Received: 17 July 2020 | Revised: 24 September 2020 | Accepted: 23 November 2020

DOI: 10.1111/pai.13426

ORIGINAL ARTICLE

WILEY

# Safety and effectiveness of omalizumab for the treatment of chronic urticaria in pediatric patients

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**Editor:** Hugh Sampson

## Abstract

**Background:** Evidence on safety and effectiveness of omalizumab for treatment of chronic urticaria in pediatric patients is scarce and limited to case reports. In particular, drug survival of omalizumab has not yet been investigated, which is a key element in the evaluation of its clinical performance. The aim of this study was to investigate safety, effectiveness, and drug survival rates of omalizumab in a daily practice cohort of pediatric patients with chronic urticaria (CU).

**Methods:** This is a multicenter study including all pediatric patients from an academic center (Wilhelmina Children's Hospital) and a general center (Diakonessenhuis Hospital) in the Netherlands, who started omalizumab treatment before the age of 18 years. Data on safety, effectiveness, time to discontinuation, and reasons for discontinuation of treatment were assessed. Drug survival of omalizumab was estimated using the Kaplan-Meier survival analysis.

**Results:** A total of 38 patients, who started treatment between January 2014 and January 2020, were included. Most patients (68.4%) used omalizumab without reporting any side effects and a complete or good response to treatment was achieved in 76.3% of patients. The 1- and 2-year drug survival rates were 62% and 50%, respectively, with well-controlled disease activity as the most frequent reason for discontinuation in 69.2% of patients, followed by ineffectiveness in 23.1% and side effects in 7.7% of patients.

**Conclusions:** This study demonstrates high safety and effectiveness of omalizumab treatment in pediatric patients with CU, which will aid clinical decision making and management of expectations when choosing omalizumab treatment for pediatric patients with CU.

KEYWORDS

angioedema, children, clinical practice, drug survival, effectiveness, omalizumab, pediatric, safety, treatment, Urticaria

**Abbreviations:** AE, angioedema; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; MID, minimal important difference; RCT, randomized controlled trial; UAS7, Urticaria Activity Score summed over 7 days; WKZ, Wilhelmina Children's Hospital.

## 1 | INTRODUCTION

Chronic urticaria (CU) has a high prevalence in the pediatric population, estimated around 0.5%,[1,2] and affects the psychologic state and quality of life considerably.[2] Current treatment guidelines recommend a stepwise approach that aims at total symptom control. In CU patients with insufficient response to four times the standard dose of H1 antihistamines, add-on therapy should be considered.[2]

Omalizumab, a monoclonal antibody against immunoglobulin E,[3] is recommended as add-on treatment in adults and adolescents (≥12 years) with CU. Studies on the safety and efficacy of omalizumab for the treatment of CSU, however, were mainly performed in adult patient populations in three randomized controlled trials (RCTs) that included 5, 18, and 10 adolescents only.[4–6] Although none of the studies reported specific outcomes of the use of omalizumab in adolescents, overall, omalizumab achieved a statistically significant reduction in disease severity scores and was well tolerated.[4–6] In addition, several case reports including a total of fifteen children aged 4-16 years describe safe and successful use of omalizumab.[7–12] Although studies on safety and efficacy of omalizumab in children with CU are scarce, the clinical safety and efficacy of omalizumab in the pediatric population have been demonstrated in large, RCTs in patients with asthma aged 6-12 [13–16] and 6-20 years (n = 246-627).[17]

Drug survival of drug therapy is a key element in the evaluation of its clinical performance.[18] In short, drug survival is the length of time patients remain on a specific drug, investigated using the technique of survival analysis.[19] Survival analysis involves a series of statistical techniques to study time until the occurrence of an event of interest, in this case the discontinuation of omalizumab. By analyzing the treatment duration and reasons for discontinuation of treatment, drug survival analysis reveals the drug's safety, tolerability, and effectiveness over time, as well as patients' and doctors' preferences. Therefore, drug survival can be used as an indicator of therapeutic success in daily practice.[19]

