TREATMENT OF SKIN DISEASES WITH THE
308 nm XENON CHLORIDE ULTRAVIOLET B LASER

Summary of Ph.D. Thesis

Eszter Baltás M.D.

Department of Dermatology and Allergology
Faculty of Medicine
University of Szeged, Hungary

2006
1. INTRODUCTION

Ultraviolet (UV) light is a form of electromagnetic radiation situated in the wavelength spectrum 100-400 nm. The region above 200 nm has been subdivided on the basis of the responses of human skin and the wavelengths contained in sunlight. Three UV regions are recognized, with UVB (280-320 nm) the most biologically active waveband.

The beneficial effect of sunlight for various skin disorders has been known since antiquity. Over the past few years, the development of irradiation devices with new emission spectra has led to an expanded role for phototherapy in dermatology.

Psoriasis vulgaris is a chronic inflammatory skin disease, affecting 2-3% of the population worldwide. It represents a lifelong burden for the patients, and has a significant impact on patients' quality of life (QoL). Clinically, it is considered a disorder of the entire skin, with the most common presentation being well circumscribed, erythematous, scaling plaques that may be symmetrically distributed. A repertoire of topical and systemic treatment and phototherapy are available for the disorder. Narrow-band (NB) UVB (311 nm, Philips TL01 bulbs) is effective in moderate and severe forms of psoriasis.

Atopic dermatitis (AD) is a chronic and often relapsing inflammatory skin condition with an incidence of 10%, that occurs most commonly during infancy and childhood. Acute inflammation with exudation favor the infantile form, and chronic inflammation with lichenification and scale increases in prevalence with age. Regardless of the stage all AD patients experience pruritus and xerosis. The disease may cause chronic and recurrent physical and psychological disability. Various forms of phototherapy (UVA1, UVAB, UVB, NB-UVB, photochemotherapy, balneophototherapy, climatotherapy and extracorporal photopheresis) have been already shown to be promising treatment options in AD. NB-UVB is an effective therapeutic modality in moderate and severe atopic eczema.

Vitiligo is an acquired idiopathic disorder, affecting 1-2% of the general population. It is characterized by circumscribed, chalk-white macules on the skin and often leads to social stigmatization of the patients. Although there is still no therapeutic panacea for vitiligo, the traditional options available - corticosteroids, topical and oral psoralen plus UVA (PUVA), NB-UVB - may lead to satisfactory results in many patients. Today NB-UVB is the first choice of treatment in adults and in children with generalized vitiligo.

Mycosis fungoides (MF) represents clinically and biologically a heterogeneous group of non-Hodgkin lymphomas. Malignant skin-homing T cells growing primarily in the skin give rise to several clinical patterns. Patients
with classical MF progress from patch stage to plaque stage and finally to tumor stage disease, and have a protracted clinical course over years or even decades. There are three main categories of therapy in MF: skin-directed therapy (SDT), biologic response modifiers, and systemic chemotherapy. The choice of an initial treatment depends on the stage of the disease and the general condition and age of the patient. Biologic response modifiers and systemic chemotherapy are used in higher stage and in refractory patch- and plaque-stage disease. SDT of early-stage MF consists of phototherapy, radiotherapy, topical application of corticosteroids, retinoids, or cytotoxic agents.

We have previously found that the 308 nm xenon chloride (XeCl) laser was more effective than the NB-UVB light for the treatment of psoriasis, suggesting that UVB laser might offer advantages over NB-UVB. The clinical efficacy of the XeCl laser in psoriasis vulgaris is therefore well documented, but in other skin diseases has not been investigated. Setting out from the data that indicate NB-UVB phototherapy to be an efficacious and safe treatment modality in dermatology, we embarked on a study of targeted phototherapy using a 308 nm XeCl laser to treat psoriasis vulgaris, focal areas of AD, vitiligo and early-stage MF.

