

ORIGINAL PAPER

From regulatory limitations to new opportunities: Real-life experience on the effectiveness of short courses of omalizumab in the treatment of chronic idiopathic urticaria

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Abstract

Economic sustainability of long-term continuous treatment of antihistamine refractory chronic urticaria with omalizumab may be an issue. We assessed the efficacy of relatively short courses (5–6 months) of omalizumab in patients with chronic idiopathic urticaria (CIU). We retrospectively studied 40 patients (observed between June 2015 and January 2019) affected by moderate-to-severe CIU refractory to anti-H1 antihistamines (up to fourfold doses). Omalizumab was administered every 4 weeks for 24 weeks, then for 20 weeks in case of a relapse of moderate-to-severe degree, then again for 24 weeks in case of a second relapse. Monthly clinical evaluations were performed. Mean disease severity significantly dropped after 1 month and further decreased thereafter, with 30 complete remissions after the first course of treatment. In 2–4 months, 18 patients had a relapse of moderate-to-severe degree. The profile of response to the second course of omalizumab was similar to the first. A third course was necessary for seven patients. No adverse effects were recorded. Courses of 5–6 months of omalizumab may induce rapid significant improvement of urticaria and many prolonged complete remissions. In case of relapse, further courses show a similar profile of response and may induce additional long-term complete remissions.

KEYWORDS

chronic idiopathic urticaria, omalizumab, real life

1 | INTRODUCTION

Urticaria is a common disease characterized by wheals and/or angioedema. Causative factors are multiple and etiological diagnosis is difficult. This is particularly true for chronic urticaria, which often remains idiopathic despite accurate diagnostic workup and significantly impairs quality of life and psychological status of patients (Cappuccio et al., 2017; Foti, Antelmi, Mistrello, Guarneri, & Filotico, 2007; C. Guarneri et al., 2017; F. Guarneri, C. Guarneri, & Cannavò, 2014; F. Guarneri, C. Guarneri, & Marini, 2014; Marzano et al., 2015; Powell, 2015; Zuberbier, 2018).

Since etiological diagnosis and treatment are not always possible or may take a long time, symptom control strategies are important in the management of chronic urticaria (Marzano et al., 2015; Powell, 2015; Zuberbier, 2018). As first-line treatment, current international guidelines suggest second-generation H1-antihistamines, which can be up dosed up to fourfold higher than recommended doses. In case of insufficient disease control, the successive step is omalizumab (Zuberbier, 2018).

Biotechnological (or “biologic”) drugs are a large, heterogeneous class of pharmacological molecules. Biologic drugs are used for the treatment of several dermatological diseases, including psoriasis (Bartolotta et al., 2018; Conti et al., 2019; Di Lernia et al., 2018; F. Guarneri,

C. Guarneri, & Guarneri, 2007; C. Guarneri, Russo, Mazzeo, & Cannavò, 2014; Kaushik & Lebwohl, 2019; Kim & Lebwohl, 2019; Stiff, Glines, Porter, Cline, & Feldman, 2018), atopic dermatitis (Moyle, Cevikbas, Harden, & Guttman-Yassky, 2019; Seegräber, Srou, Walter, Knop, & Wollenberg, 2018), and urticaria (Ferrer & Madamba, 2017; Joshi & Khan, 2017).

Omalizumab is a humanized monoclonal antibody that selectively binds to human immunoglobulin E (European Medicines Agency, 2019). Efficacy and safety of omalizumab for the treatment of chronic spontaneous urticaria were assessed in three Phase III studies published between 2013 and 2015 (Kaplan et al., 2013; Maurer et al., 2013; Saini et al., 2015). However, actual efficacy and safety of drugs can be assessed only in postmarketing studies, on a much larger sample of population and in “real-life” conditions of use. A recent meta-analysis (Tharp et al., 2018) evaluated 67 “real-life” studies on omalizumab, and 6 more papers were published thereafter until March 16, 2019.

Literature does not specify time limits for continuous treatment with omalizumab. However, Italian regulations (Agenzia Italiana del Farmaco, 2015) allow reimbursement of costs by the National Health System only for courses of 5–6 months (which can be repeated after 2 months, in case of relapses of moderate-to-severe degree). This peculiar “real-life” condition is a limit, but also an opportunity to assess the clinical response obtained with a relatively short –compared with literature– course of treatment.

