SUMMARY, CONCLUSIONS, AND DISCUSSION

This thesis deals with some therapeutical aspects of the pigment disorders non-segmental vitiligo, melasma, and Becker’s nevus.

In non-segmental vitiligo, home UVB therapy and the necessity of post-operative irradiation after punch grafting are debated.

Furthermore, following the introduction of fractional lasers in 2004, promising results in various pigment disorders such as melasma and Becker’s nevus, have been published. However, randomized clinical trials to definitely prove safety and efficacy were lacking.

Therefore, this thesis considers (i) the efficacy and safety of home UVB therapy in non-segmental vitiligo, (ii) the effect of different UV sources on outgrowth of 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.

Chapter 1 - General introduction and aims of thesis

Chapter 1 is a general introduction on the etiology, pathogenesis and current treatment options in vitiligo, melasma and Becker’s nevus.

Chapter 2 - ‘Home versus outpatient narrowband UVB therapy for the treatment of non-segmental vitiligo: a retrospective questionnaire study’

Chapter 2 shows the results of a retrospective questionnaire study in which we compared home versus outpatient NB-UVB therapy for the treatment of non-segmental vitiligo. NB-UVB therapy is usually delivered in an outpatient clinic. Therefore, vitiligo patients have to visit the clinic twice a week often during working hours and often for more than six months. In the early 1990s home NB-UVB therapy was introduced in the Netherlands. Since its introduction, safety, effectiveness and compliance concerning home treatment have been debated. This study was the first to provide data on the pro’s and cons of home UVB therapy versus clinic based UVB therapy in patients with non-segmental vitiligo.

104 consecutive patients with non-segmental vitiligo who completed total body NB-UVB therapy between March 2008 and January 2009 were asked to fill out a questionnaire on safety, efficacy and satisfaction. 64 patients got clinical UVB while 40 patients had home UVB-treatment. The overall response rate was 86%.

We concluded that patient-reported outcomes of home and clinical NB-UVB therapy were comparable. The rate of pigmentation and occurrence of side effects were similar and time investment was significantly lower in the home group. Contrary to what you expect, satisfaction with the result in the home group was significantly lower.
Home NB-UVB therapy appeared to be a valuable and safe alternative for hospital-based NB-UVB therapy for patients with vitiligo.

Chapter 3 - ‘Punch graft testing in vitiligo; effects of UVA, NB-UVB and 632.8 nm Helium-Neon laser on the outcome’

Post-operative UV-irradiation has been suggested to improve pigment outgrowth after punch grafting in vitiligo, but is time consuming while UVA and NB-UVB could promote photoageing and photocarcinogenesis. Helium-Neon laser treatment has been advocated in segmental vitiligo and may be a safe alternative for UV-irradiation.

Chapter 3 describes a randomised controlled observer-blinded study where the effects of UVA, NB-UVB and Helium-Neon laser irradiation on outcome of punch-grafting were studied in six patients with stable vitiligo. In each of four 2x2 cm depigmented test-regions, four 1.5 mm pigmented punch grafts were placed. These test-regions were randomly allocated to one of the phototherapeutic modalities twice weekly versus no therapy at all during three months. All patients were followed up for 6 months. In two patients the majority of punch grafts showed outgrowth of pigment in all treatment modalities, whereas in the other four patients the majority of punch grafts depigmented.

We concluded that stable vitiligo did not preclude failure of punch grafting. Intrinsic patient-related factors in the grafted area seemed to determine outgrowth of pigment, while the phototherapeutic modalities had minor to no effect. The number of patients who showed pigment outgrowth was too small to compare the different modalities.

Chapter 4 – ‘Non-ablative 1550 nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled pilot study’

Melasma is a common pigment disorder, which is often difficult to manage because of its refractory and recurrent nature. Treatment of choice is triple topical therapy; a topical bleaching that was first introduced in 1975 as Kligman formula and consists of hydroquinone, tretinoin and a moderately potent to potent corticosteroid. Recently, non-ablative fractional laser therapy at 1550 nm was reported as a treatment for melasma.

