Photo- and laser therapy in pigment disorders
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GENERAL INTRODUCTION
INTRODUCTION

This thesis deals with new therapies for the cutaneous pigment diseases vitiligo, melasma, and Becker’s nevus. In this introduction, they are shortly described as to what they are and what the present status of therapy is.

VITILIGO

Vitiligo is a chronic skin disease, characterized by destruction of skin melanocytes leading to sharply depigmented macules. This acquired pigment disorder is common in all races, regardless of age and sex and affects 1-2% of the world population. (1) The course of the disease is unpredictable, but is often slowly progressive. Depigmented patches may be present in a localized asymmetric form with a focal or segmental (dermatomal) distribution or in a generalised symmetric form with an acrofacial, disseminated or universal distribution. (2)

To date, no curative treatment is available. Non-surgical modalities, considered as first-line therapy, include topical corticosteroids. However, the effect of topical therapy alone is poor. (3)

Secondly, narrowband ultraviolet B (NB-UVB) therapy is another often used modality. (1,4-6) Outpatient clinic based NB-UVB therapy often is, however, a considerable burden for the patient. Classical institutional NB-UVB is effective, but time consuming as it requires two visits each week during six to 12 months. Because of these disadvantages of outpatient UVB therapy, home UVB therapy was introduced in 1979, primarily for psoriasis (7-11), and in the early 1990s for vitiligo as well. (12)

UVA has also been advocated for the treatment of vitiligo, however efficacy has shown to be poor. (3) Repeated multiple exposures to either UVA or NB-UVB result in a marked increase in the number and functional state of active melanocytes, and they are considered as some of the strongest stimuli to induce repigmentation. (13,14) However, irradiation probably promotes photoageing and photocarcinogenesis. (15-17)

Recently, the red Helium-Neon (HeNe) laser (632.8 nm) was introduced as a possible inducer of repigmentation in vitiligo. The mechanism of action thereof remains unclear, but as the HeNe laser is a low energy laser, thermal effects on the irradiated tissues are considered to be minute and effects are generally attributed to direct biostimulation of exposed cells. (15,16)

Finally, in therapy-resistant non-progressive vitiligo, autologous punch grafting is widely used; it is relatively inexpensive, easy to perform, and successful. (17,18) Post-operative irradiation (natural sun exposure, UVA, NB-UVB) has been suggested to improve pigment cell outgrowth and pigment production after skin transplantation, but is time consuming and could induce photoageing and photocarcinogenesis. (15-17)
MELASMA

Melasma is a common pigment disorder, characterized by symmetric hyperpigmented patches on the face, which often causes significant emotional and psychosocial suffering, thus negatively influencing the patient's quality of life. (20) Melasma is encountered in all skin types, but (of course) particularly in ethnic skin. (21) The pathogenesis of melasma is not fully understood. Genetic background and sun exposure seem to be the most important etiologic factors besides pregnancy, systemic drugs, hormonal medication and phototoxic or photoallergic cosmetics. (22)

Melasma is often difficult to manage because of its refractory and recurrent nature. Current treatments include topical bleaching creams, chemical peels and laser therapy. However, results are often disappointing. Treatment of choice is triple topical therapy, a combination of topical bleaching agents that was first introduced in 1975 as the ‘Kligman formula’. It contains hydroquinone, tretinoin and dexamethasone. Nowadays, dexamethasone is frequently replaced by various other moderately potent to potent corticosteroids. (23,24) The results of laser therapy and intense pulsed light therapy in melasma are generally disappointing and treatment is limited by adverse effects such as postinflammatory hyperpigmentation, especially in dark-skinned patients. Therefore, these approaches are controversial. (25,26)

Recently, non-ablative fractional laser therapy at 1550 nm was reported as a promising treatment for melasma. (27,28) At this wavelength water absorption is predominant. In fractional laser therapy multiple small sized coagulated zones are separated by surrounding untreated tissue. (29) It was reported that these microscopic treatment zones allow transport and extrusion of microscopic epidermal necrotic debris including melanin from melanocytes through a compromised dermal-epidermal junction. (29,30) Generally, a visible wound does not appear because these microscopic treatment zones have a diameter less than 100 micrometer. (29) The stratum corneum was found to be intact after 24 hours. (31,32) Moreover, as the microscopic treatment zones are surrounded by untreated tissue, recovery is relatively fast and inflammation is mild.

