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LETTER TO THE EDITOR

Effect of polymorphisms in IL-12B p40, IL-17A and IL-23 A/G genes on the response of psoriatic patients to narrowband UVB

To the Editor,

Genetics play an important role in the development of psoriasis. Moreover, interindividual genetic differences have explained the varied response of psoriatic patients to different therapeutic modalities, and the personal variations in the development of adverse drug reactions.[1]

Narrow band-UVB (Nb-UVB) offers a well-established treatment modality for psoriasis by targeting IFN-γ-producing Th1 cells, as well as several cytokines involved in the pathogenesis of psoriasis such as: interleukin 12 (IL-12), interleukin 17 (IL-17) and interleukin 23 (IL-23).[2] IL-12 is produced by activated macrophages and serves as an essential inducer of Th1 cells . Subunit beta of IL-12 is encoded by IL-12B p40 gene, which also serves as a common subunit for IL-23.[3] IL-23 is a heterodimeric cytokine produced mainly by activated myeloid cells, as well as epithelial and endothelial cells. It activates the JAK/STAT signaling cascade which stimulates memory rather than naive T cells and promotes the production of proinflammatory cytokines.[4] Th17 cells have been identified in psoriatic skin leading to the expression of high levels of Th17 cytokines (such as IL-17) locally in lesional skin. IL-17A mediates its immune regulatory function mainly by promoting the generation of proinflammatory cytokines and chemokines, which leads to the attraction of neutrophils and macrophages to the site of inflammation. IL-17A, IL-17F and the heterodimeric IL-17A/IL-17F mediate their function through IL-17 heterodimeric receptor complex comprised of IL-17RA and IL-17RC. Downstream signaling interactions of IL-17R lead to the activation of nuclear factor kappa B and mitogen-activated protein kinase, which in turn enhance the production of proinflammatory cytokines and chemokines, with subsequent myeloid cell recruitment to the inflamed tissue. This causes inflammation and erythema.[5] IL-23 plays a role in the terminal differentiation of effector Th17 cells and their pathogenicity in peripheral tissues.[6]

We intended to study the effect of polymorphisms in IL-12B p40, IL-17A and IL-23 A/G genes on the response of psoriatic patients to Nb-UVB. Following approval by the Dermatology Research Ethical committee, and after informed consents were signed, this prospective study was carried out in the outpatient clinics of the Department of Dermatology in Cairo University. During the period from January 2014 to January 2015, 100 patients with psoriasis vulgaris involving more than 20% of body surface area (58 men [58%] and 42 women [42%]; mean ± SD age 41 ± 16.6 years, range 13-71 years) were recruited. Patients with any contraindication to phototherapy or patients receiving any other lines of treatment were excluded from the study.

Three millilitre of venous blood was drawn from each patient. Samples were stored at −20°C or used directly within 24 hours for genomic DNA extraction (AxyPrep Blood Genomic DNA Miniprep Kit [Cat. No.: AP-MN-BL-GDNA-50], Axygen Biosciences, USA). Primers were provided by (Fermentas™–Lithuania). Restriction enzymes provided by New England-Biolabs® Inc. were used. (refer to supplementary, online-only data).

Baseline PASI score was calculated for each patient before starting treatment. Nb-UVB was delivered by UV cabin (Waldmann Gmbh, Germany) equipped with an integrated UV photometer, having 16TL-01/100 Watt fluorescent lamps producing Nb-UVB with an emission spectrum of 310-315 nm. Nb-UVB was given 3 times a week on non-consecutive days. Patients were started off at 70% of minimal erythema dose (MED) which was calculated for each patient.[7] The dosage was increased by 10%-20% of MED every other session, until minimal perceptible erythema was reached. Eyes and genitalia were covered during treatment. Sessions were continued until improvement of baseline PASI by 75% (PASI- 75) was achieved, or for a maximum of 36 sessions. Final response was graded as: excellent: ≥75% improvement in PASI, moderate: 50%-75% improvement in PASI, and poor when improvement in PASI was less than 50%. Patients were categorized into 2 groups; responders and non-responders according to their final response, where responders included those with an excellent or moderate response and non-responders included those with a poor response. Patients were examined weekly to detect the occurrence of any side effects such as erythema, burn, xerosis, and pruritus, or the appearance of new lesions (koebnerization).

The frequency of distribution of the different genotypes of the 3 studied cytokines is illustrated in Table 1. Thirty-eight patients (38%) had polymorphic IL-12B p40 genotypes (AB and BB), 46 patients (46%) had polymorphic IL-23 A/G genotypes (AC and CC) and 56 patients (56%) had polymorphic IL-17A genotype (AG). Thirty-five patients (35%) had polymorphism in only 1 of the studied genes, 37 patients (37%) had polymorphisms in 2 of the studied genes, 10 patients (10%) had polymorphisms in the 3 studied genes, and 18 patients (18%) had no polymorphism in any of the studied genes.

