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Remission of chronic urticaria in patients treated with omalizumab

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Abstract

Introduction: This study examined the remission probability and duration in chronic spontaneous urticaria (CSU) patients resistant to second-generation H1-antihistamines (sgAHs) undergoing omalizumab treatment.
Methods: This is a retrospective observational study of 176 adult CSU patients exhibiting a significant pruritus component (≥ 8) of the weekly urticaria activity score (UAS7) despite four daily sgAH tablets and starting omalizumab treatment with 300 mg every 4 weeks. After excluding 13 nonresponders, we analyzed 163 omalizumab responders (mean age 51.8 years, 74.4% female). The intervals between applications were increased. Discontinuation was considered for patients that remained asymptomatic on a gradually reduced dosage (to 150 mg every 12 weeks) without sgAHs.
Results: Omalizumab discontinuation was possible in 25.8% (42/163). The duration of omalizumab treatment before remission ranged from 7 to 63 months. Twenty-one patients (50.0%) maintained complete remission until the end of the observation period (September 2021) for 8 to 68 months. Of the relapsed patients, 71.4% (15/21) effectively controlled CSU with sgAHs. Six patients (28.6%; 6/21) required omalizumab reintroduction after 6 to 40 months of remission, responding favorably.
Conclusions: The study shows that a quarter of severe CSU patients achieve long-term remission. In addition, sgAHs effectively manage symptoms in a majority of relapsed cases, and those requiring omalizumab reintroduction respond favorably.

Keywords: urticaria, antihistamines, omalizumab, urticaria remission, urticaria relapse

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Introduction

Chronic spontaneous urticaria (CSU) is characterized by the occurrence of itchy wheals, angioedema, or both, without identifiable triggers, persisting for at least 6 weeks (1). It usually occurs in the form of relapses and remissions. The more severe the disease, the lower the likelihood of its remission (2–4). CSU may significantly impair the quality of life (5). Disease activity is measured with the urticaria activity score (UAS). Daily UAS values can range from 0 to 6 points, depending on the number of wheals (0 to 3) and the intensity of pruritus (0 to 3) (5, 6). Treatment is aimed at complete control of the signs and symptoms (1). The primary medications are second-generation H1-antihistamines (sgAH), which are taken regularly in a dose of one to four tablets per day. Omalizumab is commonly used to treat patients with sgAH-resistant CSU. It is an anti-IgE humanized monoclonal antibody that lowers the concentration of free IgE and downregulates high-affinity receptors for IgE (FcεRI) on mast cells and basophils, preventing their degranulation (7). Omalizumab treatment is symptomatic and has no effect on the natural course of CSU (8). We aimed to observe the probability of disease remission in patients with sgAH-resistant CSU and its duration after discontinuation of omalizumab.

Methods

This was a retrospective observational study of sgAH-resistant CSU patients that received omalizumab at the University Clinic of Respiratory and Allergic Diseases Golnik between 2014 and 2020. SgAH resistance was defined as a pruritus component of the weekly UAS (UAS7) ≥ 8 despite regular intake of sgAHs at a fourfold dosage. In Slovenia, omalizumab is reimbursed for such patients. Data on the age and sex of the patients, dates of omalizumab application, daily UAS and antihistamine use, and patient contact information were exported from the electronic portal developed in-house for tracking treatment with omalizumab. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (78/9/14).

A standard schedule for omalizumab treatment at the Golnik Clinic starts with 300 mg every 4 weeks. In patients with a complete response (UAS7 = 0), sgAHs are discontinued. In those remaining asymptomatic, the intervals between omalizumab doses are extended, and the dose is gradually reduced. If patients remain asymptomatic despite receiving 150 mg for 12 weeks, omalizumab is discontinued.

Three study groups were analyzed: 1) omalizumab non-responders, 2) omalizumab responders with remission, and 3) omalizumab responders without remission (Table 1). The three study groups were comparable in terms of age and sex distribution. In September 2021, we telephoned patients in the second group in which omalizumab had been discontinued to check whether they were still symptom-free and/or needed sgAHs. The duration of remission was calculated from the date of the last omalizumab application to the date of the telephone follow-up.

The distribution of numerical data was tested using the Kolmogorov–Smirnov test. Because data were normally distributed, parametric statistical methods were employed. Data were presented as mean ± standard deviation or mean and range. Differences

Table 1 | Classification and response rates of chronic spontaneous urticaria patients treated with omalizumab.

Group	*n/N* (%)
Omalizumab non-responders	13/176 (7.4)
Omalizumab responders	163/176 (92.6)
Remission	42/163 (25.8)
No remission	121/163 (74.2)

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between groups were tested using an independent samples *t*-test and a chi-squared test. *P*-values < 0.05 were considered significant.

Results

This study included 176 sgAH-resistant CSU patients (130 [73.9%] females, 46 [26.1%] males; mean age 51.8 ± 13.8 years). Thirteen participants (12 females, mean age 46.3 ± 13.5 years) were excluded from the analysis due to non-response to omalizumab. Consequently, 163 omalizumab responders were eligible for analysis. We were able to discontinue omalizumab in 25.8% (42 of 163) of responders (34 females, mean age 54.4 ± 13.8 years) because of complete CSU remission (i.e., no wheals and no sgAH treatment), but 74.2% (121/163) of them (85 females, mean age 51.5 ± 13.8 years) still required omalizumab (Table 1). In the remission group, the duration of omalizumab treatment before discontinuation was 24.3 ± 15.9 months (range 7 to 63 months). The average time between discontinuation of omalizumab and the end of the observation period (September 2021) was 39.6 ± 18.4 months (range 8 to 68 months). At the end of the observation period, 21 patients (50.0%) were still in complete remission for 39.2 ± 17.7 months (range 9 to 69 months), and 15 patients with a relapse were controlling their symptoms with sgAHs after a duration of complete remission of 20.8 ± 21.7 months (3 to 72 months). Omalizumab was reintroduced in six (14.3%) patients with a duration of complete remission of 21.3 ± 13.3 months (range 6 to 40 months). Three patients responded to reintroduction with immediate complete control (UAS7 = 0), but in three patients it took 6 to 12 months, and a temporary increase in the omalizumab dose to 450 (two patients) or 600 mg for 4 weeks (one patient) was needed to achieve complete control.

