ISSN 1996-3424

Asian Journal of Dermatology

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OPEN ACCESS Asian Journal of Dermatology

ISSN 1996-3424
DOI: 10.3923/ajd.2016.1.7

Research Article
Effect of Narrow Band Ultraviolet B Therapy on Serum Levels of Interleukin22 in Egyptian Patients with Psoriasis

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Abstract

Background and Objective: Psoriasis is a chronic hyper-proliferative skin disease. The IL22 and other cytokines play a role in pathogenesis of psoriasis. Narrow band-ultraviolet B (NB-UVB) is one of the treatment arsenal used in psoriasis. The aim of this prospective study was to study the changes in levels of IL22 before and after NB-UVB therapy, the relation of IL22 to severity of disease and the ability of baseline IL22 level to predict the outcome of NB-UVB therapy. **Methodology:** Thirty five patients with chronic plaque psoriasis were studied against 44 healthy volunteers as control. The IL22 levels were measured in control. The IL22 in and PASI score values were recorded in psoriasis patients at baseline and after 12 weeks of NB-UVB therapy. **Results:** Baseline IL22 level was significantly higher than control and declined after NB-UVB to insignificant values. The IL22 levels showed significant positive correlation with PASI score before and also after NB-UVB. No significant differences were recorded in IL22 levels in responders vs non-responders to NB-UVB. **Conclusion:** The IL22 levels is increased in psoriasis and could be used as a laboratory marker of the severity of disease, but could not predict the response to NB-UVB.

Key words: Psoriasis, IL22, phototherapy, NB-UVB, cytokines, PASI score

Received: August 08, 2015 Accepted: November 28, 2015 Published: December 15, 2015

Citation: Moheiddin Alghobary, Manar Sallam, Sherin Ezz-Elregal, Hanaa Morkos Abdel-Masseih and Heba Mosaad, 2016. Effect of narrow band ultraviolet B therapy on serum levels of interleukin22 in Egyptian patients with psoriasis. Asian J. Dermatol., 8: 1-7.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Psoriasis is a chronic relapsing immune mediated hyper-proliferative inflammatory skin disease that affects 2-3% of the worldwide population and causes significant morbidity[1]. The etiology and pathogenesis of psoriasis still unclear, however, substantial clinical and basic studies indicate that cellular innate and adaptive immune responses, especially the activation and release of cytokines by T cells, play critical roles in the pathogenesis of psoriasis[2]. Accumulating evidence suggests that a subset of T cells, T helper 17 (Th-17) could play an important role in the pathogenesis of psoriasis and other immune mediated inflammatory diseases. The Th-17 cells are characterized by the production of IL22 and other pro-inflammatory cytokines[3].

Interleukin22 (IL22) is a cytokine produced by several different cellular sources such as Th-17 and also Th-22 cells[4]. The IL22 was reported to induce epidermal hyperplasia and hypogranulosis. The IL22 can also synergize with the other pro-inflammatory cytokines to induce and exacerbate psoriasis[5].

Many treatment options are available for psoriasis, including narrow band ultraviolet B (NB-UVB) therapy which is proved to be an effective treatment for psoriasis, as well as other skin diseases. The NB-UVB (311-312 nm) is known to give good results in psoriasis as this represents the wavelength with the optimal "phototherapy index[6]".

Review of literature revealed a paucity of researches that addressed the changes in IL22 with NB-UVB therapy in psoriasis[7-9]. However, other studies addressed the changes in levels of IL22 and other cytokines before and after different treatments modalities, like calcipotriol[10], cyclosporin A[11] etanercept and actitretin[12] and yielded variable results.

The aim of the present work is to study the relation between IL22 blood level in psoriatic Egyptian patients before and after commencing therapy with NB-UVB, its correlation with severity of disease and also to find whether IL22 can be used to predict the response to NB-UVB in psoriatic patients or not.

MATERIALS AND METHODS

Patients: The present protocol was approved by the Medical Ethical Committee of Mansoura University Hospital. There were 35 patients enrolled with chronic plaque psoriasis vulgaris. Psoriasis was diagnosed between 4 months and 20 years before the present study. Psoriasis severity was evaluated by Psoriasis Area and Severity Index (PASI)[13]. Erythrodermic, pustular and arthropathic psoriasis were not included.

