic acceptability as it might be more suitable to divide cosmetic acceptability in different subdomains.

TREATMENT

Current treatments for vitiligo involve topical and systemic immunosuppressants, phototherapy, and surgical techniques.[29] Phototherapy is added to the topical or systemic immunosuppressant treatment in extensive and rapidly spreading disease.[29] Psoralen plus ultraviolet A phototherapy (PUVA) was the first phototherapy regimen that was used in vitiligo.[29,30] However, NBUVB is the current phototherapy of choice as it is even effective as PUVA and has a more favorable safety profile.[31] NBUVB has immunosuppressive qualities, and induces melanocyte differentiation and melanin production.[29,32] It has also been demonstrated that NBUVB is an effective treatment in childhood vitiligo.[33,34] Hypothetically, treatment of vitiligo in the early phase of the disease could potentially lead to modification of underlying disease processes, which is also the case in other auto-immune disorders such as rheumatoid arthritis. This hypothesis is supported by clinical data of patients with recent onset of vitiligo achieving significant higher repigmentation after NBUVB than patients with long-standing vitiligo.[35] In Chapter 4.1, we investigated the long-term efficacy and safety of NBUVB in 18 cases of childhood vitiligo for patients who participated 20 years ago in a clinical trial within our institute. To our knowledge, this was the first long-term follow-up study after NBUVB in childhood vitiligo. In the 20 years after participation in the previous study, 22% of patients received no additional treatment and 78% of patients received subsequent phototherapy. Patients who received phototherapy after the first study showed at present a larger affected body surface area than patients who received no additional treatment. This may suggest that in a small number of patients the vitiligo (who received no additional treatment) was not reactivated or less rapidly progressed after the first NBUVB treatment. However, the median duration between onset of vitiligo and first treatment with NBUVB was longer in the group without additional treatment. This suggests that also other factors may influence the disease process of vitiligo. The European guidelines on vitiligo state that prolonged maintenance with NBUVB treatment is not recommended, because there is a potential risk on skin photodamage due to the higher susceptibility of vitiligo skin to sunburn.[36] However, in our study none of the patients reported occurrence of either melanoma or non-melanoma skin cancer, though the number of participants is too small to draw any conclusions about risk of

skin cancer. Generally, there is a lack of data from clinical studies concerning the safety of NBUVB in childhood vitiligo. Limitations of our study are the small population size, retrospective uncontrolled design and relatively low response rate. Our data suggest that NBUVB may be a safe and effective treatment option in childhood vitiligo which in some cases might change the natural course of the disease.

Surgical treatment of vitiligo is performed in stable refractory disease. The main principle of surgical treatment in vitiligo is transplanting melanocytes from normal pigmented skin to a depigmented recipient-site. Several surgical treatment options for vitiligo are available and these options can be divided into 2 main categories: tissue grafts and cell suspension grafts. Examples of tissue grafts are punchgrafting (transplanting small punch biopsies) and suction blister grafting (transplanting epidermal suction blister grafts). Tissue grafts are suitable for smaller depigmented areas. Cell suspension grafting, also known as cell suspension transplantation (CST), is more suitable to cover larger surface areas and are composed of suspensions of keratinocytes and melanocytes.[29] Surgical treatment in stable vitiligo lesions is frequently combined with subsequent phototherapy as total repigmentation after melanocyte transplantation is uncommon. However, the role and beneficial effect of phototherapy in the surgical treatment is not known. In Chapter 4.3, we present a systematic review in which we included 39 studies investigating 1624 patients with vitiligo. The aim of this systematic review was to identify whether phototherapy improves the outcome of melanocyte transplantation in vitiligo. We found 4 studies directly comparing phototherapy with no phototherapy after melanocyte transplantation.[37-40] Two of these studies confirmed the benefit of phototherapy for melanocyte transplantation. We found 4 studies directly comparing different phototherapies with no significant differences in repigmentation between modalities. The other 32 non-comparative studies only investigated one phototherapy and due to the high heterogeneity (in terms of transplantation techniques, phototherapy regimen and follow-up duration) we were not able to pool these results. We also found a high variation in measurement instruments, which further impeded the comparison between studies. Therefore, consensus on a core set of measurement instruments is essential. We included both prospective and retrospective clinical studies, which led to low quality of the evidence and unknown biases. The results of Chapter 4.3 suggest that phototherapy might improve the outcome of melanocyte transplantation in vitiligo. Potentially, NBUVB is the most preferred phototherapy due to its immunosuppressive effects and safety profile, especially in non-segmental vitiligo. The frequency, duration, initial dose, dose adjustments, timing of phototherapy and cumulative dose of the phototherapies varied significantly between studies and no recommendation can

be made on which treatment scheme should be advised. We recommend NBUVB as standard phototherapy after melanocyte transplantation due to its mode of action and safety profile.

Recipient-site preparation before cell suspension transplantation is required to allow access to the underlying structures necessary for melanocyte adherence.[41] However, the optimal ablation depth is not known and full surface ablation can lead to persistent side-effects.[42,43] In Chapter 4.2, we reported a randomized controlled trial in which different depths and different types of ablation of the recipient site before cell suspension transplantation were compared in segmental vitiligo and piebaldism. Compared to the control site, we found repigmentation after deep full surface CO_2 ablation and superficial full surface CO_2 ablation, but no repigmentation after fractional CO_2 ablation. The superficial full surface ablation resulted in faster re-epithelialization and less persistent erythema than deeper full surface ablation. Fractional ablation did not result in effective repigmentation, although preclinical studies have reported that fractional laser can result in adequate penetration and adherence of cells.[41,44] In contrast, the necrotic eschar that is produced by the fractional CO_2 laser may theoretically impair permeation and adherence of melanocytes. Limitations of this study were the small sample size and the inclusion of both piebaldism and segmental vitiligo, because these are different depigmenting skin disorders. However, both have the same stable disease course and lack a persisting auto-immune reaction against melanocytes, which is present in non-segmental vitiligo. Previous studies in non-segmental vitiligo have shown repigmentation after laser ablation without any additional treatment like cellular grafting.[45,46] This unspecific induction of repigmentation is very unlikely in segmental vitiligo and piebaldism due to the general absence of follicular melanocytes. Furthermore, in a previous comparable study we also found no unspecific repigmentation induction after monotherapy with CO_2 laser ablation alone in a similar population.[47] We recommend that the recipient site before CST is prepared with superficial full surface ablation. Fractional CO_2 laser with the settings used in this study was not effective as a procedure for recipient-site preparation.

FUTURE DIRECTIONS

Current research is mainly focused on immunosuppressive targeted therapies to stop the progression of the disease. However, repigmentation after treatment with currently available immunosuppressants is unsatisfactory and combination therapies are recommended.[36,48-50] Additional induction of repigmentation is achieved by

phototherapy or melanocyte transplantation. To the best of my knowledge, no clinical studies have yet been performed that compare the efficacy of standard of care immunosuppressive treatments with and without cell suspension transplantation in non-segmental vitiligo. Hypothetically, standard of care combined with cell suspension transplantation could result in a promising treatment regimen in patients with non-segmental vitiligo. More clinical trials are needed to investigate the combined treatment of cell suspension transplantation and standard of care in non-segmental vitiligo. Furthermore, repigmentation after cell suspension transplantation varies widely between individual patients. Several potential factors could play a role in this variation, such as harvesting of the donor skin sample, disaggregation of epidermal cells, application of the cell suspension, viable cell counts, donor to acceptor ratio and recipient-site preparation. Further research is necessary to investigate whether these possible factors play a role in the outcome of cell suspension transplantation.

Recent basic and translational research have significantly improved the understanding of the pathogenesis of non-segmental vitiligo. These understandings could also lead to better targeted therapy for vitiligo patients. For example, blockage of the IFN-γ pathway could potentially lead to disrupting the CD8+ T-cells recruitment and subsequently stopping the melanocyte destruction. In recent basic studies, blockage of the T-cell chemokine receptor CXCR3 and its ligand CXCL10 in mice with widespread depigmentation resulted in cessation of spread and perifollicular repigmentation.[51,52] The IFN-γ pathway relies on the JAK-STAT pathway for signaling. In recent case studies, systemic treatment with JAK inhibitors (i.e. tofacitinib) of patients with non-segmental vitiligo resulted in cessation of spreading and repigmentation.[53,54] Recent basis studies have also showed that keratinocytes play a major role in the chemokine production in vitiligo.[55] Hypothetically, local disruption of the IFN-γ pathway with topical JAK inhibitors could also be an effective treatment.[56] Larger randomized controlled trials are needed to further assess the efficacy and safety of systemic and topical JAK inhibitors in the treatment of vitiligo. Furthermore, combination of these targeted therapies with therapies for repigmentation induction (i.e. phototherapy or melanocyte transplantation) could potentially lead to optimal repigmentation and is still an unexplored area of research.

Potentially, impairment of regulatory T-cells could also play a role in the pathogenesis of vitiligo.[57,58] Recent studies have shown reduced numbers and function of regulatory T-cells in vitiligo.[57,59] Regulatory T-cells normally inhibit autoimmune response and impairment of regulatory T-cell function in vitiligo may lead to less inhibition of CD8+ T-cells with subsequent ongoing melanocyte destruction. Hypothetically, replenishing

regulatory T-cells or enhancing their function in vitiligo skin might suppress disease activity and even promote repigmentation. Future research should focus on the role of regulatory T-cells in the treatment and pathophysiology of vitiligo.

Categorization of patients in different groups of disease extent leads to better comparison of results in and also helps establishing inclusion criteria for clinical trials.[60] Furthermore, these categorizations can also be used for treatment guidelines in vitiligo. Although grading of the disease extent is necessary for future clinical trials and also for daily practice, no grading scales for disease extent are yet available. Future studies should focus on establishing these grading scales for disease extent in vitiligo and ideally international consensus between patients, physicians and other stake-holders should be reached on the subject. To improve the interpretability of treatment results, also minimal important changes of repigmentation should be established. Furthermore, international consensus should be reached on what is the cut-off point for repigmentation in terms of treatment success, as this is an important reference point for treatment outcome in clinical trials and daily practice. The establishment of a minimal important change and cut off for treatment success, will aid further clinical trials to establish their primary outcomes and hence improve future research in vitiligo. Although maintenance of repigmentation is one of the core set of outcome domains in vitiligo research, very little long-term data on the efficacy of the currently available treatment is available. Future randomized controlled trials should include maintenance of repigmentation as one of their outcomes.