In chapter 4 we assessed the efficacy and safety of non-ablative 1550 nm fractional laser therapy in melasma and compared these results with the gold standard, triple topical therapy. Twenty female patients with moderate to severe melasma and Fitzpatrick skin types II-V were randomized and included in an observer-blinded study with two arms. Ten patients were treated four times with non-ablative 1550 nm fractional laser therapy at 10 mJ/microbeam while the other 10 patients were treated once daily for eight weeks with a modified triple topical therapy (hydroquinone, tretinoin and triamcinolone acetonide cream). Improvement was determined using
the physician’s global assessment (PhGA) at 3 weeks, 3 months and 6 months after the last treatment.

The PhGA had improved in both groups at 3 weeks. However, there was no difference in the PhGA between the two groups. The mean treatment satisfaction and treatment recommendation were significantly higher in the laser group at 3 weeks. However, melasma recurred in five patients in both groups after 6 months.

We concluded that non-ablative 1550 nm fractional laser therapy was safe and comparable in efficacy and recurrence rate to triple topical therapy. Furthermore we stated that it may be a useful alternative treatment option for melasma when topical bleaching is ineffective or not tolerated.

Chapter 5 – ‘Non-ablative 1550 nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled split-face study’

As non-ablative 1550 nm fractional laser therapy at 10 mJ/microbeam proved relatively safe and effective in the previous study, in chapter 5 an intra-patient study was performed to compare non-ablative 1550 nm fractional laser therapy with modified triple topical therapy, using higher settings (15 mJ/microbeam) and long term intermittent maintenance bleaching during follow-up. Twenty-nine patients with melasma were included in a randomized controlled observer-blinded study with split-face design. Each side of the face was randomly allocated to either 4-5 non-ablative 1550 nm fractional laser therapy sessions (15 mJ/microbeam, 14-20% coverage) or triple topical therapy (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1% cream). Triple topical therapy was applied once daily for 15 weeks until the last laser session. After this last treatment, patients were asked to apply triple topical therapy twice weekly on both sides of the face during follow-up. Improvement of melasma was assessed by patient’s global assessment (PGA), patient’s satisfaction, physician’s global assessment (PhGA), melanin index, and lightness (L-value) at 3 weeks, and at 3 and 6 months after the last treatment.

Mean PGA and satisfaction were significantly lower at the fractional laser side. PhGA, melanin index and L-value showed a significant worsening of hyperpigmentation as well. At 6 months follow-up, most patients preferred triple topical therapy. Moreover, 9 patients (31%) developed postinflammatory hyperpigmentation after two or more laser-sessions.

We concluded that given the high rate of postinflammatory hyperpigmentation, non-ablative 1550 nm fractional laser at 15 mJ/microbeam was not recommendable for the treatment of melasma. As laser treatment was partly in summer, this may have influenced the negative outcome.
Chapter 6 – ‘Ablative fractional laser therapy as treatment for Becker’s nevus; a randomized controlled pilot study’

Becker’s nevus is an acquired skin disorder, characterized by the development of unilateral hyperpigmented patches that eventually develop a slightly elevated surface and often hypertrichosis. Prevalence ranges from 0.25-2.5%.

To date, no effective treatment is available. Recently, non-ablative fractional laser therapy was suggested as treatment option for Becker’s nevus. Ablative fractional laser therapy might be even more effective as it results in complete ablation of microscopic treatment zones instead of coagulation, preventing a possible reuptake of melanin from the microscopic treatment zones by dermal macrophages and keratinocytes.

In chapter 6, 11 patients with Becker’s nevus, older than 18 years were included in a prospective randomized controlled, observer-blinded split lesion trial. In each patient two similar square test regions were randomized to receive either ablative fractional laser therapy at 10 mJ/microbeam, coverage 35-45%, in combination with topical bleaching (to prevent laser induced postinflammatory hyperpigmentation or topical bleaching alone (to allow comparison of the regions). Three and 6 months after the last treatment, clearance of hyperpigmentation was assessed by physician’s global assessment (PhGA), melanin index, reflectance spectroscopy, patient’s global assessment (PGA), patient’s satisfaction and histology.

At 6 months follow-up, PhGA improved in the laser treated region. Reflectance spectroscopy, melanin index, number of melanocytes and amount of dermal melanin did not significantly differ between both regions. PGA and patient’s satisfaction were 5.0 and 5.9 (visual analogue scale, 0-10). Three patients developed postinflammatory hyperpigmentation.

We concluded that ablative fractional laser therapy was moderately effective in some patients with Becker’s nevus. However, postinflammatory hyperpigmentation and relatively negative patient reported outcomes still preclude ablative fractional laser therapy from being a standard therapy.

