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Soluble tumour necrosis factor-α receptor type 1 as a biomarker of response to phototherapy in patients with psoriasis

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Abstract
The purpose of the study was to analyze the relationship between the serum concentration of soluble tumour necrosis factor-α type 1 (sTNF-R1), the severity of plaque-type psoriasis and therapeutic response. We compared sTNF-R1 in 25 patients treated with narrowband ultraviolet B (NB-UVB) radiation and 25 patients treated with systemic photochemotherapy (psoralen plus UVA – PUVA). The pretreatment Psoriasis Area and Severity Index (PASI) score and sTNF-R1 concentration were 16.32 ± 5.26 and 1.99 ± 0.40 ng ml^{-1}, respectively, in the group treated with NB-UVB, and 17.22 ± 3.48 and 2.07 ± 0.31 ng ml^{-1}, respectively, in the group treated with PUVA. The concentration of sTNF-R1 in healthy controls was 1.49 ± 0.34 ng ml^{-1} ($p<0.05$ compared with patients with psoriasis). The pretreatment PASI score correlated with sTNF-R1 in both treatment groups ($r=0.46$ and $r=0.44$, $p<0.05$). NB-UVB and PUVA gave similar therapeutic effects (the PASI score after 20 treatments was 4.42 ± 1.67 in the NB-UVB-treated group and 5.55 ± 2.10 in PUVA-treated patients); however, the sTNF-R1 concentration at the same time differed significantly: 1.52 ± 0.37 ng ml^{-1} and 1.98 ± 0.39 ng ml^{-1} ($p<0.001$), respectively. Moreover, the decline in sTNF-R1 in both treatment groups was significant only in patients in whom the duration of skin lesions was less than 3 months. The results suggest that the value of serum sTNF-R1 concentration as a marker of response to phototherapy may depend on duration of skin lesions and the treatment method.

Keywords: *Soluble tumour necrosis factor-α receptor type 1, psoriasis, narrowband ultraviolet B, systemic photochemotherapy*

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Introduction

Psoriasis is a chronic and recurrent inflammatory disorder, affecting 1–3% of the world population, and plaque-type psoriasis vulgaris is the most frequently seen clinical form of the disease (Naldi & Griffiths 2005). Two subtypes of psoriasis vulgaris have been distinguished on the basis of the age at onset and the family history of the disease: type 1 (onset around 20 years of age, usually positive family history and, in general, more a severe course of disease) and type 2, or a late-onset psoriasis (Henseler & Chrisophers 1985).

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Tumour necrosis factor-α (TNF-α) is one of the major cytokines produced by skin. The induction of the expression of intercellular adhesion molecule-1 on keratinocytes and other cell adhesion molecules (vascular adhesion molecules, E-selectin) on dermal endothelium may be critical for TNF-α-mediated inflammation in psoriasis (Terajima et al. 1998). Given the important role of TNF-α, the molecule became a target for therapy in psoriasis patients. There are two anti-TNF-α agents in current use for psoriasis in Europe and USA: etanercept (a recombinant TNF-α receptor type 2 fusion protein with the ability to bind and neutralize the activity of soluble TNF-α) and infliximab (a chimeric, human–murine, anti-TNF-α-monoclonal IgG_1 antibody, forming stable complexes with all forms of TNF-α). Both agents are effective in the treatment of chronic plaque psoriasis, and etanercept also in psoriatic arthritis (Mease et al. 2000, Chaudhari et al. 2001).

The biological activity of TNF-α is mediated by two receptors: TNF-R1 and TNF-R2, of molecular weight 55 kDa and 75 kDa, respectively (Brockhaus et al. 1990). The soluble forms of these receptors (sTNF-R1 and sTNF-R2) may act in contradictory ways: competing with cell-surface receptors or stabilizing the cytokine molecule (Aderka et al. 1992). The upregulation of the biological activity of both receptors in psoriatic tissues was found, pointing to some quantitative differences between sTNF-R1 and sTNF-R2 expression and concentration (Kristensen et al. 1993, Ettehadi et al. 1994). It has been shown that the concentration of sTNF-R1 was higher in sera of patients with psoriasis than in healthy controls and correlated with the severity of skin lesions (Griffiths et al. 1996, Kirby et al. 2001, Serwin et al. 2005).

