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Omalizumab in Chronic Urticaria: An Italian Survey

Giovanni Damiani^{a-c} Marco Diani^b Rosalynn R.Z. Conic^c Laura Colli^b
Silvia Ferrucci^c Emanuela Martina^d Anna Maria Offidani^d
Paolo Daniele Maria Pigatto^b

^aYoung Dermatologists Italian Network (YDIN), GISED, Bergamo, Italy; ^bClinical Dermatology, IRCCS Istituto Ortopedico Galeazzi, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; ^cDepartment of Dermatology, Case Western Reserve University, Cleveland, OH, USA; ^dDepartment of Clinical and Molecular Sciences – Dermatological Clinic, Università Politecnica delle Marche, Ancona, Italy

Keywords

Omalizumab · Chronic urticaria · Chronic spontaneous urticaria · Chronic inducible urticaria · Real-life prospective observational study

Abstract

Omalizumab is approved for use in chronic spontaneous urticaria (CSU); however, it is not approved for chronic inducible urticaria (CIndU). The aim of the present study was to assess the effectiveness of omalizumab in treating CSU and CIndU in Italy. This is a multicentre prospective observational real-life study involving patients with severe urticaria capable of undergoing omalizumab therapy. We enrolled 127 patients (59.1% females), ranging in age from 15 to 83 years, 69.3% had CSU alone, 26.8% had CSU and CIndU, and 3.9% had only CIndU (30.8% delayed pressure, 35.9% dermographic, 15.3% cholinergic, 12.8% cold, 5.1% aquagenic). After the first cycle of omalizumab (300 mg every 4 weeks for 24 weeks), 16 CSU patients and 10 patients (20.5%) with CIndU with or without

CSU did not require a second cycle of omalizumab (300 mg every 4 weeks for 20 weeks). The patient with aquagenic urticaria achieved remission after the first cycle. None showed a lack of response to the second cycle of omalizumab. Omalizumab is a promising drug for both spontaneous and inducible chronic urticaria. Current evidence indicates that omalizumab may be approved also for CIndU.

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Introduction

Chronic urticaria (CU) represents a complex clinical pathological entity consisting of chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) [1]. Despite the common manifestations including itch, wheals and/or angioedema that last for more than 6

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Table 1. Clinical and demographic characteristics of the enrolled sample of patients

Characteristics	Patients (n = 127)
Gender, M/F (%)	52/75 (40.9/59.1)
Age (mean ± SD), years	50.8±16.5
Disease duration (mean ± SD), months	52±65.7
Different therapies than H ₁ antihistamines	
Short-course corticosteroids, n (%)	79 (62.2)
Montelukast, n (%)	23 (18.1)
Cyclosporine, n (%)	17 (13.4)
Others (azathioprine or dapsone), n (%)	7 (5.5)
Clinical phenotype	
CSU, n (%)	88 (69.3)
CIndU, n (%)	5 (3.9)
CSU and CIndU, n (%)	34 (26.8)
CIndU phenotypes	Patients (n = 39)
Delayed pressure, n (%)	12 (30.8)
Dermographic, n (%)	14 (35.9)
Cholinergic, n (%)	6 (15.3)
Cold, n (%)	5 (12.8)
Aquagenic, n (%)	2 (5.1)

SD, standard deviation; CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria.

weeks, these entities are triggered by different stimuli and display different pathogenic mechanisms [1]. Furthermore, CIndU has been demonstrated to be a predictor of severe CSU [2].

The treatment guidelines for chronic urticaria start with H₁ antihistamines, which can be increased up to fourfold the standard dosage [3]. However, some patients do not respond, requiring additional therapy [3].

Nowadays, omalizumab, a humanized IgG1 monoclonal antibody, is considered to be the gold standard in anti-histamine-resistant patients with urticaria. However, while omalizumab has been approved for treating patients with CSU, the use for CIndU remains nonapproved. To date, the majority of evidence for omalizumab use in CIndU stems from case reports and case studies, with only three phase II studies; however, evidence for therapeutic efficacy and safety has been promising [4–6].

Furthermore, despite one decade of experience in managing eosinophilic asthma with omalizumab, its application for urticaria has started only recently. This real-life prospective observational study was designated in order to evaluate the efficacy of omalizumab in a multicentre cohort of patients seen at the dermatology-allergy outpatient clinic.

