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

Ph.D. thesis

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LIST OF ORIGINAL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. Baltas E, Nagy P, Bonis B, Novak Z, Ignacz F, Szabo G, Bor Z, Dobozy A, Kemeny L.
Repigmentation of localized vitiligo with the xenon chloride laser.
Br J Dermatol 2001; 144: 1266-7. IF: 2, 405

II. 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

III. Baltas E, Trach V, Dobozy A, Kemeny L.
The platelet-activating factor antagonist WEB 2086 gel inhibits UV-induced dermatitis on human skin.
Skin Pharmacol Appl Skin Physiol 2003; 16: 259-262. IF: 1,529

IV. Baltas E, Csoma Zs, Bodai L, Bonis B, Ignacz F, Dobozy A, Kemeny L.
Treatment of atopic dermatitis with the xenon chloride excimer laser.
JEADV (in press) IF: 1,368

V. Novak Z, Bonis B, **Baltas E**, Ocsovszki I, Ignacz F, Dobozy A, Kemeny L.
Xenon chloride ultraviolet B laser is more effective in treating psoriasis and in inducing T cell apoptosis than narrow-band ultraviolet B.
J Photochem Photobiol B 2002; 67: 32-8. IF: 1,573

CONTENTS

1 INTRODUCTION

1.1 Ultraviolet radiation

Ultraviolet (UV) radiation has been used for decades with great success and a constantly increasing rate in the management of skin diseases. UV light is a form of electromagnetic radiation situated in the wavelength spectrum 100-400 nm. The UV region above 200 nm has been artificially subdivided on the basis of the responses of human skin and the wavelengths contained in sunlight. Three regions are recognized. UVC radiation (200-280 nm) is not found in sunlight at the surface of the earth, as it is filtered out by ozone and water vapour in the atmosphere. UVB radiation (280-320 nm) is the most biologically active waveband of UV radiation in sunlight. UVA radiation (320-400 nm) is biologically less active than UVB and only partially is responsible for the sun-induced erythema.

1.2 Evolution of ultraviolet phototherapy

The beneficial effects of sunlight for various cutaneous disorders have been known since antiquity. The first artificial light source, in the form of a carbon arc, was used for the treatment of lupus vulgaris by Niels Finsen in 1903 (Brodthagen, 1979). This was replaced by the hot quartz mercury vapour lamp used by Goeckerman in 1925 for daily UV light treatment in conjunction with crude coal tar, and with anthralin by Ingram in the 1950s (Goeckerman, 1925). The next advance was the development of the fluorescent lamp in the 1960s, consisting of a low-pressure mercury vapour lamp coated with a phosphor that absorbs the 254 nm radiation, which is re-emitted at longer wavelengths in a continuous spectrum. The availability of high-intensity fluorescent UV irradiators for UVB and subsequently psoralen plus UVA (PUVA) therapy gave impetus to the first-line use of phototherapy for cutaneous disorders (Abel, 1999).

UVA therapy utilizes light energy with a bandwidth from 320 nm to 400 nm. It can be used on its own as UVA radiation or in combination with psoralen. Topical administration of extracts and parts of plants that contain natural psoralen followed by exposure to sunlight has been used as a remedy for vitiligo for thousands of years, beginning with the ancient Egyptian and Indian healers. In modern medicine, the first studies in vitiligo with topical and oral psoralens were performed originally by El Mofty in 1948, and later by Lerner *et al* (Pathak, 1992). In 1974, orally administered 8-methoxypsoralen (8-MOP) and subsequent irradiation

with UVA was a highly effective treatment for psoriasis. This new therapeutic concept was termed photochemontherapy or PUVA (Parrish, 1974). Within a few years the efficacy of PUVA were documented worldwide (Wolff, 1975). This form of therapy is currently used in the treatment of different skin diseases (Abel, 1999). Psoralens can be administered orally or applied topically in the form of solutions, creams or baths. UVA sources commonly used are fluorescent lamps or high-pressure metal-halide lamps. The typical fluorescent PUVA lamp has an emission peak at 352 nm and emits approximately only 0.5 percent in the UVB range. Several investigators have reported the influence of wavelength on therapeutic efficacy in phototherapy, mainly with regard to psoriasis (Parrish, 1981). In 1976 Fisher found wavelength of 313 nm more effective than longer wavelengths in the UVA region. Initially, broad-band (BB)-UVB light sources were applied which emit wavelengths throughout the whole spectrum of UVB light (280-320 nm). In 1981 Parrish and Jaenicke determined an action spectrum for phototherapy of psoriasis (Parrish, 1981). The most effective wavelengths were between 295 and 313 nm; the therapeutic effectiveness in that range resembled the erythemal action spectrum, peaking near 300 nm. These seminal observations provided the rationale for the development of more selective UVB phototherapy (SUP) irradiation devices (Paul, 1983). These units have a spectrum that is still broadband UVB but is enhanced in the range of 300 to 320 nm. A major breakthrough was achieved by the development of the Philips TL-01 fluorescent lamp, emitting a narrow UV band at 311-313 nm and thereby matching closely the assumed therapeutic optimum for psoriasis. A large number of clinical trials comparing BB-UVB versus 311 nm UVB phototherapy for psoriasis have been conducted (Coven, 1997). Based on these studies, it is now generally accepted that narrow-band (NB)-UVB therapy is superior to BB-UVB for psoriasis (Coven, 1997). Patients treated with 311 nm spectrum show faster clearance of skin lesions, fewer episodes of excessive erythema, and a longer period of remission. For these reasons, 311 nm UVB therapy current represents the phototherapeutic modality of choice for the treatment of psoriasis in Europe, and is being used increasingly in the United States. Over the past few years, the development of irradiation devices with new emission spectra has led to an expanded role for phototherapy in the treatment of skin diseases: psoriasis, atopic dermatitis (AD), polymorphic light eruption, mycosis fungoides (MF), pruritus, viltiligo, lichenoid graft versus host reaction.

1.3 The xenon chloride excimer laser

Earlier, we observed that supraerythemogenic fluences of UVB result in faster clearing of psoriasis, however, the limiting factor for the use of such high fluences lies with the intolerance of the uninvolved surrounding skin, since psoriatic lesions can often withstand much higher UV exposure. Because the laser light can be selectively directed towards lesional skin, and all of the energy of a 308 nm excimer laser is emitted within the action spectrum for the phototherapy of psoriasis, our group investigated the therapeutic effect of the 308 nm xenon chloride (XeCl) excimer laser for psoriasis. This laser emits its total energy at 308 nm and may therefore be regarded as a "super narrow band" UVB light source. The laser has been used to treat skin tumors and tattoos. In six patients with chronic plaque type psoriasis, we compared the efficacy of NB-UVB with 308 nm UVB laser. The number of treatments up to complete clearance with the NB-UVB was 29-33, while that with the XeCl laser was 8-10. The cumulative doses were 26-32 J/cm^2, and 2.5-8.1 J/cm^2 for the NB-UVB and XeCl laser, respectively, so the cumulative dose required for the complete clearance of psoriatic plaques was 6 times less with the XeCl laser than with NB-UVB phototherapy (Bonis, 1997). No serious side-effects were observed, just erythema, blisters, hyperpigmentation, but they were well tolerated. In summary, XeCl laser might therefore be regarded as a new and promising form of UVB phototherapy, which seems to be superior to conventional UVB sources in the treatment of psoriasis (Spann, 2001; Kemeny, 2001). The clinical efficacy of the XeCl laser in psoriasis is therefore well documented, but in other skin diseases has not been investigated so far.

1.4 The mechanisms of action of ultraviolet light

1.4.1 The mechanisms of action of ultraviolet light in T cell mediated dermatoses

UVB and UVA phototherapy are currently regarded as modalities whose mechanism of action depends upon immunomodulatory effects that are not specific for a single type of light source (Aubin, 2003). The in vivo relevance of these immunomodulatory effects is dependent on the physical properties of the UV radiation employed. On a per-photon basis, wavelengths within the UVB spectrum possess greater energy than does UVA radiation, but because of their shorter wavelength, they have a more superficial depth of penetration within the skin. As a result, UVB phototherapy primarily affects the function of epidermal keratinocytes and

Langerhans cells (Takashima, 1995), whereas UVA radiation additionally affects dermal fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes within the dermis, mast cells, and granulocytes.

UVB radiation effects the soluble mediators, e.g. it increases the interleukin (IL)-10 protein expression in human keratinocytes (Rivas, 1994), therefore suppresses the production of interferon (IFN)-γ by T lymphocytes (Grewe, 1995). UVB is capable of modulating the expression and function of adhesion molecules, e.g. intercellular adhesion molecule-1 (ICAM-1) expression can be efficiently prevented by exposing human keratinocytes to UVB radiation (Krutmann, 1990). UVB induced also down-regulation of growth factor production and abrogation of growth factor receptor expression (Takashima, 1995). The mixed lymphocyte reaction (MLR) and mixed epidermal cell lymphocyte reaction (MECLR) showed that the alloactivating capacity of cells was decreased by UVB exposure (Vermeer, 1994). UVB can also be immunosuppressive possibly at the level of antigen-presenting dendritic cells (Hart, 2000). The results of some new investigations provide evidence that UVB irradiation can induce regulatory/suppressor T cells (Aubin, 2003). According to the observations of Krueger *et al*, UVB treatment produced consistent and profound depletion of T lymphocytes from psoriatic epidermis. T cell activation appeared to be decreased even further, as judged by expression of the IL-2 receptor. Dermal lymphocytes were much less affected (Krueger, 1995).

In UV-irradiated skin, a distinct and well-circumscribed inflammatory erythema develops as a result of the activities of lipid mediators, biologically active amines, cytokines and oxygen free radicals (Kemeny, 1996; Kemeny, 1994). The UVB-induced erythema is due to the formation of DNA damage and all the other events mentioned are secondary to this. Both direct and indirect data suggest, that platelet-activating factor (PAF) may play a role in the pathomechanism of UV-induced dermatitis (Kemeny, 1996; Publ. III.).

Both UVB and UVA radiation are highly efficient in inducing apoptosis in human cells. UVB treatment caused the induction of Fas ligand on keratinocytes in human epidermis (Gutierrez-Steil, 1998). T cells, as compared with monocytes or keratinocytes, have an increased susceptibility to UV radiation-induced apoptosis; this mechanism is therefore, of particularly importance for phototherapy of T cell-mediated inflammatory (psoriasis, AD) and hyperproliferative (MF) skin diseases.

In summary, the mechanisms of action of UV light in the treatment of T cell mediated dermatoses fall into three major categories: (1) effects on soluble mediators; (2) modulation

of the expression of cell surface-associated molecules; and (3) the induction of apoptosis in pathogenetically relevant cells.

1.4.2 The mechanisms of action of ultraviolet light in vitiligo

The mechanism of action of UVB light in vitiligo is not completely understood. Similar to PUVA therapy, NB-UVB may exert its effects in vitiligo in a two-step process, both of which may occur simultaneously: (1) the stabilization of the depigmentation process, and (2) the stimulation of residual follicular melanocytes.

In the perilesional skin of vitiligo T lymphocytes and macrophages have been reported, which confirmed the involvement of cellular immunity in the pathogenesis of the disease. Well-documented immunomodulatory effects of UV radiation can explain the stabilization of the local and systemic abnormal immune responses (Parsad, 2004; Fitzpatrick, 1997; Kanwar, 2005). The action of PUVA and NB-UVB on perilesional T lymphocytes could also be the explanation for the therapeutic effect of these phototherapies in vitiligo (Fitzpatrick, 1997).

