Original paper

The relationship between Fc epsilon receptor-1α and β (*FCER1A* and *FCER1B*) gene polymorphisms in patients with chronic urticaria using omalizumab

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Abstract

Introduction: Chronic urticaria requires well-defined treatment strategies in order to achieve a maximum treatment response and maintain the quality of life. Since 2014, omalizumab has been used in chronic urticaria. However, many studies showed that some patients are resistant to omalizumab.

Aim: To determine the effects of single nucleotide changes in the *FCER1A* and *FCER1B* genes, which are thought to be related to resistance mechanisms, in our population of patients who have not responded to omalizumab treatment.

Material and methods: We included 100 patients with chronic urticaria who were treated with omalizumab and 50 healthy individuals. Frequently observed gene polymorphisms, FCER1A (rs2251746) and FCER1B (rs569108), were examined in peripheral blood samples. The regions of rs2251746 and rs569108 gene polymorphisms were amplified using fluorescently labelled probes through real-time polymerase chain reaction (PCR). The analysis was performed bioinformatically via the SNP genotype profiling program.

Results: There was no statistically significant relationship between *FCER1A* (rs2251746) and *FCER1B* (rs569108) gene polymorphisms in patients and their clinical, demographic characteristics, and the resistance to treatment ($p > 0.05$). In our study, the mean patient age was found to be higher in the CT group (44.71 ±12.5 years) compared to the TT group (37.34 ±11.5 years) only in the rs2251746 polymorphism ($p < 0.05$).

Conclusions: In our study, there was no significant relationship between *FCER1A* and *FCER1B* gene polymorphisms and resistance to omalizumab therapy. Further, multicentre, large-scale studies are needed to support our results.

Key words: omalizumab, urticaria, genetics, polymorphism, FcεRIα, FcεRIβ.

Introduction

Urticaria is an inflammatory skin disease that presents with fluffy, erythematous, oedematous, itchy papules/plaques, sometimes accompanied by angioedema due to deep dermis and subcutaneous tissue involvement. It is called 'acute urticaria' (AU) if symptoms last for less than 6 weeks with aggravations, and 'chronic urticaria' (CU) if it lasts for 6 weeks or longer [1]. Acute urticaria is usually seen in children and young adults, while chronic urticaria is more common in middle-aged women [2]. In less than half of the cases of acute urticaria, an underlying cause such as medication, infection and food can be detected, while it is more difficult to determine the cause in CU cases [3].

Immunoglobulin E (IgE) plays a role in the activation of mast cells in the pathogenesis of urticaria, leading to the release of a number of mediators and cytokines. It is one of the most important mediators in allergic reactions and causes the development of urticaria lesions. Crosslinking of immunoglobulin E with multivalent antigens to high-affinity receptor (FcεR1) induces an allergic activation and leads to secretion of inflammatory mediators and induces cytokine gene transcription. Therefore, the ligation of IgE to the high-affinity IgE receptor plays a critical role in the induction of allergic diseases [4, 5].

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FcεR1 is expressed on the surface of effector cells involved in urticaria, such as mast cells and basophils, and initiates an IgE-mediated allergic response. In some patients with chronic urticaria, auto-antibodies against the FcεR1 alpha (α) subunit and IgE are responsible for histamine secretion, which causes symptoms such as urticaria. Patients in this subgroup are considered 'autoimmune urticaria' [1, 6].

The number of studies to identify genetic polymorphisms that can contribute to understanding the pathogenesis of common diseases is increasing day by day. Studies to identify single nucleotide polymorphisms (SNPs), which make up the vast majority of polymorphisms, are among the most common. These studies aim to develop individualized treatments by defining genetic factors that affect drug absorption, metabolism and the interaction of the drug at the receptor level. Investigation of polymorphisms occurring in the *FCER1* gene region will also be useful for understanding the pathogenesis of allergic reactions. Polymorphisms in this region are likely to be associated with allergic diseases [7–9]. Thus far, polymorphisms of genes including *FCER1A, FCER1B, FCER1C, HNMT, TNF-a, TGFb1, PTPN22, CCR2, CCR5,* and *HLAA-33* and *HLADRB1 *04* have been associated with chronic urticaria [10–15].

