ORIGINAL ARTICLE

A retrospective analysis omalizumab treatment patterns in patients with chronic spontaneous urticaria: a real-world study in Belgium

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Abstract

Background Chronic spontaneous urticaria (CSU) is characterized by the repeated occurrence of persistent hives and/or angioedema for ≥6 weeks, without specific external stimuli. H_1-antihistamines have long been the standard of care of CSU, but many patients remain uncontrolled even at 4× the approved dose. Add-on therapy with omalizumab has proven effective in clinical trials, but little is known about omalizumab treatment in Belgium.

Objective To collect real-world clinical data on omalizumab treatment in adults with CSU in Belgium.

Methods This was an observational, retrospective chart review of adults with CSU, who initiated omalizumab treatment between August 2014 and December 2016 (maximum 28 months follow-up).

Results In total, 235 patients were included (median time from symptom onset to diagnosis, 5.4 months; median time from diagnosis to commencing omalizumab, 6.7 months). Treatments used before/after commencing omalizumab did not always adhere to guidelines; many patients (26.4%/11.1%) received first-generation H_1-antihistamines, while 20.4% used omalizumab monotherapy after initiating treatment. The mean interval between omalizumab administrations was 4.8 (SD 1.7) weeks; 67.8% of patients had ≥1 interval prolongation and/or shortening. Mean baseline 7-day Urticaria Activity Score (UAS7) was 32.0 (SD 6.05); this improved to 12.6 (SD 11.2) after 1 month of omalizumab. About 67.2% of patients reached UAS7 ≤ 6 (well controlled) during the study. A total of 87 patients stopped omalizumab and never restarted before the end of the observation period; the most prevalent reason was remission of symptoms (49.4% of patients), followed by lack of effect (12.6%), lost to follow-up (6.9%) and adverse events (3.4%). Headache was the most common adverse event (n = 8/82). No anaphylaxis was reported.

Conclusions This study revealed that patients initiated on omalizumab in Belgium had severe CSU at baseline, and showed substantial improvements after 1 month of treatment. Greater adherence to the prescription of guideline-recommended medications is needed for the treatment of CSU.

Received: 16 January 2019; Accepted: 23 April 2019

Conflicts of interest

HL has received honoraria for lectures and consulting, and funding to support work on this study from Novartis. AS has received honoraria for lectures from Novartis, and funding to support work on this study. VS has received honoraria for lectures and congress support, and funding to support work on this study from Novartis. MG has received honoraria for consulting and congress support, and funding to support work on this study from Novartis. JL has received honoraria for consulting, and funding to support work on this study from Novartis. MB,

LD and MM have received funding to support work on this study. RS has received congress support from CSL Behring and Shire. HR and KA are employees of Novartis.

Funding source

N.V. Novartis Pharma S.A. funded this study.

Introduction

Chronic urticaria (CU) is a common skin disorder characterized by the repeated occurrence of hives and/or angioedema for more than 6 weeks.[1,2] CU is divided into two types: chronic spontaneous urticaria (CSU), in which symptoms occur in the absence of specific external triggers, and chronic inducible urticaria (CIndU), in which symptoms occur in response to specific stimuli, such as exposure to cold, heat or pressure.[1]

Previous reports suggest that many patients are undertreated and not receiving the recommended therapy.[3–5] CSU can be debilitating and unpredictable, and has a significant negative impact on quality of life (QoL);[2] it can result in work productivity loss and absenteeism,[6] interference with sleep and daily activities,[5] and high levels of anxiety and psychological distress.[7] Thus, the EAACI/GA^{2}LEN/EDF/WAO guidelines recommended treatment using a specific algorithm that allows for stepping up or down of medications until achieving complete symptom control.[1]

For many years, H_1-antihistamines have been recommended as the standard of care in CSU,[1,8–10] but up to 60% of patients remain uncontrolled at the licensed dose.[11] For these patients, the guidelines recommend uptitrating H_1-antihistamines up to four times the licensed dose, followed by add-on therapy with omalizumab.[1] Omalizumab is very effective in the treatment of CSU; it reduces the numbers of urticarial weals and pruritus, prevents angioedema, improves QoL and has a favourable safety profile.[12–19] Ciclosporin A, also off label for urticaria, is only recommended for patients with severe disease refractory to the combination of antihistamines and omalizumab.