BECKER´S NEVUS

Becker's nevus is a relatively common skin disorder, characterized by the development of unilateral hyperpigmented patches, that eventually develop a slightly elevated, with a sometimes verrucous surface and often hypertrichosis in 56-70% of male cases. (33-35) The prevalence ranges from 0.25 to 2.5%, and is about five times more frequent in males than in females. (34-37) Little is known about the pathogenesis of the disorder, but increased androgen sensitivity of fibroblasts has been suggested as a possible etiologic factor. (38-42) Currently, no treatment is available for Becker's nevus. Studies on intense pulsed light and Quality-switched ruby laser showed disappointing
or even adverse effects.\textsuperscript{43,44} Better results have been achieved with erbium yttrium-aluminium-garnet (YAG) laser and long-pulsed alexandrite laser.\textsuperscript{44,45}

Recently, non-ablative fractional laser therapy was suggested as treatment option for Becker’s nevus.\textsuperscript{46} The main principle of fractional laser therapy is the coagulation or ablation of small columns of skin, leaving the surrounding tissue intact.\textsuperscript{29} This enhances healing of the treated and coagulated skin after treatment, minimizing the risk for unwanted effects. Ablative fractional laser therapy at 10600 nm might be even more effective in the treatment of Becker’s nevus than non-ablative fractional laser therapy, as complete ablation of microscopic treatment zones takes place instead of coagulation, preventing a possible reuptake of melanin from the microscopic treatment zones by dermal macrophages and keratinocytes.

\section*{AIMS OF THIS THESIS}

Treatment of pigment disorders is certainly challenging. In non-segmental vitiligo, home UVB therapy and the necessity of post-operative irradiation after punch grafting are debated in this thesis. Furthermore, following the introduction of fractional laser devices in 2004, promising results in various pigment disorders, especially melasma, have been published. However, randomized clinical trials to definitely prove safety and effectiveness, have as yet not been published. Therefore, this thesis discusses (i) the efficacy and safety of home UVB therapy, (ii) the effect of different light sources on outgrowth of pigment from punch grafts, in non-segmental vitiligo; (iii-v) the efficacy and safety of non-ablative and ablative fractional laser therapy in melasma and in Becker’s nevus, and finally (vi) the histopathological differences between non-ablative and ablative fractional laser.

Home UVB therapy for the treatment of vitiligo has been debated since its introduction in the early 1990s. Non-evidence based but understandable fear is often expressed about higher risks regarding inaccurate dosimetry, phototoxicity, suboptimal treatment, and unsupervised continuation of irradiations, photoageing and carcinogenicity. Chapter 2 is the first study to provide pro’s and cons of home UVB therapy versus outpatient UVB therapy in patients with non-segmental vitiligo.

Post-operative irradiation (UVA, NB-UVB, HeNe laser) has been suggested to improve pigment outgrowth after punch grafting, but is time consuming and UVA and NB-UVB could promote photoageing and photocarcinogenesis. In Chapter 3 pigment outgrowth of punch grafts after irradiation with UVA, NB-UVB and HeNe laser is compared to no phototherapy in patients with non-segmental vitiligo.

Non-ablative fractional laser therapy at 1550 nm has been reported as an effective treatment for melasma, although there is minimal evidence for its efficacy and controlled trials were lacking. In Chapter 4 is a randomized inter-patient study to assess efficacy and safety of non-ablative 1550 nm fractional laser therapy at 10 mJ/microbeam compared with the gold standard (triple topical therapy).
As non-ablative 1550 nm fractional laser therapy at 10 mJ/microbeam proved relatively safe and effective, in Chapter 5 an intra-patient study was performed to compare non-ablative 1550 nm fractional laser therapy with triple topical therapy, using more aggressive settings and long term intermittent maintenance bleaching during follow-up.

Non-ablative fractional laser therapy has been suggested as a treatment option for Becker’s nevus. Ablative fractional laser therapy might be even more effective, as complete ablation of microscopic treatment zones takes place instead of coagulation, preventing a possible reuptake of melanin from the microscopic treatment zones by dermal macrophages and keratinocytes. In Chapter 6 efficacy and safety of ablative fractional laser therapy in the treatment of Becker’s nevus was assessed.

Fractional laser therapy has become a widely accepted modality and creates multiple small sized coagulated zones, separated by surrounding untreated tissue. Histological studies have shown that permanent tissue damage is usually minimal or absent after either non-ablative or ablative fractional laser. However, histological comparisons between non-ablative and ablative fractional laser have not been published. In Chapter 7 the histological outcome of non-ablative and ablative fractional laser was compared.

REFERENCE LIST