In a study of the mechanism of repigmentation in vitiligo, Cui *et al* demonstrated that in normal skin, only active melanocytes were presented in the epidermis and inactive melanocytes were in the outer root sheaths and formed a reservoir in human skin. While in vitiligo the active melanocytes in the epidermis were totally missing, the inactive melanocytes in the outer root sheaths of hair follicles were not affected by the pathologic process (Cui, 1991). It is likely that NB-UVB, similar to PUVA therapy, stimulates the dopa-negative, amelanotic melanocytes in the outer hair root sheaths, which are activated to proliferate, produce melanin, and migrate outwards to adjust depigmented skin, resulting in perifollicular repigmentation (Cui, 1991) (Fig. 1.).

Hachiya *et al* observed that stem cell factor (SCF) with its receptor, c-kit, plays an important role in the melanocyte mitogenesis, melanogenesis and melanocyte migration, suggesting another possible mechanism of UVB-induced repigmentation (Imokawa, 1995; Hachiya, 2001). During *in vitro* culturing, melanocytes loose their pigment production. After repeated UVB (4x5 mJ/cm^2) irradiation the cells regain pigmentation, observed by Kormos *et al* (Kormos, 2004).

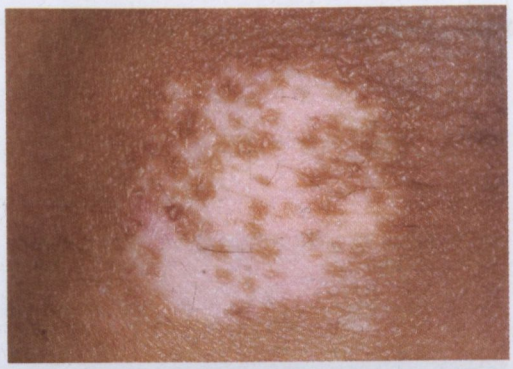

Figure 1. Perifollicular repigmentation in vitiligo.

1.5 Ultraviolet phototherapy of skin diseases

1.5.1 Phototherapy of psoriasis

Psoriasis is a hyperproliferative, inflammatory skin disease of multifactorial origin, affecting approximately 2-3% the population worldwide. In Western Europe the disease is about as common as diabetes mellitus. The symptoms may appear in various forms but either mild or severe forms of psoriasis affect the quality of life tremendously. Clinically, psoriasis is considered a disease of the entire skin, with the most common presentation being well circumscribed erythematous, scaling plaques that may be symmetrically distributed (Fig. 2.). The pathogenesis of the disease is not yet known, the search for the aetiology has concentrated on epidermal proliferation and differentiation, inflammatory changes and the dermal vasculature (Nickoloff, 2004). Although each of these broad areas might hold the answer, now it seems that skin infiltration by activated cutaneous lymphocyte-associated antigen-positive T cells appears to cause a complex inflammatory tissue phenotype, leading to the presence of activated leukocytes in skin lesions, a diverse array of cytokines produced by leukocytes and keratinocytes, proliferation of small blood vessels and epidermal keratinocytes and increased expression of leukocyte-trafficking adhesion molecules. Therefore, there is considerable evidence, that psoriasis vulgaris is mediated by activated T lymphocytes infiltrating the epidermis and the dermo-epidermal interface (Wrone-Smith, 1996). UV phototherapy is indicated for patients with generalized plaque, guttate psoriasis, or palmoplantar psoriasis who have not responded adequately to conventional therapies. The choice of initial treatment with UVB or PUVA is based on a history of previous response to treatment, skin type, severity of psoriasis, and patient considerations, including compliance and responsibility for observing the precautions to avoid potential side-effects. Today, NB-

UVB (311 nm, Philips TL01 bulbs) has become a standard therapy for plaque-type and guttate psoriasis(Barbagallo, 2001).

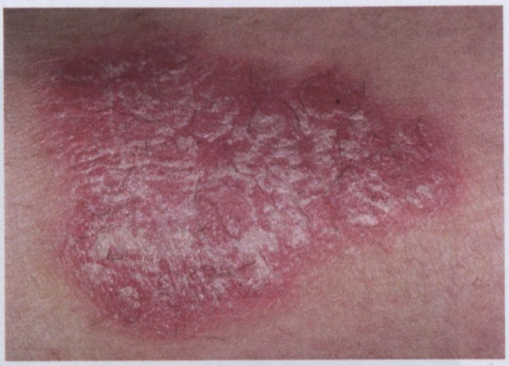

Figure 2. Erythematous, scaling, psoriatic plaque on the elbow.

1.5.2 Phototherapy of atopic dermatitis

AD is a common, multifactorial, chronic and often relapsing inflammatory skin disease with an incidence of 10% that occurs most commonly during infancy and childhood. It is characterised by cutaneous erythema, severely pruritic papular and lichenified plaques, excoriations, cracks, erosions (Fig. 3.) and is a cause of chronic and recurrent physical and psychological disability. The disease is frequently associated with elevated serum immunoglobulin E (IgE) levels and a personal or family history of AD, allergic rhinitis, and asthma. The pathogenesis of AD is primarily one of a stage-related imbalance of the ratio of T helper (TH)1/ TH2 cells, leading to the predominance of TH2 cells and their memory counterparts in acute lesions with subsequent predominance of IFN-γ in later stages. The cytokines present in involved skin as a result of this inflammatory process. In particular, IL-4, IL-5, IL-10, IL-13, and IFN-γ elicit an immune response resulting in the up-regulation of IgE, recruitment and activation of mast cells, basophiles, and eosinophils.

Management of AD entails different approaches depending on the severity, extent, and distribution of skin lesions. Various forms of phototherapy are quite effective for the treatment of AD. Specific protocols, including UVA1 at various dosages, UVAB, UVB, NB-UVB, PUVA (either oral or bath), balneophototherapy, climatotherapy and extracorporeal photopheresis (ECP) have all shown promise in the treatment of AD (Scheinfeld, 2003). The therapeutic effectiveness of UVA1 irradiation in the management of patients with AD was

first evaluated in an open study in patients with acute, severe exacerbations of the disease in 1992 by Krutman *et al* (Krutmann, 1992). NB-UVB therapy is effective against moderate to severe atopic eczema, and is well tolerated by most patients (Reynolds, 2001).

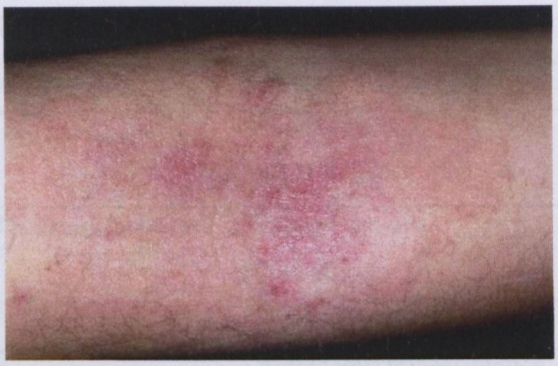

Figure 3. Infiltrated, eczematous lesion on the elbow-joint in AD.

1.5.3 Phototherapy of vitiligo

Vitiligo is a common skin disease, with a prevalence of 1% to 2%, characterized by cutaneous white macules (Fig. 4.), that seriously affect the quality of life of the patients. The pathomechanism of the disease is not fully understood, according to the convergence theory, the coexistence of various factors might lead to the symptoms. Autoimmune mechanisms with an underlying genetic predisposition are the most likely cause of vitiligo, although neurohumoral and autocytotoxic hypotheses are alternative theories or contributing mechanisms. Antibodies to melanocytes have been found by immunoprecipitation in the sera of patients with vitiligo causes damage to melanocytes in cell cultures, suggesting that the antibodies present in the sera may be involved in the pathogenesis of vitiligo (Norris, 1988). Vitiligo patients have an increased association of known autoimmune disorders including thyroiditis, pernicious anaemia, Addison's disease, diabetes mellitus and alopecia areata (Schallreuter, 1994). Lastly, patients with metastatic melanoma may develop vitiligo (Nordlund, 1983). Involvement of cellular immunity has been considered because T lymphocytes and macrophages in perilesional skin have been reported frequently. This finding is consistent with a hypothesis that lesional T cells rather than circulating antimelanocytic antibodies may be responsible for the patchy destruction of cutaneous melanocytes in vitiligo (Badri, 1993). Many treatments have been described in the literature, but these have to be individualised not only for the particular subject, but also for different

body sites on the same subject. Traditional therapies include topical, intralesional and systemic corticosteroids, topical and oral PUVA, and more recently, NB-UVB. The latter is now being used more frequently for the therapy of vitiligo in both adults in children with satisfactory results (Njoo, 2000; Njoo, 1999; Scherschun, 2001; Tjioe, 2005) (Table 1.).

Table 1. Treatment scheme for vitiligo (Njoo, 1999).

	Subtype of vitiligo	First-choice therapy	Alternative therapies
Children (<12 years)	All	Topical steroids (and UVA)	Local UVB (311 nm), topical PUVA
Adults	Localized (<2% depigmentation)	Topical steroids (and UVA)	Local UVB (311 nm), topical PUVA
	Generalized (>2% depigmentation)	UVB (311 nm)	PUVA
	Segmental	Autologous transplantation	Topical steroids (and UVA), UVB (311 nm)
	Lip-tip	Autologous transplantation	micropigmentation
	Therapy resistant an/or generalized (> 80% depigmentation)	Depigmentation with bleaching cream and/or laser	none

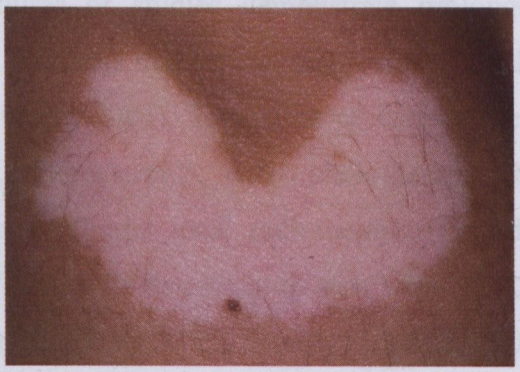

Figure 4. Circumscribed vitiligous macule on the trunk.

1.5.4 Phototherapy of early stage mycosis fungoides

MF represent 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. In general, the process begins with flat lesions (macules and patches). These erythematous patches are often associated with inflammation and pruritus (Fig. 5.). The

diagnosis is elusive as the lymphomatous cells are mature helper T cells and the lesions have an admixture of cell types that suggest inflammatory aetiology. These nondiagnostic patches can persist for years. Invasion of the epidermis is typically associated with the clinical changes of scaling and pruritus. As the cells proliferate, lesions become firmer and more varied in their surface and contour. The clinical progression of the disease than proceeds at variable rates with the development of cutaneous nodules and tumors or erythroderma (Table 2.). Recent advances in the understanding of the molecular and biologic behaviour of T cells in this disorder - the propensity of the cells to home to the skin, to function in an activated state, and to achieve clonal dominance – have had a tremendous influence on the development of treatments (Girardi, 2004). The affected T cells in MF are characterised by a predominant CD4+ phenotype with frequent loss of CD7 (pan-7 cell antigen) and often demonstrate T cell receptor rearrangement. These atypical T cells are initially epidermotropic, but can infiltrate the dermis, lymph nodes, bone marrow, or other systemic organs over time.

