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Antihistamine-resistant chronic spontaneous urticaria: 1-year data from the AWARE study

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Background

Previous reports indicate that patients with chronic spontaneous urticaria (CSU) are undertreated and that physicians show poor adherence to guideline recommendations. Awareness of CSU has improved in recent years, but it remains unclear if this has improved the management of these patients in clinical practice.

Objective

To describe disease burden, quality of life (QoL), and treatment patterns of patients with H₁-antihistamine-refractory CSU in Germany.

Method

AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) is a global prospective, non-interventional study of chronic urticaria in the real-world setting, supported by the manufacturer of omalizumab. Patients (18–75 years) were included who had H₁-antihistamine-refractory CSU for ≥ 2 months. Disease characteristics, pharmacological treatments, and QoL (dermatology life quality index [DLQI], chronic urticaria QoL questionnaire, and angioedema QoL questionnaire) are reported for patients enrolled in Germany.

Results

After 1 year in AWARE, CSU remained uncontrolled (urticaria control test [UCT] score < 12) in 432 of 1032 (42.2%) patients. QoL impairment remained high after one year, with 28.2% of patients reporting that CSU had a moderate/very large/extremely large effect on the DLQI. Most patients did not receive guideline-recommended treatments at the end of the one-year observation period. Changes in treatments were most evident at the first patient visit, with an increase in patients

receiving omalizumab vs. prior therapy from 8.5% to 21.4%, and a decrease in those receiving no treatment from 29.9% to 12.8%. These changes were associated with reduced hives, angioedema, UCT scores, and QoL scores at Month 3, but only modest improvements thereafter. Of 528 patients with uncontrolled CSU and who were eligible for treatment escalation, only 3% received up-dosing of H₁-antihistamines and only 5% were initiated on omalizumab during one year of treatment.

Conclusions & Clinical Relevance

This study highlights a significant discrepancy between recommendations for managing CSU in international guidelines, and in real-world clinical practice in Germany.

Keywords

Angioedema, chronic spontaneous urticaria, quality of life, urticaria

Introduction

Chronic urticaria (CU) is a common skin disorder characterized by the repeated occurrence of hives (wheals) and/or angioedema (swellings in the deeper layers of the skin), for more than 6 weeks.[1] CU is divided into two types: chronic spontaneous urticaria (CSU), in which symptoms occur without 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. CSU is more common than CIndU and accounts for about two-thirds of all CU cases.[2]

CSU is unpredictable and debilitating, and has a significant negative impact on the quality of life (QoL).[2] CSU can result in work productivity loss and absenteeism,[3] interference with sleep and daily activities,[4] and high levels of anxiety and psychological distress.[5] Moreover, CU-associated

angioedema can cause significant quality of life (QoL) impairment,[3, 4] owing to its unpredictable development and/or functional impairment,[6] which instills fears of suffocation.[7, 8]

H₁-antihistamines have long been the standard of care in CSU,[9-11] but up to 60% of patients remain uncontrolled at the approved dose.[12] The EAACI/GA²LEN/EDF/WAO guideline for urticaria recommends to use approved doses of second-generation H₁-antihistamines as first-line treatment, followed by increased dose (up to 4× approved dose) as second-line therapy.[1] Off-label drugs, such as ciclosporin, leukotriene receptor antagonists, and H₂-antihistamines, have been added to H₁-antihistamines in daily clinical practice, but have limited use owing to unfavorable safety profiles or poor evidence for their efficacy.[1] The 2017 update and revision of the EAACI/GA²LEN/EDF/WAO urticaria guideline provides strong recommendation for the use of omalizumab as add-on third-line therapy to H₁-antihistamines,[1] which is supported by several studies that demonstrate its efficacy and safety.[7, 8, 13-18]

It was previously reported that physicians showed poor adherence to guidelines in the diagnostic and therapeutic management of CSU in Germany.[19] In addition, AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation), a prospective, non-interventional, global (36 countries) study, examined real-world treatment patterns, burden of disease, and rates of healthcare resource utilization of patients with CU who are refractory to treatment with H₁-antihistamines.[20] Baseline findings of the AWARE study in Germany revealed that patients with H₁-antihistamine-refractory CSU had high rates of angioedema and comorbid CIndUs, had impaired health-related QoL, and were undertreated.[20]

