

EXPERT OPINION

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Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice

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Objective: To collect data on the efficacy and safety of omalizumab in 110 patients from 9 Spanish hospitals suffering from chronic spontaneous urticaria (CSU) refractory to conventional treatment.

Methods: A retrospective, descriptive analysis was performed, showing the data of 110 patients suffering from refractory CSU who received omalizumab as an off-label treatment in 9 Spanish hospitals from October 2009 to September 2012.

Results: Ninety (81.8%) patients exhibited a complete or significant response, 12 (10.9%) had partial response, and 8 (7.2%) showed no response. Sixty-six (60%) patients were able to stop all concomitant medications, remaining asymptomatic treated with omalizumab alone. No serious adverse events were reported.

Conclusions: Omalizumab shows excellent efficacy and safety profile in a large series of CSU patients in real-life practice. This drug will contribute to settle the debt with CSU patients contributing to restore their quality of life.

Keywords: chronic spontaneous urticaria, chronic urticaria, CSU, omalizumab

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1. Introduction

Chronic spontaneous urticaria (CSU) is defined by continuous or recurring episodes of spontaneous, transient (< 24 h) dermal wheals and pruritus, with or without angioedema, which can persist for at least 6 weeks. CSU has a great impact on patients' quality of life. Updated guidelines recommend non-sedating antihistamines at conventional doses as a first-line treatment, and, where there is no response, increasing off-label dose up to fourfold. Short courses of systemic corticosteroids are only recommended for acute exacerbations. Up to now, the only third-line treatment with an evidence-based recommendation is cyclosporine [1,2]. Omalizumab has shown to be very effective in improving the symptoms of chronic urticaria [3-12].

In the present study, we collected data on the efficacy and safety of omalizumab in 110 patients from 9 hospitals suffering from refractory CSU to available treatments.

2. Methods

A retrospective descriptive analysis was carried out comprising 110 patients from 9 hospitals who presented with refractory CSU and were treated with omalizumab

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as an off-label treatment. We included CSU patients with or without associated physical urticaria, CSU with angioedema, and chronic autoimmune/autoreactive urticaria (CAU) defined as CSU with positive autologous serum skin test (ASST) and/or autologous basophil CD63 expression assay (Table 1).

The patients were treated from October 2009 to September 2012. Refractory CSU was defined as having uncontrolled symptoms for at least 6 weeks despite administration of different available treatments (detailed as previous treatments in Table 1) for 4 weeks according to the last published EAACI/GA²LEN/WAO/EDF guidelines [1]. Although the treatment protocols were not exactly the same for all centers included, 150 or 300 mg of omalizumab was administered subcutaneously every 2 or 4 weeks independent of patient body weight and total serum immunoglobulin E (IgE) levels. Omalizumab was used in all patients as an off-label treatment as approved by the Spanish Agency for Drugs and Health Products, and by each pharmacy hospital committee that include written informed consent.

We defined complete response as disappearance of hives and pruritus; significant response, when minimal symptoms with no need of rescue medication (antihistamines); and partial response was classified as reduction of more than one level of therapy compared to baseline. Patients were classified as nonresponders when neither remission nor any improvement in symptoms was experienced during the treatment period. Assessment of disease activity was performed before and after treatment using the Urticaria Activity Score (UAS) [1,13] in a subgroup of 38 patients.

Omalizumab was administered through four different protocols: 150 mg every 2 weeks or every 4 weeks, or 300 mg at the same frequencies. One of the protocols called for discontinuation of treatment after 3 months on 300 mg of omalizumab, reintroducing the drug in doses administered every 2 or 3 months as needed when symptoms reappeared. In total, 110 patients received 2009 omalizumab (150 mg) doses.

2.1 Statistical analysis

The categorical variables were described as absolute and relative frequencies, while continuous variables were reported as the mean and standard deviation or range. Descriptive statistics were performed using SPSS software version 19.0 (SPSS, Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered to indicate statistical significance.