A systematic review of 84 observational studies indicated that findings from clinical trials underscore the real-world effectiveness of omalizumab in the management of CSU;[20] however, there was no data for Belgium in the systematic review, and there is little published information on the use of omalizumab in daily clinical practice in this country. This study was designed to describe omalizumab treatment patterns since becoming available in Belgium for CSU to better understand omalizumab dosing, treatment outcomes, patients' characteristics and healthcare burden in the real-world setting.

Methods

Study design

This was a non-interventional, observational, multi-centre, retrospective, descriptive chart review performed in 16 centres in Belgium, where omalizumab is known to be used to treat patients with CSU. Omalizumab was funded via a medical need program from August 2014 based on a diagnosis of CSU for ≥6 months and 7-day urticaria activity score (UAS7)≥16 and via the public healthcare system from 1 June 2015 onwards based on a diagnosis of CSU for ≥6 months and UAS7 ≥ 28. Funding of omalizumab treatment via the medical need program or national reimbursement was not mandatory for inclusion.

The data for this study were retrieved retrospectively from patients' medical records at the participating dermatology and internal medicine centres. The study was designed, implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology,[21] and the STROBE guidelines.[22]

Patients

Patients (≥18 years old) were included who had a diagnosis of CSU and had received ≥1 treatment with omalizumab and ≥1 follow-up visit between August 2014 and December 2016. Patients were excluded if they participated in any randomized trial in CU during the observation period or if they were treated with omalizumab for any off-label indication.

Demographics and baseline characteristics

Demographic data collected included age and gender. Baseline characteristics included date of CSU symptom onset and diagnosis; severity of CSU disease by means of Dermatology Life Quality Index (DLQI; range 0–30) and UAS7 (range 0–42);[23] CSU relevant medical history; and work/school attendance. UAS7 scores/ranges are defined as: urticaria-free (0); well-controlled (1–6); mild (7–15); moderate (16–27); and severe (28–42).[24] Change in UAS7 after starting omalizumab was determined.

Omalizumab treatment exposure and outcome

Omalizumab dosing, frequency of administration, duration and treatment intervals, as well as reasons for treatment delay or interruption were analysed. Treatments used before commencing and in combination with omalizumab were examined.

CSU-related healthcare resource use

The number and nature of urticaria tests, the number of CSU-related emergency room admissions and length of stay, patient referrals and the number of CSU consultations were analysed.

Table 1 Demographics and baseline characteristics

Category	Total population (*N* = 235)
Demographics	
Age in years	46.2 ± 15.4
Female, *n* (%)	159 (67.7)
Male, *n* (%)	76 (32.3)
Disease characteristics, *n* (%)	
Comorbid CIndU	113 (49.3)
Symptomatic dermographism	71 (31.0)
Angioedema	93 (40.6)
No medical history	36 (15.7)
Atopy	32 (14.0)
Onset of symptoms, diagnosis and start of omalizumab treatment, median (range)	
Time from onset of symptoms to diagnosis of CSU, months	5.4 (0.0–456.0)†
Time from onset of CSU symptoms to omalizumab start, months	23.5 (0.3–503.0)†
Time from diagnosis of CSU to omalizumab start, months	6.7 (0.0–425.5)†
Other CSU medications	
Number of combined medications before commencing omalizumab	2.0 ± 1.7
Number of concomitant medications after commencing (in combination with) omalizumab	0.6 ± 0.9

Data are mean ± standard deviation unless otherwise stated.
†For three patients, the date of onset of CSU symptoms was unknown and arbitrarily encoded as being similar to the date of diagnosis.

Adverse events

The type, severity and clinician's assessment of causality of adverse events during omalizumab treatment were recorded.

Results

Patient characteristics

In total, 235 patients were included in this chart review, the majority of whom were female (67.7%), and the mean age was 46.2 years (Table 1). The mean observation period was 15.7 (SD 7.8) months. Of these, 70.2% of patients were treated in university hospitals (39.6% dermatology; 30.6% internal medicine), 9.8% in peripheral hospitals (all dermatology) and 20.0% in private dermatology practices. Patients treated in private practices had a mean of 11.9 CSU-related consultations compared with 9.2 and 8.6 for university hospital dermatology and internal medicine specialties, respectively, and 8.7 for peripheral hospitals. Patients were mainly referred by their general practitioner (n = 98; 41.7%) or by other dermatologists (n = 58; 24.7%).