To diminish subjectivity, PASI was evaluated by the same dermatologist. The PASI score, was recorded twice; at the baseline and at the end of 12 weeks treatment. A reduction of PASI score by 50% or more of the baseline level is considered as response to NB-UVB, while <50% reduction is considered as non response to treatment[14].

The patients included in our study had no other autoimmune diseases or systemic diseases and they did not receive any systemic treatment as immunosuppressive drugs or phototherapy for at least three months prior to the first PASI score evaluation, first blood sample collection and NB-UVB treatment.

Phototherapy: The NB-UVB irradiation (311±2 nm) was administered using eight mercury low pressure lamps (Philips TL-01) with a spectrum of 305-315 nm, maximum wavelength of 311 nm were installed in a Waldmann cabinet (UVB-TL-01), Waldmann Medizintechnik, Villingen-Schwenningen, Germany). The initial dose was 0.1-0.3 J cm^2 depending on the phototype of the patient. The distance between the patients and lamps were around 30 cm. Patients were given three sessions/week with increments of 0.1 J cm^2/session, until irritation or a maximum dose of 2.5 J cm^2 was reached. Treatment was continued for 12 weeks.

Control group: Forty four healthy volunteers, including 22 male and 22 female, without psoriasis and also without other autoimmune diseases or systemic diseases and with normal hematological and biochemical values were taken as control.

Serum IL22 detection: Three milliliters venous blood samples were collected on sterile plane tube and were allowed to stand for 30 min at room temperature then centrifuged at 300 g for 5 min. Sera immediately separated and stored at -20°C until the time of analysis.

IL22 assay kit: The RayBio® Human IL22 Enzyme-linked Immunosorbent Assay (ELISA) kit is an *in vitro* ELISA for the quantitative measurement of human IL22 in serum, plasma, cell culture supernatants and urine. This assay employs an antibody specific for human IL22 coated on a 96 well plate. Standards and samples are pipetted into the wells and IL22 present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-human IL22 antibody is added. After washing away unbound

biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and colour develops in proportion to the amount of IL22 bound. The stop solution changes the colour from blue to yellow and the intensity of the colour is measured at 450 nm RayBiotech. Results are expressed in pico-gram per millilitre.

Statistical analysis: Statistical analysis was performed using SPSS 16.00 pg. Data were first subjected to test for normal distribution (Kolmogrov-Smirnov test). Student t and Paired t test was used for parametrically distributed variants. Mann-Whitney and Wilcoxon mated-pair rank summation test were used for non-parametrically distributed variants. Spearman correlation test was used to study correlation between IL22 and PASI score.

RESULTS

Thirty psoriatic cases completed the study, including 15 males and 15 females. Their ages ranged from 14-65 years (mean age 45.6±14.3 years). The duration of the disease ranged from 1-21 years with a mean 7.5±5.3 years (Table 1). Control group included 44 subjects (22 males and 22 females) with mean age of 41.4±6.8 years. No significant difference was recorded in age distribution between the study group and the control group ($p = 0.091$).

IL22 changes before and after NB-UVB: The IL22 was measured in all patients and controls. Before treatment, psoriasis patients showed significant higher baseline levels IL22 than control ($p = 0.0001$). After treatment, IL22 was reduced and significant difference was recorded in psoriatic cases compared to baseline ($p<0.0001$), while insignificant difference was recorded compared to control ($p = 0.3935$, Table 2).

PASI score changes before and after NB-UVB: At baseline, the mean PASI score was 19.7633±6.6854. A significant decrease in the mean PASI score after phototherapy to was recorded to 9.1867±5.0221 ($t = 11.801$, p-value 0.000, (Table 3)).

Table 1: Patient characterization, PASI score and IL22 levels before and after NB-UVB