Few Italian studies exist on “real-life” use of omalizumab in chronic urticaria, and, with two exceptions, they describe populations of less than 20 patients. We present our experience on 40 patients treated in about 3.5 years in our clinic.

2 | METHODS

The study was performed at the Dermatology Unit of the University Hospital “Gaetano Martino” of Messina (Italy), upon authorization of the local Ethical Committee. The clinical files of patients treated with omalizumab between June 2015 and January 2019 for antihistamine refractory chronic idiopathic urticaria (CIU) were retrospectively examined.

Based on the literature and our experience (C. Guarneri et al., 2017; F. Guarneri, C. Guarneri, & Cannavò, 2014; Marzano et al., 2015; Powell, 2015; Zuberbier, 2018), all cases of noninducible chronic urticaria (duration: 6 or more weeks) underwent extensive laboratory workup (hematocrit, hemoglobin level, white blood cell count, differential blood cell count, total eosinophil count, liver and kidney function tests, erythrocyte sedimentation rate, antistreptolysin titer, thyroid function test, urinalysis, examination of stools for parasites and occult blood, and serum levels of C-reactive protein, glucose, proteins, complements, iron, ferritin, transferrin). When appropriate, patients were also checked with other specialists for autoimmune, rheumatological, endocrine, infectious, odontostomatologic, otorhinolaryngologic, gastroenterological, hematological, allergic, cardiovascular, respiratory, renal/urinary, and/or neuropsychiatric diseases, and additional laboratory/

instrumental tests suggested by these specialists were performed. Urticaria was classified as idiopathic when the above diagnostic procedures failed to identify known causes. Oral antihistamines (standard dose, then up dosing) and short courses of systemic glucocorticosteroids were used as first-line therapy (Zuberbier, 2018), and omalizumab was considered in case of inadequate disease control after 30 days. Because of Italian regulations (Agenzia Italiana del Farmaco, 2015), patients were considered eligible for treatment with omalizumab when, despite the use of antihistamines, their urticaria activity score (UAS) and UAS in the last 7 days (UAS7) were higher than 3 and 16, respectively. In line with these regulations, omalizumab was administered for 24 weeks (300 mg every 4 weeks). After this period, a second course of 20 weeks was prescribed in case of relapse, with the same eligibility criteria. When a further relapse occurred thereafter, treatment was started again, with another course of 24 weeks.

Sex, clinical history, age at first visit in our Unit, time of onset of urticaria, UAS7 at each administration of omalizumab, type and dose of other drugs used for urticaria before and during treatment with omalizumab, duration of relapse-free interval after each course of omalizumab, and need for additional courses of omalizumab were recorded. Mean, SD, minimum, maximum, and quartiles of quantitative data, and absolute and relative frequency of qualitative data were calculated. Groups were compared using Student's *t* test for quantitative variables with normal distribution, Mann–Whitney *U* test for quantitative variables without normal distribution, and chi-squared test for qualitative variables. In all tests, $p < .05$ was considered significant.

3 | RESULTS

In the study period, 40 patients (17 M, 23 F) with moderate-to-severe antihistamine refractory CIU underwent treatment with omalizumab in our Dermatology Unit. Their mean age was 51.33 ± 17.76 years (range 17–80, first quartile 42.75, median 52.5, third quartile 66.25), without significant differences between males and females (males 50 ± 17.26 years, females 52.3 ± 18.44 , $p = .69$). Age at the onset of urticaria was between 13 and 79 years (mean 42.96 ± 17.01), reported disease duration was 8.37 ± 10.80 years (range: 6 weeks to 40 years). Also for these parameters, differences between males and females were not significant ($p = .59$ and $.87$, respectively). Antihistamines used before treatment with omalizumab were in decreasing order of frequency, cetirizine (15 patients), bilastine (14 patients), rupatadine (6 patients), ebastine (3 patients), fexofenadine (2 patients), levocetirizine (1 patient), and unspecified (1 patient). All patients had used one type of antihistamine, except two of them, who had used cetirizine and fexofenadine. Thirty-three subjects had also undergone short courses of systemic glucocorticosteroids, namely, deflazacort (12 patients), methylprednisolone (9 patients), betamethasone (4 patients), prednisone (4 patients), and unspecified (4 patients).

