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Aims and Scope

Acta Dermatovenerologica Croatica (ADC) aims to provide dermatologists with up-to-date information on all aspects of the diagnosis and management of skin and venereal diseases. Accepted articles regularly include original scientific articles, short scientific communications, clinical articles, case reports, reviews, reports, news and correspondence. ADC is guided by a distinguished, international editorial board and encourages approach to continuing medical education for dermatovenerologists.

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Advancing the Mission

In the past year we made a steady progress in global participation, with some increases in article submissions from Poland, Bosnia and Herzegovina, Bulgaria, and Brazil. The Editorial Board will continue its efforts to ensure further global participation in the *Acta Dermatovenerologica Croatica* (ADC).

We begin Volume 12 with more optimism. Issue by issue, the Journal will transform into more prestigious publication. Our intent is to transfer to the reader a better knowledge of the diseases present in various geographic regions and to appreciate more the challenges our colleagues are faced with in the diagnosis and treatment of these disorders. We will strive to prioritize and publish articles that would make high impact.

We will try to continue with our work on electronic publication. At the time we have various technical and financial problems and no sponsor initiative to aid in the transmission of the medical literature to developing countries. An option under consideration is to contact SOROS to help with offering our electronic journal to libraries in Eastern Europe at a discount.

The practice of medicine and dermatovenerology remains art and a calling. We will continue to do our best to highlight the written and visual form of our knowledge and bring emphasis and reinforcement to this art with commentaries, letters, book reviews, and perhaps biographies. We will continue to focus on our mission of worldwide participation to bring new information, updates in dermatology and venerology, as well as special cases.

Our intention for this Volume 12 is to fulfill the parameters set and for our Journal to become more widely accepted, with higher impact and better outlook.

Looking forward to continue progress this year,

Prof. Jasna Lipozenčić, MD, PhD,
Editor-in-Chief
Acta Dermatovenerologica Croatica

Acta Dermatovenerol Croat 2004;12(1):2-6 ORIGINAL SCIENTIFIC ARTICLE

Serum Concentrations of Transforming Growth Factor $_1$ in Patients with Psoriasis Vulgaris

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SUMMARY Psoriasis is a common chronic cutaneous disease affecting 1-3% of general population. Its pathogenesis is not fully understood, but the involvement of several cytokines has clearly been established. The aim of the present study was to evaluate serum concentrations of transforming growth factor (TGF)- $_1$ in patients with psoriasis vulgaris and to correlate these concentrations with severity of psoriasis and several other clinical parameters. Sixty patients with psoriasis and 38 healthy persons (control group) were included into the study. TGF- $_1$ was measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits. Serum concentrations of TGF- $_1$ in patients with psoriasis were significantly increased compared with the controls (42.9±9.9 *vs.* 37.7±6.0 ng/mL, respectively, p=0.004). Patients with more severe disease (PASI <24 points) had significantly higher serum concentration of TGF- 1 than those with mild psoriasis (PASI<24 points; p<0.001). Moreover, serum TGF- $_1$ concentration significantly correlated with disease severity (p=0.001). In patients with pre-existing infections of the respiratory tract, the concentrations of serum TGF- $_1$ were significantly decreased (p=0.03). Since serum concentrations of TGF- $_1$ are increased in patients with psoriasis, TGF- 1 might be used as a marker of psoriasis activity.

KEY WORDS *cytokines; psoriasis; transforming growth factor beta*

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease affecting 1-3% of general population (1). It is characterized by increased proliferation and disturbed differentiation of keratinocytes, dermal/epidermal inflammatory infiltrations of lymphocytes and neutrophils, and enhanced angiogenesis in early psoriatic lesions (1,2). Etiopathogenesis of psoriasis remains unclear, although influence of some genetic and environmental factors has been recognized (3,4). Numerous reports indicated a significant role of cytokines excreted by activated keratinocytes and inflammatory infiltrate cells in the pathogenesis of psoriasis (5-7).

Transforming growth factor beta (TGF-) may be found in humans in three isoformes: TGF- $_1$, TGF- $_2$, and TGF- $_3$. Although they demonstrate similar properties *in vitro*, their functions are very different *in vivo*. TGF- $_1$ is produced by different

cells, including activated inflammatory infiltrate cells and keratinocytes. TGF- $_1$, although regarded as a growth factor, possesses strong immunosuppressive activity, in some experiments even stronger than cyclosporine. Moreover, TGF- $_1$ inhibits keratinocytes proliferation, activates angiogenesis, stimulates fibroblasts proliferation, and production of extracellular matrix elements by these cells (8,9).

The aim of our study was to evaluate TGF- $_1$ expression in the sera of patients with psoriasis vulgaris, and to assess its usefulness as a marker of clinical intensity of psoriasis. Another aim was to define possible correlation between the examined cytokine concentrations and selected triggering factors and the clinical course of the disease.

PATIENTS AND METHODS

Patients

The study was performed among 60 patients with psoriasis vulgaris (19 women and 41 men) divided into several subgroups according to nine criteria (Tables 1 and 2). The mean (SD) age of patients was 36.1 11.7 years (range, 18-61), and mean duration of the disease was 14.6 10.1 years, ranging between 1 month and 37 years. Skin lesion intensity ranged from 7.0 to 48.4 points as measured according to Psoriasis Area and Severity Index (PASI) (10,11). The age at onset of psoriasis in our patients was between 4 and 56 years (21.5 10.3 years). None of the patients had ever been treated with any systemic immunosuppressive agent, and they had not been given any topical antipsoriatic preparations for at least 1 month before the collection of the blood samples. The control group consisted of 38 age- and sex-matched healthy individuals.

Table 1. The examined and the control group divided into subgroups according to gender and age criteria

Selection criteria	Examined group (no of patients)	Control group (no of patients)
total number	60	38
aged <40 years	34	25
aged >40 years	26	13
men	41	26
women	19	12

Table 2. Distribution of the examined (psoriatic) group into subgroups according to criteria reflecting various elements in the course of disease.

Selection criteria	Examined group (no of patients)
total number	60
PASI 24	31
PASI 24	29
recurrences 1 month	23
recurrences > 1 month	37
psoriasis type I	55
psoriasis type II	5
infection influence	21
without infection influence	39
familial history - significant	18
familial history - not significant	42
full remissions	30
partial remission	30
disease duration 20 years	40
disease duration 20 years	20

Measurements of TGF- $_1$ Serum Concentration

Eight milliliters of peripheral blood were collected from all subjects during the exacerbation of the disease. After the 30 minutes at room temperature, the blood was centrifuged for 10 minutes and the serum was aspirated and frozen at –70°C. TGF- $_1$ was measured by enzyme-linked immunosorbent test (ELISA) with a commercially available kit from R&D Systems (Minneapolis, MN, USA), at sensitivity of <0.7 pg/mL in a sample volume of 100 L. The assays were performed strictly according to the manufacturer's instructions. Extinction was measured at 450 nm with a Microplate Reader EL-311 automatic analyzer (Boehring GmbH, Marburg, Germany). Results were calculated from the standard curve of recombined human TGF- $_1$ and were expressed as pg/mL.

Statistical Analysis

Statistical analysis was performed with Student t-test, Cox-Cochran test, variance multifactorial system analysis, and Spearman rank correlation test. P-values less than 0.05 were considered statistically significant.

RESULTS

Mean serum concentration of TGF- $_1$ in the group of psoriatic patients was significantly higher than that in the control group (42.9±9.96 ng/mL *vs.* 37.7±5.96 ng/mL, respectively, p=0.004). The similar significant differences in serum concentrations of TGF- $_1$ were observed between the subgroups of male patients (44.4±10.6 ng/mL) and male controls (37.4±5.72 ng/mL, p=0.003) and between patients (43.8±10.6 ng/mL) and healthy controls (37.3±6.00 ng/mL) younger than 40 years of age (p=0.007; Fig. 1). No such differences were observed between female patients and female controls or between patients older and younger than 40 years of age (Fig. 1).

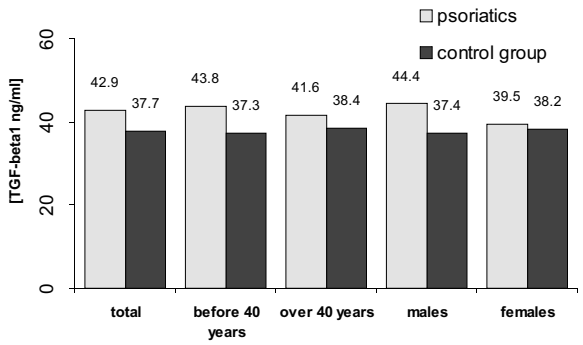

Figure 1. Serum concentrations of transforming growth factor (TGF)- $_1$ in patients with psoriasis vulgaris and healthy controls divided into subgroups according to sex and age.

The serum concentration of TGF- $_1$ in male subjects was 44.4±10.6 ng/mL, which was significantly higher than in female subjects (39.5±7.52 ng/mL, p=0.019; Fig. 2). Patients with lower severity of psoriasis, i.e. PASI <24 points, had significantly lower serum concentrations of TGF- $_1$ than the group of patients with more intensive psoriatic lesions, i.e. PASI <24 points (37.3±6.11 ng/mL *vs*. 48.8±9.86 ng/mL, respectively; p<0.001) (Fig. 2). Moreover, serum concentration of TGF- $_1$ was significantly lower in patients who experienced upper respiratory truck infection than those without a history of such infections (39.1±18.0 ng/mL *vs*. 44.9±10.3 ng/mL, respectively, p=0.03) (Fig. 2). Analysis of influence of sex, PASI score, and history of infections on the serum concentration of TGF- $_1$ by variance multifactorial system revealed that the global variability resulted mainly from PASI value.

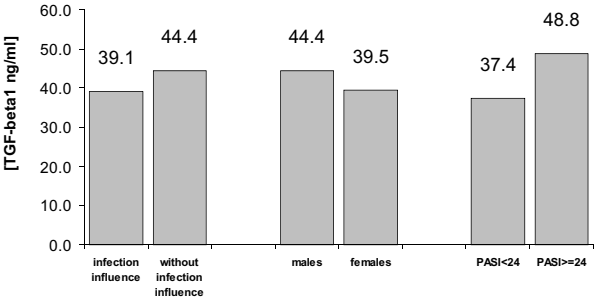

Figure 2. Serum concentrations of transforming growth factor (TGF)- $_1$ in patients with psoriasis vulgaris according to different criteria.

Moreover, serum TGF- $_1$ concentrations significantly correlated with severity of psoriasis (r=0.51, p=0.001; Fig. 3). Patient age, duration of psoriasis, duration of the last outbreak of disease, family history of psoriasis, type of psoriasis (type I or II), and achievement of full or partial remissions did not influence TGF- $_1$ concentration in the sera of our patients with psoriasis vulgaris (data not shown).

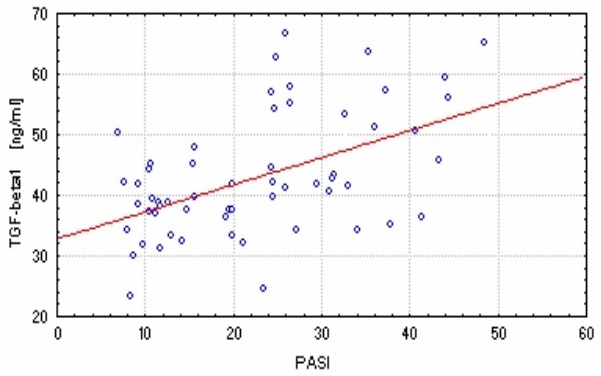

Figure 3. Correlation between serum concentrations of transforming growth factor (TGF)- $_1$ and psoriasis activity (PASI), r=0.51, p<0.001.

DISCUSSION

We found significantly increased concentration of TGF- $_1$ in the sera of patients with psoriasis vulgaris. Moreover, the severity of psoriasis significantly correlated with the serum concentration of TGF- $_1$. Analysis of variance showed that among all separately analyzed factors, PASI had the strongest influence on the concentration of TFG- $_1$ in psoriatic patients. Published data on TGF- $_1$ in psoriatic individuals are very limited. Bonifati *et al* (12) showed increased serum concentrations of TGF- $_1$ in psoriatic patients and also demonstrated

relationship between serum TGF- $_1$ concentrations and intensity of psoriatic lesions, which is in accordance with our results. Although Flisiak *et al* (13) were not able to demonstrate significant differences in plasma concentrations of TGF- $_1$ between patients with psoriasis and healthy controls, they found significant correlation between the plasma TGF- $_1$ and disease severity. Moreover, they found activity of TGF- $_1$ in the scales, but there was no correlation between its concentration in the scales and PASI. Plasma concentrations of TGF- $_1$ were not increased in psoriatic patients and did not show any significant correlation with severity of the disease. The observed discrepancy between studies performed by Bonifati *et al* (12), our study, and findings by Flisiak *et al* (13) could be due to the fact that Flisiak *et al* (13) studied TGF- $_1$ in the plasma not in the sera. It is well known that the main source of TGF- $_1$ in blood are platelets (9).

In the present study, as well as in other studies, the increased serum concentrations of TGF- $_1$ in patients with psoriasis (12) and the positive correlation between its concentration and PASI (12,13) suggested that this parameter could be used as a marker of disease activity. However, we must emphasize that serum concentrations of TGF- $_1$ found by Bonifati *et al* (12) before and after effective antipsoriatic treatment were almost the same. This finding, in only 15 patients, is not surprising, as several investigators demonstrated increased serum concentrations of various cytokines and adhesion molecules in active psoriasis, but did not find their significant decrease after treatment (7,14,15).

Increased serum concentrations of TGF- $_1$ were also found in other inflammatory diseases, such as systemic lupus erythematosus, glomerulonephritis, and rheumatoid arthritis. They were also increased in diseases with associated sclerosis, including scleroderma and hepatic cirrhosis, and other diseases, such as acquired immunodeficiency syndrome (AIDS). Therefore, the increase in serum TGF- $_1$ concentration is probably not specific phenomenon for psoriatic process (8,16).

At present, the role of increased serum concentration of TGF- $_1$ in patients with psoriasis is still unclear. Flisiak *et al* (13) stated that observed correlation between TGF- $_1$ concentration and PASI could be due to vascular expansion with activation of endothelial cells in psoriasis, which are important source of TGF- $_1$. TGF- $_1$ has been shown to be a potent chemoattractant for neutrophils, monocytes, and mast cells. Moreover, TGF- $_1$ may induce angiogenesis and may increase production of Th1 type cytokines (IL-2 and IFN-) by activated T-cells (8,9). Recent studies confirmed psoriasis to be Th1-related disease (17) and all the above mentioned processes could be involved in the pathogenesis of psoriasis (1,2). It cannot be not excluded that TGF- $_1$ is a molecule regulating keratinocytes homeostasis in psoriasis, influencing their proliferation and differentiation. TGF- $_1$ is mainly found in the stratum granulosum and stratum corneum of the epidermis (8). Although significant difference in TGF- $_1$ expression on mRNA level between psoriatic epidermis and healthy skin could not be demonstrated (18,19), Kane *et al* (20) found enhanced expression of TGF- $_1$ protein in psoriatic lesions.

In conclusion, based on the literature data and our own study, it seems that TGF- $_1$ could be involved in the pathogenesis of psoriasis. However, its exact mechanism is not clear. It is also difficult to clearly determine the cellular source of increased serum concentration of TGF- $_1$ in psoriasis. Therefore, further studies are necessary to define the exact role of this multifunctional cytokine in psoriatic process. Nevertheless, the present study suggests usefulness of the TGF- $_1$ measurements in the sera of patients with psoriasis as a marker of the activity of their disease.

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Acta Dermatovenerol Croat 2004;12(1):7-11 CLINICAL ARTICLE

Naphthalanotherapy Reduces Angiogenetic Factor in Psoriatic Lesion

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SUMMARY Immunohistochemical analysis (cell immunophenotyping before and after 3 weeks of treatment with naphthalan oil) was performed on biopsy specimens from 10 patients with psoriasis vulgaris. To determine the angiogenetic factor in psoriatic lesions, immunohistochemical staining on 3- m paraffin block sections was performed by using monoclonal anti-factor VIII antibody. There was a significant difference in the mean number of new blood vessels before and after the therapy (15.1 *vs.* 6.7). It seems that naphthalan therapy reduces number of new blood vessels and has effect on neovascularization in patients with psoriasis.

KEY WORDS F VIII factor of angiogenesis; immunohistochemistry; psoriasis; naphthalan treatment

INTRODUCTION

Naphthalan is a natural, naphthene-based earth oil used for the treatment of psoriasis at the Naftalan Special Hospital in Ivanić Grad, Croatia. It is a thick, dark-brown liquid of a characteristic aromatic odor. In contrast to other related oils, Naphthalan has a high specific weight (0.93-0.97) and mostly contains compounds of stearic structure. Therapeutic properties of Naphthalan have been known since ancient times (1,2). The antipsoriatic properties of heavy naphthene oil (Naphthalan®) make the basis of antipsoriatic treatment regimen that has been successfully used over the last decade at the rehabilitation hospital in Ivanić Grad.

Vulgar psoriasis is a chronic relapsing skin disease affecting 2%-3% of the total population worldwide (3,4). The disease is characterized by precipitated epidermopoiesis with consequential formation of scales on the skin and scalp, and specific nail lesions. Psoriatic arthritis develops in 3%-5% of psoriasis patients (2,3). In Croatia, 1%-2% of the population are affected, whereas psoriatic patients account for 6%-8% of all patients treated at departments of dermatology (5). The disease shows a familial clustering and affects consecutive generations. It usually runs a relapsing remitting course, with varying clinical behavior and different age at

disease onset. There is a novel concept in the pathogenesis of psoriasis, demonstrating the characteristic and well known psoriasiform epidermal hyperplasia to be a secondary lesion in the sequence of pathogenetic events in psoriasis caused by migration of the inflammatory infiltrate cells from the dermis to the epidermis (4).

In 1972, Folkman suggested that psoriasis was an angiogenesis-dependent disease and identified vasoproliferation as a suitable target for the development of anti-psoriatic drug. However, advance in our understanding of the angioproliferation in psoriasis has been made only recently. The therapeutic implication of the angiogenesis in psoriasis has been studied by many investigators (7-11). The factors that control angiogenesis in psoriasis are of interest not only to dermatologists, but also to pathologists. The ultimate aim is to reveal a critical pathway that can be modulated in the treatment of psoriasis.

Role of Angiogenesis in Psoriasis

Psoriasis is primarily a lymphocyte-driven disease – pronounced dermal microvascular expansion in skin lesions suggests that psoriasis is angiogenesis-dependent (6). The key histopathological changes in psoriatic lesions are epidermal hyperplasia, accumulation of inflammatory cells (T-lymphocytes, monocytes, and neutrophils), and expansion of the superficial microvasculature. This microvasculature is composed of capillary loops arising from terminal arterioles in the upper-horizontal dermal vascular plexus, passing up into dermal papilla, and arching back to connect with post-capillary venules in the horizontal plexus. Psoriatic skin has dilated and elongated superficial capillaries passing into the dermal papillae, with multiple vascular segments in the papillary tip. Immunostained microvessels in the biopsy material from lesions and non-affected skin areas in psoriatic patients have demonstrated a fourfold increase in the endothelium of the superficial microvasculature in psoriatic lesions but not in the deeper vasculature. The changes in the microvasculature occur early in the development of psoriatic lesions (4).

Microvessels undergoing angiogenesis display an altered pattern of integrin expression, reflecting the key role of integrins in mediating cell-matrix interaction and endothelial cell activation. Creamer *et al* (7) demonstrated a threefold increase in the expression of v_3 integrin on the endothelium of superficial microvasculature in psoriatic skin, suggesting a functional role for v_3 integrin in psoriatic angioproliferation. Increased expression in v_3 expression in microvessels of the psoriatic skin has been confirmed by Nickoloff *et al* (8). Angiogenesis is an important component of acute and chronic psoriatic skin lesions, as they are erythematous and display a tendency to bleed after the removal of scale (8). Further experiments have demonstrated no up-regulation of $_1$ integrins on psoriatic microvessels, but a down-regulation of $_4$ integrin on the endothelium in psoriatic lesions as compared with that in non-psoriatic skin (7). Subsequent research has also identified microvascular proliferation in plaque disease, with a monoclonal antibody to the proliferation marker Ki-67 revealing a 3.1%-endothelial proliferation index (9).

Keratinocytes in psoriatic skin lesions are a major source of proangiogenic cytokines (4,10). Several angiogenic factors from psoriatic epidermis have been identified, including interleukin-8, tumor necrosis factor- , transforming growth factor- , endothelial cell stimulating angiogenesis factor, thymidine phosphorylase (TP), and vascular endothelial growth factor (VEGF) (4,10). Thus, psoriatic epidermal hyperplasia may involve increased expression of a keratinocyte mitogen (TGF-) rather than deficient expression of a growth inhibitor (TGF-) (10).

Angiopoietins have recently been identified as the major ligands of the endothelial-specific receptor Tie 2 (11). Angiopoietin 1 induces Tie 2 signaling as a receptor activator and maintains blood vessel formation, whereas angiopoietin 2 destabilizes vessels by blocking Tie 2 signaling as an antagonist of angiopoietin 1 and acts with vascular endothelial growth factor to initiate angiogenesis (11). The studies demonstrated that angiopoietins 1 and 2 and Tie 2 were up-regulated in psoriatic skin lesions compared with non-affected skin in psoriasis patients (11).

Chronic inflammation of the tissue underlying the epidermis in psoriatic skin creates a strong angiogenic signal. Several studies have shown a high detectable blood flow in the psoriatic plaques (9-11).

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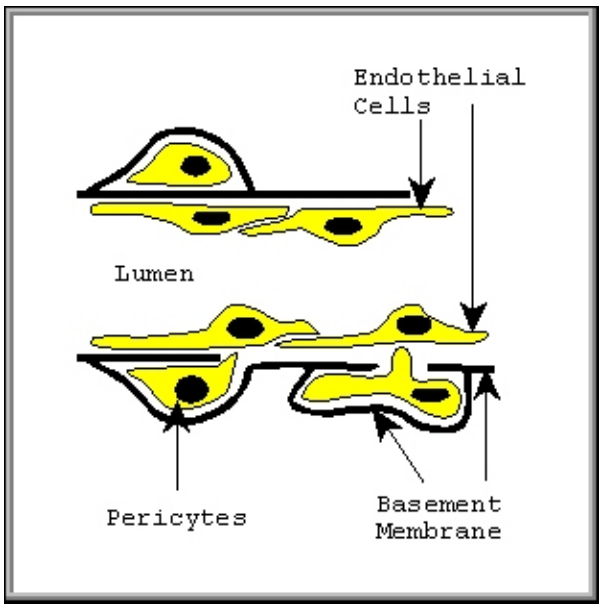

Figure 1. The mechanism of angiogenesis (ref. 12,13).

Angiogenesis Mechanism

In mature (non-growing) capillaries the vessel wall is composed of an endothelial cell lining, a basement membrane, and a layer of cells called pericytes, which partially surround the endothelium (Fig. 1). The pericytes are contained within the same basement membrane as the endothelial cells and occasionally make direct contact with them.

Angiogenic factors bind to endothelial cell receptors and initiate the sequence of angiogenesis (12,13). When the endothelial cells are stimulated to grow, they secrete proteases, which digest the basement membrane surrounding the vessel. The junctions between endothelial cells are altered, cell projections pass through the space created, and the newly formed sprout grows towards the source of the stimulus.

