Introduction

Chronic urticaria (CU) is a dermatological disease characterized by the rapid appearance of itchy hives, angioedema or both, lasting for 6 weeks or more [1]. Approximately 0.5–1% of the general population suffers from CU and over 60% of cases are classified as chronic spontaneous (previously termed idiopathic) urticaria (CSU), for which no obvious triggers can be identified [2,3]. The average duration of CSU is generally up to 5 years, although more severe cases can last considerably longer [2,4]. The EAACI/GA2/LEN/EDF/WAO urticaria guidelines suggest using daily non-sedating (second generation) H1-antihistamines as first-line treatment [1]. As second-line therapy, an increase up to four times the licensed antihistamine dose may be beneficial, but around 45% of patients fail to respond [5]. For these cases, omalizumab is recommended as add-on therapy, as third-line treatment option.

Omalizumab is a humanized monoclonal antibody recognizing the Fc portion of the immunoglobulin E (IgE) molecule. It is thought to reduce IgE- and FcεRI-mediated mast cell and basophil activation [6,7], with a similar outcome on both mast cells and basophils. Launched around 20 years ago to treat patients with severe asthma non responsive to standard treatment it is currently used in several other allergic conditions includingrefractory CSU since 2013, displaying high efficacy and safety, especially when compared to first- and second-line therapies.

Since then, a number of studies have been published, especially in real-life settings, aimed at finding the best strategy to administer omalizumab to optimize the treatment outcome.

According to the review by Tonacci et al. [8], omalizumab 300 mg administered every 4 weeks appears to be the most effective and safe dose for the treatment of CSU, showing rapid response time. This approach displays minor adverse effects, and appears to be safe also when administered to pregnant women and their offspring. However, after the discontinuation of the drug, relapses may occur, with urticaria activity scores (UAS7) returning to pre-treatment levels in some cases,

along with a poorer quality of life . In such cases, retreatment is advisable in order to increase patients' quality of life. Nevertheless, it is not clear which strategies in terms of dose and/or timing of omalizumab administration are the best to achieve good retreatment response. Within this framework, a literature review on studies about retreatment with omalizumab in CSU was carried out and results are presented and critically discussed in the present article.

Materials and Methods

We performed a literature search in PubMed until January 2020 by using logical combinations of the following terms: 'urticaria, chronic', 'urticaria, idiopathic', 'urticaria, chronic spontaneous', 'omalizumab', 'anti-IgE' and 'retreatment'. We included reports of original data, including double blind placebo-controlled, randomized controlled trials (DBPC-RCT), RCTs, open controlled trials, observational studies, and retrospective trials. We excluded: (1) case reports, systematic reviews, review articles, meta-analyses, as well as papers not published in English language.

Results

According to the inclusion and exclusion criteria mentioned above, a handful of studies were retrieved. Overall literature search results are displayed in Table 1.

Study	No. of patients	Treatment	Retreatment	Results
Metz et al., 2014 [9]	25 patients with CSU and/or CIndU (aged 18-74 years; 18 women)	150 to 600 mg/month subcutaneously in 2- to 4-week intervals	Retreatment initiated after the recurrence of symptoms. All patients received the same dose of omalizumab in the same interval as the last successful treatment before discontinuation	Rapid and complete response after the first injection within the first 4 weeks of retreatment for all patients
Mandel et al., 2018 [10]	18 patients with refractory CSU (aged 25–74 years; 14 women)	300 mg every 4 weeks for 6 months	3 patients retreated with the same treatment as the initial one	Complete response (UAS7 = 0) within 16 weeks; good response (UAS7 ≤ 6) within one week
Nettis et al., 2018 [11]	31 patients with refractory CSU (mean age: 48.1 ± 13.4; 22 women)	300 mg every 4 weeks for 24 weeks subcutaneously (first treatment course)	Retreatment (second and third treatment course) at least 8 weeks after the end of the previous course	First course: complete response for all patients, relapse within 5-20 weeks. Second course: complete response in 93.5% of patients. Symptoms remission within 5-16 weeks after their last injection. Third course: complete remission in 93.8%. ≥ 8 weeks after the administration of the last dose, 68.7% had relapse of CSU. Complete therapeutic response in 4.9 weeks (first course), 3.8 weeks (second course), 1.8 weeks (third course)
Nettis et al., 2018 [12]	24 patients with refractory CSU (mean age: 48.0 ± 13.7; 14 women)	300 mg every 4 weeks for 24 weeks (first treatment course)	300 mg every 4 weeks for 24 weeks (second course) after 8–16-week follow-up	First course: good efficacy; relapse within 9-19 weeks. Similar efficacy during re-treatment, with slightly lower efficacy compared to the first course
Türk et al., 2018 [13]	25 patients with CSU	300 mg/4 weeks for at least 3 months	In all patients with complete or partial response:	58% had complete response at the end of treatment. At the