The results of the first course of omalizumab are shown in Figure 1. Before treatment (T0), UAS7 was between 16 and 32 (mean 23 ± 4.2). Six patients (one with UAS7 = 32, two with UAS7 = 31, two with UAS7 = 29, and one with UAS7 = 28) also reported angioedema,

FIGURE 1 UAS7 score in the first course of treatment with omalizumab. Numbers in parentheses indicate the patients involved at each stage. T0–T5: doses of omalizumab, T6: follow-up at 1 month. UAS7, urticaria activity score in the last 7 days

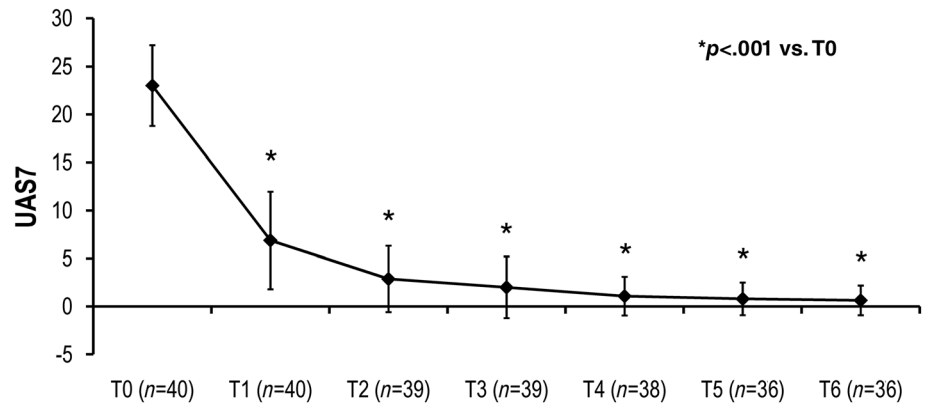
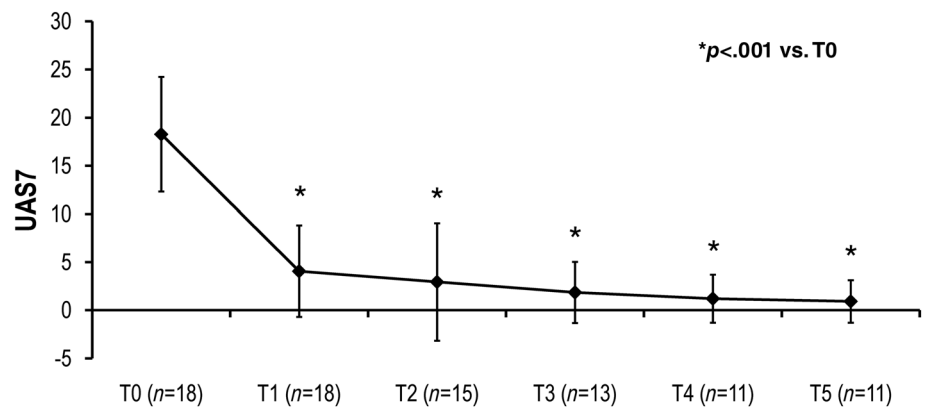


FIGURE 2 UAS7 score in the second course of treatment with omalizumab. Numbers in parentheses indicate the patients involved at each stage. T0–T5: doses of omalizumab, T6: follow-up at 1 month. UAS7, urticaria activity score in the last 7 days



on 2–7 days in the last week (mean 3.3 ± 1.5 days). A statistically significant clinical improvement was observed 4 weeks after the first administration of omalizumab (T1), when a mean UAS7 score of 6.88 ± 5.08 was recorded ($p < .001$), with a range of values between 0 and 18 and nine cases of complete remission. The mean number of days per week with angioedema decreased to 1.3 ± 1.0 (range 0–3). After 8 weeks, one woman who had achieved complete clearance of urticaria decided to stop treatment, against medical advice, and had no relapses thereafter (until the end of the study period). The remaining 39 patients experienced significant improvement at 8 weeks (mean UAS7 score 2.87 ± 3.46 , $p < .001$ vs. T1 and T0). Mean UAS7 further decreased, at a lower rate, in the subsequent 16 weeks. Three of these 39 patients decided to stop treatment before 24 weeks, against medical advice, because of complete remission: one of them stopped treatment after four doses, two after five doses. Two of these three patients had no relapses until the end of the study period, while one experienced a relapse of urticaria 2 months after drug withdrawal.