Greater awareness of CSU has been achieved in recent years. In 2014 and 2018, revisions and updates of the international EAACI/GA²LEN/EDF/WAO guideline on urticaria were published.[1, 9]. Urticaria Day (www.urticariaday.org), a global initiative to raise awareness of urticaria, was first celebrated in 2013, and each year since then, on October 1st. In 2015, GA²LEN initiated the global network of Urticaria Centers of Reference and Excellence (UCARE; www.ga2len-ucare.com), and the

urticaria network (www.urticaria.net) started the global Chronic Urticaria REgistry (CURE; www.urticaria-registry.com)[21]. In recent years, numerous urticaria schools and preceptorships, as well as global forums (GA²LEN Global Urticaria Forum; www.globalurticariaforum.org) were held,[22] and the number of CSU publications increased each year (from 98 in 2013 to 178 in 2017). This greater awareness of CSU and guidelines for the management of this disease should help to improve the management of CSU in daily practice.

Here, we examine changes in treatment, symptoms, and health-related QoL (HR-QoL) up to 1 year of the AWARE study to determine if there have been any improvements in the management of patients with H₁-antihistamine-refractory CSU.

Methods

Patient population

Enrollment in the AWARE study occurred in urticaria centers and office-based dermatological practices in Germany, between March 2014 and December 2014. Patients were included if they had a medically-confirmed diagnosis of CU that had been present for longer than 2 months and that was resistant to treatment with at least the approved dose of H₁-antihistamines. Patients were also required to be ≥18 years of age and able to provide informed consent. Patients were excluded from the study if difficulties were anticipated with patient follow-up or if they were participating in a CU indication (or similar) clinical trial. Although patients with CIndU were also included in the AWARE study, this manuscript focuses on patients with a diagnosis of CSU.

Ethical approval for the AWARE study was obtained from Charité Ethikkommission in Berlin, Germany (September, 2013; approval number EA1/243/13) and from urticaria specialist centers where needed according to local regulations. AWARE was sponsored by the manufacturer of omalizumab.

Patient-reported outcomes

Patient demographics, disease characteristics and activity (Urticaria Control Test [UCT]), QoL assessments (Dermatology Life Quality Index [DLQI]), and treatment patterns were analyzed at Baseline and at subsequent visits roughly every 3 months. Patients were asked by their physician if they experienced hives and/or angioedema within the previous 6 months at Baseline, and within the previous 3 months at subsequent visits (i.e., the period between each visit).

The UCT retrospectively assesses patients' burden of disease over the previous 4 weeks; a score of ≥ 12 points (range from 0 to 16 points) indicates that a patient's urticaria is controlled and a score of < 12 points indicates that the urticaria is uncontrolled.[23] UCT is a useful tool to monitor disease status over time, and to guide treatment decisions in patients with uncontrolled disease (i.e., UCT score < 12).

The dermatology life quality index (DLQI), chronic urticaria QoL questionnaire (CU-QoL) and, for those with angioedema, angioedema QoL questionnaire (AE-QoL) were used to assess the impact of CSU on patients' QoL. DLQI is a validated, dermatology-specific 10-item questionnaire with six subheadings: symptoms and feelings; daily activities; leisure; work and school; personal relationships; and treatment. The DLQI score ranges between 0 and 30, with higher scores indicative of a greater QoL impairment.[24]

The AE-QoL is a 17-item questionnaire that includes four subdomains: functioning; fatigue/mood; fears/shame; and food (each item is answered on a Likert scale ranging from 0 [not important] to 4 [very important]).[25, 26] The CU-QoL is a 23-item questionnaire used to assess the effect of CU on patients' overall functioning, sleep, itching/embarrassment, mental status, swelling/eating, and limits looks (each item is marked on a Likert scale ranging from 1 [not at all] to 5 [very much]).[27] The total scores of the CU-QoL and AE-QoL questionnaires are transferred to scales ranging from 0 to 100, with higher scores reflecting greater impairment in QoL.