In this thesis, several blind spots in vitiligo research have been addressed. However, many challenges in vitiligo research still remain and future studies should address these important issues. Future research will expectedly gain more insight in the pathophysiology and clinical pathway of vitiligo which will further color the white spots of vitiligo.

REFERENCES

1 Alikhan A, Felsten LM, Daly M *et al*. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *Journal of the American Academy of Dermatology* 2011; **65**: 473-91.

2 Nordlund JJ, Kirkwood JM, Forget BM *et al*. Vitiligo in patients with metastatic melanoma: a good prognostic sign. *Journal of the American Academy of Dermatology* 1983; **9**: 689-96.

3 Koh HK, Sober AJ, Nakagawa H *et al*. Malignant melanoma and vitiligo-like leukoderma: an electron microscopic study. *Journal of the American Academy of Dermatology* 1983; **9**: 696-708.

4 Quaglino P, Marenco F, Osella-Abate S *et al*. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**: 409-14.

5 Hartmann A, Bedenk C, Keikavoussi P *et al*. Vitiligo and melanoma-associated hypopigmentation (MAH): shared and discriminative features. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* 2008; **6**: 1053-9.

6 Sosa JJ, Currimbhoy SD, Ukoha U *et al*. Confetti-like depigmentation: A potential sign of rapidly progressing vitiligo. *Journal of the American Academy of Dermatology* 2015; **73**: 272-5.

7 Teulings HE, Willemsen KJ, Glykofridis I *et al*. The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. *Pigment cell & melanoma research* 2014; **27**: 1086-96.

8 Ezzedine K, Lim HW, Suzuki T *et al*. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment cell & melanoma research* 2012; **25**: E1-13.

9 Zaima H, Koga M. Clinical course of 44 cases of localized type vitiligo. *The Journal of dermatology* 2002; **29**: 15-9.

10 Hann SK, Chang JH, Lee HS *et al*. The classification of segmental vitiligo on the face. *Yonsei medical journal* 2000; **41**: 209-12.

11 van Geel N, Speeckaert R, Melsens E *et al*. The distribution pattern of segmental vitiligo: clues for somatic mosaicism. *The British journal of dermatology* 2013; **168**: 56-64.

12 Whitton ME, Pinart M, Batchelor J *et al*. Interventions for vitiligo. *The Cochrane database of systematic reviews* 2015; **2**: Cd003263.

13 Rodrigues M, Ezzedine K, Hamzavi I *et al*. New discoveries in the pathogenesis and classification of vitiligo. *Journal of the American Academy of Dermatology* 2017; **77**: 1-13.

14 Speeckaert R, van Geel N. Vitiligo: An Update on Pathophysiology and Treatment Options. *Am J Clin Dermatol* 2017.

15 De Vet HC. *Measurement in Medicine: practical guides to biostatistics and epidemiology*, Vol. 8. Cambridge: University Printing House. 2011.

16 van Geel N, Lommerts J, Bekkenk M *et al.* Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *The Journal of investigative dermatology* 2016; **136**: 978-84.
17 Williamson PR, Altman DG, Blazeby JM *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; **13**: 132.
18 Vrijman C, Linthorst Homan MW, Limpens J *et al.* Measurement properties of outcome measures for vitiligo. A systematic review. *Archives of dermatology* 2012; **148**: 1302-9.
19 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.
20 Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010; **19**: 539-49.
21 Hamzavi I, Jain H, McLean D *et al.* Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Archives of dermatology* 2004; **140**: 677-83.
22 Komen L, da Graca V, Wolkerstorfer A *et al.* Vitiligo Area Scoring Index and Vitiligo European Task Force assessment: reliable and responsive instruments to measure the degree of depigmentation in vitiligo. *The British journal of dermatology* 2015; **172**: 437-43.
23 Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* 2005; **210**: 194-9.
24 Komen L, van der Kraaij GE, van der Veen JP *et al.* The validity, reliability and acceptability of the SAVASI; a new self-assessment score in vitiligo. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2145-51.
25 Terwee CB, Bot SD, de Boer MR *et al.* Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; **60**: 34-42.
26 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment cell & melanoma research* 2015; **28**: 363-9.
27 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159-74.
28 Ezzedine K, Sheth V, Rodrigues M *et al.* Vitiligo is not a cosmetic disease. *Journal of the American Academy of Dermatology* 2015; **73**: 883-5.
29 Rodrigues M, Ezzedine K, Hamzavi I *et al.* Current and emerging treatments for vitiligo. *Journal of the American Academy of Dermatology* 2017; **77**: 17-29.
30 Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Archives of dermatology* 1997; **133**: 1525-8.
31 Bae JM, Jung HM, Hong BY *et al.* Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2017; **153**: 666-74.
32 De Francesco V, Stinco G, Laspina S *et al.* Immunohistochemical study before and after narrow band (311 nm) UVB treatment in vitiligo. *European journal of dermatology : EJD* 2008; **18**: 292-6.

33 Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *Journal of the American Academy of Dermatology* 2000; **42**: 245-53.

34 Sen BB, Rifaioglu EN, Ekiz O *et al.* Narrow-band ultraviolet B phototherapy in childhood. *Cutaneous and ocular toxicology* 2014; **33**: 189-91.

35 Hallaji Z, Ghiasi M, Eisazadeh A *et al.* Evaluation of the effect of disease duration in generalized vitiligo on its clinical response to narrowband ultraviolet B phototherapy. *Photodermatol Photo* 2012; **28**: 115-9.

36 Taieb A, Alomar A, Bohm M *et al.* Guidelines for the management of vitiligo: the European Dermatology Forum consensus. *The British journal of dermatology* 2013; **168**: 5-19.

37 Lim JT. Repigmentation of vitiligo with autologous blister-induced epidermal grafts. *Annals of the Academy of Medicine, Singapore* 1999; **28**: 824-8.

38 Zhang DM, Hong WS, Fu LF *et al.* A randomized controlled study of the effects of different modalities of narrow-band ultraviolet B therapy on the outcome of cultured autologous melanocytes transplantation in treating vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2014; **40**: 420-6.

39 Ebadi A, Rad MM, Nazari S *et al.* The additive effect of excimer laser on non-cultured melanocyte-keratinocyte transplantation for the treatment of vitiligo: A clinical trial in an Iranian population. *Journal of the European Academy of Dermatology and Venereology* 2015; **29**: 745-51.

40 Barman KD, Khaitan BK, Verma KK. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]* 2004; **30**: 49-53.

41 Al-Hadidi N, Griffith JL, Al-Jamal MS *et al.* Role of Recipient-site Preparation Techniques and Post-operative Wound Dressing in the Surgical Management of Vitiligo. *Journal of cutaneous and aesthetic surgery* 2015; **8**: 79-87.

42 Lommerts JE, Meesters AA, Komen L *et al.* Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomised controlled trial comparing full-surface and fractional CO2 laser recipient site preparations. *The British journal of dermatology* 2017.

43 Silpa-Archa N, Griffith JL, Williams MS *et al.* Prospective comparison of recipient-site preparation with fractional carbon dioxide laser vs. dermabrasion and recipient-site dressing composition in melanocyte-keratinocyte transplantation procedure in vitiligo: a preliminary study. *The British journal of dermatology* 2016; **174**: 895-7.

44 Oni G, Lequeux C, Cho MJ *et al.* Transdermal delivery of adipocyte-derived stem cells using a fractional ablative laser. *Aesthet Surg J* 2013; **33**: 109-16.

45 Shin J, Lee JS, Hann SK *et al.* Combination treatment by 10 600 nm ablative fractional carbon dioxide laser and narrowband ultraviolet B in refractory nonsegmental vitiligo: a prospective, randomized half-body comparative study. *The British journal of dermatology* 2012; **166**: 658-61.

46 Bayoumi W, Fontas E, Sillard L *et al.* Effect of a preceding laser dermabrasion on the outcome of combined therapy with narrowband ultraviolet B and potent topical steroids for treating nonsegmental vitiligo in resistant localizations. *The British journal of dermatology* 2012; **166**: 208-11.
47 Komen L, Vrijman C, Tjin EP *et al.* Autologous cell suspension transplantation using a cell extraction device in segmental vitiligo and piebaldism patients: A randomized controlled pilot study. *Journal of the American Academy of Dermatology* 2015; **73**: 170-2.
48 Oiso N, Suzuki T, Wataya-Kaneda M *et al.* Guidelines for the diagnosis and treatment of vitiligo in Japan. *J Dermatol* 2013; **40**: 344-54.
49 Whitton ME, Pinart M, Batchelor J *et al.* Interventions for vitiligo. *Cochrane Database Syst Rev* 2015: CD003263.
50 Whitton M, Pinart M, Batchelor JM *et al.* Evidence-based management of vitiligo: summary of a Cochrane systematic review. *The British journal of dermatology* 2016; **174**: 962-9.
51 Richmond JM, Masterjohn E, Chu R *et al.* CXCR3 Depleting Antibodies Prevent and Reverse Vitiligo in Mice. *The Journal of investigative dermatology* 2017; **137**: 982-5.
52 Rashighi M, Agarwal P, Richmond JM *et al.* CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med* 2014; **6**: 223ra23.
53 Liu LY, Strassner JP, Refat MA *et al.* Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *Journal of the American Academy of Dermatology* 2017; **77**: 675-82 e1.
54 Craiglow BG, King BA. Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy. *JAMA dermatology* 2015; **151**: 1110-2.
55 Richmond JM, Bangari DS, Essien KI *et al.* Keratinocyte-Derived Chemokines Orchestrate T-Cell Positioning in the Epidermis during Vitiligo and May Serve as Biomarkers of Disease. *The Journal of investigative dermatology* 2017; **137**: 350-8.
56 Rothstein B, Joshipura D, Saraiya A *et al.* Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *Journal of the American Academy of Dermatology* 2017; **76**: 1054-60 e1.
57 Klarquist J, Denman CJ, Hernandez C *et al.* Reduced skin homing by functional Treg in vitiligo. *Pigment cell & melanoma research* 2010; **23**: 276-86.
58 Dwivedi M, Laddha NC, Arora P *et al.* Decreased regulatory T-cells and CD4(+) /CD8(+) ratio correlate with disease onset and progression in patients with generalized vitiligo. *Pigment cell & melanoma research* 2013; **26**: 586-91.
59 Tu CX, Jin WW, Lin M *et al.* Levels of TGF-beta(1) in serum and culture supernatants of CD4(+) CD25 (+) T cells from patients with non-segmental vitiligo. *Archives of dermatological research* 2011; **303**: 685-9.
60 van Geel N, Boniface K, Seneschal J *et al.* Meeting report: Vitiligo Global Issues Consensus Conference Workshop "Outcome measurement instruments" and Vitiligo International Symposium, Rome, Nov 30-Dec 3rd. *Pigment cell & melanoma research* 2017; **30**: 436-43.