### 2. AIMS OF THE STUDY

The specific aims of our study were:

1. To extend our previous data on the therapeutic efficacy of the 308 nm XeCl laser in the treatment of psoriasis.
2. To investigate the therapeutic efficacy of the XeCl laser in the treatment of atopic dermatitis.
3. To investigate the therapeutic efficacy of the XeCl laser in the treatment of vitiligo.
4. To investigate the therapeutic efficacy of the XeCl laser in the treatment of mycosis fungoides.
3. PATIENTS AND METHODS

3.1. Psoriasis vulgaris

Twenty-one patients (48 plaques) with chronic plaque type psoriasis were treated. A 308 nm XeCl excimer laser (Lambda Physik LPX 105 E, Göttingen, Germany) was used: its output consisted a train of short pulses (15 nanoseconds) at 5.5 mJ/cm² per pulse (the size of the light spot is 3x3 cm). Minimal erythema dose (MED) was established in uninvolved, unexposed skin. The laser therapy was given 3 times weekly until the treated plaques cleared. XeCl laser phototherapy was performed with different impulse intensities (0.06 mJ/cm² and 20 mJ/cm²) or impulse frequencies (1 Hz and 20 Hz), the cumulative doses and the number of treatments up to complete clearance were measured in the two groups. Local psoriasis severity index (LPSI) scores were determined for each plaque following each treatment: erythema, induration and desquamation were rated according to a five-point scale. Statistical analysis was performed by bilateral comparison study and Wilcoxon signed ranks test. A probability level of p<0.05 was considered statistically significant.

3.2. Atopic dermatitis

Fifteen patients with AD lesions localized exclusively on the flexor surfaces of the extremities (less than 20% of the body surface) were enrolled in the study. Phototesting and laser treatment were carried out with the XTRAC laser (PhotoMedex Incorporation, PA, USA) instrument. The patients were treated twice weekly for 4 weeks.

Local eczema area severity index (EASI) was used to determine the severity of the AD. The local EASI score is the sum of the scores of four clinical symptoms (erythema, infiltration, lichenification and excoriation), that are graded from 0 to 3 (0: absent, 1: mild, 2: moderate, 3: severe). The patients were rated according to the intensity of itching during a 24-hours period, using a 10 cm visual analogue scale. The aim of the QoL questionnaire (10 questions) was to measure the impact of the symptoms on the patient’s quality of life during the previous week. The severity of the AD was scored at the baseline visit, and then once weekly during the laser treatment. Statistical analysis were performed with Friedman’s non-parametric repeated measures ANOVA, followed by the Student-Newman-Keuls multiple comparison procedure. A probability of p<0.05 was considered statistically significant.
3.3. Vitiligo

Six patients with vitiligo were included in the study. Phototesting was not done, as the lesional skin of all patients was considered to be Fitzpatrick skin phototype I. The vitiligous patches were treated twice weekly for six months with the 308 nm XeCl excimer laser (Lambda Physik LPX 105 E, Göttingen, Germany). The patients were without any other treatment for six months prior to the study. They were otherwise healthy and no additional treatment or medication was allowed during the study. Improvement compared with baseline examination was recorded in percentage depending on the extent of repigmentation.

3.4. Mycosis fungoides

Four patients with limited patch-stage MF were included in the study. The diagnosis of MF was established by the clinical appearance of the lesions and confirmed histologically by conventional microscopy and immunohistochemical staining. T cell receptor rearrangement was examined with polymerase chain reaction. Determination of the stage of MF was based on the tumor-node-metastasis (TNM) classification. All of the patients had stage IA disease. Stage IA MF is confined to the skin with less than 10% patches and plaques covering the skin surface (i.e., T1N0M0). Phototesting and laser treatment were carried out with the XTRAC laser (PhotoMedex Incorporation, PA, USA) instrument. Before treatment, all patients were phototested to determine the MED of the 308 nm UVB. The irradiation doses were 2 MED. The treatment was administered two or three times weekly until the clinical clearance or minimal residual activity (improvement > 90%) was achieved. Clinical response was rated as follows: complete remission (no disease activity present), partial remission (decrease of disease activity > 50%), and progression of the disease (increase of disease activity > 25%).
4. RESULTS