The phototherapy, especially narrowband ultraviolet B (NB-UVB) radiation and photochemotherapy (psoralen plus ultraviolet A – PUVA), are frequently treatments of choice in patients with chronic, plaque-type psoriasis (Hönigsmann 2001, Naldi & Griffiths 2005). The mechanism of phototherapy, although not fully examined, involves the modulation of secretion and activation of anti-inflammatory and immunosuppressive cytokines, including TNF-α (Schwarz & Luger 1989, Köck et al. 1990, Neuner et al. 1994, Olaniran et al. 1996, Piskin et al. 2004).

In a previous study we demonstrated that elevated sTNF-R1 correlated with the severity of skin lesions in patients with active psoriasis and declined after treatment with NB-UVB (Serwin et al. 2005). The aim of the present study was to compare sTNF-R1 serum concentration as a marker of therapeutic response in patients treated with NB-UVB and with PUVA, in relation to the severity of the clinical picture and the duration of skin lesions.

Material and methods

Subjects, treatment and assessment methods

The study was carried out in 50 patients with early-onset (before 40 years of age) plaque-type psoriasis vulgaris (skin phototype II and III – persons who have basic white skin colour and tan after sunburn), selected from patients treated with phototherapy at the Department of Dermatology and Venereology of the Medical University of Bialystok and the Daily Care Department of Specialist Dermatological–Venereological Out-patient's Clinic in January–September 2005 in whom concomitant systemic disorders were excluded on the basis of medical history and laboratory tests. For the purpose of the study these patients were additionally divided into two groups: those in whom skin lesions had lasted less than 3 months and were not treated

during that period, and those in whom worsening of the skin condition lasted longer and did not respond to topical treatment applied previously. Patients were randomly included to two treatment groups: the group treated with NB-UVB ($n=25$, 14 women and 11 men) and the group treated with systemic PUVA ($n=25$, 11 women and 14 men). The treatment schedule comprised 20 irradiations three times a week (on Monday, Wednesday and Friday), starting with 50% of minimal erythema dose (NB-UVB), or with 70% of minimal phototoxic dose (PUVA). TL-01® lamps (wavelength 311–313 nm) and Arimed PUVA® lamps (wavelength 320–340 nm) were used as sources of irradiation (Cosmedico Medizintechnik GmbH, Schwenningen, Germany). One hour before UVA treatment patients took 8-methoxypsoralen in soft gelatin capsules orally at a dose of 0.6 mg kg^{-1}.

The assessment of skin lesions and the serum concentration of sTNF-R1 was performed before treatment (T0), and after 10 and 20 treatments (T10 and T20, respectively) and, additionally, 1 month after the end of treatment (Tx). During the whole period patients were asked to apply only topical emollients on the skin. The severity of psoriatic lesions was assessed using the Psoriasis Area and Severity Index (Fredriksson & Petersson 1978), taking into consideration the extent of body surface affected, intensity of erythema, scaling and induration. Theoretically, the PASI score can range from 0 to 72. Samples of 5 ml of venous blood were collected in Vacutainer® tubes after overnight fasting. After centrifugation (15 min at 2000*g*) sera were collected and stored at $-76^{\circ}C$ until analyzed. The serum concentration of sTNF-R1 was measured using a quantitative sandwich enzyme immunoassay technique with a human monoclonal antibody (sensitivity <0.3 pg ml^{-1}, sample volume 50 µl, 1:10 serum dilution; Quantikine® R&D Systems, Inc. Minneapolis, MN, USA). Monoclonal antibodies specific for sTNF-R1 were pre-coated onto a microplate. Standards and samples were pipetted in duplicate into the wells and any sTNF-R1 present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for sTNF-R1 was added to the wells. Following the wash to remove any unbound antibody–enzyme reagent, a substrate solution was added to the wells and colour developed in proportion to the amount of sTNF-R1 bound in the initial step. The colour development was stopped and the optical density of each well was determined within 30 min, using a microplate reader set to 540 nm. The average of duplicate optical density readings for each standard, control and sample was calculated. The sTNF-R1 concentrations were read from the curve drawn on the log/log paper from the data on optical density for the standards versus the concentration of the standards, then multiplied by the dilution factor of 10.

Control sera were taken and analyzed in the same manner from 20 generally healthy volunteers aged 20–55 years (12 men and 8 women, admitted for minor surgical procedures – excision of common moles or other benign skin lesions). Family history of psoriasis was excluded in controls. All patients and controls gave their informed consent. The study protocol was approved by the Bioethical Committee of the Medical University of Bialystok.