SUMMARY AND CONCLUSIONS

CHAPTER 6.1

SUMMARY AND CONCLUSIONS

Vitiligo is a common acquired skin disease characterized by depigmentation of the skin which affects approximately 0.5-1% of the world's population. Vitiligo is a disfiguring and psychologically devastating skin disease caused by selective destruction of melanocytes. Two main subtypes of vitiligo, non-segmental and segmental, can be distinguished. The pathogenesis of both subtypes is considered to be different. The main focus of this thesis was to answer important questions in the clinical pathway of vitiligo. The clinical pathway of a patient with suspected vitiligo can be divided into the diagnosis (Chapters 2.1-2.3), measurement (Chapters 3.1-3.4) and treatment (Chapters 4.1-4.3) of vitiligo. In Chapters 2.1 and 2.2, we investigated the prevalence of melanoma-associated leukoderma and whether expert in the field can differentiate between melanoma-associated leukoderma and vitiligo. The objective of Chapter 2.3 was to study the characteristics, the chance and possible predictors of progression of focal vitiligo. In Chapters 3.1, 3.2 and 3.3, we investigated whether the Vitiligo Extent Score and the Self Assessment Vitiligo Extent Score are valid, reliable and responsive measurement instruments to measure the extent of depigmentation in vitiligo. In Chapter 3.4, the validity and reliability of another measurement instrument, the Vitiligo Cosmetic Acceptability Scale, was assessed. The objective of Chapter 4.1 was to assess the long-term outcome after narrowband ultraviolet B phototherapy (NBUVB) in childhood vitiligo. In Chapter 4.2, we assessed the efficacy and safety of less invasive recipient-site preparations before cell suspension transplantation. The objective of the systematic review in Chapter 4.3, was to assess whether phototherapy has a beneficial effect on the outcome of surgical treatment in vitiligo. The overall objective of this thesis was to color the white spots in vitiligo by coloring the blind spots in vitiligo research.

Chapter 2.1 – Vitiligo-like depigmentations as the first sign of melanoma: a retrospective case series from a tertiary vitiligo center.

Vitiligo-like skin depigmentation can occur in patients with melanoma and this phenomenon is called melanoma-associated leukoderma (MAL). Many dermatologists are not aware of the diagnosis of MAL, and may easily misdiagnose and treat these patients as having nonsegmental vitiligo, thereby overlooking the underlying melanoma. The prevalence of MAL and its clinical characteristics are not well established. In Chapter 2.1, we retrospectively analyzed the clinical presentation, type of depigmentation and disease course of patients with MAL who were diagnosed at the Netherlands Institute for Pigment Disorders from 2009 to 2014. Additionally, we reviewed patients with MAL identified from a questionnaire study that evaluated the lifetime prevalence of melanoma in 1307 patients with vitiligo. Seven patients initially diagnosed with nonsegmental vitiligo could be identified as having MAL, which gives a prevalence of MAL in these cohorts of 0.15%. The identified cases concerned older patients with fair

skin types and with a sudden onset of highly progressive atypical depigmentations refractory to topical treatment and NBUVB. In conclusion, although MAL is a rare disease, awareness of this phenomenon and correct diagnosis of these patients is crucial to limit further melanoma treatment delay. A total body inspection on suspect melanocytic lesions should be performed and a history on removed melanocytic lesions should be recorded in any patient presenting with vitiligo.

Chapter 2.2 – Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field.

Melanoma-associated leukoderma (MAL) is a depigmenting disorder that can occur spontaneously in patients with melanoma. The differences in clinical presentation between MAL and vitiligo are not well defined. This may lead to misdiagnosing MAL as vitiligo, resulting in delayed detection and treatment of melanoma. The objective of Chapter 2.2 was to assess whether experts in the field can distinguish between MAL and vitiligo, and to assess if discriminative features can be identified. We designed an image comparison study in which 4 experts in the field blindly assessed photographs followed by medical history of 11 patients with MAL and 33 with vitiligo. The assessors misdiagnosed 72.7% of MAL cases and marked 80.0% of them as typical vitiligo. The median age at onset of the leukoderma was higher (55 years, $P = 0.001$) in MAL. No discriminative morphological features were found. Limitation of this study was sampling bias because of inclusion in our tertiary referral center for vitiligo. In conclusion, the clinical presentation of leukoderma in patients with melanoma resembles that of vitiligo. We propose "melanoma-associated vitiligo" as the more appropriate term for leukoderma in patients with melanoma. Clinicians should be aware that depigmentation in vitiligo can also be caused by melanoma-associated vitiligo and a total body inspection should be performed.

Chapter 2.3 – Focal vitiligo: long-term follow-up of 52 cases.

Focal vitiligo is characterized by depigmented patches located in a small area without a typical segmental distribution. Focal vitiligo is classified as an undetermined type of vitiligo and a more definitive diagnosis can be made when the lesions have not evolved into non-segmental or segmental vitiligo after a period of 1-2 years. However, the chance of progression is not known and may lead to treatment-indecision. The objective of Chapter 2.3 was to study the characteristics of patients with focal vitiligo and possible predictors of progression. In Chapter 2.3, we conducted a survey-study in patients with the initial diagnosis of focal vitiligo between January 2005 and June 2010. Focal vitiligo was defined as either a small acquired isolated depigmented lesion

without typical segmental distribution or two to three small acquired lesions localized in a non-segmental area with a maximum of 5 cm. We identified 128 eligible patients and the response rate was 40.6% (n = 52 completed questionnaires). The median follow-up duration was 7 years. Progression to non-segmental vitiligo occurred in 23%. In 11.5% of the patients, progression to non-segmental vitiligo occurred within 2 years after onset. Nevertheless, even after a first stable period of more than 2 years, another 11.5% of patients advanced to non-segmental vitiligo. No associated prognostic factors at baseline of progression to non-segmental or long-lasting focal vitiligo were found. In Chapter 2.3, focal vitiligo progressed to typical non-segmental vitiligo, but not towards typical segmental vitiligo. In conclusion, focal vitiligo is a rare subtype of vitiligo and most patients have long-lasting focal lesions after onset of the disease. There seem to be no clinical signs that predict progression in focal vitiligo.

Chapter 3.1 – Development and validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative.

The clinical assessment of vitiligo involves an estimation of the affected body surface area. The most commonly used method is the "palm of hand 1% rule" as integrated in the Vitiligo Area Scoring Index. However, this method can be challenging and time consuming. In Chapter 3.1, we introduced a new measurement tool: the Vitiligo Extent Score (VES). In the first part of the study, the VES was developed and subsequently optimized during a pilot scoring session. In a subsequent stage, the inter- and intrarater reliability of the VES were tested. Live scoring showed an excellent interrater reliability for the VES (intraclass correlation VES: 0.924 vs. Vitiligo Area Scoring Index: 0.846). Subsequent scoring on pictures was comparable with the live evaluation and demonstrated an excellent intrarater reliability. A high intraclass correlation for the VES (intraclass correlation VES: 0.923 vs. Vitiligo Area Scoring Index: 0.757) was also found in an additional subgroup of patients with extensive vitiligo. Moreover, user-friendliness and timing were scored very favorably. In conclusion, the VES allows us to accurately and easily monitor the affected body surface area in a standardized way. Moreover, our results provide evidence that the VES can be proposed as a promising tool to measure the vitiligo extent in clinical trials and in daily practice.

Chapter 3.2 – Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES).

The Vitiligo Extent Score (VES) was introduced in Chapter 3.1 as a new physicians' score for the clinical assessment of the extent of vitiligo. However, a good patient self-assessment score was still lacking. The objective of Chapter 3.2 was to develop and

validate a simplified version of the VES as a patient-reported outcome measure. After extensive pilot testing, patients were asked to score their vitiligo extent twice with an interval of 2 weeks using the Self Assessment Vitiligo Extent Score (SA-VES). The scores were compared with the physicians' evaluation (VES). The SA-VES demonstrated very good test-retest reliability (intraclass correlation = 0.948, 95% confidence interval [CI]: 0.911-0.970) that was not affected by age, skin type, or vitiligo distribution pattern. According to patients, the SA-VES was easy to use (22% very easy; 49% easy; 29% normal) and required <5 minutes in the majority of patients (73%, <5 minutes; 24%, 5-10 minutes; 2%, 10-15 minutes). Comparison of the SA-VES and the VES demonstrated excellent correlation (r = 0.986, P < .001). Limitation of the study was that only a few patients were included that had darker skin type. In conclusion, the results of Chapter 3.2 demonstrated excellent reliability of the SA-VES and excellent correlation with its investigator-reported counterpart (VES). This patient-oriented evaluation method provides a useful tool for the assessment of vitiligo extent.

Chapter 3.3 – Prospective evaluation of the responsiveness of the Vitiligo Extent Score (VES) and Self-Assessment Vitiligo Extent Score (SA-VES).

The VES and SA-VES are valid and reliable measurement tools to measure the extent of vitiligo. In Chapter 3.3, we measured the responsiveness of the VES and SA-VES prospectively during 6 months of NBUVB. We included 30 patients with vitiligo and followed them during 6 months of NB-UVB therapy. Before and 6 months after start of NBUVB, patients were asked to fill in a questionnaire comprising questions concerning baseline characteristics, SA-VES and improvement after treatment. One independent vitiligo expert assessed the VES on the photographs taken before and 6 months after start of NBUVB. Measurement of the responsiveness was based on hypotheses testing; when 75% or more of the hypotheses were confirmed the VES and SA-VES were marked as responsive. After 6 months of NBUVB, 24 patients were seen for follow-up and included in the data-analysis. Median age was 42 years (interquartile range (IQR): 38-57) and 33% of patients were males. The degree of depigmentation at inclusion was 2.6% (median, IQR: 1.0-8.6%) and repigmentation after 6 months of follow-up was 29.1% (median, IQR: 15.0-43.4%). We confirmed ≥ 75% of hypotheses of both the VES and the SA-VES. The main limitation of this study was the low number of included patients. In conclusion, the responsiveness of the VES and SA-VES is promising, but further research in a larger patient population is needed to confirm our study findings.