4.1. Psoriasis vulgaris

Forty-eight plaques of 21 psoriatic patients were treated effectively with the XeCl laser, the LPSI scores decreased continuously and rapidly after each treatment. In order to optimize certain parameters of the UVB phototherapy, we examined whether the therapeutic effect of the XeCl laser depends on the intensity and frequency of the laser impulses. The initial dose was 0.6 MED, which was increased by 20% on each subsequent treatment. The mean cumulative doses up to complete clearance of the psoriatic plaques were 4.06 J/cm² and 4.05 J/cm² for impulse intensities of 20 mJ/cm² and 0.06 mJ/cm² respectively. The mean number of treatments was 9.2 in both cases. Using XeCl laser with an impulse frequency of 1 Hz or 20 Hz, the mean cumulative doses were 4.6 J/cm² and 4.3 J/cm². The mean number of treatments was 8 in both groups. There was no significant difference in the decrease in LPSI scores using either 1 Hz or 20 Hz impulse frequency. The treatment was well tolerated and no serious side-effects were observed during the laser therapy.

4.2. Atopic dermatitis

Of the 15 patients enrolled in the study, one was dropout because of non-compliance. Fourteen patients completed the study. Depending on the skin type and the MED, the initial doses in the individual patients ranged from 150-450 mJ/cm². The mean cumulative dose of UVB was 1.66 J/cm². The mean reduction in the intensity of erythema, infiltration, excoriation and lichenification was 58%. At the completion of the laser therapy, each score was significantly lower than the initial values. Before the laser treatment, the EASI scores ranged between 3 and 14 (mean 8.5). At the end of the treatment period, the EASI scores were significantly lower (between 0 and 15, mean: 3.57) as compared with the initial values. Before the laser treatment the QoL scores ranged between 4 and 11 (mean 6.57), whereas at the end of the treatment period they were between 0 and 6 (mean 1.71), significantly lower than the baseline values. After one month of phototherapy we observed 81% reduction in the itching score. The score values of erythema, infiltration, excoriation and itching decreased significantly after one week of treatment while the intensity of lichenification reduced after two weeks. EASI scores decreased also significantly upon the total treatment period showing the most dramatic decrease in the first two weeks. No serious side-effects or discomfort were observed. There was no exacerbation at the one-month follow-up.
4.3. Vitiligo

Four patients completed the six-month treatment regimen; two were lost because of non-compliance after 5 weeks. The initial dose was 49.5 mJ/cm\(^2\), the mean cumulative dose of UVB was 50.7 J/cm\(^2\) (31.5-70.8 J/cm\(^2\)). Repigmentation generally started eight weeks after the beginning of the laser therapy, with 1-3 mm pigmented macules and continued during therapy in a typical, perifollicular pattern. After six months one patient responded with 95% repigmentation, two individuals showed 75% and one showed repigmentation in less than 50% of the area treated. There was no loss of the pigmentation at the three-month follow up. No phototoxic or photoallergic reactions, perilesional hyperpigmentation were observed. Side-effects were minimal, including mild erythema and pruritus, which resolved spontaneously.

4.4. Mycosis fungoides

Four patients with early-stage MF achieved complete clinical remission with a marked reduction in size and infiltration of the patches. Clinical healing was obtained in 6 to 14 sessions (average: 9), with a cumulative dose ranging from 2.8-7.4 J/cm\(^2\) (mean: 4.4 J/cm\(^2\)). A slight erythema and transient hyperpigmentation was observed in the treated areas with spontaneous resolution after two weeks following the end of the treatment. No serious or unpleasant side-effects were observed. There was no exacerbation of the skin symptoms at the six-month follow-up.

5. DISCUSSION

In the present study we extended our previous investigations on the therapeutic efficacy of the excimer laser in psoriasis vulgaris, introduced a new and efficient (photo) therapeutic approach for vitiligo, limited atopic dermatitis and patch-stage mycosis fungoides.