Statistical analysis

Results are reported as observed. Means, medians, standard deviation (SD), minimum and maximum are stated for quantitative values, and absolute and relative frequencies for categorical measurements.

Results

Demographics and clinical characteristics

Patient demographics and clinical characteristics of the AWARE patients in Germany have been previously published in detail.[20] Overall, 1550 patients with H₁-antihistamine-refractory CSU were included into the analysis population; 71.3% (n=1105/1550) were enrolled at office-based dermatologists, whereas 28.7% (n=445/1550) were enrolled in outpatient clinics of hospitals. The mean ($\pm$ SD) age was 47.1 $\pm$ 15.6 years, and 70.1% (n=1086) were female. The mean ($\pm$ SD) time since CSU was diagnosed was 4.9 $\pm$ 7.4 years, and the mean ($\pm$ SD) body weight was 77.9 $\pm$ 17.4 kg. Of note, 22% (n=341) of the patients with CSU had CIndU as a comorbidity.

CSU remained uncontrolled in many patients after 1 year in AWARE

At Baseline, 91.1% (n=1407/1545) of patients reported that they experienced hives at least once within the previous 6 months. Subsequent visits showed that although reports of hives (occurring at least once during the 3 months between each visit) decreased throughout the observation period, 59.1% (n=600/1015) of patients reported that they were still affected after 1 year of follow-up (**Figure 1**). Rates of angioedema were also high at Baseline, with 43.9% (n=678/1544) of patients reporting that they experienced at least one episode within the previous 6 months; at Month 12, 16.1% (n=163/1011) reported having experienced angioedema within the previous 3 months.

At Baseline, 78.2% (n=1188/1520) of patients with CSU had uncontrolled urticaria (UCT score

<12); while after 1 year of follow-up, although there was an improvement in disease control, 42.2% (432/1032) still experienced uncontrolled symptoms (**Figure 1**). Mean ($\pm$ SD) UCT score overall was 7.7 ± 4.3 at Baseline; this improved to 10.5 ± 4.0 at Month 3, following which they remained at similar levels (11.1 ± 4.0 at Month 6; 11.3 ± 3.9 at Month 9; 11.7 ± 3.7 at Month 12). At Month 12, patient with hives reported a mean ($\pm$ SD) UCT score of 10.5 ± 3.5 , while for those not reporting hives it was 13.4 ± 3.3 .

Quality of life impairment remained high in many patients after 1 year in AWARE

At Baseline, 55.7% of patients reported that CSU had a moderate, very large or extremely large effect on their QoL, as measured by DLQI; at Month 3, this proportion of patients decreased to 36.9%. The extent of this initial improvement was not seen across Months 6 (32.7%) to 12 (28.2%; **Figure 2**). Mean DLQI ($\pm$ SD) score at Baseline was 8.3 ± 6.9 ; this improved to 5.2 ± 5.6 at Month 3, following which the scores remained similar (4.7 ± 5.4 at Month 6; 4.5 ± 5.4 at Month 9; 4.1 ± 5.0 at Month 12).

Similarly, mean ($\pm$ SD) CU-QoL total scores improved more between Baseline (36.5 ± 20.0) and Month 3 (26.4 ± 18.9), with smaller improvements up to Month 12 (21.8 ± 17.6) (**Figure 2**). The most affected subdomains of the CU-QoL questionnaire were itching/embarrassment (Baseline: 48.8 ± 26.3 ; Month 12: 25.0 ± 22.1), sleep (Baseline: 45.6 ± 26.7 ; Month 12: 32.2 ± 25.5), and mental status (Baseline: 41.6 ± 26.1 ; Month 12: 28.1 ± 25.3).

The impact of angioedema on QoL, as assessed by mean ($\pm$ SD) AE-QoL, was high, 42.8 ± 22.9 (**Figure 2**). Improvements were observed across visits, but the impact on QoL remained high at Month 12 (28.8 ± 19.9). The most affected subdomains of the AE-QoL questionnaire were fears/shame (Baseline [mean $\pm$ SD]: 49.3 ± 28.2 ; Month 12: 32.2 ± 24.9), and fatigue/mood (Baseline: 44.0 ± 26.2 ; Month 12: 34.8 ± 25.4).