Continued capillary sprout growth is dependent upon several processes: the stimulus for growth (angiogenic factors or hypoxia) must be maintained; the endothelial cells must secrete the proteases required to break down the adjacent tissue; the cells themselves must be capable of movement/migration; and endothelial cell division must take place to provide the necessary number of cells (this takes place at a site behind the growth front of the sprout). Neighboring blind-ended sprouts then join together to form a capillary loop, this later matures into a vessel like the one from which it arose. Hence, inhibiting neovascularization would be an indirect means of counteracting psoriatic plaque formation. This supports observations that the psoriasis-initiating factor resides in the keratinocytes and that a significant vascular proliferation is required to cause hyperplasia of the epidermis.

Angiogenesis-Dependent Diseases

The development of some other dermatological and non-dermatological diseases is also dependent on neoangiogenesis, e.g. in angiofibroma, neovascular glaucoma, arteriovenous malformations, arthritis (including rheumatoid arthritis), lupus, other connective tissue disorders, Osler-Weber syndrome, pyogenic granuloma, retrolental fibroplasias, scleroderma, hemangioma, and hypertrophic scars (12).

Anti-angiogenesis Therapies in the Treatment of Psoriasis

Many effective treatments have an anti-angiogenic activity. Vitamin D_3 analogue shows an antiproliferative action on keratinocytes, thus having anti-angiogenic activity. Topical calcipotriol in psoriasis acts via modulation of angioproliferative pathways in the superficial microvasculature (4). Acitretin, a major synthetic retinoid, is used for topical treatment of psoriasis, whereas tazarotene is a retinoid with topical efficacy showing anti-angiogenic activity via modulation of keratinocyte VEGF production. Hernandez *et al* (14) demonstrated that cyclosporine A (CyA) inhibits angiogenesis induced by VEGF and that this effect is mediated via the inhibition of cyclo-oxygenase (Cox)-2, the transcription of which is activated by VEGF in endothelial cells. Recently there has been a renewed interest in anti-angiogenic effects of razoxane, one of the most successful anti-psoriatic drugs, on human tumors. There is evidence suggesting a biological similarity in the effects of angiopoietin 2 and razoxane on the vasculature, implying that the drug may mediate the vessel stabilizing activity of angiopoietin 2 (4).

MATERIAL AND METHODS

Study group included five female and five male patients with psoriasis vulgaris. Every patient took a 30-minute naphthalan oil bath once a day five days

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a week (except weekend). The clinical improvement at the end of the study correlated with the vessel quantification in biopsy specimen. Biopsy specimens of 0.5 mm in diameter of the whole dermis obtained from the same part of the skin lesions from the patients with of psoriasis vulgaris were submitted to immunohistochemical analysis (cell immunophenotyping) before and after the 3-week treatment with Naphthalan oil. Immunohistochemical staining was performed on 3- m paraffin block sections by using anti-factor VIII antibody (Dako, Glostrup, Denmark). Sections were incubated for 30 minutes at room temperature with primary antibody at 1:100 dilution. After washing, the sections were stained with biotinylated multi-link (swine, anti-rabbit, mouse, and goat immunoglobulin) (Dako) at a 1:1,000 dilution, followed by staining with streptavidin-biotin-peroxidase complex (Dako) at 1:1,000 dilution. The reaction was visualized by DAB staining and slides were contrast-stained with hematoxylin and embedded in a synthetic medium (DPX).

The vessel quantification was done for the dermis of each skin sample as a total positive cell count per mm sample.

RESULTS

The mean vessels number in dermis of psoriatic patients was 15.1 (range, 10-25) before the treatment, and 6.7 (range, 4-12) after the treatment. The immunohistochemical staining with anti-factor VIII antibody was performed for visualization of blood vessels in patients before the therapy. The endothelial cells were stained with factor VIII, revealing many multiplied blood vessels (Fig. 2A). After the therapy, the same method showed a decrease in the number of blood vessels in the lesions (Fig. 2B).

DISCUSSION

In psoriatic skin lesions, there is an expanded superficial microvasculature in close proximity to overlying epidermis; this spatial relationship is critical to fulfill the metabolic needs of hyperplastic keratinocytes and to provide an enlarged endothelial surface area for inflammatory trafficking (4). Epidermal changes in psoriasis induced by an altered differentiation program of the keratinocytes develop along with profound hyperproliferation, acanthosis, parakeratosis, and the lack of granular layer. Abnormal proliferation is due to an increased number of germinative keratinocytes *per* skin surface area, accelerated cell cycle (15), and increased recruitment of actively cycling lymphocytes from a resting pool and on cytokines (15-17). In human skin model of psoriasis, lymphocyte-dependent angiogenesis was proven, with active participation of multiple cell types including natural killer T-cells, keratinocytes, macrophages, and microvascular endothelial cells (8). Our understanding of the molecular and cellular mechanisms involved in psoriatic angioproliferation has advanced in last thirty years. The factors that control angiogenesis in psoriasis are of interest for novel therapeutic strategies in the treatment of psoriasis (4).

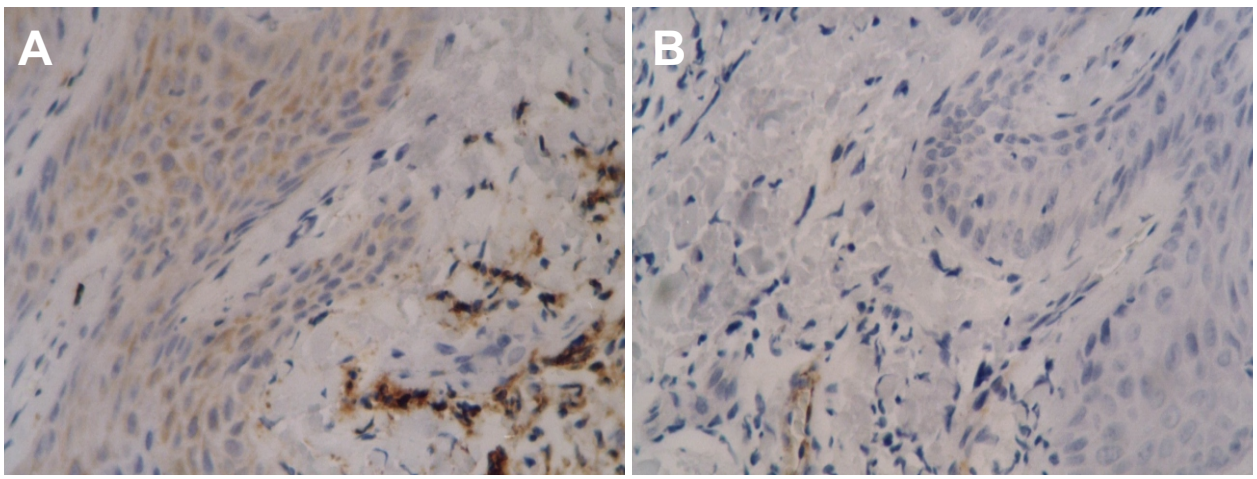

Figure 2. The immunohistochemical staining with anti-factor VIII in patients before (**A**) and after (**B**) naphthalanotherapy. After naphthalanotherapy, blood vessels in dermis were rare in comparison with the findings before the therapy. Contrast-staining with hematoxylin x 200.

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Consequently, normalization of these processes may positively influence the course of the disease. Since both markers are up-regulated by naphthalan, we may assume that this oil can induce keratinocyte differentiation and that it strongly inhibits the proliferation of keratinocytes (16).

Naphthalan also inhibits the angiogenesis in psoriatic dermis. Our results have shown decreased mean vessel number after naphthalanotherapy. Sweet and Smoller (18) and Creamer and Barker (19) found similar results.

There are many ways to treat psoriasis patient. Relatively new approaches in psoriasis treatment are using anti-angiogenic agents. Angiogenic factors initiate the sequence of angiogenesis and the cells are capable of movement/migration. The switch to the angiogenic phenotype involves a change between positive and negative regulators of the growth of microvessels. Naphthalan induces the decrease in the blood vessels number and acts as an anti-angiogenic agent.

CONCLUSION

Although this preliminary approach on possible therapeutic use of naphthalan as a new angiogenic agent to treat psoriasis has proven its anti-angiogenic properties, further studies are needed. The mean number of new blood vessels in dermis of our psoriatic patients after naphthalanotherapy was decreased after 3 weeks of therapy. It seems that naphthalanotherapy has an effect on the neovascularization in patients with psoriasis.

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The Compilation and Edition of the First Color Atlas of Dermatology by Robert Willan (1757-1812), Thomas Bateman (1778-1821), and Ashby Smith (?-1831) from 1790 to 1817

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SUMMARY An account is given of the development of early dermatologic iconography, mostly in watercolors and copper prints, as a consequence of late Enlightenment perspectives and the development of a visually-dependent concept in a text-dominated discipline of dermatology. The first great atlases in the field of dermatology by Robert Willan (1757-1812) and Jean-Louis Alibert (1768-1837), and by M. N. Devergie (1784-1842) in venereology, are addressed and Willan's work is elaborated in detail.

KEY WORDS dermatology; history of medicine; iconography

At the crossroads, when texts and pictures came to lie athwart…

Karl Holubar

INTRODUCTION

In the second half of the 18th century, plants, animals, and diseases (including dermatoses) were systematized, and the Enlightenment period brings to mind the names of Carl von Linné, François Boissier de Sauvages, and Joseph von Plenck. Linné honored his medical colleagues and contemporaries by naming plants after them, e.g., *Sauvagesia*, a tropical weed, or *Fothergilla*, an American shrub (after John Fothergill, 1712-1780, a dedicated botanist and the most well known physician in London at the time). All this notwithstanding, it soon became obvious that words alone would not suffice to describe phenomena in medicine or beyond. As Barbara Maria Stafford put it, and Claudia Benthien reiterated, the text-based culture began to change into a visually dependent culture (1,2). Dermatology, because of the ubiquitous visibility of symptoms, and ophthalmology, dealing with the optical sense *per se*, were in the forefront of drawing and painting in medicine, as evidenced by the earliest paintings (water colors) from 1782 preserved in the archives of the Royal Society of Medicine in London

and the Institute for the History of Medicine in Vienna.

PHYSICIANS-PAINTERS

The three historically most important schools in dermatology – London, Paris, and Vienna – produced a series of impressive atlases over the following century. The unique fact that many physicians in Vienna were painters made us search for physician-painters elsewhere. A long list of painters among dermatologists in Vienna included Carl von Rzehaczek, Lorenz Matthäus Carl Rigler, Anton Elfinger, Carl and Julius Heitzmann, Salomon Ehrmann, Carl Henning and others. In ophthalmology, there were Georg Joseph Beer, Friedrich und Eduard Jäger, father and son; again Carl von Rzehaczek, and the Heitzmann brothers (3-5). In Alibert's atlas from 1806 (6) and Marie-Nicolas Devergie's atlas from 1833 (7), no physician-painters could be identified – Moreau-Valvile and Dupont aîné seem to have been the artists principally employed by these authors. In the Willan-Bateman series of editions from 1798 to 1817, this was different (8-12). Thomas Bateman contributed a series of drawings and paintings for the atlas. Interestingly, one plate (# xxvi), presenting *roseola annulata* and *roseola infantalis*, bears the signature *R. W. delin*^{t} in the left lower corner, proving that also Robert Willan (9) himself produced pictures for his epochal book (Fig. 1). This is evident only in the 1817 edition (9), but not in the earlier one from 1808 (11). Bateman signed his work using either his full name or initials.

ROBERT WILLAN

Willan was the first to produce dermatological pictures in a book, which may be found in the first fascicle of his drawings of cutaneous diseases from 1798 (10). In the introduction to that book he wrote: "In order to convey distinct ideas on the subject, I shall elucidate every genus by colored engravings representing some of its most striking varieties. This method is new, and will be attended with many advantages…". Alibert followed Willan's suit eight years later, although with few referrals to earlier texts: "*Pour imprimer un plus grand sceau d´authenticité á ce que j´ai écrit, pour ajouter á l´énergie et á la puissance de mes discours, pour perpétuer et animer en quelque sorte tous mes tableaux, j´ai cru devoir recourir á l´artifice ingénieux du pinceau et du burin*" (1).

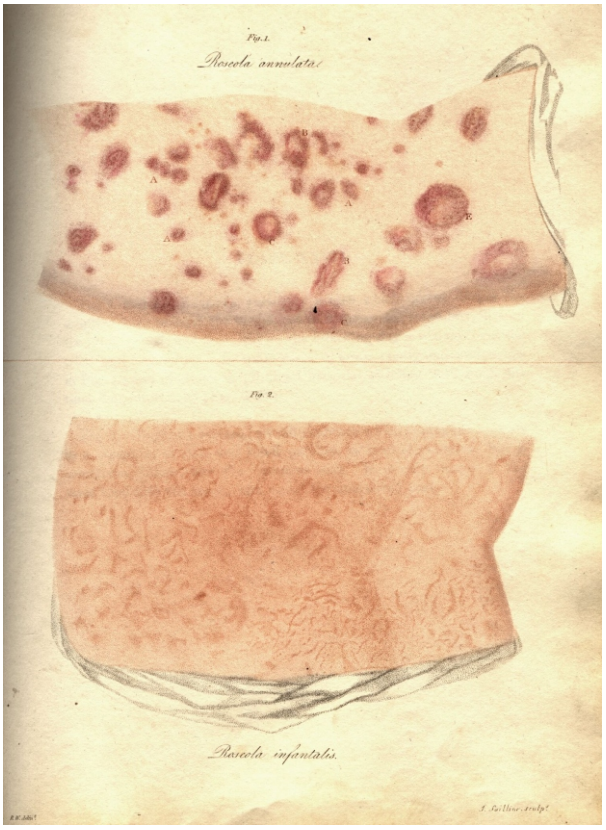

Figure 1. Robert Willan, signed R.W.delin^{t} , J Sailliar, sculp^{s}, plate xxvi, roseola, in the Bateman edition of 1817 (without Willan's initials in the 1808 edition).

For the sake of completeness, it shall be mentioned that the last and posthumous edition of Boissier de Sauvages' *Nosolgia methodica*, edited by C. F. Daniel in Leipzig in 1791, did contain one page of small color pictures. However, these illustrations cannot be compared with Willan's because of lack of clarity, lesser quality, and minute format.

Willan's 1798 edition (10) carried seven plates (some depicting more than one area affected by disease). Willan's edition from 1808 (11), called "volume I", exhibited 33 plates with one or more separate illustrations. Ashby Smith's edition from 1814 (12) had only two pictures, again showing more than one area each (Fig. 2), whereas the cumulative edition by Bateman from 1817 comprised 72 plates of which 18 were done by the hand of Thomas Bateman himself, and one by Willan (9). After Willan's death in April 1812, his wife Mary (Smith)-Willan did not confide the plates to Bateman but rather to Willan's step son-in-law, Ashby

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Figure 2. Ashby Smith edition from 1813, plate ii, *porrigo scutulata*; signed: Syd Edwards del.; Selliers fc.

Figure 3. Bateman edition from 1817, plate lxv, sycosis menti, signed drawn by T.B., eng^{d} by J Stewart.

Smith. It seems that Bateman made up by himself for what he did not have, or was entrusted with by Willan earlier, just to equip the 1817 edition with sufficient pictures. This latter fact proves Bateman's mastership on the graphical level as well, which compares well to the Vienna physician-painters (Fig. 3).

For contrast, Alibert's magnificent atlas numbers 55 plates, mostly done by Moreau Valvile, and stippled by Salvatore Tresca (6). Devergie (not Marie-Guillaume-Alphonse D., 1798-1879, but Marie-Nicolas D., 1784-1842, also referred to as Devergie aîné) numbered up to 161 plates by Dupont aîné, with some of them missing. His is definitely the most extraordinary and impressive atlas of venereal diseases of all times (7) (Fig. 4).

So what may have made Willan to go into depicting skin lesions? Do we have any indications of his motives? The answer could be twofold. First, he was an extraordinary gifted person, a keen observer, dealing with innumerable patients in the Carey Street Dispensary and his own office for more than 20 years. Second, the quagmire of dermatologic diagnoses and his personal education in the classic languages of Latin and Greek played a decisive role. Munk's Roll in the Royal College of Physicians mentions Willan as accomplished classical scholar who even called his horses by classical names, e.g. Odysseus and Telemachus. Where did he learn Greek and Latin? In Sedbergh, Yorkshire, where he was born? A rather small place. Could there have been a grammar school teaching Latin and Greek?

THE THREE YORKSHIRE MEN

Next to the Wellcome Institute in London is the house (and library) of the Society of Friends (Quakers). Suffice it to mention that Willan, as much as his collaborator Thomas Bateman (1778-1821), was a Quaker, as was John Fothergill (1712-1780), Willan's mentor. The three Yorkshire men. Dropping into the Quaker bookshop serendipitously during a recent research stint in London yielded an unexpected result. No biographies of the above persons

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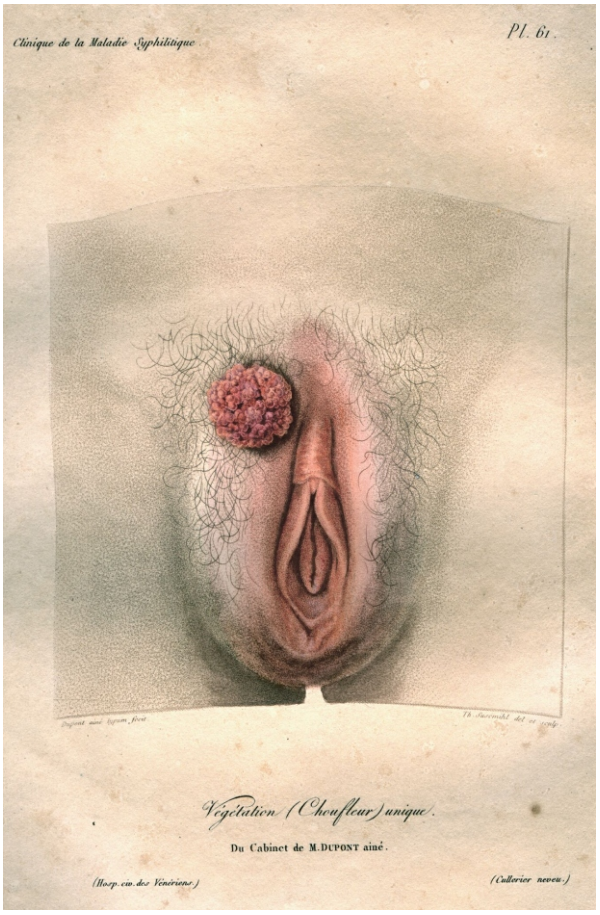

Figure 4. M. N. Devergie, 1833, plate 61, végétation (choufleur) unique, signed Th Susémihl del et sculp, Dupont aîné typum fecit.

were on sale but a student searching other material busied himself next to the counter, sifting through old publications and, by physical proximity, eavesdropped on the question of such biographies being available or not. Browsing through such material, he saw an article on Fothergill and spoke up. It was a brochure from 1979, at sale for a few pennies, recalling the bicentennial of the foundation by Fothergill, of the School of Friends in Ackworth, Yorkshire. There it read that Fothergill himself went to the grammar school at Sedbergh "*where he learnt Latin and Greek*" (14).

The archives of the Medical Society of London treasure letters of Thomas Bateman to Richard Willan, brother of Robert. In one of these letters, dated August 19, 1812 (Robert died on April 7 that year), it reads: "…*he* (Robert) *received his school education solely at the Grammar School at Sedbergh under a namesake of my own."* We may speculate that this fact of Mr. Bateman, (of unknown but possible relation to Thomas Bateman), tutoring Robert Willan at the Sedbergh grammar school, is one of the roots of the close, almost filial relationship Thomas had to his teacher.

Herewith the riddle is solved – Willan who attended the very same school half a century after Fothergill, must have acquired knowledge of classical languages in his hometown. How then relate Latin and Greek to depicting dermatoses?

Quite easily, once the author is familiar with Greek and Latin in general and medical history in particular. The introduction to Willan's "Volume I" from 1808 (11) sufficiently proves both points, and also underlines, what has been quoted above from Munk's Roll. Willan did go after the literal meaning of dozens of old terms, when and where they were applied, wrote that the same names were used differently, or different designations given to the same condition at various body areas. Here is a quotation from the American edition of Willan's "Volume I" (12):

"This will appear from comparing their accounts of Pityriasis, Ceria, Achores, Meliceris, Melitagra; Exanthemata, Helcydria, and Psydracia capitis; Sycose and Lychenose tubercles of the chin; Madarosis, Milphosis, Ptilosis, Alopecia, and Ophiasis… they [the Greek] also paid attention to the cutaneous blemishes, termed Phaci, Ephelides, Chalazia, Thymia, Peliomata, Celides, Rhagades, Tyli, Myrmeciae, Acrochordones, etc." Almost all these terms were used with correct plural and singular, and only some were anglicized. Many of these words mean much the same. A differentiation by letters or words must appear insufficient looking at this queue of terms and the urge to depict what is meant becomes understandable. Drawing or painting was much more in focus in schools, as it is today, as much as calligraphy. Given a certain talent, the drive to draw or paint by one's own hand, would be a logical consequence. In Willan, we recognize a classical scholar, a physician devoted to the diseases of the skin, and a thinker aware of the myriad of names and the insufficiency of what these names mean with respect to what they were applied. Plenck's approach alone looked promising to him as a written concept. And on this he built, by simpli-

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fication and more exact definition of lesions, which he then sought to present to the reader's eye graphically. The result was an epochal oeuvre, phenomenal in its clarity of description and illustration at the same time. Why did it take so long?

From the early 1780s onwards, Willan worked in the Carey Street Dispensary. In 1787, the Medical Society of London invited treatises on topics selected by the society, for winning the John Fothergill Medal (15,16). The first one was awarded to Dr. John Falconer of Bath but not handed in to the prize-winner on the day selected, i.e. Fothergill's birthday on March 8, but later on. The medal had not been ready in time. The second medal, however, was awarded *lege artis* on March 8, 1790. Robert Willan was awarded for an essay entitled "*cuticulam curare paratus*". This was the basis of his later volume. In the preface of the first fascicle, printed in 1798, Willan apologizes to the reader and explains the lapse of almost eight years due to technical difficulties. Later fascicles followed through the years up to 1808, the year when the so-called "Volume I" was edited, one year before an American edition appeared in Philadelphia. Thereafter, Willan's health deteriorated and in 1811 he left England for Funchal, Madeira, where he died on April 7, 1812. The two heirs, one by family and the other by dedication, ran into frictions because Mary (Smith) Willan handed the papers (and prints?) to Ashby Smith and not to Thomas Bateman, who seemed to have had sufficient material from earlier years of cooperation with Willan to compile posthumous editions of the master's work. Both started to edit Willan's work and the respective prefaces of their volumes, Batemans, dated May 25, 1813 (8), and Ashby Smith's, dated September 24, 1814 (13), attest to that sufficiently. Bateman finished the edition on October 1, 1817, embellishing many copies by his own hand. Ashby Smith finished his version of Willan's compilation in 1821, with still another volume of lesser importance and a different title and without illustrations (17). Bateman was most definitely Willan's dermatological successor and as an artist capable as his teacher, as evidenced by the wide circulation of his editions, which speak in favor of even greater graphical talent. His 1817 (9) preface makes that clear: "in order, however, to fulfil the wishes of the profession by the completion, as far as it was in my power, of the series of engravings begun by Dr. Willan, I have purchased the copyright of that work together with the drawings and engravings procured by him, and have now brought that series to a conclusion."