There are three main categories of therapy in MF: (1) skin-directed therapy (SDT); (2) biologic response modifiers, and (3) systemic chemontherapy (Girardi, 2004; Gathers, 2002). Biologic response modifiers and systemic chemontherapy are used in higher stage disease and refractory patch- and plaque-stage disease (Girardi, 2004) (Table 3.). The accessibility of the lesions, along with the failures of studies demonstrate prolonged survival using more aggressive systemic therapy, confirms that topical therapeutic modalities are the treatment of choice for localized MF (Girardi, 2004). Treatment of early stage MF consists of various options such as topical corticosteroids, UV phototherapy, bexarotene gel, topical chemontherapy (nitrogen mustard) and local radiotherapy (Girardi, 2004). When treating patients with early stage MF it may be beneficial to start with NB-UVB therapy and, if there is progression or no response, switch to PUVA therapy (Diederen, 2003).

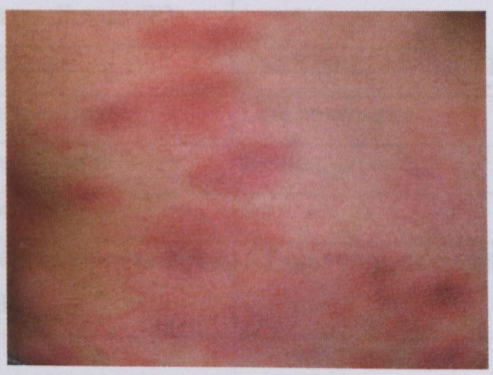

Figure 5. Erythematous patches in early stage MF.

Table 2. Classic tumor-node-metastasis (TNM) staging of mycosis fungoides (Willemze, 1997).

TNM	Definition
Tumor 1	Patches, plaques, or both involving <10% of body surface area
T2	Patches, plaques, or both involving >10% of body surface area
T3	One or more cutaneous tumors
T4	Erythroderma
Node 0	Lymph nodes clinically uninvolved
N1	Lymph nodes clinically enlarged but not histologically involved
N2	Lymph nodes clinically nonpalpable but histologically involved
N3	Lymph nodes clinically enlarged and histologically involved
Metastasis 0	No visceral disease
M1	Visceral disease
Bone marrow 0	No circulating atypical cells (Sezary cells)
B1	Circulating atypical cells (Sezary cells)

Stage	Definition
IA	T1N0M0
IB	T2N0M0
IIA	T1-2N1M0
IIB	T3N0-1M0
IIIA	T4N0M0
IIIB	T4N1M0
IVA	T1-4N2-3M0
IVB	T1-4N0-3M1

Table 3. Therapeutic options in the management of MF (Girardi, 2004).

Limited patch-or plaque disease (T1)	Widespread patch –or plaque disease (T2)	Tumors (T3)	Erythroderma (T4)
Topical steroids	Phototherapy	TSEB with or without RT	TSEB plus ECP
Phototherapy	Nitrogen mustard	Oral bexarotene	Oral bexarotene
Bexarotene gel	Oral bexarotene	Denileukin difitox	Chlorambucil
Nitrogen mustard	Methotrexate	RT	Denileukin difitox
Radiotherapy (RT)	Total-skin electron-beam (TSEB)	RT plus nitrogen mustard	ECP
		RT plus phototherapy	IFN α–2b
		IFN α–2b	PUVA plus IFN α–2b

2 AIMS OF THE STUDY

We have previously found that the 308 nm 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 (Bonis, 1997).

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.

The specific aims of our study were:

1. To extend our previous data on the therapeutic efficacy and safety of the 308 nm XeCl laser for the treatment of psoriasis.
2. To investigate the therapeutic efficacy of the XeCl laser in the treatment of AD.
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 MF.

3 PATIENTS AND METHODS

3.1 Investigations in psoriasis

3.1.1 Patients

48 plaques of 21 patients with chronic plaque type psoriasis were treated with XeCl laser phototherapy. Informed consent was obtained before the start of the study. Upon entry to the study, the patients had not been treated with systemic antipsoriatic medication for a minimum of 4 weeks.

3.1.2 Irradiation

For each patient, a minimal erythema dose (MED) was established in uninvolved, unexposed gluteal skin. XeCl laser therapy was given 3 times weekly until the treated plaques had cleared completely. The initial dose was 0.6 MED, which was increased by 20% on each subsequent treatment. A 308 nm XeCl excimer laser (Lambda Physics LPX 105 E, Göttingen, Germany) was used: its output consisted of a train of short pulses (15 nanoseconds) at 5.5 mJ/cm^2 per pulse, the size of the light spot is 3 cm x 3 cm. In two groups of patients, XeCl laser phototherapy was performed with different impulse intensities (0.06 mJ/cm^2 and 20 mJ/cm^2) or impulse frequencies (1 Hz and 20 Hz), and the cumulative doses and the number of treatments up to complete clearance were determined. In five patients, symmetrical psoriatic plaques were irradiated with the same energy density with XeCl laser, but the frequency of laser impulses was 1 Hz or 20 Hz, and local psoriasis severity index (LPSI) scores were determined for each plaque following each treatment. LPSI is a widely used scoring system for assessment of severity of psoriasis. For each plaque, erythema, induration and desquamation are rated according to a five-point scale. The LPSI score then can vary from 0 to 15, with higher scores representing greater degree of psoriatic severity.

3.1.3 Data analysis

The comparisons were performed by bilateral comparison study and Wilcoxon signed ranks test. A probability level of $p<0.05$ was considered statistically significant.

3.2 Investigations in atopic dermatitis

3.2.1 Patients

Fifteen patients with AD entered the study after receiving full information on the procedure and purpose of the trial. The mean age was 17.3 years (range from 13 to 24); there were 9 females and 6 males. The patients satisfied the diagnostic criteria of Hanifin and Rajka (Hanifin, 1980). They had lesions exclusively on the flexor surfaces of the upper and/or lower extremities. Less than 20% of the body surface was affected. A wash-out period of two weeks after topical corticosteroid treatment and four weeks after systemic treatment was required before starting phototherapy.

3.2.2 Irradiation

Phototesting and laser treatment were carried out with the XTRAC laser (Photomedex Incorporation) instrument. This is a 308 nm excimer laser based on a self-contained gas system of XeCl. The output is initiated by a foot switch and consists of a train of short pulses, delivered through a fiberoptic hand piece, with pulse repetition of up to 200 Hz. The energy of each light impulse is 3 mJ, with a pulse-width of 30 nanoseconds, the beam diameter is 2 cm. The laser allows fixed fluences to be delivered, starting from 100 mJ/cm^2 with 50 mJ/cm^2 increments up to a maximum dose of 2100 mJ/cm^2. Prior to treatment, all patients were phototested in order to determine the MED of the excimer laser, by exposing the buttock to a geometrical dose range between 100 and 350 mJ/cm^2 (Fig. 6.). Phototherapy was started after a one-week period with a topical emollient (Repair®, Yamanouchi). The initial irradiation dose was 50 mJ/cm^2 less than the MED. The dose was increased by 50 mJ/cm^2 each week. The laser pulses were not overlapped, and just right up to the margin of the affected areas were treated. The patients were treated twice weekly, never on consecutive days. The total treatment period was 4 weeks, for a maximum of 8 treatment sessions, but fewer if the lesions cleared. During the study, no additional topical or systemic treatments were allowed, with the exception of the Repair® emollient. The eyes were protected with UV-blocking goggles.

We used the local eczema area severity index (EASI) to determine the severity of the AD (Barbier, 2004). The local EASI score is the sum of the scores of four clinical symptoms (erythema, infiltration, lichenification and excoriation), these being graded from 0 to 3 (0: absent, 1: mild, 2: moderate, 3: severe). The patients rated the intensity of itching during the

24-h period, using a 10-cm visual analogue scale, with 0 cm indicating "no itching" and 10 cm indicating "worst itching imaginable". The aim of the quality of life (QL) questionnaire (10 questions) was to measure how much the skin problem had affected the patients (0: not at all, 1: mildly, 2: moderately, 3: very much) during the past week. Photographs were taken one week before the commencement of laser therapy and at the completion of the therapy. The severity of the AD was scored after the one-week wash-out period at the baseline visit, and then once weekly during the laser treatment.

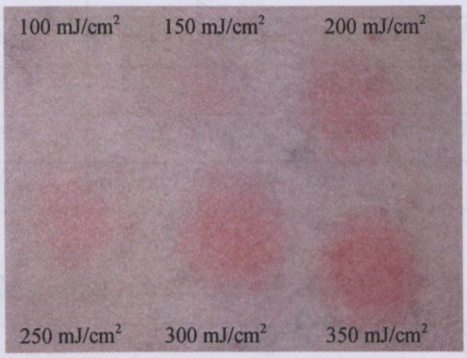

Figure 6. Determination the MED by exposing the buttock to a geometrical dose range between 100 and 350 mJ/cm^2 UVB. The MED of this patient was 150 mJ/cm^2.

3.2.3 Data analysis

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 to be statistically significant.

3.3 Investigations in vitiligo

3.3.1 Patients

Six patients with localized vitiligo were included in the study, five women and one man with a mean age of 27.3 years, ranging form 24 to 45 (Table 4.). Three individuals had Fitzpatrick skin type II and three had type III skin (Table 5.) (Astner, 2004). All of them had localized, stable vitiligo: three patients presented the focal subtype, three had the segmental form. The mean duration of the disease was 9 years, ranging from 5 to 14. All patients had been treated unsuccessfully with topical corticosteroids and other phototherapies before. The patients were without any treatment for six months prior to the study. They were otherwise healthy and used

3.3.3 Data analysis

On the initial visit, a complete history and skin examination were performed. Photographs were taken before the first treatment, after three and six months of treatment, and three months following termination of the laser therapy. Improvement compared with baseline examination was recorded in percentage depending on the extent of repigmentation. Patient compliance was noted in terms of attendance frequency for treatment.

3.4 Investigations in early stage mycosis fungoides

3.4.1 Patients

Four patients with limited patch-stage MF were included in the study (Table 6.). The mean age was 60.7 years (range from 37 to 71); there were 2 females and 2 males. In all patients, the diagnosis of MF was established by the clinical appearance of clinical lesions and confirmed histologically by conventional microscopy and immunohistochemical staining. T cell receptor rearrangement was examined with polymerase chain reaction (PCR). Stage of disease was classified based on the TNM classification (Table 2.). All of the patients had stage IA disease. Stage IA is MF confined to the skin with less than 10% patches and plaques covering the skin surface (i.e., T1N0M0 in the TNM classification). After giving informed consent, all patients were required to discontinue any topical treatment for at least 4 weeks, any systemic treatment for at least 1 month before starting laser treatment.

Table 6. Profile of patients with MF.