Most patients do not receive guideline-recommended CSU treatments

In general, CSU patients did not receive guideline-recommended treatments (**Figure 3**). Pre-enrollment, 29.9% (n=463/1550) of patients reported that they were receiving no treatment and 17.7% (n=274/1550) were receiving treatments that were not guideline-recommended. Furthermore, pre-enrollment guideline-recommended treatment was received by only half of the patients; 17.3% (n=268/1550) were receiving first-line therapy with non-sedative H₁-antihistamines at the approved dose, 23.9% (n=370/1550) were receiving second-line therapy with non-sedative H₁-antihistamines at increased dose, and 11.3% were receiving third-line therapies (omalizumab, 8.5% [n=131/1550]; montelukast, 2.3% [n=36/1550]; ciclosporin, 0.5% [n=8/1550]).

After 1 year, the numbers of patients not receiving guideline-recommended CSU treatments remained high, with 20.2% (n=228/1130) still receiving no treatment after one year, and 17.4% (n=197/1130) of patients receiving treatments that were not guideline-recommended. Further analysis of patients receiving no treatment confirmed that, of 145 patients with available UCT and symptom data at 1 year, 66.2% (n=96/145) were not fully controlled on the UCT or still experienced hives and/or angioedema. In contrast, only 33.8% (n=49/145) had fully controlled CSU (UCT=16) and were free of symptoms; 83 patients receiving no treatment had missing UCT or symptom data at 1 year.

CSU patients with uncontrolled disease are not switched to effective treatment

In a sub-analysis of 528 patients with uncontrolled urticaria (UCT<12; **Table 1**), 36.9% (n=195/528) were receiving the approved dose of H₁-antihistamines at Baseline, while 63.1% (n=333/528) were receiving them at increased dose. Escalation of treatment from the approved dose to increased dose H₁-antihistamines was low throughout the 1-year observation period; ranging from 0% to 6.7% at the visits during that time (**Table 1**). In the few patients who received up-dosing from the approved to increased dose of H₁-antihistamines, this was associated with a greater

improvement in UCT scores, compared with the mean UCT overall and for those who did not switch to this treatment (**Supplementary Table 1**).

Escalation of treatment to omalizumab in patients who were insufficiently controlled with H₁-antihistamines at increased dose ranged from 0% to 11.1% (**Table 1**). Across Months 3 to 12, rates of treatment escalation to omalizumab in this subpopulation of patients were all <2%. In the 11.1% of patients switched to treatment with omalizumab at Baseline, there was a corresponding increase in mean UCT score at Month 3 among those who switched, compared with the overall mean UCT score and for that of those who did not switch to this treatment (**Supplementary Table 2**).

Discussion

These 1-year results from AWARE in Germany confirmed that, although international guidelines and effective treatment options are available, CSU remains undertreated, with many patients still receiving no treatment or only the approved dose of second-generation H₁-antihistamines despite being refractory to them. Enrolled patients had a long time until diagnosis was established and many may have been uncontrolled for years. Previous studies in CSU have shown that longer disease duration is associated with longer time to remission and more severe disease,[28, 29] indicating a great need for earlier treatment and better disease management.

According to the 2014 CU guidelines (i.e., the relevant guidelines at the time of the AWARE study),[9] all patients with CSU that is insufficiently controlled by the approved dose of second-generation H₁-antihistamines (first-line) should be up-dosed to 2–4× the approved dose of second-generation H₁-antihistamines (second-line), followed by add-on therapy with omalizumab, montelukast or ciclosporin (third-line); however, this guidance was not followed for a substantial number of patients in AWARE. After one year, 37.6% of patients were still receiving treatment that was not guideline recommended. Of those 66.2% received no treatment at all despite being

symptomatic. Unfortunately, owing to the registry nature of this study, the reasons for not following CU guideline recommendations were not recorded.