Recently, the drug survival of omalizumab has been studied in an adult Dutch CU population.[20] This study showed a 1-, 2- and 3-year overall drug survival of omalizumab of 77%, 61%, and 55%, respectively, mostly determined by well-controlled disease activity, demonstrating high safety and effectiveness in daily practice.[20] In pediatric patients with CU, however, daily practice data of treatment with omalizumab are lacking. Furthermore, the drug survival of omalizumab in pediatric patients with CU has not yet been investigated. The primary aim of this study is to investigate safety and effectiveness of omalizumab in a daily practice cohort of pediatric patients with CU.

**Key Message**

Omalizumab is approved and recommended as add-on treatment in adults and adolescents (≥12 years) with chronic urticaria (CU). However, studies on the safety and effectiveness of omalizumab for the treatment of CU in pediatric patients are scarce and limited to case reports. This article provides data demonstrating safety and effectiveness of omalizumab use in a large pediatric population with CU. Current management guidelines are mainly derived from results of studies with adult patients. Hence, our results strongly contribute to recommendations in guidelines.

## 2 | METHODS

### 2.1 | Patient and data collection

All patients in the Wilhelmina Children's Hospital (WKZ)—part of the University Medical Center Utrecht and the Diakonessenhuis Hospital—a general hospital in Utrecht (Netherlands), who were diagnosed with CU and were prescribed omalizumab before the age of 18, were screened for inclusion.

All variables used in the study, regarding information on patient characteristics, treatment characteristics, and disease activity, were extracted from the electronic patient record. Chronic urticaria disease activity was assessed using the Urticaria Activity Score 7 (UAS7)[2]. The smallest difference between UAS7 scores with clinical relevance, the minimal important difference (MID), was defined as a decrease in the UAS7 score of 10 points.[21]

Start- and stop data of omalizumab, response to treatment, side effects, and reasons for treatment discontinuation were captured. Only the first treatment episode with omalizumab was used for analyses. If omalizumab treatment was discontinued and restarted within a 90-day timeframe, the subsequent dosage was considered part of the initial treatment episode; otherwise, it was considered as new treatment episode.

All patients were treated according to the local treatment protocol based on the international guidelines.[22] Briefly, treatment with omalizumab was initiated in children with high disease activity scores (UAS7 ≥ 16) despite the use of antihistamines in fourfold the licensed dose for children. Initial treatment consisted of 300 mg omalizumab every 4 weeks, with an increase to 450 or 600 mg in case of insufficient treatment response (UAS7 > 16) after the 6th administration. If treatment was effective, a down-dosing schedule was initiated that entailed progressively increasing the dosing interval by 1 week every visit up to 8 weeks.[23] Omalizumab was discontinued if good disease control was maintained after an interval of 8 weeks.

Treatment response was classified as "complete"—(UAS7 score = 0), "good"—(0 < UAS7 score < 7), "partial"—(UAS7 score > 6; MID ≥ 10) or "poor"—(UAS7 score > 16; MID < 10) and was evaluated at second administration (T2) and at end of treatment or datalock. In case of missing activity scores, treatment response was determined by four different authors independently, based on the physicians' description in the patients' charts.

An assessment outcome of being symptom-free or being satisfied, with minor symptoms only, equals a complete and good response, respectively, whereas the description of an insufficient or lacking response equals a partial or poor response, respectively. Any discrepancies were resolved by consensus.

### 2.2 | Statistical analyses

Statistical analyses were performed by using IBM SPSS Statistics (25.0.0.2). Comparisons of measures at different time points were made using a paired t test or Wilcoxon-signed rank test for continuous variables. Statistical significance was assumed for $P \leq .05$.