Modern dermatology was built on Robert Willan's (1757-1812) work and on account of his eminent merits for the discipline, he was rightfully elected "the dermatologist of the millennium" at a session of the Royal Society of Medicine on February 23,1999). His life and tragic death at age 55 in Madeira have been the subject of many papers that followed since. In any case, he was the one who started to equip texts describing skin diseases with proper color prints and thereby foreshadowed what was to come in the 19th century. Next to the two men mentioned, J. L. Alibert and M. N. Devergie, there were the atlases of Erasmus Wilson (18), Ferdinand Hebra (19), Radcliffe Crocker (20), and many others. At the end of the century, photography and moulages started to replace watercolors and engravings or lithographs.

POST SCRIPTUM

Ashby Smith was Willan's step son-in-law, who accompanied Willan to Madeira and remained by the master's side until his death. He was a member of the Royal College of Surgeons – aside to that nothing more can be said about him, not even year of his birth. The year of his death, i.e. 1831, however, is recorded in Franz Ehring's encyclopedic book, *Skin Diseases:* Five Centuries of Scientific Illustration (21) and can be verified through the Royal College of Surgeons in London. After all, Ashby Smith may be a double surname, or, as sometimes customary in the Anglo-Saxon world, a surname, e.g. his mother's maiden name used as a first name or middle name, or simply a first name. Sometimes Ashby-Smith is hyphenated. The question remains, therefore, if he should be placed under "A" or under "S" in an alphabetic reference list. I chose the former variant just because his name(s) appear always in full and not as "A. Smith". This, on the other hand, may be due to the way people with frequently encountered family names, e.g. Smith, use to write their other names in order to avoid being mistaken for other "Smiths". After all, Moriz Kaposi mentioned that possibility as one of the reasons why he wanted to change his name.

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Acta Dermatovenerol Croat 2004;12(1):18-25 REVIEW

The Genetics of Psoriasis

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SUMMARY There is considerable epidemiologic evidence that genetic component plays a key role in the pathogenesis of psoriasis. The disease is multifactorial in origin and shows polygeneic inheritance. In the last decade, there have been significant advances in our understanding of the genetic basis of this common disease. Susceptibility gene characterization and knowledge of the immune basis of psoriasis have better defined the disease pathways involved in the pathogenesis of psoriasis. A number of genetic loci have been identified by genome wide-linkage scans. In particular, the importance of PSORS 1 linkage characterization is emphasized, as this information will help develop more specific diagnostic and prognostic tools.

KEY WORDS genes; psoriasis; susceptibility loci; PSORS 1

INTRODUCTION

Psoriasis is a common inflammatory hyperproliferative skin disease affecting 2% to 3% of the Caucasian population in North America and most of the European countries (1). The disease can be localized to small skin areas or generalized. In 5-10% of cases, psoriasis is associated with seronegative, potentially disabling arthritis (2). However, association with some intestinal inflammatory diseases and acquired immunodeficiency syndrome (AIDS) has also been reported (3,4). Although psoriasis is rarely fatal, it can be debilitating because of its unfavorable effects on the quality of life and social stigmatization (5).

Psoriasis is a heterogeneous disease – it may manifest in a number of distinct clinical subtypes. The most common clinical subtype is *psoriasis vulgaris* (PV), accounting for approximately 85% of all cases (2). *Guttate psoriasis* (GP) is an important clinical variant that most frequently occurs in adolescents and young adults. It is characterized by sudden onset of widely dispersed small red scaly plaques, mainly over the trunk and proximal limbs. GP is often associated with a preceding streptococcal throat infection (6). In most cases, the disease is self-limiting (acute GP), but a significant proportion of patients develop PV later in life. Also, these patients often have a family history of psoriasis (7). Other less common clinical subtypes include generalized pustular psoriasis (GPP), palmoplantar pustular psoriasis (PPP) and erythrodermic psoriasis (2).

Histologically, PV is characterized by epidermal hyperproliferation and altered differentiation, angiogenesis, and epidermal and dermal leukocyte infiltration (2).

Both sexes are equally affected, and 75% of patients develop psoriasis before age 40. Initial manifestation of PV usually occurs in the third decade of life. Two peaks of age at onset have been described. The first peak is between 20 and 30 years, and the majority of psoriasis patients belong to this group. The second, smaller peak occurs at 50-60 years. A hypothesis is that, in analogy to diabetes mellitus, there are two types of non-pustular psoriasis. Type I with early onset is human leukocyte antigen (HLA)-associated psoriasis with strong family history and more severe clinical course. Type II is sporadic and characterized by late onset (after age 40); it is not associated with HLA and usually manifests in a milder form of the disease (8).

The etiology and pathogenesis of psoriasis remains to be defined. However, it is clear that psoriasis is a multifactorial disease in which both genetic and environmental factors are responsible for the occurrence and phenotypic expression of the disease (9). Environmental factors include streptococcal infections, some medications, trauma, and stress (2). Several lines of evidence point to a prominent role of T-cells in the pathogenesis of psoriasis, and it is now generally accepted that psoriasis is the most prevalent T-cell mediated inflammatory disease in humans (10).

The genetic basis of psoriasis has long been recognized by clinicians because of familial clustering. The mode of inheritance does not follow Mendelian patterns. These observations have been supported by large epidemiologic studies. On the basis of results of a classic epidemiologic study including more than 10,000 individuals from the Faroe Islands (Denmark), Lomholt (11) concluded that psoriasis was genetically determined. The incidence of psoriasis on the Faroe Islands was 2.8%, and 91% of psoriasis patients had a positive family history. Lomholt (11) proposed a multifactioral mode of inheritance of psoriasis in which genetic components end external factors jointly influence the onset and course of the disease.

Further evidence for genetic involvement in psoriasis came from demographic, epidemiologic, serologic, family, and twin studies, as well as from numerous reports on the association of the disease with HLA Cw6 antigen (12). A number of twin studies were performed to elucidate the genetic variability of dissimilar concordance rates in monozygotic and dizygotic twin pairs. The concordance rate indicates how often twin pairs are both affected or both unaffected in contrast to being discordant when one is affected and the other one is not. Analyzing 219 twin pairs, Farber *et al* (13) found that the median concordance of psoriasis in monozygotic twins was 65% in contrast to 23% in dizygotic twins. The conclusions were that psoriasis followed a multifactioral mode of inheritance, and that a heritable component contributed to a distinct disease pattern. Monozygotic affected twins more often show similar age at onset as well as similar distribution patterns, course, and severity of the disease than dizygotic twins in whom no such trends have been observed (13).

Because of the autoimmune and genetic predisposition of psoriasis, early genetic studies were focused on HLA association as these genes are involved in antigen presentation to T-cells. The HLA genes located within the major histocompatibility complex (MHC) display a high degree of polymorphism (more allelic forms of the gene). Associations between psoriasis and HLA B13, B57, B37, B39, Cw2, and Cw6 from HLA class I have been identified (14-18), with HLA-Cw6 showing the strongest and most consistent association in most ethnic groups (19). The MHC genes characteristically display strong linkage disequilibrium (co-segregation of marker and disease allele, a reflection of physical proximity and recombination fraction, since certain alleles occur together more frequently than expected by chance) because of low recombination frequencies between them, resulting in the presence of conserved or ancestral haplotype (20). Later studies have shown strong association of psoriasis with many extended haplotypes, of which nearly all contain Cw6.The role HLA class II DR and DQ antigens in psoriasis has been intensively investigated since 1981. Schmitt Egenolf *et al* (21) published one of the first reports on the association between DNA-typed HLA class II alleles and type I psoriasis. They found a significantly higher frequency of HLA-DRB1*0701 (DRB1*0701 is a subtype of DR7) in patients with psoriasis type I than in

control group. The same group of authors also introduced an extended haplotype EH 57.1 (57 deduced from B57) – Cw6-B57-DRB1*0701-DQA1*0201-DRB1*0303 (22). By comparing the frequencies of the extended haplotype EH57.1 in 35% of psoriasis type I and 2% of controls, they calculated a 26-fold risk of psoriasis development (22). An extended haplotype is a combination of several distinct alleles, which is nearly always inherited as a full complex having remained essentially unchanged throughout evolution. Ikaheimo *et al* (23) studied 64 Finnish patients and confirmed earlier finding of Cw6 as a single gene, which showed a stronger correlation with psoriasis than the complete Cw6-DR7-DQA1*0201 haplotype. Jenisch *et al* (24) showed the HLA class II DRB1*0701 and DQB1*0303 haplotypes to increase susceptibility to psoriasis only in the presence to Cw6. A recent study of 29 patients from UK revealed that all patients with guttate psoriasis carried HLA Cw*0602 allele (6).

Association has been found between HLA and many other diseases, such as insulin-dependent diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and celiac disease (25-27). All these diseases are polygenic disorders originating from concert operation of different genes. Therefore, the patterns of heredity are complex and hard to decipher. Non-HLA and HLA genetic components interact in the outbreak of disease. This may also hold true for the inheritance of nonpustular psoriasis.

Given that psoriasis is a complex disease displaying wide variation in phenotype and clinical response, a number of susceptibility genes are probably responsible for its expression. Since 1990, a multilocus model of inheritance has been accepted as an explanation of psoriasis (12). Since that time, several genome-wide scans with paramateric and nonparametric approaches have been performed, aiming to detect linkage with any psoriasis susceptibility loci. In eight studies, significant evidence for such a linkage have been reported for psoriasis susceptibility 1 (PSORS 1) region located on the short arm of chromosome 6 and specifically within MHC (28-35) (Table 1).

PSORS 1 confers a high risk for psoriasis. It has been estimated that the HLA-associated PSORS 1 alleles account for 35-50% of familial clustering observed in psoriasis (28,29). Research groups from all over the world are focusing their efforts on defining the major susceptibility allele within PSORS 1 (36).

Table 1. Candidate loci in psoriasis identified by genetic linkage study

Locus	Chromosomal location	Authors (year)	Ref. No.
PSORS1	6p21.3	Trembath *et al* (1997)	28
		Nair *et al* (1997)	29
		Burden *et al* (1998)	30
		Jenisch *et al* (1998)	31
		Capon *et al* (1999)	32
		Samuelsson *et al* (1999)	33
		Enlund *et al* (1999)	34
		Veal *et al* (2001)	35
PSORS 2	17q24-25	Tomfohrde *et a*l (1994)	56
		Nair *et al* (1997)	29
		Samuelsson *et al* (1999)	33
		Enlund *et al* (1999)	34
PSORS 3	4q34	Mathews *et al* (1996)	58
		Samuelsson *et al* (1999)	33
PSORS 4	1q21	Capon *et al* (1999)	59
		Bhalerao & Bowcock (1998)	1
PSORS 5	3q21	Enlund *et al* (1999)	60
		Samuelsson *et a*l (1999)	33
PSORS 6	19p13-p34	Lee *et al* (2000)	61
		Veal *et al* (2001)	35
PSORS 7	1p35-p34	Veal *et al* (2001)	35
PSORS 8	16q12-13	Nair *et al* (1997)	29
		Karason *et al* (2003)	62
	20p	Trembath *et al* (1997)	28
		Nair *et al* (1997)	29
	19p-13	Lee *et al* (2000)	61

SUSCEPTIBILITY LOCI FOR PSORIASIS

PSORS 1

The first complete sequence and gene map of human MHC was reported in 1999 by the MHC Sequencing Consortium (37). This region is located on chromosome 6 (6p21.3), which is among the first multi-megabase regions of the human genome to be completely sequenced. When it was discovered

50 years ago, the region was thought to specify histocompatibility genes. However, the nature of these genes has only been resolved in the last two decades. The average gene density (including pseudogenes) over the entire 3.6-Mb is 1 gene *per* 16 kilobases (kb). Although many of the 224 identified loci are still of unknown function, the MHC Sequencing Consortium estimate that about 40% of the expressed genes have an immune system function. Over 50% of MHC have been sequenced twice in different haplotypes, providing an insight into the extraordinary polymorphism end evolution of this region (36). The MHC genes involved in the functioning of the immune system may be potential candidates for psoriasis susceptibility (Fig. 1).

PSORS 1 contains HLA Cw6. To date, no functional role has been assigned to HLA-C. However, HLA Cw6 may play a role in determining the age of psoriasis onset. Type I psoriasis shows a much stronger HLA Cw6 association compared with type II psoriasis (38). Guttate psoriasis is also characterized by an early onset and strong association with HLA Cw6 (6).

It has also been observed that patients with psoriasis may have different clinical features depending on whether they are HLA-Cw6 positive or negative. HLA Cw6-positive patients often show an earlier age at onset and more extensive plaques on their arms, legs and trunk, more severe form of the disease, and a higher incidence of Koebner's phenomenon. Dystrophic nail changes and psoriatic arthritis are more common in HLA Cw6 negative patients (17,39,40).

Type I psoriatics generally have a propensity to a more widespread and recurrent disease compared with type II patients (8). Alternatively, HLA Cw6 may simply represent a genetic marker of psoriasis susceptibility since type I psoriasis is characterized by a strong family history of psoriasis (8). Not all patients with psoriasis carry the Cw6 allele, and not all HLA-Cw6-bearing haplotypes confer an

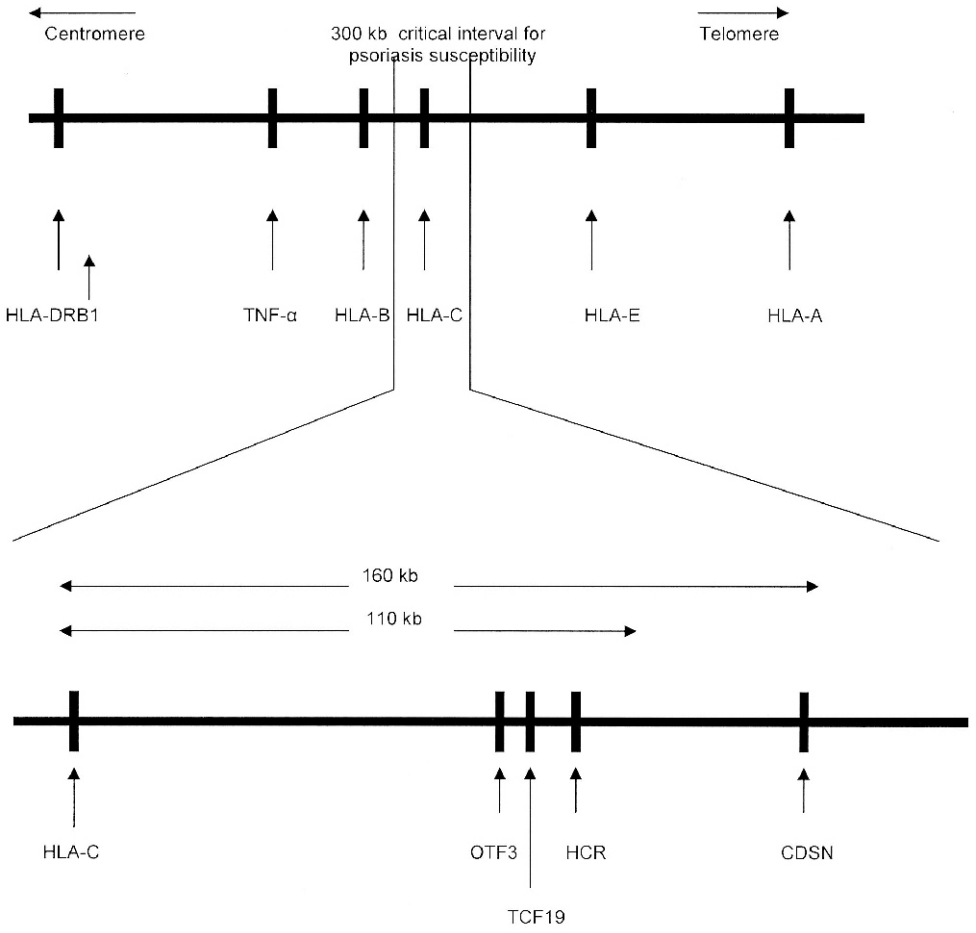

Figure 1. PSORS 1 on chromosome 6p21.3 with known candidate genes (modified according to ref. 9).

equal risk for psoriasis development (31). The strong HLA Cw6 association found in many ethnic groups may be the result of linkage disequilibrium with a nearby gene on the same chromosome. It is now widely accepted that HLA Cw6 is probably a marker for PSORS 1 gene rather than the major susceptibility allele itself (9,41-43).

Linkage disquilibrium mapping has refined the PSORS 1 susceptibility region to an approximately 300-kb interval around HLA-C (Fig. 1). This interval has been sequenced and besides HLA-C, four other genes have been described: OTF 3 (POU5F1), TCF 19 (SC1), HCR (Pg8), and corneodesmosine (CDSN).

Gonzalez *et al* (44) have reported on association with one allele of OTF3 gene in a Spanish population, although they acknowledged that OTF3 was a somewhat unlikely candidate for susceptibility for psoriasis, as the gene encoded a transcriptional factor playing a major role in embryonic stem cell lineage commitments.

Teraoka *et al* (45) analyzed TCF 19 coding for cell regulator, expressed in the G1-S phase of the cell cycle, but failed to observe any association.

HCR and CDSN deserve special mention, as there is a strong genetic and functional evidence for their role in the pathogenesis of psoriasis. The HCR gene has lately been under intense scrutiny (Fig. 1). It is located 110 kb telomeric of HLA-C in the critical region for psoriasis susceptibility. Sequencing analysis showed that HCR was highly polymorphic. HCR was first identified as a putative structural component of skin-related tissues, as it presented trichohyalin, myosin, and laminin homologies (46). Asumalahti *et al* (47) demonstrated the gene to be ubiquitously expressed but upregulated in psoriatic epidermis. They also tested HCR as a PSORS 1 candidate by analyzing 17 intragenic single-nucleotide polymorphisms (SNPs) in a Finnish population sample. Their study disclosed a significant association between psoriasis and two-SNP haplotypes bearing two Arg›Trp substitutions (HCR*Trp-Trp allele). In addition, functional studies suggest that HCR is a regulator of keratinocyte differentiation and proliferation, providing additional support for HCR candidacy in psoriasis pathogenesis (47).

The CDSN gene is located 160 kb telomeric of HLA-C in class I region and codes for corneodesmosin, a desmosomal protein involved in keratinocyte cohesion and desquamation (48,49) (Fig. 1). A recent study demonstrated CDSN overexpression and altered distribution in psoriatic epidermis, which are disease-specific changes, as they have not been observed in other inflammatory skin diseases, such as atopic dermatitis and lichen planus (50). The CDSN gene is highly polymorphic and its polymorphism occurs at a frequency of 1/65 kb at least (51).

The linkage and association with psoriasis vulgaris has been demonstrated for an allele of the CDSN gene defined by SNPs +619 (Ser›Phe) and +1243 (Ser›Leu) giving amino acid substitution (41,52). Given the high CDSN polymorphism, SNP haplotypes rather than single alleles are likely to influence protein structure. A high-risk haplotype including high-risk alleles +619, +1236, and +1243 has shown a significant association with psoriasis (53). Based on its genomic position and putative biologic function, CDSN is an attractive candidate gene for psoriasis susceptibility.

Other Candidate Loci for Psoriasis Susceptibility

It is now clear that a number of genetic risk factors besides PSORS 1 may play a role in psoriasis. Bowcok *et al* (54,55) first demonstrated the existence of a predisposing locus other than HLA in some families. Some of the other non-MHC candidate loci for psoriasis susceptibility are of particular interest. The linkage to 17q24-q25 (PSORS 2) demonstrated by Tomfohrde *et al* (56) has been replicated by other groups in a variety of populations in the USA, Sweden, and Ireland (29,33). The search for this gene is under way (57).

The linkage of psoriasis susceptibility with regions other than PSORS 1 and PSORS 2 has been reported in multiply affected families from different geographic locations: 4qter (PSORS 3) in a group of Irish families (58), 1q21 (PSORS 4) in a family from Lazlo region in Italy (59), 3q21 (PSORS 5) in a set of Swedish families (60), 19p13 in German families (61), and 16q in Icelandic families (62). The candidate interval on 19p13 (PSORS 6) contains a gene that codes for ICAM-1, a ligand for lymphocyte function-associated antigen (LFA) that acts as a major cell adhesion molecule mediating leukocyte migration in psoriasis. PSORS 4 on chromosome

1q21 contains the epidermal differentiation complex, a cluster of genes expressed during epidermal differentiation. It also contains other skin expressed genes, including loricrin, involucrin, and filagrin, a psoriasin which is overexpressed in psoriatic skin and acts as a potent chemotactic inflammatory protein for CD4+ (63). Several immune related genes have been mapped on chromosome 1p (PSORS 7), including the gene encoding for EPS 15, a highly specific intercellular substrate for the epidermal growth factor receptor, which is overexpressed in psoriatic epidermis (35). It is interesting that some psoriasis susceptibility loci coincide with the loci identified for other inflammatory and autoimmune diseases, such as chromosome 1q for atopic dermatitis, 3q21 and 17q24.3 for rheumatoid arthritis, and 16 p for inflammatory bowel disease (54). This is an important finding because clinically distinct autoimmune diseases may be controlled by a common set of susceptibility genes.

The identification of multiple loci for psoriasis susceptibility has stressed that psoriasis is a heterogeneous disease with different genetic causes. It is also important that epistasis (interaction) exists between some susceptibility loci. For example, the penetrance of PSORS 1 is only 10%, and the presence of psoriasis in PSORS 1-positive patients is thought to be caused by epistasis with other loci (55).

In an effort to confirm the previously reported linkage to psoriasis, the International Psoriasis Genetics Consortium analyzed 942 affected sibling pairs from 710 pedigrees for 53 microsatellites spanning 14 psoriasis candidate regions (64). This large collaborative study is likely to facilitate further research efforts to determine and characterize the susceptibility loci for psoriasis. These data provide unequivocal evidence for a major role of a gene or genes within the MHC class I region. Other loci are likely to confer a lower risk of disease causation (64).

Psoriasis is probably a multigeneic disease, with multiple susceptibility genes working in a concert to produce the abnormal phenotype (65).

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Acta Dermatovenerol Croat 2004;12(1):26-29 REVIEW

New Trends in the Immunopathogenesis of Psoriasis

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SUMMARY Psoriasis is a chronic hypeproliferative inflammatory skin disease characterized by abnormal keratinocyte hyperproliferation and differentiation, intra-epidermal accumulation of neutrophil granulocytes, and dermal inflammatory infiltrate that mostly consists of T-cells. Today, psoriasis is definitely recognized as a T-cell-mediated inflammatory disease. Infiltration of T-cells seems to be the primary event that precedes the keratinocyte hyperproliferation. It is suggested that systemic lymphocyte activation is followed by the local accumulation of specific CD4+ T-cells and subsequently by the activation of intradermal CD8+ T-cells. So far, it seems that CD4+ T-cells create an appropriate type-1 cytokine environment for CD8+ T-cells activation that eventually trigger the psoriatic cascade. Thus, T-cells are responsible for initiation and maintenance of psoriasis. The precise mechanism how activated T-cells trigger psoriasis is yet unknown. However, it seems that the specific immune reaction to a putative antigen, mediated by T-cells leads to creation of psoriatic lesions. The immune reaction constantly driven by bacterial superantigens or epidermal self-antigens eventually leads to development of psoriatic lesions. The psoriatic process is a dynamic process that includes interaction between Th1- and Tc1-cells as well as between T-cells and keratinocytes. The better understanding of the immunopathogenesis of psoriasis would allow for development of specific T-cell-targeted and/or cytokine-targeted new therapies.

KEY WORDS cytokines; immunopathogenesis; keratinocytes; psoriasis; T lymphocytes

INTRODUCTION

Psoriasis is a chronic hypeproliferative inflammatory skin disease characterized by abnormal keratinocyte hyperproliferation and differentiation, intra-epidermal accumulation of neutrophil granulocytes, and inflammatory vascular changes (1). Immunologically, psoriasis is characterized by a dense mononuclear inflammatory infiltrate, particularly in the dermis, which mostly consists of T-cells (2). Psoriasis is now generally recognized as a T-cell-mediated inflammatory disease. Infiltration of T-cells seems to be the primary event that precedes the keratinocyte hyperproliferation (3). The suggested mechanism is that systemic lymphocyte activation is followed by the local accumulation of specific CD4+ T-cells and subsequent activation of intradermal CD8+ T-cells (4).