3. Results

Clinical features and demographics of the sample and outcomes after treatment with omalizumab are summarized in Table 1.

Ninety (80.8%) patients with CSU achieved a complete response or significant response. Twelve patients (10.9%) achieved partial response and only 8 (7.2%) showed no

response at all, even after doubling doses for 2 months or shorten period of administration in five of them. Thirty-eight patients, in whom UAS was used before and after treatment, showed a significant reduction, from 5.34 ± 0.88 to 0.66 ± 1.3 ; ($p < 0.005$). The use of concomitant medication significantly decreased ($p < 0.005$), and 66 (60%) patients were able to withdraw all medications, remaining asymptomatic with omalizumab treatment alone. Forty-one patients (37.3%) discontinued use of omalizumab (after 1 – 18 months) due to a complete response; of these, omalizumab had to be reintroduced in 20 (47.5%) patients due to symptoms that slowly relapse, and the symptoms disappeared between the first week and 2 months of treatment in 18 of them (90%). There were no changes in treatment protocol. Until now, 21 (19.1%) of patients remain asymptomatic without omalizumab treatment. No serious adverse events were reported.

We did not find differences when we compared efficacy and time of response among different doses or scheduled protocols, even considering the different types of CSU included in the analysis and subanalysis (CSU with or without associated physical urticaria, CSU with angioedema, and CAU patients).

4. Discussion

Nonsedating anti-H1 antihistamines remain the first-line treatment option for chronic urticaria. Standard licensed dose often fails, and therefore to increase the dose up to four times is recommended. Although anti-H1 dose increases, good control is not achieved in many patients requiring the immunomodulation. Since the first reports of isolated cases [3], omalizumab has emerged as a promising agent due to its excellent efficacy/safety profile. A Phase I single-blind, placebo-controlled study first demonstrated efficacy and safety in 12 patients with autoimmune serologies [4]. A Phase II dose-escalation study that was double-blind and placebo-controlled [7] and another open-label study in patients lacking autoimmune serologies confirmed these data [8]. Subsequently several studies [9–11] also showed an excellent response to the drug. Recently, a large multicenter, randomized, double-blind, placebo-controlled Phase III study [12] showed a significant improvement of itch-severity score, UAS7, and number of hives compared with placebo using 150 and 300 mg of omalizumab every 4 weeks during 3 months for a 3-month period in CSU patients. Complete response was obtained in 23 and 53% of patients with 150 and 300 mg, respectively. This trial supports the therapeutic efficacy observed in our series using different protocols with fixed doses of 150 or 300 mg. Previously, excellent rates of response using adjusted omalizumab doses [4,6] as well as fixed doses [7,8] were observed in CSU patients. Omalizumab is effective independent of body weight or total IgE levels to treat CSU patients, at least at doses of 150 mg every 4 weeks.

Table 1. Clinical and demographic characteristics.