Drug survival rates of omalizumab were calculated by the Kaplan-Meier method and displayed in survival curves for overall drug survival (event: discontinuation due to any reason) and survival curves for different reasons of discontinuation (events: well-controlled disease activity, ineffectiveness, side effects, or combination of side effects and ineffectiveness). Patients who did not discontinue treatment at the time of datalock or were lost to follow-up were censored. Data were compared with previously published data of drug survival in adult CU patients.[20] The log-rank (Mantel-Cox) test was used to compare the survival curves of adult and pediatric patients. To identify whether determinants were associated with discontinuation of treatment, a univariate Cox regression model was performed. Those determinants with a $P \leq .2$ were entered into a multivariate Cox regression model with backward selection. In the multivariate Cox regression model, determinants with a $P \leq .05$ were considered statistically significant.

This study was approved by the Medical Ethics Review committee in both participating centers [protocol number 19-808/C]. Exemption regarding obtaining informed consent was granted according to the General Data Protection Regulation (GDPR). Analyses were performed with completely pseudonymized data.

**TABLE 1** Patient characteristics

| | Total |
|---|---|
| Gender (female) | 22 (57.9%) |
| Age at start omalizumab (y), median (IQR) | 14.9 (12.9-16.0) |
| Age at start omalizumab (categorized) | |
| <6 y | 1 (2.6%) |
| 6-12 y | 5 (13.2%) |
| 12-16 y | 20 (52.6%) |
| 16-18 y | 12 (31.6%) |
| Main diagnosis | |
| CSU | **29 (76.3%)** |
| CSU with AE | 17 |
| CSU with CIndU | 5 |
| CSU with AE and CIndU | 3 |
| AE | **2 (5.3%)** |
| AE with CIndU | 1 |
| CIndU | **7 (18.4%)** |
| CIndU with CSU | 3 |
| CIndU with AE | 3 |
| Autoimmune disease[a] | 2 (5.3%) |
| Duration of CU at start of omalizumab (mo), median (IQR)[b] | 20.5 (12.5-48.2) |
| Duration of CU at start of omalizumab (categorized) | |
| <1 y | 9 (23.7%) |
| 1-2 y | 12 (31.6%) |
| 2-5 y | 9 (23.7%) |
| 5-10 y | 8 (21.1%) |

[a]One patient (male, 16.8 y old) suffered from diabetes mellitus type 1, and one patient (female, 14.9 y old) suffered from diabetes mellitus type 1 and hypothyroidism

[b]Duration of CU estimated in 18 patients (47.4%)

## 3 | RESULTS

### 3.1 | Patient and treatment characteristics

Of 56 screened patients, 18 were excluded because: (a) they received omalizumab for indications other than CU (N = 14); (b) treatment was never initiated (N = 2); or (c) the initial diagnosis of CU was corrected after start of treatment (N = 2). In total, 38 patients (57.9% female), who started treatment between January 2014 and January 2020, were included from the two centers—WKZ (n = 28) and Diakonessenhuis Hospital (n = 10).

Patient characteristics are shown in Table 1. The median age of all patients at start of omalizumab was 14.9 years with the youngest patient being 3.6 years and the oldest patient being 17.7 years. Six patients (15.8%) were younger than 12 years at start of treatment. The majority of patients (76.3%) presented mainly with spontaneous wheals, whereas 17.5% and 5.0% presented with chronic inducible urticaria (CIndU) and angioedema (AE), respectively. Based on self-reported triggers, the CIndU patients had cold urticaria (n = 3), cholinergic urticaria (n = 2), and symptomatic dermographism (n = 2). In total, 32 patients experienced multiple components of CU. Omalizumab treatment was initiated a median of 20.5 months after the first onset of CU. There were no differences between the patients from the two participating centers.

The majority of patients (92.1%) were treated with antihistamines throughout omalizumab treatment, the majority being treated with antihistamines four times a day. Besides antihistamines, montelukast and corticosteroids were used simultaneously during omalizumab treatment in 7.9% and 2.6% of patients, respectively. Detailed treatment characteristics are shown in Table S1.

Half of the patients (50.0%), of whom two patients restarted treatment within 90 days after discontinuation, were continuously treated with omalizumab. In total, 13 patients (34.2%) discontinued omalizumab treatment, of whom two patients restarted treatment after 212 and 226 days. Six patients (15.8%) were lost to follow-up.