Materials and Methods

This is a multicentre prospective observational real-life study involving patients with severe urticaria, who fulfil the criteria for omalizumab use, and are seen at one of the three university centres (Galeazzi Hospital in Milan, Policlinico in Milan and Department of Dermatology in Ancona). The current dosage criteria for omalizumab in Italy is 300 mg subcutaneously every 4 weeks in patients who (1) are aged >12 years, (2) have a urticarial activity score (UAS) of >3 or a UAS7 (urticarial activity score over 7 days) >16, and (3) are unresponsive to a 4 times increased dosage of antihistamines [7, 8]. The treatment is administered over two cycles; the first one is 24 weeks, followed by an 8-week “wait and see” period, after which the second cycle is administered for 20 weeks [8]. Additional treatment cycles are considered not approved use, in apparent contradiction with the chronic behaviour of CU. CIndU patients previously unresponsive to the approved treatments were shifted to the not approved use of omalizumab. Patients with a history of urticaria longer than 6 weeks and unresponsive to antihistamines from September 2015 to June 2017 were recruited. All patients kept an electronic diary using the Urticaria app (Version 1.3, Novartis Farma S.p.a.) in order to homogenize recorded items, namely age, gender, UAS7, Dermatologic Quality of Life index, wheels location and number [9]. The UAS7 score was used to categorize patients into four groups: urticaria-free (UAS = 0, complete response), well controlled disease (UAS7 = 1–6 points; optimal response), mild urticaria (UAS7 = 7–15 points; partial response), moderate and severe urticaria (UAS7 = 16–27 and >27 points; non-response).

Results

We enrolled 127 patients (59.1% females), ranging in age from 15 to 83 years (Table 1). The mean duration of disease was 52 ± 65.7 months (range 6–540), and urticaria was present in 96% of our patient cohort for more than 1 year, and more than 5 years in 53% of the cases. Our sample was characterized by 69.3% CSU alone, 26.8% CSU and CIndU, and 3.9% only CIndU. In detail, CIndU patients were divided into 30.8% delayed pressure, 3.9% dermatographic, 15.3% cholinergic, 12.8% cold, and 5.1% aquagenic. Atopy as presence of atopic dermatitis, allergic asthma or allergic rhinitis or constitutional eczema was found in 22.8% of patients. Autologous serum skin test and autologous plasma skin test were positive in 28.3%. Furthermore, antithyroid peroxidase antibodies were present in 14.2% of patients. In addition to H₁ antihistamines, 62% of our cohort previously used short course corticosteroids, 18.1% montelukast, 13.4% cyclosporine, and 5.5% others. All CU patients displayed a UAS7 of more than 27 before starting the omalizumab therapy. Among all CU patients, 8.7% had a UAS7 of >27, 19.7% 16–27, 29.1% 7–15, 26% 1–6, and 16.5% 0 points

Fig. 1. Evaluation of UAS7 during the first and second cycles of omalizumab in patients with chronic urticaria (CSU and CIndU). %, percentage of patients that have the specified score.