	(age: 31-49; 18 women)		discontinuation of omalizumab after 6 months; retreatment at the same initial dose if the recurred disease couldn't be controlled with concomitant medications	3rd month, 32% had complete response. Eleven patients experienced relapse, omalizumab was restarted in 10 of them. After the re-initiation of omalizumab, 5 had complete response and 5 had partial response. Seven patients achieved remission after discontinuation. Time from the last omalizumab dose was 8 weeks / 18 months
Matucci et al., 2019 [14]	30 patients with CSU (age: 20-70; 22 women)	300 mg/4-week intervals for 6 administrations	Retreatment with the same protocol in relapsing patients; in case of a second relapse, a third treatment was performed	Cycle 1: After 6 months, 83.4% were responders, 13.3% partial responders, 3.3% did not respond. Time to achieve a partial or complete response: 5.8 ± 1 weeks. 79.1% relapsed within 12.5 ± 4.0 weeks. Cycle 2: 14/15 improved their symptoms (57.1% complete remission). Mean response time: 5.0 ± 1.3 vs 6.1 ± 1.4 weeks (first cycle). 53.8% relapsed. Cycle 3: 7/7 had complete remission
Vollono et al., 2019 [15]	32 patients with CSU (age: 27-72; 22 women)	Subcutaneous 300 mg/ 4 weeks as add-on to H1-antihistamines for 6 months	300 mg every 4 weeks for 5 months in case of recurrence in an 8-week treatment interruption	13 patients completed 2 cycles of treatment, 10 patients had completed 1 cycle of treatment, 8 patients had undergone 1/2 cycle of treatment. Mild, transient local skin immediate reactions observed in one patient. 20 patients added second-generation H1-antihistamines due to persistence of pruritus and wheals after 2–4 weeks of treatment with omalizumab monotherapy.

Table 1. Studies retrieved in the literature search.

The works retrieved included a relatively low number of patients, mostly women, and were all concordant in stating that the first subcutaneous dose of omalizumab should be 300 mg

administered every 4 weeks, with the exception of Metz et al.[9], where the initial dose and administration interval differed according to the dose and interval used to obtain a remission during the first treatment course.

Where information on dosage was available, retreatment was carried out with the same dose of omalizumab administered during the previous round. Overall, retreatment with omalizumab was safe and effective in nearly all cases, with minor side effects reported, including mild, transient local immediate skin reactions [15]. Furthermore, the time to achieve complete remission decreased with subsequent treatment cycles. As observed by Nettis et al. [11], patients showed an average complete remission after 4.9 weeks during the first treatment course, dropping to 3.8 and 1.8 on the second and third retreatment courses, respectively, hence demonstrating an increased rapidity of response to treatment after multiple cycles.

Another important strategy to consider is how to choose the best timing for retreatment. From our review it is difficult to draw definite conclusions, since all the studies adopted different timing protocols and all of them obtained satisfying results. However, both the studies by Metz et al. [9], where the timing was adapted according to the occurrence of relapses, and Nettis et al. [11], where omalizumab was administered at least 8 weeks after the end of the previous course, achieved optimal results.

Conclusions

The present review confirms the optimal efficacy and safety of omalizumab to treat refractory CSU in most cases. Overall, retreatment seems to provide the best results in terms of efficacy using the same dose as in the first cycle, usually 300 mg injected subcutaneously every 4 weeks. In any case, the interval between two subsequent treatment courses should be controlled and not exceed 8 weeks, to avoid delayed efficacy.

Future studies should address retreatment efficacy on larger samples, also trying to reduce the current gender bias by including more male subjects with CSU treated with omalizumab..

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Omalizumab retreatment in patients with chronic spontaneous urticaria: a systematic review of published evidence

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Key words: Chronic urticaria, Omalizumab, retreatment, therapy.

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ABSTRACT

A systematic review of the current literature on retreatment with omalizumab of patients with relapsing chronic spontaneous urticaria was performed. Published evidence shows that retreatment is safe and clinically effective, and that time to complete clinical response reduces as the number of retreatments increases.

Introduction

Chronic urticaria (CU) is a dermatological disease characterized by the rapid appearance of itchy hives, angioedema or both, lasting for 6 weeks or more [1]. Approximately 0.5–1% of the general population suffers from CU and over 60% of cases are classified as chronic spontaneous (previously termed idiopathic) urticaria (CSU), for which no obvious triggers can be identified [2,3]. The average duration of CSU is generally up to 5 years, although more severe cases can last considerably longer [2,4]. The EAACI/GA2/LEN/EDF/WAO urticaria guidelines suggest using daily non-sedating (second generation) H1-antihistamines as first-line treatment [1]. As second-line therapy, an increase up to four times the licensed antihistamine dose may be beneficial, but around 45% of patients fail to respond [5]. For these cases, omalizumab is recommended as add-on therapy, as third-line treatment option.

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