In recent years, the use of omalizumab, a monoclonal antibody, has been increasing in the treatment of chronic urticaria patients who do not respond to antihistamines. Omalizumab binds to the C3 part of the free-circulating IgE molecule in the blood and prevents antibody-mediated allergic and immunological reactions. The C3 region is also the binding region of IgE to FcεR1. Omalizumab cannot bind to FcεR1-bound IgE on the target cell surface. The expression of FcεR1 on the target cell surface is related to the level of circulating IgE antibodies. With appropriate doses of omalizumab, free IgE levels rapidly decrease to zero and accordingly, the FcεR1 on the target cell surface decreases as well. In this way, the binding of IgE to FcεR1 also decreases [16, 17]. However, certain studies have reported that some patients do not benefit from omalizumab treatment [18–20].

Aim

In our study, we aimed to determine the effects of single nucleotide changes in the *FCER1A* and *FCER1B* genes, which are thought to have an effect on the resistance mechanism in the Turkish population in patients with no response to omalizumab therapy. The genomic profile we aimed to depict within the scope of our study would reveal the genomic profile based on the response to the treatment of our population as well as being effective in the identification of the treatment-resistant patient group. Our study includes very comprehensive data of molecular medicine as it will compare the genomic profile of the relevant polymorphisms, with the patient age, gender and other clinical features.

Material and methods

Subjects

We included a total of 100 chronic urticaria patients under omalizumab treatment who had presented to the dermatology outpatient clinic between January 2019 and June 2019 and 50 healthy individuals (control group) and evaluated *FCER1A* and *FCER1B* gene polymorphisms. The study included patients aged 18–80 years who were under follow-up for chronic urticaria disease, who used or are still using omalizumab for at least 3 months, and who agreed to participate in the study and gave written informed consent. However, individuals younger than 18 years or older than 80 years of age, patients diagnosed with chronic urticaria, but not receiving omalizumab treatment, and patients with genodermatosis were excluded from the study.

Fifty healthy volunteers aged between 18 and 80, who had presented to the dermatology outpatient clinic with other complaints and no pathology detected as a result of routine tests and who did not have a known chronic disease, constituted the control group.

After having recorded the clinical and demographic characteristics of the patients participating in the study in the case data form, the *FCER1A* (rs2251746) and *FCER1B* (rs569108) gene polymorphisms were tested by sending the blood samples to the medical biology laboratory in the cold chain. In addition, data related to the management of patients were evaluated and recorded. The urticaria activity score (UAS7) values of patients were recorded before and after omalizumab treatment, and patients using antihistamine and/or immunosuppressive medication (prednisolone/cyclosporin) with omalizumab were noted as well. The relationship between rs2251746 and rs569108 gene polymorphisms and the clinical, demographic and treatment approach of the patients were evaluated using statistical analysis tests. The study was approved by the Local Ethics Committee (Approval date: 09.11.2018, no. 08/2018).

DNA isolation and genotyping

GF-1 Blood DNA Extraction Kit (Vivantis Technologies, Malaysia) was used for extraction of genomic DNA from peripheral blood of subjects according to the manufacturer's instructions. The *FCER1* gene rs2251746 variant and *FCER1B* gene rs569108 variant were detected by Taqman Assays (Thermo Scientific, USA). SNP genotyping was performed by Real-Time PCR amplifications that were 25 µl containing 2.25 µl at the concentration of 3–20 ng genomic DNA diluted in distilled water, 12.50 µl of 2xTaqpath ProAmp Master Mix (2X) (Thermo Scientific, USA) and 1.25 µl of 20× Taqman SNP Assay mix (Thermo

Scientific, USA). Manufacturer's instructions were used for the amplification conditions.

