



Omalizumab in chronic spontaneous urticaria: steroid sparing effect

Alessia Gatta, Loredana Della Valle, Anila Farinelli, Enrico Cavallucci, Roberto Paganelli & Mario Di Gioacchino

To cite this article: Alessia Gatta, Loredana Della Valle, Anila Farinelli, Enrico Cavallucci, Roberto Paganelli & Mario Di Gioacchino (2018) Omalizumab in chronic spontaneous urticaria: steroid sparing effect, Journal of Dermatological Treatment, 29:sup3, 6-9, DOI: [10.1080/09546634.2018.1527988](https://doi.org/10.1080/09546634.2018.1527988)

To link to this article: <https://doi.org/10.1080/09546634.2018.1527988>



Accepted author version posted online: 24 Sep 2018.
Published online: 03 Jan 2019.



Submit your article to this journal [↗](#)



Article views: 136



View related articles [↗](#)



View Crossmark data [↗](#)



Citing articles: 1 View citing articles [↗](#)

ARTICLE



Omalizumab in chronic spontaneous urticaria: steroid sparing effect

Alessia Gatta, Loredana Della Valle, Anila Farinelli, Enrico Cavallucci, Roberto Paganelli and Mario Di Gioacchino

Department of Medicine and Science of Ageing, Specialization School of Allergy and Clinical Immunology, G. D'Annunzio University, Chieti, Italy

ABSTRACT

Omalizumab has been recognized to be effective in the treatment of chronic spontaneous urticaria (CSU). The Italian Medicines Agency authorizes two omalizumab courses, only for patients with CSU unresponsive to antihistamines, and this schedule may limit omalizumab use. Unfortunately, in the majority of CSU, the schedule is unsatisfactory because symptoms usually recur shortly after discontinuation of treatment. A case of a patient needing more than two treatment courses with omalizumab is reported, in order to discuss the rationale for its long-term use. Patient had needed systemic steroids almost continuously for 4 years. Two severe glucocorticoid-associated adverse events (GAEs) occurred during long-term treatment. Omalizumab 300 mg monthly was started with immediate disappearance of the urticarial lesions. Beneficial effects waned shortly after discontinuation of treatment, and further steroid use was needed. A second omalizumab course showed the same clinical pattern, with prompt response and recurrence of symptoms after suspension. Therefore, we decided to repeat the 6 months omalizumab treatment as soon as symptoms recurred, to avoid further emergency steroid treatments and GAEs. This experience suggests that long-term use of omalizumab could be useful. Evidences show that omalizumab is effective and safe for re-treatment and long-term use of responding patients after recurrence.

ARTICLE HISTORY

Received 20 February 2018
Accepted 19 September 2018

KEYWORDS

Chronic spontaneous urticaria; steroid-dependent urticaria; autologous serum and plasma skin test; omalizumab

Introduction

Chronic spontaneous urticaria (CSU) is a cutaneous disorder of unknown origin. A combination of immune, genetic, and environmental factors is involved in its pathogenesis. Pivotal steps are degranulation of cutaneous mast cells and release of chemical mediators, among whom histamine is the most important in causing symptoms. Current guidelines recommend second-generation non-sedating H1-antihistamines as first-line treatment, in addition to short courses of corticosteroid during the exacerbations. However, almost half of CSU patients continue to have symptoms even with very high doses of antihistamines. In these patients, cyclosporine A (1), montelukast and omalizumab have been suggested as third-line therapy (2). However, cyclosporine A and steroids are unsuitable for long-term use owing to considerable side effects. Moreover, results from trials evaluating the use of montelukast in the management of CSU are inconsistent (3). On the contrary, omalizumab, besides its positive effects, has a good safety profile. Its long-term use could be useful for patients responding to treatment and recurring after discontinuation. Nevertheless, omalizumab has been licensed by the Italian Medicines Agency (IMA) for use in CSU, with the recommendation to give two courses of treatment, the first for 6 months and the second for 5 months, with two months interval in between, in case of symptoms reappearing (4).