Age(y) /Sex	Skin type	Affected area	Previous therapy	TNM/Stage	Duration of disease
62/F	III	leg, trunk	topical corticosteroids, PUVA, retinoid	T1N0M0/IA	9 years
53/M	II	arm	topical corticosteroids, PUVA	T1N0M0/IA	12 years
71/M	III	trunk, leg, arm	topical corticosteroids, PUVA	T1N0M0/IA	10 years
37/F	III	Trunk	topical corticosteroids	T1N0M0/IA	3 months

3.4.2 Irradiation

Phototesting and laser treatment were carried out with the XTRAC laser (Photomedex Incorporation) instrument. The energy of each light impulse is 3 mJ, with a pulse-width of 30 nanoseconds, the beam diameter is 2 cm. The laser allows fixed fluences to be delivered, starting from 100 mJ/cm^2 with 50 mJ/cm^2 increments up to a maximum dose of 2100 mJ/cm^2. Before treatment, all patients were phototested to determine the MED of the 308 nm UVB by exposing an uninvolved area of skin to a dose range between 100 and 350 mJ/cm^2. The irradiation doses were twice the MED. Treatment was administered three times or twice weekly until clinical clearance or minimal residual activity (improvement > 90%) was achieved. During the study, no additional topical or systemic treatments were allowed.

3.4.3 Data analysis

Clinical evaluations were performed every session. Photographs were taken before the first treatment and after termination of the laser therapy. Clinical response was rated as follows: complete remission (no disease activity present), partial remission (decrease of disease activity > 50%), and progressive disease (increase of disease activitiy > 25%).

4 RESULTS

4.1 Results is psoriasis vulgaris

48 plaques of 21 psoriatic patients were treated with the XeCl laser. In order to optimize certain parameters of the UVB phototherapy, we examined whether the therapeutically effect of the XeCl laser depends on the intensity and frequency of the laser impulses.

The mean cumulative doses up to complete clearance of the psoriatic plaques were 4.06 and 4.05 mJ/cm^2 for impulse intensities of 20 and 0.06 mJ/cm^2, respectively (data not shown); the mean number of treatments was 9.2 in both cases. When the XeCl treatment was carried out with an impulse frequency of 1 or 20 Hz, the mean cumulative doses were 4.6 and 4.3 mJ/cm^2, the mean number of treatments was 8 (data not shown). None of these differences proved statistically significant. When the irradiation was performed with 1 or 20 impulses/s, there was also no significant difference in the decrease in LPSI scores (Fig. 7/a, 7/b). Representative clinical pictures are presented in Figure 8.

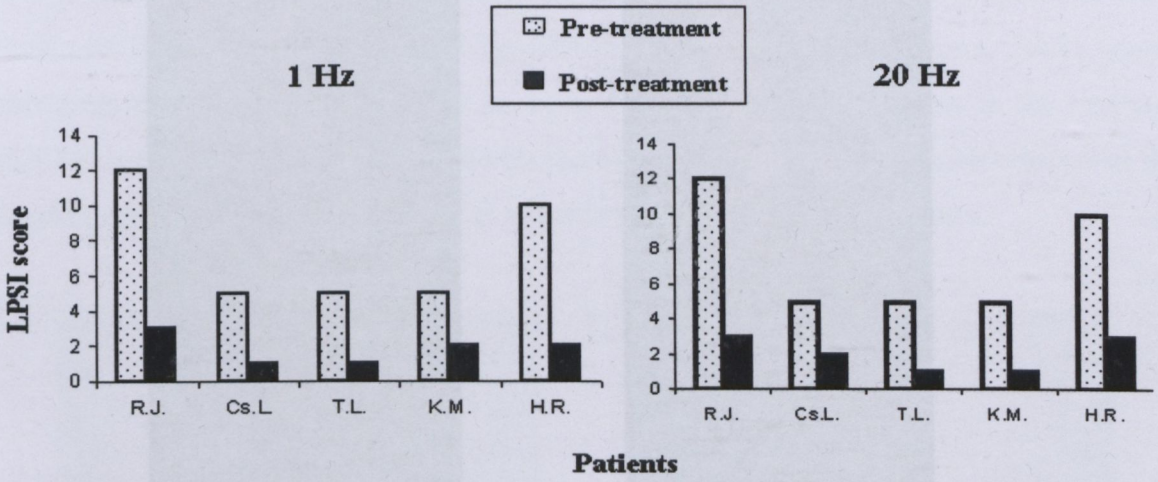

Figure 7a. The local psoriasis severity index (LPSI) scores measured before and after treatments with XeCl laser with 1 Hz or 20 Hz impulse frequencies. Symmetrical psoriatic plaques of 5 patients were compared. The initials of the patients are represented under the bars.

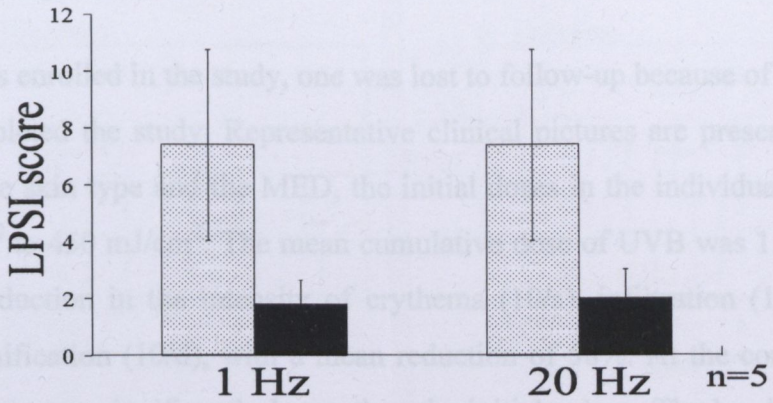

Figure 7b. The average±standard deviation of local psoriasis severity index (LPSI) scores measured before and after treatments with XeCl laser with 1 Hz or 20 Hz impulse frequencies. Symmetrical psoriatic plaques of 5 patients were compared. The differences proved to be statistically not significant measured by Wilcoxon signed ranks test.

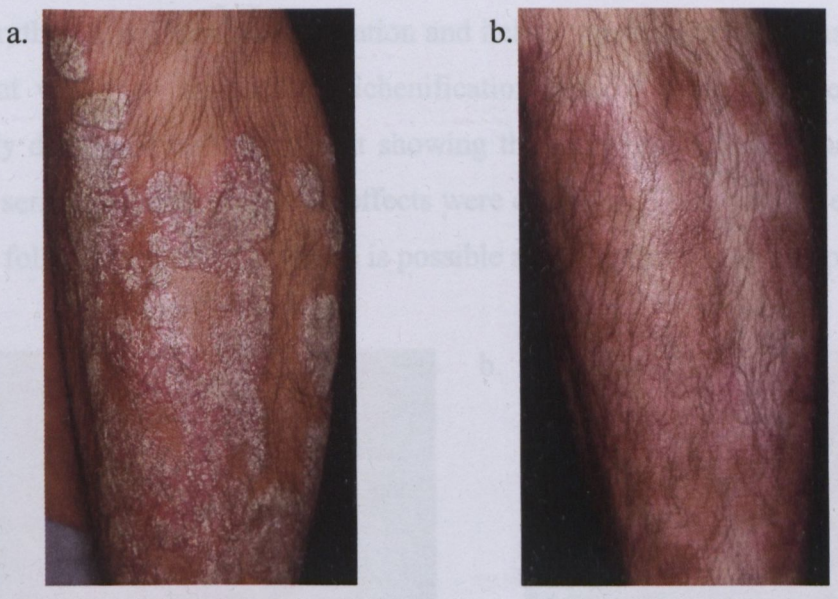

Figure 8. Psoriatic plaque on the leg before (a.) and after 1 month (b.) of laser treatment. After treatment (b.) erythema and transient hyperpigmentation was evidenced in the treated areas with spontaneous resolution.

4.2 Results in atopic dermatitis

Of the 15 patients enrolled in the study, one was lost to follow-up because of non-compliance. 14 patients completed the study. Representative clinical pictures are presented in Figure 9. Depending on the skin type and the MED, the initial doses in the individual patients ranged from 150 mJ/cm^2 to 450 mJ/cm^2. The mean cumulative dose of UVB was 1.66 J/cm^2. Figure 10 shows the reduction in the intensity of erythema (10/a), infiltration (10/b), excoriation (10/c) and lichenification (10/d), with a mean reduction of 58%. At the completion of laser therapy, each score was significantly lower than the initial values. The local EASI scores are presented in Figure 10/e. 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 between 0 and 15 (mean 3.57), and significantly lower as compared with the initial values. Figure 10/f depicts the QL data. Before the laser treatment the QL 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), and significantly lower than the baseline values. Figure 10/g demonstrates an 81% reduction in the itching score after one month of phototherapy, from 2-8 (mean 5.57) to 0-4 (mean 1.02). The score values of erythema, infiltration, excoriation and itching significantly decreased after one week of treatment while the intensity of lichenification reduced after two weeks. EASI scores significantly decreased upon treatment showing the most dramatic decrease in the first two weeks. No serious or unpleasant side-effects were observed. There was no exacerbation at the one-month follow-up, although relapse is possible as with other phototherapies.

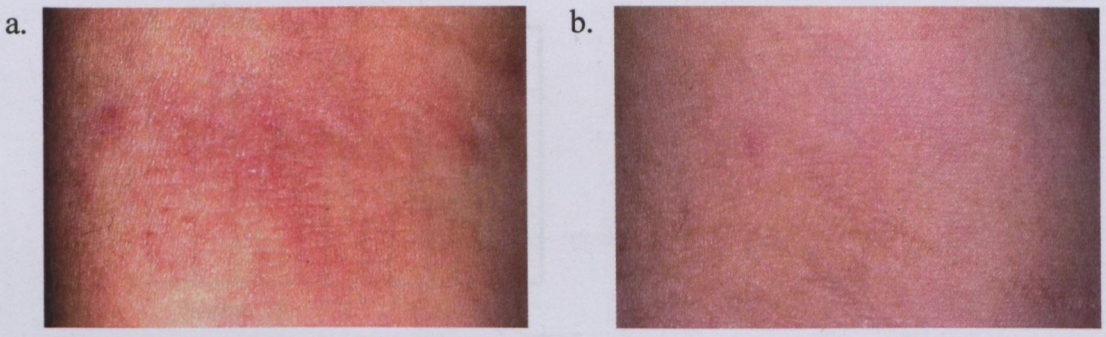

Figure 9. Lesions of AD on the elbow-joint before (a.) and after 1 month (b.) of laser treatment.