Statistical analysis

The SPSS 23.0 package program was used to evaluate the data in the study. The χ^2 and/or the Fisher's exact tests were used for comparison of the categorical variables between the groups. While the *t*-test in the independent groups was used to compare the continuous variables between two groups; the One-Way Analysis of Variance (ANOVA) was used to test the difference between more than two groups. The results of the analysis of the categorical variables were given as frequency and percentage values, while the mean ± standard deviation, median, minimum and maximum values were used to summarize the continuous data analysis results. A *p*-value of less than 0.05 was accepted as statistically significant.

Results

A total of 150 subjects, including 100 chronic urticaria patients and 50 healthy controls, were included in our study. Of the chronic urticaria patients, 66% were female (n = 66) and 34% were male (n = 34). There were 24 (48%) women and 26 (52%) men in the control group. The ages of patients with CU were between 20 and 69 years, and the mean age was 39.74 ±12.37 years. In the control group, the age of participants ranged between 18 and 65 years, and the mean age was 31.74 ±9.69 years (Table 1). The disease duration of the participants was 1–20 years and the mean disease duration was 6.08 ±3.71 years The duration of omalizumab use ranged between 3 months and 72 months, and the mean duration was 17.36 ±11.05 months. Total IgE levels were normal (< 100 kU/l) in 42 (42%) patients and high (> 100 kU/l) in 52 (52%) patients (Table 1).

In our study, 57 patients were using only omalizumab, and 39 patients were using an antihistaminic drug in addition to omalizumab. Of the remaining 4 patients, 3 were using antihistamine and cyclosporine, and one was using prednisolone in addition to these drugs. The weekly mean and standard deviation of the UAS7 (urticaria activity score) was 19.47 ±7.38 points (min.–max. = 6–37) before the omalizumab treatment, while it was 1.73 ±2.20 points (min.–max. = 0–7) after treatment. According to these results, we found that 87 (87%) patients benefited from treatment and 13 (13%) patients were resistant to treatment. Seventy percent of the patients had no concomitant disease. There was asthma in 7%, asthma and diabetes in 1%, accompanying psychiatric disorder in 10%, autoimmune disease in 4%, and accompanying diabetes, hypertension or cardiovascular disease in 8% of the patients (Table 1).

When we evaluated the rs2251746 polymorphism in the patient group, we detected the TT genotype in 64 (64%) individuals, CT genotype in 32 (32%) individuals and homozygous CC genotype in 4 (4%) individuals. In the healthy control group, we detected the TT genotype in 32 (64%) individuals, CT genotype in 17 (34%) individuals and the homozygous CC genotype in 1 (2%). When we evaluated the rs569108 polymorphism, we detected the homozygous AA genotype in 93 (93%) patients and 7 heterozygous AG genotypes in 7 (7%) patients. In the healthy control group, 47 (94%) subjects had homozygous AA and 3 (6%) subjects had heterozygous AG genotypes. The CC genotype was not found in either of the two groups. We compared the polymorphism characteristics of the patient and the control groups and there was no statistically significant difference between them ($p > 0.05$) (Table 2).

There was no significant difference between the genders in terms of genetic polymorphism in the control and the patient groups ($p > 0.05$). We evaluated the relationship between the treatment response and genetic polymorphism. There was no significant difference in polymorphism between the patients who benefited from the treatment and those who were resistant to treatment (Table 3).

We evaluated the relationship between the serum total IgE level and polymorphism in patients who participated in the study. There was no significant relationship between the total IgE level and polymorphism (Table 4).

In the patient group, the clinical features of the patients were compared according to the rs225176 polymor-

Table 1. Demographic characteristics of patients with chronic urticaria

Parameter	Results
Gender	66 (66.0%) females 44 (34.0%) males
Age	39.740 ±12.37
Disease duration	6.08 ±3.7 years
Omalizumab usage time	17.360 ±11 months
Total IgE level	42 (42%) patients < 100 58 (58%) patients > 100
UAS7	Before treatment: 19.7 ±7.3 After treatment: 1.73 ±2.2
Response to omalizumab treatment	Number of patients responding to treatment: 87 (87%) Number of treatment-resistant patients: 13 (13%)
Concomitant diseases	No accompanying disease: 70 (70%) Asthma/atopy: 1 (1%) Asthma/diabetes: 1 (1%) Psychiatric diseases: 10 (10%) Autoimmune disease: 4 (4%) DM, HT, CVD: 8 (8%)

DM – diabetes mellitus, HT – hypertension, CVD – cardiovascular disease.