Chapter 3.4 – Pilot study on the validity and reliability measurement of a new patient reported outcome measure in vitiligo: the Vitiligo Cosmetic Acceptability Scale (VICAS).

Cosmetic acceptability of repigmentation is marked as a core outcome domain in vitiligo. Nevertheless, no tool is available to measure this important domain. In Chapter 3.4, we tested the validity and reliability of a new tool to measure the cosmetic acceptability: the Vitiligo Cosmetic Acceptability Scale (VICAS). The VICAS is comprised of one question 'How satisfied are you with the cosmetic aspect of the repigmentation?' answered on a 5-point Likert Scale (very dissatisfied to very satisfied). We included 30 patients with non-segmental vitiligo. After 26 weeks of NBUVB, 26 patients were included for data-analysis. The affected body surface area at inclusion was 6% (median, IQR: 3-12%) and 19% repigmentation (median, IQR: -15–46%) was found after 6 months. Measurement of the construct validity was based on hypotheses testing and when ≥ 75% of hypotheses were confirmed we would mark the VICAS as a valid tool. However, only 1 of 4 hypotheses was confirmed in Chapter 3.4. The intra-observer reliability was fair (κ=0.391, week 26 vs. week 28) and for 37% of patients the VICAS was easy to very easy in use. In conclusion, the VICAS is a fairly reliable measurement instrument. However, the validity of the VICAS was not confirmed and it remains unclear whether the VICAS is a useful measurement instrument to assess the cosmetic acceptability of repigmentation in vitiligo. Further consensus should be reached on whether and how we should measure cosmetic acceptability.

Chapter 4.1 – Twenty-year follow-up using a postal survey of childhood vitiligo treated with narrowband ultraviolet B phototherapy.

NBUVB is an effective treatment option in childhood vitiligo. To date, no data are available on the long-term efficacy and safety of NBUVB in childhood vitiligo. In Chapter 4.1, we designed a long-term follow-up survey-study after our prospective clinical trial of 20 years prior in which 51 children with non-segmental vitiligo were treated with NBUVB for a maximum period of 1 year. Of the 51 patients who participated in the first study, a total of 18 patients returned a completed questionnaire. Median follow-up duration was 20 years and median current age 32 years. Current affected body surface area was lower than before inclusion in the first study. In Chapter 4.1, only a small percentage of patients (22%) did not receive any additional treatment after the first study and these patients had lower affected body surface area than patients who received additional treatment after the first study (0.6% vs 5.3%, respectively). This may suggest that in a small number of patients, the vitiligo was not reactivated or only slowly progressed after the first NBUVB. None of the patients reported occurrence of either melanoma

or nonmelanoma skin cancer. Limitations of Chapter 4.1 are the small population size, retrospective uncontrolled design and low response rate. Our data suggest that NBUVB may be a safe and effective treatment option in childhood vitiligo which in some cases may change the natural course of the disease.

Chapter 4.2 – Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomized controlled trial comparing full surface and fractional CO_2 laser recipient-site preparations.

Autologous non-cultured cell suspension transplantation is an effective treatment for repigmentation in segmental vitiligo and piebaldism. Full surface laser ablation is frequently used to prepare the recipient-site before cell suspension transplantation, even though optimal laser settings and ablation depth are unknown. The objective of Chapter 4.2 was to assess the efficacy and safety of less invasive recipient-site preparations. In a randomized, observer-blinded, controlled trial we compared different recipient-site preparations before cell suspension transplantation in segmental vitiligo and piebaldism. In each patient, we randomly allocated three CO_2 laser recipient-site preparations (i.e. 209 and 144 µm full surface, fractional) and a control (no treatment) to four depigmentations. After six months we assessed repigmentation and side effects. We included 10 patients with vitiligo (n=3) and piebaldism (n=7). Compared to the control site, we found more repigmentation after 209 µm (median 68.7%, p=0.01) and 144 µm (median 58.3%, p=0.007) full surface ablation, but no repigmentation after fractional ablation (median 0.0 %, p=0.14). In conclusion, superficial full surface CO_2 laser ablation with a depth of 144 µm is an effective recipient-site preparation before cell suspension transplantation while fractional CO_2 laser is not.

Chapter 4.3 – The role of phototherapy in the surgical treatment of vitiligo: a systematic review.

Vitiligo is frequently treated with the combination of phototherapy and melanocyte transplantation. However, the additional benefit of phototherapy is unclear. Moreover, the optimal type and regimen of phototherapy is unknown. The objective of the systematic review in Chapter 4.3 was to identify whether phototherapy improves the outcome of melanocyte transplantation in vitiligo. We searched and screened for eligible studies in the databases of MEDLINE, EMBASE and CENTRAL. We included all clinical studies investigating melanocyte transplantation combined with phototherapy. After screening and selection of abstracts and full-texts, we found 39 eligible clinical studies with 1624 patients. The eligible studies investigated several phototherapy modalities, such as NBUVB (n=9), psoralen combined with ultraviolet A (PUVA, n=19),

ultraviolet A (UVA, n=1), monochromatic excimer light or laser (MELi and MELa, n=4) and active sunlight exposure (n=9). Four studies directly compared phototherapy versus no phototherapy and two studies confirmed the benefit of phototherapy for melanocyte transplantation. We found no significant differences in repigmentation in studies directly comparing phototherapy modalities. The overall quality of the studies was moderate to poor and high heterogeneity between studies was found. We found limited evidence that phototherapy improves the outcome of melanocyte transplantation in vitiligo. There is insufficient evidence to recommend a specific type or regimen of phototherapy. More studies should be performed investigating the additional benefit of different phototherapies and the preferred moment of phototherapy.

CHAPTER 6.2

SAMENVATTING EN CONCLUSIES

Vitiligo is een verworven huidziekte die voorkomt bij ongeveer 0.5-1% van de algehele wereldbevolking. Vitiligo is een ontsierende aandoening die wordt veroorzaakt door een selectieve destructie van melanocyten in de huid, waardoor witte plekken ontstaan. Vitiligo is niet besmettelijk of levensbedreigend, maar patiënten kunnen wel psychologische problemen ontwikkelen die de kwaliteit van leven ernstig kunnen verminderen. Twee subtypes van vitiligo worden onderscheiden, namelijk non-segmentale en segmentale vitiligo, waarvan verondersteld wordt dat de pathogenese van beide subtypes verschillend is. Dit proefschrift richt zich op het beantwoorden van belangrijke vragen binnen het klinische proces van vitiligo. Het klinische proces van een patiënt met verdenking op vitiligo bestaat uit de diagnose (hoofdstukken 2.1-2.3), het meten (hoofdstukken 3.1-3.4) en de behandeling (hoofdstukken 4.1-4.3) van vitiligo. In de hoofdstukken 2.1 en 2.2, hebben we de prevalentie van melanoomgeassocieerde leukoderma onderzocht en of experts in het vakgebied melanoomgeassocieerde leukoderma kunnen onderscheiden van vitiligo. Het doel van hoofdstuk 2.3 was om de patiëntkarakteristieken, mogelijke voorspellers van en kans op progressie van focale vitiligo te onderzoeken. In de hoofdstukken 3.1, 3.2 en 3.3, hebben we onderzocht of de Vitiligo Extent Score en de Self Assessment Vitiligo Extent Score valide, betrouwbare en responsieve meetinstrumenten zijn om de uitgebreidheid van depigmentatie in vitiligo te meten. In hoofdstuk 3.4 hebben we de validiteit en betrouwbaarheid van een ander meetinstrument, de Vitiligo Cosmetic Acceptability Scale, onderzocht. Het doel van hoofdstuk 4.1 was om de lange-termijn uitkomsten van smalband ultraviolet-B lichttherapie (NBUVB) in kinderen met vitiligo te onderzoeken. In hoofdstuk 4.2, hebben we de effectiviteit en veiligheid van minder invasieve voorbehandelingen van de receptor-plek voorafgaand aan cel suspensie transplantatie onderzocht. Het doel van de systematische review in hoofdstuk 4.3 was om te onderzoeken of lichttherapie een voordelig effect heeft op het resultaat van de chirurgische behandeling in vitiligo. Het overkoepelende doel van dit proefschrift was de witte vlekken van vitiligo in te kleuren door de blinde vlekken in het vitiligo-onderzoek te verkleinen.

Hoofdstuk 2.1 – Vitiligoachtige depigmentatie als eerste teken van melanoom: een retrospectieve case serie van een tertiair vitiligocentrum.

Vitiligoachtige depigmentatie van de huid kan ontstaan in patiënten met melanoom en dit fenomeen wordt ook wel melanoomgeassocieerde leukoderma (MAL) genoemd. Veel dermatologen zijn zich niet bewust van de diagnose MAL en kunnen deze patiënten abusievelijk diagnosticeren en behandelen als non-segmentale vitiligo. Hierdoor wordt de diagnose van het onderliggende melanoom gemist met uitstel van adequate behandeling van het melanoom als gevolg. De prevalentie van MAL en de klinische kenmerken zijn relatief onbekend. In hoofdstuk 2.1 hebben we retrospectief

de klinische presentatie, het type depigmentatie en ziektebeloop bekeken van MAL-patiënten die gezien werden tussen 2009 en 2014 in het Nederlands Instituut voor Pigmentstoornissen (SNIP). Daarnaast hebben we MAL-patiënten geanalyseerd die hadden deelgenomen aan een vragenlijststudie over de levensduurprevalentie van melanoom in 1307 patiënten met vitiligo. Wij hebben zeven patiënten die initieel waren gediagnosticeerd als non-segmentale vitiligo kunnen identificeren als MAL-patiënt, wat resulteert in een geschatte prevalentie van MAL in deze cohorten van 0,15%. De geïdentificeerde gevallen bestonden uit oudere patiënten met lichte huidtypes en met een plotsteling ontstaan van zeer snel progressieve atypische depigmentaties die refractair waren voor topische behandeling en NBUVB-lichttherapie. Dit onderzoek geeft aan dat het bewustzijn en correct diagnosticeren van MAL, ook al komt het weinig voor, cruciaal is om de vertraging in melanoombehandeling te beperken. Een algehele huidinspectie op verdachte melanocytaire laesies zou uitgevoerd moeten worden en tijdens de anamnese zou gevraagd moeten worden naar eventueel eerder verwijderde melanocytaire laesies in het verleden bij elke patiënt die zich presenteert met vitiligo.

