Coloring the spots

Diagnosis, measurement instruments and treatment in vitiligo

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Citation for published version (APA):
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. 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. 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. 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. 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. 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. 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. 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. Patients with long-lasting focal vitiligo showed similar characteristics as non-segmental vitiligo and were mainly located on predilection 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. Stable segmental vitiligo normally responds well to surgical
treatment and patients with long-lasting vitiligo also responded well to surgical treatment. 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. 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. Measurements form the basics of diagnosis, prognosis and evaluation of the results of medical interventions. 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. 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).

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’. Up to this date, the Vitiligo Area Severity Index (VASI) 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) $\geq 0.9$). 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%). 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. 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. 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. 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. 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. A limitation of 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%). 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) 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. 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. 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. 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. Nevertheless, the current consensus is still that cosmetic acceptability of repigmentation should be measured in vitiligo. 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. Phototherapy is added to the topical or systemic immunosuppressant treatment in extensive and rapidly spreading disease. Psoralen plus ultraviolet A phototherapy (PUVA) was the first phototherapy regimen that was used in vitiligo. However, NBUVB is the current phototherapy of choice as it is even effective as PUVA and has a more favorable safety profile. NBUVB has immunosuppressive qualities, and induces melanocyte differentiation and melanin production. It has also been demonstrated that NBUVB is an effective treatment in childhood vitiligo. 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. 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. 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. 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. 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. However, the optimal ablation depth is not known and full surface ablation can lead to persistent side-effects. 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 CO₂ ablation and superficial full surface CO₂ ablation, but no repigmentation after fractional CO₂ 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. In contrast, the necrotic eschar that is produced by the fractional CO₂ 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. 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 CO₂ laser ablation alone in a similar population. We recommend that the recipient site before CST is prepared with superficial full surface ablation. Fractional CO₂ 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. 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.\textsuperscript{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.\textsuperscript{53,54} Recent basis studies have also showed that keratinocytes play a major role in the chemokine production in vitiligo.\textsuperscript{55} Hypothetically, local disruption of the IFN-γ pathway with topical JAK inhibitors could also be an effective treatment.\textsuperscript{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.\textsuperscript{57,58} Recent studies have shown reduced numbers and function of regulatory T-cells in vitiligo.\textsuperscript{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. 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 stakeholders 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.
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