Table 2. Comparison of the rs2251746 and rs569108 polymorphism characteristics of the patient and control groups

Polymorphism	Control group		Patient group		*P*-value
	N	%	*N*	%	
rs2251746:					
CC	1	(2)	4	(4)	0.858
CT	17	(34)	32	(32)	
TT	32	(64)	64	(64)	
rs569108:					
AA	47	(94)	93	(93)	1.00
AG	3	(6)	7	(7)	
GG	0		0		

Table 3. Comparison of the relationship between the treatment response and polymorphism

Polymorphism	Group (patient)/response to treatment				*P*-value
	Responding to treatment		Treatment-resistant		
	N	%	*N*	%	
rs2251746:					
CC	2	(2.3)	2	(15.4)	0.073
CT	29	(33.3)	3	(23.1)	
TT	56	(64.4)	8	(61.5)	
rs569108:					
AA	81	(93.1)	12	(92.3)	0.916
AG	6	(6.9)	1	(7.7)	
GG	0		0		

Table 4. Comparison of the relationship between the total IgE level and polymorphism

Polymorphism		Total IgE		Total	*P*-value
		≤ 100	> 100		
rs569108:					
AA	*n*	38	55	93	0.449
	%	40.9	59.1	100.0	
AG	*n*	4	3	7	
	%	57.1	42.9	100.0	
rs2251746:					
CC	*n*	3	1	4	
	%	75.0	25.0	100.0	0.312
TT	*n*	24	40	64	
	%	37.5	62.5	100.0	
CT	*n*	15	17	32	
	%	46.9	53.1	100.0	

phisms and there were no significant differences in the clinical features ($p > 0.05$) other than the patient age. Among the 3 genotypes, there was a significant difference regarding age between CT and TT groups in the patient group ($p = 0.020$). Besides, there was no significant difference between the rs569108 polymorphism groups in terms of clinical features ($p > 0.05$).

Discussion

Urticaria is a common reactive skin disease that affects 15–30% of the society and is a frequent cause of consultations in hospitals. Hives that last for more than 6 weeks are considered 'chronic urticaria', which constitutes 25% of urticaria and the point prevalence is 0.5–1% [1, 21]. Currently, the underlying causes and pathophysiological mechanisms of CU are still not fully understood. Allergic diseases are extremely complex and arise through the interaction between genetic and environmental factors. The number of genetic studies on allergic diseases, especially asthma, has increased steadily over the past few years. Similar to asthma and other allergic diseases, genetic mechanisms are thought to be related to the pathogenesis of CU [15]. In a study with a large population of CU patients, the authors reported that the disease showed an increased prevalence among first-degree relatives compared to the general population [22].

Chronic urticaria is a disease that requires well-defined treatment strategies to obtain a maximum treatment response and maintain the quality of life. The efficacy, safety, and tolerability of omalizumab, which has been used since 2014 in patients with chronic urticaria who have not responded to standard dose H_1 antihistamine therapy, have been demonstrated in phase-III studies [23–25]. In the current literature, studies are ongoing to seek answers to questions such as determining clinical-laboratory indicators, optimal treatment duration, dose, and treatment intervals, post-remission management and effectiveness of post-relapse therapy in order to predict the individual treatment response and optimizing the omalizumab therapy.

In their study with CU patients using omalizumab, Bongiorno *et al.* reported that mild to moderate CU symptoms (UAS7: 7–11 points) persisted despite the use of omalizumab in 14.3% of patients [19]. In their study with 93 CU patients using omalizumab, Ertas *et al.* reported resistance to treatment in 14% of patients [20]. It is still unclear why some patients are resistant to anti-IgE therapy. In our study, we observed resistance to treatment in 13% of cases, which is consistent with the literature mentioned above.

