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Type I and Type IIb Autoimmunity in Chronic Spontaneous Urticaria Patients: Evaluating the Clinical Response to Omalizumab

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Abstract

This study aimed to evaluate the clinical response to omalizumab in patients with Type 1 and Type IIb autoimmunity suffering from chronic spontaneous urticaria (CSU) and to compare the difference in laboratory data. A retrospective study was conducted from September 2019 to December 2022 in the Center of Allergy and Immunology in Tbilisi, Georgia, involving 39 patients (95% females, 5% males, average age 35.82 years). Total IgE and ANA antibodies were taken as markers of autoimmunity. The study included patients who still had high disease activity despite using a fourfold dose of non-sedating antihistamines. Patients were prescribed omalizumab according to international guidelines with an interval of 4 weeks for at least 3 months. Disease activity was determined using the urticaria activity score (UAS7), and patients were divided into three groups according to CSU activity: low, moderate, and high disease activity. Response to omalizumab was assessed as non-responders, partial responders, and complete responders. The results showed that Type I autoimmunity had a higher percentage of complete responders than Type IIb (55.5% vs. 18.3%). Non-responder rates were higher in Type IIb than in Type I (72.7% vs. 18.5%). The median total IgE levels were significantly higher in Type I than in Type IIb (138 vs. 23.95 kU/I). The median duration of the disease was significantly shorter in Type I than in Type IIb (9 vs. 27 months). No significant differences were found between the two groups regarding age, angioedema, CRP levels, H. pylori infection rates, anti-TPO IgG levels, eosinopenia, and basopenia.

In conclusion, this study suggests that the clinical response to omalizumab differs depending on the type of autoimmunity. Type I autoimmunity patients had a better response to omalizumab than Type IIb. The median duration of the disease was significantly shorter in Type I than in Type IIb. Further studies are needed to evaluate the mechanism underlying the difference in response to omalizumab and the use of different treatment options for patients with different types of autoimmunity.

Keywords: *chronic spontaneous urticaria, omalizumab, Type I and Type IIb autoimmunity*

Introduction

Omalizumab has emerged as a crucial therapy for individuals suffering from chronic spontaneous urticaria (CSU) who do not respond to antihistamines, even when administered in doses higher than those recommended by the manufacturer[1]. Around 70% of patients (referred to as fast responders) experience a quick decline in UAS7 levels when treated with Anti-IgE, whereas an additional 15% of patients (called slow responders) have a similar response over 3-4 months. The remaining 15% appear to be resistant to the treatment[2]. There have been several studies conducted in recent times which have demonstrated a correlation between the initial total IgE levels and the clinical response observed after treatment with the drug [3,4]. Identifying an IgE-mediated auto-allergic mechanism in many CSU patients explains the rapid response observed in severely affected individuals upon being treated with omalizumab[5]. At the same time, there are data on Type IIb autoimmunity with a poor clinical response to omalizumab and a good response to cyclosporine [6]. Based on two types of mast cell degranulating signals, two endotypes of CSU, auto-allergic and autoimmune, are proposed. The first is known as type I autoimmune CSU mediated by IgE autoantibodies and the second – aiCSU, known as type IIb autoimmune CSU, in which IgG autoantibodies, and probably IgM and IgA, are responsible for direct activation of mast cells through binding to high-affinity IgE receptors. According to existing studies, total IgE, anti-TPO, autologous serum skin test (ASST), basophil histamine release assay (BHRA), and other tests have been used to determine mainly two types of autoimmunity mechanisms[7]. It is important to find simple and cost-effective markers to distinguish between forms of autoimmunity. We used total IgE and ANA antibodies in our study. Our study aims to evaluate the clinical response to omalizumab in patients with type I and type IIb autoimmune disease and the difference in laboratory data between the two groups.

Methods

This retrospective study was conducted from September 2019 to December 2022 at the Center of Allergy and Immunology in Tbilisi, Georgia (GA²LEN Urticaria Center of Reference and Excellence). Thirty-nine adults and adolescents (≥ 12 years old) with a diagnosis of CSU, confirmed by an allergologist according to the international Guideline[1], were included. The study included patients with high disease activity despite using a fourfold dose of non-sedating antihistamines. According to international guidelines, these patients have been prescribed omalizumab at intervals of 4 weeks for at least three months.