The burden of CSU was evident from the substantial numbers of patients reporting that CSU was uncontrolled (UCT < 12) and that it affected their QoL (moderate to extremely large effect on DLQI), particularly at Baseline. At Month 12, many patients still reported experiencing hives (59.1% [n=600/1015]) and angioedema (16.1% [n=163/1011]), with just under half of patients (42.2% [n=432/1023]) scoring UCT<12, thus indicating that the majority of patients with active disease had uncontrolled symptoms. Previous studies have shown that CSU can severely affect patients' QoL,[30-32] with a high emotional burden and rates of psychiatric comorbidities.[33, 34] Improvements in HR-QoL, UCT score, and the presence of hives or angioedema were seen throughout the 1-year period, but they were more substantial at earlier visits. This improvement between Baseline and Month 3 could be attributed to the overall higher use of pharmacological treatments compared with pre-enrollment and/or the higher rate of treatment escalation in patients with uncontrolled urticaria; however, escalation of therapy to recommended second- and third-line treatments was lower than expected throughout the one-year observation period. In addition, although improvements were seen in the signs and symptoms of CSU and HR-QoL, 48.9% of patients still experienced uncontrolled disease at Month 12. Many of these patients may have benefited from a timely treatment escalation.

Increased dose H₁-antihistamines have long been regarded as an effective treatment for CSU[35] and can achieve symptom control in more patients than those using the approved dose.[36-38] A recent meta-analysis of randomized, double-blind studies of H₁-antihistamine up-dosing in patients with CSU found that up-dosing improved itching, but not the number of hives in patients who are inadequately controlled by the approved dose.[12] In AWARE, substantial improvements in UCT

were observed in patients who were up-dosed to increased dose H₁-antihistamines; however, the number of patients whose dose was escalated was very low considering the high numbers of patients still receiving the approved dose of H₁-antihistamines at Month 12, despite being refractory to this treatment.[38]

Omalizumab was the first drug approved for use in patients with CSU who remain symptomatic despite H₁-antihistamine treatment and it is currently the only licensed third-line treatment.[39] In AWARE, similar substantial improvements in UCT were observed for patients who were escalated to omalizumab as those who up-dosed from the approved to increased dose H₁-antihistamines, but the number of patients who were escalated was lower than would be expected according to the guidelines. Several randomized controlled trials (RCTs) have shown that omalizumab effectively controls the symptoms of CSU,[13, 16-18, 40-42] improves the QoL,[13, 16-18, 40-44], reduces the frequency and severity of angioedema in H₁-antihistamine-refractory CSU,[7] as well as the fears of suffocation or of suffering from a life-threatening episode of angioedema.[8] The results of these randomized control trials and those of AWARE support the need for greater implementation of second- and third-line therapies according to treatment guidelines.

In many healthcare systems, CSU patients are initially seen by a primary care physician. Some might be not familiar with the international CU guidelines and hence do not prescribe guideline-recommended treatments.[19] In this German study, 71.3% of patients were enrolled at office-based dermatologists and 28.7% in outpatient clinics of hospitals, but no major differences in the escalation of therapy were observed between them. Physician and patient preferences may play a role in the infrequent up-dosing of H₁-antihistamines. Some physicians may feel there is conflicting evidence for the efficacy of up-dosing H₁-antihistamines or may not up-dose as it is an off-label dosage in Germany.[12] Some patients have concerns about side effects, loss of efficacy or dependency associated with up-dosing H₁-antihistamines,[38] and may choose not to up-dose for these reasons. Regarding biologic treatments, cost and reimbursement criteria can determine whether physicians choose omalizumab over other treatments, but these should in principle not be

deciding factors in Germany where it is fully reimbursed by health insurance for qualifying patients.

Poor physician experience with omalizumab may also be an issue.[19]

Due to the registry nature of AWARE, the number of patients for which data is available varies between visits, as well as across the parameters measured; therefore data should be interpreted with caution. The numbers of patients whose treatment was escalated from the approved dose to increased dose H₁-antihistamines, and from increased dose H₁-antihistamines to omalizumab, was very low across all visits, therefore any associations with changes in UCT score should be interpreted with caution. Further studies are required to determine any true association between escalation of these treatments and subsequent improvements in UCT scores.