The median post-treatment follow-up was 18.5 months (min. 1.2 months; max. 72.5 months).

The UAS7 scores at baseline and end of treatment were available for 20 children and the median score decreased significantly from 25.5 at baseline to 0.60 at end of treatment ($P = .0001$). At end of treatment or at datalock, treatment response was based on UAS7 scores in 26 patients (68.4%) and on the physicians' documentation in 12 patients (31.6%). Overall, most patients were complete responders (39.5%) or good responders (36.8%), of which 36.8% of patients had achieved this response at the second administration. Ultimately, six patients (15.8%) were partial responders and three patients (7.9%) were poor responders. Response to omalizumab in CSU and/or AE patients and CindU patients was comparable with 77.4%, respectively, 71.4% of patients achieving a complete or good response ($P = .850$). Among the patients who presented with CIndU, response was partial or lacking in only two patients in whom their CIndU was triggered by cold.

Almost all patients (97.4%) started omalizumab treatment with a dose of 300 mg. Throughout omalizumab treatment, 300 mg was the maximum dose in 71.1% of patients. Ten patients, aged between 12 and 16.8 years, received a higher dose: six patients (15.8%) and four patients (10.5%) were treated with a dose of, respectively, 450 and 600 mg at least once. There were no differences in the specific patient characteristics gender, age, BMI, disease duration, and disease activity at start of treatment between patients treated with standard and high dose of omalizumab.

## 3.2 | Side effects

In total, twelve children reported one or more side effects. The most frequent reported side effect was headache (n = 5, 41.7%). Other reported side effects were fatigue (n = 2, 16.8%), flu-like symptoms (n = 1, 8.3%), injection site reaction (n = 1, 8.3%), arthralgia/joint pain (n = 1, 8.3%), and hair loss (n = 1, 8.3%). None of these side effects led to discontinuation of omalizumab. The parents of one patient (8.3%) attributed loss of concentration due to omalizumab treatment. This was the reason for discontinuing omalizumab after six administrations in this patient. These observations are presented in Table 2. The use of higher doses of omalizumab (450 and 600 mg) was not associated with an increase of side effects.

## 3.3 | Drug survival

Overall, 13 (34.2%) patients discontinued treatment. The most frequent reason for discontinuation of omalizumab was well-controlled disease activity in nine (69.2%) patients. Other reasons for treatment

**TABLE 2** Side effects during omalizumab treatment

| Patient | Sex | Age[a] | No. of administrations | Maximum dose during treatment (mg) (no.) | Most important reported side effect | Additional reported side effects | Reason for discontinuation? |
|---|---|---|---|---|---|---|---|
| 1 | F | 10.6 | 11 | 300 | Headache | Fatigue, dizziness, injection site reaction | No |
| 2 | M | 8.5 | 12 | 300 | Injection site reaction | — | No |
| 3 | F | 17.5 | 8 | 300 | Headache | Fatigue, nausea, dizziness | No |
| 4 | F | 16.8 | 11 | 300 | Arthralgia/joint pain | Headache, flu-like symptoms | No |
| 5 | F | 15.4 | 12 | 450 (1) | Hair loss | — | No |
| 6 | F | 11.1 | 19 | 300 | Fatigue | Arthralgia/joint pain | No |
| 7 | F | 15.9 | 30 | 300 | Fatigue | Headache, itchy arms | No |
| 8 | F | 14.9 | 8 | 300 | Headache | Stomach ache, nausea | No |
| 9 | F | 14.7 | 4 | 300 | Flu-like symptoms | — | No |
| 10 | M | 13.4 | 11 | 450 (3) | Loss of concentration | — | Yes |
| 11 | F | 16.3 | 25 | 300 | Headache | — | No |
| 12 | M | 12.9 | 3 | 300 | Headache | — | No |

[a]Age (y) at start of omalizumab treatment.

discontinuation were ineffectiveness in three patients (23.1%) and side effects in one patient (7.7%).