Patients were divided into two groups according to autoimmunity. Total IgE and ANA antibodies were taken as markers of autoimmunity. Namely, the first group is Type I autoimmunity with high total IgE (> 43 kU/l) and negative ANA, and Type IIb autoimmunity with low total IgE (< 43 kU/l) and positive ANA.

Disease activity was determined using the urticaria activity score (UAS), which was calculated as the sum of the itch (no = 0, mild = 1, moderate = 2, intense = 3) and the wheal score (no wheals = 0, < 20 wheals/24 hr = 1, 20–50 wheals/24 hr = 2, > 50 wheals/24 hr = 3) for seven consecutive days (UAS7, minimum = 0, maximum = 42). Response to omalizumab was assessed as non-responders (a reduction in UAS7 of less than 30%), partial responders (a reduction in UAS7 of 30% to 89%), and complete responders (a reduction of 90% or more from baseline in UAS7), respectively.

According to the manufacturer's instructions, total IgE levels were measured using the ImmunoCAP system (Thermo-Fisher, Uppsala, Sweden). ANA was detected using HEp-2 cells and an indirect fluorescent antibody technique. The result would be reported as a titer. The cut-off value to define positive ANA was 1:80. Thyroid microsomal antibodies were detected by radioimmunoassay (cut off > 34 kU/l). Serum CRP concentrations were measured by ELISA using commercially available reagents (reference range < 6.0 mg/L). H. Pylori was detected by a stool antigen test.
Statistical analysis: Differences in continuous variables between test samples were analyzed using a t-test for independent samples and the Mann-Whitney U test. The Chi-Square test was used to see differences in categorical variables. Normally distributed data are presented as mean ± SD, and nonnormally distributed data are expressed as a median. Date were analyzed using SPSS software version 22.0 (IBM Corporation, New York, USA). Statistical significance was defined as $p < 0.05$.

Results

Of the 39 patients in this study, 95% (n=37) were females, and 5% (n=2) were males. Average age 35.82 years (range 12-71). The results indicate that Type I autoimmunity had a higher percentage of complete responders (CR) than Type IIb (55.5% vs. 18.3%). Non-responder (NR) rates were higher in Type IIb than in Type I (72.7% vs. 18.5%). The median total IgE levels were significantly higher in Type I than in Type IIb (138 vs. 23.95 kU/I). The median duration of the disease was markedly shorter in Type I than in Type IIb (9 vs. 27 months). The study did not find significant differences between the two groups regarding age, angioedema, CRP levels, H. pylori infection rates, anti-TPO IgG levels, eosinopenia, and basopenia. All data are collected in Table 1.

Table 1 - Comparison between the study populations' baseline clinical and serological characteristics.

	Group1 Type I autoimmunity (Total IgE high > 43, ANA -) n=28	Group 2 Type IIb autoimmunity (Total IgE high < 43, ANA +) n=11	p-value
Gender (Female)	92%	100%	
Age (years) (mean ± SD, Range)	34.63	40.25	0.368
complete responders (CR)	55.5%	18.3%	**0.004***
partial responders (PR)	26%	9%	0.758
Non responders (NR)	18.5%	72.7%%	**0.012***
Angioedema	42%	60%	0.351
duration of diseases (month) median	9	27	**0.019***
Total IgE kU/I (median)	138 (min-max 8.6-1297)	23.95 (min-max 5.73-386)	**0.02***
CRP	24.57+42.96	22.71+39.67	0.444
H.pylori +	32%	27%	0.085
anti-TPO IgG +	50%	36.6%	0.867
Eosinopenia (<0.05 × 10^9/L)	0.24	0.21	0.847
Basopenia (<0.01 × 10^9/L)	0.06	0.02	0.478

Note: CRP- C reactive protein, H.pylori – Helicobacter pylori, IgG-anti-TPO - anti-thyroid peroxidase immunoglobulin G. *statistically significant values are shown in bold