The findings of the AWARE study revealed a significant discrepancy between recommendations in international treatment guidelines and the real-world treatment of patients with CSU, whose lives are seriously burdened by their disease. Initial improvements in symptom control and HR-QoL plateaued after Month 3 when fewer changes to patients' treatments were implemented, especially regarding the escalation of therapy to second- and third-line options. Current guideline recommendations (i.e. the daily use of H₁-antihistamines [up to 4× standard doses], followed by add-on therapy with omalizumab [third line] and ciclosporin [fourth line]) are effective and should be implemented for patients whose symptoms remain uncontrolled (UCT < 12) on their current medication.

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Figure 1. Prevalence of (A) hives^a and (B) angioedema^a, and (C) the proportion of patients with uncontrolled (UCT <12) or controlled (UCT ≥12) disease^b among patients with CSU

^aPatients were asked if they experienced hives or angioedema within the previous 6 months at Baseline and within the previous 3 months at subsequent visits (i.e., the period between each visit); ^bUCT is a measurement of disease control during the 4 weeks prior to each assessment. The number of subjects with available data at each visit varied because of the registry nature of AWARE.

CSU, chronic spontaneous urticaria; UCT, urticaria control test.

Figure 2. Quality of life of patients with CSU, as measured by (A) DLQI, (B) CU-QoL and (C) AE-QoL

The number of subjects with available data at each visit varied because of the registry nature of AWARE.

AE-QoL, angioedema quality of life questionnaire; CU-QoL, chronic urticaria quality of life questionnaire; DLQI, dermatology life quality index

Figure 3. Numbers (and percentages) of patients receiving different treatments at each visit

^aE.g. ketotifen, dapson, etc.; ^bE.g. 'as needed'

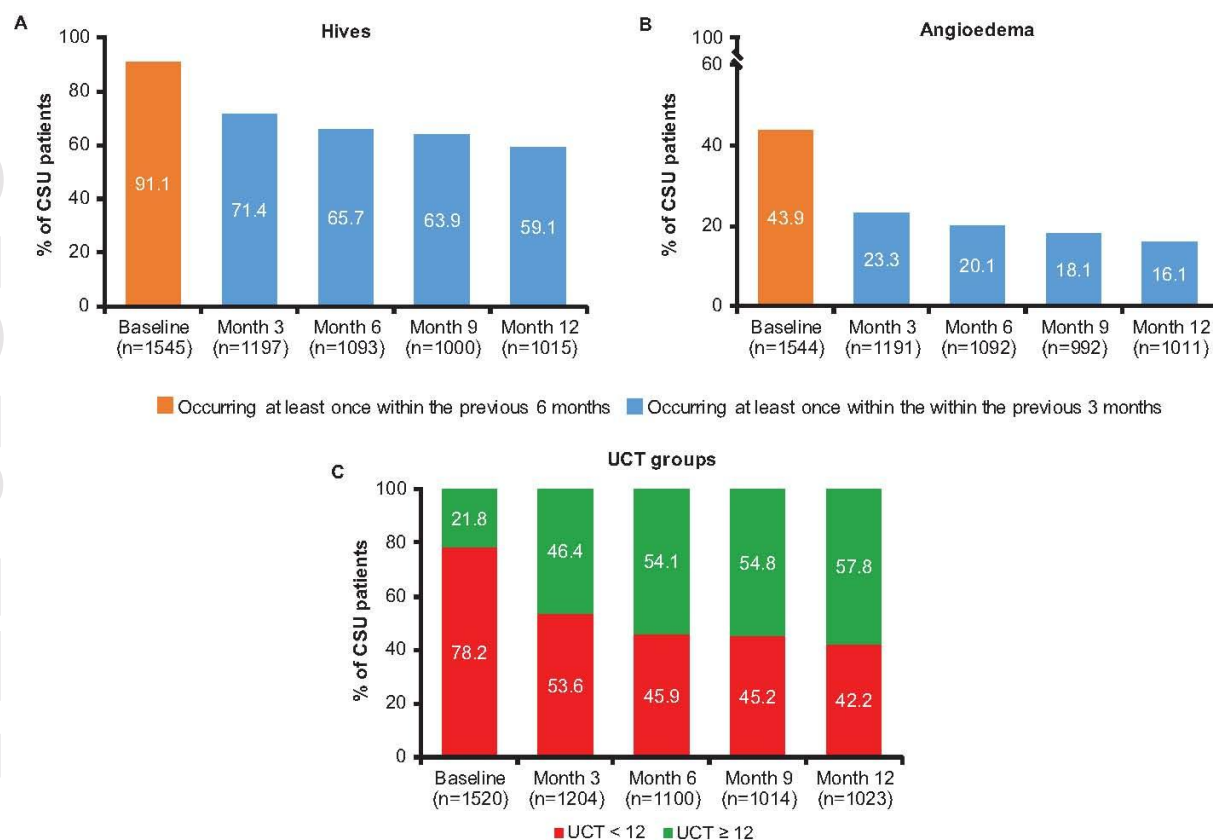
Guideline-recommend treatments are shown in color. Patients in the 2nd gen. H₁-AH once-daily or increased frequency groups were only included in these groups if they were not receiving add-on third-line medications (i.e., omalizumab, ciclosporin, or montelukast); patients in the omalizumab, ciclosporin, and montelukast groups may have been receiving concomitant H₁-AH once-daily or at increased frequency in accordance with guideline recommendations.