Statistical analysis

Because sTNF-R1 concentrations and PASI score values presented a Gaussian distribution, for statistical analysis of the result, the two-sided Student's *t*-test for

comparison of mean values, and Pearson's correlation coefficient (r) for estimation of the strength of the association between parameters, were used (Statistica 5.1 '97 PL software, StatSoft, Cracow, Poland). The level of significance was set at 0.05.

Results

The sociodemographic and clinical data of patients are presented in Table I. The duration of the disease ranged from 5 to 49 years. In ten patients (40%) in the NB-UVB group and in 14 (56%) in the PUVA group the worsening of skin lesions lasted less than 3 months. The pretreatment PASI value was insignificantly higher in patients who were treated with photochemotherapy (Table II). All patients completed the scheduled 20 treatments. The total biological dose of NB-UVB was 0.701–1.120 J cm^{-2} and that of UVA 33–43 J cm^{-2}.

Treatment results

The treatment results were good and, moreover, were maintained for up to 1 month in all patients in both groups. After 20 treatments (T20) the PASI value remained higher in patients treated with PUVA than in those treated with NB-UVB (Table II). The decline in PASI score was quite similar in patients with skin lesions lasting less than 3 months or longer (Table III). Twenty-one patients (84%) treated with NB-UVB and 19 patients (76%) treated with PUVA ($p>0.05$) achieved at least 75% of decline in PASI score value at T20. One month after the end of treatment the PASI value was almost the same in the two groups.

Relationship between serum sTNF-R1 concentration and PASI score during treatment with NB-UVB and PUVA

The pretreatment serum concentration of sTNF-R1 was 2.07 ± 0.42 ng ml^{-1} in patients and 1.49 ± 0.34 ng ml^{-1} in controls ($p<0.01$). The concentration correlated with pretreatment PASI scores in patients treated with NB-UVB and with PUVA

Table I. Baseline sociodemographic and clinical characteristics of patients treated with narrowband ultraviolet B (NB-UVB) radiation and photochemotherapy (psoralen plus UVA, PUVA).

	Treatment group	
	NB-UVB ($n=25$)	PUVA ($n=25$)
Age (years)		
Mean value ± standard deviation	38.21 ± 11.40	43.40 ± 12.18
Range	21–60	22–59
Family history of psoriasis, n (%)	17 (68)	15 (60)
Age of psoriasis onset (years)		
Mean value ± standard deviation	18.89 ± 11.11	22.93 ± 8.71
Range	4–40	10–40
Duration of current relapse (months)		
Mean value ± standard deviation	4.42 ± 3.36	5.13 ± 3.04
Range	1–12	1–12
Psoriasis Area and Severity Index score (range)	7.11–23.40	11.40–24.61

Table II. Psoriasis Area and Severity Index (PASI) score and soluble tumour necrosis factor-α concentration (sTNF-R1) in patients during treatment with narrowband ultraviolet B (NB-UVB) radiation and photochemotherapy (psoralen plus UVA, PUVA). Values are mean ± SD.

	PASI score			sTNF-R1 (ng ml^{-1})		
Time of examination	NB-UVB ($n=25$)	PUVA ($n=25$)	p-Value	NB-UVB ($n=25$)	PUVA ($n=25$)	p-Value
T0[a]	16.32 ± 5.26	17.22 ± 3.48	NS	1.99 ± 0.40	2.07 ± 0.31	NS
T10[b]	8.57 ± 3.33	11.23 ± 3.39	<0.01	1.55 ± 0.38	2.06 ± 0.35	<0.001
T20[c]	4.42 ± 1.67	5.55 ± 2.10	<0.05	1.52 ± 0.37	1.98 ± 0.39	<0.001
Tx[d]	4.50 ± 1.60	4.85 ± 1.79	NS	1.51 ± 0.44	1.94 ± 0.22	<0.001
p (T0–Tx)	<0.01	<0.01		<0.001	NS	

[a]Pretreatment; [b]after ten treatments; [c]after 20 treatments; [d]1 month after the end of treatment; NS, not statistically significant.

($r=0.46$ and $r=0.44$, respectively, $p<0.05$). The pretreatment correlation coefficients between sTNF-R1 and PASI score in patients with short-lasting psoriatic lesions were: $r=0.69$ and $r=0.84$ in the NB-UVB and PUVA groups, respectively ($p<0.05$). In those with long-lasting lesions the coefficients were $r=0.35$ and $r=0.33$, in the NB-UVB and PUVA groups, respectively ($p>0.05$). At the end of treatment the correlation became inverse and not statistically significant. No significant correlation between the duration of the disease and sTNF-R1 was found.