In the total population, 27 patients (11.5%) did not attend school or work for a mean duration of 1.2 (SD 5.3) days per month because of CSU-related problems before omalizumab treatment. In contrast, 16 patients (6.8%) did not attend school or work for mean duration of 0.5 (SD 3.3) days per month since omalizumab initiation. Before omalizumab treatment, 13 (5.5% of total population) patients had a prior CSU-related emergency room admission for angioedema (n = 6), rash (n = 5), anxiety (n = 2) and infection (n = 1); one patient was admitted for two reasons. During the observation period, two patients had a CSU-related emergency room admission while on omalizumab, one for angioedema and one for rash.

It should be noted that although omalizumab reimbursement became available during the course of this study (June 2015), the median time from symptom onset to omalizumab start was similar between those who were enrolled before and after reimbursement (Table 1); the median time from CSU diagnosis to omalizumab start was shorter for those enrolled after reimbursement (5.5 months) compared with those enrolled before (9.1 months). It should also be noted that 81 patients received omalizumab funding via the Medical Need Program, 208 received national reimbursement (71 of whom were previously funded via the Medical Need program), eight patients had their treatment paid for by other funding, and 19 patients had no funding information.

The mean number of diagnostic tests per patient was 2.7, the most common of which were differential blood count in 75.3% of patients (n = 177/235), immunoglobulin (Ig) E levels in 41.3% (n = 97/235) and CIndU provocations tests in 29.4% (n = 69/235); 13.6% of patients had no diagnostic test for CU (Fig. 1). The mean IgE level was 257.7 IU/mL, with a large distribution (range 2.0–2914.0 IU/mL, median 106.0 IU/mL). Angioedema was reported in 40.6% of patients and 49.3% suffered from comorbid CIndU, of which symptomatic dermographism was the most common (31.0%); all other CIndUs occurred in less than 10% of patients. Other comorbidities of interest included atopy (14.0% of patients) and allergic asthma (7.4%).

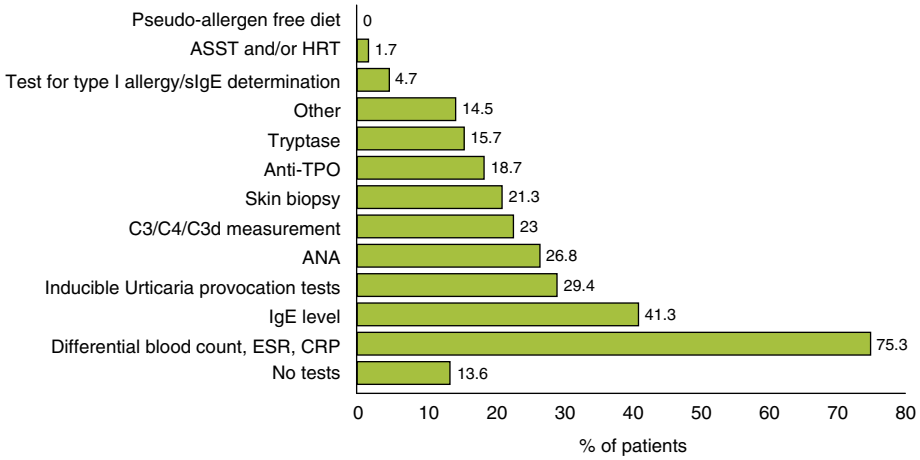

Figure 1 Summary of diagnostic tests. ANA, antinuclear antibody; ASST, autologous serum skin test; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRT, histamine release test; IgE, immunoglobulin E; TPO, thyroid peroxidase.

Table 2 Proportion of the total population (N = 235) using selected treatments (in order of guideline recommendations) before and after initiating omalizumab treatment

Category	Before omalizumab	Combined with omalizumab
Second-generation H_1-antihistamine (any dose)	87.7% (n = 206)	74.5%† (n = 175)
Ciclosporin	16.6% (n = 39)	7.2%† (n = 17)
Montelukast	40.9% (n = 96)	25.5%† (n = 60)
Corticosteroids	42.6% (n = 100)	13.6%† (n = 32)
First-generation H_1-antihistamine (any dose)	26.4% (n = 62)	11.1%† (n = 26)
No medication	0.0% (n = 0)	20.4%‡ (n = 48)

†Medications were used at least once since initiating omalizumab treatment.
‡Monotherapy (never any concomitant medication in addition to omalizumab during the treatment period).