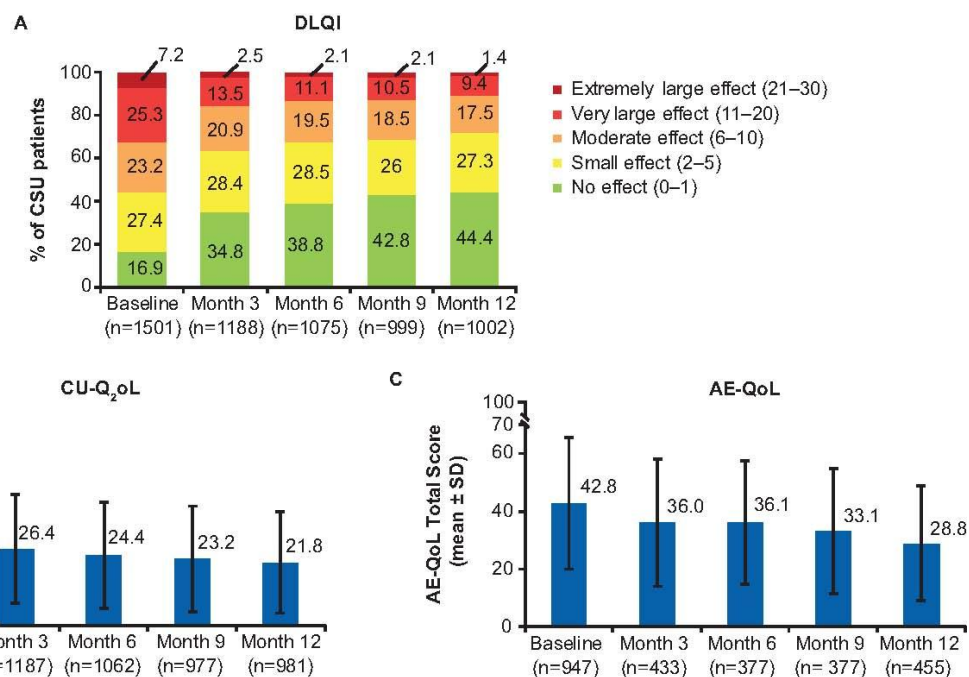
gen., generation; H₁-AH, H₁-antihistamine