Serum sTNF-R1 concentration during treatment

In both treatment groups the concentration of sTNF-R1 diminished during treatment but the decrease was significant only in patients treated with NB-UVB; the difference was seen after ten treatments (Table II). In PUVA-treated patients the sTNF-R1 did not change significantly. In both groups an important decrease in sTNF-R1 was observed in patients with short-lasting skin lesions (Table III). sTNF-R1 remained at almost the same level in patients with long-lasting psoriasis.

Discussion

Two TNF-α receptors that play an important role in the regulation of TNF-α activity have distinctly different locations within psoriatic lesions (Kristensen et al. 1993). Moreover, some findings indicated that sTNF-R1 (or p55) may play a more significant role in the modulation of cytokine activity: the mean absolute concentration of immunoreactive TNF-R1 was higher that that of sTNF-R2 in extracts of lesional psoriatic skin; plasma concentrations of sTNF-R1 were higher in psoriasis patients than in healthy controls; and the concentration of TNF-R1 in patients predominated over TNF-R2. The authors suggested that local and systemic release of soluble TNF-α receptors, in particular that of p55, may serve to regulate the effects of TNF-α in psoriasis (Ettehadi et al. 1994). Thus, the sTNF-R1 became an interesting molecule as a marker for the activity of the disease (Griffiths et al. 1996, Kirby et al. 2001, Serwin et al. 2005).

The present study is an extension of previous work on the relevance of sTNF-R1 as an indicator of severity of disease and the therapeutic response in patients with psoriasis. We attempted to verify whether elevated sTNF-R1 concentration could be

Table III. The concentration of soluble tumour necrosis factor-α concentration (sTNF-R1, ng ml^{-1}) and Psoriasis Area and Severity Index (PASI) score (mean value ± SD) in patients with short- and long-lasting skin lesions during treatment with narrowband ultraviolet B (NB-UVB) radiation and photochemotherapy (psoralen plus UVA, PUVA).

	Treatment					
	NB-UVB			PUVA		
	Duration of skin lesions			Duration of skin lesions		
Time of examination	<3 months ($n=10$)	≥3 months ($n=15$)	*p*-Value	<3 months ($n=14$)	≥3 months ($n=11$)	*p*-Value
T0[a]						
sTNF-R1	2.08 ± 0.36	1.89 ± 0.35	NS	2.09 ± 0.42	2.04 ± 0.28	NS
PASI	17.12 ± 3.71	15.54 ± 2.59	NS	16.70 ± 4.06	17.30 ± 3.75	NS
T10[b]						
sTNF-R1	1.49 ± 0.28	1.85 ± 0.26	<0.05	2.05 ± 0.33	2.07 ± 0.39	NS
PASI	9.58 ± 3.82	7.56 ± 1.84	<0.05	11.70 ± 4.95	11.16 ± 3.36	NS
T20[c]						
sTNF-R1	1.36 ± 0.23	1.71 ± 0.29	<0.01	1.92 ± 0.22	2.05 ± 0.33	<0.01
PASI	4.83 ± 1.39	4.14 ± 1.68	NS	5.69 ± 3.54	5.34 ± 1.68	NS
Tx[d]						
sTNF-R1	1.37 ± 0.25	1.65 ± 0.19	<0.01	1.80 ± 0.20	2.07 ± 0.24	<0.05
PASI	4.24 ± 1.81	4.07 ± 1.69	NS	4.48 ± 1.76	4.85 ± 0.85	NS
p (T0–Tx)						
sTNF-R1	<0.01	NS		<0.05	NS*	
PASI	<0.01	<0.01		<0.01	<0.01	

[a]Pretreatment; [b]after ten treatments; [c]after 20 treatments; [d]1 month after the end of treatment; NS, not statistically significant.

