IL17A (rs2275913 G>A) and IL17F (rs2397084 T>C) Gene Polymorphisms: Relation to Psoriasis Risk and Response to Methotrexate.

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Abstract

Background The relation of IL17 polymorphisms to psoriasis risk and response to methotrexate has not been previously studied in Egyptians.

Objectives To study the relation of IL17A (rs2275913 G>A) and IL17F (rs2397084 T>C) polymorphisms to psoriasis risk and assess their predictive role as regards response to methotrexate.

Patients & Methods IL17A (rs 2275913) and IL17F (rs 2397084) polymorphisms were evaluated in 100 healthy subjects and 100 patients with chronic plaque psoriasis by real time-PCR. Patients were given methotrexate weekly intramuscularly (0.6mg/kg) for 12 weeks.

Results IL17F TT genotype was more frequent in patients (87%) than controls (68%), while TC genotype was more frequent in controls (32%) than patients (13%). TT genotype was associated with increased risk of psoriasis whereas the TC allele was associated with a decreased risk. There was no significant difference regarding IL17A GG, GA and AA genotype frequencies between patients and controls. PASI ≥75% was achieved in 22 patients (73.3%) with the TT genotype and 8 patients (26.7%) with TC genotype (p=0.019).

Conclusion IL17F (rs2397084 T>C) TT genotype could be considered a susceptibility marker in Egyptian patients. Psoriatic patients with TT genotype and T allele of IL17F (rs2397084 T>C) are likely to show a better response to methotrexate.

Introduction

Psoriasis is a multigenic, T-cell mediated immunological disease. (Georgescu et al. 2019) [1] Beside TNF-α and IL-23, growing body of evidence from literature supports the role of the newer the IL-17 family in the pathogenesis and treatment outcome of psoriasis. (Puscas et al. 2019) [2]

Interleukin 17 family comprises six structurally related cytokines (IL17A-F), the most important members of which are IL-17A, followed by IL-17F. They are believed to play a central role in psoriasis pathogenesis through their pro-inflammatory effect on keratinocytes and neutrophils. (Bialecka et al. 2016) [3]

Methotrexate has been used as a standard monotherapy for treating psoriasis for decades and still continues to be used by virtue of its effectiveness, affordability and relative safety. Besides, its antiproliferative effect, it is believed to exert an anti-inflammatory effect through its effect on inflammatory cells and cytokines. Methotrexate has been shown to reduce IL17 expression and serum levels in psoriasis and rheumatoid arthritis patients. (Li et al. 2012) [4] However, variation in patients' response to methotrexate still remains incompletely understood. (Warren et al. 2009) [5]The genetic markers to predict the response to methotrexate treatment are not firmly established and there is paucity of pharmacogenetic studies in literature. It is possible that certain gene polymorphisms involved in the

pathogenesis of psoriasis may allow to select patients likely to respond to methotrexate. (Warren et al. 2009) [5]

IL-17A and IL-17F genes are located on chromosome 6p12. (Park et al. 2005; Prieto-Perez et al. 2015) [6, 7] Several IL17 gene polymorphisms have been described in literature and were associated with risk of developing several autoimmune, inflammatory and infectious diseases. Single nucleotide polymorphisms (SNPs) for IL17A (rs2275913: A > G) and IL17F (rs2397084: T > C, rs11465553: G > A, rs763780: T > C) genes were shown to affect amino acid sequences. (Bialecka et al. 2016) [3]

The implications of IL17 polymorphism to psoriasis susceptibility in general and in Egyptian patients however is not yet fully established. The relation of IL17 polymorphism to response to methotrexate has not been previously studied.

We aimed to study the association of IL17A (rs2275913 G > A) and IL17F (rs2397084 T > C) gene polymorphisms to psoriasis risk in a cohort of Egyptian patients and evaluate any predictive role to response to methotrexate.

Patients & Methods

Patients

This prospective study was conducted on 200 subjects, divided into two groups; group I of 100 healthy control individuals and group II composed of 100 patients with chronic plaque psoriasis. All study subjects were recruited from attendants of the dermatology outpatient clinic of Alexandria Main University Hospital from September 2016 to April 2018. A written informed consent was obtained from all subjects. The study protocol followed the International Ethical Guidelines of the 1975 Declaration of Helsinki and was approved by the local institutional ethical committee. Inclusion criteria were patients with chronic plaque psoriasis of either sex, aged more than 16 years of age with PASI score >10%.