Discussion

The study aimed to evaluate the clinical response to omalizumab in patients with Type 1 and Type IIb autoimmunity and the difference in laboratory data. Patients were divided into two groups according to autoimmunity - Type I autoimmunity with high total IgE ((> 43 kU/l) and negative ANA and Type IIb autoimmunity with low total IgE (<43 kU/l) and positive ANA. The response to omalizumab was assessed as non-responders, partial responders, and complete responders. The results showed that Type I autoimmunity had a higher percentage of complete responders than Type IIb, while non-responder rates were higher in Type IIb than in Type I. The median total IgE levels were significantly higher in Type I than in Type IIb, and the median duration of the disease was considerably shorter in Type I than in Type IIb. No significant differences were observed between the two groups regarding age, angioedema, CRP levels, H. pylori infection rates, anti-TPO IgG levels, eosinopenia, and basopenia.

Recent reports characterised 2 possible endotypes according to the type of mast cell degranulation signals: type I autoimmune CSU mediated with IgE autoantibodies to auto-allergens (or autoallergy), and type IIb autoimmune CSU mediated with autoantibodies that target activating mast cells receptors. These 2 endotypes of autoimmune hypersensitivity have been postulated as etiologic in most CSU patients. There is a need to develop diagnostic tests to differentiate these two endotypes of CSU to tailor the appropriate treatment and help each patient achieve remission [8]. The study's findings suggest that total IgE levels and ANA can help identify patients with Type I and Type IIb autoimmunity and predict their response to omalizumab [9,10]. Many studies indicate that total IgE levels affect the response to omalizumab. Baseline total IgE levels above 43 IU/l and twofold or more increased IgE levels at week 4 were correlated with the improvement of CSU at week 12 of treatment as assessed by UAS[11]. Weller et al. found that elevated total IgE levels were common in complete responders (77.5%), and rarely detected in non-responders (20%) to omalizumab[12]. Asero has recently confirmed that most early responders to omalizumab have elevated baseline total IgE [13]. The response to omalizumab in severe chronic spontaneous urticaria (CSU) largely depends on the autoimmune or autoallergic endotype of the disease, and total IgE levels are the most reliable prognostic marker for omalizumab response. The study concludes that thyroid autoimmunity alone cannot be used as a clinical predictor of omalizumab response in patients with severe CSU. Total IgE levels remain the only and most reliable prognostic marker for omalizumab response in these patients[14]. According to our results, too, there was no difference in thyroid autoimmunity.

The study's limitations include small sample size, retrospective design, and lack of a control group. Further studies with a larger sample size, prospective design, and a control group are needed to validate the findings. Nevertheless, the study provides important insights into the use of omalizumab in patients with CSU and different types of autoimmunity. Overall, the study highlights the importance of personalised medicine in managing CSU patients, considering their autoimmunity status and laboratory data.

Conclusion

This study evaluated the clinical response to omalizumab in patients with chronic spontaneous urticaria (CSU) and Type I and Type IIb autoimmunity. The results showed that Type I autoimmunity had a higher percentage of complete responders than Type IIb, while non-responder rates were higher in Type IIb than in Type I. The median duration of the disease was significantly shorter in Type I than in Type IIb. These findings suggest that omalizumab may be more effective in Type I autoimmunity than Type IIb autoimmunity in CSU patients.

The results of our study indicate that total IgE and ANA, two simple and inexpensive tests, can be used to predict the efficacy of omalizumab. Further studies are needed to evaluate the mechanism underlying the difference in response to omalizumab and the use of different treatment options for patients with different types of autoimmunity.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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I და IIb ტიპის აუტოიმუნურობა ქრონიკული სპონტანური ურტიკარიით პაციენტებში: ომალიზუმაბით მკურნალობის ეფექტურობის შეფასება

ბიძინა კულუმბეგოვი [1,2], მაია გოთუა [1], თინათინ ჩიქოვანი [2]

[1]ალერგიისა და იმუნოლოგიის ცენტრი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