Case No.	Sex	Age (years)	Duration (years)	Skin phototype	PASI before	PASI after	Response to NB-UVB	IL22 before	IL22 after
1	Female	32	15	III	16.8	7.2	Yes	3.2	1.4
2	Male	52	4	IV	16.2	5.1	Yes	0.6	0.3
3	Male	31	14	III	16.4	7.4	Yes	2.2	1.3
4	Male	51	3	III	11.6	4.3	Yes	0.4	0.2
5	Female	14	6	IV	19.8	9.7	Yes	3.3	1.5
6	Female	62	5	III	12.9	4.2	Yes	4.3	4.2
7	Male	64	15	III	7.6	3.2	Yes	1.0	0.3
8	Male	47	21	III	15.2	3.2	Yes	2.2	1.1
9	Male	45	10	III	15.2	5.4	Yes	4.3	2.8
10	Male	59	8	III	26.9	10.5	Yes	15.8	7.9
11	Female	60	5	III	24.5	11.3	Yes	11.4	5.8
12	Male	53	4	III	25.0	12.4	Yes	16.5	6.4
13	Male	32	6	III	30.0	10.5	Yes	19.3	6.4
14	Female	30	8	III	20.7	9.8	Yes	4.3	2.2
15	Male	54	11	III	23.4	8.5	Yes	5.8	1.4
16	Female	65	1	III	11.6	4.3	Yes	2.5	1.4
17	Female	24	7	III	21.9	18.7	No	15.4	10.3
18	Male	30	9	III	32.1	5.5	Yes	35.5	20.3
19	Female	50	10	IV	25.0	15.0	No	4.3	3.3
20	Male	25	1	III	21.9	9.7	Yes	16.5	9.4
21	Female	35	5	III	16.4	10.4	No	7.9	7.0
22	Female	45	1	III	15.2	6.5	Yes	4.4	2.3
23	Male	50	6	IV	25.0	20.7	No	11.5	6.7
24	Male	65	8	III	7.8	3.0	Yes	2.3	1.3
25	Female	60	7	IV	30.0	11.6	Yes	88.1	20.3
26	Female	56	2.5	III	26.4	17.6	No	7.9	3.3
27	Female	55	1	III	14.4	4.3	Yes	87.4	6.0
28	Male	45	2	III	28.8	18.7	No	64.5	35.4
29	Male	52	20	III	15.0	5.3	Yes	11.5	6.8
30	Female	25	10	III	19.2	11.6	No	70.6	50.2

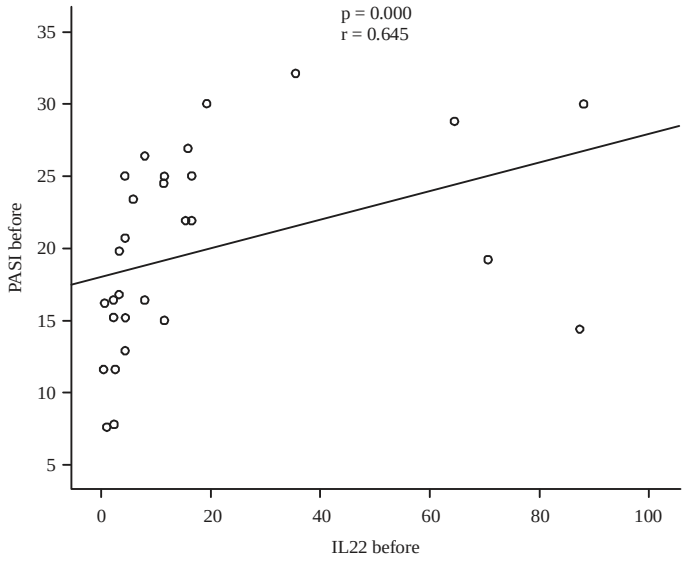

Fig. 1: Correlation between PASI score and IL22 levels before NB-UVB therapy (spearman test)

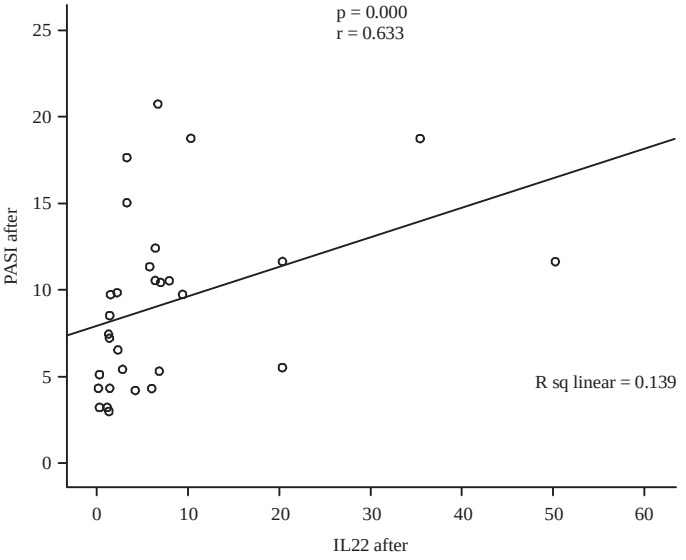

Fig. 2: Correlation between PASI score and IL22 levels after NB-UVB therapy (spearman test)