We excluded pregnant and lactating women, patients with severe skin infection, lung diseases, chronic liver failure, leukopenia, aplastic anemia, neoplastic diseases and those with a history of allergy to methotrexate.

All patients were subjected to thorough personal, family and drug history taking and clinical evaluation of onset, and duration of psoriasis. A complete general physical examination was performed and a local dermatologic examination including grading of the disease severity according to the Psoriasis Area and Severity Index (PASI) score, before the start of medication and 12 weeks after treatment with intramuscular methotrexate 0.6mg/kg/week was conducted. PASI 75% was calculated at the end of the study.

Methods

Two mL of whole blood were withdrawn aseptically using sterile vacutainer K2 EDTA tubes. Samples were transferred to the lab immediately and stored at -20 c till the time of DNA extraction

DNA Extraction, amplification and quantification: (Hebron HR 2009)[8]

QIAamp DNA Blood Mini Kit (Qiagen, USA) was used to extract genomic DNA was extracted from PMC according to the manufacturer's instructions. The quantity and purity of the DNA was assessed by the NanoDrop 2000 (Thermo Scientific, USA).

The IL17A (rs 2275913) and IL17F (rs 2397084) SNPs genotyping was performed using the 5' nuclease Allelic discrimination assays. The PCR reaction mix contained 10 µL TaqMan® Universal PCR Master Mix (Applied biosystems, USA), 20 ng DNA/reaction, 1 µL of TaqMan® SNP Genotyping Assay 20x (Assay ID: C_3219460_20 and C_15903863_10 respectively) and DNAase free water to a final reaction volume of 20 µL. Thermal cycling profile was conducted using Rotorgene Q real-time PCR system (Qiagen, Germany) as follows: initial AmpliTaq Gold enzyme activation at 95 °C for 10 min, and 40 denaturation cycles at 95 °C for 15 seconds and annealing/extension for 1 minute at 60 °C.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were chi-square test for categorical variables to compare between different groups and fisher’s exact or monte carlo correction for chi-square when more than 20% of the cells have expected count less than five. Odd ratio (OR) was used to calculate the ratio of the odds and 95% confidence interval of an event occurring in one risk group to the odds of it occurring in the non-risk group.

Results

Demographic characteristics of the studied groups:

Control group I included 52 males and 48 females, whereas the patients group II included 58 males and 42 females. The mean age in the control group I and patients group II was 39.58 ± 16.53 years and 42.70 ± 14.09 years respectively. There was no significant difference regarding age and gender between patients and control subjects (p=0.076, p=0.723). Psoriasis disease duration ranged from 1-35 years with a mean duration of 10.90 ± 4.48 years. A positive family history of psoriasis was reported in 65% of the patients and 10% of the controls. This difference was statistically significant (p<0.0001) PASI scores

before therapy ranged from 22.13-55.30 with a mean score of 38.2 ± 7.79. PASI score after 12 weeks of therapy ranged from 2.40-20.10 with a mean score of 10.98 ± 4.48. This difference was statistically significant ($p<0.001$). Mean percentage of PASI reduction 12 weeks after treatment was 71.19% ± 12.54.

Genotype and allele frequency of IL17A polymorphism (rs2275913 G>A) in the control and patients groups:

There was no significant difference regarding GG genotype frequency between patients (70%) and controls (74%) ($p=0.146$). GA genotype frequency was more frequently observed in psoriasis patients (21%) than controls (10%). The AA genotype was observed in 16% of controls and 9% of patients ($p=0.146$).