In the present paper, we report the typical case of a patient suffering from severe CSU, who had a good response to treatment with omalizumab but recurred after the second course of therapy, and we discuss the opportunity to administer long-term omalizumab.

Case report

The patient DG (male, 39 years old) was referred to the outpatient clinic of the Allergy Unit of the University hospital in Chieti in 2015, for severe urticaria/angioedema diffuse all over the body surface, which had first presented in 2011. No other diseases were recorded, except for Hashimoto's disease, currently under treatment with L-thyroxine.

At the beginning of the disease, antihistamine treatment controlled the symptoms. Starting from the end of 2012, several frequent acute episodes occurred, almost monthly, with access to the emergency unit and systemic (i.v.) steroid treatment each time. Oral steroid treatment was started in April 2013, because antihistamines were ineffective. After some months, steroids were discontinued and the patient was treated with ciclosporin A (5 mg/kg/day) for 5 months with some beneficial effects. In January 2014, serum creatinine increased and ciclosporin was stopped. Three months later, steroid treatment was restarted because of recurrence of CSU. In January 2015, the patient had a spontaneous rib fracture and in April, he was referred to the diabetes center for the occasional finding of hyperglycemia.

In September 2015, after steroid suspension, he was first seen at our clinic with a UAS = 5 and UAS7 score = 35. The autologous serum and plasma skin tests were positive. Antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), protein electrophoresis, triptase, complete blood count, C3, C4 and C1 inhibitors were within normal values; CRP and D-dimer were slightly elevated. Monthly omalizumab 300 mg subcutaneous injections were started. After the third injection, urticaria disappeared nearly completely. The patient achieved total resolution of the

symptoms after 4 months, and the treatment was interrupted after the sixth injection. The patient was admitted to the emergency unit for urticaria/angioedema 30 days later, and i.v. steroids were administered. In the following days, the symptoms recurred and antihistamines were again ineffective. Two months after the last dose, a new course of omalizumab was started, with the patient showing $UAS=6$ and $UAS7$ score $=38$. Also on this occasion, prompt beneficial effects were evident with total disappearance of the urticarial lesions after the second injection. The treatment was suspended after 5 months, as recommended by the Italian Medicines Agency, but symptoms reappeared shortly as after the first course of treatment, and steroids were used. The following period of omalizumab treatment was similarly effective; 3 weeks after the last interruption the patient returned to our unit with acute urticaria with angioedema, and steroids, once again, were used.

Discussion

Although the effectiveness of omalizumab is well demonstrated, in chronic urticaria, its mechanism of action remains unclear and several hypotheses were suggested. The most recent studies have shown that a rapid response to omalizumab therapy in chronic urticaria is more likely to result from the elimination of an activating signal, in this case IgE, rather than from the generation of a negative inhibitory signal (5).

Omalizumab binds to circulating IgE, with reduction of IgE-mediated response (6–8).

Basopenia is often associated to CSU due to the migration of basophils from blood to skin, and omalizumab causes a reversion of basopenia with improvement of basophil IgE receptor function. Indeed, histamine increase in whole blood has been noted in omalizumab-treated patients compared to placebo in omalizumab trials (9), and the improvement in basopenia in active CSU is associated with reduced clinical symptoms, suggesting that basophil recruitment to the skin is directly related to CSU symptoms. Thus, omalizumab may reverse a mechanism that recruits basophils to the skin and suppresses their IgE receptor pathway.

The presence of autoantibodies against thyroid antigens, FcεRI, and IgE suggests that autoimmunity might contribute to the pathogenesis of chronic urticaria at least in a subset of patients (10–13).