Table 2: Serum IL22 levels in control and psoriatic cases before and after treatment

Group	No.	Median	Range	Z	p-value
Controls	44	5.70	1.40-15.10	5.968*	<0.0001
Cases before treatment	30	16.50	4.30-45.50	4.226**	<0.0001
After treatment		6.50	2.30-50.20	0.853***	0.3935

*Control vs cases at baseline (Mann-Whitney test), **Cases before vs cases after treatment (Wilcoxon test), ***Control vs cases after treatment (Mann-Whitney test)

Table 3: PASI score in psoriatic patients before and after NB-UVB

PASI before NB-UVB (No. = 30) Mean±SD	PASI after NB-UVB (No. = 30) Mean±SD	t	p-value
19.7633±6.6854	9.1867±5.0221	11.801*	0.000

*Paired t-test

Table 4: Baseline IL22 in responders vs non responders to NB-UVB

Group	No.	Median	Range	Z	p-value
Responders	23	4.3	0.4-88	1.547*	0.122
Non responders	7	11.5	4.3-70.6		

*Mann-Whitney test

Correlation between PASI score and IL22 levels: Significant positive correlation was recorded between IL22 level and PASI score before phototherapy as shown in Fig. 1 ($r = 0.645$, $p = 0.000$). This significant positive correlation was also recorded after treatment as shown in Fig. 2.

IL22 as a predictor of response to NB-UVB: Response to NB-UVB was determined by reduction of the PASI score by 50% or more of the baseline level. Accordingly, 23 cases were responders (76.67%) while 7 cases (23.33%) were non responders to NB-UVB. Baseline IL22 levels were not statistically different in both groups (p = 0.122, Table 4). This means that baseline IL22 level can't be used to predict the response to NB-UVB.

DISCUSSION

In the current work, the baseline IL22 level was almost three folds that of the control group. After NB-UVB, a reduction in IL22 levels to figures close to that of the control levels was recorded. This means that the IL22 was reduced with improvement of psoriasis with NB-UVB therapy. Similarly, PASI score level, as a marker of the severity of disease, declined significantly after 12 weeks treatment with NB-UVB, pointing to clinical improvement and reduction of the severity of disease. These finding of reduced PASI score and IL22 after NB-UVB point to not only the effectiveness of NB-UVB as a successful treatment of psoriasis, but could also point to the value of IL22 as a laboratory marker of severity of psoriasis. The significant positive correlations recorded between PASI score values and IL22 levels before and also after treatment with NB-UVB add another support to this finding.

The value of IL22 as a marker of psoriasis severity could be explained in the light of its role in pathogenesis of psoriasis. The IL22 production is reported to be upregulated in psoriatic skin[3]. The IL22 is also reported to be an inducer of epidermal keratinocytes proliferation. The IL22 plays a role in Signal Transduction and Activation of Transcription (STAT3) activation with the help of IL17[15]. The IL22 stimulates Vascular Endothelial Growth Factor (VEGF) production in keratinocytes[16]. Furthermore, the production of IL22 enhances acanthosis and dermal inflammation via interaction with IL23[5,17].

In this study, the response rate to NB-UVB was 76.67% at 12 weeks therapy, while 23.33% of cases were non-responders. Univariate analysis of baseline IL22 levels failed to demonstrate a significant difference in IL22 levels between responders and non-responders to NB-UVB therapy. This means that baseline IL22 level could not be used as a predictors of the outcome of therapy by NB-UVB.