Chapter 7 – ‘Increased formation of fibrosis after treatment with ablative versus non-ablative fractional laser therapy’

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. The aim of this study was to compare the histological outcome of non-ablative and ablative fractional laser.

In chapter 7, in a randomized controlled observer-blinded study, biopsies of 18 patients (ashy dermatosis n=4, postinflammatory hyperpigmentation n=6, Becker’s nevus n=8) were treated with ablative or non-ablative fractional laser were compared.
In each patient, two similar test-regions were randomised to receive either fractional laser with intermittent topical bleaching (to prevent laser-induced postinflammatory hyperpigmentation) or topical bleaching alone (to allow comparison of the regions). Patients with ashy dermatosis and postinflammatory hyperpigmentation were treated with non-ablative 1550 nm fractional laser (15 mJ/microbeam, 14-20% coverage), whereas patients with Becker’s nevus were treated with ablative fractional laser (10 mJ/microbeam, 35-45% coverage), for a total of three to five sessions. Biopsies were obtained 3 months after the last treatment, and analyzed by a blinded dermatopathologist.

At follow-up, development of fibrosis was seen significantly more often in patients treated with ablative as compared to non-ablative fractional laser. We concluded that ablative fractional laser therapy may have induced formation of fibrosis, whereas treatment with non-ablative fractional laser therapy did not.

Further research whether this fibrosis is due to the used laser settings or the disorder is mandatory. Also, whether formation of fibrosis has to be regarded as dermal remodeling or a subtle subclinical form of scarring should be investigated in future histopathologic studies.

**DISCUSSION**

**Vitiligo**

To date, NB-UVB therapy is the most effective therapy for non-segmental vitiligo. We showed that patient-reported outcomes of home and outpatient NB-UVB therapy were comparable with regard to repigmentation and occurrence of side effects. Therefore, home NB-UVB therapy is a valuable alternative to clinic based NB-UVB therapy. Concerns among dermatologists about higher risks regarding inaccurate dosimetry, phototoxicity, suboptimal treatment, and unsupervised continuation, proved to be unfounded. Moreover, as time investment was significantly less and patients can perform NB-UVB therapy at any time at their own home, it means a significant step forward in the treatment of non-segmental vitiligo.

Secondly, we showed that in patients treated with autologous minigrafting, intrinsic patient-related factors in the grafted area seemed to determine outgrowth of pigment, while the phototherapeutic modalities had minor to no effect. Moreover, we concluded that stable vitiligo did not preclude failure of punch grafting. Since no real time parameters for disease activity in vitiligo are known, a minigraft-test probably still is the best way to predict the outcome of minigrafting.

In future research, a prospective comparison between home versus outpatient NB-UVB therapy, and the necessity of post-treatment procedures after punch grafting, should be investigated.
**Melasma**
In patients with melasma, non-ablative 1550 nm fractional laser therapy at 10 mJ/microbeam was safe and comparable in efficacy and recurrence rate to triple topical therapy (50%). Therefore, it may be a useful alternative treatment option for melasma when topical bleaching is ineffective or not tolerated. However, given the high rate of postinflammatory hyperpigmentation, non-ablative 1550 nm fractional laser at 15 mJ/microbeam was not recommendable in the treatment of melasma. Caution should be advocated using non-ablative 1550 nm fractional laser in melasma, especially in spring and summer. As shown in chapter 4 and 5, more aggressive settings inherently lead to more side-effects. Non-ablative fractional laser is not a final solution nor a quick fix for melasma, as melasma is known to be recalcitrant and recurrent.

Because these two papers are the first randomized trials comparing fractional laser to triple topical therapy, more randomized studies are mandatory. As there is only one paper on long term treatment with triple topical therapy, in future studies, the long term intermittent treatment of triple topical therapy combined with non-ablative fractional laser may be considered.

**Becker’s nevus**
Ablative fractional laser therapy was moderately effective in some patients with Becker’s nevus. However, postinflammatory hyperpigmentation and relatively negative patient reported outcomes still preclude ablative fractional laser therapy from being a standard therapy.

In future research, a larger cohort of patients should be recruited in order to compare treatment outcomes in different skin types and different characteristics of Becker’s nevus. Moreover, given the high rate of laser-induced postinflammatory hyperpigmentation, optimization of laser parameters is mandatory in future research.