Treatment patterns before and after commencing omalizumab

Before commencing omalizumab, 87.7% of patients received second-generation H_1-antihistamines (Table 2); of these, 42.7% (n = 88/206) were receiving them at the approved dose, while 15.5% (n = 32/206), 6.3% (n = 13/206) and 35.4% (n = 73/206) were updosed to 2×, 3× and 4× the approved dose, respectively. Of the 26.4% of patients who received first-generation H_1-antihistamines before commencing omalizumab, 87.1% (n = 54/62) received them at the approved dose, while 8.1% (n = 5/62), 1.6% (n = 1/62) and 3.2% (n = 2/62) were updosed to 2×, 3× and 4× the approved dose, respectively. In total, 95.3% (n = 224/235) of patients received a first- or second-generation H_1-antihistamine before omalizumab.

After initiating omalizumab, 74.5% of patients received concomitant second-generation H_1-antihistamines at least once; of these, 65.7% (n = 115/175) received them at the approved dose, 40.0% (n = 70/175) were updosed to 4× the approved dose. Of the 11.1% of patients who received first-generation H_1-antihistamines after commencing omalizumab, 84.6% (n = 22/26) were receiving them at the approved dose, while 11.5% (n = 3/26) were updosed to 2–4× the approved dose. One-hundred-seventy-nine patients (76.2%) received first- or second-generation H_1-antihistamines in combination with omalizumab. Patients received first- or second-generation H_1-antihistamines in combination with omalizumab for 48.9% and 74.9% of the time while on omalizumab, respectively. Before omalizumab treatment, corticosteroids were used by 42.6% (n = 100/235) of patients at least once, while 13.6% (n = 32/235) used them in combination after commencing omalizumab.

Before commencing omalizumab, 31.1% (n = 73/235) of patients were treated with monotherapy, 32.2% (n = 76/235) with dual therapy and 20.0% (n = 47/235) with triple therapy. After commencing omalizumab, it was used as monotherapy in 20.4% (n = 48/235) of patients, 34.4% (n = 81/235) of patients had one other CSU medication in combination (dual therapy), and 27.7% (n = 65/235) had two CSU medications added (triple therapy) as the maximum number of CSU treatments combined during the observation period.

The mean duration of omalizumab treatment within the observation period was 11.9 (SD 7.6) months; 54.0% of patients were treated for 1 year; 20.4% were treated for 1.5 years; and the remaining 25.5% were treated more than 1.5 years. The majority of patients (93.6%) received omalizumab 300 mg; however, 4.3% (n = 10/235) received 450 mg, 0.9% (n = 2/235) 600 mg, 13.2% (n = 31/235) 150 mg and 0.4% (n = 1/235) 75 mg at least once during the observation period. Most patients (84.3%) had no dose change during the omalizumab treatment period.

