Treatment of vitiligo
Njoo, M.D.

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CHAPTER I

General introduction and Aims of the studies
There seem to be differences among physicians in their approach towards the treatment of patients with vitiligo. Studies in the United States of America (USA) concluded that many physicians consider the disease as a trivial cosmetic disorder and do not offer treatment. In The Netherlands, there is also concern about variability in decisions whether or not to offer therapy in vitiligo and if so, by which modality. A questionnaire among Dutch patients with vitiligo revealed that about 90% of the respondents were told by their physicians that “they should just live with their pigmentary disorder” and that “there was no treatment for it”. In contrast, some physicians are of the opinion that vitiligo should not be regarded as an “untreatable disorder”. Patients with vitiligo should be informed of the available treatment modalities and their expected results.

Interrogating Dutch dermatologists about the rationale for not offering treatment to patients with vitiligo can shed light on the situation in the Netherlands. Such an inventory may also reveal points of inconsistency among those who do offer treatment, in terms of arguments for making treatment choices and selecting strategies. At present, explicit guidelines for the treatment of vitiligo have not yet been developed in The Netherlands. Such guidelines can assist the physician in daily clinical decision making for patients with vitiligo. In addition, therapeutic regimens should be updated regularly with newly obtained clinical and experimental data.

Aims of the studies

Chapter 2 offers a review of the literature on vitiligo as a pigmentary disorder. Historical aspects, epidemiology, clinical picture, differential diagnosis and psychosocial aspects of vitiligo are discussed. Furthermore, current concepts regarding the pathogenesis of this pigmentary disorder are reviewed. Treatment strategies of currently most applied therapies in vitiligo are described.

In chapter 3, literature and clinical studies are presented in 7 different subchapters. Chapter 3.1 describes the results of a written survey concerning the management of vitiligo that was sent to all practicing dermatologists in The Netherlands. The survey aimed at documenting practice variation and to highlight bottlenecks in current treatment policies. The results of this survey may indicate important clinical issues that may be addressed in future guidelines.

Chapter 3.2, 3.3, and 3.4 describe the several steps that are involved in the making of evidence-based guidelines for the treatment of vitiligo. Each year, many clinical trials
that report on the effectiveness and safety of various different therapies for vitiligo are published. In addition, several guidelines and review articles have been published on categories of patients with vitiligo that should receive therapy and, if so, which treatment should be applied \textsuperscript{4,6,7}. Many of these recommendations were based on personal preferences; they may contain biased and misleading information. Some were the product of informal or formal institutional consensus meetings, at best supported by a limited number of references to scientific literature\textsuperscript{9}. Furthermore, there is concern that only a few randomized controlled trials (RCTs) have been performed in vitiligo. Treatment results as described in noncontrolled trials should be interpreted with caution. Moreover, no studies have been performed to compare these therapies in terms of effectiveness and side effects.

According to the principles of evidence-based medicine, the best medical care is provided by integrating the best external evidence, as obtained from clinically relevant studies, into clinical management decisions in daily practice. By combining all relevant studies in a systematic review one can increase the power and precision of estimates on effectiveness and side-effects profiles \textsuperscript{10,11}. The development of guidelines for the choice of the most effective and safest therapy in vitiligo should also be based on the available evidence in literature. Therefore, we performed systematic reviews of the available literature on the most applied forms of nonsurgical and autologous transplantation therapies, with regard to both effectiveness and safety. The results of these studies are described in chapters 3.2 and 3.3 respectively. Based on the data presented in chapters 3.1, 3.2, and 3.3, guidelines for the treatment of vitiligo have been developed, disseminated and implemented into daily practice (chapter 3.4). An additional systematic review on depigmentation therapies for vitiligo universalis has also been incorporated in these guidelines.

The last 3 chapters describe experimental and clinical studies in vitiligo. Chapter 3.5 contains a report on the association of the Koebner phenomenon with disease activity and therapeutic responsiveness in 61 adults with vitiligo vulgaris. To date, there are no clinical markers available to assess disease activity. Such an assessment of disease activity can be essential in the choice of the most effective therapy for the disease. A novel scoring system, the "vitiligo disease activity (VIDA) score", is proposed as a semi-quantitative measure of disease activity.

Many investigators consider the treatment of vitiligo in children to be a separate issue. For children, the classical therapy with psoralens must be used with caution because of
the phototoxic and systemic effects. In general, oral psoralen plus UV-A (or “PUVA”) is not recommended for children younger than 12 years. In some institutes psoralens are only applied topically. It is known that repigmentation by PUVA is a long and tedious process that can take months to years of therapy on end. Especially in children, there is concern that long-term risks of carcinogenesis as well as premature aging of the skin would be increased. At present, most physicians only offer adjunctive therapies, such as camouflage or sunprotective measures, to cope with the color differences and the lack of melanin in their skin. Moreover, studies have shown that the effects of vitiligo on the quality of life these children are underestimated. Recently, narrowband UV-B phototherapy was shown to be an effective and safe therapeutic modality in adult vitiligo. Chapter 3.6 describes the results of an open prospective clinical study on the effectiveness, safety and the impact on the quality of life of this novel phototherapy in 51 children with generalized vitiligo.

In rare cases of vitiligo universalis, the depigmentation is so widespread that active therapy will probably not result in a cosmetically acceptable grade of repigmentation. Treatment in such cases is directed to achieve a uniform, completely depigmented skin color. Monobenzylether of hydroquinone (MBEH) is presently used worldwide to remove disfiguring residual pigment in patients with vitiligo universalis. Depigmentation by MBEH is however a long process and many (cutaneous and ocular) side effects have been reported with this drug. Because of these side effects, the use of MBEH has been restricted in The Netherlands. In chapter 3.7, the long-term effectiveness and safety of depigmentation therapy using topical 4-methoxyphenol (4-MP) cream and/or Q-switched ruby (QSR) laser are evaluated in 16 patients with vitiligo universalis. Clinical data are obtained from retrospective and follow-up studies.

The results of these studies are summarized and put in perspective in chapter 4. Conclusions are drawn regarding the treatment of vitiligo and the implications of novel clinical and experimental data for current therapeutic regimens. Finally, recommendations are made for future clinical trials in vitiligo.
GENERAL INTRODUCTION AND AIMS OF THE STUDIES

REFERENCES