The 1- and 2-year overall drug survival was 62% and 50%, respectively, mostly determined by well-controlled disease activity (Figure 1). The overall drug survival rates of pediatric patients and adult patients[20] were not significantly different ($P = .227$). However, the drug survival curves related to discontinuation due to well-controlled disease activity—which were compared since this was the most frequent reason of treatment discontinuation in both adult- and pediatric patients—differed significantly ($P = .032$; Figure S1).

Determinants of drug survival were analyzed by Cox regression analysis (Table 3). None of the factors, including age at start of omalizumab treatment, gender, disease duration, disease activity at baseline, or the main diagnosis, appeared to affect discontinuation of treatment. No factors were entered into a multivariate Cox regression.

## 4 | DISCUSSION

This study represents the largest daily practice cohort study of pediatric patients with CU being treated with omalizumab to date. We provide long-term safety, effectiveness, and drug survival data on omalizumab for treatment of chronic urticaria in pediatric, spanning a timeframe of 6 years. The safety profile of omalizumab was reassuring since most patients (68.4%) used omalizumab without reporting any side effects and only mild side effects. The side effects, mainly headache and fatigue, were reported by twelve patients (31.6%). The majority of patients (76.3%) achieved a good or complete response at end of treatment or datalock, whereas 15.8% and 7.9% of patients were partial and poor responders, respectively. Our results showed a 1- and 2-year drug survival of 62% and 50%, respectively, mainly determined by well-controlled disease activity.

Previously published work on safety and effectiveness of omalizumab treatment in patients with CU is limited to a small number of adolescents (n = 33) included in three RCTs[4–6] and fifteen pediatric patients aged 4-16 years[7–12] described in case reports. None of the RCTs presented specific outcomes from use of omalizumab in adolescents. All case reports describe a complete or good (UAS7 ≤ 6) response to omalizumab in 86.7%, respectively, 13.3% of patients, with a treatment duration varying from 3 to 20 months.[7–12] None of these patients reported any side effects. However, the potential outcome reporting bias inherent to case reports and the lack of specific outcomes from use of omalizumab in adolescents in the RCTs complicate the comparison of our data with published work.

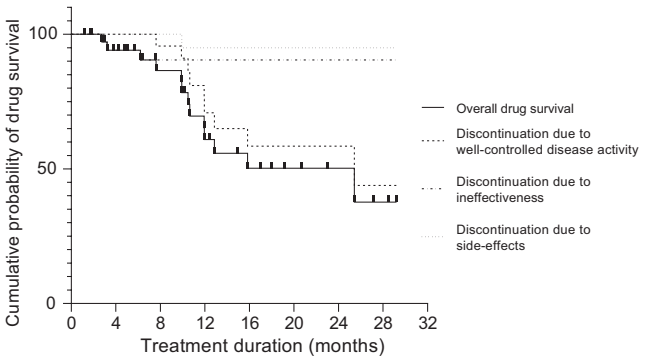


**FIGURE 1** Drug survival of omalizumab in pediatric patients

Our results concur with the results derived from other studies in adult patients with CU. The effectiveness of omalizumab found in our study is comparable to daily practice studies in adult patients, with complete and good response rates varying between 64% and 83%.[20,24–26] In addition, the overall 1- and 2-year drug survival rates found in this pediatric population are not statistically different from previously published drug survival rates in adult patients with CU.[20] However, the drug survival curves related to discontinuation due to well-controlled disease activity in pediatric and adult patients were statistically different ($P = 0.032$), suggesting that pediatric patients are more likely to discontinue treatment due to well-controlled disease activity compared to adult patients. This, however, needs to be investigated in larger studies.