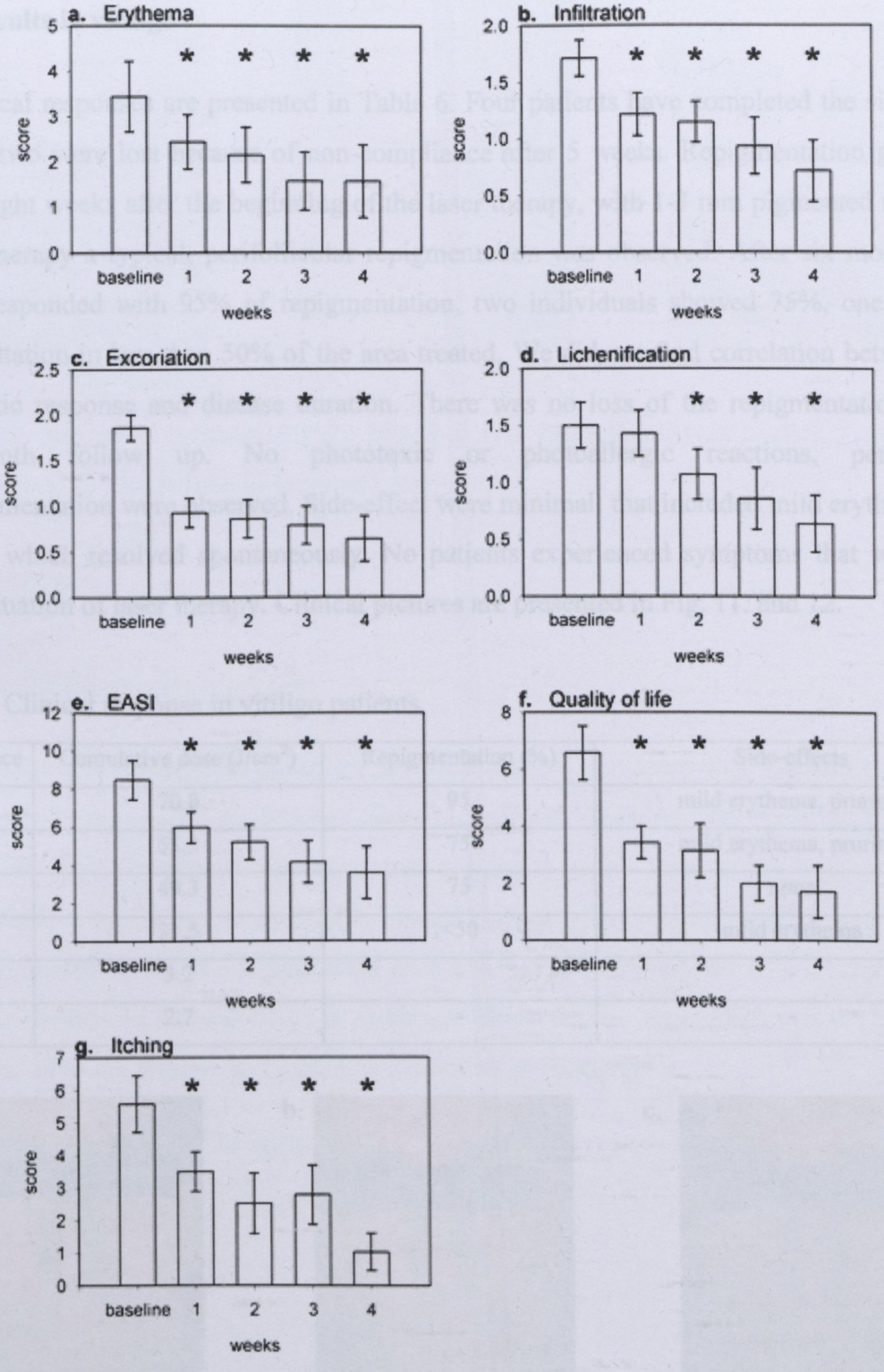

Figure 10. The scores of erythema (a), infiltration (b), excoriation (c), lichenification (d), EASI (e), QL (f), itching (g) significantly decreased during the laser treatment. All values are expressed as means ± standard error. The asterisks indicate statistically significant differences ($P<0.05$) in comparison with the baseline values.

4.3 Results in vitiligo

The clinical responses are presented in Table 6. Four patients have completed the six-month therapy, two were lost because of non-compliance after 5 weeks. Repigmentation generally started eight weeks after the beginning of the laser therapy, with 1-3 mm pigmented macules. During therapy a typical, perifollicular repigmentation was observed. After six months one patient responded with 95% of repigmentation, two individuals showed 75%, one showed repigmentation in less then 50% of the area treated. We did not find correlation between the therapeutic response and disease duration. There was no loss of the repigmentation at the three-month follow up. No phototoxic or photoallergic reactions, perilesional hyperpigmentation were observed. Side-effect were minimal: that included mild erythema and pruritus, which resolved spontaneously. No patients experienced symptoms that warranted discontinuation of laser therapy. Clinical pictures are presented in Fig. 11. and 12.

Table 6. Clinical response in vitiligo patients.

Compliance	Cumulative dose (J/cm^2)	Repigmentation (%)	Side-effects
+	70.8	95	mild erythema, pruritus
+	51.3	75	mild erythema, pruritus
+	49.3	75	none
+	31.5	<50	mild erythema
-	3.2	-	-
-	2.7	-	-

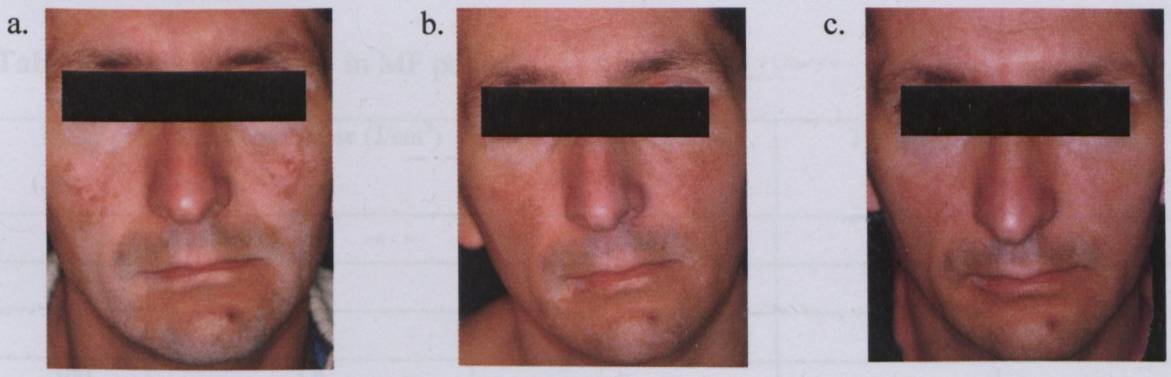

Figure 11. Vitiligous macules on the face before laser therapy (a.), after 3 months of treatment (b.), after 6 months of laser therapy (c.).

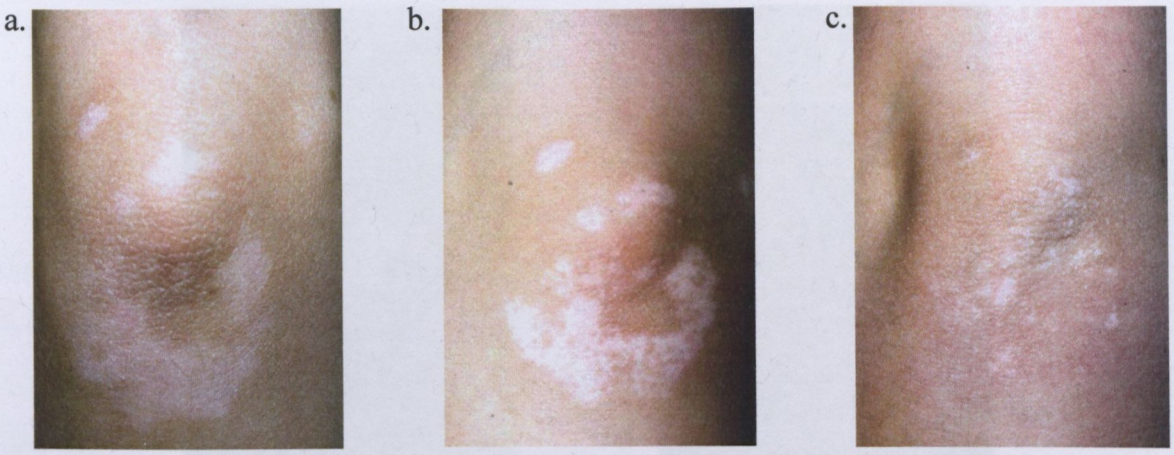

Figure 12. Vitiligous macules on the elbow before laser therapy (a.), after 3 months of treatment (b.), after 6 months of treatment (c.).

4.4 Results in mycosis fungoides

Four patients were treated, all achieved complete clinical remission with a marked reduction in size and infiltration of the patches (Fig. 13.). Clinical healing was obtained in 6 to 14 sessions (average: 9), with a cumulative dose ranging from 2.8 J/cm^2 to 7.4 J/cm^2 (mean: 4.4 J/cm^2) (Table 7.). A slight erythema and transient hyperpigmentation was evidenced in the treated areas with spontaneous resolution after two weeks following the end of treatment. No serious or unpleasant side-effect were observed. There was no exacerbation at the six-month follow-up, although relapse is possible as with other phototherapies.

Table 7. Clinical response in MF patients.

MED (J/cm^2)	Cumulative dose (J/cm^2)	Number of sessions	Treatment interval (weeks)
200	2.8	7	4
200	3.6	9	5
250	7.6	14	6
300	3.6	6	3

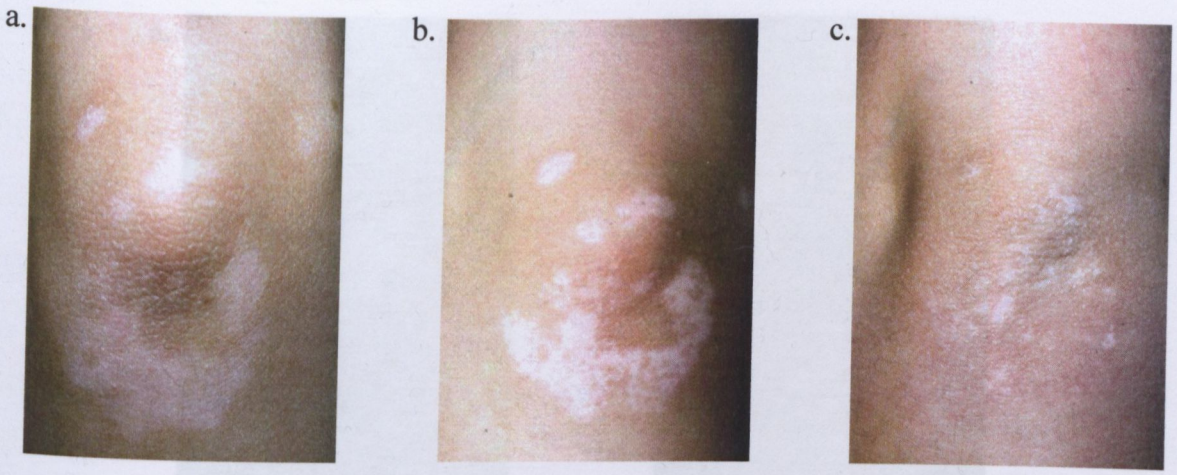

Figure 12. Vitiligous macules on the elbow before laser therapy (a.), after 3 months of treatment (b.), after 6 months of treatment (c.).

4.4 Results in mycosis fungoides

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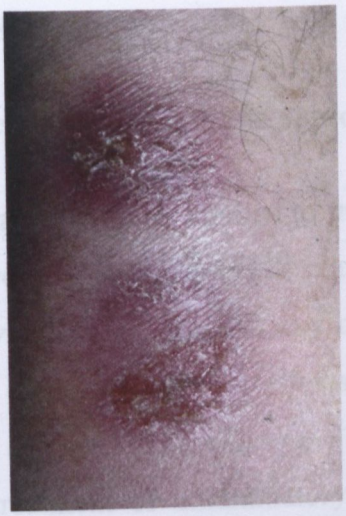
a.



b.

