Coloring the spots

*Diagnosis, measurement instruments and treatment in vitiligo*

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**Citation for published version (APA):**

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INTRODUCTION
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. The name vitiligo is probably derived from the Latin word for defect (vitium).

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

**BURDEN OF THE DISEASE**

Vitiligo is a disfiguring asymptomatic disease, although itch has been reported as a rare symptom. 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 and lower than in healthy controls. Different factors contributing to this impairment in quality of life have been described, such as female gender, extent of vitiligo, darker skin types and localization of the depigmented lesions on visible areas. Furthermore, impairment in quality of life in vitiligo patients also appears to be associated with perceived stigmatisation. 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. Furthermore, patients with vitiligo also face several psychosocial difficulties, such as problems in sexual function, sleep disturbances, anxiety and lowered self-esteem. Therefore, vitiligo should not be considered as a cosmetic disease, but as a disfiguring and psychologically devastating skin disease that requires medical treatment.

**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. 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. 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. Recent genome-wide association studies have identified 50 genetic loci that contribute to the risk on developing vitiligo. 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. The autoimmune 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. Several provoking factors for vitiligo have been identified, such as exposure to chemical products containing phenols and skin trauma.

The current pathogenesis hypothesis for segmental vitiligo is a somatic mosaicism. 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. 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.

**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).

**Differential diagnosis**

The diagnosis of vitiligo is in most cases straightforward. The main differential diagnoses for vitiligo are other depigmentary or hypopigmentary skin disorders such as piebaldism, pityriasis alba and progressive macular hypopigmentation. An overview of the differential diagnosis of vitiligo with the key features for differentiation from vitiligo can be found in Table 1.
The most alarming differential diagnosis of vitiligo is melanoma-associated leukoderma. 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. The depigmentation in melanoma-associated leukoderma occurs spontaneously before or after the detection of melanoma and most frequently occurs during treatment with immunotherapy. 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. However, in 20.5% of all melanoma-associated leukoderma cases the depigmentation occurs before the diagnosis of melanoma. 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. 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. 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.

**Classification**

Vitiligo is generally divided into 2 subtypes: non-segmental and segmental vitiligo (Figure 1). 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. 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. A third subtype, the undetermined/unclassified type, has recently been defined by the Vitiligo Global Issues Consensus Conference. 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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piebaldism</td>
<td>Midline depigmentation; present at birth; lesions contain islands of normal pigment</td>
<td>Dominantly inherited; other affected family members</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>White forelock, some with depigmented patches</td>
<td>Other stigmata of the syndrome, including hearing loss</td>
</tr>
<tr>
<td>Multiple ash leaf macules of</td>
<td>Multiple, well-demarcated, hypopigmented macules</td>
<td>Other cutaneous signs of TS, epilepsy, and other organ involvement</td>
</tr>
<tr>
<td>tuberous sclerosis (TS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomelanosis of Ito</td>
<td>Blaschkoid hypopigmentation present at birth</td>
<td>May or may not have other stigmata</td>
</tr>
<tr>
<td><strong>Inflammatory conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>Poorly demarcated hypopigmented macules; scale, erythema may be seen; most commonly in children with skin of color</td>
<td>Does not fluoresce with Wood’s lamp; evidence of eczema may be noted</td>
</tr>
<tr>
<td>Postinflammatory hypopigmentation</td>
<td>Poorly demarcated hypopigmentation in an area of previous inflammation; may see primary dermatosis (eg, seborrheic dermatitis, eczema)</td>
<td>Decreased number of melanocytes with or without other inflammatory patterns</td>
</tr>
<tr>
<td>Lichen sclerosus et atrophicus</td>
<td>Typically on genitals; atrophic skin with or without fissures; figure-of-eight pattern surrounding vaginal introitus and anus</td>
<td>Lichenoid inflammation; epidermal atrophy; sparing of melanocytes</td>
</tr>
<tr>
<td>Discoid lupus erythematosis</td>
<td>Head, face, and neck erythematosus, scaly macules and plaques with scarring, dyspigmentation and alopecia</td>
<td>Interface dermatitis with sparing of melanocytes</td>
</tr>
<tr>
<td>Hypopigmented sarcoidosis</td>
<td>Hypopigmented macules or patches; may be other manifestations of sarcoidosis</td>
<td>Histopathology reveals noncaseating granulomas</td>
</tr>
<tr>
<td><strong>Cutaneous malignancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides (hypochromic variant)</td>
<td>Especially seen in skin of color; bathing suit distribution; with/without scale and signs of inflammation</td>
<td>Epidermotropism; atypical lymphocytes</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired progressive macular hypomelanosis</td>
<td>Young adults; trunk (especially lower back and axillae)</td>
<td>Wood’s lamp may reveal <em>P.acnes</em> (pink fluorescence)</td>
</tr>
<tr>
<td>Tinea versicolor</td>
<td>Hypopigmentation; trunk</td>
<td>Positive skin scraping with potassium hydroxide preparation; green fluorescence of untreated lesions</td>
</tr>
</tbody>
</table>
Table 1 - (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprosy (tuberculoid or indeterminate)</td>
<td>Hypopigmented, hypoaesthetic white patches</td>
<td>Skin smear and biopsy specimen reveal <em>Mycobacterium leprae</em></td>
</tr>
<tr>
<td>Pinta (late-stage)</td>
<td>Depigmented lesions, typically on distal extremities or other exposed part of the body</td>
<td>Rapid plasma reagin-positive; spirochetes on dark-field microscopy or histopathology</td>
</tr>
</tbody>
</table>

**Exogenous causes**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic guttate hypomelanosis</td>
<td>Exogenous UV-light exposure causing nonprogressive 1-5 mm hypomelanotic macules in older adults; chronically sun-exposed sites; no leukotrichia</td>
<td></td>
</tr>
<tr>
<td>Trauma-induced hypo- or depigmentation</td>
<td>Geometric shapes and history of trauma or surgical intervention</td>
<td></td>
</tr>
</tbody>
</table>

**Segmental disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus depigmentosus</td>
<td>At birth or first few years of life; grows in proportion to child; usually hypopigmented, has a jagged border, and lacks leukotrichia</td>
<td>Normal number of melanocytes histologically but decreased melanin</td>
</tr>
<tr>
<td>Nevus anaemicus</td>
<td>Presents at birth; mostly on the upper aspect of the chest; poorly demarcated white macule with surrounding erythema</td>
<td>Merges with surrounding skin with diascopy; no accentuation with Wood's lamp examination</td>
</tr>
</tbody>
</table>

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
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.\textsuperscript{66} The aims of treatment in vitiligo are to stop progression of the disease and to induce repigmentation.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{vitiligo_algorithm}
\caption{Treatment algorithm for vitiligo.\textsuperscript{66}}
\end{figure}

TIMS, topical immunomodulators (TIMs); \textsuperscript{*} depending on localisation, \textsuperscript{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.\textsuperscript{67}
Introduction

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). 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. Moreover, phototherapy also has side-effects such as increased risk of skin cancer and premature skin aging. 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. NBUVB is also an effective treatment option in childhood vitiligo. No data are available on the long-term efficacy and safety of NBUVB in childhood vitiligo.

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. 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. 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. 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. 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.
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. 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. The chance of progression of focal vitiligo is not known and no prognostic factors have yet been identified. 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.\textsuperscript{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.\textsuperscript{5,73} The objective of Chapter 4.1 was to assess the long-term outcome after NBUVB in childhood vitiligo.\textsuperscript{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\textsubscript{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.
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