Allergology International xxx (2017) 1–5

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original Article

Treatment and retreatment with omalizumab in chronic spontaneous urticaria: Real life experience with twenty-five patients

Murat Türk*, İnsu Yılmaz, Sakine Nazik Bahçecioğlu

Division of Allergy and Clinical Immunology, Department of Chest Diseases, Erciyes University School of Medicine, Kayseri, Turkey

ARTICLE INFO

Article history:
Received 21 February 2017
Received in revised form
15 April 2017
Accepted 23 April 2017
Available online xxx

Keywords:
Anti-IgE antibody
Management
Omalizumab
Retreatment
Urticaria

Abbreviations:
ANA, anti-nuclear antibody;
CMS, concomitant medication score;
CRP, C-reactive protein; CSU, chronic spontaneous urticaria; ESR, erythroid sedimentation rate; Tg, thyroglobulin; TPO, thyroid peroxidase; UAS, urticaria activity score

ABSTRACT

Background: Previous data have shown the high efficacy of omalizumab in chronic spontaneous urticaria (CSU). However, factors that may be effective on the response to therapy, relapse rates after drug discontinuation, and efficacy of retreatment remain unclear. This study aimed to determine the efficacy of omalizumab in CSU refractory to conventional therapy, to identify possible factors affecting treatment response and relapse, and also to evaluate the efficacy of retreatment on relapsed disease.
Methods: The data of CSU patients treated with 300 mg/month omalizumab for at least 3 months were retrospectively analyzed. In order to evaluate the efficacy of treatment and retreatment, baseline and follow-up concomitant medication score (CMS) and urticaria activity score (UAS) were calculated. Possible factors affecting treatment response and relapse were identified.
Results: Twenty-five patients were included. The median duration of omalizumab therapy was 6 (6–12) months. Of the patients with baseline UAS 6 (5.5–6) and CMS 13 (10–15), 8 (32%) had complete response (UAS = 0) and 2 (8%) were non-responders after 3 months of therapy. None of the complete responders were positive for IgG-anti-TPO. After discontinuation of omalizumab therapy, 11 (61%) patients experienced relapse and 10 of them received retreatment with omalizumab. Half of the patients had complete response, and half had partial response (UAS = 1–4) after retreatment. No treatment related adverse events were documented.
Conclusions: Omalizumab has high efficacy in both the treatment and retreatment of CSU; however, relapse rates after discontinuation are high. Autoimmune markers may be helpful in predicting treatment response and relapse.

Introduction

Chronic spontaneous urticaria (formerly called chronic idiopathic urticaria) (CSU) is a disease characterized by recurrent itching, wheals and/or angioedema that lasts for more than 6 weeks in the absence of a precipitating external factor. Since the disease may sometimes last for years,[1] it negatively affects the patients' quality of life and may cause socioeconomical problems. Non-sedating H1-antihistamines are the drug of choice for the first-line treatment and up to a four-fold dose increase is recommended if there is no improvement.[2] However, high dose antihistamines are ineffective in approximately half of the patients,[3] and in these cases leukotriene receptor antagonists, cyclosporine A, H2-antihistamines or systemic glucocorticoid combinations are also used in addition to H1-antihistamines.[2,4] Recently, studies on the high efficacy of omalizumab in patients that are refractory to conventional therapy have been reported. Use of omalizumab in CSU patients was approved both in the USA and the EU in 2014 and it became the first drug approved for use in patients refractory to H1-antihistamines.[5,6]

Omalizumab (Xolair®, Novartis, Switzerland) is a monoclonal humanized IgG antibody that attaches to unbound IgE and prevents its attachment with the high or low-affinity receptors (FcεRI and FcεRII) on mast cells, basophils, eosinophils and lymphocytes. Thus it causes a decrease in free IgE levels and a down-regulation of receptors on cell membranes.[7] Its mechanism of action in CSU is not fully understood. As a modification of allergic response is not aimed at it is in asthma, a fixed dose of the therapy is recommended. Even though the doses may differ among centers, the evidence-based highest efficient dose is 300 mg/4 weeks.[8,9]

Most previous studies including real life data are based on drug efficacy. Knowledge on the optimal duration of treatment and

* Corresponding author. Division of Allergy and Clinical Immunology, Department of Chest Diseases, Erciyes University School of Medicine, 38039 Melikgazi, Kayseri, Turkey.
E-mail address: mrttrk@gmail.com (M. Türk).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2017.05.003

Please cite this article in press as: Türk M, et al., Treatment and retreatment with omalizumab in chronic spontaneous urticaria: Real life experience with twenty-five patients, Allergology International (2017), http://dx.doi.org/10.1016/j.alit.2017.05.003

management after therapy discontinuation are not clear. Data on the possible effective factors on treatment response, relapse rates and retreatment efficacy are very limited. Thus in this study we aimed to establish efficacy of omalizumab in CSU refractory to conventional therapy, to identify factors that may be effective on therapeutic response and relapse, and to evaluate the efficacy of retreatment in relapsed cases.

Methods

This single-centered retrospective study evaluated the data of patients diagnosed with CSU that were treated with omalizumab from 2013 to 2016. The center is located within the university hospital and it is the only reference allergy-clinical immunology clinic in the city and the surrounding region.

Patients who were treated with omalizumab without any break for at least 3 months were included. Omalizumab was administered 300 mg/4 weeks to every patient at the outpatient clinic under surveillance. Concomitant medications were adjusted at monthly controls according to the clinical response. The baseline and follow-up concomitant medication scores (CMS) of patients were calculated retrospectively. Symptom scores were obtained from patient charts.

