Clinical and patient reported outcomes in vitiligo
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GENERAL INTRODUCTION AND AIMS OF THE THESIS
VITILIGO

Vitiligo is a chronic skin disease, in which white skin patches arise due to loss of pigment-producing melanocytes. This skin disease is common in all races, regardless of age and sex and affects 0.5-1% of the world population.1 The first signs of vitiligo can arise at any age but in 50% of the patients affected, the onset is before the age of 20 years. The most common clinical pattern is the so-called subtype generalized or non-segmental vitiligo.2,3 The Vitiligo European Task Force (VETF) defines non-segmental vitiligo as ‘an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increase in size with time corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes’.4 Other subtypes of vitiligo are localised types, such as segmental, focal and mucosal vitiligo. In some patients, depigmentation spreads over more than 80% of the whole body. This type of vitiligo is known as universal vitiligo.2

Generally, vitiligo does not lead to significant physical morbidity, but vitiligo can have an impact on the quality of life of the patients. Many vitiligo patients, for instance, suffer from psychosocial distress and social stigmatization.5-7 Because skin colour plays a major role in an individual’s perception of health, wealth, worth and desirability, pigment disfigurement may influence social interactions,8 and may even lead to social exclusion. It is for this reason, that vitiligo has been declared to be one of the major medical problems in India.9;10 However, in Western-European countries vitiligo, although associated with other auto-immune diseases,2 is often considered as a harmless, cosmetic skin disorder. The importance of treating vitiligo patients is therefore often underestimated.7;11;12 It is important to recognize and to pay attention to the psychosocial impact of this disease.10

TREATMENT OF VITILIGO

Although vitiligo can as yet not be cured, several treatment options are available. These treatments are intended to reduce disease activity and/or induce repigmentation in existing vitiligo patches, and thereby to improve quality of life.

Narrowband ultra violet B phototherapy (NB-UVB) was introduced in 1997 and is now widely accepted to be the most effective therapy for vitiligo. It has largely replaced the classical ultra violet A phototherapy combined with the photosensitizer psoralen (PUVA) which was less effective and had more side-effects.13 It is assumed that by its immunomodulating effect, NB-UVB inhibits disease activity and promotes melanocyte migration and proliferation.14 In 2002, the 308-nm xenon chloride excimer laser (EL) was introduced as a treatment for vitiligo.15-25 EL was reported to be more effective than NB-UVB treatment.26,27 Another putative advantage of EL over NB-UVB would be the selective targeting which spares non-affected skin and reduces the cumulative UV dose.
Topical therapy with corticosteroids or calcineurin inhibitors can be considered for limited lesions, but is most effective in combination with phototherapy or natural sunlight.\textsuperscript{28,29} Surgical therapies can be considered for stable vitiligo patches that are resistant or respond unsatisfactory to non-surgical therapies due to an insufficient remaining reservoir of melanocytes in these lesions. Melanocyte transplant techniques include suction blister grafting, split-thickness skin grafting, punch grafting and melanocyte cell suspension. In the Netherlands Institute for Pigment Disorders (NIPD) the autologous punch grafting technique is routinely used as a surgical therapy. This technique is relatively simple and has shown to be effective for stable localised and generalized vitiligo.\textsuperscript{30} Punch grafting followed by either EL\textsuperscript{31} or NB-UVB\textsuperscript{32} was found to be effective in inducing repigmentation in vitiligo patients. The efficacy of EL versus NB-UVB after punch grafting in vitiligo patients has not been evaluated.

**OUTCOME MEASURES IN VITILIGO**

The aim of treatment is to induce repigmentation and to achieve a better quality of life. Good clinical measures are essential to measure the efficacy of a therapy in terms of repigmentation. The Vitiligo Area Scoring Index (VASI)\textsuperscript{33} was introduced as a quantitative parametric score. The VASI is calculated using a formula that includes contributions from all body regions. A few years later, in the Vitiligo European Task Force (VETF), a system was proposed which combines analysis of extent, stage of disease (staging), and disease progression (spreading).\textsuperscript{4} These two measurements are subjective clinical assessments. In addition, a variety of other scoring systems is in use to evaluate treatment outcome in terms of repigmentation,\textsuperscript{3} making cross-study comparisons difficult. Moreover, most outcome measures rely on a subjective clinical assessment, which cannot exclude inter-observer bias and may therefore have limited accuracy and reproducibility.