The evidence accumulated in the last decade strongly suggests that psoriasis is a T-cell-mediated disease. The important role of T-cells in psoriasis pathogenesis was first suggested after effectiveness of cyclosporine was observed in the treatment of psoriasis (5). Cyclosporine was found to se-

lectively inhibit interleukin-2 (IL-2) and interferon- (IFN-) release from CD4+ T-cells. Further evidence includes the successful use of diphtheria fusion toxin (DAB_{389}IL-2) in psoriasis treatment (6). DAB_{389}IL-2 is a potent immunotoxin only to T-cells expressing IL-2 receptor (IL-2R). Finally, experiments on a severe combined immunodeficient (SCID) mouse confirmed the key role of activated T-cells in the initiation and persistence of psoriatic process (7). In the SCID mouse, only injection of autologous CD4+ T-cells from the psoriatic patient could induce transformation of engrafted symptomless skin into a typical psoriatic lesion.

THE ROLE OF T-CELLS IN PSORIASIS

Several studies have confirmed the important role of T-cells in triggering the psoriatic process (8,9). So far, it seems that CD4+ T-cells create an appropriate cytokine environment for CD8+ T-cells activation that eventually trigger the psoriatic cascade (10). Thus, interaction between CD4+ and CD8+ T-cells leads to creation of psoriatic lesions.

The availability of numerous monoclonal antibodies has enabled the immunohistochemical characterization of the inflammatory infiltrate within the psoriatic lesions. Immunohistochemical studies showed increased number of T-cells in the epidermis and dermis of psoriatic plaques (11,12). T-cells infiltrating dermis are mainly of type 1 helper CD4+ T lymphocytes (Th1) and those infiltrating the epidermis are mostly type 1 cytotoxic CD8+ T-cells (Tc1). Both, activated Th1 and Tc1 lymphocytes, are highly overrepresented in psoriatic lesions where they express increased level of HLA-DR and IL-2R surface molecules as markers of persistent activation (13). The Th1 and Tc1 subsets seem to represent a major effector T-cell population within the psoriatic lesions. Infiltrating T-cells create a type 1 cytokine microenvironment within the psoriatic lesions with type 1 cytokines IFN- , tumor necrotizing factor- (TNF-) and IL-2, but not IL-4 or IL-5 (14). Such particular cytokine pattern is sufficient in inducing typical psoriatic changes, mainly keratinocyte hyperproliferation (IL-6 and IFN-) and accumulation of neutrophil granulocytes (IL-8) in the epidermis (15). Activated keratinocytes also produce wide range of cytokines that enhance activation and chemotaxis of T-cells in the skin (IL-6 and IL-8) or even induce the increased expression of particular adhesion molecules (IL-1) important in T-cell trafficking (16). Therefore, T-cells and keratinocytes are equal partners in the persistent dialogue during the creation of psoriatic lesions.

HOW T-CELLS MEDIATE PSORIASIS?

The precise mechanism how activated T-cells trigger psoriasis is yet unknown. However, it seems that the specific immune reaction to a putative antigen mediated by T-cells leads to creation of psoriatic lesions (17). The only difference between “normal” and “psoriatic” immune reaction is in the duration of the process. Normally, immune response stops after elimination of an antigen. Psoriatic immune reaction continues until the formation of characteristic psoriatic plaque. Thus, it is clear that T-cells are responsible for initiation and maintenance of psoriasis (18). The real nature of putative psoriatic antigen is yet unknown, but it is now recognized that bacterial endotoxins acting as superantigens or a particular epidermal self-antigen are capable of triggering psoriasis (19,20).

The first step in psoriatic immune reaction seems to be the capture of antigen by epidermal Langerhans cells (Lc) and their subsequent activation (21). Langerhans cells are antigen-presenting cells that mature during the activation process and subsequently express markers of activation (CD80, CD86, and CD40). Activated Lc cells migrate to the skin-draining lymph nodes where T-cell activation occurs. Indeed, activated Lc cells are found in high amount in the epidermis and dermis of psoriatic lesions (22). Antigens are enzimatically processed within the Lc cells and subsequently presented on their surface to activate naïve T-cells.

The activation of T-cells is a complex process of stimulation the T-cell antigen-receptor (TCR) complex and T-cell costimulation through particular surface receptors (23). The recognition of an antigen peptide presented on the surface of antigen-presenting cells in the complex with either major histocompatibility complex (MHC) I or MHC II is an initial step in the T-cell activation. Peptide antigens are recognized by T-cell antigen-receptor complex on the surface of T-cells. If a match between a peptide and particular T-cell antigen-receptor complex occurs, the first activation signal is send to T-cells and IL-2 and IL-2R (CD25) are subsequently syn-

thesized. For the optimum T-cell activation and subsequent clonal expansion, accessory co-stimulation is required (24). The accessory signals are obtained through interaction between CD28 on T-cells and CD80 and CD86 on the surface of antigen-presenting cells and between CD40L on T-cells and CD40 on antigen-presenting cells. The result of such coordinated stimulation is increased transcription of IL-2, IFN- , and TNF that induce expansion of particular T-cell clone and differentiation toward type 1 effector cells (25). The interaction between CD40 and CD40L induce transcription of IL-12, a major cytokine driving type-1 differentiation characterized by IL-2, IFN- , and TNF release (26). It is now recognized that psoriasis is a type-1 disease mediated by type-1 cytokines (27,28). Indeed, high concentration of type-1 cytokines is found in psoriatic lesions.

During the maturation process, T-cells express particular skin homing receptor, cutaneous lymphocyte-associated antigen (CLA) that traffics activated T-cells back to the skin (29). It is a glycoprotein that interacts with E-selectin or P-selectin on endothelial cells of cutaneous microvessels, subsequently slowing down the rolling T-cells. The endothelial cells release wide range of chemokines (TARC and MIG) that induce lymphocyte function associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) expression on the surface of T-cells (30). These adhesion molecules interact with intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on the endothelial cells and subsequently extravasate into dermis. The chemotactic gradient of a wide range of chemokines (RANTES, TARC, and MIG) produced by endothelial cells, keratinocytes, monocytes and Lc cells traffics T-cells into epidermis and dermis (31). Actually, IFN- and TNF- from T-cells stimulate the synthesis of those chemokines that attract Th1 cells to dermis and Tc1 cells toward the epidermis. Wide range of chemokines and their receptors on T-cells are highly expressed in psoriatic lesions (32).

Finally, effector part of immune response occurs in the skin. In the dermis, after antigen stimulation, Th1 cells release large amounts of IFN- that induce expression of ICAM-1, CD40, and MHC-II molecules on keratinocytes. In addition, Th1 cells stimulate TNF- release by dermal macrophages. LFA-1+Tc1 cells interact with ICAM-1 on keratinocytes and migrate to epidermis (33,34). Intra-epidermal Tc1 cells release IFN- and stimulate keratinocyte hyperproliferation and abnormal differentiation, the key markers of psoriatic phenotype. Furthermore, IFN- and TNF- from Tc1 cells stimulate IL-8 release from activated keratinocytes. IL-8 release attracts neutrophil granulocytes into epidermis, forming the so-called Munro's abscesses (35). Activated keratinocytes secrete wide range of chemokines (MIG and IP-10) and cytokines (IL-6) that either amplify lymphocyte trafficking and adhesion to endothelial cells or enhance further keratinocyte proliferation. Finally, keratinocytes synthesize particular angiogenic cytokines, such as vascular endothelial growth factor (VEGF), which induce typical vascular changes in psoriatic lesions (36). Hence, the vicious circle is closed. The immune reaction driven by bacterial superantigens or epidermal self-antigens, described herein, is constantly going on until psoriatic lesions are created.

CONCLUSION

The psoriatic process is a dynamic process that includes interaction between Th1 and Tc1 cells, as well as between T-cells and keratinocytes. The better understanding of the psoriasis immunopathogenesis would enable development of specific T-cell-targeted and/or cytokine-targeted new therapies.

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Acta Dermatovenerol Croat 2004;12(1):30-34 REVIEW

Psoriasis Treatment – Yesterday, Today, and Tomorrow

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SUMMARY In this historical review the authors investigated the treatment of psoriasis through the centuries. There are numerous obstacles in search for the description of psoriasis vulgaris in the works of the great physicians in the antiquity. Most remedies have been developed empirically. During the last two centuries, innumerable drugs have been employed in the treatment of psoriasis. Today dermatologists use the rotational treatment to diminish adverse drug events. In the future psoriasis will probably be cured with the new biological agents.

KEY WORDS psoriasis; treatment; history

INTRODUCTION

Today, psoriasis is a well-known skin disease, in whose etiopathogenesis take part genetic factors, environmental factors, and immunologic mechanisms. It is hard to understand the impossibility to find description of psoriasis in the works of great physicians of the passed centuries in spite of the frequency of disease, its long lasting course, and typical lesions and localization. Probably in the elapsed age the description of skin diseases, considered *morbi in pulchredine*, was not precise, the terminology not standardized, the translation from one language to others was difficult, and different authors called the same disease differently, while different diseases bore the same name.

In the Egyptian Ebers papyrus that had been written at the time of the 18th Dynasty (15th century BC), one may find descriptions of many skin diseases, such as *šuf. t* for scale, but it is impossible to recognize psoriasis (1). Some believe that the disease called *zaraath* (translated in Greek as *lepra*) in the Bible was either leprosy or psoriasis (2). The confounding of these two diseases created great problems to psoriatics for a long time. Hippocrates used the word *psora* that meant scale and itch for itchy lesions on the eyelids and genitals, so this surely was not psoriasis although he used tars and climate to treat skin diseases (3). It seems that in the books of A. Cornelius Celsius, who lived during the Roman Empire in the 1st century AD, there is the first description of psoriasis, but under the name of impetigo; the disease was treated with medicaments containing pitch and sulfur (4). The word *psora* was also mentioned in the books of the other encyclopedist Pliny, but he did not describe the dis-

ease (5). Galen from Pergamo was the first one who used the term *psoriasis*, but only for an itchy eruption of the scrotum (6). Recently, Holubar wrote about the semantic aspects of the word *psoriasis* (7).

During the dark Middle Ages, the medicine was full of superstition, ignorance, and mysticism and gave little attention to skin diseases. Perhaps the Arabian physicians first distinguished psoriasis from other skin diseases, what happened in the 8th century AD. They also used a kind of psychotherapy to treat the disease (8).

In the 18th century, the great Swedish naturalist and physician Carl Linnaeus introduced the binomial terminology and first classified the plants in a comprehensible manner. Later on, he proposed to classify the diseases in his *Genera Morborum* (9). Short after, Joseph Plenck in Vienna, also a great expert in botany who compiled a list of about 800 medicinal plants, compiled the book *Doctrina de Morbis Cutaneis* in 1776, in which he classified about 120 skin diseases into 14 classes after the elementary lesions, which he only marginally defined. He also paid little attention to psoriasis and its therapy, and used the old term *impetigo* for that disease (10). It was the English physician Robert Willan who, in his work *On Cutaneous Disease* from 1798, developed a simpler and better classification of skin diseases after the elementary lesions (11). He used the term *psoriasis* for the papulosquamous disease and partly differentiated psoriasis from leprosy. His work was continued and completed by his disciple Thomas Bateman.

At the beginning of the 19th century, the great French physician Jean Louis Alibert worked and taught at the Hospital of St. Louis in Paris. He also tried to systematize skin diseases and proposed a “tree of skin diseases”, which made only greater confusion. Psoriasis was classified in the group of dartrous dermatoses together with leprosy (12).

It was Ferdinand von Hebra who, around 1850, working in Vienna at the Allgemeine Krankenhaus finally separated psoriasis from leprosy and also classified skin diseases not only on the basis of gross anatomy, but also, after Karl Rokitansky, used the microscopic criteria in the classification of diseases (13).

THE LAST TWO CENTURIES

After these preliminary remarks, it becomes clear that we can speak about the treatment of psoriasis from the beginning of the 19th century. The treatment was topical and/or systemic. Arsenic was among the first drugs that were used systemically. In 1806, Thomas Girdlestone was the first who used potassium arsenate as *solutio Fowleri,* usually 6 drops 3 times a day (14). This solution was introduced into medicine in 1780 by the English physician and pharmacist Fowler (15). The drug is easily absorbed from the gastrointestinal tract and deposited in various organs, especially in the skin and hair. It acts through inhibiting some enzymes.

Hebra and Kaposi also proposed *solutio Fowleri* and *pilulae asiaticae* in the treatment of psoriasis (13). It seems that arsenic compounds mostly improved psoriasis guttata, but sometimes also other forms of the disease. In 1869, arsenic acid was also injected subcutaneously. Because psoriasis is a chronic disease, with time this therapy led to accumulation of arsine and toxicity, with patients developing pigmentations, keratoses, and cancers of the skin, liver, bladder, and larynx. In spite of these adverse reactions, arsine had remained in use until the middle of the 20th century and the introduction of corticosteroids in the therapy of psoriasis.

Mercury was used for centuries in the treatment of syphilis and skin diseases. In 18th century, Turner cured psoriasis with injunctions of an ointment containing ammoniated mercury *(hydrargiri amidochlorati)* (16). Mercury ointment was also used by Bateman and other physicians during the 19th century. In 1895, Brault (17) used organic mercury compound injections in the treatment of arthritis psoriatica. Even in 1972 Jadassohn and Kogoj (18) recommended a mercury ointment for psoriasis capillitii.

The local or internal (intramuscular) use of sulfur and salicylic acid in treatment of skin disease has been known for a long time. Hebra and Kaposi used it in various ointments. Later, many diseases as well as psoriasis were considered infectious and an antibacterial treatment was introduced (iodine, phenol, or acetic acid).

In the middle of the 19th century in India, Chrysarobin was used in the treatment of dermatomycoses and psoriasis, i.e. long before the English physician Balmanno Squire (19) in 1876 wrote about its use

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for psoriasis. The drug was present in the Goa (or Bahia) powder, obtained from the center of the trunk of the tree *Andira Araroba* (vataireopis araroba), which grows in some parts of Brasil. Today this plant is hard to find and also only few botanists know of it (20). Chrysarobin is an antranone that easily oxidizes; its concentration in the powder was very variable. This drug was used in the form of 1-5% ointment and when applied, it caused irritation, itching, and colored the skin and linen. Chrysarobin was not to be used on the face because it provoked keratitis. The drug was effective, but also expensive and toxic. So, attempts were made to synthesize a similar substance with little side effects. At the end of 19th century, the development of chemistry and technology especially in Germany and England favored these attempts: first antrarobine obtained had no effect on psoriasis; later in 1916, the synthesis of dithranol (cignolin or antralin) permitted treating psoriasis in a better way (21). It was applied as ointment or paste (0.1%) or, as today, in a stick for short contact therapy.

Yet, Hippocrates used tars in the treatment of skin disease (pine tar), and tars were also used during the last two centuries. Little improvement was obtained with wood tars (pine, birch, juniper, or pix betulina) containing acetic acid and phenolcarbonic acid. Because of their acidic reaction, they irritated the skin. They were incorporated in ointments, paste, and oils and applied directly on the skin or used for baths (22).

Bituminous tars, such as ichthyol, were also used. Like wood tars, they are not photosensitizing. A greater improvement was the introduction of coal tar obtained from distillation of coal in the manufacture of illuminating gas. This substance is phototoxic (under UVA and visible rays). In 1925, Goeckerman (23) used coal tar in conjunction with ultraviolet light irradiation. This method is today one of the most efficient treatments for psoriasis.

The beneficial effect of sun on skin diseases had already been known among the old civilizations, who left us the knowledge of heliomarinotherapy, which is still used in the treatment of psoriasis (24). Finsen introduced artificial ultraviolet radiation in medicine at the beginning of 20th century. Alderson, in the twenties of the last century, reported an improvement with UV in psoriasis (24). In the last decade, lamps were developed with wavebands between 300 and 320 nm and narrow spectrum around 311 nm, together with PUVA therapy. In 1973, Tronnier and Schule (25) first observed a good improvement of psoriasis after the topical use of psoralen and UVA. Soon after Parish *et al* (26) used oral psoralens and UVA irradiation. This treatment is highly effective and produces long lasting remissions.

At the middle of the 20th century, corticosteroids were introduced into medicine. The local application of cortisone and hydrocortisone was without any effect on psoriasis. Changing the steroid molecule permitted obtaining more potent steroids, like fluocinolone acetonide, betamethasone valerate, and clobetasol propionate, which were effective in clearing most cases of psoriasis. Their efficacy can be enhanced with occlusive dressing or use in combination with salicylic acid, tars, and other. The drawbacks of this therapy are atrophy of the skin, suppression of the hypothalamus-pituitary-adrenal axis, and tachyphylaxis. Internal use of corticosteroids is recommended only in problematic cases.

Among other drugs employed in the treatment of psoriasis there are cytostatics and antimetabolits. Particular mention deserves methotrexate, which can give satisfactory response in severe cases, but – it is hepatotoxic (27). There were also attempts to treat psoriasis with diets low in fat, vegetarian, or with low or high contains of potassium (28,29).

In recent years, the internal use of cyclosporine, an immunosuppressive drug, has shown good results in the treatment of the disease, but a problem has been its nephrotoxicity (30). Analogs of vitamin D slowing epidermopoiesis can be used topically to improve psoriasis. In the erythrodermic and pustular form of psoriasis a great step was the introduction of systemic retinoids etretinate and acitretin (31). They act through the nuclear receptors RAR and RXR and on the expression of genes important for the proliferation and differentiation of keratinocytes. Retinoids can be used in combination with PUVA.

So, to avoid the adverse effects of all these potent drugs, we use combined or rotational therapy, i.e. we change the treatment after a course. The success of immunotherapy or psoriasis in the last years and advances in the elucidating the patho-

genesis of the disease (32) have permitted us to believe in the future use of drugs that act on specific receptors, such as IL-2, cytokines, chemokines, or on some molecules on the surface of lymphocytes (33). These new drugs derived from living organisms, so-called the biologic agents, such as humanized or recombinant monoclonal antibodies and fusion proteins, will find more employment in the future. They can act on molecules such CD4, CD2, molecules of the antigen-presenting cells, or on endothelial cells. Other may block some of the proinflammatory cytokines, like tumor necrosis factor , or perhaps interleukins that change the TH1 to TH2 immune response (34-37). Some of these "biologics" have been shown effective and safe in the treatment of other autoimmune diseases and thus in psoriasis as well, with the possibility to obtain long lasting remissions. The progress in psoriasis genetics and in pharmacogenetics will permit a better and individualized treatment of the disease (38).

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Acta Dermatovenerol Croat 2004;12(1):35-41 REVIEW

Update on the Psoriasis Therapies

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SUMMARY New psoriasis therapies offer a great hope for the people who suffer from chronic inflammatory skin diseases. Psoriasis and psoriatic arthritis are the diseases that can be treated with biological therapy, which targets either the interaction between an antigen-presenting cell and the T-cell, or cytokines, such as tumor necrosis factor alpha (TNF-), that are presumed to be involved in the pathogenesis of psoriasis vulgaris and psoriatic arthritis. Current biologic therapies now seem to hold promise of potentially excellent effect, with the toxicities associated with existing therapies: phototherapy (PUVA or UVB), retinoids, cyclosporin, methotrexate (MTX). Topical therapy will continue to be used in combination with new biological therapies for residual psoriatic plaques. In this paper, we highlight the current psoriasis treatments, new biologic therapies, and their use in practice.

KEY WORDS psoriasis vulgaris; therapy; novel immunotherapies for psoriasis; biologic therapies for psoriasis

INTRODUCTION

Psoriasis is a chronic lifelong skin disease affecting 2% of the population worldwide (1). Psoriasis has been traditionally divided into mild, moderate, and severe form, based on the percentage of body surface area involvement. Understanding the pathophysiology of psoriasis, coupled with advances in molecular research, has led to the development of targeted biologic treatments for patients with psoriasis, especially plaque psoriasis. T lymphocytes play an important role in initiating the reaction of immune system and the inflammatory responses that result in development of psoriatic plaque. The hallmark feature of psoriasis is thickened, erythematous, scaly plaques, most commonly on predilection sites (elbows, knees, scalp, and sacrum). There is a genetic basis to the disease, with multiple loci of numerous chromosomes being identified and their role further elucidated (2). The determined immunogenic inflammatory disorder is based on ongoing autoreactive Th-1 response (2). Psoriasis is now considered to be a T-cell-mediated (auto) immune disease, in which cytokines and chemokines play an essential role, with lymphocyte activation as a key step in the process. It is demonstrated that psoriasis is a granulocyte-mediated disease; the presence of large granulocyte infiltrations and hyperexpression of interleukin-8 (IL-8) suggest that IL-8 plays a signifi-

cant role in psoriasis. Various factors induce relapse or exacerbation of psoriasis, including psychological stress, skin trauma, medications, and infection (2). Psoriasis can have significant adverse effect on patient's physical, psychological, and social life. A wide spectrum of clinical presentations of psoriasis includes plaque psoriasis, psoriasis inversa, eruptive psoriasis, erythtodermic psoriasis, generalized form of psoriasis, psoriasis pustulosa, and psoriasis arthropatica (3). Psoriasis plaques show epidermal hyperproliferation, epidermal and dermal inflammation, and enhanced angiogenesis in early lesions (1). A significant proportion (30%) of patients suffers from joint manifestations of the disease, which has generally a negative impact on the quality of their life (4). Treatment of psoriasis is aimed at symptomatic relief and improved quality of life. The current management of psoriasis depends on the severity of disease, quality of life, risk versus benefit assessment of various treatment strategies, and a patient's response to prior treatment (5). Consensus statement for psoriasis treatment is in the final stages of development by the American Academy of Dermatology (6).

PRACTICAL CONSIDERATIONS IN THE TREATMENT OF PSORIASIS

The management of psoriasis is a complex issue for both patients and physicians. Patients with psoriasis represent a large population in European countries, and approximately 2 million Americans are afflicted with moderate to severe plaque psoriasis (4). These patients are faced with significant limitations of traditional psoriasis therapies. While some systemic treatments have good short-term effects, their side effect profiles prohibit their long-term use in the treatment of this chronic disease. Current standard therapies, such as phototherapy, methotrexate, and cyclosporine, are associated with long-term safety concerns, risk of birth defects, organ toxicity, and carcinogenicity.

Patients with mild, localized form of the disease normally receive topical therapy with calcipotriene, tazarotene, coal tar, anthralin or topical corticosteroids. Patients with moderate, resistant form of disease are candidates for phototherapy, broadband or narrow-band ultraviolet (UVB), or psoralen plus UVA (PUVA) phototherapy, which may be applied separately or in combination with topical therapy or systemic retinoids.

Patients with moderate-to-severe disease and with or without concomitant psoriatic joint disease, or those in whom phototherapy/PUVA therapy is precluded, are candidates for systemic therapy with retinoids, methotrexate, or cyclosporine. Patients unresponsive to traditional topical therapy and phototherapy, those with good quality of life, and those with localized disease pose a challenge to clinicians (3,4,6). Rotational therapy is limited by the duration of safe treatment with conventional therapies.

Conventional psoriasis therapies (topical treatments, phototherapy, and systemic agents such as methotrexate, cyclosporine, and acitretin) leave many needs unmet. Common psoriasis treatment depends on patient's age, type of psoriasis, concomitant diseases, and triggering factors.