UVB has been widely used in the treatment of different skin diseases. Initially, broad-band (BB)-UVB light sources were applied, which emit wavelengths throughout the whole UVB range (290-320 nm). Further research led to the introduction of the more selective NB-UVB phototherapy operating at 311-313 nm. In the past few years we have developed a 308 nm “super narrow-band” laser-based phototherapy for the treatment of psoriasis. In 1997 we found that the XeCl UVB laser therapy is more effective, than conventional NB-UVB in the treatment of psoriasis vulgaris. The cumulative dose of UVB was 6 times
less using XeCl laser than NB-UVB for the complete clearance of psoriatic plaques (Bónis, 1997).

In this work we compared the antipsoriatic efficacy of the XeCl excimer laser when the irradiation was performed at different light intensities and impulse frequencies. Our results showed that the laser therapy was highly effective in all of the treated psoriatic plaques, the LPSI scores decreased rapidly following each treatment. All patients tolerated the treatment well and no serious side-effect was observed. We did not find significant differences in the therapeutic efficacy of the excimer laser using different treatment settings.

One of the major mechanisms of action of UVB light in the treatment of psoriasis vulgaris seems to be a cytotoxic effect on the infiltrating T cells, where the mechanism of cell death is most probably apoptosis. In our previous in vitro studies we compared the apoptosis-inducing capacity of the different light sources: the XeCl UVB laser was found to be a more potent inductor of T cell apoptosis than NB-UVB light. There are several explanations for this difference. Although NB-UVB emits most of its energy in the wavelength interval 311-313 nm, its emission spectrum contains longer wavelengths, which may exert a less cytotoxic effect on T cells. On the other hand, the intensity of XeCl laser light is much higher than that of NB-UVB light. The XeCl laser emits its energy in nanoseconds, while the performance of NB-UVB irradiation requires minutes. Additionally, the higher apoptosis-inducing efficacy of the XeCl laser might explained by the differences in the biological effects of coherent laser light from those of incoherent light. Our in vitro experiments are in concordance with our in vivo results suggesting that the more effective induction of T cell apoptosis might be responsible for the greater clinical efficacy of the XeCl laser as compared with NB-UVB light.

Carcinogenic potential of different UV therapies increases with the cumulative UV dose during life. We presumed after our pilot study, that the lower therapeutic cumulative dose with the XeCl laser - needed for clinical healing in psoriasis - involves a lower risk of carcinogenesis. Additionally, the majority of the psoriatic patients suffer from mild to moderate psoriasis, affecting 10-20% of the total body surface area. The XeCl laser is selectively directed toward lesional skin and spares the surrounding normal skin from unnecessary carcinogenic UV radiation exposure. The clinical efficacy and safety of the XeCl laser for the treatment of psoriasis was confirmed later by other studies (Spann, 2001; Trehan, 2002; Asawanonda, 2000; Feldman, 2002; Gerber, 2003).

Management of AD entails different approaches depending on the severity, extent, and distribution of skin lesions. The most frequently applied effective forms of phototherapy include NB-UVB and PUVA in patients with moderate to severe disease. In the present study we have shown that XeCl UVB laser is
highly effective for the treatment of AD lesions. The severity of erythema, infiltration, excoriation, lichenification, itching and the EASI score values significantly decreased during the treatment. All of our patients observed clinical improvement and reported a significant improvement in the quality of life. Our results suggest that the xenon chloride laser is an effective and well-tolerated treatment for localized AD. However, randomized clinical studies should be performed to show its efficacy in combination with conventional treatment modalities.