Hoofdstuk 2.2 – Melanoomgeassocieerde leukoderma en vitiligo kunnen niet onderscheiden worden op basis van geblindeerde beoordeling door experts in het vakgebied.

Melanoomgeassocieerde leukoderma (MAL) is een depigmentatiestoornis die spontaan kan optreden in melanoom-patiënten. De verschillen in klinische presentatie tussen MAL en vitiligo zijn niet welomschreven. Dit kan leiden tot het onjuist diagnosticeren van MAL als vitiligo, resulterend in late detectie en behandeling van het melanoom. Het doel van hoofdstuk 2.2 was om te beoordelen of experts in het vakgebied onderscheid kunnen maken tussen MAL en vitiligo en om te kijken of er onderscheidende eigenschappen kunnen worden gevonden. We hebben hiervoor een vergelijkingsstudie van foto's opgezet waarbij vier experts in dit vakgebied geblindeerd foto's van 11 MAL-patiënten en 33 vitiligopatiënten hebben geanalyseerd, gevolgd door het beoordelen van de medische voorgeschiedenis. De beoordelaars hebben 72,7% van de MAL-gevallen onjuist gediagnosticeerd en deze in 80% van de gevallen aangeduid als typische vitiligo. De mediane leeftijd van ontstaan van leukoderma was hoger (55 jaar, P = 0,001) in MAL. Geen onderscheidende eigenschappen in klinische presentatie werden gevonden. Beperking van deze studie was de steekproefbias door het includeren in een tertiair verwijzingscentrum voor vitiligo. Concluderend, de klinische presentatie van leukoderma in patiënten met melanoom lijkt op die van vitiligo. Wij stellen voor dat "melanoomgeassocieerde vitiligo" een correctere benaming is voor leukoderma in

melanoompatiënten. Clinici zouden zich ervan bewust moeten zijn dat depigmentatie in ogenschijnlijke vitiligo-patiënten ook veroorzaakt kan worden door melanoom-geassocieerde vitiligo en dat een algehele huidinspectie moet worden uitgevoerd.

Hoofdstuk 2.3 – Focale vitiligo: langdurige follow-up van 52 patiënten.

Focale vitiligo wordt gekenmerkt door gedepigmenteerde maculae die gelokaliseerd zijn in een klein gebied zonder een typische segmentale distributie. Focale vitiligo is gedefinieerd als een niet-geclassificeerd type van vitiligo en een meer definitieve diagnose kan worden gemaakt wanneer de laesies zich niet hebben ontwikkeld tot non-segmentale of segmentale vitiligo na een periode van 1-2 jaar. Daarentegen is de kans op progressie niet bekend en dit kan leiden tot besluiteloosheid omtrent de behandeling. Het doel van hoofdstuk 2.3 was om de patiëntkarakteristieken van focale vitiligo en mogelijke voorspellers voor progressie te onderzoeken. In hoofdstuk 2.3 hebben wij een vragenlijststudie gedaan in patiënten die de diagnose van focale vitiligo kregen tussen januari 2005 en juni 2010. Focale vitiligo werd gedefinieerd als een kleine verworven geïsoleerde gedepigmenteerde macula zonder typische segmentale distributie of als 2-3 kleine verworven laesies gelokaliseerd in een non-segmentaal gebied van maximaal 5 cm. We hebben 128 geschikte patiënten gevonden en het responspercentage was 40,6% (n = 52 voltooide vragenlijsten). De mediane follow-up duur was 7 jaar. In 23% van de gevallen was progressie naar non-segmentale vitiligo opgetreden. In 11,5% van deze patiënten trad de progressie naar non-segmentale vitiligo op binnen 2 jaar na het ontstaan van de ziekte. Desalniettemin, zelfs na een initiële stabiele fase van meer dan 2 jaar, ontwikkelde nog eens 11,5% van de patiënten uiteindelijk non-segmentale vitiligo. Wij hebben geen prognostische factoren voor progressie naar non-segmentale of aanhoudende focale vitiligo gevonden. Focale vitiligo ontwikkelde zich in de loop der tijd in sommige gevallen wel in non-segmentale vitiligo, maar niet in segmentale vitiligo. Resumerend, focale vitiligo is een zeldzaam subtype van vitiligo en de meeste patiënten hebben aanhoudende focale vitiligo na het ontstaan van de ziekte. Er lijken geen klinische kenmerken te zijn die progressie in focale vitiligo kunnen voorspellen.

Hoofdstuk 3.1 – Ontwikkeling en validatie van de Vitiligo Extent Score (VES): een internationale samenwerking.

De klinische beoordeling van vitiligo omvat een schatting van het aangedane lichaamsoppervlakte. De meest gebruikte methode is de 1%-handpalm regel, welke geïntegreerd is in de Vitiligo Area Scoring Index. Echter, deze methode is ingewikkeld in gebruik en tijdrovend. In hoofdstuk 3.1 hebben wij een nieuw meetinstrument geïntroduceerd: de Vitiligo Extent Score (VES). In het eerste deel van de studie hebben wij

de VES ontwikkeld en geoptimaliseerd in een proefscoringssessie. In de daaropvolgende fase is de betrouwbaarheid van de VES tussen en binnen beoordelaars getest. Het scoren van live patiënten toonde een excellente tussenbeoordelaarsbetrouwbaarheid voor de VES (intraclass correlatie VES: 0,924 vs. Vitiligo Area Scoring Index: 0,846). Het scoren op foto's was vergelijkbaar met de live evaluatie en demonstreerde een excellente binne nbeoordelaarsbetrouwbaarheid. Een hoge intraclass correlatie voor de VES (intraclass correlatie VES: 0,923 vs. Vitiligo Area Scoring Index: 0,757) werd ook gevonden in een additionele subgroep met patiënten die uitgebreide vitiligo hadden. Bovendien werden de gebruikersvriendelijkheid en timing als goed beoordeeld. Met de VES kunnen we dus gemakkelijk en accuraat op een gestandaardiseerde manier de hoeveelheid aangedaan lichaamsoppervlakte monitoren. Daarnaast laten onze resultaten zien dat de VES een veelbelovend meetinstrument is om de uitgebreidheid van vitiligo te meten in klinisch onderzoek en in de dagelijkse praktijk.

Hoofdstuk 3.2 – Ontwikkeling en validatie van een patiënt-gerapporteerde uitkomstmaat in vitiligo: de Self Assessment Vitiligo Extent Score (SA-VES).

De Vitiligo Extent Score (VES) is geïntroduceerd in hoofdstuk 3.1 als een nieuwe klinische score voor artsen om de uitgebreidheid van vitiligo te meten, maar een goed meetinstrument voor zelfevaluatie voor patiënten ontbrak tot op heden. Het doel van hoofdstuk 3.2 was om een gesimplificeerde versie van de VES als patiëntgerapporteerde uitkomstmaat te ontwikkelen en valideren. Na een uitgebreide testfase werden patiënten gevraagd om de uitgebreidheid van hun vitiligo twee keer te scoren met een interval van 2 weken met behulp van de Self Assessment Vitiligo Extent Score (SA-VES). Wij hebben deze scores vergeleken met de scores van de arts (VES). De SA-VES toonde een zeer goede binnenbeoordelaarsbetrouwbaarheid (intraclass correlatie = 0,948; 95%-betrouwbaarheidsinterval: 0,911-0,970) welke niet beïnvloed werd door leeftijd, huidtype of distributie patroon. Volgens patiënten was de SA-VES gemakkelijk tot zeer gemakkelijk in gebruikt (22% zeer gemakkelijk; 49% gemakkelijk; 29% normaal) en voor het grootste deel van de patiënten vergde het <5 minuten om de SA-VES in te vullen (73%, <5 minuten; 24%, 5-10 minuten; 2%, 10-15 minuten). Vergelijking van de SA-VES en VES liet een excellente correlatie zien (r = 0,986, P < 0,001). Beperking van de studie is dat weinig patiënten zijn geïncludeerd die een donker huidtype hadden. De resultaten van hoofdstuk 3.2 demonstreren een excellente betrouwbaarheid van de SA-VES en een excellente correlatie met het door artsen gerapporteerde equivalent (VES). Deze patiënt-georiënteerde evaluatie methode is een bruikbaar instrument om de uitgebreidheid van vitiligo te meten.

Hoofdstuk 3.3 – Prospectieve evaluatie van de responsiviteit van de Vitiligo Extent Score (VES) en de Self Assessment Vitiligo Extent Score (SA-VES).

De VES and SA-VES zijn valide en betrouwbare meetinstrumenten om de uitgebreidheid van vitiligo te meten. In hoofdstuk 3.3 hebben wij prospectief de responsiviteit van de VES en SA-VES tijdens 6 maanden van NBUVB-lichttherapie onderzocht. We hebben 30 patiënten geïncludeerd met vitiligo en hen 6 maanden gevolgd tijdens behandeling met NBUVB. Patiënten werden voor en 6 maanden na start van de NBUVB-lichttherapie gevraagd om een vragenlijst in te vullen betreffende patiëntkarakteristieken, de SA-VES en de verbetering na behandeling. Eén onafhankelijke vitiligo expert heeft de VES op foto's van voor en 6 maanden na NBUVB-behandeling beoordeeld. Het beoordelen van de responsiviteit was gebaseerd op het testen van hypotheses; wanneer 75% of meer van de hypotheses werden bevestigd zouden de VES en SA-VES gekenmerkt worden als responsief. Na 6 maanden van NBUVB hebben wij 24 patiënten terug gezien en hen geïncludeerd in de data-analyse. Mediane leeftijd was 42 jaar (interkwartielafstand (IQR): 38-57) en 33% van de patiënten was man. De mate van depigmentatie bij inclusie was 2,6% (mediaan, IQR: 1,0-8,6%) en repigmentatie na 6 maanden van follow-up was 29,1% (mediaan, IQR: 15,0-43,4%). We hebben ≥ 75% van de hypotheses van zowel de VES als de SA-VES kunnen bevestigen. De belangrijkste beperking van deze studie is het lage aantal geïncludeerde patiënten. De responsiviteit van de VES en SA-VES is veelbelovend en verder onderzoek in een grotere patiëntenpopulatie is nodig om onze resultaten te kunnen bevestigen.