The CMS of patients were calculated in a similar way to previous studies: antihistamines (regular dose, 2 points; 4 times the regular dose, 8 points), oral glucocorticoids (<11 mg, 5 points; 11–25 mg, 10 points; >25 mg, 15 points), cyclosporine 3.0 mg/kg (8 points), hydroxychloroquine (6 points) and montelukast (2 points).[10] Therapeutic efficacy was evaluated by urticaria activity score (UAS). According to this, at their monthly follow-up, patients were asked to score their symptoms categorically as wheals (none: 0 points, <20 wheals: 1 points, 20–50 wheals: 2 points, >50 wheals: 3 points) and pruritus (none: 0 point, mild: 1 point, moderate: 2 points, severe: 3 points), making up 0–6 points in total.[2,11]

According to the responses to omalizumab, patients were grouped as follows: complete responders (UAS = 0 and no increase in symptoms during follow-up), partial responders (UAS = 1–4), and non-responders (UAS $\geq$ 5 or gradually increasing UAS at follow-up). The patient characteristics of the complete and partial control groups were compared.

In all patients with complete or partial response, discontinuation of omalizumab was tried at a time after 6 months. Retreatment was initiated if the recurred disease couldn't be controlled with concomitant medications. The characteristics of patients who were symptomatic and asymptomatic after discontinuation of omalizumab were compared. At the time of the study, 4 patients had not completed their 6 month-therapy and 1 patient was resistant to all therapies. Therapy discontinuation was not tried in these 5 patients and they were excluded from that comparison. Study design is summarized in Figure 1. Data related to other possible triggers and comorbidities such as serum total IgE, phadiatop and sIgE for food mix, vitamin B12, thyroid autoantibodies, eosinophil counts, rheumatological markers, fecal *Helicobacter pylori* antigen, C-reactive protein (CRP), erythroid sedimentation rate (ESR), anti-endomysium and anti-gliadin autoantibodies were recorded retrospectively. Possible effects of these variables on clinical response were evaluated.

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Parameters were expressed as median (25–75 interquartile range; IQR) unless stated otherwise. Chi-square, Mann–Whitney U and repeated measures ANOVA tests were used for comparing variables.

Table 1
Patient characteristics.

Variables (N = 25)	Median (IQR)
Age	39 (31.8–49)
Female gender; n (%)	18 (72)
Comorbidities; n (%)	
Hypothyroidism	5 (20)
Asthma	4 (16)
Diabetes mellitus	2 (8)
Rheumatologic disorders	1 (4)
CRP; mg/L	3.4 (3.3–11.2)
Eosinophil count; %	1.7 (0.9–2.8)
Eosinophil count; cells/mL	130 (79–195)
Total IgE; IU/mL	226 (56–340)
ESR; mm/h	10 (4–20)
ANA positivity; n (%)	6 (24)
Phadiotop positivity; n (%)	9 (36)
Food mix positivity; n (%)	1 (4)
IgG anti-TPO positivity; n (%)	7 (28)
IgG anti-Tg positivity; n (%)	3 (12)
Anti-endomysium positivity; n (n = 10)	0
AGA-IgG positivity; n (n = 10)	1
AGA-IgA positivity; n (n = 10)	1
Fecal *H. Pylori* antigen positivity; n (n = 21)	11

IQR, Interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, Anti-nuclear antibody; TPO, Thyroid peroxidase; Tg, Thyroglobulin; AGA, Anti-gliadin antibody.

Results

Patient characteristics are listed in Table 1. The majority of patients were female (72%), young and had few comorbidities. IgE levels prior to therapy were slightly high. Seven patients (28%) were positive for anti thyroid peroxidase (IgG-anti-TPO) and 3 (12%) were positive for anti thyroglobulin (anti-Tg) autoantibodies. Six patients (24%) had anti-nuclear antibody (ANA), one of them also had SS-A and SS-B positivity. Nine patients (36%) were positive for at least one of ANA, IgG-anti-TPO and IgG-anti-Tg antibodies. Fecal *H. pylori* antigen was positive in 11 patients.

Median time from appearance of urticaria symptoms to omalizumab therapy was 44 (15–72) months. Baseline median CMS was 13 (10–15) and UAS was 6 (5.5–6). At the third and sixth months CMS and UAS had decreased to 2 (0–6) and 1 (0–1), respectively (Table 2).

During the first three months, all patients had improved CMS and UAS. After three months, 2 patients experienced worsened symptoms and increased need for concomitant medication. They were accepted as non-responders and omalizumab therapy was discontinued after the 6th month and 10th month. One patient's prior systemic steroid and cyclosporine treatments were stopped until the 3rd month, but systemic steroid therapy was restarted due to symptomatic worsening. However, since the symptoms were still better than they were before omalizumab treatment, she was accepted as a partial-responder and continued omalizumab treatment. The data of these three patients are given in Table 3.

Fourteen (58%) patients had complete response at the end of their therapies. At the 3rd month, 8 patients (32%) had complete response. None of these complete-responders had IgG-anti-TPO autoantibody positivity when compared to partial-responders ($p = 0.058$). The time from first symptoms to omalizumab therapy was also markedly shorter in complete responders; however, the difference was not statistically significant [22 (7–51) months and 47 (18–80) months, respectively, $p = 0.12$]. Relapse ratios did not differ significantly between these two groups ($p = 0.63$) (Table 4). Fecal *H. pylori* antigen, phadiatop, ANA and IgG anti-Tg positivity, and CRP levels also did not differ between these groups. Non-responders were not included in statistical analyses since the number of patients was very low (n = 2).

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