Moreover, 40–45% of patients with CSU have IgG against FcεRI and/or IgE that causes subunit cross-link and leads to histamine release from basophils and mast cell degranulation (14). Omalizumab binds IgE and causes a loss of membrane-bound IgE with a subsequent reduction of FcεRI in skin mast cells, so rendering them less susceptible to activation by IgG–anti-IgE and IgG–anti-FcεRI (15).

Coagulation may play a role in the pathogenesis of CSU (16). Plasma markers of thrombin generation are elevated in patients with active CSU, and decrease during remission (17).

Currently, there is no identification of possible markers predicting a response to omalizumab in patients with CSU. However, patients with CSU show different patterns of response to omalizumab: quick versus slow remission and complete versus partial versus no remission. There are reports showing that high total IgE levels are linked to fast CSU relapse after cessation of omalizumab (18). Therefore, the assessment of pre- and post-treatment IgE levels may help to improve the management of CSU (18). In addition, both positive basophil histamine release assay and autologous serum skin test predict a slow response to

omalizumab, suggesting that this drug works via reducing FcεRI expression in these patients (19).

Omalizumab is effective in CSU and rapidly induces clinical remission in the majority of cases. A large double-blind, randomized, placebo-controlled trial showed that more than half of treated patients achieved a $UAS7 \leq 6$, and 34% of patients were completely symptom-free ($UAS7=0$) (20). However, symptoms usually recur 4–16 weeks after the treatment is discontinued in the majority of patients, although there are reports of longer times of remission in selected cases, sometimes for several months; only very few patients had an immediate and complete disappearance of symptoms after a single dose of omalizumab (21,22). Despite the ongoing follow-up of those patients, it is still unclear whether the remission has been spontaneous, as frequently observed in the natural course of urticaria, or whether the drug is particularly effective in selected patients.

Safety and efficacy of long-term use of omalizumab has been reported in several real-life studies (23–32).

Al-Ahmad described the clinical course of patients with severe recalcitrant chronic urticaria that was treated with omalizumab for periods up to 4 years (24). The improvement was maintained throughout 4th year of therapy and treatment was well tolerated.

Fiorino et al reported a similar long-term clinical course in a patient that was disease-free for 4 year under omalizumab treatment. No immediate or delayed side effects were ever noticed during the period when 49 injections were administered (25).

Clinical experience from more than 1250 injections in 51 patients over four years indicates that omalizumab is a rapidly acting, highly effective and safe drug in CU patients (26). In this retrospective analysis, in all patients with complete remission of symptoms, omalizumab was discontinued every 6–12 months to assess disease activity including time to relapse.

Another retrospective study from the United States, who use omalizumab in CU patient for longer than 1 year, suggested that periodic attempts at weaning patients with CU from omalizumab should be attempted because there could be a chance of spontaneous remission. However, restarting omalizumab after recurrence seems effective and safe (27).

Furthermore, many studies suggested how to manage a long-term omalizumab therapy for refractory chronic spontaneous urticaria (26–31).

Some authors considered reasonable to start with the lower dose (150 mg omalizumab every 4 weeks) and to increase the dose if patients do not respond. An alternative approach was to start with the higher dose, which was then reduced if appropriate.

For example, Ensina et al treated with omalizumab 47 CSU patients refractory to high-dose antihistamines. The average number of administrations was 11.4 (range 2–87). Complete response was seen in 84.6% of patients who started with 300 mg, and in 60% of those who started with 150 mg every 4 weeks and no severe adverse events were reported (28).

Dose intervals can also be adjusted, making them more frequent if urticaria activity increases just prior to the next administration, or extending the interval to achieve the minimum effective dosage in cases where complete remission is achieved.

This different step up/step down approach, with personalized doses regimen, were effective in long-term control of symptoms, avoiding the use of corticosteroids (31).

The randomized, double-blind XTEND-CIU (Xolair Treatment Efficacy of LoNger Duration in Chronic

Idiopathic Urticaria Study showed that continued treatment with omalizumab prevented relapse and improved quality of life.