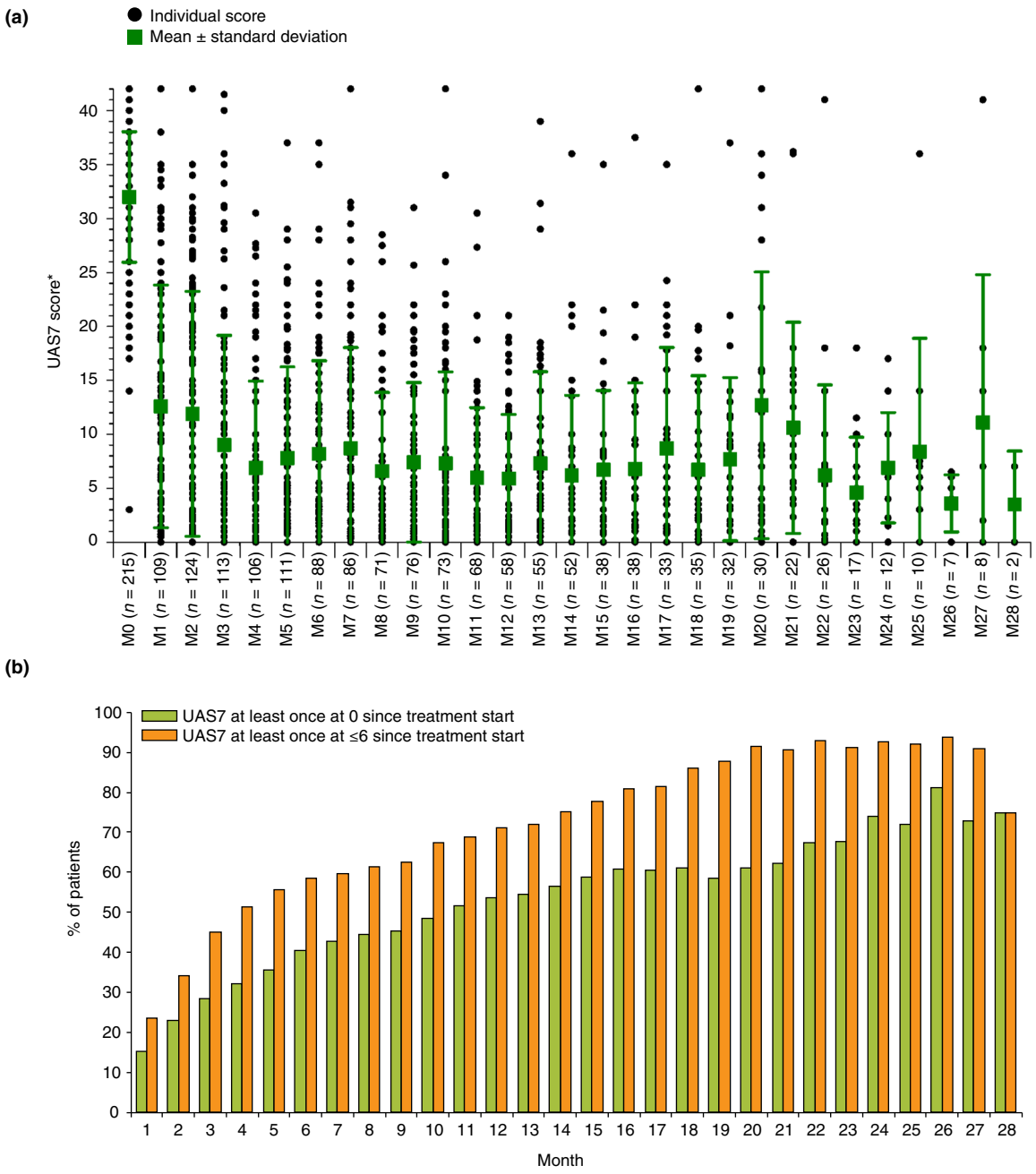

Figure 2 (a) UAS7 characteristics over time. (b) Evolution over time of patients with at least one UAS score of 0 and ≤6 since omalizumab treatment initiation. M, month; UAS7, 7-day urticaria activity score. *One patient had a UAS7 score of 0 recorded at an unknown time-point. This result is not included in the graph.

The mean interval between omalizumab administrations was 4.8 weeks; 32.2% of patients received omalizumab at a consistent 4-week interval. At least once during the observation period, 61.7% had a prolonged (≥5 weeks) treatment interval, while 19.6% had a shortened (<3 weeks) interval; some patients (13.5%) had both a prolongation and shortening. In total, 10.6% of patients had ≥1 treatment interruption. Practical reasons were the most common cause of treatment interval prolongation (56.1%) or treatment interval shortening (57.5%). Other reasons for interval prolongation were temporary interruption

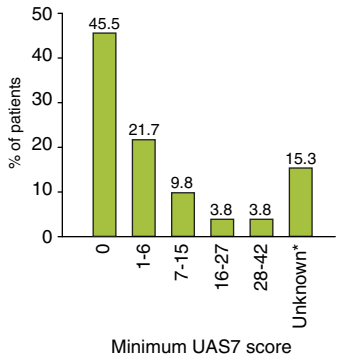

Figure 3 Number of Patients reaching different UAS7 during the observation period as their lowest score (unique scores, not cumulative). *Patients with no UAS score determined since omalizumab treatment.

of treatment (18.2%), tapering (40.2%) and other reasons (3.8%). Other reasons for interval shortening were lack of efficacy (32.5%). In most patients, the 4-week interval was at least once prolonged/shortened, but in general by pooling all interval data only 15.4% were prolonged and 3.2% shortened.