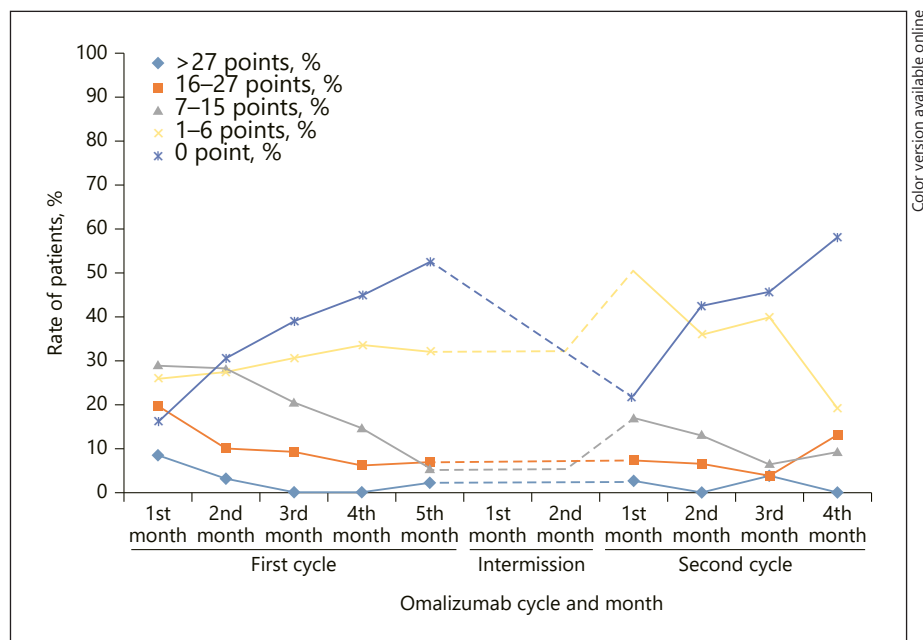
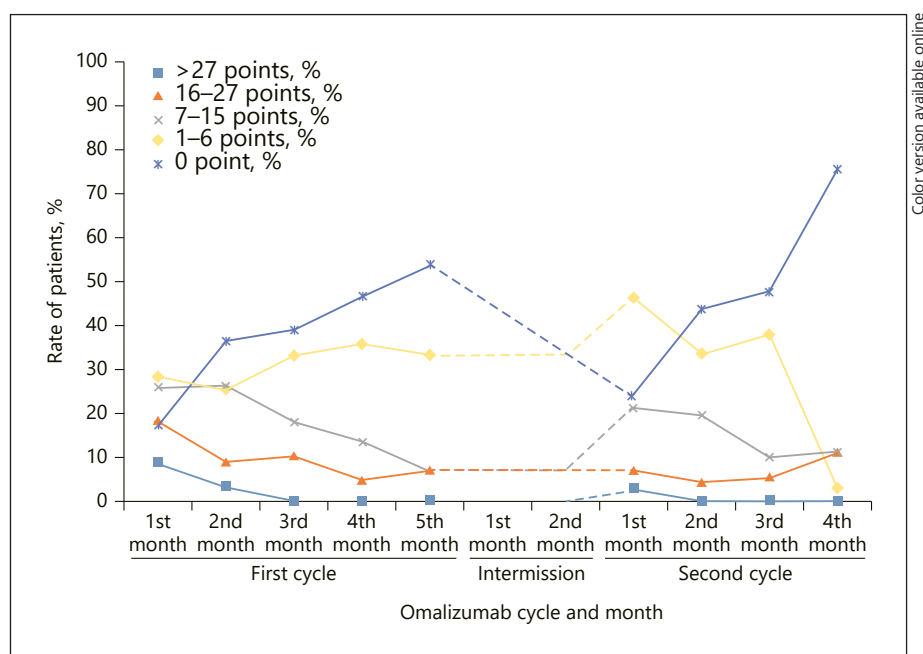


Fig. 2. Evaluation of UAS7 during the first and second cycles of omalizumab in patients with chronic spontaneous urticarial (CSU). %, percentage of patients that have the specified score.



after the first months of therapy (Fig. 1). A second cycle of omalizumab was not needed in 25 patients (Fig. 1). Furthermore, 77.1% of CU patients who underwent a second cycle of therapy achieved optimal (UAS7 = 1–6) or complete response (Fig. 1).

Of those with CSU, 86.4% of patients experienced optimal response (UAS7 = 1–6), or complete response, and

after the second cycle only 18.4% had mild or moderate urticaria (Fig. 2). Notably after the first cycle, 15 CSU patients did not require further omalizumab treatment (Fig. 2).

Regarding patients with CIndU, 82% obtained optimal (UAS7 = 1–6) or complete response after the first cycle of omalizumab and 10 patients did not require another cycle