not only a marker of severity of the disease but also whether it can be useful in predicting the response to the two most frequently used methods of phototherapy. The concentration of sTNF-R1 in controls was almost identical to that in the previous study, but the pretreatment concentration in patients with psoriasis was higher, which may result from the higher PASI score, which correlated with sTNF-R1 in both studies. Similarly, the sTNF-R1 concentration in the NB-UVB-treated group almost reached the level observed in healthy controls (Serwin et al. 2005). Two findings in the present study merit discussion. First, the response of sTNF-R1 in the two treatment groups differed significantly; second, this response was different in patients with short- and long-lasting skin lesions. The patients studied (and controls) were selected to constitute an almost homogeneous group, taking into consideration the age, general health status (concomitant disorders were excluded), family history and the history of skin lesions. The difference in sTNF-R1 concentration during the therapy can be explained, at least in part, by higher PASI values in patients treated with PUVA compared with NB-UVB after 20 treatments. However, correlation between these two values was not significant at that moment and the difference between sTNF-R1 in the two groups remained after 1 month, when the PASI values were almost equal.

The different influence of UVB and PUVA on the molecule must be considered in discussing this finding. The detailed mechanisms of the action of NB-UVB and PUVA in psoriasis are not well defined but they involve a combination of effects including

alteration in cytokine expression, which is far beyond the purpose of this study. It has been previously found that the serum levels of sTNF-R1 decreased after treatment (PUVA and coal tar with UVB) in patients with chronic plaque psoriasis, and mirror the fall in PASI, but these levels did not return to control values (Kirby at al. 2001). The causes of this phenomenon may be several, including the duration of the skin disease, or the duration of the current relapse and, finally, the severity of the skin lesions and persistent residual inflammation, as PASI score does not achieve zero value in these patients. The authors have not analyzed the sTNF-R1 response separately for different treatment methods, probably because the number of patients was rather small – four in each treatment group (Kirby et al. 2001). Studies on the influence of UVB on the molecule are rare and cannot be directly applied for the comparison, because they were performed only *in vitro* and gave contradictory results (Trefzer et al. 1993, Barr et al. 1999). In the keratinocyte supernatant, sTNF-R1 concentration remained unchanged after UVB irradiation at the dose of 100 J m^{-2}, despite the reduction in expression of the cell-surface receptor (Trefzer et al. 1993). Three erythema doses of solar-stimulating radiation (comprising 93% of UVB effective energy) resulted in a transient decrease in sTNF-R1 in suction blister exudates, followed by an increase with maximal values 48 h after UV exposure (Barr et al. 1999). Studies on the influence of PUVA on soluble TNF-α receptors are lacking.

The UVB is a potent stimulus of TNF-α synthesis and release (Schwarz & Luger 1989, Köck et al. 1990). In contrast, PUVA has opposite effects on the production and secretion of TNF-α by epidermal cells (Schwarz & Luger 1989) and peripheral blood mononuclear cells (Neuner et al. 1994, Olaniran et al. 1996). Because TNF-α can act in an autocrine manner and modulate *in vitro* expression of TNF-R1 (Trefzer et al. 1993), the contradictory action of UVB and PUVA on the cytokine may contribute, in part, to different concentrations of serum sTNF-R1 in patients treated with NB-UVB and with PUVA. We suggest that UVA, by penetrating the skin tissue deeper than NB-UVB, influences the upregulation of TNF-R1 in dermal blood vessels, the specific location of this receptor in psoriatic lesions (Kristensen et al. 1993), and also the maintenance of sTNF-R1 at an almost stable, high level. The serum concentration of soluble TNF-α receptors in patients with psoriasis can also be modulated by various other factors, which require further studies.

We have demonstrated for the first time that the biological response of sTNF-R1 to treatment in psoriasis depends on the duration of the skin lesions – it is more expressed in patients with worsening of skin lesions lasting less than 3 months. Similar studies are lacking, but we can suggest that long-lasting inflammatory phenomena contribute to establishment of a kind of 'equilibrium' of multiple biological molecules, a status that is more difficult to modulate by therapy.

Conclusions

Our findings suggest that increased sTNF-R1 level is not only a marker of the severity of the clinical picture in patients with active plaque-type psoriasis but may also reflect the duration of the aggravation of the disease. The serum sTNF-R1 concentration is significantly influenced by treatment only in some psoriasis patients, namely in these with short-lasting skin lesions and treated with NB-UVB. Thus, the elevated baseline sTNF-R1 has a relative value in predicting therapeutic response. The reason for

different concentrations of sTNF-R1 in patients during treatment with NB-UVB and PUVA requires further studies.

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References

Aderka D, Engelmann H, Maor Y, Brakebusch C, Wallach D. 1992. Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. Journal of Experimental Medicine 175:323–329.