Local Therapy for Psoriasis

Local therapy is very useful and includes keratolitics, tars ointment, anthralin (dithranol), topical corticosteroids (class II-IV), analognes of D3 vitamin (calcipotriol and tacalcitol), topical retinoids (tazarotene gel 0.1%), phototherapy (UVB; narrow/band; or broad/band), naphthalanotherapy, heliomarinotherapy, spa therapy, PUVA-bath, and PUVA-cream. If current topical treatments are ineffective, the combination with systemic therapy is necessary.

Systemic Therapy for Psoriasis

Systemic psoriasis therapy ensured long-term therapy safety and includes photochemotherapy (PUVA-oral); retinoids (acitretin); retinoids + PUVA (RE-PUVA), methotrexate, cyclosporine, mycophenolate mofetil, and fumar acid ester (leflunomide). However, thick psoriatic plaques are still particularly problematic to treat. Systemic agents are expected to provide improved long-term therapy, efficacy, and prolonged remission. Because psoriasis is a chronic immunoinflammatory skin disorder, options for clinical therapy are limited when conventional therapies cease to be safe due to long duration. Since treatment discontinuation results in eventual relapse, the need for long-term efficacy and safety of the therapy is evident.

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Psychosocial therapy (relaxing group therapy or self-training) is necessary to prolong remission of psoriasis (4).

IMMUNOSUPPRESSIVE THERAPY FOR PSORIASIS

According to pathobiological findings in psoriasis, the therapeutic use of immunosuppressant agents, such as methotrexate, cyclosporine A, mycophenolate mofetil, fumar acid ester, tacrolimus, and pimecrolimus, in psoriasis has been effective despite the side effects.

Methotrexate

Methotrexate is not a new immunosuppressive agent. It has been used for decades in the treatment of resistant chronic plaque psoriasis, eruptive psoriasis, erythroderma, and especially psoriatic arthritis. Applied in total weekly doses of 7.5-20 mg either orally, intravenously, or intramuscularly, methotrexate is an effective immunosuppressant without immunoproliferative action (7). Before and every 4-8 weeks during the therapy with methotrexate, liver and renal function must be checked.

Mycophenolate Mofetil

Mycophenolate mofetil has been used as an effective immunosuppressive in the treatment of psoriasis for 25 years. Today, this drug is experiencing a sort of renaissance as an agent for the treatment of autoimmune diseases. Although there are no large randomized, placebo controlled studies of mycophenolate mofetil among patients with psoriasis, smaller studies have found good effect in 11 patients with daily doses of 2 g mycophenolate mofetil during 3 weeks, with the reduction of Psoriasis Area and Severity Index (PASI) score by 40-70% (8). The lower dose is not recommended.

Leflunomide

Fumar acid ester, or *leflunomide*, is useful through many years. Leflunomide, a new immunosuppressive agent, has shown good effect in the treatment psoriatic arthritic and psoriatic patients (7). The pharmacological action of newly developed immunosuppressive agents is based on action on calmodulin-dependent calcineurin serin phosphatase, regulation of transcription factors genes (especially for IL-2, IL-4, GM-CSF, and IL-3), production of cytokines, and psoriatic inflammation cascade. Cyclosporin A and FK 506 have suppressive action on IL-1 and IL-8 expression in psoriatic epidermis and on expression of IL-8 receptor on keratinocytes (7).

Cyclosporine A

Cyclosporine A is effective immunosuppressive agent for twenty years in transplantation medicine and especially in atopic dermatitis therapy. In patients with severe and resistant psoriasis cyclosporine A is useful in spite of nephrotoxicity and hepatotoxicity. Cyclosporine A in the treatment of psoriasis in dose of 3-4 mg/kg/day for 8 weeks, or 5 mg/kg/day after 4-8 weeks, as well as in dose 1-14 mg/kg/day/ for a week is effective, although it is also associated with well-known toxicities, including dose-dependent renal impairment and hypertension (7). The dose can be reduced according to the effect after 4-week interval from 0.5-1 mg/kg/day to the maintenance dose. However, relapse of psoriasis is possible after cessation of the cyclosporine A therapy. In patients with hypertension, cyclosporine A therapy can be continued with simultaneous administration of calcium antagonists (nifedipine or isradipine).

Immunosuppressive Macrolactams

Tacrolimus and ascomycin macrolactam derivate pimecrolimus (ASM 981) are chemicaly very similar. Tacrolimus (FK 506) has an “allyl”-group at position 21, whereas ascomycin has an “ethyl”-group, which are bounded on cytoplasmatic protein$_{12}$ (FKBP$_{12}$), alternatively named macrophylin$_{12}$. Like cyclosporine A, they both inhibit phosphatase calcineurin. Tacrolimus has inhibitory effects on expression of IL-8 receptor on psoriatic keratinocytes and in atopic skin, where it inhibits the expression of high affinity IgE receptors (Fc RI) on dendritic epidermal cells. Systemically administered tacrolimus has been proven effective in transplanted patients with psoriasis (7). In the largest control study among 50 patients, tacrolimus was administered in daily doses of 0.05 mg/kg/bw, and increased after 3-6 weeks to 0.10 (0.15) mg/kg/bw for 6 weeks if the previous dose had not been effective enough (7). However, in 19 out of 50 patients the therapy had to be stopped because of side effects. After 9 weeks of tacrolimus therapy, the reduction of PASI score

was observed in 83% of patients and 47% of participants in placebo group (7). Efficacy of local use of tacrolimus has been proven not only in psoriasis therapy, but also in the therapy of inflammatory dermatoses.

Pimecrolimus inhibits the release of mast cell proinflammatory mediators and TNF- with influence on lymphocytes. Pimecrolimus has been used for the treatment of psoriasis since 1996, and has proven efficacy and advantage in comparison with corticosteroids. Orally administered at doses of 5 mg-20 mg, or 40 mg (20 mg twice a day, or 30 mg/twice a day), pimecrolimus is useful in the treatment of severe psoriatic plaques, where it reduces PASI score by 60% (40 mg) or even 75% (60 mg). For systemic immunosuppression, it is necessary to administer high doses of pimecrolimus (7).

A new macrolide, rapamycin (sirolimus), has been recently introduced as an immunosuppressant after transplantation. However, little information is available on the use of sirolimus in the treatment of psoriasis. Sirolimus inhibits T lymphocyte activation and proliferation, which occurs in response to antigenic and cytokine stimulation. Reitamo *et al* (9) found synergistic therapeutic effect (70.5% reduction of PASI score) of sirolimus with cyclosporine A in patients with severe plaque psoriasis. Monotherapy of sirolimus with daily dose of 0.5 mg, 1.5 mg, or 3.0 mg/mm^2 body surface has no significant advantage (9).

THE ERA OF NEW THERAPEUTICS

Based on the immunological basis of psoriasis, selective T-cell targeting in psoriasis gives a novel approach to improve clinical outcomes. The efficacy of therapeutic agents that target T-cells, such as anti-CD_4 monoclonal antibodies, cyclosporin, and interleukin-2 fusion toxin has provided further evidence that psoriasis is a T-cell mediated disease. Suppressive treatment inhibits the production of cytokines, reduction of inflammation and hyperproliferation of keratinocytes, apoptosis and targeting T-cells in blood and skin.

The majority of T-cells in psoriatic plaques are CD45RO+ memory-effector T-cells that migrate into the skin (6,10,11). Novel immunotherapies for psoriasis are based on targeting antigen presentation and costimulation, T-cell activation and leukocyte adhesion, activation of proinflammatory mediators, and administration of anti-inflammatory cytokines.

In psoriatic plaques, there is predominance of Th_1 cytokines, namely interferon gamma (IFN-) and IL-2. For T-cells to gain access to skin, they must bind to endothelial cells and move out to peripheral circulation and into the dermis where they can bind to keratinocytes. This process is mediated by the up-regulation of adhesion molecules on the surface of endothelial cells, including E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular-cell adhesion molecule 1 (VCAM-1). E-selectin is the endothelial ligand for cutaneous lymphocyte antigen (CLA) on memory T-cells. In psoriasis, there is a focal expression of ICAM-1 on keratinocytes, allowing T-cells to bind and subsequently induce the psoriatic process (12).

Targeting cells with intravenous infusions anti-CD_4+ monoclonal antibodies has led to significant improvements in the treatment of patients with psoriasis.

Numerous discoveries have supported the concept that psoriasis is an immune T-cell-mediated disease, including the effect of cyclosporin, the effects of various immunosuppressive therapies on T-cells, the efficacy of a T-cell toxin, anti-CD_4 and –CD_3 antibodies for psoriasis, and the recent development on an animal model (6). Currently, there are over 40 biologic agents under evaluation (and at different stages of development) targeting different molecular entities. These agents are those that effect T lymphocyte-mediated processes on those that alter cytokine activity (10-12). Some targets of biologic agents for T-cells are LFA-1/ICAM-1 (CD11a subunit): efalizumab; LFA-3: CD2-alefacept; Anti-CD_2: MEDI-507: Siplizumab; Anti-CD25: dalizumab, basiliximab; IL-2-coupled diphtheria toxin DAB_{398} IL-2. Targets of anticytokine are TNF- : etanercept, infliximab; INF- (Protein design lab, in trials) (6). Alefacept is the first biologic agent approved in 2003 for the treatment of moderate-to-severe psoriasis.

New Approaches in Psoriasis Treatment

By selectively targeting a specific portion of the immune system, the new generation of biologic

products can provide remitting or suppressing effect. A greater understanding of the immunologic basis of psoriasis has enabled development of new treatments that selectively target a specific position in the immune system (12,13). Several basic strategies have emerged, each with the common goal of reducing or eliminating the pathogenic effects of T-cells (13). These investigation strategies have led to the development of a new generation of biologic products that can provide either a disease remitting or disease suppressing effect.

STRATEGIES FOR BIOLOGIC TREATMENT

Targeting Pathogenic T-Cells

Targeting pathogenic T-cells is based on the selective blocking of the CD_2 receptor on $CD45RO^+$ T-cells. Potential therapies can lead to selective apoptosis of pathogenic T-cells while sparing $CD45RA^+$ nad've T-cells. Human LFA-3-IgG_1 fusion protein is a biologic agent (genetically engineered), which binds to CD_2 on the surface of T-cells and thereby blocks the interaction of CD_2 with natural LFA-3 and prevents T-cell activation (subsequently reducing pathogenic $CD45RO^+$ T-cells over expressing CD_2 molecules) (12,14). Targeting T-cells with anti-CD4 monoclonal antibodies (MoA) and selective blockade of activated T-cells induces improvement in psoriasis. MoAs are produced by fusing a normal, activated antibody-producing B-cell with a myeloma cell. The result of this cell fusion is a hybrid cell, which has the immortal-growth properties. The clones of B-cell hybridomas are a source of large quantities of MoA used for therapeutic, diagnostic, and research purpose (12,13).

Human Interleukin-2 (IL-2) effects are based on selective blockade of activated T-cells. The selective blocker of activated T-cells, but not keratinocytes, is a fusion protein composed of human interleukin-2 and fragments of diphtheria toxin (DAB_{398} IL-2, or IL-2 diphtheria toxin) (14,15). Reduction in tissue-infiltrating T-cells, keratinocyte proliferation, and epidermal thickness correlates with administration of IL-2 diphtheria toxin and improvement of psoriasis.

Interleukin 2 fusion toxin (DAB_{398} IL-2, a receptor-targeted cytotoxin), is a recombinant fusion protein proved to be effective in the selective destruction of cells expressing high-affinity IL-2 receptors. In severe cases of psoriasis, it is administered intravenously at doses of 100 kU/kg or 200 kU/kg, 5 times daily for a week, followed by a 23-day assessment period. The treatment cycle is repeated once for a total of 10 doses over the 56-day (12). Clinical and histological improvements induced by the IL-2 toxin show that psoriasis is linked to skin infiltrates.

Inducing Immune Deviation

T-cells in psoriasis primarily release Th_1 cytokines (IL-2, INT-), which lead to the release of inflammatory cytokines, such as TNF- and IL-1. Administration of Th_2 cytokines to reduce Th_1 response is a potential therapy for psoriasis. Recombinant human IL-10 (Th_2 cytokine) is effective at suppressing lesions (13,14).

Inhibiting T-Cell Activation

The primary or costimulatory signals for activation are blocked by reducing immune response in psoriasis. Disease-suppressing agent would likely require a chronic administration without interruption. CTL A 4-Ig is a fusion protein that selectively inhibits T-cell activation by blocking CD28; CD80 is a costimulatory signal required for T-cell activation (13,14).

Inhibiting Cytokines

Inflammatory cytokines released by cells in psoriatic lesions perpetuate the inflammatory process. Binding and eliminating this cytokines could alter the course of psoriasis. Therapies that bind and block the activity of the cytokine TNF- are recombinant TNF-receptor fusion proteins (13).

Biological Therapy Agents for the Treatment of Psoriasis

Biological therapy agent for the treatment of psoriasis is etanercept (fusion protein composed of human TNF type II receptor [TNF-RII] and human IgG_1 Fc region), which specifically binds TNF- , blocks interaction with cell-surface TNF receptors, and inhibits TNF- -mediated inflammation, cell infiltration, and keratinocyte proliferation. It can be administered as at-home subcutaneous injection twice a week (15).

Efalizumab (humanized monoclonal antibody to the CD11a chain of LFA-1) blocks T-cell activation and reactivation; binding and traffic into dermis and epidermis. Efalizumab is currently assessed by Food and Drug Administration (FDA) USA for its possible application in the treatment of psoriasis (16). Efalizumab (anti-CD11a, Raptiva , Genentech) is a humanized monoclonal IgG_1 antibody that binds to CD11a (the -subunit of LFA-1) and prevents LFA-1 from interacting with ICAM-1. A single infusion of efalizumab in doses 0.03-10.0 mg/kg demonstrated significant clinical improvement and led to an improvement in PASI scores during 2-10 weeks, decreased T-cell migration into psoriasis plaques, and decreased ICAM-1 expression, which suggested a decrease in the secretion of pro-inflammatory cytokine. Subcutaneous home administration of efalizumab offers an interesting new therapeutic option for the treatment of psoriasis and a potentially safer long-term therapy (16).

Infliximab is a chimeric monoclonal antibody to TNF- composed of murine-variable regions and human IgG Fc region, which specifically binds TNF- , inhibits TNF- -mediated inflammation, and induces apoptosis in monocytes (15,17).

A year ago, FDA approved the use of alefacept (fusion protein composed of the external domain LFA-3 and a human IgG1 Fc-region), which eliminates pathogenic T-cells by binding to natural killer (NK) cells and blocks T activation, for the treatment of psoriasis. It is administered as in-office intravenous push or intramuscular injection once weekly (16,17).

Etanercept and infliximab are in phase III trials for the treatment of psoriasis.

According Asadullah *et al* (18), new immunomodulatory therapies for the treatment of psoriasis in clinical development (Phases I-III) are as follows: action of the function of antigen-presenting cells: CTLA-4 (BMS 188667), LFA-3TIP (amivene/alefacept), Anti-CD80 antibodies (IDEC 114), Calcitriols (rocaltrol), Fumaric acid esters (fumaderm); T-cell inhibitors: Macrolides [FK506 (tacrolimus), SDZASM981 (pimecrolimus) and sirolimus (rapamycin)], Anti-CD2 antibodies [MEDI507 (siplizumab)], Anti-CD3 antibodies (OKT3,HuM291), Anti-CD4 antibodies (BB14), Mycophenolate mofetil (cellcept), IL-2-coupled *diphtheria* toxin (DAB3 98IL-2), Anti-CD25 antibodies (basiliximab, dalizumab); Inhibitors of adhesion: Anti-CD11a antibodies [hu1124 (efalizumab)], Anti CD6 antibodies (bort1); Inhibitors of proinflammatory cytokine/mediator action: Anti-IL-8 antibodies (ABX-IL8), Anti-TNF-receptors [etanercept (enbrel)], LTB4-receptor antagonist (VLM 295), Anti-IFN- antibodies.

Administration of Anti-inflammatory Cytokines IL-4, IL-10, and IL-11

Local immunosuppressive macrolides, such as tacrolimus (FK 506) and ascomycin derivate (ASM 981) pimecrolimus, have been very useful especially for the treatment of facial skin lesions in atopic dermatitis and psoriasis. However, according clinical trials tacrolimus has not been an ideal therapeutic agent in case of psoriasis (7,18).

According to the Consensus Statement on new immunomodulatory therapy in psoriasis, there are many ways to help our patients with psoriasis. We must take into account that all modalities in psoriasis treatment are good, from local therapy, systemic therapy, phototherapy, heliomarinototherapy, combined therapy with local agents, sequentional therapy with good immunosuppressants like MTX/fumaric acid; cyclosporin/UV-therapy; fumaric acid/UV-therapy; and MTX/UV-therapy (7,17,18).

CONCLUSION

Conventional psoriasis therapies leave many needs unmet. Systemic agents need to have improved long-term safety, whereas long-term efficacy and convenience should be improved in topical agents. Biologic therapies are targeted treatments that have been shown efficacious in managing moderate-to-severe plaque psoriasis. They are generally safe and well-tolerated, with little likelihood for major organ toxicity, bone marrow toxicity, teratogenecity, or drug interaction. The new biologic agents may well transform the way that moderate to severe psoriasis is treated.

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Phototherapy of Psoriasis: Review and Update

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SUMMARY Along with topical and systemic therapy, phototherapy is one of the three fundamental treatment options for managing psoriasis. The use of UVB continues to be one of the most important therapeutic interventions for mild to moderate psoriasis. An advance in UVB phototherapy has been the introduction of narrowband UVB lamps (311 nm). UVB lamps are superior to conventional broadband UVB in clearing psoriasis. PUVA is very effective therapy and is still the most effective form of phototherapy for severe, extensive form of the disease. Therez has been a trend towards whole-body PUVA-bath. Advantages of PUVA bath are lack of gastrointestinal side effects and no need for post-treatment eye photoprotection because there is no systemic photosensitization. UVB and PUVA can be administered in combination with a variety of topical and systemic treatments to achieve more effective results more quickly. The most recent form of phototherapy, 308-nm excimer laser, holds promise for becoming a useful tool in the treatment of stable, localized psoriasis.

KEY WORD keratectomy; photorefractive, excimer laser; psoriasis; phototherapy; photochemotherapy

INTRODUCTION

The beneficial influence of sunlight on a broad variety of diseases has been recognized since ancient times, and a variety of therapies have been developed based on these observations. Niels Finsen used the first artificial light source, in the form of a carbon arc, for the treatment of lupus vulgaris in 1893. He won the Nobel Prize in 1903 for this pioneering application of UV light in medical treatment. Phototherapy of psoriasis with artificial light sources has a history of almost 80 years, ever since Goeckerman, in 1925, introduced a combination of topical crude coal tar and subsequent UV irradiation (1). Today, phototherapy represents one of the three therapeutic options for managing psoriasis, along with topical and systemic therapy.

UVB PHOTOTHERAPY

Phototherapy is the use of artificial UVB delivered by fluorescent lamps without the addition of exogenous photosensitizers. The UVB radiation is absorbed by endogenous chormophores. The best-characterized chromophore for UVB is nuclear DNA. Absorption of UV by nucleotides leads to DNA photoproduct formation, mainly pyrimidine dimers (2). Despite the quantitative predominance of the dimers, the pyrimidine pyrimidone photoproduct is probably biologically more significant (3).

UVB exposure is known to cause a reduction of DNA synthesis (4,5). It can be used to suppress the accelerated DNA synthesis in psoriatic epidermal cells. Besides the effect on cell cycle, UV induces

prostaglandin release and alters cytokine expression and secretion (6). One important aspect of phototherapy is its effect on the cutaneous immune response. UV-induced systemic immune suppression has also been linked to the formation of pyrimidine dimers (7). UV light is known to have direct immunosuppressive effects on decreasing Langerhans cells as well as indirect effects on specific cytokines and adhesion molecules. What is also clear is that UV photons induce an overall selective reduction in T-cells within psoriatic skin through apoptosis (8).

The use of UVB continues to be one of the most important therapeutic interventions for mild to moderate psoriasis. Since UVB is easier to administer and does not involve administration of oral photosensitizing medication, this form of phototherapy is often chosen before PUVA. In addition, factors that suggest use of UVB therapy in comparison with PUVA therapy are brief history of psoriasis, as it is possible that maintenance treatment will be unnecessary (acute guttate psoriasis); less then 30% of the body surface involved by disease before treatment; thin, macular psoriasis; young age; and skin type I or II (9).

Conventional UVB lamps deliver radiation over entire UVB spectrum (280-320 nm). Advancement in UVB-based phototherapy was the introduction of fluorescent light bulbs (TL-01) that deliver monochromatic light at 311 nm UVB. The primary impetus for developing narrowband UVB (NB UVB) were the detailed psoriasis action spectrum studies. In 1976, Fisher (10) indicated that the wavelength of 313 nm was the most effective in treating the disease. In 1981, Parrish and Jaenicke (11) expanded this line of investigation. They determined that UV wavelengths longer than 313 nm were not as effective in resolving psoriasis, whereas wavelengths shorter than 300 nm only produced UV burns without clearing psoriasis. Patients treated with the narrow-band UVB lamps (311 nm) showed faster clearing of psoriatic lesions, fewer episodes of excessive erythema, and a longer period of remission when compared with broadband sources (12-17). When TL-01 phototherapy and oral PUVA were compared, narrow-band UVB was almost as effective as PUVA (18-20). However, patients with higher baseline PASI scores responded significantly better to PUVA than to narrow-band UVB (18).

The advantages of narrow-band UVB over oral PUVA therapy are as follows: shorter treatment time; no systemic effects since oral drugs are not required; less burning incidents; no need for post-treatment eye photoprotection; allowed use in children and pregnant and lactating women (21,22).

A recent study has shown that TL-01 UVB is more efficient than trimethoxypsoralen (TMP) bath-PUVA (23).

In Europe, narrow-band UVB has completely supplanted broadband UVB, whereas in North America it has not been adopted as quickly, primarily because the lamps had not been available in the US until 1998.

It is standard in narrow-band UVB therapy to first obtain a minimal erythema dose (MED) and to initiate treatment at 70% of the MED (8,21). Subsequent dose increments can be 10-20% over the previous narrow-band UVB dose (21,24). Another approach is to use skin type-dependent starting doses and fixed increments depending upon the patient's erythema response. The minimal frequency of treatment is 3 times a week, although 4 or 5 treatments each week are preferable. Upon clearing the treatment is either discontinued or the maintenance therapy is introduced (one or two treatments weekly for one or two months). It is generally felt that maintenance therapy keeps patients clear of disease. On the other hand, the efficacy and requirements of maintenance are controversial because of the additional radiation load delivered to the patient skin (6). More multicentric trials are necessary to quantify the long-term risks and assess the role of maintenance therapy.

UVB can be administered in combination with a variety of topical and systemic treatments to achieve more effective results more quickly.

Topical corticosteroids are frequently used together with UVB phototherapy, but there is no consensus as to whether they enhance the therapeutic response to UVB (25). When UVB is administered with topical corticosteroids, the duration of remission is shortened (26).

Topical salicylic acid, which is often used in the treatment of psoriasis, can decrease the effectiveness of phototherapy by providing photoprotection (24,27).

The combination of calcipotriol and UVB (either broadband or narrow-band) leads to a better clearing of psoriatic lesions than UVB monotherapy, especially in the terms of rapidity of action and UVB-sparing effect (lower cumulative dose) (28-32). It is important to instruct patients to apply calcipotriol after phototherapy.

De Rie *et al* (33) found that calcipotriol ointment and cream blocked UVB transmission when applied immediately before UVB radiation.

Several studies have shown that the addition of tazarotene to UVB phototherapy promotes more effective and faster clearing of psoriasis than does UVB monotherapy (34-36).