At the end of the first course of treatment, the mean UAS7 score of the remaining 36 patients was 0.64 ± 1.55 (range 0–7), with 30 cases of complete resolution. Compared to T0, UAS7 improved on average by 97.67%. One patient reported one episode of angioedema in the last week.

During treatment, progressive decrease of UAS7 was observed in 28 of the 36 patients, while the remaining 8 experienced temporary worsening after initial improvement. This happened after the third dose in four cases (in one patient UAS7 increased from 6 to 10, and in

the other three increased from 0 to 2, 3, and 7, respectively), after the fourth dose in one case (UAS7 increased from 3 to 4), and after the fifth dose in three cases (in one patient UAS7 increased from 4 to 7, and in the other two increased from 0 to 2 and 3, respectively). Seven of these eight patients had one episode of worsening, followed by decrease of UAS7, while one of them experienced an increase of UAS7 from 0 to 2 in two occasions, after the third and fifth doses.

After the first course of omalizumab (complete or voluntarily interrupted), 22 patients reported no relapse or few episodes of mild urticaria until the end of the study period. Conversely, 18 patients (including one who had voluntarily interrupted treatment before 24 weeks) had a relapse which required retreatment (UAS7 > 16), in a period between 2 and 4 months after last administration of omalizumab (mean 2.60 ± 0.68 months). Three of them (one with UAS7 = 29, two with UAS7 = 16) also reported angioedema, on 2–4 days in the last week (mean 2.7 ± 1.2 days). These 18 patients were not significantly different from the other 22 for sex (8 males and 10 females vs. 9 males and 10 females, $p = .82$), age (53.89 ± 14.45 vs. 49.23 ± 20.16 years, $p = .40$), age of onset of urticaria (43.78 ± 12.77 vs. 42.30 ± 20.11 years, $p = .78$), baseline UAS7 (23.11 ± 4.86 vs. 22.91 ± 3.69 , $p = .89$), UAS7 after 24 weeks of treatment with omalizumab (0.89 ± 2.00 vs. 0.32 ± 0.84 , $p = .27$), mean improvement from baseline at T1 ($73.96\% \pm 24.51\%$ vs. $67.86\% \pm 16.54\%$, $p = .37$) or after the entire course of omalizumab ($96.37\% \pm 8.10\%$ vs. $98.73\% \pm 3.30\%$, $p = .26$).

As shown in Figure 2, the mean UAS7 at the beginning of the second course of omalizumab was 18.28 ± 5.95 , significantly lower than

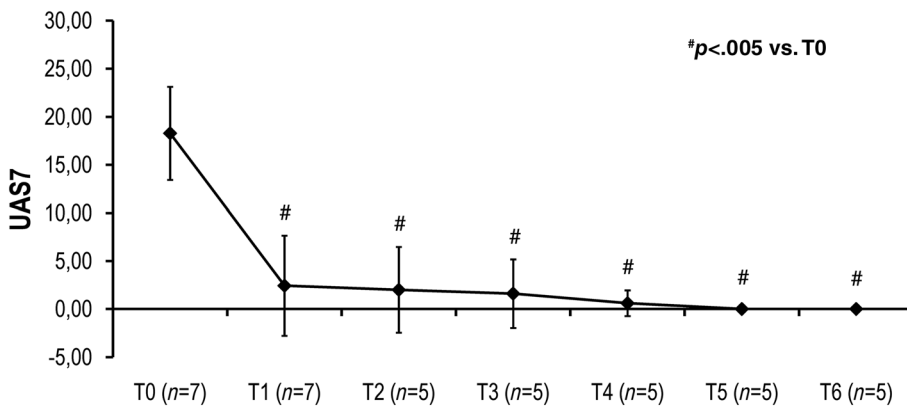


FIGURE 3 UAS7 score in the third course of treatment with omalizumab. Numbers in parentheses indicate the patients involved at each stage. T0-T5: doses of omalizumab, T6: follow up at 1 month. UAS7, urticaria activity score in the last 7 days