For the 43 patients who stopped omalizumab treatment and did not restart during the observation period for remission of symptoms, nine patients (20.9%) were treated with omalizumab for less than 6 months and 34 patients (79.1%) were treated longer than 6 months. The interval between treatment stop and the end of the observation period was <1 month for 14 of these patients (32.6%), 1–2 months for nine patients (20.9%), 2–3 months for one patient (2.3%) and longer than 3 months for 19 patients (44.2%).

Table 3 Severity, seriousness and causality of adverse events

Category	Total population (*N* = 235)
Patients with any adverse event, *n* (%)	52 (22.1)
Severity, *n* (%)	
Mild	28 (11.9)
Moderate	22 (9.4)
Severe	5 (2.1)
Seriousness, *n* (%)	
Fatal	0 (0.0)
Life-threatening	0 (0.0)
Hospitalization	1 (0.4)
Disability–Incapacity	3 (1.3)
Birth defect	0 (0.0)
Not significant	49 (20.9)
Causality, *n* (%)	
Possibly related to omalizumab	26 (11.1)
Unrelated to omalizumab	13 (5.5)
Unknown	21 (8.9)

Evolution of UAS7 score

The mean baseline UAS7 was 32.0 (SD 6.1); this improved to 12.6 (SD 11.2) after one month of omalizumab treatment (Fig. 2a). The number of patients for whom a UAS7 score was reported differs per month; 15.3% had no UAS score available during the observation period. During the observation period, 67.2% (n = 158/235) of patients reached UAS7 ≤ 6 (well controlled; Fig. 2b); 9.8%, 3.8% and 3.8% reached UAS7 of 7–15, 16–27 and 28–42, respectively; five patients (2.5%) remained at UAS7 > 28 during the omalizumab treatment period. During the observation period, 42.6% of patients (n = 106/235) became urticaria-free (UAS7 = 0) after a mean of 4.0 ± 4.6 months treatment with omalizumab. The 52 patients who reached a minimum UAS7 ≤ 6, but not 0, needed a mean of 6.8 (SD 6.1) months treatment with omalizumab to achieve a well-controlled state (Fig. 3).

Work/school absenteeism before and after commencing omalizumab

In total, 27 patients (11.5%) reported an absenteeism from work or school before omalizumab treatment, with an average of 1.2 days absent per month. After commencing omalizumab, 16 patients (6.8%) reported an absenteeism, with an average of 0.5 days per month.

Adverse events

In total, 82 adverse events (AEs) were reported (0.35 AEs per patient) in 52 patients (22.1% of the total population) during the observation period. Of these, 29 AEs in 26 patients were possibly related to omalizumab (Table 3). Six severe AEs (SAEs; 7.3%) were reported in five patients (2.1%). Of these SAEs, one case of headache and one combined case of flu, nausea, dizziness, fatigue and constipation were possibly related to omalizumab; while one case of arthralgia with hospitalization, one case of extreme somnolence (not significant), one case of urticaria worsening with hospitalization and one case of stress (not significant) had unknown association with omalizumab. There were no reports of anaphylaxis. Causality was unknown for 31 cases in 21 patients.

Discussion

This patient chart review provides good insight into omalizumab treatment in Belgium, with a large patient cohort and more than 2 years of data. The findings revealed that patients initiated on omalizumab in Belgium had severe CSU at baseline (mean UAS7 = 32.0), and most had been treated with H_1-antihistamines for a relative long time prior to starting omalizumab. Patient demographics and clinical characteristics in this study are representative of the general population of patients with CSU.[5] The difficult journey to diagnosis and treatment of patients with CSU was confirmed by the long periods of time between symptom onset to diagnosis, and from diagnosis to omalizumab

treatment initiation. After reimbursement of omalizumab in Belgium, the median time from CSU diagnosis to omalizumab start was shortened by 3.6–5.5 months; however, better care is still needed to shorten the long period from symptom onset to diagnosis.