Hoofdstuk 3.4 – Pilotonderzoek naar de validiteit en betrouwbaarheid van een nieuwe patiënt-gerapporteerde uitkomstmaat in vitiligo: de Vitiligo Cosmetic Acceptability Scale (VICAS).

Cosmetische aanvaardbaarheid van repigmentatie is gekenmerkt als een van de kernuitkomst domeinen in vitiligo. Desalniettemin is er nog geen meetinstrument beschikbaar om dit belangrijke domein te meten. In hoofdstuk 3.4 hebben we de validiteit en betrouwbaarheid getest van een nieuw instrument die de cosmetische aanvaardbaarheid van repigmentatie meet in vitiligo: de Vitiligo Cosmetic Acceptability Scale (VICAS). De VICAS bestaat uit één vraag 'Hoe tevreden bent u met het cosmetisch aspect van uw repigmentatie?' en wordt beantwoord op een 5-punts schaal (zeer ontevreden tot zeer tevreden). We hebben 30 patiënten met non-segmentale vitiligo geïncludeerd en na 26 weken van NBUVB-lichttherapie hebben we 26 patiënten geïncludeerd voor data-analyse. Het mediane aangedane lichaamsoppervlakte bij inclusie was 6% (IQR: 3-12%) en 19% mediane repigmentatie (IQR: -15–46%) werd

gevonden na 6 maanden. Het meten van de constructvaliditeit berustte op het testen van hypotheses en wanneer ≥ 75% of hypotheses werden bevestigd zouden we de VICAS kenmerken als een valide meetinstrument. Echter hebben we maar 1 van de 4 hypotheses kunnen bevestigen in hoofdstuk 3.4. De binnenbeoordelaarsbetrouwbaa rheid was redelijk (κ=0.391, week 26 vs. week 28) en voor 37% van de patiënten was de VICAS gemakkelijk tot zeer gemakkelijk in gebruik. De VICAS is dus een redelijk betrouwbaar meetinstrument. Daarentegen, werd de validiteit van de VICAS niet bevestigd en blijft het onduidelijk of de VICAS een bruikbaar meetinstrument is om de cosmetische aanvaardbaarheid van repigmentatie te meten in vitiligo. Verdere consensus is nodig om te bepalen of en hoe we cosmetische aanvaardbaarheid zouden moeten meten.

Hoofdstuk 4.1 – Vragenlijststudie met twintig jaar follow-up van vitiligo op kinderleeftijd behandeld met NBUVB.

NBUVB is een effectieve behandeloptie in vitiligo op kinderleeftijd. Tot op heden is er geen data beschikbaar over de lange-termijn effectiviteit en veiligheid van NBUVB in vitiligo op kinderleeftijd. In hoofdstuk 4.1 hebben we een lange-termijn follow-up vragenlijststudie gedaan in 51 kinderen met non-segmentale vitiligo die hadden deelgenomen aan een eerder prospectief klinisch onderzoek van 20 jaar geleden waarin zij werden behandeld met NBUVB voor een maximale periode van 1 jaar. Van de 51 patiënten die hadden deelgenomen in het eerste onderzoek, hebben in totaal 18 patiënten een ingevulde vragenlijst teruggestuurd. Mediane follow-up duur was 20 jaar en mediane huidige leeftijd was 32 jaar. Het huidige aangedane lichaamsoppervlakte was lager dan voor inclusie in de eerste studie. In hoofdstuk 4.1 heeft alleen een klein percentage van de patiënten (22%) geen additionele behandeling gehad na de eerste studie en deze patiënten hadden een lager aangedaan lichaamsoppervlakte dan de patiënten die additionele therapie hadden gehad na de eerste studie (0,6% vs. 5,3%, respectievelijk). Dit zou kunnen betekenen dat in een klein aantal van de gevallen, de vitiligo niet gereactiveerd was of alleen langzaam vorderde na de eerste NBUVB-lichttherapie. Geen van de patiënten rapporteerde het ontstaan van melanoom of niet-melanoom huidkanker. Beperkingen van de studie in hoofdstuk 4.1 zijn de kleine populatiegrootte, retrospectieve ongecontroleerde studieopzet en het lage responspercentage. Onze resultaten doen vermoeden dat NBUVB een veilige en effectieve behandeloptie zou kunnen zijn in vitiligo op kinderleeftijd en dat het in sommige gevallen eventueel het ziektebeloop kan veranderen.

Hoofdstuk 4.2 – Autologe celsuspensietransplantatie in segmentale vitiligo en piebaldisme: een gerandomiseerd gecontroleerd onderzoek naar CO_2-laservoorbehandeling van het volledige oppervlakte en fractionele CO_2-laservoorbehandeling van de receptorplek.

Autologe niet-gekweekte celsuspensietransplantatie is een effectieve behandeling voor repigmentatie in segmentale vitiligo en piebaldisme. Laserablatie van de volledige oppervlakte is een frequent gebruikte methode als voorbehandeling van de receptorplek voor celsuspensietransplantatie, desondanks zijn de optimale laserinstellingen en ablatiediepte niet bekend. Het doel van hoofdstuk 4.2 was om de effectiviteit en veiligheid van minder invasieve voorbehandelingen van de receptorplek te onderzoeken. In een gerandomiseerd, beoordelaargeblindeerd, gecontroleerd onderzoek hebben we verschillende voorbehandelingen voor celsuspensietransplantatie vergeleken in segmentale vitiligo en piebaldisme. In elke patiënt hebben we drie CO_2-laservoorbehandelingen (i.e. 209 en 144 µm volledige oppervlakte ablatie en fractionele ablatie) en een controleplek (geen voorbehandeling) gerandomiseerd toegewezen aan vier depigmentaties. Na 6 maanden hebben we de repigmentatie en bijwerkingen bekeken. We hebben 10 patiënten met segmentale vitiligo (n=3) en piebaldisme (n=7) geïncludeerd. Vergeleken met de controleplek, hebben we meer repigmentatie gevonden na 209 µm (mediaan 68,7%, p=0,01) en 144 µm (mediaan 58,3%, p=0,007) ablatie van het volledige oppervlakte, maar geen repigmentatie na fractionele ablatie (mediaan 0,0 %, p=0,14). Resumerend is dus superficiële volledige oppervlakte ablatie met een CO_2-laser met een diepte van 144 µm een effectieve voorbehandeling voor celsuspensietransplantatie, maar fractionele CO_2-laser niet.

Hoofdstuk 4.3 – De rol van lichttherapie in de chirurgische behandeling van vitiligo: een systematische review.

Vitiligo wordt frequent behandeld met de combinatie van lichttherapie en melanocytentransplantatie. Desalniettemin is het additionele voordeel van lichttherapie onduidelijk. Bovendien is het optimale type en regime van lichttherapie niet bekend. Het doel van de systematische review in hoofdstuk 4.3 was om te identificeren of lichttherapie de uitkomst na melanocytentransplantatie verbeterd. We hebben gezocht in en de geschikte studies geselecteerd uit de databases van MEDLINE, EMBASE en CENTRAL. We hebben alle klinische onderzoeken geïncludeerd die hebben gekeken naar melanocytentransplantatie in combinatie met lichttherapie. Na screening en selectie van de abstracts en de gehele tekst, hebben we 39 geschikte klinische studies

met 1624 patiënten gevonden. De geschikte studies hebben gekeken naar verschillende lichttherapie modaliteiten, zoals NBUVB (n=9), psoralenen gecombineerd met ultraviolet A (PUVA, n=19), ultraviolet A (UVA, n=1), monochromatisch excimer licht of laser (MELi of MELa, n=4) en actieve zonlicht blootstelling (n=9). Vier studies hebben direct lichttherapie versus geen lichttherapie vergeleken en twee studies bevestigden het voordeel van lichttherapie na melanocytentransplantatie. We hebben geen significante verschillen in repigmentatie gevonden in de studies die de verschillende lichttherapie modaliteiten direct hebben vergeleken. De algehele kwaliteit van de studies was matig tot slecht en we vonden een hoge heterogeniteit tussen de studies. We hebben beperkt bewijs gevonden dat lichttherapie de uitkomst van melanocytentransplantatie in vitiligo verbetert. Er is onvoldoende bewijs om een specifieke lichttherapie modaliteit of regime aan te bevelen. Meer studies zouden moeten worden uitgevoerd om het additionele voordeel van de verschillende lichttherapieën en het aangewezen moment van lichttherapie te onderzoeken.

ADDENDUM

LIST OF CONTRIBUTING AUTHORS

Dr. H.E. Teulings
Department of Dermatology and Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Dr. A. Wolkerstorfer
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Drs. L. Nieuweboer-Krobotova
Zuwe Hofpoort Hospital, Woerden, the Netherlands

Prof. dr. R.M. Luiten
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Dr. M.W. Bekkenk
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Dr. J.P.W van der Veen
Medisch Centrum Haaglanden, The Hague , the Netherlands.

Dr. K. Ezzedine
Epidémiologie en Dermatologie et Evaluation des Thérapeutiques, UPE-Université Paris-Est, Service de Dermatologie, Hôpital Henri Mondor, Paris, France

Prof. dr. N. Van Geel
Department of Dermatology, Ghent University Hospital, Ghent, Belgium

Dr. A. Hartmann
Department of Dermatology, University of Erlangen, Erlangen, Germany

Dr. R. Speeckaert
Department of Dermatology, Ghent University Hospital, Ghent, Belgium

Prof. dr. P.I. Spuls
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Y. Schilder
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Prof. dr. M.A. de Rie
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Dr. C.A.C. Prinsen
VU University Medical Center, Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, Amsterdam, The Netherlands

Dr. V. Eleftheriadou
Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, United Kingdom

Dr. A. Taïeb
National Reference Center for rare skin diseases, Hoˆpital St-Andre´, University Hospital Center of Bordeaux, Bordeaux, France

Dr. M. Picardo
San Gallicano Dermatology Institute, Via Elio Chianesi, Roma, Italy

Dr. M.D. Njoo
Department of Dermatology, Ziekenhuisgroep Twente, Almelo/Hengelo, The Netherlands.