<i>n</i> (Total)	110
Gender (female)	73 (66.4%)
Age (years)	45 (range 17 – 74)
Positive test	
ASST (n = 27)	12 (44.4%)
Autologous basophil CD63 expression assay (n = 16)	3 (18.8%)
Total IgE (IU/ml) (n = 107)	133 (range 2 – 1042)
Any specific IgE (atopy) (n = 57)	34 (59.6%)
Antinuclear antibodies (n = 54)	6 (11.1%)
Antithyroid antibodies (n = 72)	10 (13.9%)
Thyroid substitutive therapy (n = 77)	6 (7.8%)
Type of urticaria*	
CSU	110 (100%)
CAU (n = 35) [‡]	15 (42.9%)
PhysU [§]	39 (35.5%)
AO	7 (6.4%)
Duration [¶]	
< 6 months	4 (3.6%)
6 – 12 months	10 (9.1%)
1 – 5 years	42 (38.2%)
> 5 years	5 (49.1%)
Disease activity (p < 0.005)	
UAS (pre-omalizumab) 38 patients	5.34 (range 3 – 6)
UAS (post-omalizumab) 38 patients	0.66 (range 0 – 6)
Previous treatments	
High antihistamine doses (three- to fourfold)	84 (76.4%)
Systemic steroids	85 (77.3%)
Calcineurin inhibitors (cyclosporine, Tacrolimus)	31 (28.8%)
Montelukast	15 (13.6%)
Others (methotrexate, doxepin, H2-antihistamines, antimalarials, dapsone, etc.)	17 (15.5%)
Treatment with omalizumab (months)	11.423 (range 1 – 48)
Omalizumab doses	
150 mg/2 weeks	(9.1%)
150 mg/4 weeks	54 (49.1%)
300 mg/2 weeks	5 (4.5%)
300 mg/4 weeks	28 (25.5%)
Others (150 – 300/ 6 – 24 weeks)	13 (11.8%)
Response to omalizumab	
Complete or significant response	90 (81.8%)
Partial	12 (10.9%)
No response	8 (7.2%)
Time for response after starting omalizumab [#] (n = 58)	
First week	31 (53.4%)
First month	5 (8.6%)
1 – 6 months	22 (37.9%)
Any medication after omalizumab	66 (60%)
Stop omalizumab	41 (42.6%)
Reintroduction omalizumab	20 (48.8%)
Response after reintroduction	18 (90%)

Results are expressed as number of patients or mean with range in brackets.

*The number of urticaria patients is higher than 100% because some patients presented with more than one type.

[‡]ASST and/or Autologous Basophil CD63 expression assay available from 35 patients.

[§]Mainly dermatographic urticaria or delayed pressure urticaria, associated to CSU.

[¶]Duration: time from onset of symptoms until beginning of omalizumab treatment.

[#]Data available from 58 patients.

AO: Angioedema; CAU: Chronic Autoimmune/Autoreactive Urticaria; CSU: Chronic Spontaneous Urticaria; PhysU: Physical Urticaria.

We show descriptive data from a large retrospective case report including 110 patients suffering from refractory CSU who were treated with omalizumab. The present study has the limitation to be retrospective. Different doses and

administration protocols were used. However, due to the large number of patients treated and doses administered (2009) over 3 years, we offer useful information that could shed some light on this entity.

The main finding is that omalizumab is able to induce a fast – in some cases even within few hours after its administration – and effective response in 81% of CSU patients. Of the 110 patients included, 41 discontinued use of omalizumab, 21 remained free of symptoms, and 20 required a reintroduction of the treatment. It is interesting to note that, in our series, omalizumab is equally effective regardless different urticaria subtypes (CSU with or without associated physical urticaria, CSU with angioedema, or CAU). Omalizumab did not lose effectiveness, and after its reintroduction was effective again in 18 of the 20 patients in whom the drug was withdrawn. These are new and important findings that were not previously pursued in formal trials. These trials are designed to assess fast and immediate efficacy omalizumab long-term outcomes and loss of effectiveness along time which seems not to be the case. For how long this drug should be used to obtain a complete response without relapse of symptoms is a challenge that should be faced in future prospective studies.

Furthermore, omalizumab seems to be a very safe drug in patients with CSU, showing a better effective/toxicity profile than other recommended alternative treatments such as

long-term period of corticosteroids or calcineurin inhibitors (cyclosporine or tacrolimus).

In summary, we present data of omalizumab use in CSU along 3 years including > 2000 doses. In this study we show that omalizumab has an excellent profile in terms of efficacy/adverse events, with a response rate of 81% with a low percentage (7%) of patients with refractory CSU exhibiting a lack of response. Omalizumab is already included as a third-line therapy for CSU, both in the EAACI guidelines [1] and the recent WAO guidelines [2]. Our findings confirm this recommendation. Nevertheless, additional studies are needed to determine its exact place in urticaria treatment, as well as the best dose protocol and administration scheme. However, its unique combination (thus far) of efficacy and safety suggests that it may be the drug of choice for patients refractory to antihistamines.

Declaration of interest

All authors are medical advisors for Novartis. Ana Gimenez-Arnau is a medical advisor for Genentech.

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