The G allele was observed in 79% and 80.5% of the control and patients groups respectively, while the A allele was observed in 21% and 19.5% of the controls and patients respectively. There was no significant difference between patients versus control subject group regarding both G and A allele frequencies ($p=0.759$). (Table 1)

Genotype and allele frequency of IL17F polymorphism (rs 2397084 T>C) in the control and patients groups:

Genotype TT was significantly more frequently observed in the patients group (87%) than the control group (68%), while genotype TC was significantly more frequent in controls (32%) than patients (13%). ($p=0.005$). TT genotype was statistically associated with increased risk of psoriasis occurrence (OR=3.148) whereas the TC allele was associated with a decreased susceptibility to develop psoriasis (OR=0.318). (Table 1)

There was a significant difference between patients and control groups regarding both T and C allele frequency where the T allele was significantly more observed in psoriatic patients (93.5%) than in controls (84%), and the allele C was more frequent in controls (16%) than patients (6.5%) ($p=0.009$). (Table 1)

The T allele was found to be significantly associated with increased risk of psoriasis (OR=2.740) whereas the C allele was statistically associated with reduced risk to develop psoriasis (OR=0.365). (Table 1)

Table 1
Genotype and allele frequency of IL17A (rs 2275913 A>G) and IL17F (rs2397084 T>C) polymorphisms.

		Group I		Group II		p[a]	OR	95% C.I
		No.	%	No.	%			
IL17A	Genotype	(n = 100)		(n = 100)				
	GG	74	74.0	70	70.0	0.146	0.820	0.38 – 1.76
	GA	10	10.0	21	21.0		2.394	0.84 – 6.78
	AA	16	16.0	9	9.0		0.519	0.19 – 1.44
	Allele frequency							
		(n = 200)		(n = 200)				
	G	158	79.0	161	80.5	0.759	1.097	0.61 – 1.99
	A	42	21.0	39	19.5		0.911	0.50 – 1.65
IL17F	Genotype	(n = 100)		(n = 100)				
	TT	68	68.0	87	87.0	0.005[a*]	3.149*	1.370 – 7.239
	TC	32	32.0	13	13.0		0.318*	0.138 – 0.730
	Allele frequency							
		(n = 200)		(n = 200)		0.009[a*]		
	T	168	84.0	187	93.5		2.740*	1.261 – 5.952
	C	32	16.0	13	6.5		0.365*	0.168 – 0.793

IL17A (rs 2275913 A>G) polymorphism genotypes and alleles were not statistically different among patients and controls. IL17F (rs2397084 T>C) polymorphisms TT genotype and T allele are associated with increased risk of psoriasis. . IL17F (rs2397084 T>C) polymorphisms TC genotype and C allele are associated with reduced risk of psoriasis.

a: Chi square test

p: p value for comparing between the two groups

*: Statistically significant at $p \leq 0.05$

OR: Odds ratio

CI: Confidence interval

Group I: healthy group

Group II: psoriatic patients

IL17F (rs 2397084 T>C) polymorphism genotype and PASI ≥75% response

PASI ≥75% was achieved in 22 patients (73.3%) with the TT genotype and only 8 patients (26.7%) with TC genotype. (p=0.019) (Table 2)

IL17 A (rs2275913 G>A) polymorphism genotype and PASI ≥75% response:

PASI ≥75% was achieved in 18 patients (60%) of GG genotype, 8 patients (26.7%) with GA and 4 patients (13.3%) with AA genotype. (p=0.339) (Table 2)

Table 2
Relation between clinical response and IL17F (rs2397084 T>C) and IL17A (rs 2275913 A>G) polymorphisms genotypes.

		Responder (PASI≥75%)		p[a]
		No.	%	
IL17F		(n= 30)		
	TT	22	73.3	0.019*
	TC	8	26.7	
IL17A		(n= 30)		
	GG	18	60.0	0.339
	GA	8	26.7	
	AA	4	13.3	

IL17F (rs2397084 T>C) polymorphisms TT genotype was associated with better clinical response than TC genotype. IL17A (rs 2275913 A>G) genotypes did not differ according to clinical response.

a: Fisher Exact

*: Statistically significant at p ≤ 0.05

IL17F (rs 2397084 T>C) allele frequencies and PASI ≥75%

response

PASI ≥75% was achieved in 52 patients (86.6%) with T allele and 8 patients (13.4%) with the C allele (p =0.023). (Table 3)

IL17 A (rs2275913 G>A) allele frequencies and PASI ≥75% response

PASI ≥75% response was achieved by 44 patients (73.3%), and 16 patients (26.7%) in group a with allele G and A respectively (p =0.118). (Table 3)

Table 3
Relation between clinical response and IL17F (rs2397084 T>C) and IL17A (rs 2275913 A>G) polymorphisms allele frequencies.