Re-treatment, when needed, could be accomplished safely and effectively.

The study had two phases: an initial 24-week open-label period ($n=205$; all patients were given omalizumab 300 mg subcutaneously every 4 weeks), and a follow-on 24-week double-blind phase ($n=134$; patients were randomized to continue omalizumab or switch to placebo). Placebo treated patients experienced relapse more often (60.4%) than omalizumab-treated patients (21%).

The percentage of patients with clinical worsening 12 weeks after omalizumab discontinuation was similar whether the patient had discontinued after 24 weeks of treatment (placebo-treated patients) or 48 weeks of treatment (omalizumab-treated patients who completed 48 weeks of treatment; 23 of 53 [43.4%] vs 32 of 71 [45.1%], respectively; $p=1.00$). During the double-blind period, no new adverse events were identified, including no evidence of allergic reactions associated with stopping and restarting omalizumab (32).

No disease-modifying properties can be attributable to omalizumab, even when administered for prolonged treatment. At present, omalizumab can be considered a symptomatic treatment, as symptoms constantly recur within weeks or months. With this in mind, the recommendation of the IMA to limit the use of omalizumab to the moderate-severe resistant cases of spontaneous urticaria seems logical. However, the limitation to two courses of treatment (6 plus 5 months with two months' interval) appears not to be supported by scientific data. In fact, omalizumab is indicated for patients with spontaneous chronic urticaria resistant to antihistamine treatment and severe CSU needing steroid treatment. As in the patient presented in this report, when steroid treatment lasts for a long time the patient is most likely at risk of steroid-associated adverse events, such as fractures, hypertension, diabetes, gastrointestinal complications, pneumonia, urinary tract infection, cataract, myocardial infarction and stroke. In the present case, the patient had a spontaneous rib fracture and hyperglycemia. In a study on the cost of glucocorticoid-associated adverse events (GAE) in rheumatoid arthritis (33), the authors reported that in a six-month period of observation the above-mentioned diseases were significantly more frequent in glucocorticosteroid users than in nonusers. Furthermore, steroid users incurred significantly higher costs than nonusers for the treatment of glucocorticoid-associated adverse events, and in addition, users had higher mortality than nonusers. Physicians and policy makers should consider the potential costs of GAEs when deciding on the availability (and duration) of treatment options.

Our experience suggests that long-term use of omalizumab could be useful for patients that respond to treatment and recur after discontinuation. Dose and administration interval could be individualized in order to improve each patient response. Published evidences support this possibility and should be considered for changes in regulation.

Patient consent

The patients gave consent to the inclusion of material pertaining to himself into this article, he acknowledged he cannot be identified via the paper; the Authors fully anonymized patient's material.

Acknowledgements

Medical writing assistance of this paper was provided by Laura Brogelli, on behalf of Content Ed Net; this assistance was funded by Novartis.

Disclosure statement

The authors report no conflicts of interest.

Funding

This supplement was funded by Novartis.