Available data suggest that adherence to guideline recommendations is poor, leading to an unmet need within the CU population.[5,25–29] Furthermore, the majority of data on CU inadequately controlled with H_1-antihistamines is limited to patient populations derived from specialized urticaria centres, which may not represent the general CU population due to limited numbers.[30,31] Results from this study confirmed these findings in Belgium, where treatments used prior to commencing and in combination with omalizumab did not always adhere to guidelines. Many patients received first-generation H_1-antihistamines, despite widespread agreement that these should no longer be prescribed owing to their pronounced anticholinergic effects and sedative actions, as well as their interactions with alcohol and CNS-acting drugs, interference with rapid eye movement sleep and impact on learning and performance.[1,2,32] Indeed, guidelines recommend that modern second-generation H_1-antihistamines, which are minimally or non-sedating and free of anticholinergic effects, should be prescribed as standard of care.[1] However, the data in this study are in contrast to these guidelines, since H_1-antihistamines were updosed to 4× the approved dose in only 35.4% of patients; however, this could be associated with the requirement of patients to only be resistant to H_1-antihistamines at the approved dose for reimbursement in Belgium. Corticosteroid use was also high both before and after initiation of omalizumab. Recent evidence has shown that short-term use of corticosteroids is associated with a 2- to 5-fold increase in the incidence of acute adverse events, including sepsis, venous thromboembolism and fracture, compared with background rates.[33,34]

Montelukast and ciclosporin were both used as add-on therapies before and after commencing omalizumab. Both of these treatments were previously recommended as third-line add-on therapies to H_1-antihistamines during this study; however, montelukast is no longer recommended owing to the poor level of evidence for its efficacy, and ciclosporin is only recommended as standard therapy owing to not being licensed and its inferior safety profile compared with omalizumab.[1] It should be noted that the previous guidelines were the relevant guidelines during this study, which accounts for the relatively high use of montelukast (40.9%) and ciclosporin (16.6%) prior to initiating omalizumab.[8] In the updated guidelines, ciclosporin is recommended to only be prescribed for patients with severe disease that is refractory to combined treatment with H_1-antihistamines (at any dose) and omalizumab.[1]

The updated guidelines provide strong recommendation for the use of omalizumab as third-line therapy in patients who are unresponsive to high doses of H_1-antihistamines.[1] This recommendation is based on numerous studies confirming the effectiveness of omalizumab in the treatment of CSU and its favourable safety profile.[12–19] Indeed, the results of this chart review support this recommendation, through the rapid and substantial decrease in disease activity from severe at baseline (mean UAS7 = 32.0) to mild after one month of omalizumab (mean UAS7 = 12.6). These benefits continued to improve with time, with the lowest mean UAS7 of 3.5 (i.e. well-controlled urticaria) after 28 months of omalizumab treatment. Although the data are limited, improvements were noted in work/school absenteeism and CSU-related ER admissions following omalizumab treatment initiation. These findings support the need for earlier diagnosis and treatment initiation in CSU, with a further need for escalation of treatment to add-on omalizumab in patients who are inadequately treated with H_1-antihistamines.

Recent studies suggest that dose interval adjustments may benefit some patients who respond early or late to omalizumab, requiring longer or shorter intervals between administrations, respectively.[35–38] As reimbursement of omalizumab in Belgium is only for a 4-week dosing regimen, there is very little flexibility with treatment intervals. Still, in this study, many patients had a prolongation (≥5 weeks) or shortening (<3 weeks) of a treatment interval, with 'practical reason' being the most common reason for prolongation, and 'lack of efficacy' being the most common for interval shortening. The reported rate of discontinuations for remission of symptoms was high, but as only 44.2% of these patients were stopped for longer than 3 months, so these data should be interpreted with caution.

Potential limitations of the present study are its non-interventional character, and the likelihood of missing data and patients lost to follow-up due to the long observation period. Indeed, few patients had data available on the effect of CSU on QoL, so this could not be assessed. However, non-interventional studies are the preferred means of collecting real-world data, which provides meaningful insight into patient treatment in clinical practice. The findings of this study are not only useful for physicians in Belgium, but for those worldwide who adhere to the EAACI/GA^{2}LEN/EDF/WAO guidelines.

This chart review revealed that patients initiated on omalizumab in Belgium had severe CSU at baseline, and showed substantial improvements after one month of treatment and continued benefit for up to 28 months of treatment with omalizumab. Findings also identified a need for greater adherence to the prescription of guideline-recommended medications before starting and in combination with omalizumab in Belgium.

Acknowledgements

Medical writing support was provided by Martin Wallace, PhD of Novartis Ireland, Ltd, which was funded by N.V. Novartis Pharma S.A., Belgium in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The study was sponsored by N.V. Novartis Pharma S.A.

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