These findings in terms of the relation between IL22 levels and the severity of psoriasis add a support to previous work in this field. Coimbra *et al.*[7] studied IL22 levels and other cytokines (IL17, IL23, IL8, vEGF, TNF-aplha) in 34 psoriatic cases in Portugal vs 20 control. Their patients were subjected to PUVA and NB-UVB and reached similar conclusion to ours. This study included close number of Egyptian psoriatic cases (30 vs 34) compared to Coimbra *et al.*[7] and we reached similar conclusion in terms of relation of IL22 to severity of psoriasis. Babanin[9] reached similar conclusion compared to ours in terms of the increased baseline level of IL22 compared to control and the decline after 12 weeks NB-UVB to control values. The authors also reported that the use of erythemogenic doses of NB-UVB could improve the results in non responders to suberythemogenic doses of NB-UVB. In the study of Eysteinsdottir *et al.*[8] high baseline IL22 and other cytokines was also reported to decline in 6 cases of psoriasis treated by NB-UVB 3 times/week for 8 weeks compared to healthy control. The authors also reported even more decline in IL22 levels in another 6 psoriatic cases who were bathed in geothermal seawater twice daily then subjected to NB-UVB 5 times/week for only two weeks. Although done in a smaller number of cases compared to our study, the shorter time needed to reach better results by bathing in geothermal seawater before NB-UVB could represent an advantage of this technique and more work is needed in this field. Shimauchi *et al.*[18] studied IL22 and Vascular Endothelial Growth Factor (VEGF) in 28 psoriatic Japanese patients (19 psoriasis vulgaris, three pustular psoriasis and six psoriasis arthropathica) before and after biologic treatment (16 ustekinumab, six for adalimumab and six for infliximab). High baseline IL22 and VEGF that declined with therapy was found. The author concluded that IL22 and VEGF could be used as a sensitive biomarker of psoriasis severity. Compared to this study, we included almost the same number of cases (30 vs 28), but with different ethnicity (Egyptians vs Japanese), only psoriasis vulgaris (no psoriatic arthropathy or pustular forms), different therapy (NB-UVB vs biologic) and we reached similar conclusion in terms of the value of IL22 as a marker of severity of psoriasis.

On the other hand, the relation of IL22 to severity of psoriasis was questioned by Caproni *et al.*[12]. The authors studied 30 plaque psoriatic Italian patients who were given etanercept and another 30 patients who were given acitretin for 12 weeks vs 10 healthy control. Before and after treatment, PASI was calculated and serum levels of IL17, IL22 and IL23 were investigated. After treatment, PASI was significantly lower for both groups. However, etanercept- treated patients showed lower psoriasis area and severity index than acitretin-treated ones. Psoriasis patients showed higher IL17 and IL22 levels than controls, while no IL23 was found in any serum. Furthermore, a significant positive correlation between IL17 levels-but not IL22 and PASI score was found. The authors explained the absence of IL23 by suggesting a role of this cytokine in early cases of psoriasis only or by its rapid clearance by local autocrine or paracrine mechanism, but

they did not offer adequate explanation of the absence of correlation between PASI score and IL22 levels inspite of its high values in psoriatic patients compared to control.

Recently, Dyring-Andersen *et al.*[10] studied 18 psoriatic Danish patients treated by topical calcipotriol vs vehicle, applied on two similar lesions twice daily for two weeks. Among 16 cases that completed the study, the response assessment was done clinically as well as by biopsy and *in situ* measurement of frequency of CD8+IL17+T and IL22+ or IFN-c+cells by immunohistochemical study and flow cytometry. The authors recorded significant decrease in CD8+IL17+T cells in skin-derived cells from calcipotriol-treated skin, which was further supported by the absence of CD8+IL17+T cells in immunohisto-chemical staining of calcipotriol-treated skin. No changes in the frequency of IL22+ or IFN-c+cells in calcipotriol vs vehicle group were observed. The authors concluded that improvement of psoriasis severity by calcipotriol therapy is then related to reduction in CD8+IL17+T cells and not IL22+ or IFN-c+cells. The apparent contradictory findings in terms of relation of IL22 to psoriasis severity could be explained mainly by the difference of *in situ* measurement by skin biopsy and immune-histochemistry vs *in vivo* measurement of blood samples. Other variations in number of cases (30 vs 16) and different ethnicity (Egyptians vs Danish) and different treatment (NB-UVB vs topical calcipotriol) could also play a role in this issue.

In this study, univariate analysis failed to demonstrate significant difference between the responders and non responders to NB-UVB therapy in terms of IL22 level. This means that IL22 could not be used to predict the outcome of this treatment modality. Unfortunately, review of literature failed to yield enough research for comparison in terms of the predictive value of IL22 for the outcome of NB-UVB therapy. However, failure of IL22 to predict the response to biologic treatment in 28 Japanese psoriatic patients was reported by Shimauchi *et al.*[18].

Some limitations were encountered during conduction of this study. The most important is that it would be more beneficial to study more cytokines, like IL17, IL23 and IL8 to have a more comprehensive view that would help in better understanding of the pathogenesis of psoriasis.

CONCLUSION

From this study, It can concluded that IL22 level could serve as a good laboratory marker that correlates well with psoriasis severity, but could not be used as a predictor of the outcome of therapy with NB-UVB.

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