The Ingram method uses UVB light and topical anthralin. The healing is more rapid and the cumulative UVB dose lower than with monotherapy (37, 38).

The Goeckerman regimen (UVB + tar) is not clearly superior to UVB monotherapy and has ceased to be acceptable in recent years (25,39).

The treatment of psoriasis with acitretin combined with UVB is emerging as a viable clinical strategy. The combination of this retinoid with UVB enhances the efficacy of phototherapy while sharply reducing the cumulative UV dose as well as the total number, frequency, and duration of therapy. Moreover, patients whose psoriasis does not clear with monotherapy will often achieve significant clearing with the combination of acitretin and phototherapy (40-44). When retinoids and UVB phototherapy are combined, the doses of retinoids necessary for clearing can be dramatically reduced. Doses of 10-30 mg may be sufficient to completely clear patients on a regimen of UVB phototherapy, but at low doses, side effects are significantly less common.

Regimen combining methotrexate and UVB may potentially reduce the total dose of methotrexate required to achieve control over the disease, which presumably lowers the risk of hepatotoxicity (45). However, this regimen is rarely used, since methotrexate enhances the probability of UV-induced skin tumors (39).

The main short-term side effects of UVB are erythema (sunburn reaction) and dry skin with pruritus. Slightly erythematogenic UVB doses are considered necessary to clear psoriasis effectively, but severe sunburn reactions should be avoided. Well-known ocular side effects of UVB include conjunctivitis and keratitis, and therefore both the patient and the phototherapy technician should always wear eye protective glasses.

The most important potential long-term toxicities of UVB phototherapy are photoaging and an increased risk of cutaneous cancer. Although UVB is a known carcinogen, research does not indicate that broadband UVB treatment for psoriasis has been associated with an increase in the risk of skin cancer (44,46). The exception is high-exposure broadband UVB (>300 treatments) that may be associated with an increased risk of genital tumors in men treated without shielding (47). The actual risk of cancer due to narrowband UVB is unknown at the moment and will await long-term follow-up studies for the results to be seen due to the long latent period for human UV carcinogenesis.

PUVA PHOTOCHEMOTHERAPY

Photochemotherapy (PUVA) is a therapeutic method that uses psoralen and exposure to long-wave ultraviolet A radiation (320-400 nm).

Psoralens are tricyclic furocoumarins naturally occurring in certain plants, most of them being also synthetically produced. Psoralens can be used systemically, topically, or as bath therapy. Currently, the most commonly prescribed psoralen is methoxsalen (8-MOP). The use of bergapten (5-MOP) in Europe has been increasing because 5-MOP is less phototoxic agent. The incidence and severity of adverse events, such as nausea, vomiting, pruritus, and erythema, is 2-11 times more frequent with 8-MOP than with 5-MOP (48). The synthetic furocoumarin, trimethylpsoralen (TMP), is used for bath-water-delivered PUVA mainly in Scandinavia. 8-MOP and 5-MOP are available as oral preparations, which contain either crystals, or micronized crystals, or solubilized psoralens in a gel matrix. The liquid preparation induces earlier, higher, and more reproducible peak plasma concentrations than the crystalline preparation (6).

PUVA mechanism of action includes production of oxygen-dependent and oxygen-independent photochemical reactions. Type I reactions are oxygen-independent and exemplified by the formation

of DNA cross-links and development of cyclobutane rings. A DNA cross-link is a covalent bond that remains as a defect in the DNA. DNA-psoralen cross-links inhibit DNA replication and cause cell cycle arrest. The type II reaction is dependent upon the generation of reactive oxygen species, which primarily results in damage of cell and mitochondrial membranes (49). Psoralen photosensitization leads to an alteration of cytokine and cytokine receptor expression, as well as cytokine secretion (50). Infiltrating lymphocytes are strongly suppressed by PUVA, with variable effects on different T-cells subsets (51).

PUVA is very effective therapy and is still the most effective form of phototherapy for severe extensive disease PUVA therapy should be given advantage over UVB therapy in case of long history of psoriasis; more than 30% of the body surface involved by the disease before treatment; thick plaques; involvement of the palms and soles; nail disease; failure to respond to UVB phototherapy; very active, aggressive disease with marked inflammatory component; and skin type III or IV (9).

Oral PUVA timing for UVA exposure depends on the drug formulation used. With 8-MOP-liquid (0.6 mg/kg) and 5-MOP-liquid (1.2 mg/kg), it is 1 h and 2 h before exposure, respectively, whereas with crystalline tablets it is 2 h for 8-MOP and 2.5 h for 5-MOP, respectively (6). The choice of initial UVA dose is of paramount importance. There are very big inter-individual differences in the phototoxic response. Individual phototoxic response is assessed by determining minimal phototoxic dose (MPD).

Two therapeutic protocols of PUVA-treatment for psoriasis were developed simultaneously. The European PUVA Study (EPS) protocol includes MPD as initial dose, followed by four exposures per week (52). The weekly UVA dose increase is 0.5 to 2.0 J/cm^2, depending on the patient's phototoxic and pigment response. Dermatologists from the USA mostly use the United States Cooperative Clinical Trial (USCCT) protocol (53). The initial UVA dose is determined according to the patient's skin type. PUVA therapy is performed 2-3 times per week, with a 0.5-1.5 J/cm^2 increase in the UVA radiation dose. According to the protocol for PUVA therapy adopted by the British Photodermatology Group (BPG), the initial dose is 50% of MPD, followed by only two weekly exposures with a considerable increase in the weekly dose and reduced risk of cumulative phototoxicity (54). The respective success rates reported by the USCCT and EPS are essentially similar: 88.0% *vs*. 88.8% treatment response better than marked improvement. However, in the former trial, the median number of exposures until clearing was higher (25 *vs.* 20) and therefore the duration of the clearing phase was twice (12.7 *vs.* 5.3 weeks) as long as in the latter (53,54). When patients reach a plateau in their response, a tapering maintenance therapy can be performed, enabling them to gradually decrease the frequency of treatments before discontinuing phototherapy. Still, it is well known that patients, allowed to continue with long-term maintenance PUVA therapy with resultant high cumulative numbers of treatment, were the ones who had the highest risk of squamous cell carcinomas (55,56).

PUVA bath therapy has been popular in Scandinavia for many years, and has recently attracted interest worldwide. Patients spend 15 to 20 minutes in 150 L of water containing 0.5-5 mg/L of 8-MOP or 0.2-0.5 mg/L TMP at 30-37°C (57). TMP is traditionally used in Scandinavian countries and the United Kingdom, whereas 8-MOP is used in most other countries. The temperature of the water should be at least 30°C because it has been shown that the photosensitizing capacity of 8-MOP decreases at water temperature below 30°C (58). UVA radiation is given immediately after the bath, as the desired phototoxic effect vanishes rapidly after 20-30 minutes (59,60). Advantages of PUVA-bath are the lack of gastrointestinal (nausea and vomiting) and hepatic (increased liver transaminases) side effects and no need for post-treatment eye photoprotection because there is no systemic photosensitization. Disadvantages are increased complexity and associated costs (increased nursing time and greater costs of topical preparations). Several studies have shown that PUVA-bath is as effective as, or even more effective than, oral-PUVA. The total UVA dose was 2-6 times lower with PUVA-bath (61-65).

As with phototherapy, PUVA can be combined with other treatments to improve efficacy and reduce possible side effects.

The combination of PUVA with topical corticosteroids has produced controversial results, with

some authors claiming that the combination results in faster clearing without shortening the duration of remission, whereas other authors claim that the addition of topical corticosteroids to a regimen of PUVA therapy results in shorter remissions (66,67).

Two studies have shown that calcipotriol improves the response of psoriasis to PUVA (68,69). However, there have been no clinical trials of tazarotene or tacalcitol in combination with PUVA published, and the response to PUVA enhanced with tazarotene or tacalcitol has been reported only anecdotally (70,71).

The combination of PUVA with oral retinoids (acitretin only) may be ideal because the treatments also reduce one another's side effects. The number of treatments required for clearing is dramatically reduced when an oral retinoid is added to the PUVA regimen. The total amount of UVA exposure required is also pronouncedly reduced (42,44,72,73). The doses of oral retinoids required are much lower. Because the carcinogenicity of PUVA seems to be related to the total dose administered, retinoids can be viewed as a PUVA-sparing therapy. Retinoids should be applied first for 2 weeks. This flattens lesions and reduces scales, facilitating PUVA therapy.

In view of the possible long-term side effects (immunosuppression and skin carcinogenesis), the combination of PUVA and cyclosporin A, or PUVA and methotrexate cannot be recommended (49,74, 75).

Erythema is the most common acute side effect of PUVA therapy. It is well known that erythema from PUVA is delayed by 48-72 hours or longer in case of severe reaction compared with that from UVB, which usually peaks within 24 hours. Patients frequently complain of generalized pruritus, which is mostly caused by dryness of the skin. PUVA therapy can cause another type of pruritus, commonly called "PUVA itch" – a deep, burning sensation. It is a symptom of phototoxicity. Oral administration of psoralens can induce systemic side effects in the absence of light. Therapy with 8-MOP is not infrequently disrupted by acute gastrointestinal adverse reactions, mostly nausea and vomiting. Hepatic adverse effects of psoralens are uncommon, except in case of a pre-existing liver dysfunction (76,77). Careful ophthalmologic evaluation before the treatment and eye protection during and after UVA exposure are both necessary to avoid acute inflammation of the conjunctiva and cornea. Although experimental data indicated a risk of premature cataract formation, prospective studies did not find an increased frequency of cataracts in patients treated with oral PUVA therapy (78-80).

The major concern with prolonged and repeated phototherapeutic regimens is the induction of promotion or skin cancers. High-dose exposure to oral PUVA is associated with a persistent dose-related increase in the risk of squamous cell cancer, even among patients lacking substantial exposure to other carcinogens (55,81,82). A meta-analysis of the PUVA Follow-up Study and other trials showed a 14-fold incidence of squamous cell cancer in patients who received high-dose PUVA (>200 treatments or >2,000 J/cm^2) compared with those ho received low-dose PUVA (<100 treatments or <1,000 J/cm^2) (83). Since male genitalia are particularly sensitive to the development of squamos cell cancer, it has been advocated that male genitals must be shielded during all of the PUVA exposures (84). Unlike the case with squamous cell carcinoma, the risk of basal cell carcinoma did not significantly increase with the degree of long-term PUVA exposure (46,47,55).

It is not clear whether exposure to PUVA increases the risk of malignant melanoma. Except for anecdotal reports, malignant melanoma has not been observed in PUVA-treated patients until recently, and no increase in melanoma incidence has been found in a large number of studies performed so far. However, in 1997 Stern *et al* (85) reported an increased risk of malignant melanoma developing 15 years after first treatments and most notable among patients who had received 250 or more treatments. In their PUVA Follow-Up Study in 2001, Stern *et al* (55) detected seven additional invasive melanomas and the risk seemed to be increasing with time. Although their findings have not been confirmed by other multicentric trials, they are alarming since the association between exposure to ultraviolet light and development of melanoma has been well established in both humans and experimental animals (25).

While an increased frequency of skin cancer was observed in patients treated with oral PUVA

therapy, it was not observed in patients treated with PUVA bath therapy. Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis (86). In addition, no association between cutaneous cancer and 8-MOP bath PUVA was found in 158 Finnish psoriatic patients (87). These data on the long-term safety of PUVA bath are encouraging but no premature conclusions should be drawn (6).

EXCIMER LASER TREATMENT OF PSORIASIS

A new alternative for treating psoriasis by phototherapy is the 308-nm xenon chloride excimer laser. Bonis *et al* (88) compared 311-nm narrowband UVB phototherapy ith the 308-nm excimer laser. The 308-nm excimer laser required 6.47-fold less irradiation and 3.6-fold fewer treatments than 311-nm UVB phototherapy to achieve complete clearance of psoriatic changes. Two studies have shown that a single high-dose (8-16 MED) excimer laser treatment can be effective for localized plaque-type psoriasis (89,90). The higher fluences, however, were associated with painful blistering eruptions. In a multicenter study, 84% of patients reached improvement of 75% or more after 10 or fewer treatments (91). In the most recent study, 66% of patients were at least 90% clear after a maximum of 10 treatments, with MED starter dose (92).

Excimer laser has several advantages over UVB phototherapy. This device allows specific targeting of affected sites without needless exposure of unaffected skin. The excimer laser can effectively clear psoriatic plaques in fewer treatments with lower cumulative dose than the standard phototherapy. Potential limitations of laser therapy for psoriasis include relative cost of treatment, time constraints when treating a large surface area (the spot size is less than 2 cm^2), and the unknown risk of carcinogenicity. The 308-nm excimer laser holds promise for becoming a useful tool in the treatment of stable, localized psoriasis (93).

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Acta Dermatovenerol Croat 2004;12(1):51-54 REVIEW

Heliomarinotherapy in Psoriasis

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SUMMARY Heliomarinotherapy is an important therapeutical option in the treatment of psoriasis. Investigations on heliomarinotherapy carried out at the Dead Sea and compared with results obtained in Veli Lošinj, Croatia showed that the remissions of psoriasis after such treatment were long lasting, side effects slight, and use of corticosteroids not necessary.

KEY WORDS psoriasis; heliomarinotherapy; climate factors; UV radiation

INTRODUCTION

Psoriasis is a relatively frequent autoimmune inflammatory skin disease present in 1-3% of the population, sometimes affecting the joints (1). One-third of the cases are patients below twenty years of age (type I psoriasis).

It is well known that psoriasis is a result of pronounced hyperproliferation of keratinocytes (2). Recent investigation has demonstrated the importance of environmental as well as genetic and immunological factors in the origin of psoriasis. Psoriasis, as an autoimmune disease, is caused by an autoimmune reaction to an epidermal and/or dermal autoantigene (3). The visible changes of the skin, scaling of the scalp, and the chronic course of the illness influence the psychological state of these patients and reduce their quality of life (4). Heliomarinotherapy is one of the oldest treatment modalities for psoriasis. Since antiquity, the effects of climatic factors have been known to have positive influence on the health and skin diseases. The Egyptians and other people of the ancient world worshipped the sun as their god and were aware of what an enormous influence this star had on life on earth. The Greek physicians understood what meaning the light, water, and air had for life, and Hippocrates described the influence of diverse climatic factors and sea water on health and disease, and considered natural factors to cause illnesses (5).

The importance and benefits of climatic factors and their influence on human health are well known, but in case of irrational exposure, they can

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provoke different pathological states. In addition to various external factors, genetic factors also play a significant role (6). Sunrays, wind, air temperature, air pressure, and humidity may have beneficial effects on psoriatic skin lesions, which depend on the intensity of these factors and vary according to geographical latitudes, distance from the sea, altitude, season, time of day, and weather.

Long time ago, dermatologists investigated the effect of climatic factors on the structure and function of the skin, e.g. on the capillaries and circulation in them, the amount of oxygen they contain, on sweating and functioning of sebaceous glands, on the state of the hair, the senses, intensity of itching, on production of D_3 vitamin from cholesterol, which can all provoke the manifestation and/or deterioration of numerous skin diseases in psoriasis (6).

The application of sunlight in the treatment of skin disease is called heliotherapy; the use of sunlight and baths in seawater is called heliomarinotherapy; and the use of aerosol with seawater is called heliomarinothalassotherapy.

The treatment of various diseases with seawater – thalassotherapy – is very old. Pliny wrote that Roman and Arabian physicians know about hydrotherapy. In the New Age, the first establishments for hydrotherapy were founded in England and Italy (Viareggio) at the beginning of the 19th century (7). Stüttgen *et al* (8) divided climatic factors in several groups as follows: photoactinic complex, which includes diverse types of rays (visible light, ultraviolet rays, infrared rays, cosmic rays); hygrothermic complex, which comprises air temperature, air humidity, and rainfall; physical complex, which includes air pressure and wind; electricity, which is present in the atmosphere; and chemical complex, which includes the amount of oxygen in the air, carbon dioxide, dust, smoke and waste gases from engines and industrial plants.

HELIOMARINOTHERAPY

Long ago it was noted that heliomarinotherapy, i.e. treatment with seawater and sun, has a beneficial effect on skin diseases, especially on psoriasis. Application of this physical natural factor is based on the fact that sunrays combined with seawater have a stronger effect, for which ultraviolet rays are mostly responsible (UVA and UVB). Coblentz (1934) grouped them on the basis of their biological effects into long-wave, middle-wave, and short-wave UV rays (9). Today, we are aware of the importance of UV index for our skin during the year and in the different geographic regions. Ultraviolet rays make up approximately 1% of all rays coming from the sun to the earth; nevertheless, they have a large amount of energy and can considerably affect the skin. UVA rays, or long-wave rays of 320-400 nm, make up 95% of UV rays reaching the earth's surface. Their energy is relatively small, but they penetrate into the dermis, enabling a quick browning of the skin. The long exposition to UVA has significant effects on photoaging of the skin. In dermatotherapy, UVA is usually used with photosensitizers as they act antiproliferatively on keratinocytes and produce depletion of lymphocytes from the epidermis and dermis. UVB rays, middle-wave rays of 290-320 nm, produce erythema and skin inflammation probably due to the release of mediators, such as prostaglandins (E2 and F2), histamine, and cytokines (IL-1, IL-6, and IL-8). The most effective UV rays are those of 311 nm. Therapeutically, they act through inhibition of DNA synthesis by inducing apoptosis of lymphocytes in the epidermis. UVC rays or short UV rays (wavelength of 200-290 nm) are germicidal. They are not to be found on the earth's surface since they are practically completely absorbed by the ozone in the stratosphere. Visible light can produce photodermatoses, whereas infrared rays can contribute to chronic skin damage, e.g. aging from UVA rays.

Based on beneficial effects of UV rays in psoriasis, a special apparatus has been developed that enables application of UVA rays in the treatment of psoriatic patients the whole year round. It should be emphasized that Prof A. Vukas established the Center for UVB and PUVA therapy in Rijeka, Croatia, the first one in this region of Europe, in 1974 (10). The Center was situated at the Rijeka Hospital Department of Dermatology and Venerology, site Sušak (10). At the Department of Dermatology and Venerology, Zagreb University Hospital Center, the same type of Center for UVA and PUVA therapy was established in 1978 by Vera Pasini-Omeljčenko.

The Dead Sea (Israel) is well known for successful treatment of psoriasis by means of heliomarinotherapy, without harmful topical or internal

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therapy. The Dead Sea (390 m under sea level) has an enormous salt content (33%). Mostly, patients from northern Europe are treated there. Results are excellent considering that improvement has been observed in 88% of the treated (11). Therapy usually lasts 4 weeks and during this interval, patients with skin type 4 receive about 3.11 J/cm^2 of the skin, or 148 erythema doses (MED), which is less than what patients receive with phototherapy in continental Centers (12). With respect to the development of skin cancer, this therapy is less dangerous than UV therapy, especially that performed in hospitals, where large doses are applied.

The most frequent side effects observed during heliomarinotherapy are slight solar dermatitis (8.22%), edema of the legs (2%), and herpes simplex (12). Recently, Shani *et al* (13) have described even better results, obtaining remissions in their patients up to 7 months, which are the longest remissions achieved in the treatment of psoriasis with any method applied so far. Moreover, the costs of this long treatment for psoriatic patients from the Scandinavian Peninsula as well of those from Italy, Austria, Germany, and France is covered by their health insurance (14). Of interest are also comparative studies of psoriasis treatments at the Dead Sea. In cases where only seawater from the Dead Sea was applied, improvement was observed in 28% of patients, whereas treatment consisting of mere sunbathing led to improvement in 73% of patients (15). The research in the treatment of psoriasis with heliomarinotherapy carried out on the Canarian Islands has also shown great efficacy of this kind of therapy, with an improvement in 86.3% of patients (16) and a positive influence on the patient's quality of life (17).

Heliomarinotherapy in Veli Lošinj

In Croatia, heliomarinotherapy has been developed in the Hospital of Veli Lošinj, located on the southeast part of the island of Lošinj, Croatia. In 1880, Professor A. Haračić begun measuring the climatic factors in Veli Lošinj, and published his results in Vienna. Soon after, Austrian physicians Clar, Schrotter (pulmologist), Lang (dermatologist), and others visited the island and reported to the Austrian government that the climate was beneficial, so that in 1892 Veli Lošinj became a "Kurort". Children were cured there as well as adults with lung allergies and skin diseases. Živković (18) studied the efficacy with heliomarinotherapy in 1,450 psoriatic patients and established that in 32% psoriatic skin lesions disappeared completely, whereas 55% of patients showed considerable improvement. Such good results achieved in 87% of patients certainly provide proof of the efficacy of this kind of therapy, which is also followed by long remissions lasting 5.5 months on average (18). Rožmanić *et al* (19) obtained similar results some years later: of 312 psoriatic patients, 31% had a complete regression of the lesions, whereas 58% had a good regression after having received a total of 2,581 sun hours/year. Apart from the efficacy of the sunrays and the seawater, this method also has certain significance with respect to psychological relaxation due to lovely surroundings, free of pollution. Our sea contains elements such as salt, Mg, Ca, J, P, and many oligoelements. It contains ten times less salt (3.7%) than the Dead Sea, but recent research performed in 2001 by German authors has indicated that balneophototherapy gives the same results irrespective of whether sea or fresh water are used (20). The mechanisms through which heliomarinotherapy acts have not been completely elucidated, but probably include thermal, chemical, and immunomodulatory effects.

Today, we must protect these regions from hasty development of industries and contamination, which have unfortunately already reached a critical point in many seas. Our mission to help the 2% of psoriatic patients in Croatia involves helping the renewal of the Hospital for Heliomarinotherapy in Veli Lošinj. During the winter months, application of ultraviolet rays is possible with the use of various devices and according to diverse schemes.

CONCLUSION

Heliomarinotherapy is a useful method for psoriatic patients. We had good results with this treatment applied in the treatment of psoriasis in Veli Lošinj, where the clear sea and clean air are pleasurable for the patients. Under the control of dermatovenerologists (to prevent side effects), this method offers long lasting remission of psoriasis and spares patients from chronic administration of topical corticosteroids, which is very important in patients with chronic relapsing diseases.

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Does the Measles Epidemic in Croatia at the Beginning of the 21st Century Tell us Something?

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Vjesnik, Zagreb, 4 January 2004. "As we were close to eradicating measles from the list of infectious diseases in Croatia, epidemiologists – to put it mildly – are not happy about the epidemics that has recently broken out in our country," says Dr Ira Gjenero-Margan, Head of the Infectious Diseases Epidemiology Division of the Croatian Institute of Public Health in Zagreb. Considering the satisfactory level of public health measures, measles were expected to appear only in part of the population with decreased immunity, i.e. in those who were not vaccinated and were in contact with infected persons.

Although six to eight infected persons is the usual annual toll from measles in Croatia, at present this number exceeds 20 patients, with all accompanying symptoms (Fig. 1). This number gives basis for calling it an epidemic, and there are some indications that the number of people infected with measles will increase. All we know is that the measles has been brought from France (by an adult carrier), where, like in other west European countries, systematic vaccination of the population is not carried out, whereas in Croatia vaccination has been obligatory since 1968. The source of disease was a single adult, at the Stančić Center for Occupational Therapy and Rehabilitation of Physically and Mentally Challenged Persons in Dugo Selo, near Zagreb. The measles was clinically present in five inmates, and 19 inmates who were in close contact with the infected persons have been under suspicion of having been infected. Most of them have never been vaccinated against measles.