Barr RM, Walker SL, Tsang W, Harrison GJ, Ettehadi MW, Graves MW, Young AR. 1999. Suppressed alloantigen presentation, increased TNF-α, IL-1, IL-1Ra, IL-10, and modulation of TNF-R1 in UV-irradiated human skin. Journal of Investigative Dermatology 112:692–698.

Brockhaus M, Schoenfeld H-J, Schlaeger E-J, Hunziker W, Lessauer W, Loetscher H. 1990. Identification of two types of tumor necrosis factor receptors on human cell lines by monoclonal antibodies. Proceedings of the National Academy of Sciences USA 87:3127–3131.

Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. 2001. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. Lancet 35:1842–1847.

Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp DR. 1994. Elevated tumor necrosis factor alpha (TNF-α) biological activity in psoriatic skin lesions. Clinical & Experimental Immunology 96:146–151.

Fredriksson T, Petersson V. 1978. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 157:238–244.

Griffiths CEM, Boffa MJ, Gallatin WM, Martin S. 1996. Elevated levels of circulating intercellular adhesion molecule-3 (cICAM-3) in psoriasis. Acta Dermato-Venereologica (Stockholm) 76:2–5.

Henseler T, Chrisophers E. 1985. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. Journal of the American Academy of Dermatology 13:450–456.

Hönigsmann H. 2001. Phototherapy for psoriasis. Clinical and Experimental Dermatology 26:343–350.

Kirby B, Boffa MJ, Nayak N, Gallatin WM, Martin S, Griffiths CEM. 2001. The effect of treatment on serum levels of soluble intercellular adhesion molecules and tumour necrosis factor-receptor 1 in psoriasis. British Journal of Dermatology 145:1027–1028.

Köck A, Schwarz T, Kirnbauer R, Urbanski A, Perry P, Ansel JC, Luger TA. 1990. Human kernatinocytes are a source for tumor necrosis factor. Evidence for synthesis and release upon stimulation by endotoxin or ultraviolet light. Journal of Experimental Medicine 172:1609–1614.

Kristensen M, Chu CQ, Eedy DJ, Feldman M, Brennan FM, Breathnach SM. 1993. Localization of tumor necrosis factor-alpha (TNF-alpha) and its receptors in normal and psoriatic skin: epidermal cells express the 55-kD but not the 75-kD TNF receptor. Clinical and Experimental Immunology 94:354–362.

Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet 356:1627–1632.

Naldi L, Griffiths CEM. 2005. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. British Journal of Dermatology 152:597–615.

Neuner P, Charvat B, Knobler R, Kirnbauer R, Schwarz A, Luger TA. 1994. Cytokine release by peripheral blood mononuclear cells is affected by 8-methoxypsoralen plus UV-A. Photochemistry and Photobiology 59:182–188.

Olaniran AK, Baker BS, Paige DG, Garioch JJ, Powels AV, Fry L. 1996. Cytokine expression in psoriatic skin lesions during PUVA therapy. Archives of Dermatological Research 288:421–425.

Piskin G, Tursen U, Sylva-Steenland RMR, Bos JD, Teunissen MBM. 2004. Clinical improvement in chronic plaque-type psoriasis lesions after narrow-band UVB therapy is accompanied by a decrease in the expression of INF-γ inducers – IL-1, IL-18 and IL-23. Experimental Dermatology 13:764–772.

Schwarz T, Luger TA. 1989. New trends in photobiology: effect of UV irradiation on epidermal cell cytokine production. Journal of Photochemistry and Photobiology B 4:1–13.

Serwin AB, Sokolowska M, Chodynicka B. 2005. Soluble tumor necrosis factor α receptor type 1 in psoriasis patients treated with narrowband ultraviolet B. Photodermatology, Photoimmunology and Photomedicine 21:210–211.

Terajima S, Higaki M, Igarashi Y, Nogita T, Kawashima M. 1998. An important role of tumor necrosis factor-α in the induction of adhesion molecules in psoriasis. Archives of Dermatological Research 290:246–252.

Trefzer U, Brockhaus M, Lötscher H, Parlow F, Budnik A, Grewe M, Christoph H, Kapp A, Schöpf E, Luger TA, Krutmann J. 1993. The 55-kD tumor necrosis factor receptor on human keratinocytes is regulated by tumor necrosis factor-alpha and by ultraviolet B radiation. Journal of Clinical Investigation 92:462–470.