No statistically significant difference existed between responders and non-responders as regards to the distribution of the different genotypes of any of the studied cytokines (IL-12, $P = .241$) (IL-23,

TABLE 1 Frequency of distribution of the different genotypes of the 3 studied cytokines and comparison between responders and non-responders

	Number (percent) of patients (total = 100)	Number (percent) of responders (total = 87)	Number (percent) of non-responders (total = 13)	*P* value*
IL-12 genotypes				
AA wild (common)	62 (62%)	55 (63.2%)	7 (53.8%)	.241 (NS)
AB heteromutant	28 (28%)	25 (28.7%)	3 (23.1%)	
BB homonutant	10 (10%)	7 (8.0%)	3 (23.1%)	
IL-23 genotypes				
AA wild (common)	54 (54%)	45 (51.7%)	9 (69.2%)	.242 (NS)
AC heteromutant	27 (27%)	26 (29.9%)	1 (7.7%)	
CC homomutant	19 (19%)	16 (18.4%)	3 (23.1%)	
IL-17 genotypes				
GG wild (common)	44 (44%)	39 (44.8%)	5 (38.5%)	.666 (NS)
AG heteromutant	56 (56%)	48 (55.2%)	8 (61.5%)	

NS, non-significant.
**P* value is significant < .05.

TABLE 2 Comparison between different therapeutic indices in relation to number of genes affected

	One polymorphic gene (N = 35)	Two polymorphic genes (N = 37)	Three polymorphic genes (N = 10)	*P* value*
Baseline PSAI	9.86 ± 4.59	10.40 ± 3.92	9.71 ± 4.46	.675 (NS)
PSAI Final	3.02 ± 1.91	3.42 ± 2.85	3.00 ± 1.89	.871 (NS)
Percent of improvement (%)	68.11 ± 14.25	66.11 ± 22.49	67.22 ± 18.93	.985 (NS)
Number of sessions at which initial improvement started	5.26 ± 2.47	5.00 ± 1.71	5.56 ± 2.74	.982 (NS)
Cumulative dose at initial improvement	2.49 ± 1.33	2.21 ± 0.75	2.63 ± 1.65	.865 (NS)
Total cumulative dose	57.82 ± 21.53	64.68 ± 22.41	64.31 ± 25.60	.294 (NS)

NS, non-significant.
**P* value < .05 is significant.

P = .242) (IL-17, *P* = .666; Table 1). The number of polymorphic genes did not affect various therapeutic indices (Table 2).

Twenty-five patients (25%) reported side effects; 1 (1%) reported erythroderma, 1 (1%) reported Koebner phenomenon, 2 (2%) reported xerosis, 10 (10%) reported itching and 11(11%) reported erythema. They included 8 patients (32%) with polymorphic IL-12B p40 genotypes, 12 patients (48%) with polymorphic IL-23 A/G genotypes, 18 patients (72%) with polymorphic IL-17A genotype and 3 patients (12%) had no polymorphic genotypes. The development of side effects was not significantly associated with any of the polymorphisms tested (IL-12, *P* = .551) (IL-23, *P* = .426) (IL-17, *P* = .099).

The lack of a statistically significant difference in the prevalence of mutant genotypes of (IL-12p40; IL-23A/G; IL-17A) between responders and non-responders indicates that these polymorphisms have no influence on the response of psoriatic patients to Nb-UVB. Over and above the presence of more than 1 gene polymorphism had no significant effect on therapeutic indices.

Upon further review of the literature, and in accordance with our findings, Bialecka et al.[8] found no influence of polymorphisms in IL17A and IL17F on the response of psoriatic patients neither to topical treatment alone, nor to combining topical treatment and Nb-UVB. To the best of our knowledge, no similar studies were conducted assessing IL-12 or IL-23 polymorphisms.

Although each cytokine polymorphism independently did not promote the development of side effects, the highest number of patients developing side effects was those with polymorphic IL-17 followed by IL-23. This may be attributed to the proinflammatory nature of both cytokines, and the fact that IL-23 increases the production of IL-17.

Other studies found the response to Nb-UVB not to be influenced by polymorphisms in other cytokines involved in the pathogenesis of psoriasis such as IL-6.[9] On the other hand, Toll-like receptor 9 promotor polymorphism was found to be associated with a better response to Nb-UVB.[10]

In conclusion, the response of psoriatic patients to Nb-UVB seems to be unaffected by the currently studied polymorphisms. Further multicenter studies with larger sample size are required. Studying the effect of other gene polymorphisms such as IL-23R gene and IL12 B p70 on the response to Nb-UVB is also needed.

CONFLICT OF INTEREST

None declared.

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[Correction added on 21 June 2018 after first online publication: One of the author names was previously incorrect and has been corrected in this version.]

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