before the first course ($p = .007$). Also in this case, a significant decrease was observed after the first dose (eight patients with $\text{UAS7} = 0$, mean $\text{UAS7} 3.54 \pm 5.08$, $p < .001$), and further progressive improvement occurred with subsequent administrations. The 11 patients who completed the course of treatment achieved a final mean UAS7 of 0.91 ± 2.21 (nine complete remissions); none of them reported angioedema in the last week. One of the 18 patients was lost at follow-up after the second dose, when she had achieved a reduction of her UAS7 from 29 to 15 and remission of angioedema, while for 6 the second course of omalizumab was in progress at the end of the study period (January 2019). Two of these six patients had achieved a reduction of their UAS7 from 20 to 10 and from 15 to 3, respectively, after first dose, while two had achieved a reduction of their UAS7 from 22 to 3 and from 15 to 0, respectively, after three doses. The two remaining patients had received four doses of omalizumab, with improvement in one case (UAS7 from 21 to 2) and no variation of the initial UAS7 of 7 in the other. Progressive decrease of UAS7 was observed in 9 of the 11 patients who completed the second course of omalizumab. In one of the other two cases, UAS7 decreased from 29 (baseline) to 7 after the first dose, raised to 23 after the second dose, then progressively decreased to a final score of 3 at the end of the course. In the other case, UAS7 decreased from 21 to 0 after 4 weeks of treatment, then raised to 7 after 2 months and did not change until the end of the course.

Seven patients who had achieved complete remission with the second course of omalizumab experienced another relapse of moderate-to-severe urticaria ($\text{UAS7} > 16$) after 2–3 months (mean time: 2.50 ± 0.50 months). Two of them, with $\text{UAS} = 17$, also reported angioedema on 2 days in the last week. These 7 patients and the rest of the study population did not differ significantly for sex (3 males and 4 females vs 14 males and 19 females, $p = .98$), age (55.71 ± 11.80 vs. 50.39 ± 18.79 years, $p = .35$), age of onset of urticaria (49 ± 11.78 vs. 41.68 ± 17.81 years, $p = .20$), baseline UAS7 (23 ± 5.89 vs. 23 ± 3.87 , $p = 1$), UAS7 after the first course of treatment with omalizumab (1 ± 1.91 vs. 0.55 ± 1.48 , $p = .58$), mean improvement from baseline at T1 ($74.02 \pm 23.29\%$ vs. $69.88 \pm 20.13\%$, $p = .67$) or after the entire first course of omalizumab ($95.93 \pm 7.38\%$ vs. $98.04 \pm 5.72\%$, $p = .50$).

The response of these seven patients to the third course of omalizumab is shown in Figure 3. Initial mean UAS7 score was 18.29 ± 4.86 . As of January 2019 (end of study period), five patients had

completed this course, achieving complete remission of urticaria. One of them had experienced temporary worsening during both previous courses, but this was not observed in the third. Worsening after three doses (UAS7 increased from 0 after first and second doses to 8 after third dose), followed by progressive improvement, was instead observed in another of these five patients, who had never shown such behavior previously.

Of the two patients who did not complete the third course of omalizumab, one had decided, against medical advice, to stop treatment after achieving complete remission of urticaria and angioedema in 8 weeks, while the other had received a single dose within the time limits of the study period, achieving a decrease of UAS7 from 16 to 0 and remission of angioedema. As of January 2019, the five patients who completed the third course and the one who decided to stop it before completion have been in clinical remission for 1–5 months (mean 3.5 ± 1.74).

4 | DISCUSSION

Our data confirmed the good efficacy of omalizumab observed in Phase III studies (Kaplan et al., 2013; Maurer et al., 2013; Saini et al., 2015). Among our 40 patients, nine (22.5%) achieved complete remission and 19 (47.5%) good disease control ($\text{UAS7} \leq 6$) within 4 weeks after the first dose of omalizumab, in line with literature (Kaplan et al., 2016). However, improvements were rather fast not only for these “early responders”: 16 patients achieved complete remission after 8 weeks (two doses) and 22 after 12 weeks (three doses), while those who achieved good disease control ($\text{UAS7} \leq 6$) were the vast majority of our study population (35/40, 87.5%) already after 8 weeks (two doses). For the 29 patients who achieved complete remission at the end of the first course of treatment, the mean time to obtain such result was 11.31 weeks, while for the 35 patients who completed the first course with a UAS7 score of 6 or less, the mean time to achieve that result was 6.74 weeks.