Drs. A.A. Meesters
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Dr. L. Komen
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Drs. S.E. Uitentuis
Department of Dermatology and the Netherlands Institute for Pigment Disorders, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

CONTRIBUTION OF THE AUTHORS PER ARTICLE

Vitiligo-like depigmentations as the first sign of melanoma: a retrospective case series from a tertiary vitiligo centre.

H.E. Teulings: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.

J.E. Lommerts: analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

A. Wolkerstorfer: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

L. Nieuweboer-Krobotova: revising the article critically for important intellectual content and final approval of the version to be published.

R.M. Luiten: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

M.W. Bekkenk: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

J.P.W van der Veen: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field.

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.

H.E. Teulings: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published and final approval of the version to be published.

K. Ezzedine: contributions to acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.
N. van Geel: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
A. Hartmann: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
R. Speeckaert: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
P.I. Spuls: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.
R.M. Luiten: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.
M.W. Bekkenk: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

Focal vitiligo: long-term follow-up of 52 cases.

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.
Y. Schilder: contributions to acquisition of data and final approval of the version to be published.
M.A. de Rie: revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to design, revising the article critically for important intellectual content and final approval of the version to be published.
M.W. Bekkenk: contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative.

N. van Geel: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

M.W. Bekkenk: contributions to conception and design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.

A. Wolkerstorfer: contributions to conception and design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.

C.A.C. Prinsen: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.

V. Eleftheriadou: revising the article critically for important intellectual content and final approval of the version to be published.

A. Taieb: revising the article critically for important intellectual content and final approval of the version to be published.

M. Picardo: revising the article critically for important intellectual content and final approval of the version to be published.

K. Ezzedine: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.

R. Speeckaert: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES).

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

N. van Geel: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.
M.W. Bekkenk: contributions to conception and design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to conception and design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
C.A.C. Prinsen: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.
V. Eleftheriadou: revising the article critically for important intellectual content and final approval of the version to be published.
A. Taieb: revising the article critically for important intellectual content and final approval of the version to be published.
M. Picardo: revising the article critically for important intellectual content and final approval of the version to be published.
K. Ezzedine: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
R. Speeckaert: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.
Prospective evaluation of the responsiveness of the Vitiligo Extent Score (VES) and Self Assessment Vitiligo Extent Score (SA-VES).
J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author
M.W. Bekkenk: contributions to revising the article critically for important intellectual content and final approval of the version to be published.
R. Speeckaert: contributions to analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.
N. van Geel: contributions to conception, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

A. Wolkerstorfer: contributions to conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.
C.A.C. Prinsen: contributions to design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Pilot study on the validity and reliability measurement of a new patient reported outcome measure in vitiligo: the Vitiligo Cosmetic Acceptability Scale (VICAS).

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author
M.W. Bekkenk: contributions to revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Twenty year follow-up using a postal survey of childhood vitiligo treated with narrowband ultraviolet-B phototherapy.

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.
M.D. Njoo: contributions to acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published. Corresponding author
M.A. de Rie: revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to design, revising the article critically for important intellectual content and final approval of the version to be published.
M.W. Bekkenk: contributions to conception and design, interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomised controlled trial comparing full-surface and fractional CO_2 laser recipient site preparations.

J.E. Lommerts: contributions to design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.
A.A. Meesters: contributions to design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
L. Komen: contributions to conception and design, revising the article critically for important intellectual content and final approval of the version to be published.
M.W. Bekkenk: contributions to design, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published.
M.A. de Rie: contributions to design, revising the article critically for important intellectual content and final approval of the version to be published.
R.M. Luiten: contributions to design, revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

The role of phototherapy in the surgical treatment of vitiligo: a systematic review.

J.E. Lommerts: contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. Corresponding author.
S.E. Uitentuis: contributions to acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.
M.W. Bekkenk: revising the article critically for important intellectual content and final approval of the version to be published.
M.A. de Rie: revising the article critically for important intellectual content and final approval of the version to be published.
A. Wolkerstorfer: contributions to design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published.

BIBLIOGRAFIE

Lommerts JE, Teulings HE, Ezzedine K *et al.* Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field. *Journal of the American Academy of Dermatology* 2016; **75**: 1198-204.

Lommerts JE, Schilder Y, de Rie MA *et al.* Focal vitiligo: long-term follow-up of 52 cases. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2016; **30**: 1550-4.

van Geel N, Lommerts J, Bekkenk M *et al.* Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *The Journal of investigative dermatology* 2016; **136**: 978-84

Lommerts A. Vitiligo: een update. *Nederlands Tijdschrift voor Dermatologie en Venereologie* 2016; **26**: 149-54.

Lommerts JE, Njoo MD, de Rie MA *et al.* Twenty-year follow-up using a postal survey of childhood vitiligo treated with narrowband ultraviolet B phototherapy. *The British Journal of Dermatology* 2017; **177**: e60-e

Lommerts JE, Meesters AA, Komen L *et al.* Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomised controlled trial comparing full-surface and fractional CO2 laser recipient site preparations. *The British Journal of Dermatology* 2017; **177**:1293-1298

van Geel N, Lommerts JE, Bekkenk MW *et al.* Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES). *Journal of the American Academy of Dermatology* 2017; **76**: 464-71

Teulings HE, Lommerts JE, Wolkerstorfer A *et al.* Vitiligo-like depigmentations as the first sign of melanoma: a retrospective case series from a tertiary vitiligo centre. *The British journal of dermatology* 2017; **176**: 503-6

van Geel N, Boniface K, Seneschal J *et al.* Meeting report: Vitiligo Global Issues Consensus Conference Workshop "Outcome measurement instruments" and Vitiligo International Symposium, Rome, Nov 30-Dec 3rd. *Pigment cell & melanoma research* 2017; **30**: 436-43.

Eggen CAM, Lommerts JE, van Zuuren EJ *et al.* Laser treatment of congenital melanocytic nevi: a systematic review. *The British Journal of Dermatology* 2017, **Epub**

van Geel N, Wolkerstorfer A, Lommerts JE *et al*. Validation study of the Vitiligo Extent Score-plus (VESplus). *Journal of the American Academy of Dermatology* 2017; **Epub**

van Geel N, Bekkenk M, Lommerts JE *et al*. The Vitiligo Extent Score (VES) and the VESplus are responsive instruments to assess global and regional treatment response in patients with vitiligo. *Journal of the American Academy of Dermatology* 2018; **Epub**

PHD PORTFOLIO

Name PhD-student	Janny Elizabeth Lommerts
PhD Period	October 2014 – June 2018
Promotores	Prof. dr. M.A. de Rie
	Prof. dr. R.M. Luiten
Co-promotores	dr. A. Wolkerstorfer
	dr. M.W. Bekkenk

1. PhD Training

	Year	ECTS
General courses		
Basic Course Legislation and Organization for Clinical Researchers (BROK)	2014	0.9
Practical Biostatistics	2015	1.1
Scientific Writing in English for Publication	2016	1.5
Clinical data management	2016	0.3
	Total	**3.8**

Seminars, workshops and masterclasses		
Weekly scientific meeting of department	2014-2018	3
Masterclass Medical Business	2016	0.6
	Total	**3.6**

Presentations		
Annual meeting American Academy of Dermatology, Washington, U.S.A. *Oral presentation:* Melanoma-associated vitiligo or vitiligo?	2016	0.5
Annual meeting Dutch Society for Experimental Dermatology, Lunteren, The Netherlands *Poster presentation:* Vitiligo Extent Score (VES): reliability of a new measurement tool in vitiligo.	2016	0.5
Annual Skin Regeneration Symposium, Cambridge, U.K. *Oral presentation:* ReCell in vitiligo and piebaldism patients: preliminary data of RCT on the recipient site preparation.	2016	0.5
Annual meeting European Academy of Dermatology and Venereology, Vienna, Austria *Oral poster presentation:* It is difficult to differentiate between melanoma-associated leukoderma and vitiligo: an image comparison study by experts in the field.	2016	0.5

Vitiligo International Symposium, Rome, Italy *Oral presentation:* The role of phototherapy in the surgical treatment of vitiligo: a systematic review.	2016	0.5
Vitiligo International Symposium, Rome, Italy *Poster presentation:* Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomized controlled trial on the recipient site preparation.	2016	0.5
International Pigment Cell Conference, Denver, U.S.A. *Oral presentation:* VItiligo Cosmetic Acceptability Scale (VICAS): preliminary results on the validity and reliability of a new measurement tool to measure the cosmetic acceptability in vitiligo.	2017	0.5
International Pigment Cell Conference, Denver, U.S.A. *Oral presentation:* Laser treatment of congenital melanocytic nevi: a systematic review.	2017	0.5
International Pigment Cell Conference, Denver, U.S.A. *Poster presentation:* Melasma Extent Score (MES): development, validation and reliability testing of a new outcome measure in melasma.	2017	0.5
International Pigment Cell Conference, Denver, U.S.A. *Poster presentation:* Autologous cell suspension grafting in segmental vitiligo and piebaldism: a randomized controlled trial on the recipient site preparation.	2017	0.5
International Pigment Cell Conference, Denver, U.S.A. *Poster presentation:* Prospective measurement of the responsiveness of the Vitiligo Extent Score (VES) and Self-Assessment VES (SA-VES) during NB-UVB therapy in vitiligo patients.	2017	0.5
	Total	**6.0**

(Inter)national conferences		
Annual meeting European Academy of Dermatology and Venereology, Amsterdam, The Netherlands	2014	1.0
Annual meeting Dutch Society for Experimental Dermatology, Lunteren, The Netherlands	2015	0.5
Annual meeting Dutch Society for Experimental Dermatology, Lunteren, The Netherlands	2016	0.5
Annual meeting American Academy of Dermatology, Washington, U.S.A.	2016	1.25
Annual Skin Regeneration Symposium, Cambridge, U.K.	2016	0.75
Annual meeting European Academy of Dermatology and Venereology, Vienna, Austria	2016	1.0
Vitiligo International Symposium, Rome, Italy	2016	0.75
International Pigment Cell Conference, Denver, U.S.A.	2017	1.25
Annual Cochrane Skin Group Meeting 2018, Amsterdam, the Netherlands	2018	0.5
	Total	**7.5**

2. Teaching

Supervising master student for master thesis, Y. Schilder, Vrije Universiteit	2015	1.0
Supervising master student for master thesis, P. Smeets, Vrije Universiteit	2016	1.0
	Total	**2.0**

3. Parameters of esteem – Awards

Award for best poster presentation, Annual meeting Dutch Society for Experimental Dermatology, 2016, Lunteren, The Netherlands
Travel grant, International Pigment Cell Conference, 2016, Denver, U.S.A.