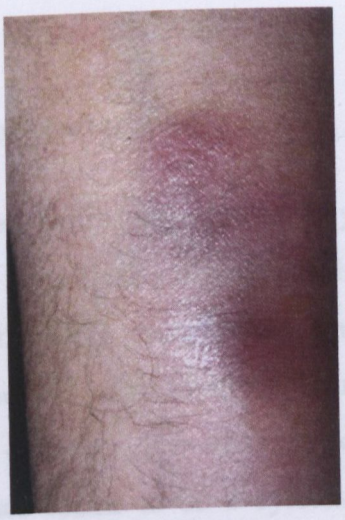


Figure 13. Infiltrated MF lesions on the forearm of a patient before (a.) and after (b.) laser treatment. After treatment (b.) erythema and transient hyperpigmentation was evidenced in the treated areas with spontaneous resolution.

5 DISCUSSION

5.1 Xenon chloride laser in the phototherapy of psoriasis vulgaris

UV phototherapy is widely applied to treat different dermatoses. The prototypic skin disease showing a favorable response to UV phototherapy is psoriasis vulgaris (Fischer, 1976). There is growing evidence that the efficacy of UVA and UVB phototherapy may not simply be attributed to antiproliferative effects, but most likely involves immunomodulatory consequences (Morita, 1997; Gilmour, 1993). One of the major mechanisms of action of UVB light in the treatment of inflammatory dermatoses seems to be a cytotoxic effect on the infiltrating T cells, where the mechanism of cell death is most probably apoptosis (Ozawa, 1999; Aragane, 1998).

Earlier, we found that XeCl UVB laser clears psoriatic plaques more efficiently, than conventional NB-UVB. The cumulative dose required for the complete clearance of psoriatic plaques was 6 times less with the XeCl laser than with NB-UVB phototherapy (Bonis, 1997). The high clinical efficacy of the XeCl laser for psoriasis was later confirmed by other studies. Asawanonda *et al* determined the dose-response relationship of XeCl laser for psoriasis. They used 8 different fluences from 0.5 to 16 MED. The use of such high fluences resulted in a prolonged remission of psoriasis, even after a single treatment. They could demonstrate that fluence was the single most important determinant in the clinical clearing of psoriasis (Asawanonda, 2000). Trehan *et al* also investigated the antipsoriatic efficacy of one single high fluence XeCl laser treatment. 11 of 14 patients showed significant improvement within 1 month, and 5 still demonstrated persistent areas of clearing at 4 months (Trehan, 2002). Another studies established the high efficacy of XeCl laser in chronic inverse psoriasis (Mafong, 2002) and scalp psoriasis(Gupta, 2004). According to a multicenter open trial from 5 dermatology practices including 124 patients, 84% of the patients achieved at least 75% clearing in after 10 or fewer treatments. No serious side-effects were observed, just erythema, blisters, hyperpigmentation, but they were well tolerated (Feldman, 2002).

In order to expand our earlier pilot study, in the present study we investigated the efficacy of the XeCl laser for the treatment of psoriasis. All 21 patients tolerated the treatment well and no serious side-effects were observed. The XeCl laser phototherapy was highly effective in all of the treated plaques, the LPSI scores decreasing quickly following each visit (Publ. V.) Conventional UVB sources emit polychromatic continuous incoherent light, whereas the XeCl laser emits coherent, monochromatic UVB light in short impulses, which permits the

variation of certain important phototherapeutic parameters, such as impulse frequency and light intensity. Earlier, when psoriatic skin was irradiated with multiple MED doses of XeCl laser, the application of higher frequency of laser impulses led to the induction of stronger erythema (unpublished data). These observations indicated that the frequency of impulses influences the biological effect of phototherapy. In the present study, we compared the antipsoriatic efficacy of the XeCl laser when the irradiation was performed at different intensities and impulse frequencies. We did not find significant differences in either of the investigated parameters. In our previous clinical study, treatment of psoriasis with the XeCl laser proved to be more effective than with NB-UVB. We therefore compared the apoptosis-inducing capacities of two different UVB sources: the XeCl UVB laser was found to be a more potent inductor of T cell apoptosis than was NB-UVB light (Publ. V.) There can be several explanations for this difference. Although the NB-UVB light source emits most of its energy in the wavelength interval 311-313 nm, its emission spectrum contains longer wavelengths too, 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 be explained by the differences in the biological effects of coherent laser light from those of incoherent light.

Our *in vitro* experiments were paralleled by the *in vivo* results of the use of the XeCl laser for the treatment of psoriasis, suggesting that the more effective induction of T cell apoptosis may be responsible for the greater clinical efficacy of the XeCl laser as compared with NB-UVB light (Publ. V.).

Carcinogenicity of different UV therapies increases in parallel with the cumulative UV dose during life (Lavker, 1995). We found earlier, that the cumulative dose needed for healing was more than 6 times less with the XeCl laser than with NB-UVB therapy (Bonis, 1997). We presumed, that the lower therapeutic cumulative dose therefore involves a lower risk of carcinogenesis. Additionally, as the majority of the psoriatic patients suffer from mild to moderate psoriasis, affecting only 10-20% of the total body surface, and the XeCl laser is selectively directed toward lesional skin, the laser treatment results in sparing the surrounding normal skin from unnecessary carcinogenic UV radiation exposure.

In summary, our results suggest that the XeCl laser is a new and promising form of UVB phototherapy, which seems to be superior to conventional UVB sources in the treatment of psoriasis (Spann, 2001; Kemeny, 2001; Publ. V.).

5.2 Xenon chloride laser in the phototherapy of atopic dermatitis

The management of AD entails different approaches, depending on the severity, extent and distribution of the skin lesions. The mainstays of topical therapy include the regular use of emollients, coupled with antimicrobials, corticosteroids and immunomodulators. For severe disease, systemic medication such as cyclosporine A can be used for limited periods. Phototherapy is effective for the treatment of AD (Scheinfeld, 2003). UVA1 at various dosages, UVAB, UVB, NB-UVB, PUVA (either oral or bath), balneophototherapy, climatotherapy and ECP have all shown promise in the treatment of AD (Prinz, 1994; Scheinfeld, 2003; Simon, 2000).

The most frequently applied effective forms of phototherapy include NB-UVB and PUVA in patients with moderate to severe AD (Der-Petrossian, 2000). Although insufficient human data are available, it is supposed that long-term NB-UVB therapy may involve a lower risk of skin cancer than that of PUVA therapy (Slaper, 1986).

In the present study, the XeCl UVB laser proved effective for the treatment of localized AD. The mean cumulative dose required for the complete clearance of AD was (5 times) less with the XeCl laser than compared with NB-UVB therapy (Reynolds, 2001). All of our patients observed clinical improvement and QL improvement. The score values of erythema, infiltration, excoriation, lichenification and itching significantly decreased during the treatment. EASI scores significantly decreased upon treatment showing the most dramatic decrease in the first two weeks.

In conventional phototherapy and photochemontherapy the whole body is exposed to UV radiation, the region of action of the 308 nm excimer laser can be restricted to the involved areas. The side-effects, and especially the carcinogenicity, of the different types of UV therapy increase with the cumulative UV dose to which a person is exposed throughout life. With our treatment modality, only the affected areas are treated by UVB light, so that the risks of carcinogenesis and other UVB side-effects occurring on the surrounding skin are much lower.

Our results suggest that the xenon chloride laser is effective and well-tolerated treatment for localized atopic dermatitis (Publ. IV.). However, randomised clinical studies should be performed to show its efficacy in combination with conventional treatment modalities.

5.3 Xenon chloride laser in the phototherapy of vitiligo

Phototherapy alone or in combination is a well-established and widely used treatment for vitiligo. Previously PUVA appeared to be the best method in providing reasonable hope for achieving repigmentation. Both topical and systemic PUVA are used, but short-term and long-term side-effects should be accurately evaluated. Long periods of treatment are required and the results are not always satisfactory. The NB-UVB phototherapy that was firs introduced for the treatment of psoriasis, is now widely used to treat vitiligo. Some studies have compared the efficacy of NB-UVB therapy to topical PUVA in treating generalized vitiligo, conclude that NB-UVB was as efficient as topical PUVA, but had fewer adverse effects (Westerhof, 1997). Based on meta-analysis of the literature it has been reported that of the non-surgical repigmentation techniques class 3 corticosteroids and NB-UVB therapy were the most effective and safest for both localized and generalized vitiligo (Njoo, 1999; Njoo, 1998; Kanwar, 2005; Tjioe, 2005). Oral PUVA was associated with the highest rates of side-effects, while no side-effects were reported with UVB (Njoo, 1999; Njoo, 1998). Recently NB-UVB has been reported effective and safe in adults and children with vitiligo (Njoo, 2000; Scherschun, 2001). Using UVB microphototherapy, the vitiligous patches could be electively treated with BB-UVB light, and this BB-UVB microphototherapy might be a treatment of choice for patients with localized vitiligo according to the study of Lotti et al. (Lotti, 1999). The lack of exposure of the uninvolved skin to UV radiation results in a less risks of short-term and long-term side-effects such as accelerated photoaging and photocarcinogenesis. The 308 nm XeCl laser provide similar advantages for localized vitiligo, as the uninvolved skin can be excluded from the treatment. Additionally, the use of 308 nm XeCl laser might offer further advantages for vitiligo treatment. Although there are no comparative studies using different UVB light sources in vitiligo, in psoriasis NB-UVB was more effective than BB-UVB (Coven, 1997), and XeCl laser was found to be more effective than NB-UVB light (Kemeny, 2001; Bonis, 1997). Hong *et al* reported the 308 nm laser therapy more effective than NB-UVB therapy in the treatment of vitiligo (Hong, 2005). The greater clinical efficacy of XeCl laser compared to NB-UVB light in psoriasis might be partly due to its deeper penetrance into the skin, 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 (Publ. V.). As repigmentation in vitiligo is probably due to the activation of melanocytes in the hair follicles (Feldman, 2002), the deeper penetrance of the XeCl laser might result the good

therapeutical results achieved with this light source. Additionally, conventional UVB sources emit polychromatic continuous incoherent light, while XeCl laser emits coherent, monochromatic UVB light in short impulses, and the biological effects of coherent laser light and incoherent light with the same wavelength might differ. Indeed, we could show recently, that irradiation of T cells with XeCl laser in vitro induced a higher number of apoptotic cells than obtained with the NB-UVB light in the same dosages (Publ. V.), suggesting that in addition to its deeper penetrance into the skin, other factors might also contribute to the greater clinical efficacy of the laser.

In the present study we investigated the efficacy of the XeCl laser for the treatment of vitiligo. Four patients completed the six-month therapy. One patient responded with 95% of repigmentation, two individuals showed 75%, one showed repigmentation in less than 50% of the area treated. No serious side-effects were observed. We found the 308 nm XeCl laser useful and well-tolerated in the treatment of localized vitiligo (Publ. I., II.). The clinical efficacy of the XeCl laser for the treatment of vitiligo (Feldman, 2002; Taneja, 2003; Leone, 2003; Hadi, 2004) and resurfacing-induced leukoderma (Friedman, 2001) was confirmed later by other studies.

In summary, the XeCl UVB laser might therefore be regarded as a treatment of choice in the phototherapy of localized vitiligo.