It has been reported that there may be a later development of resistance in patients responding well to omalizumab treatment [26, 27]. However, the reasons

for this have not been fully explained. In a statement on possible mechanisms of resistance development, it has been suggested that the pathomechanisms that cause histamine release in CU are many and their relative importance may vary from 1 patient to another or may change over time in the same patient. Omalizumab can only affect some, not all, of these mechanisms [28].

FcεR1 is a multimeric cell surface receptor to which the Fc fragment of IgE binds with high affinity. FcεR1 is expressed on the surface of effector cells involved in urticaria, such as mast cells and basophils, and initiates an IgE-mediated allergic response [7]. Therefore, it would be useful to examine polymorphisms occurring in the *FCER1* gene region to elucidate the pathogenesis of allergic reactions and even predict the response to treatment.

There are very few studies in the literature exploring the relationship between *FCER1A* and *FCER1B* gene polymorphisms and CU, or the relation of the treatment response with *FCER1A* and/or *FCER1B* gene polymorphisms. Guo *et al.* conducted the first study to investigate the relationship of *FCER1A* genetic polymorphisms (rs2298805, rs10908073 and rs2494262) with chronic spontaneous urticaria (CSU) in Chinese patients and the relation of these polymorphisms with the treatment efficacy of non-sedative H_1-antihistamines. They reported that while rs2494262 and rs10908073 polymorphisms were not significantly related to the CSU risk and the response to antihistamines, they found that the rs2298805 polymorphism was significantly related to the risk of CSU and total serum IgE level. They also showed that the rs2298805A allele carriers responded better to non-sedative H_1-antihistamines used in the treatment of CSU [10].

In another study, Choi *et al*. investigated the relationship between *FCER1B*, *HRH1*, *HRH2*, and *HNMT* gene polymorphisms and response to H1-antihistamines in 63 Korean patients with CU. They reported that CU patients with *FCER1B* -109C/C homozygous variant required a significantly lower cumulative H_1-antihistamine dose compared to those with T/C and T/T genotypes, and also CU patients with *FCER1B* -RsaI_in2A/A homozygous variant required a significantly lower cumulative H_1-antihistamine dose compared to those with G/A and G/G genotypes [29].

However, there has been no study in the literature investigating the relationship between *FCER1A* and *FCER1B* gene polymorphisms and the therapeutic efficacy of omalizumab. To the best of our knowledge, this is the first study to investigate *FCER1A* and *FCER1B* gene polymorphisms that may have an effect on the resistance mechanisms to omalizumab.

In our study, we investigated the relation of rs2251746 among *FCER1A* gene polymorphisms (CC, CT, TT genotypes) and rs569108 among *FCER1B* gene polymorphisms (AA, AG, GG genotypes) with response to omalizumab treatment; however, we did not find a significant difference between the treatment responders and treatment-resistant patients in terms of polymorphism. In both groups, among the rs2251746 polymorphisms, there were mostly TT genotype and the least CC genotype determined, while, among the rs569108 polymorphisms, the subjects had mostly the AA genotype and the least genotype was AG.

FCER1A is an important immune-related gene that encodes the alpha chain (FcεR1α) of the high-affinity IgE receptor, which is the ligand-binding subunit and initiates the IgE-mediated allergic response. Some recent studies have shown that SNPs in the *FCER1A* gene are associated with serum IgE levels. *FCER1A* is a candidate gene that leads to an increase in the serum IgE level and to clinical atopy [10, 30].