CURRICULUM VITAE

Janny Elizabeth (Annelies) Lommerts is geboren op 19 januari 1990 te Arnhem. De lagere schooltijd bracht zij deels door in Dieren en deels in Heerhugowaard. In 2001 ging zij naar het Murmellius Gymnasium in Alkmaar, waar zij in 2007 haar eindexamen behaalde. Na het succesvol afronden van de propedeuse Farmacie aan de Rijks Universiteit Groningen, is zij in 2008 gestart met de opleiding geneeskunde aan de Vrije Universiteit in Amsterdam. Tijdens de co-schappen werd de interesse voor dermatologie gewekt, waarna zij in 2014 een semi-arts stage heeft afgerond bij de afdeling Dermatologie in het St. Antonius Ziekenhuis in Nieuwegein. Hierop volgde een wetenschappelijke stage aan het Nederlands Instituut voor Pigmentstoornissen (SNIP) onder begeleiding van dr. A. Wolkerstorfer. In 2014 is zij gestart met haar promotieonderzoek naar vitiligo onder begeleiding van prof. R.M. Luiten, prof. M.A. de Rie, dr. M.W Bekkenk en dr. A. Wolkerstorfer. Tijdens dit promotietraject, werkte zij ook als basisarts in het Nederlands Instituut voor Pigmentstoornissen (SNIP). In oktober 2016 startte zij haar opleiding tot Dermatoloog onder begeleiding van dr. J.R Mekkes in het Academisch Medisch Centrum.

DANKWOORD

Dit proefschrift was niet tot stand gekomen door de bijdrage van enkele belangrijke personen. Ondanks dat een van mijn stellingen luidt: 'Nait soezen, moar broezen' (vrij vertaald geen woorden maar daden); wil ik toch graag stil staan bij het bedanken van deze personen.

Beste *prof. dr. M.A. de Rie*, beste *Menno*, bedankt dat u als promotor mijn promotietraject in goede banen heeft willen leiden. Ik heb uw opmerkingen tijdens mijn thesis-besprekingen als zeer waardevol ervaren en doordat u wat meer afstand had van het onderwerp maakte dit het ook erg inzichtelijk.

Beste *prof. dr. R.M. Luiten*, beste *Rosalie*, ik wil u bedanken voor uw kritische feedback en dat ik hierdoor mijn proefschrift naar een hoger niveau heb kunnen tillen. Dank voor de nuttige opmerkingen en tips tijdens de pigmentbijeenkomsten, congressen en thesisbesprekingen.

Beste *dr. A. Wolkerstorfer* en *dr. M.W. Bekkenk*, beste *Albert* en *Marcel*, op inhoudelijk vlak had ik zeker geen betere co-promotoren kunnen wensen. Ik wil jullie beiden bedanken voor het vertrouwen in mij en de tijdsinvestering in het begeleiden van mijn promotietraject. Beste *Albert*, jouw enthousiasme omtrent het onderzoek hebben mijn interesse en plezier in onderzoek doen aangewakkerd en dit heeft ook zeker een bijdrage geleverd aan de snelheid van het afronden van mijn proefschrift. Beste *Marcel*, bedankt dat je deur altijd open staat voor een praatje. Jouw enthousiasme en rechtlijnigheid hebben mij tijdens het onderzoek zeer geholpen en gestimuleerd.

Ook de overige leden van mijn promotiecommissie, *prof. dr. P.I. Spuls, prof. dr. R. Hoekzema, prof. dr. H.J.C. de Vries, prof. dr. W. Bergman* en *dr. M.M.C. Leeflang,* wil ik graag bedanken voor het kritisch beoordelen van mijn proefschrift en deelname aan mijn commissie. Dear *prof. dr. T Passeron*, thank you for participating in my defence committee and for your important work in the research of pigment disorders.

Beste *prof. dr. N. Van Geel* en *dr. R. Speeckaert*, beste *Nanja* en *Reinhart*, vanaf het begin van mijn promotie hebben we samen gewerkt aan de studies naar de nieuwe meetinstrumenten in vitiligo. Ik wil jullie beiden zeer bedanken voor de mogelijkheid die jullie me hebben gegeven om hieraan deel te nemen. Ook bedankt voor de samenwerking en gezellige scoringsmeetings in Gent en Amsterdam.

Beste *dr. H.E. Teulings*, *dr. J.P.W. van der Veen*, *dr. I. Nieuweboer-Krobotova* en *dr. M.D. Njoo*, bedankt voor deelname en waardevolles bijdrages aan de studies. Dear *dr. K. Ezzedine, dr. A. Hartmann, dr. V. Eleftheriadou, dr. A. Taieb* and *dr. M. Picardo*, thank you for actively contributing to the studies and for the inspirational work in the field of vitiligo-research. Beste *dr. C.A.C. Prinsen*, beste *Sanna*, bedankt voor je kritische blik en bijdrage aan de meetinstrument-studies. Ik heb veel geleerd van je feedback op de studies.

Beste *Arne, Karien* en *Lisa*, vanaf het moment dat ik bij jullie op de onderzoekskamer kwam voelde ik me welkom. Bedankt voor jullie enthousiasme, tips over het onderzoek en de gezellige momenten. Beste *Karina* en *Gabrielle*, bedankt voor jullie hulp bij het opzetten en uitvoeren van de cel suspensie transplantatie studie. Ook jullie bedankt voor de tips en feedback. Beste *Sanne*, bedankt voor je deelname aan de systematische review. Ik heb met een gerust hart mijn werkplek op de onderzoekskamer aan je overgedragen en heb er alle vertrouwen in dat jij jouw promotietraject naar vitiligo met vlag en wimpel gaat volbrengen. Beste *collega-onderzoekers* en *mede-AIOS*, ik wil jullie graag bedanken voor jullie interesse in mijn onderzoek, nuttige tips en de gezellige momenten.

Beste *dr. J.R. Mekkes* en *andere dermatologen* van het AMC, bedankt dat jullie mij als AIOS hebben opgenomen in jullie opleidingsgroep. Ik ben ook zeer dankbaar voor de flexibiliteit en ruimte die ik heb gekregen om mijn proefschrift te voltooien.

Beste *Bernice, Carmen* en *Mariska*, bedankt voor jullie administratieve hulp bij het voltooien van mijn proefschrift en bedankt voor de gezellige gesprekken. Beste *Selma* en *ander ondersteunend personee*l van de afdeling dermatologie van het AMC, bedankt voor jullie interesse en medewerking aan enkele studies van mijn proefschrift. Beste *Yvonne* en *Philippe*, bedankt voor jullie bijdrage aan de studies en dat jullie bij mij jullie wetenschappelijke stage hebben gelopen.

Lieve *familie, schoonfamilie* en *vrienden*, ondanks dat ik niet met iedereen vaak inhoudelijk over mijn promotieonderzoek heb gepraat, heb ik toch de laatste periode veel steun en lieve woorden van jullie mogen ontvangen en ik wil jullie hiervoor bedanken, Lieve *Sarah* en *Berdien,* bedankt voor jullie hulp als paranimfen tijdens de laatste fase van mijn promotie en de ondersteuning tijdens deze bijzondere dag.

Lieve *oma Olsder*, de afgelopen paar jaar heeft u meerdere keren gevraagd wanneer ik nou eens ging promoveren en nu is het eindelijk zo ver. U houdt er erg van om op te scheppen over al uw kleinkinderen tegenover uw huisgenoten, dus ik hoop erg dat u er bij kan zijn tijdens mijn promotie zodat u weer een beetje kan opscheppen.

Lieve *Evan*, lieve zwager, bedankt voor je humor en gezelligheid. Lieve *Felize* en *Annalua*, ook al zijn jullie nog klein, ik wil jullie bedanken voor de vreugde die jullie mij brengen als ik op jullie mag passen.

Lieve *Bruno*, lieve broer, bedankt dat je me hebt geleerd om altijd buiten mijn eigen referentiekader te denken en bedankt dat wij als gezin door jou onze grenzen hebben verlegd.

Lieve *Berdien*, lieve zus, je bent een inspiratie voor mij als hardwerkende liefdevolle moeder. Ik ben erg trots op jou hoe je naast je succesvolle carrière ook nog eens een hele succesvolle mama bent. Als zus wil ik je graag bedanken voor je onvoorwaardelijke steun, lieve woorden en interesse in mijn onderzoek.

Lieve *mama*, wat ben je een topvrouw. Ik vind het zo knap hoe jij in je eentje je bedrijf hebt opgezet en met jouw werk vele mensen over de hele wereld hiermee kan helpen. Je bent echt een voorbeeld voor velen en ook zeker voor mij. Bedankt dat je altijd voor mij klaar staat en dat je me hebt geleerd dat je hard moet werken om dingen te bereiken.

Lieve *papa*, wat lijk ik toch veel op jou. Naast uiterlijk (valt nog over te twisten), maar ook zeker in karakter. Ik weet nog goed dat ik als vierjarige in 1994 bij jouw promotie mocht zijn, wat vond ik dit spannend en nu sta ik er zelf! Bedankt dat ik altijd bij je terecht kan met moeilijke vraagstukken en dat je mij aanspoort om mijn passies achterna te gaan.

Lieve *papa* en *mama*, bedankt dat jullie het mogelijk hebben gemaakt dat wij veel van onze dromen hebben kunnen realiseren en dat jullie er altijd voor ons zijn.

Lieve *Wim*, bedankt voor je eindeloze geduld en relativeringsvermogen. Zonder jou had ik dit boekje nooit af kunnen maken. Je bent altijd zo ontzettend lief en begripvol voor me geweest als ik weer eens in de stress zat of tot laat met mijn onderzoek bezig was. Bedankt dat je mij scherp houdt en dat je me aan het lachen maakt. Ik kijk heel erg uit naar onze toekomst samen, ik heb je lief.