Measles is a primarily children's acute disease caused by the Morbillivirus, which belongs to a genus of viruses of the Paramyxoviridae subfamily. In the initial phase, measles can be similar to a cold with sometimes very high fever, conjunctivitis, and cough, but with a characteristic maculo-papulous rash, enanthem on the buccal mucosa, and the so-called Koplik's spots, formations of small punctate blue-white lesions on the bright red background, present in 80% of the patients. The symptoms disappear within 4-7 days after the appearance of the rash and the disease gradually subsides with rest, high fever decreases and cough disappears. In case when the weakened organism is attacked by bacteria, the most frequent complica-

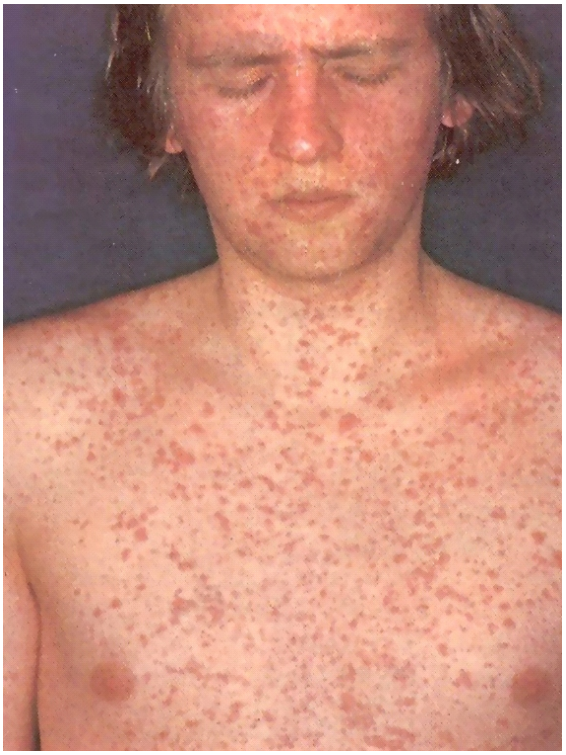

Figure 1. Characteristic maculo-papulous rash in a measles patient.

tions are otitis media, pneumonia, and, most seriously, encephalitis (1). The patient is contagious one day before the appearance of the symptoms and four days after. There is no specific drug for treatment, but the exposition to infection does not exclude vaccination. Presently, all the persons under the age of 25 years have been vaccinated. The disease can be prevented, or its appearance can be significantly reduced, if active immunization is received within three days of the contact with the measles virus, and passive immunization within six days.

In the last five years, smaller or large-scale measles epidemics have been described among children <1 year of age with no history of vaccination and once vaccinated 15-year-old children in Poland (2,255 cases of measles were reported in children in 1997-1998) (2). In Japan, 69 cases were reported during 1998 and 1999 (3), 111 cases were reported in Ireland in the period from 1999 to 2000 (4), and 55,000 measles cases were reported in Korea in the 2000-2001 period (5).

According to the data of the World Health Organization (WHO), almost 40 million people were reported to have contracted measles worldwide during 2000, with a total of 770,000 measles-associated deaths, and 28 million cases reported to have had secondary complications after being infected with the Morbillivirus (6). It has been estimated that the number of fatalities among children of the underdeveloped countries of Africa and South East Asia amounted to 1.7 million in 2000, with 46% of measles-related deaths (7).

Epidemiological studies have shown that a vaccination level exceeding 90%, with bivalent vaccine and by intensive vaccination measures, can effectively eradicate measles. During recent measles epidemics in Croatia, the Epidemiology Division of the Croatian Institute of Public Health in Zagreb has informed all health institutions on anti-measles procedures and protocols, such as reporting suspicious disease signs, obligatory isolation of patients, and serological testing for proving the disease (RT-PCR test). All the health institutions in Croatia were ordered to review the measles vaccination status in persons <35 years of age. Persons previously not vaccinated should be vaccinated against measles with a mono-component vaccine.

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UPCOMING MEDICAL MEETINGS

Continuing Medical Education Course

UPDATE ON PSORIASIS

Zagreb, Croatia

October 15-16, 2004

The Continuing Medical Education Course is organized by the Chair of Dermatovenerology, Zagreb University School of Medicine, under the auspices of Academy of Medical Sciences of Croatia.

Known experts in the field of psoriasis will also participate in the Course.

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Report From the Annual Meeting of the Austrian Dermatovenerological Society

Graz, Austria, November 21-23, 2003

This year's Meeting of the "Österreichische Gesellschaft für Dermatologie und Venerologie (ÖGDV), organized by Professor Werner Aberer, currently President of the Society, was as successful as always. The International Meeting held in Graz, Austria, November 21-23, 2003, was attended by approximately 400 participants not only from Austria, but also from Switzerland, Germany, Slovenia, Hungary, Italy, United Kingdom, and Croatia. About 50 firms were present at the pharmaceutical exhibition that was part of the whole event.

On Saturday, November 22, 2003, Albert Finlay (Cardiff), as a guest of the ÖGDV, gave a lecture on "Quality of life index in dermatology" within the "Ferdinand von Hebra Memorial Lecture." Dr Finlay, as an expert in this field, has a large experience in confirming the dermatology quality of life index (DQLI) for many dermatological diseases like psoriasis, atopic dermatitis, and many others. The DQLI is very important measure of psoriasis patient's quality of life and even better than PASI score or SCORAD index for assessment of quality of life in atopic dermatitis patients.

Very interesting was a lecture given by Prof. Diepgen, who presented fundamentals of modern medicine and talked about the Cochrane library and evidence-based medicine. Prof. Sterry held a very instructive lecture about ISO certification.

There were 11 interesting clinical cases presented, followed by rich discussions. A poster presentation offered about 27 posters, and every day, there were lectures given by invited speakers from abroad.

On Sunday, November 23, 2003, president of the Collegium Internationale Allergologicum, and elected president of the European Academy for Dermatology and Venerology, Professor Johannes Ring delivered a very competent "Joseph von Plenck memorial lecture" entitled "Skin, Allergy and Environmental problems", focused on modern dermatology in 21st century, especially on allergies and atopy.

Congratulations to Prof. Aberer for excellent organization.

Prof. Jasna Lipozenčić, MD, PhD

Marko Polo´s Diary

Stella Fatović-Ferenčić, ESHDV representative of Croatia

12th EADV Congress, Barcelona, Spain, October 15-18, 2003

The city of Gaudi, towered by the impressive spikes of the Sagrada Familia, hosted a huge crow of 8,000 participants of the European Academy of Dermatovenerology (EADV) Congress during several rainy days in October last year. The warmth of our hosts and their hospitality made us nothing but enchanted in this pulsing center of commercial and administrative power, the city where Joan Miró, Salvador Dalí, and Pablo Picasso moved the borders of art and sensitivity. The History day started as usual with a guided tour to the Hospital de la Santa Creu i Saint Pau. The long period devoted to the construction of the hospital is a demonstration of its complexity, size, and creative architecture. We were fascinated with the sensitivity of the architects who created a place were patients would feel surrounded with dignity, with colorful stained-glass windows, and beautiful gardens they could wander through all day long. I couldn't resist but think how colors and gardens are usually neglected details in hospital architecture of our time. After the tour, we were brought to a room where the Alibert Lecture was given, entitled The honor of living, by Professor Mascaró.

The History symposium Masters in Dermatovenerology, which took place the next afternoon, acquainted us with the lives and legacy of Joseph Plenck (1735-1807), Ferdinand-Jean Darier (1856-1936), José E. Olavide (1836-1901), Jaume Peyri (1877-1950), Luca Stulli (1772-1828), Franziszek Krysztalowicz (1869-1931), and Alfred Blascho (1858-1922).

The following day, an editorial board meeting of the Journal of the European Academy of Dermatovenerology took place at the Hotel Catalonia Plaza. Introduction of the electronic submission of manuscripts and web-based peer review system was discussed, and we were all pleased to hear that the Impact Factor of the Journal has risen in 2003. The marketing objectives for the forthcoming year would have to reflect the growth of the journal in both its print and electronic forms.

Saturday, another rainy and gray day, enchanted us by a visit to the Cusi Museum of Pharmacy at El Masnou, in the region known as El Maresme, north of Barcelona. The Cusi museum of Pharmacy houses objects and antiques of pharmacy acquired, preserved, studied, and exhibited by a pharmacist Joaquim Cusi i Furtunet. Although exhibiting mostly the preparation of ophthalmic products, the Museum also contains collections of diverse pharmaceutical and medical accessories, ceramics and glass, mortars, and collection of illustrations and paintings of medical instruments, as well as an outstanding library of 6,000 volumes of old books and writings.

Visit of Coleman Jacobson to Zagreb's Dermatology Clinic, November 7, 2003

Dr. Jacobson has held all academic ranks from Clinical Instructor to Clinical Professor at the Southwestern Medical School of the University of Texas and has been Chief of the Division of Dermatology at Baylor University Medical Center and the Derma-

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tology Service at the Children's Medical Center, Dallas, Texas. He is former President and Chairman of the Board of Trustees of the Dermatology Foundation, and he also served as Executive Vice President of the International Society of Dermatology (ISD). As a true Texan, he charmed everyone with his openness in communication and a typical sense of humor. I took him to the Dermatology Clinic at Zagreb School of Medicine, where Professor Ivan Dobrić, Head of the Clinic, and his staff organized a warm welcome. While listening to case reports and discussions and during a visit tour around the premises, I felt proud and assured that the attempts our dermatologists make in the field are ambitious and promising.

Hydrotherapy: Approaches and Paradoxes – Symposium, Croatian Academy of Sciences and Arts, November 25, 2003

The year of 2003 was proclaimed the Year of Fresh Water and the symposium entitled Hydrotherapy: Approaches and Paradoxes held in the building of the Croatian Academy of Sciences and Arts was our contribution to this occasion. Water has a deep symbolical meaning in all cultures and religions and since ancient times, it has been linked to the creation, birth and life, destruction and death. The use of water in healing has been known since the dawn of civilization. Hydrotherapy gained in popularity during the 18th and 19th century and still preserves its place within medicine. The experts from different disciplines (medicine, history, religion, geology, and biology) who participated at the symposium brought different viewpoints into the discussion. The event was pervaded by the cross-cultural, symbolic, and religious meaning of water, its significance in early medical conceptions, therapeutic applications, and place in public health activities throughout history. Two presentations were given by dermatologists: Andrija Stanimirović spoke about climatotherapy at the Dead Sea in the treatment of psoriasis, whereas Jasna Lipozenčić and Marija Kanižaj-Vlahovski delivered a talk on the use of water in maintaining the physiological status of skin and in the treatment of dermatoses.

Good for the itch, Marko Polo was taught when he reached a hot spring in southern Iran more then 700 years ago. He took a bath in a big hot spring at Cheshmeh Genu, where locals still bathe in mineral-rich water. People travel, times change, cultures mix, yet the human link to water in all segments of life remains equally strong.

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The world is waiting, sretan vam put !

stella@hazu.hr

****

ERRATUM:

In my paper on Joseph Planck (1735-1807), Acta Dermatovenerologica Croatica 2003;11:207-11, the Hebrew caption was spelled wrongly. It should read:

אין נביא בעירו

I ask the reader's apology.

Karl Holubar, Vienna

Book Review

Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldshmith LA, Katz SI, editors. Fitzpatrick's Dermatology in General Medicine, 6th edition. New York: McGraw-Hill, Medical Publishing Division; 2003. Set: ISBN 0-07-138076-0.

Format: hard cover, two volumes, 2,850 pages, 280 chapters, 37 sections. Volume 1: ISBN 0-07-138066-3, Volume 2: ISBN 0-07-138067-1.

This is a new, sixth edition of Fitzpatrick's Dermatology in General Medicine (DIGM), reminding us of the first edition of this classic and definitely best known textbook in dermatology, which was published by the same publisher in 1971. The preceding, fifth, edition was issued in 1999. Every new edition of Fitzpatrick's DIGM has shed new light and brought novel concepts to the dermatologic profession and science. It is a classic medical book in the field of dermatology useful to physicians, scientists, and students all over the world. However, it is primarily intended for dermatologists and residents in dermatology.

The first, introductory part and chapter 1, referring to the history of dermatology and providing a concise historical survey of the profession, were written by Prof Karl Holubar from Vienna and Assist. Prof. Stella Fatović-Ferenčić from Zagreb. Other segments of the first part are dedicated to dermatologic propedeutics. The material is presented in a modern and convenient style, additionally elucidated by all kinds of illustrations, thus bringing it closer primarily to the young generations of dermatologists. The more so, all chapters of the book are accompanied by a large body of references, most of them very recent.

The second part of the book is dedicated to the biology and development of the skin. There are 34 chapters, which deal with the genetics, structure, and development of skin; epidermal kinetics; differentiation and keratinization; skin as a protective organ; and biology of melanocytes, hair follicles, nails, extracellular matrix, blood vessels, and basal membrane. A special chapter is dedicated to the endothelium, neurobiology, and wound healing. The sixth section of the second part of the book deals with immunity and skin as an immune barrier, whereas the effect of HLA system on disease susceptibility and role of cytokines and chemokines are dealt with in special chapters. The same holds for lymphocytes, regulation of the production and activation of neutrophils, eosinophils, and basophils, molecular and cellular biology of mastocytes, complement system, and eicosanoids. Three chapters refer to carcinogenesis, i.e. chemical and viral carcinogenesis, photocarcinogenesis, and oncogenes. The last chapter in the second part of the book is the chapter on photoimmunology. The entire second part of the book is richly illustrated, with excellent schematic presentations and microphotographs, rendering this highly complex material very reader-friendly, which especially holds for the chapter on melanocyte biology.

The third part of Fitzpatrick's DIGM is dedicated to the diseases manifesting on the skin and mucosa. This huge material is divided into 12 sections and as many as 101 chapters. The section on non-cutaneous manifestations of skin diseases elaborates psychological aspects of skin diseases and pathophysiology and clinical aspects of pruritus, with special reference to the diagnosis and management of these disorders. Section 8 deals with the epidermis and diseases associated with inflammatory lesions of the epidermis, and kinetics

and differentiation impairments. Description is provided of psoriasis and psoriatic arthritis, with the latest concepts on their pathogenesis and treatment. Clinical picture, novelties in the pathogenesis and management of other diseases associated with keratinization disorder, e.g., parapsoriasis, pityriasis rosea, and pityriasis rubra pilaris, are thoroughly and conveniently presented. Special attention is paid to the association of parapsoriasis with skin lymphoma. A relatively new term of clonal dermatitis is mentioned. Also, it is emphasized that the so-called parapsoriasis group of diseases is characterized by the potential transformation to cutaneous lymphoproliferative diseases, which is accompanied by clone progression of certain T-cells produced by mutation. Clonal dermatitis has been postulated to represent a stage in the progression of precursor diseases to skin lymphomas.

Along with a detailed description of particular entities, the chapter dedicated to ichthyosiform dermatoses provides a survey of clinical features and associated symptoms, etiologies (gene, protein, and function) and histologic characteristics of this group of diseases. The chapter is enriched by excellent clinical photos.

Section 9 describes a group of bullous dermatoses as epidermal cohesion disorders, presenting a number of new concepts on erythema multiforme, pemphigus, bullous pemphigoid, and cicatricial pemphigoid. Special chapters deal with paraneoplastic pemphigus, linear IgA dermatosis and chronic bullous diseases of childhood, herpes gestationis, impetigo herpetiformis, and Hailey-Hailey disease. The chapter on hereditary bullous epidermolyses is provided by excellent clinical and micromorphological pictures and schematic presentations that make this complex dermatologic issue easier and convenient to comprehend. Considerable attention is also dedicated to the diseases associated with sebaceous gland disorders, especially acne. The chapter on acne provides a thorough survey of therapeutic options for this common cutaneous disease of the young.

Dermatologic oncology begins with section 11 on epithelial precancerous lesions. Consistently with the majority of current dermatologic textbooks, Bowen's disease, erythroplasia of Queyrat, and erythroplasia are described among precancerous lesions. Special chapters are dedicated to planocellular and basal cell carcinoma. In the chapter on planocellular carcinoma, verrucous carcinomas are described as a group of planocellular, exophytic, slowly growing carcinomas at the sites exposed to chronic irritation. According to the site of development, there are four types of this tumor: oral florid papillomatosis, anogenital type described by Buschke and Loewenstein, epithelioma cuniculatum, and type IV that may develop in other regions of the trunk and extremities. Detection of type 6, 11, 16, and 18 HPV in the epithelioma cuniculatum points to the possible evolution of this tumor from vulgar verruca.

Section 12 refers to melanocyte disorders. Albinism, vitiligo, and many other pigmentation disorders associated with various diseases and syndromes as well as physical impacts are thoroughly described. Special chapter deals with benign melanocyte hyperplasias and neoplasms, atypical nevi, and melanoma. The chapter on melanoma brings a survey of therapeutic options, some of them perhaps finding wide application in the near future, e.g., vaccination and monoclonal antibodies.

Special section provides a detailed survey of inflammatory and non-neoplastic diseases of the dermis. Special chapter is dedicated to vascular anomalies and tumors of the skin and subcutaneous tissue, illustrated with impressive clinical pictures. The chapter on Kaposi's sarcoma brings a lot of new data on the disease pathogenesis.

The section on cutaneous changes in disorders of altered reactivity describes various forms of immunodeficiency. Special chapters are dedicated to urticaria and angioedema, contact allergic dermatitis, and graft-*versus*-host disease (GvHD). Atopic dermatitis and seborrheic dermatitis are described in detail.

Section 17, which deals with skin changes due to mechanical and physical factors, describes skin lesions caused by exposure to heat and cold. Special chapters are dedicated to radiobiology and radiotherapy of skin diseases. This text is very concise, evidently written by experts, and certainly useful to every dermatologist, particularly those engaged in dermatologic radiotherapy. Mention should be made of the chapters on skin problems in patients having undergone extremity amputation or

with stoma. A chapter on sports dermatology is for the first time found in a dermatologic textbook.

The section on skin diseases caused by drugs and chemical agents gives an account of occupational skin diseases, mucocutaneous complications of antineoplastic therapy, and skin changes associated with cytokine (especially interferon) and growth factor therapy, and drug abuse.

The fourth part of Fitzpatrick's DIGM is entitled Dermatology and Medicine, and contains eight sections and 50 chapters. Three chapters in section 20 are dedicated to various skin diseases related to specific life periods: pregnancy, infancy, childhood, and adolescence. Further chapters describe skin changes in nutritional, metabolic, and hereditary diseases. Skin alterations in the disorders associated with amino acid metabolic errors, skin amyloidoses, porphyrias, Fabry's disease, and skin changes in fat metabolism disorders are described in detail. Descriptions of the diseases and skin lesions are accompanied by numerous tables, schematic presentations, and photographs. Skin changes in hereditary diseases of the connective tissue are briefly and clearly presented in the respective chapters. A detailed account of xeroderma pigmentosum is given in the chapter on heritable diseases with increased sensitivity to cellular injury.

Skin changes in hematologic diseases are concisely and systematically presented in a special chapter. The convenient and precise description is substantiated by a table of skin symptoms in particular hematologic diseases, given on five pages. Primary and secondary skin lymphomas are described in special chapters, with special reference to the diagnosis and therapeutic options. The classification of lymphomas according to the World Health Organization is provided in addition to the EORTC classification of primary skin lymphomas. The description of Langerhans histiocytoses (previously called histiocytosis X) is accompanied by very impressive photographs of these rare and severe diseases.

Skin changes associated with diseases of the gastrointestinal tract and hepatobiliary tract, renal diseases, peripheral vascular diseases, diabetes mellitus and other endocrine diseases are presented in the respective chapters.

Section 26 deals with the group of rheumatic, multisystem diseases. A very detailed account is given of lupus erythematosus, dermatomyositis, scleroderma, systemic necrotizing arteritis, cutaneous necrotizing venulitis, and pigmented purpuric dermatosis.

Section 27 deals with cutaneous manifestations of other organ system diseases, i.e. sarcoidoses, malignant diseases (cutaneous paraneoplastic syndromes), neurocutaneous diseases, tuberous sclerosis complex, neurofibromatoses, and Behçet's disease. The description of skin lesions is very clear and concise, thus definitely highly useful to many physicians of various specialties.

The fifth part of Fitzpatrick's DIGM describes diseases due to microbial agents, infestations, bites, and stings. This part of the book is abundant in various useful data from general microbiology. A special account is given of the staphylococcal scalded skin syndrome, enriched with excellent photographs and microphotographs.

Section 29 covers fungal diseases with cutaneous involvement. Superficial fungal infections, onychomycoses, tinea nigra, piedra, candidiasis, pityriasis versicolor, and deep fungal infections are described, with special reference to systemic mycoses. These are followed by viral diseases of the skin, with due attention paid to the classification, replication, and cellular events during various viral infections. Skin lesions in diseases caused by human immunodeficiency virus (HIV) are presented in special chapters. Description of skin alterations caused by prions and rickettsiae points to the comprehensiveness and richness of the data offered in the Fitzpatrick's DIGM.

Section 31 provides a detailed account of sexually transmitted diseases, describing syphilis, endemic (nonvenereal) treponematoses, chancroid, lymphogranuloma venereum, granuloma inguinale, and gonorrhea. Section 32 is dedicated to leishmaniasis, cutaneous toxoplasmosis, cysticercosis, and other helminthic infections. Several chapters refer to dermatologic issues related to outdoor activities, such as snake bites and jellyfish burns. The issues are presented concisely and illustrated with excellent photographs, useful not only to a dermatologist but also to every other specialist.

A novelty in a dermatologic textbook is the inclusion of evidence-based dermatology. Practical evidence-based medicine (EBM) is predicated on find-

ing and using the best evidence. Potential sources of evidence include understanding the etiology and pathophysiology of disease and logic, personal experience, colleagues or experts, textbooks, articles published in journals, and reviews.

Special section deals with topical therapy and its principles. Abundant data are provided on topical agents in dermatology, i.e. corticosteroids, retinoids, antibiotics, antimycotics, sunscreens, keratolytics, immunomodulators, and other topical agents, as well as on cosmetics and skin care in dermatologic practice. In the segment on systemic therapy, an account is given of systemic corticosteroids, sulfones, antimalarials, retinoids, cytostatics, antihistaminics, antibiotics, antiviral agents, systemic antimycotics, immunosuppressants, and novel biologic drugs used in the management of psoriasis.

The last chapters of Fitzpatrick's DIGM deal with phototherapy, photodynamic therapy, use of laser in dermatology, and surgical techniques used in cosmetic dermatology, and tumor surgery. A chapter on skin resurfacing by use of laser is a novel topic in dermatologic literature, and so are the chapters on the use of botulinum toxin in cosmetic medicine, hair transplantation and alopecia reduction, and on nail surgery.

The subject index provided at the end of the book is very comprehensive, written on 139 pages.

The review of Fitzpatrick's DIGM, a textbook written by more than 400 authors, definitely deserves by its contents, systematic presentation, and relevance to be distinguished from all other dermatologic textbooks. In Fitzpatrick's DIGM, the basic and clinical dermatologic science have been best and most conveniently integrated, making it a pivotal dermatologic book in the world medical literature, convincingly pointing to the role of dermatology in the medicine in general. Indeed, it is a great pleasure and true fortune to have this valuable book in one's own library.