When we evaluated rs2251746 (TT, CT, CC genotypes), one of the *FCER1A* gene polymorphisms in our study, we did not find a significant difference between the patient and the control group. Zhou *et al*. reported that rs2427837 and rs2251746 gene polymorphisms in *FcεR1α* were a genetic risk factor for high serum IgE levels. However, in the same study, no significant difference was observed in the distribution of rs2427837A/G and rs61828219 T/G genotypes between CU patients and the healthy control group [7]. Another large-scale study in which genome-wide association studies (GWAS) were conducted showed that rs2251746 and rs2427837 polymorphisms found in the *FCER1A* gene were of great importance in the regulation of total IgE levels, and revealed that the *FCER1A* gene was a new susceptibility gene for IgE levels [31]. However, in our study, we did not find a significant relationship between rs2251746 polymorphism and serum total IgE levels in CU patients.

In our study, we examined the relationship between rs2251746 polymorphism and clinical and demographic characteristics of the CU patients (age, gender, disease duration, duration of omalizumab use, concomitant diseases, UAS7 values before and after treatment); however, we did not find a significant relationship in terms of other features except age. The mean age was significantly higher in the CT group compared to the TT group (44.71 ±12.5 years vs. 37.34 ±11.5 years).

Regulation of FcεR1 expression is crucial for receptor functions. It is known that both the expression of the FcεR1β subunit and the serum levels of IgE are important regulatory factors on FcεR1 gene expression. FcεR1β regulates the receptor response to IgE by amplifying the receptor signal. IgE-FcεR1 binding leads to over-expression of the receptor with an increase in the total FcεR1α content on the surface. This process can be reversed by removing IgE, which causes a decrease in receptor function and FcεR1α content [32]. This important function of the FcεR1β subunit has been the focus of attention in many studies on allergic disease pathogenesis. To date, few studies have been conducted to determine the relationship between CU and FCER1B gene polymorphism [33].

In our study, rs569108 (AA, AG, GG genotypes), which is one of the *FCER1B* gene polymorphisms, was not significantly different between the patients and healthy controls, and no GG genotype was found in either of the two groups.

In a study investigating the *FCER1B* gene polymorphism in patients with CU, there was no significant relationship between *FCER1B* C-109T gene polymorphism and the CSU; however, compared to *FCER1B* C allele carriers, T allele carriers had a higher risk of developing CSU [33].

Another study investigated the relations of *FCER1B* gene polymorphisms (rs1441586 and rs569108), and the *FcεR1γ* gene polymorphisms (rs11587213 and rs2070901) with aspirin-induced urticaria. There was no significant difference in terms of allele and genotype frequencies in all of the CU patients, including the aspirin-induced urticaria group and the aspirin-tolerant group. On the other hand, atopy was determined significantly more frequently in aspirin-induced CU patients having the AG/GG genotypes compared to the AA genotype of the rs569108 allele amongst the *FCER1B* gene polymorphisms and rs11587213 allele amongst FcεR1γ gene polymorphisms, respectively [34].

Studies have reported that the *FCER1B* gene polymorphism is associated with atopy, total serum IgE level, bronchial hyperactivity, asthma and basophilic histamine secretion activity in asthmatic patients [35–37]. However, in our study, we did not find a significant relationship between the rs569108 polymorphism and asthma/atopy, and the serum total IgE levels in CU patients. In our study, we also examined the relation of the rs569108 polymorphism with clinical and demographic characteristics of patients (age, gender, disease duration, duration of omalizumab use, concomitant diseases, UAS7 scores before and after treatment), but we did not find a significant relationship.

Conclusions

There was no significant relationship between *FCER1A* (rs2251746) and *FCER1B* (rs569108) gene polymorphisms and the clinical, demographic and treatment-related features in our study. However, our study is the first study in the literature investigating the usefulness of *FCER1A* and *FCER1B* gene polymorphisms as a pharmacogenetic marker in evaluating the response to omalizumab treatment. Clinical heterogeneity and the effect of environmental factors on the genetic background, the relatively small number of participants in the study and the unknown data about the relevant polymorphism in Turkey have decreased the power of our study. Further, large-scale studies are needed to determine the relationship between *FCER1A* and *FCER1B* polymorphisms and the response to omalizumab.

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Ethical approval

Date: 09.11.2018, number: 08.

Conflict of interest

The authors declare no conflict of interest.

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