		Responder (PASI≥75%)		p*[a]
		No.	%	
IL17F (allele)		(n=60)		
	T	52	86.6	0.023[a]
	C	8	13.4	
IL17A (allele)		(n=60)		
	G	44	73.3	0.118[a]
	A	16	26.7	
IL17F (rs2397084 T>C) polymorphisms T allele was associated with better clinical response than C allele. IL17A (rs 2275913 A>G) alleles did not differ according to clinical response. a: Fisher Exact *: Statistically significant at p ≤ 0.05.				

Discussion

Psoriasis is a chronic immune-mediated inflammatory disease that affects about 2%-4% of the population. Etiopathogenesis involves multifactorial environmental and polygenic factors. (Puscas et al. 2019) [2] Genetic factors are believed to influence the risk of developing psoriasis, clinical type, age of onset, severity as well as the risk of comorbidities. (Batalla et al. 2015; Coto et al. 2011) [9, 10]

Interleukin-17 comprises a family of six cytokines (IL-17A-F). IL-17A, IL-17B, IL-17C, and IL17F are proinflammatory cytokines that induce other inflammatory cytokines such as TNF and IL-1 and stimulate neutrophil chemotaxis. Furthermore, interleukin-17 increases the expression of IL-23R. IL-17 are primarily produced from Th17 cells and to a lesser degree from other immune cells as CD8+ cells, neutrophils, B cells, natural killer T cells, gamma delta T cells, and LTi cells. (Chiu et al. 2012) [11] IL-17A is considered the key cytokine in the inflammatory process of psoriasis because it has a direct influence on the activation and hyperproliferation of keratinocytes. (Furiati et al. 2019) [12]

Evidence from literature has implicated an important a role of interleukin-17 (IL-17), not only in psoriatic inflammation but also in treatment outcome. (Puscas et al. 2019) [2] Genetic studies have suggested important roles of components of the IL-17 as well as IL-23 signaling pathways in the development of psoriasis. The best known IL-17 polymorphisms are single nucleotide polymorphisms (SNPs) for IL17A (rs2275913: A>G) and IL17F rs2397084: T>C, rs11465553: G>A, rs763780: T>C. (Bialecka et al. 2016) [3]

The aim of this study was to study the association of IL17A (rs2275913 G>A) and IL17F (rs2397084 T>C) polymorphisms to the risk of developing psoriasis in a cohort of Egyptian patients with chronic plaque psoriasis and asses the presence of a possible predictive role to response to methotrexate.

A positive family history of psoriasis was significantly higher in our cohort of patients than controls suggesting a significant genetic background. Most of our patients were of the early onset psoriasis type. Naldi L et al (Naldi L 2011)[13] similarly reported a significantly higher family history of psoriasis among their psoriatic patients compared to the healthy controls. Early onset psoriasis (also referred to as type I) is known to start before 40 years of age, with peak onset at 16–22 years of age in opposition to late-onset psoriasis (also termed type II psoriasis) that starts at or after age 40 years, with a peak age of onset between 57 and 60 years. (Gladman DD 2005) [14] Early onset psoriasis is strongly associated with class I HLA alleles and patients usually have a family history. In contrast, type II psoriasis is more commonly sporadic with an unclear genetic background. (Schmitt-Egenolf M 2000)[15]

In the present study, a significant reduction of PASI score was observed 12 weeks after methotrexate therapy. Haider et al (Haider et al. 2014)[16] reported a 66% reduction of PASI score after 8 weeks of subcutaneous weekly methotrexate therapy in their patients. Methotrexate continues to be an affordable effective treatment option for patients with moderate to severe chronic plaque psoriasis whose condition requires systemic therapy or who failed to respond to topical treatment alone. Its therapeutic effect can be partly explained by inhibition of DNA synthesis by competitive inhibition of dihydrofolate reductase, accounting for its antiproliferative effect. However, this is not the sole mechanism of its therapeutic effect in psoriasis. A further anti-inflammatory effect through induction of immune cell apoptosis and inhibition

of T-cell activation has been suggested by invitro studies. (Meephansan et al. 2011) [17] Methotrexate was shown to reduce the numbers of T cells and monocytes in the skin and decrease expression of adhesion molecules. (Rentenaar et al. 2004) [18] Furthermore, methotrexate therapy was shown to be associated with reduction of serum interleukin-17 and 23 levels in psoriasis patients. (Elghandour et al. 2013) [19] It was suggested that methotrexate suppresses IL17 mRNA expression thereby decreasing IL-17 production. (Li et al. 2012) [4]

A significant percentage of our patients achieved a PASI 75 response. Similarly, Warren et al (Warren et al. 2017)[20] reported a 41% of patients achieving PASI 75 response. The slightly higher response can be attributed to the longer course of 16 weeks of methotrexate therapy.