5.4 Xenon chloride laser in the phototherapy of early stage mycosis fungoides

SDT is used more common in early stage MF, in which the infiltrate is characterized histologically by relative sparse and superficial lymphocytic accumulation. SDT is used as first line therapy, as adjuncts, or for maintenance (Gathers, 2002). SDT has included nitrogen mustard (mechlorethamine), topical carmustine, UVB, PUVA, localized radiation. The results of phototherapy with BB-UVB in the treatment of MF have been reported previously (Ramsay, 1992; Resnik, 1993; Diederen, 2003). Ramsey *et al* reported results from a retrospective study of 37 patients with histologically proven MF who were treated with BB-UVB. Of these patients, 84% had patch-stage disease, and 13% had plaque-stage disease. Of these patients 71% achieved a complete remission. The median time to remission was 5 months. None of the patients with plaque-stage disease were responsive to UVB treatment. Resnik *et al* and Vorderheid *et al* reported similar results in their 15-year follow-up study of 31 patients with histologically proven cutaneous T cell lymphoma (CTCL) who were treated

with UVB (Resnik, 1993). Of these patients, 21 were classified as having stage IA disease, 9 had stage IB disease, and 1 had stage IIA disease according to the TNM system. An objective clinical response was observed in 85% of the patients, with 74% achieving a complete clinical and histological response to therapy. The maximum duration of the remission ranged from 5 months to more than 15 years (median: 51 months). The patients with plaque-stage disease tended to respond less favourably. In the study by Clark *et al*, 8 patients with histologically proven patch-stage MF were treated with NB-UVB three times weekly using a standard protocol (Clark, 2000). Complete clearance of MF was achieved in 6 patients in a mean of 9 weeks or 26 treatments and 4 patients obtained prolonged remissions. Mean time to remission was 20 months. Partial response to NB-UVB was associated with rapid relapse. Diederen *et al* reported results from a retrospective study of 56 patients with early stage MF (stage IA and IB). 21 patients were treated with NB-UVB, 35 patients were treated with PUVA. NB-UVB treatment leads to complete remission in 81% of patients, to partial remission in 19% of patients, and none showed progressive disease. PUVA treatment leads to complete remission in 71% of patients, partial remission in 29% of patients, and none showed progressive disease. The mean relapse-free interval for patients treated with UVB was 24.5 months (range: 2-66 months) and for patients treated with PUVA 22.8 months (range: 1-43 months). They concluded, that NB-UVB is an effective treatment for early stage MF. It has several advantages over treatment with BB-UVB and PUVA. When treating patients with early stage MF it may be beneficial to start with NB-UVB therapy and, if there is progression or no response, switch to PUVA therapy (Diederen, 2003). In 2004 Nistico *et al* reported the 308 nm XeCl excimer laser effective in the treatment of MF. Ten lesions from five patients were treated until complete remission was achieved. The first treatment session started at a dose of twice the MED, and increased by 150-500 mJ/cm^2 during the following sessions. The number of treatments varied from 4 to 10, with a 7-10 day interval according to the response of the patients. The cumulative doses ranged from 6 to 12 J/cm^2. After 12 months follow-up the lesions were in complete remission. Slight erythema and transient hyperpigmentation was observed, which resolved spontaneously (Nistico, 2004). Passeron *et al* find the 308 nm XeCl laser effective and well tolerated in early stage MF (Passeron, 2004).

The exact mechanism of action of NB-UVB therapy is probably due to apoptosis induction in malignant T cell clones. *In vitro* experiments show that UVB decreases the allo-activating and antigen-presenting capacity of Langerhans cells and increases IL-2 and IL-6 production by human keratinocytes (Duthie, 1999; Guckian, 1995). Increased tumor necrosis factor (TNF)

has also been detected after UVB irradiation. Possibly, UV light suppresses the function of the neoplastic population of clonal T cells in the skin and serves as an immune up-regulator (Duthie, 1999).

In our study, four patients were treated and all achieved complete clinical remission with a marked reduction in size and infiltration of the patches. Although the number of patients is limited, the clinical healing observed in all 4 patients demonstrates the benefits of this new technique. These results are obtained 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. In summary, our results showed the efficacy of the 308 nm excimer laser in clearing localized patch-stage MF.

6 SUMMARY

The 308 nm XeCl laser is not unknown in dermatology. The laser emits coherent, monochromatic UVB light in short impulses. The laser treatment is selectively directed toward lesional skin and results in sparing the surrounding normal skin from unnecessary carcinogenic UV radiation exposure. In 1991 it has been tried to remove tattoos and skin tumors using its thermal coagulation effect (Loe, 1990). In 1997 we have found the XeCl excimer laser more effective than the NB-UVB in the treatment of psoriasis (Bonis, 1997; Kemeny, 2001). The clinical efficacy and safety of XeCl laser for the treatment of psoriasis was confirmed later by other studies (Spann, 2001; Trehan, 2002; Asawanonda, 2000; Feldman, 2002; Gerber, 2003; Publ. V.). In 2001 we have found the laser effective and well tolerated in the treatment of localized vitiligo (Publ. I., Publ. II.). The clinical efficacy of the XeCl laser for the treatment of vitiligo (Taneja, 2003; Hadi, 2004; Leone, 2003) was confirmed later by other studies. In addition, the XeCl laser was also effective in the phototherapy of resurfacing-induced leukoderma (Friedman, 2001), hypopigmented scars and striae (Goldberg, 2003; Alexiades-Armenakas, 2004). Recently we have found the XeCl UVB laser effective for the treatment of AD (Publ. IV.). 308 nm laser was found to be effective in the treatment of early stage MF (Nistico, 2004; Passeron, 2004), and also for oral lichen planus (Kollner, 2003; Trehan, 2004). The 308 nm XeCl laser treatment is approved by the Food and Drug Administration (FDA) for the treatment of psoriasis, vitiligo and AD.

One of the major mechanisms of action of UVB light in the treatment of different dermatoses seems to be a cytotoxic effect on the infiltrating T cells, where the mechanism of cell death is most probably apoptosis (Ozawa, 1999; Aragane, 1998). In our investigations the XeCl laser induced T cell apoptosis *in vitro* and was found to be a more potent inductor of T cell apoptosis than NB-UVB light (Publ. V.)

Based - at least partly - on our investigations with the 308 nm excimer laser, a number of new phototherapeutical devices utilizing targeted phototherapy have been developed, and revolutioned the phototherapy of skin diseases.

New results:

1. We extended our pervious data on XeCl laser treatment for psoriasis, and could show the efficacy and safety of 308 nm laser for psoriasis. The clinical efficacy did not depend on light intensity or on laser impulse frequency.
2. We have shown for the *first time* that XeCl laser is effective for the treatment of AD.
3. We have shown for the *first time* that XeCl laser is effective for the treatment of vitiligo.
4. The XeCl laser proved to be effective in the treatment of patch-stage MF.

7 Abbreviations

UV:	Ultraviolet
PUVA:	Psoralen plus ultraviolet A
8-MOP:	8-methoxypsoralen
BB-UVB:	Broad-band ultraviolet B
SUP:	Selective UVB phototherapy
NB-UVB:	Narrow-band ultraviolet B
AD:	Atopic dermatitis
MF:	Mycosis fungoides
XeCl:	Xenon chloride
IL:	Interleukin
IFN:	Interferon
ICAM:	Intercellular adhesion molecule
MLR:	Mixed lymphocyte reaction
MECLR:	Mixed epidermal cell lymphocyte reaction
PAF:	Platelet-activating factor
SCF:	Stem cell factor
IgE.	Immunoglobulin E
TH:	T helper cell
ECP:	Extracorporeal photopheresis
SDT:	Skin directed therapy
TNM:	Tumor-node-metastasis
RT:	Radiotherapy
TSEB:	Total-skin electron-beam therapy
MED:	Minimal erythema dose
LPSI:	Local psoriasis severity index
EASI:	Eczema area severity index
QL:	Quality of life
Phe:	Phenylalanine
PCR:.	Polymerase chain reaction
CTCL:	Cutan T cell lymphoma
TNF:	Tumor necrosis factor
FDA:	Food and Drug Administration

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9 REFERENCES

Abel EA. Phototherapy: UVB and PUVA. *Cutis*. 1999;64:339-342.

Alexiades-Armenakas MR, Bernstein LJ, Friedman PM et al. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. *Arch Dermatol*. 2004;140:955-960.

Aragane Y, Kulms D, Metze D et al. Ultraviolet light induces apoptosis via direct activation of CD95 (Fas/APO-1) independently of its ligand CD95L. *J Cell Biol*. 1998;140:171-182.

Asawanonda P, Anderson RR, Chang Y et al. 308-nm excimer laser for the treatment of psoriasis: a dose-response study. *Arch Dermatol* 2000;136:619-624.

Astner S, Anderson RR. Skin phototypes 2003. *J Invest Dermatol*. 2004;122:xxx-xxxi.

Aubin F. Mechanisms involved in ultraviolet light-induced immunosuppression. *Eur J Dermatol*. 2003;13:515-523.

Badri AM, Todd PM, Garioch JJ et al. An immunohistological study of cutaneous lymphocytes in vitiligo. *J Pathol*. 1993;170:149-155.

Barbagallo J, Spann CT, Tutrone WD et al. Narrowband UVB phototherapy for the treatment of psoriasis: a review and update. *Cutis*. 2001;68:345-347.

Barbier N, Paul C, Luger T et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol*. 2004;150:96-102.

Bonis B, Kemeny L, Dobozy A et al. 308 nm UVB excimer laser for psoriasis. *Lancet*. 1997;350:1522.

Brodthagen H. Stamps commemorating medicine: "Niels Finsen". Physician, photobiologist, nobel laureate. *J Dermatol Surg Oncol*. 1979;5:649.

Clark C, Dawe RS, Evans AT et al. Narrowband TL-01 phototherapy for patch-stage mycosis fungoides. *Arch Dermatol*. 2000;136:748-752.

Coven TR, Burack LH, Gilleaudeau R et al. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. *Arch Dermatol*. 1997;133:1514-1522.

Cui J, Shen LY, Wang GC. Role of hair follicles in the repigmentation of vitiligo. *J Invest Dermatol*. 1991;97:410-416.

Der-Petrossian M, Seeber A, Honigsmann H et al. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J Dermatol*. 2000;142:39-43.

Diederen PV, van Weelden H, Sanders CJ et al. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. *J Am Acad Dermatol.* 2003;48:215-219.

Duthie MS, Kimber I, Norval M. The effects of ultraviolet radiation on the human immune system. *Br J Dermatol.* 1999;140:995-1009.

Feldman SR, Mellen BG, Housman TS et al. Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. *J Am Acad Dermatol* 2002;46:900-906.

Fischer T, Alsins J. Treatment of psoriasis with trioxsalen baths and dysprosium lamps. *Acta Derm Venereol.* 1976;56:383-390.

Fitzpatrick TB. Mechanisms of phototherapy of vitiligo. *Arch Dermatol.* 1997;133:1591-1592.

Friedman SRGRG. Use of 308-nm excimer lasr for postresurfacing leukoderma. *Arch Dermatol.* 2001;137:824-825.

Gathers RC, Scherschun L, Malick F et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. *J Am Acad Dermatol.* 2002;47:191-197.

Gerber W, Arheilger B, Ha TA et al. Ultraviolet B 308-nm excimer laser treatment of psoriasis: a new phototherapeutic approach. *Br J Dermatol.* 2003;149:1250-1258.