Safety outcomes of our study are comparable to outcomes of both pediatric patients with asthma and adult patients with CU, who are treated with omalizumab. Three RCTs in pediatric patients with asthma demonstrated well tolerated and safe use of omalizumab, with discontinuation due to side effects in 0.4%-1.2% of patients whereas side effects were reported in up to 93.4%.[14–16] In these RCTs, pediatric patients with asthma reported (naso)pharyngitis, sinusitis, and upper respiratory tract infection as the most common side effects.[14–16] Headache, which was the most frequently reported side effect in our study, was mentioned in 13.8%-36.0% of patients.[14–16] Real-world data in pediatric patients with asthma suggest higher rates of discontinuation due to side effects, with fatigue as the most frequently reported side effect.[27,28] This is comparable to earlier results, where headache and fatigue were the most frequently reported side effects in adult patients with CU.[29] The percentage of patients using a dose of omalizumab higher than 300 mg in our study (26.3%) was very similar to the percentage recently published in adult patients (27.0%).[30] In addition, similar to our results, patient characteristics did not differ significantly between patients treated with standard or higher dose.[30] Interestingly, in both pediatric and adult CU patients, the incidence of side effects during high dose treatment was not elevated compared to standard treatment. Loss of concentration, which was the only side effect that led to discontinuation in our study (in one patient), was mentioned in neither RCTs nor real-world data of pediatric patients with asthma or adult patients with CU.

Although being the largest daily practice cohort of pediatric patients treated with omalizumab published to date, the small number of patients remains a limitation of this study. Due to this limitation, no determinants for drug survival could be analyzed in a multivariate Cox regression model. However, this cohort was recruited from one academic and one general hospital in the Netherlands, where the largest number of pediatric patients is treated. Hence, this cohort is likely to have high external validity. In addition, we believe

**TABLE 3** Univariate Cox regression: Determinants of drug survival in pediatric patients with CU

| | Hazard ratio [95% CI] | *P*-value |
|---|---|---|
| Age at start of omalizumab treatment | 1.06 [0.88-1.26] | .55 |
| Gender | 2.03 [0.63-6.55] | .24 |
| Disease duration | 0.99 [0.97-1.01] | .30 |
| Disease activity at baseline | 1.04 [0.97-1.11] | .26 |
| CIndU[a] | 0.58 [0.12-2.67] | .48 |
| Angioedema[a] | 1.05 [0.13-8.33] | .96 |

*Note:* Data are presented as hazard ratio with 95% confidence interval.
[a]Patients with CIndU respectively Angioedema compared to patients with CSU

an accurate representation of the real-world use of omalizumab could be rendered through detailed and complete collection of data. Nevertheless, our study accentuates the need for additional, larger-scale studies to investigate omalizumab treatment in this population.

In conclusion, our study demonstrates high safety and effectiveness of omalizumab in pediatric patients with CU. We have shown that omalizumab has a good overall survival rate, with well-controlled disease activity being the main reason for discontinuation, confirming the safe and effective use of omalizumab in this population. These findings will aid clinical decision making and management of expectations when choosing omalizumab treatment for pediatric patients with CU.

## CONFLICT OF INTEREST

AK received research funding from Novartis and is a member of the national and international advisory board from Novartis for CSU. HR is a member of the national advisory board from Novartis for CSU. CD, MAA, MG, YM, JR, and MS have no conflict of interest to declare.

## AUTHOR CONTRIBUTION

**Coco Dekkers:** Conceptualization (equal); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (equal); Project administration (equal); Validation (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Mehran Alizadeh Aghdam:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal). **Marlies de Graaf :** Conceptualization (equal); Investigation (supporting); Writing-review & editing (supporting). **André Knulst:** Conceptualization (equal); Supervision (supporting); Writing-review & editing (supporting). **Yolanda Meijer:** Investigation (supporting); Writing-review & editing (supporting). **Juul van den Reek:** Formal analysis (supporting); Methodology (supporting); Writing-review & editing (supporting). **Marike Stadermann:** Data curation (supporting); Investigation (supporting); Supervision (supporting); Writing-review & editing (supporting). **Heike Röckmann:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal).

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13426.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Dekkers C, Alizadeh Aghdam M, de Graaf M, et al. Safety and effectiveness of omalizumab for the treatment of chronic urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2021;32:720–726. https://doi.org/10.1111/pai.13426