Phototherapy alone or in combination with topical agents is a well-established and widely used treatment for vitiligo. As the repigmentation in vitiligo is probably due to the activation of melanocytes in the hair follicles, the deeper penetrance of the XeCl laser might be responsible for the good therapeutic results that we achieved with this light source. Previously PUVA appeared to be the best method in providing reasonable hope for achieving repigmentation; recently NB-UVB has been reported effective in adults and children with vitiligo. Although there are no comparative studies in vitiligo using different UVB light sources, we found that in psoriasis the XeCl laser was more effective than NB-UVB light (Kemény, 2001; Bónis, 1997). The greater clinical efficacy of XeCl laser in psoriasis might be partly due to its deeper penetrance into the skin (unpublished data), as irradiation of the psoriatic skin with XeCl laser induced higher number of apoptotic T cells in the dermis than with the NB-UVB light. In our present investigations we showed that the 308 nm XeCl laser is useful and well-tolerated in the treatment of localized vitiligo. The clinical efficacy of the XeCl laser for the treatment of vitiligo was confirmed later by other studies (Taneja, 2003; Hadi, 2004; Leone, 2003). In addition, the laser was also effective in the phototherapy of resurfacing-induced leukoderma (Friedman, 2001), hypopigmented scars and striae (Goldberg, 2003; Alexiades-Armenakas, 2004).

MF is a malignancy of clonal skin-homing CD4+ T lymphocytes and is the most common form of cutaneous T cell lymphomas. Treatment options for early-stage MF include various topical agents, radiotherapy and phototherapy. In our study, four patients were treated with the 308 nm UVB laser and all achieved complete clinical remission with a marked reduction in size and infiltration of the patches. Although the number of subjects is limited, the clinical healing observed in all four patients demonstrates the benefit of this new technique. The complete healing of the patches was achieved rapidly, allowing a low rate of cumulative doses. More follow-up is needed, but as in other studies, a prolonged period without recurrences may be expected. Compared with NB-UVB phototherapy, which is usually used when lesions cover more than 10% of skin surface, the 308 nm excimer laser has the ability to deliver high fluences selectively to the target lesion and to induce a more
significant apoptosis in the lymphocytes. Our results showed the efficacy of the 308 nm excimer laser in clearing MF that is limited to a few lesions. The clinical efficacy of the XeCl laser for the treatment of MF was proven in other studies (Nistico, 2004; Passeron, 2004).

In summary, our results clearly show that the XeCl laser is a new and promising form of UVB phototherapy in dermatology. Based on our and others investigations with the 308 nm excimer laser, a number of new phototherapeutic devices utilizing targeted phototherapy have been developed, and revolutioned the phototherapy of skin diseases.

6. SUMMARY

1. We extended our previous data on the XeCl laser treatment for psoriasis, and showed the efficacy of the 308 nm laser for psoriasis using different light intensities or laser impulse frequencies.
2. We have shown for the first time that the XeCl laser is an effective treatment for atopic dermatitis.
3. We have shown for the first time that the XeCl laser is a novel and highly effective therapeutic tool for vitiligo.
4. We have proved that the XeCl laser is an efficient treatment option in patch-stage mycosis fungoides.
7. ACKNOWLEDGEMENT

I wish to thank Professor Dr. Lajos Kemény and Professor Dr. Attila Dobozy for providing me the excellent opportunity to work in a highly inspiring environment at the Department of Dermatology and Allergology, and for guiding my scientific and clinical work.

I express my gratitude to my colleagues, Dr. Béla Bónis, Dr. Zoltán Novák, Dr. Zsanett Csoma, Dr. Nóra Eiler, Dr. Szilvia Czakó, Dr. Ágnes Kinyó for always being ready to help me.

My special thanks to Ferenc Ignác from the Department of Optics and Quantum Electronics for his cooperation during my work.

I am grateful to Professor Zsolt Bor and Professor Gábor Szabó from the Department of Optics and Quantum Electronics and to Dr. Marianna Zana from the Department of Psychiatry.

I wish to thank the help of László Bodai in the statistical analyses.

I would like to thank the technical help of Andrea Gyimesi and Péter Klapcsik.

I am especially grateful to my Mother and Father for their continuous help and endless support. I’m thankful for my family and friends encouraging me to accomplish this work.
8. LIST OF PUBLICATION

List of original papers related to the subject of the thesis


2. Baltas E, Csoma Zs, Ignacz F, Dobozy A, Kemeny L. Treatment of vitiligo with the 308 nm xenon chloride excimer laser. *Arch Dermatol* 2002; 138: 1619-20. IF: 2,761


List of original papers connected to the subject of the thesis


List of abstracts related to the subject of the thesis