Aida Pašić, MD, PhD

ANNOUNCEMENTS

4th World Congress of the International Academy of Cosmetic Dermatology, Cairo, Egypt, April 12-18, 2004. Contact Larry Millikan, MD, Tulane University Medical School of Dermatology. TB-36, 1430 Tulane Avenue, New Orleans, LA 70112. Fax +1 504 587 73382

Update on Atopic Eczema/Dermatitis Syndrome, Cavtat, Croatia, April 25-28, 2004. Contact: Prof. Jasna Lipozenčić, Department of Dermatology and Venerology, Zagreb University Hospital Center, Šalata 4, 10000 Zagreb; *jasna.lipozencic@zg.tel.hr*; *www.cybermed.hr/4dermkh*

Second EADV International Spring Symposium, Budapest, Hungary, April 29-May 1, 2004. Contact: *info@eadvbudapest2004.com*; *www.eadvbudapest2004.com*

66th Annual Meeting of the Society for Investigative Dermatology, St. Louis, Missouri, May 4-7, 2004. Contact: Kate Rader, Meetings Manager, 820 W. Superior Avenue, 7th Floor, Cleveland, OH 44113; phone: 216/579-9300; fax: 216/579-9333; e-mail: *Krader@sidnet.org*

31st Annual Joint Meeting of Society for Cutaneous Ultrastructure Research and European Society for Dermatopathology, Rome, Italy, May 6-8, 2004. Contact: *www.prex.it/congressi/scur/index.html*

9th International Congress of Dermatology, Beijing, China, May 19-22, 2004. Contact: ICD2004 Secretariat, International Department, Chinese Medical Association, 42 Dongsi Xidajie, Beijing 100710, China; *ICD2004@chinamed.com.cn*; *www.chinamed.com.cn/dermatology*

International Symposium "Frontiers in Allergy and Autoimmunity", Mainz, Germany, May 21-22, 2004. Contact: *Anja.Oberlaender@uni-mainz.de*

15th Ljudevit Jurak International Symposium on Comparative Pathology; Main Topic: Head & Neck Pathology, Zagreb, Croatia, June 4-5, 2004. Contact: *www.kbsm.hr/jurak/symposium.htm*

7th Congress of the European Society of Contact Dermatitis, Copenhagen, Denmark, June 6-8, 2004. Contact: Organizing Secretariat PREXY S.r.l. – Vialle Monza 20125 Milano, *Liss@ics.dk*; *congressi@prex.it*, *www.iscd2004.info*

23rd Congress of the European Academy of Allergology and Clinical Immunology, Amsterdam, Netherlands, June 12-16, 2004. Contact: Dept. Allergology, University Hospital Rotterdam, dr. Molewaterplein 40, NL-3015 GD Rotterdam, The Netherlands; *degroot@algo.azr.nl*; *www.congrex.com/eaaci2004*

28th Annual Meeting of the Israel Society of Dermatology and Venereology, Eilat, Israel, June 16-17, 2004. Contact: Prof. Sarah Brenner, The Tel Aviv Sourasky Medical Center, Weizman Street, Tel Aviv 64239, Israel; tel: 972 3 6974287; fax: 972 3 6974810

10th Congress of the European Confederation of Medical Mycology, June 17-20, 2004, Wroclaw, Poland. Contact: Congress Care, Muntelbolwerk 1, P.O. Box 440, 5201 AK's-Hertogenbosch, The Netherlands; *info@congresscare.com*, *www.congresscare.com*

4th European Congress of Aestetic Medicine and 6th Congress of the Swiss Society of Aestetic Medicine, Zuerich, Switzerland, June 25-26, 2004. Contact: Pro Services Consulting - Patricia Lafitte, Chemin des Baules 14, CH - 1268 Begnins - Switzerland; Phone +41 (022) 366 08 10; Fax: +41 (022) 366 08 15; *patricialafitte@deckpoint.ch*; *www.ssme.ch*

X World Congress of Pediatric Dermatology, Rome, Italy, July 7-10, 2004. Contact: Triumph Congressi, Via Lucilio, 60, 00136 Rome, Italy; *dermo@gruppotriumph.it*

19th Continuing Medical Education Course for Practical Dermatology and Venerology, Munich, Germany, July 25-30, 2004. Contact: *www.fortbildungswoche.de*

American Academy of Dermatology, Academy '04, New York, USA, July 28-August 1, 2004. Contact: American Academy of Dermatology, Department of Meetings & Conventions, 930 E Woodfield Road, Schaumburg, IL 60173; fax: 847 330 1090

7th Dresden Symposium on Autoantibodies, Dresden, Germany, September 1-4, 2004. Contact: *k_conrad@rcs.urz.tu-dresden.de*

3rd Congress of the Dermatovenerologists, Struga, Macedonia, September 15-18, 2004.; Contact: Congress Secretariat, Clinic of Dermatovenerology, Vodnjanska 17, 91000 Skopje, Macedonia; Phone: +389 2 3147-205; Phone-Fax: +389 2 3134-042; *makderm@unet.com.mk*

Allergie Kongress 2004, Aachen, Germany, September 15-19, 2004. Contact: *Gerhard.Schultze-Werninghaus@ruhr-uni-bochum.de*; *www.allergie-kongress-2004.de*

1st Croatian Congress of Psychodermatology, Cavtat, Croatia, September 23-26, 2004. Contact: Prof. Mirna Šitum, Department of Dermatology and Venerology, Clinical Hospital "Sestre milosrdnice", Vinogradska 29, 10000 Zagreb, Croatia; *msitum@kbsm.hr*

7th International Congress of Dermatology, Teheran, Iran, September 29-October 2, 2004. Contact: *info@iranderm.org*; *www.iranderm.org*

25th Annual Meeting of the International Society of Dermatologic Surgery, Barcelona, Spain, October 6-9, 2004. Contact: *isds2004@mccann.es*; *www.isds2004.com*

6th Dermatology and Dermatopathology Meeting of the Turkish Society of Dermatopathology, Istanbul, Turkey October 7, 2004. Contact: Rana Yavuzer Anadolu, M.D., Ankara Uni Koza sok. 114-86, 00670 Ankara Turkey; phone: 90-312-3245724: *ranaadolu@hotmail.com*

Update on Psoriasis, Continuing Medical Education Course organized by Chair of Dermatovenerology of the University School of Medicine Zagreb, Šalata 4, 10000 Zagreb, Croatia, October 15-16, 2004. Contact: Prof. Jasna Lipozenčić, Šalata 4, 10000 Zagreb, Croatia. Phone./Fax: +385-1-4920-014; e-mail: *jasna.lipozencic@zg.tel.hr*

Therapeutic Innovation in Dermatology and Dermatocosmetology, Bangkok, Thailand, October 23-25, 2004. Contact: *thadapiaru.@thaicosderm.org*

4th International Congress on Autoimmunity, Budapest, Hungary, November 3-7, 2004. Contact: fax:0041 22 732 2850; phone 0041 22 908 0488

13th Congress of the European Academy of Dermatology and Venerology, Florence, Italy, November 17-21, 2004. Contact: *president@eadv2004.org*; *registration@eadv2004.org*; *www.eadv2004.org*

10th World Congress on Cancers of the Skin, Vienna, Austria, March 19-23, 2005. Contact: Elfriede Pomp, Department of Dermatology, University of Vienna, Vienna General Hospital, Waehringer Guertel 18-20, A-1090 Vienna, e-mail: *info@wccs.at*; *www.wccs.at*

Spring Symposium of the European Academy of Dermatology and Venerology, Sofia, Bulgaria, 2005. Contact: Bulgarian Dermatological Society; *dermven@bg.com*

8th Congress of the European Society for Pediatric Dermatology, Budapest, Hungary, May 5-7, 2005. Contact: *www.convention.hu*; *www.espd2005.com*

World Allergy Congress – 19th International Congress of Allergology and Clinical Immunology and 24th Congress of the European Academy of Allergology and Clinical Immunology, Munich, Germany, June 26-July 1, 2005. Contact: *wac2005@congrex.se www.congrex.com/wac2005*

14th IACD (International Academy of Cosmetic Dermatology) World Congress, Paris, France, July 3-5, 2005. Contact: *iacd2005@mci-group.com*; *www.iacd-paris2005.com*

16th Biennal Meeting of the International Society for Sexually Transmitted Diseases Research (ISSTDR), Amsterdam, Netherlands, July 10-13, 2005. Contact: *isstdr@aidsfonds.nl; www.isstdr.org*

6th World Congress on Melanoma, Vancouver, B.C., Canada, September 2-9, 2005. Contact: Venue West Conference Services Ltd., Vancouver, B.C., Canada; *congress@venuewest.com*

15th World Congress of the International Union of Phlebology, Rio de Janeiro, October 2-7, 2005; Contact: RIO UIP 2005 - Secretary, Rua Santa Clara, 494 - Sorocaba - 108030-421 SP - Brasil; Phone: 55 (15) 231-6619; Fax: 55 (15) 221-4074/232-9241; *inspemoc@dglnet.com.br*; *angelo.scuderi@flebologiabrasil.com.br*; *www.flebologiabrasil.com.be*

14th Congress of the European Academy of Dermatology & Venerology, London, October 12-15, 2004. Contact: Congress President; tel: 34 93 200 7083; fax: 34 93 209 3152; e-mail: president@eadv2005.org; website: *www.eadv.org*

21st World Congress of Dermatology, Buenos Aires, Argentina, October 1-5, 2007. Contact: *info@dermato 2007.org*

INSTRUCTIONS TO AUTHORS

ACTA DERMATOVENEROLOGICA CROATICA (ADC) is a quarterly peer-reviewed journal, indexed in Index Medicus/MEDLINE and Excerpta Medica/EMBASE. It publishes original scientific articles, short scientific communications, clinical articles, case reports, reviews, reports, news and comments, and announcements in the fields of dermatology and venerology.

General Guidelines

Type the complete manuscript double-spaced, on one side of A4 bond paper, with a left side margin of at least 4 cm.

The manuscripts should not exceed 12-15 typed pages in case of original scientific papers, and 6-8 pages in case of short communications, clinical articles, case reports, and reviews.

The manuscripts should be written in English. The authors are responsible for ensuring that the English used is suitable for publication. All material is assumed to be submitted exclusively to this journal.

All manuscripts are subject to peer review.

Preparation of Manuscripts for Submission

Title Page

The title page should carry (a) the title of the paper, which should be concise but informative; (b) full name of each author, with institutional affiliation; (c) name(s) of department(s) and institution(s) to which the work should be attributed; (d) name and address (with telephone and fax numbers as well as the e-mail adress) of the author to whom requests for reprints should be addressed; (f) source(s) of support in the form of grants, equipment, drugs, or all of these; and (g) a short running head of not more than 40 characters (count letters and spaces) at the foot of the title page.

Second Page

The second page should carry a summary of not more than 250 words, followed by three to six key words from the Medical Subject Headings (MeSH) list of Index Medicus.

Manuscript

The text of observational and experimental is usually, but not necessarily, divided into sections with the headings Introduction, Material (Patients) and Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their contents, especially Results and Discussion sections. Other types of articles, such as case reports, reviews, and editorials, are likely to need other format.

Abbreviated terms should be written in full the first time they are used in the text, with abbreviation in parentheses.

Underline the words that must be printed in italic.

References should be identified in the text by arabic numerals in parentheses, and be numbered and listed consecutively at the end of the manuscript in the order in which they are first cited in the text.

Indicate in the text where the illustrations (figures and tables) should be inserted.

Tables and figures should be provided each on a separate sheet of paper after the references. Descriptive legends to figures should be typed double-spaced on a separate sheet of paper, whereas figures should be submitted in an envelope, with the number, the name of the (first) author, and title of the manuscript on the back: each table should be typed on a separate sheet of paper, numbered in the order in which they are first cited in the text, with a title and descriptive legend. Terms used in tables should not be abbreviated.

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When reporting experiments on human subjects, indicate whether the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration from 1975 as revised in 1983. Do not use patients, names, initials or hospital numbers, especially any illustrative material.

Statistics

Describe statistical methods and provide enough data to enable a knowledgeable reader to assess the reported results him or herself. Please state the statistical package (version, manufacturer) used for statistical analysis.

Acknowledgements

Please specify: (a) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chairman; (b) acknowledgements of technical help; (c) acknowledgements of financial and material support, specifying the nature of support; (d) financial relationship that may be a source of conflict of in-

terest. Technical help should be acknowledged in a separate paragraph as well as other contributions.

References

References should be typed double-spaced on a separate sheet of paper. The Vancouver style, proposed by the International Committee of Medical Journal Editors, is used (Engl J Med 1991,324:421-8, BMJ 1991,302:338-41, or *www.icmje.org*) . Examples of correct forms of references are given below:

Journal article

Standard journal article (list all authors, but if their number exceeds six, give six followed by et al.)

You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1989;79:311-4.

Chapter in a book

Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, editors. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

Article not in English

Massone L, Borghi S, Pestarino A, Piccini R, Gambini C. Localisations palmaires purpuriques de la dermatite herpetiforme. Ann Dermatol Venerol 1987;114:1545-7.

Conference paper

Harley NH. Comparing radon daughter dosimetric and risk models. In: Gammage RB, Kaye SV, editors. Indoor air and human health. Proceedings of the Seventh Life Sciences Symposium; 1984 Oct 29-31; Knoxville (TN). Chelsea (MI):Lewis, 1985:69-78.

Disertation

Youssef NM. School adjustment of children with congenital heart diseases (dissertation). Pittsburgh (PA): University of Pittsburgh; 1988.

Submission of Manuscripts

Manuscripts should be printed on paper and submitted in triplicate, with one copy on a floppy disk, and sent to:

Editorial Office

Department of Dermatology and Venerology

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Manuscripts on Disks

Floppy disks should be 3.5-inch (1.44 MB) IBM formatted and labeled with the name of the author.

The file, the word-processing program, and version used should be indicated by pen. MS-Word for Windows is preferred, although manuscripts prepared using any other IBM-compatible word-processor are acceptable.

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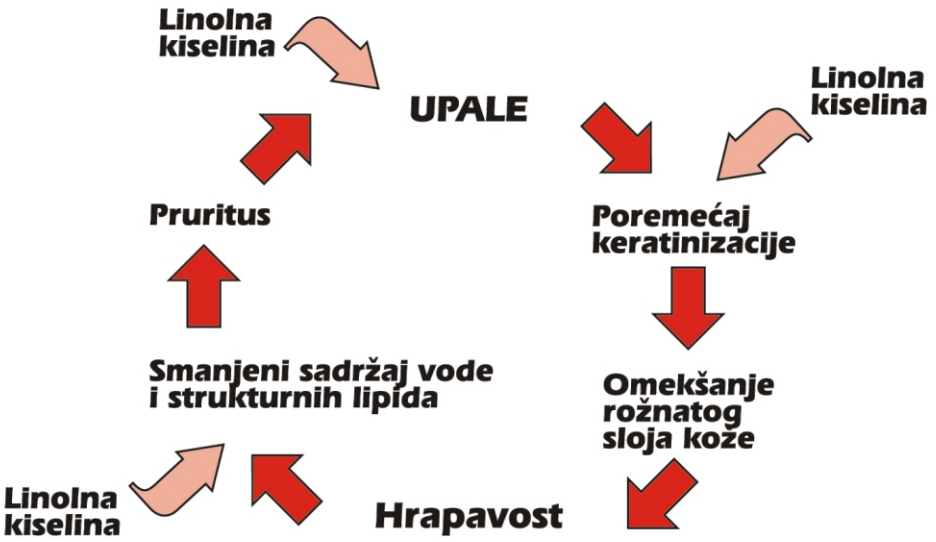
Lijek je izbora kod suhih dermatoza najviše zahvaljujući **linolnoj kiselini**, "**kamenu-temeljcu**" zdrave kože.

LINOLA-FETT u visoko lipofilnoj podlozi sadržava kao djelatnu tvar linolnu kiselinu - nezasićenu masnu kiselinu, koja je najvažniji sastojak ceramida u stratumu corneumu.



UČINKOVITOST **LINOLA-FETT** kreme dokazana je u više kliničkih studija u slijedećim terapijskim indikacijama:

- **suha koža**
- **neurodermitis (atopijski dermitis)**
- **psorijaza**
- **ekzemi**
- **suhoća vulvae**

Kod blažih oblika suhih dermatoza (u akutnoj fazi) **LINOLA-FETT** može se primijeniti i kao mono-terapija.

ODLIČNA PODNOŠLJIVOST - kako **ne** sadržava konzervanse, kortikosteroide, i antioksidanse uporaba **LINOLA-FETT** masne kreme **sigurna je i bez rizika od nuspojava**. Stoga se i može primjeniti kod **dojenčadi i kod male djece**.

PREDNOSTI TERAPIJE sa **LINOLOM-FETT** (s linolnom kiselinom):

- **značajno smanjuje transepidermalni gubitak vode**
- **dugotrajno vlaži kožu**
- **produžuje periode bez uporabe kortikosterida**
- **smanjuje pruritus**
- **linolna kiselina djeluje protuupalno**
- **značajno smanjuje eritem**
- **moguća dugotrajna uporaba bez štetnih posljedica**

DOZIRANJE I NAČIN PRIMJENE: **LINOLA-FETT** masnu kremu nanijeti na kožu nekoliko puta dnevno. Kod **radioterapije kremu je prije zračenja potrebno nanijeti na kožu u debljem sloju**.

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e-mail: REMEDIA@hi.hinet.hr

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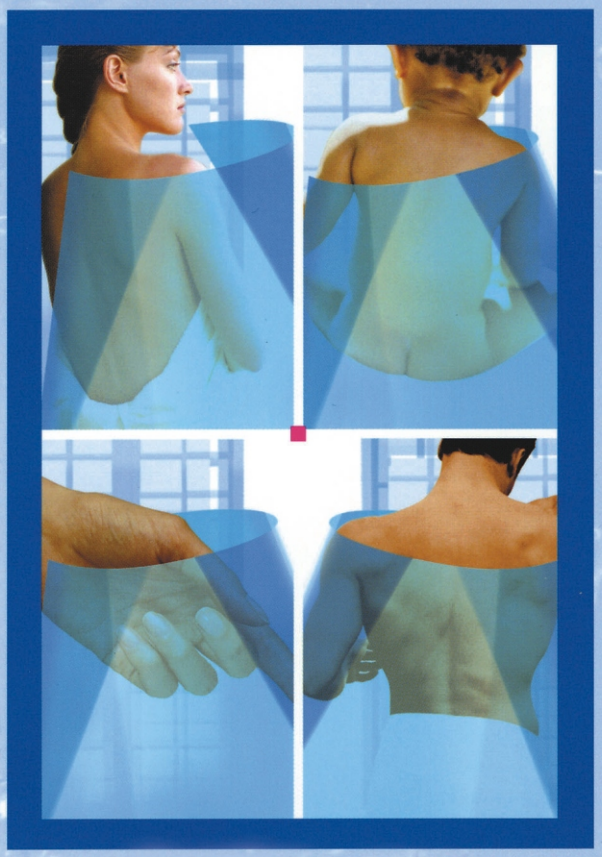

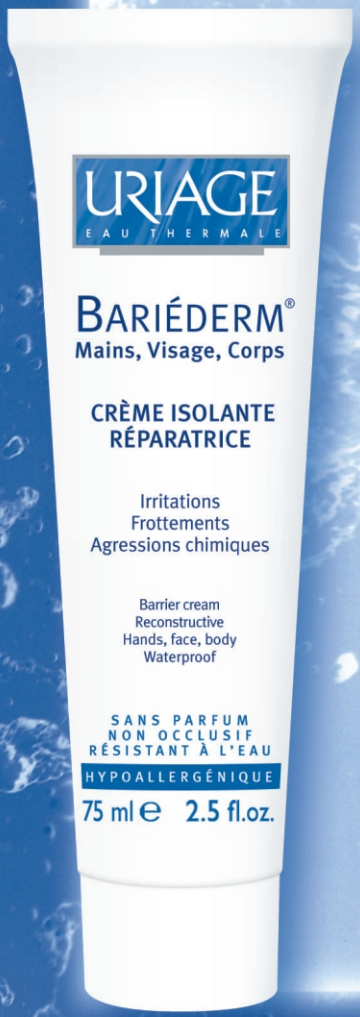

Dvostruki učinak

Zaštita i reparacija

Sve vrste kontaktnih dermatitisa:

- akutni iritativni dermatitis
- kronični iritativni dermatitis
- alergijski kontaktni dermatitis

formasana d.o.o. Ilica 100, 10000 Zagreb, tel: 01/ 3909 922, fax: 01/3909 920

URIAGE
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Za lice i tijelo
Za novorođenčad, dojenčad i djecu

INDIKACIJE

Atopijski dermatitis, iritativni dermatitis, suha koža

- Sklonost atopiji
- Pelenski osip
- Perioralne iritacije
- Ekcemi, ispucala i oštećena koža

DJELUJE ANTISEPTIČKI, PROTUUPALNO I POSPJEŠUJE ZACJELJIVANJE

UPORABA

2-3 puta dnevno nanijeti na opranu i osušenu kožu, na suhe, nadražene ili oštećene dijelove kože lica i tijela

PRILAGOĐENO OSJETLJIVOJ DJEČJOJ KOŽI

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KOŽA OSJETLJIVA NA SUNCE

BDF Beiersdorf

Djelotvorna i sigurna zaštita od alergija izazvanih djelovanjem sunca

INTENZIVNA ZAŠTITA DJECE OD ALERGIJA NA SUNCE

Problem kod male djece:

- Vlastiti zaštitni sustav još nije u cijelosti razvijen.
- Nedostatna zaštita danas-veći rizik od kasnijih trajnih oštećenja kože.
- Snažno opterećenje kože uslijed djelovanja sunca radi učestalog boravka na otvorenom i u vodi.

Rješenje:

Eucerin® Intenzivna dječja zaštita specijalno za malu djecu (od 7. mjeseca i stariju).

Losion za sunčanje za malu djecu s mikropigmentom SPF 25

- Ne sadrži kemijske zaštitne svjetlosne filtere.
- Ne sadrži mirise, boje i alkohol.
- UV-stabilan i posebice otporan na vodu.
- Za djecu od 7. mjeseca i stariju.

Rezultat:

Djelotvorna intenzivna zaštita male djece od:

- Sunčanih opekotina.
- Trajnih oštećenja kože uvjetovanih UV-zračenjem.
- Isušenja kože.

ZAŠTITA OD ALERGIJA IZAZVANIH DJELOVANJEM SUNCA

Problem:

- Simptomi: nadražaj na svrbež, crvenilo, mjehurići i stvaranje kvržica.
- Pogođeno područje: lice, dekolte, ruke, noge.
- Uzročnici: slobodni radikali koji nastaju uslijed djelovanja UV-zračenja.

Rješenje:

Krema-gel SPF15 i 25 za zaštitu protiv alergija na sunce

- Jedinstvena aktivna stnična zaštita alfa-glukozil-rutinom (AGR) i vitamin E.
- Preko 90% UVA-filtera primjereno australskom standardu.
- Bez boja, mirisa i emulgatora.
- Vodootporan.
- Klinički dokazano štiti od alergija izazvanih suncem.

Rezultat:

- Nadražaj na svrbež, crvenilo, stvaranje mjehurića i kvržica se uspješno izbjegavaju.
- 93,1% testiranih osoba djelotvornost ocijenilo vrlo dobrom.

Specijalno namijenjeno za ekstremno povišenu osjetljivost na svjetlo i nepodnošljivost na djelovanje sunca:

Ultra zaštitna krema za sunčanje za tijelo i lice SPF 50 plus

Posebno za preporučiti kod:

- Ekstremno osjetljive svjetle kože.
- Ožiljaka, smetnji kod pigmentacije, mrlja uzrokovanih trudnoćom.
- Pilinga, tretmana laserom.
- Fotosenzibilizacije uvjetovane lijekovima.
- Nepodnošljivost, alergija na sunce.

Gel poslije sunčanja za zaštitu kože ugrožene alergijom

- Hladi i obnavlja kožu opterećenu sunčanjem.
- Aktivna zaštita stanica alfa- glukozil-rutinom AGR i vitaminom E.
- Bez mirisa.

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MEDICINSKI PROGRAM ZA NJEGU KOŽE