Gilmour JW, Vestey JP, George S et al. Effect of phototherapy and urocanic acid isomers on natural killer cell function. *J Invest Dermatol.* 1993;101:169-174.

Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. *N Engl J Med.* 2004;350:1978-1988.

Goeckerman WH. The treatment of psoriasis. *Northwest Med.* 1925;24:229-237.

Goldberg DJ, Sarradet D, Hussain M. 308-nm Excimer laser treatment of mature hypopigmented striae. *Dermatol Surg.* 2003;29:596-598.

Grewe M, Gyufko K, Krutmann J. Interleukin-10 production by cultured human keratinocytes: regulation by ultraviolet B and ultraviolet A1 radiation. *J Invest Dermatol.* 1995;104:3-6.

Guckian M, Jones CD, Vestey JP et al. Immunomodulation at the initiation of phototherapy and photochemotherapy. *Photodermatol Photoimmunol Photomed.* 1995;11:163-169.

Gupta SN, Taylor CR. 308-nm excimer laser for the treatment of scalp psoriasis. *Arch Dermatol.* 2004;140:518-520.

Gutierrez-Steil C, Wrone-Smith T, Sun X et al. Sunlight-induced basal cell carcinoma tumor cells and ultraviolet-B-irradiated psoriatic plaques express Fas ligand (CD95L). *J Clin Invest.* 1998;101:33-39.

Hachiya A, Kobayashi A, Ohuchi A et al. The paracrine role of stem cell factor/c-kit signaling in the activation of human melanocytes in ultraviolet-B-induced pigmentation. *J Invest Dermatol.* 2001;116:578-586.

Hadi SM, Spencer JM, Lebwohl M. The use of the 308-nm excimer laser for the treatment of vitiligo. *Dermatol Surg.* 2004;30:983-986.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;Suppl. 92:44-47.

Hart PH, Grimbaldeston MA, Finlay-Jones JJ. Mast cells in UV-B-induced immunosuppression. *J Photochem Photobiol B.* 2000;55:81-87.

Hong SB, Park HH, Lee MH. Short-term effects of 308-nm xenon-chloride excimer laser and narrow-band ultraviolet B in the treatment of vitiligo: a comparative study. *J Korean Med Sci.* 2005;20:273-278.

Imokawa G, Miyagishi M, Yada Y. Endothelin-1 as a new melanogen: coordinated expression of its gene and the tyrosinase gene in UVB-exposed human epidermis. *J Invest Dermatol.* 1995;105:32-37.

Kanwar AJ, Dogra S, Parsad D et al. Narrow-band UVB for the treatment of vitiligo: an emerging effective and well-tolerated therapy. *Int J Dermatol.* 2005;44:57-60.

Kemeny L, Bonis B, Dobozy A et al. 308-nm excimer laser therapy for psoriasis. *Arch Dermatol* 2001;137:95-96.

Kemeny L, Ruzicka T. Lipidmediatoren. *Hautarzt.* 1994;45:582-591.

Kemeny L, Trach V, Dobozy A. Effect of locally applied WEB 2086, a platelet-activating factor antagonist, on inflammatory skin conditions in mice. *Arch Dermatol Res.* 1996;288:492-494.

Kollner K, Wimmershoff M, Landthaler M et al. Treatment of oral lichen planus with the 308-nm UVB excimer laser--early preliminary results in eight patients. *Lasers Surg Med.* 2003;33:158-160.

Kormos B, Kenderessy-Szabo A, Szabad G et al. Investigation of proliferation and pigmentation in normal human adult epidermal melanocytes cultured in chemical-free medium. J.Invest Dermatol. 123, A46. 2004.

Krueger JG, Wolfe JT, Nabeya RT et al. Successful ultraviolet B treatment of psoriasis is accompanied by a reversal of keratinocyte pathology and by selective depletion of intraepidermal T cells. J Exp Med. 1995;182:2057-2068.

Krutmann J, Czech W, Diepgen T et al. High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. *J Am Acad Dermatol.* 1992;26:225-230.

Krutmann J, Kock A, Schauer E et al. Tumor necrosis factor beta and ultraviolet radiation are potent regulators of human keratinocyte ICAM-1 expression. *J Invest Dermatol.* 1990;95:127-131.

Lavker RM, Gerberick GF, Veres D et al. Cumulative effects from repeated exposures to suberythemal doses of UVB and UVA in human skin. *J Am Acad Dermatol.* 1995;32:53-62.

Leone G, Iacovelli P, Paro VA et al. Monochromatic excimer light 308 nm in the treatment of vitiligo: a pilot study. *J Eur Acad Dermatol Venereol.* 2003;17:531-537.

Loe E, Biltz H, Koort J et al. [Possible advantages of Excimer lasers in dermatology: an in vitro comparison of ArF and XeCl Excimer, Ar+ and Nd: YAG lasers]. *Z Hautkr.* 1990;65:556-561.

Lotti TM, Menchini G, Andreassi L. UV-B radiation microphototherapy. An elective treatment for segmental vitiligo. *J Eur Acad Dermatol Venereol.* 1999;13:102-108.

Mafong EA, Friedman PM, Kauvar AN et al. Treatment of inverse psoriasis with the 308 nm excimer laser. *Dermatol Surg.* 2002;28:530-532.

Morita A, Werfel T, Stege H et al. Evidence that singlet oxygen-induced human T helper cell apoptosis is the basic mechanism of ultraviolet-A radiation phototherapy. *J Exp Med.* 1997;186:1763-1768.

Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest.* 2004;113:1664-1675.

Nistico S, Costanzo A, Saraceno R et al. Efficacy of monochromatic excimer laser radiation (308 nm) in the treatment of early stage mycosis fungoides. *Br J Dermatol.* 2004;151:877-879.

Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol* 2000;42:245-253.

Njoo MD, Spuls PI, Bos JD et al. Nonsurgical repigmentation therapies in vitiligo. Meta-analysis of the literature. *Arch Dermatol.* 1998;134:1532-1540.

Njoo MD, Westerhof W, Bos JD et al. The development of guidelines for the treatment of vitiligo. Clinical Epidemiology Unit of the Istituto Dermopatico dell'Immacolata-Istituto di Recovero e Cura a Carattere Scientifico (IDI-IRCCS) and the Archives of Dermatology. *Arch Dermatol.* 1999;135:1514-1521.

Nordlund JJ, Kirkwood JM, Forget BM et al. Vitiligo in patients with metastatic melanoma: a good prognostic sign. *J Am Acad Dermatol.* 1983;9:689-696.

Norris DA, Kissinger RM, Naughton GM et al. Evidence for immunologic mechanisms in human vitiligo: patients' sera induce damage to human melanocytes in vitro by complement-mediated damage and antibody-dependent cellular cytotoxicity. *J Invest Dermatol.* 1988;90:783-789.

Ozawa M, Ferenczi K, Kikuchi T et al. 312-nanometer ultraviolet B light (narrow-band UVB) induces apoptosis of T cells within psoriatic lesions. *J Exp Med.* 1999;189:711-718.

Parrish JA, Fitzpatrick TB, Tanenbaum L et al. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. *N Engl J Med.* 1974;291:1207-1211.

Parrish JA, Jaenicke KF. Action spectrum for phototherapy of psoriasis. *J Invest Dermatol.* 1981;76:359-362.

Parsad D, Pandhi R, Dogra S et al. Clinical study of repigmentation patterns with different treatment modalities and their correlation with speed and stability of repigmentation in 352 vitiliginous patches. *J Am Acad Dermatol.* 2004;50:63-67.

Passeron T, Zakaria W, Ostovari N et al. Efficacy of the 308-nm excimer laser in the treatment of mycosis fungoides. *Arch Dermatol.* 2004;140:1291-1293.

Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *J Photochem Photobiol B.* 1992;14:3-22.

Paul BS, Stern RS, Parrish JA et al. Low-intensity selective UV phototherapy. A clinical trial in outpatient therapy for psoriasis. *Arch Dermatol.* 1983;119:122-124.

Prinz B, Nachbar F, Plewig G. Treatment of severe atopic dermatitis with extracorporeal photopheresis. *Arch Dermatol Res.* 1994;287:48-52.

Ramsay DL, Lish KM, Yalowitz CB et al. Ultraviolet-B phototherapy for early-stage cutaneous T-cell lymphoma. *Arch Dermatol.* 1992;128:931-933.

Resnik KS, Vonderheid EC. Home UV phototherapy of early mycosis fungoides: long-term follow-up observations in thirty-one patients. *J Am Acad Dermatol.* 1993;29:73-77.

Reynolds NJ, Franklin V, Gray JC et al. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001;357:2012-2016.

Rivas JM, Ullrich SE. The role of IL-4, IL-10, and TNF-alpha in the immune suppression induced by ultraviolet radiation. *J Leukoc Biol.* 1994;56:769-775.

Schallreuter KU, Lemke R, Brandt O et al. Vitiligo and other diseases: coexistence or true association? Hamburg study on 321 patients. *Dermatology.* 1994;188:269-275.

Scheinfeld NS, Tutrone WD, Weinberg JM et al. Phototherapy of atopic dermatitis. *Clin Dermatol* 2003;21:241-248.

Scherschun L, Kim JJ, Lim HW. Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. *J Am Acad Dermatol.* 2001;44:999-1003.

Simon JC, Pfieger D, Schopf E. Recent advances in phototherapy. *Eur J Dermatol* 2000;10:642-645.

Slaper H, Schothorst AA, van der Leun JC. Risk evaluation of UVB therapy for psoriasis: comparison of calculated risk for UVB therapy and observed risk in PUVA-treated patients. *Photodermatol.* 1986;3:271-283.

Spann CT, Barbagallo J, Weinberg JM. A review of the 308-nm excimer laser in the treatment of psoriasis. *Cutis.* 2001;68:351-352.

Takashima A. UVB-dependent modulation of epidermal cytokine network: roles in UVB-induced depletion of Langerhans cells and dendritic epidermal T cells. *J Dermatol.* 1995;22:876-887.

Taneja A, Trehan M, Taylor CR. 308-nm excimer laser for the treatment of psoriasis: induration-based dosimetry. *Arch Dermatol.* 2003;139:759-764.

Tjioe M, Otero ME, van de Kerkhof PC et al. Quality of life in vitiligo patients after treatment with long-term narrowband ultraviolet B phototherapy. *J Eur Acad Dermatol Venereol.* 2005;19:56-60.

Trehan M, Taylor CR. High-dose 308-nm excimer laser for the treatment of psoriasis. *J Am Acad Dermatol* 2002;46:732-737.

Trehan M, Taylor CR. Low-dose excimer 308-nm laser for the treatment of oral lichen planus. *Arch Dermatol.* 2004;140:415-420.

Vermeer BJ, Hurks M. The clinical relevance of immunosuppression by UV irradiation. *J Photochem Photobiol B.* 1994;24:149-154.

Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. *Arch Dermatol.* 1997;133:1525-1528.

Willemze R, Kerl H, Sterry W et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood.* 1997;90:354-371.

Wolff K, Honigsmann H, Gschnait F et al. Photochemotherapy of psoriasis: clinical experiences with 152 patients. *Dtsch Med Wochenschr.* 1975;100:2471-7, 1497.

Wrone-Smith T, Nickoloff BJ. Dermal injection of immunocytes induces psoriasis. *J Clin Invest.* 1996;98:1878-1887.