Noteworthy, and not often considered in previous studies, is the duration of the results achieved at the end of the first course of therapy, a course which is relatively short (6 months) compared with those reported in the majority of literature. More than half of our patients (22/40, 55%), who had achieved complete or, in three cases, almost

complete (UAS7 = 2–3) control of the disease, maintained their results and did not require further administration of omalizumab until the end of the study period (mean disease-free time 12.19 ± 9.56 months, range 2–38). To the best of our knowledge, the time limit of 6 months for continuous treatment with omalizumab is defined only in Italian regulations. Thus, our data can be compared with those of studies performed by Italian authors (Bongiorno et al., 2016; Damiani et al., 2019; Mandel et al., 2018; Nettis, 2018; Romano et al., 2015). Romano et al. reported a higher rate of complete resolution than in our study, but in a smaller population (6/9 patients, 67%), while Bongiorno et al. reported, in a group of 18 patients, a 35.7% rate of complete resolution, followed by relapse within 1–4 months in all cases. The same number of patients ($n = 18$) was studied by Mandel et al., who recorded 10 complete resolutions (58.8%) and recurrence in three cases, after 4, 5, and 7 months, respectively. In this study, the mean follow-up period was 9.5 months (range 1–28). Nettis et al. reported a 67.8% rate of complete resolution in patients younger than 65 years and 56.7% in patients aged 65 years or more (322 in total), and 173 patients (104 aged less than 65 years and 15 aged 65 years or older) did not need a second course of treatment with omalizumab. Finally, Damiani et al. observed complete resolution in a percentage of patients similar to ours, but subjects who did not need a second course of omalizumab were 25 in a study population of 127 (15/88 when considering only those with chronic spontaneous urticaria). The reasons of the above differences are unknown. However, variability could be due, at least in part, to enrolment criteria: some authors studied CIU patients, while others included all types of spontaneous urticaria and even inducible urticaria, because omalizumab showed efficacy also in these forms of the disease (Arasi et al., 2015; Bongiorno et al., 2016; Damiani et al., 2019; Kaplan et al., 2016; Mandel et al., 2018; Nettis, 2018; Romano et al., 2015; Tharp et al., 2018).

In our study, in line with the literature (Damiani et al., 2019; Mandel et al., 2018; Nettis, 2018), clinical responses to the first, second, and third courses of omalizumab were similar. This characteristic is important because some patients are subject to relapses of moderate-to-severe degree after a course of treatment (mean disease-free interval is about 2.5 months) and need periodic retreatment. Gradual increase of the interval between injections and/or tapering of treatment after remission are interesting possibilities suggested by some authors (de Montjoye et al., 2018; Sussman et al., 2014; Vadasz, 2017), and further clinical research appears warranted to assess their possible usefulness in inducing longer and more stable remission of urticaria in these patients.

As for safety, no local or systemic adverse reaction occurred in our population during the treatment with omalizumab. This is in line with the literature, which reports that a minority of patients experiences adverse effects, usually mild (mainly local reactions at the site of injection).

In conclusion, our data confirm that omalizumab is an effective and safe treatment for antihistamine refractory CIU, and is able to induce rapid significant improvements and, in many cases, prolonged disease remission after a course of 5–6 months of treatment, a period remarkably shorter than those considered by the majority of authors.

Further courses of omalizumab, which may be administered in case of relapses, show a similar profile of response, and may induce prolonged complete remission in some cases. Upon confirmation on a larger scale, these findings could help to optimize the cost-benefit ratio in the use of omalizumab for the treatment of CIU.

CONFLICT OF INTERESTS

Valeria Papaiani received consulting fees from Novartis. Claudio Guarneri received grants, consulting fees, fees for participation in data monitoring boards, and payment for lectures from Novartis. Serafinella Patrizia Cannavò received consulting fees, support for travel to meetings, and payments for lectures from Novartis. The other authors have no conflict of interest to disclose.

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