კვლევის მიზანი იყო I და IIბ ტიპის აუტოიმუნურობის მქონე ქრონიკული სპონტანური ურტიკარიით (ქსუ) დაავადებულ პაციენტებში ომალიზუმაბზე კლინიკური პასუხის შეფასება. რეტროსპექტული კვლევა ჩატარდა 39 პაციენტზე (95% ქალი, 5% მამაკაცი, საშუალო ასაკი 35.82 წელი), რომლებიც 2019 წლის სექტემბრიდან 2022 წლის დეკემბრამდე მკურნალობდნენ ალერგიისა და იმუნოლოგიის ცენტრში (თბილისი, საქართველო). აუტოიმუნურობის მარკერებად გამოვიყენეთ შრატში საერთო IgE-ს დონე და ANA ანტისხეულების არსებობა. კვლევაში შედიოდნენ პაციენტები, რომლებსაც, არასედაციური

ანტიჰისტამინური პრეპარატების ოთხმაგი დოზით გამოყენების მიუხედავად, ჰქონდათ დაავადების მაღალი აქტივობა. პაციენტებს, საერთაშორისო გაიდლაინების მიხედვით, დაენიშნათ ომალიზუმაბი 4 კვირის ინტერვალით მინიმუმ 3 თვის განმავლობაში. დაავადების აქტივობა განისაზღვრა ურტიკარიის აქტივობის ქულის (UAS7) გამოყენებით. ქსუ-ის აქტივობის მიხედვით პაციენტები დაიყო სამ ჯგუფად: დაბალი, საშუალო და მაღალი დაავადების აქტივობით. პასუხი ომალიზუმაბზე შეფასდა როგორც: არამოპასუხე, ნაწილობრივ მოპასუხე და სრულად მოპასუხე.

შედეგებმა აჩვენა, რომ I ტიპის აუტოიმუნურობის შემთხვევაში სრულად მოპასუხე პაციენტების პროცენტული მაჩვენებელი სტატისტიკურად სარწმუნოდ მაღალია, ვიდრე IIბ ტიპის შემთხვევაში (55.5%/18.3%). ომალიზუმაბზე არამოპასუხეთა სიხშირე უფრო მაღალი იყო IIბ ტიპის დროს, ვიდრე I ტიპის შემთხვევაში (72.7%/18.5%). მედიანური საერთო IgE დონე მნიშვნელოვნად მაღალი იყო I ტიპის დროს, ვიდრე IIბ ტიპის შემთხვევაში (138 vs. 23.95 kU/I). დაავადების ხანგრძლივობა მნიშვნელოვნად უფრო ნაკლები იყო I ტიპის, ვიდრე IIბ ტიპის დროს (9 vs. 27 თვე). ამ ორ ჯგუფს შორის მნიშვნელოვანი განსხვავება არ დაფიქსირებულა ასაკის, ანგიოედემის, C-რეაქტიული ცილის დონის, H.pylori ინფექციის სიხშირის, ანტი-TPO IgG დონის, ეოზინოპენიის და ბაზოპენიის თვალსაზრისით.

შეიძლება დავასკვნათ, რომ კლინიკური პასუხი ომალიზუმაბზე ქსუ-ის აუტოიმუნურობის ტიპის მიხედვით განსხვებულია. I ტიპის აუტოიმუნურ პაციენტებს აქვთ უკეთესი პასუხი ომალიზუმაბზე, ვიდრე IIბ ტიპისას. ასევე დაავადების ხანგრძლივობა I ტიპის აუტოიმუნურ ჯგუფში მნიშვნელოვნად ნაკლებია ვიდრე მეორე ჯგუფში. საჭიროა შემდგომი კვლევები, რათა შეფასდეს მექანიზმი, რომელიც საფუძვლად უდევს ომალიზუმაბზე რეაგირების განსხვავებულობას და სხვადასხვა ტიპის აუტოიმუნური პაციენტებისთვის მკურნალობის სხვადასხვა ვარიანტების გამოყენებას.

საკვანძო სიტყვები: *ქრონიკული სპოინტანური ურტიკარია, ომალიზუმაბი, I და IIბ ტიპის აუტოიმუნურობა*