Only few studies use an objective measurement tool to score repigmentation, such as a digital image analysis system (DIAS).\textsuperscript{34-44} As it is digitally analyzed, this measurement can overcome most of the limitations mentioned. Subjective and objective repigmentation measurements after punch grafting have not been compared so far.

Good measures of patient reported outcomes (PROs) are also essential to measure the efficacy of a therapy in terms of quality of life.\textsuperscript{45} PROs are reports or assessments of any aspect of a patient’s health status and/or treatment impact that come directly from the patient, without the interpretation of the responses by anyone else.
HEALTH RELATED QUALITY OF LIFE

Health-related quality of life (HRQL) is a multi-dimensional construct which reflects the patients’ evaluation of the impact of a disease and/or treatment on their physical, psychological, and social functioning and well-being.\textsuperscript{46-48}

In vitiligo patients, HRQL can be assessed with generic questionnaires and/or dermatology-specific HRQL questionnaires. Disease specific HRQL instruments are not yet available for vitiligo. Generic HRQL questionnaires can be used for all diseases. They allow comparisons with other medical conditions, not just skin diseases, as well as comparison with the general population. These questionnaires do not focus on all areas of a specific disease, but they give an overall description of quality of life. An example of a generic HRQL questionnaire is the widely used Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36).\textsuperscript{49} Dermatology-specific HRQL questionnaires are developed to assess impact on quality of life specific to skin diseases. With these questionnaires it is possible to make comparisons between different skin diseases. The Skindex-29\textsuperscript{50} and the Dermatology Life Quality Index (DLQI),\textsuperscript{51} are widely used dermatology-specific HRQL questionnaires.

Using a combination of a generic (such as the SF-36) and a dermatology-specific HRQL questionnaire (such as the Skindex-29), a wide range of domains and aspects of quality of life can be assessed. Moreover, both types of instruments may measure different but complementary domains and aspects of patients’ health.\textsuperscript{52,53} A number of studies has examined HRQL in patients with generalized vitiligo.\textsuperscript{6,10,54-63} These studies used mainly dermatology-specific questionnaires and reported that in general, vitiligo had a negative impact on HRQL, particularly on psychosocial functioning. The patient-specific characteristics associated with HRQL have not been studied. Moreover, no data are available on the HRQL of patients with universal vitiligo or on the impact of childhood vitiligo on adult life.

AIMS OF THIS THESIS

The aims of this thesis are first to investigate the clinical and patient reported outcomes (PROs) of vitiligo treatment (Chapter 2, 3 and 4), and second to gain insight into the health-related quality of life (HRQL) and other PROs in generalized and universal vitiligo and in adult patients who had vitiligo in childhood (Chapter 5, 6 and 7).

As there are different outcome measures used in vitiligo research, it is necessary to know the quality and validity of these existing clinical measures. Improvement of the indicated imperfections in these clinical measures will lead to better decision making in patient care for vitiligo. In Chapter 2 a systematic review summarizing the available evidence of the measurement properties of clinician, patient and observer reported outcomes in vitiligo treatment is described. Chapter 3 describes a study comparing repigmentation rates as judged by computerised measurement, clinicians and patients after punch grafting in vitiligo patients. In
Chapter 4, the percentage of repigmentation is measured to compare the excimer laser with narrowband ultraviolet B phototherapy, as post-treatment regimens in vitiligo patients who underwent punch grafting.

In Chapter 5, in order to draw a profile of vitiligo patients who suffer most and thereby need special attention, the burden of vitiligo is described. The generic and dermatology-specific HRQL in sociodemographically and clinically distinct subgroups of patients with generalized vitiligo is investigated. Furthermore, associations between HRQL and sociodemographic and clinical patient characteristics are explored.

As little is known about universal vitiligo, we describe the characteristics of patients with universal vitiligo in Chapter 6. Moreover, these characteristics are compared with those of patients with generalized vitiligo. Furthermore, the HRQL of patients with universal vitiligo is compared with that of patients with generalized vitiligo.

In Chapter 7 the social and psychosexual development and current HRQL of adult patients suffering from vitiligo since childhood are compared with those of a group of healthy controls. Moreover, these outcomes in patients reporting negative childhood experiences are compared with those of patients who do not report negative childhood experiences related to vitiligo. It is our hope that the results of this thesis will contribute to the improvement of the quality of care and the quality of life of patients with vitiligo.
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