Discussion

Our study showed that a quarter of sgAH-resistant CSU patients treated with omalizumab achieved remission, with half of them maintaining remission for several years.

The studies published to date show different results regarding the natural history of CSU (2, 3, 9), influenced by the composition of the study population. Various studies have employed different criteria for CSU remission (10). Published studies have shown that 30% to 80% of patients recover 1 to 5 years after symptom onset (2, 3). Numerous studies have attempted to identify predictors of CSU prognosis. Patients with severe and prolonged disease have a poorer prognosis than those with milder disease (2, 3). Symptomatic dermographism carries the best prognosis, whereas cold urticaria has the poorest (9). The presence of angioedema had no significant influence on prognosis differences (11). In a UK study, 5% of patients reported symptoms lasting longer than 5 years (12). An Israeli prospective study of 139 patients reported that CSU lasted over a year in more than 70% of patients and over 5 years in 14% (13). In 330 adult patients with CSU in Sweden, the median symptom duration was 2 to 4 years (14). In a Dutch study of 153 CSU patients, the remission rate was 29% in 5 years and 49% in 10 years (11). A Korean study of 329 CSU patients found remission rates of 10.8% after 1 year, 18.8% in the 2nd year, and 32.9% after 5 years (15).

It is important to distinguish between remission and complete control of symptoms as outcome measures. Complete remission means the absence of the disease without additional therapy (16), whereas complete control of symptoms means the absence of the disease with regular therapy, such as sgAHs (10). A study of 137 adult patients (mean age 46.5 ± 18.8 years; 66.4% women) with CSU from three Italian university hospitals was published (17). Their treatment protocol was based on a system of reimbursement for omalizumab by the Italian health insurance fund. Patients initially received six 300 mg doses of omalizumab every 4 weeks. In this study, remission was defined as UAS7 < 6 when treated with sgAH; however, in our study remission was defined as UAS7 = 0 without sgAHs. In the aforementioned study, 46.7% of patients were satisfactorily controlled after stopping treatment after 6 months. The others relapsed and received omalizumab for a further 20 weeks. At the end of the second cycle, 72.8% of patients were satisfactorily controlled. About half of them were still well controlled after 1 year, and most of them also after 4 years. Patients were less likely to achieve control if they were 60 years or older; had symptoms lasting 22 months or more before starting omalizumab; exhibited a baseline UAS7 < 30, baseline wheal score ≥ 9, and baseline pruritus score < 15; or had undergone two consecutive omalizumab courses. Total serum IgE levels (< 45 kU/l) and positive autologous serum skin test results were not significantly associated with a higher risk of relapse (17).

A retrospective study of 47 adult patients that had been successfully treated with omalizumab at standard doses between 2013 and 2020 was published (18). In patients that had their CSU completely under control (UAS7 = 0) after the introduction of omalizumab, the interval between doses was prolonged. If the disease was completely under control even after two 8-week intervals, omalizumab was discontinued. Recurrence was defined as UAS7 > 16 at any time during follow-up after discontinuation of omalizumab. Omalizumab was discontinued in 47 of 102 patients (46.1%). Twenty-five patients (58.1%) were still in remission, and 18 (41.9%) relapsed at a median follow-up of 12.2 months. In 14 patients (77.7%), relapses did not respond to antihistamines, but re-treatment with omalizumab was successful (complete control of symptoms). The likelihood of relapse was higher in patients under 40 years of age. Previous studies have shown an increased risk of relapse in patients with a longer duration of CSU, a higher UAS7 score at baseline, or a slow response to omalizumab (19, 20). Both studies showed comparable results to our study. Twenty-one of 42 (50.0%) patients in our study maintained complete remission for an average of 39.2 months (3.3 years). Fifteen (35.7%) patients controlled their symptoms with sgAHs after maintaining complete remission for an average of 20.8 months. Omalizumab was reintroduced in six (14.3%) patients. All responded to reintroduction: three with an immediate complete response and three with a delayed complete response. It should be noted that the outcome of a single study is strongly influenced by the definition of remission. In our study, the remission criterion was the most stringent (UAS7 = 0), and so the percentage of patients that discontinued omalizumab and those that remained in remission is slightly lower.

Our study has certain limitations. Apart from being a retrospective and open study, we did not analyze the predictors of remission, nor did we compare the characteristics of patients that achieved remission with those that did not. However, the strengths of our study are the selection of a large group of patients with severe sgAH-resistant CSU and a rather long follow-up period.

Conclusions

This study shows that, in patients with severe CSU, remission occurs in a quarter of patients and can last for several years. A sig-

nificant proportion of patients can effectively control symptoms with sgAHs after relapse. Patients that were retreated after discontinuation of omalizumab responded well to reintroduction. Long-term follow-up of these patients is required to draw more precise conclusions, particularly regarding the duration of remission.

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