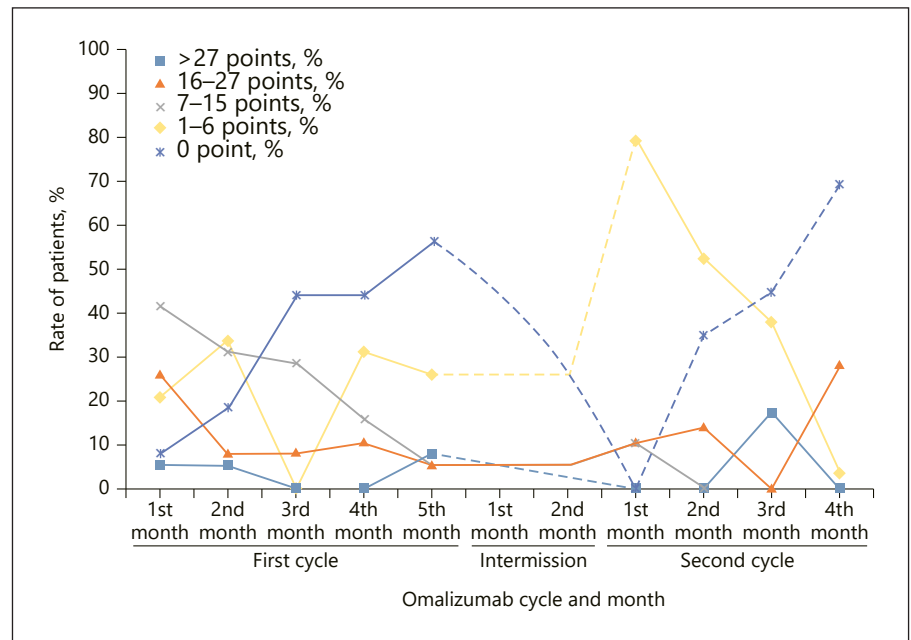


Fig. 3. Evaluation of UAS7 in the first and second cycles in patients with chronic inducible urticarial (CIndU). %, percentage of patients that have the specified score.

(Fig. 3). Remarkably, among these 10 patients was a patient with aquagenic urticaria. After the second cycle 72.4% of the remaining patients obtained an optimal (UAS7 = 1–6) or complete response (Fig. 3).

Discussion

Omalizumab has previously been proven safe and efficacious in CSU [10], and our data replicate prior findings. Despite the fact that omalizumab is used off label for CIndU, there are several case reports and trials that demonstrate its therapeutic efficacy [11]. In this study, we observed that, after the first cycle, 10 patients with CIndU did not require a second cycle of omalizumab. Since the first reported case of efficacy in CIndU, omalizumab was regarded as a possible therapeutic solution in inducible urticaria [12]. Furthermore, prior evidence for the use of omalizumab in CIndU which consisted mostly of small case series, also demonstrated a safe and effective profile [11]. Recently, Maurer et al. [11] reviewed omalizumab use for CIndU and found limited evidence for use in cold urticaria, symptomatic dermographism and solar urticaria. Little evidence is present in regard to aquagenic and vibratory urticaria. Interestingly, in our sample both patients with aquagenic urticaria responded to omalizumab. Another necessary pitfall for evaluating evidence for omalizumab use in CIndU patients were heterogeneous

dosages, which did not allow a precise comparison of clinical responses [11]. The rapid response to omalizumab in CIndU patients was in line with the literature and during the second cycle all patients achieved a complete response [11]. In the literature, the co-occurrence of CIndU and CSU is attested from 4 to 76% [13] and is currently interpreted as a negative prognostic factor of severe urticaria [7, 14]. Current evidence highlights that (a) upon interrupting omalizumab therapy after the end of the cycles a significant number of patients re-experienced urticaria, (b) urticaria is an umbrella term that encloses several clinical entities with different pathogeneses, (c) omalizumab is an effective drug for controlling CIndU with or without CSU, and (d) aquagenic urticaria may benefit from omalizumab.

Our results suggest that the treatment of CSU in patients with inducible urticaria can improve the response of CIndU and can lead to remission of both diseases. Additionally, we observed remission in 10 CIndU patients (62, 5%) with or without CSU (only 2 patients have isolated dermographic urticaria). In conclusion, our sample displayed a safe and effective profile in patients with chronic urticaria, and no debilitating side effects occur during the observation period. In combination with prior studies and current evidence, the authors suggest treating patients with CU, both CSU and CIndU, continuously with omalizumab; however, further studies are mandatory to optimize evidence.

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committees on human research. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.D. wrote the manuscript; G.D., M.D., E.M., and S.F. collected data; A.M.O. analysed data; P.D.M.P. corrected the English, organized and planned the entire study.

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