We report that IL-17F (rs2397084 T>C) TT genotype was associated with increased risk of psoriasis occurrence whereas the TC allele was associated with a decreased risk to develop psoriasis. The T allele was also significantly associated with increased risk of psoriasis whereas the C allele was statistically associated with reduced risk to develop psoriasis. This suggests that IL17F (rs2397084 T>C) polymorphism could serve as a marker of susceptibility to develop psoriasis in our Egyptian patients. This is could be explained by the fact that IL17F (rs2397084 T>C) gene polymorphism has been shown to change amino acid sequences. (Bialecka et al. 2016) [3] Bialecka et al (Bialecka et al. 2016)[3] reported no association between IL17F (rs2397084 T>C) polymorphisms and psoriasis susceptibility in a Polish population. This is probably a reflection of racial or ethnic differences.

Our observed higher frequency of IL17A (rs2275913 G>A) GG and GA genotypes among our psoriasis patients than controls and opposingly higher frequency of AA genotype in controls was insignificant. The G allele was more frequently observed in patients while the A allele was more frequent in controls. However, no significant difference was observed. We suggest that IL17A (rs2275913 G>A) polymorphism cannot be regarded as a susceptibility marker among Egyptian patients. However, this observation should be verified by other studies involving larger number of patients is needed before reaching such conclusion.

Kim et al (Kim et al. 2017)[21] similarly reported no association between IL17A (rs2275913 G>A) polymorphism and psoriasis in a Korean population. Bialecka et al (Bialecka et al. 2016)[3] reported no association between IL17A (rs2275913 G>A) polymorphisms and psoriasis susceptibility in a Polish population.

In the present study, TT genotype of IL17F (rs2397084 T>C) polymorphism and T allele were associated with a better treatment response (PASI 75) to methotrexate compared to the TC genotype and carriers of the C allele. Similarly, Bialecka et al (Bialecka et al. 2016)[3] observed that carriers of the C allele of IL17F (rs2397084 T>C) polymorphism needed a greater number of NB-UVB phototherapy sessions to respond compared to carriers of the T allele.

We report that IL17A (rs2275913 G>A) polymorphism genotypes GG, GA, AA and the haplotypes G and A were not related to treatment response to methotrexate. This was in agreement to the observations

reported by Bialecka et al (Bialecka et al. 2016)[3] that IL17A (rs2275913 G>A) polymorphisms were not related to PASI score changes after topical vitamin D3 analogue and NB-UVB phototherapy.

To the best of our knowledge, this is the first report that IL17F (rs2397084 T>C) polymorphism could be regarded as a marker of susceptibility to psoriasis in Egyptian patients with the TT genotype representing an increased susceptibility to develop psoriasis and the TC genotype presenting decreased risk to develop psoriasis. IL17A (rs2275913 G>A) polymorphism cannot be regarded as a marker of susceptibility to psoriasis in Egyptian patients. Further, psoriatic patients with TT genotype and T allele of IL17F (rs2397084 T>C) polymorphism are likely to show a better therapeutic response to the commonly used methotrexate treatment than the TC genotype and carriers of the C allele. We did not observe any relation of IL17A (rs2275913 G>A) polymorphism genotypes and alleles to treatment response to methotrexate.

Declarations

Ethics approval and consent to participate :

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Approval of the local institutional ethics committee (IRB 00012098) was obtained (approval number 0304835). Written informed patients consents were taken.

Patients consent for publication:

consents for publication were obtained from the patients.

Conflict of interests:

none

Funding:

none

Availability of data and materials:

The analyzed data sets are available from the corresponding author upon reasonable request.

Author contributions:

Ashraf Hamza, Salma Omar, Nasren Ramadan contributed equally in the study design, statistical analysis of data and interpretation of the results.

Reham Abo Elwafa performed the laboratory tests and participating in writing and revision of the manuscript with the other three authors.

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