References

1. Di Gioacchino M, Di Stefano F, Cavallucci E, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc.* 2003;24:285–290.
2. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of urticaria. *Allergy.* 2018;73:1393–1414.
3. Generali JA, Cada DJ. Montelukast: Chronic Urticaria. *Hosp Pharm.* 2015;50:583–585.
4. 21-8-2015 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA Serie generale - n. 193, Allegato 1.
5. Gericke J, Ohanyan T, Church MK, et al. Omalizumab may not inhibit mast cell and basophil activation in vitro. *J Eur Acad Dermatol Venereol.* 2015;29:1832–1836.
6. Kaplan AP, Gime nez-Arnaud AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. *Allergy.* 2017;72:519–533.
7. MacGlashan DW, Jr, Bochner BS, Adelman DC, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol.* 1997;158:1438–1445.
8. Metz M, Staubach P, Bauer A, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. *Theranostics.* 2017;7:1266–1276.
9. Saini SSRK, Hsieh HJ, Sterba PM, et al. Whole blood histamine concentration response to omalizumab in patients with chronic idiopathic/spontaneous urticaria: post hoc analysis of ASTERIA I, ASTERIA II and GLACIAL studies. *J Allergy Clin Immunol.* 2014;133:AB117.
10. Konstantinou GN, Asero R, Ferrer M, et al. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. *Allergy.* 2013;68:27–36.
11. Altrichter S, Peter HJ, Pisarevskaja D, et al. IgE mediated autoallergy against thyroid peroxidase – a novel pathomechanism of chronic spontaneous urticaria? *PLoS One.* 2011;6:e14794.
12. Marone G, Casolaro V, Paganelli R, et al. IgG anti-IgE from atopic dermatitis induces mediator release from basophils and mast cells. *J Invest Dermatol.* 1989;93:246–252.
13. Valenta R, Mittermann I, Werfel T, et al. Linking allergy to autoimmune disease. *Trends Immunol.* 2009;30:109–116.
14. Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest.* 1995;96:2606–2612.
15. Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol.* 2008;122:569–573.
16. Eggel A, Baravalle G, Hobi G, et al. Accelerated dissociation of IgE-FcεRI complexes by disruptive inhibitors actively

- desensitizes allergic effector cells. *J Allergy Clin Immunol*. 2014;133:1709–1719.
17. Takahagi S, Mihara S, Iwamoto K, et al. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. *Allergy*. 2010;65:649–656.
 18. Ertas R, Ozyurt K, Atasoy M, et al. The clinical response to omalizumab in CSU patients is linked to and predicted by IgE levels and their change. *Allergy*. 2018;73:705–712.
 19. Gericke J, Metz M, Ohanyan T, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2017;139:1059–1061.e1.
 20. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101–109.
 21. Asero R, Casalone R, Iemoli E. Extraordinary response to omalizumab in a child with severe chronic urticaria. *Eur Ann Allergy Clin Immunol*. 2014;46:41–42.
 22. Song CH, Stern S, Giruparajah M, et al. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2013;110:113–117.
 23. Silva PM, Costa AC, Mendes A, et al. Long-term efficacy of omalizumab in seven patients with treatment-resistant chronic spontaneous urticaria. *Allergol Immunopathol (Madr)*. 2015;43:168–173.
 24. Al-Ahmad M. Long-term efficacy of omalizumab in patients with treatment-resistant chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2015; 135:AB128.
 25. Fiorino I, Loconte F, Rucco AS, et al. Long-term treatment of refractory severe chronic urticaria by omalizumab: analysis of two cases. *Postep Derm Alergol*. 2014;XXXI:332–334.
 26. Metz M, Ohanyan T, Church MK, et al. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci*. 2014;73:57–62.
 27. Har D, Patel S, Khan DA, et al. Outcomes of using omalizumab for more than 1 year in refractory chronic urticaria. *Ann Allergy Asthma Immunol*. 2015;115:126–129.
 28. Ensina LF, Rodrigues S, Juliani AP, et al. Omalizumab in chronic spontaneous urticaria: a Brazilian real-life experience. *Int Arch Allergy Immunol*. 2016;169:121–124.
 29. Pinto Gouveia M, Gameiro A, Pinho A, et al. Long-term management of chronic spontaneous urticaria with omalizumab. *Clin Exp Dermatol*. 2017;42:735–742.
 30. Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014; 112:70e174.
 31. Ensina LF, de Lacerda AE, Machado LM, et al. Long-term omalizumab therapy for refractory chronic spontaneous urticaria: a real-life experience. *Ann Allergy Asthma Immunol*. 2015;115:536.
 32. Mauer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2018;141:1138–1139.e7.
 33. Pisu M, James N, Sampsel S, et al. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. *Rheumatology (Oxford)*. 2005;44:781–788.