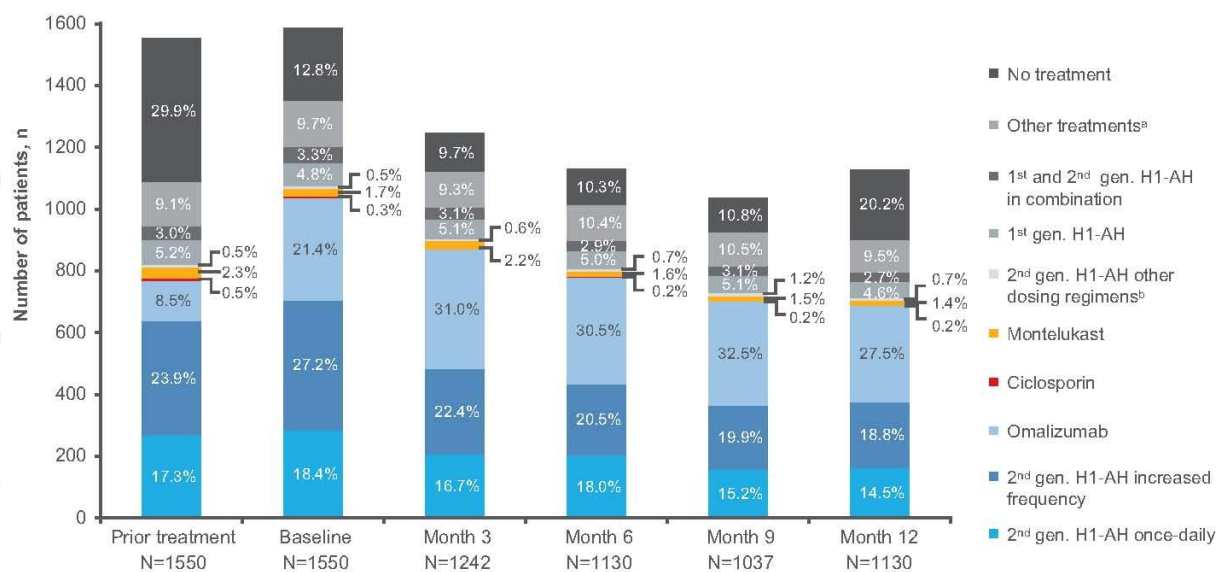
Table 1. Escalation of therapy in patients with UCT < 12.

Category, % (n/M)	Baseline	Month 3	Month 6	Month 9	Month 12
Approved dose to increased dose H ₁ - AH	5.6 (11/195)	1.6 (2/124)	0.0 (0/90)	6.7 (5/75)	0.0 (0/66)
Increased dose H ₁ - AH to omalizumab	11.1 (37/333)	1.1 (2/187)	1.5 (2/132)	1.9 (2/106)	0.0 (0/109)

H₁-AH, H₁-antihistamine; n, number of patients with treatment escalation; M, number of patients with UCT < 12 at each visit







Supplementary Tables

Table 1. Escalation of therapy in patients with UCT < 12, from the approved (≥ 3 months) of H₁-AHs to increased dose H₁-AHs. Corresponding UCT scores pre-escalation and at the subsequent visit post-escalation are shown.

		Switched to increased dose H ₁ -AHs		No Switch		Total	
Visit	Escalation Status	n	UCT, mean $\pm$ SD	n	UCT, mean $\pm$ SD	N	UCT, mean $\pm$ SD
Baseline	Pre ^a	11	5.4 $\pm$ 2.8	184	6.4 $\pm$ 3.0	195	6.3 $\pm$ 3.0
Month 3	Post ^b	8	12.6 $\pm$ 3.5	135	9.7 $\pm$ 3.9	143	9.9 $\pm$ 3.9
	Pre ^a	2	7.5 $\pm$ 2.1	122	7.7 $\pm$ 2.9	124	7.7 $\pm$ 2.9
Month 6	Post ^b	2	9.5 $\pm$ 3.5	103	9.9 $\pm$ 3.4	105	9.9 $\pm$ 3.4
	Pre ^a	0	n/a	90	8.2 $\pm$ 2.5	90	8.2 $\pm$ 2.5
Month 9	Post ^b	0	n/a	69	9.4 $\pm$ 3.9	69	9.4 $\pm$ 3.9
	Pre ^a	5	8.8 $\pm$ 3.9	70	7.5 $\pm$ 2.7	75	7.6 $\pm$ 2.8
Month 12	Post ^b	5	6.8 $\pm$ 5.0	59	10.3 $\pm$ 3.9	64	10.0 $\pm$ 4.1

^aPatients were escalated to increased dose H₁-AHs at this visit; ^bPatients were escalated at the previous visit and have available data at this visit. H₁-AH, H₁-antihistamine; SD, standard deviation; UCT, urticaria control test

Table 2. Escalation of therapy in patients with UCT < 12, from increased dose H₁-AHs (≥ 3 months) to treatment with omalizumab. Corresponding UCT scores pre-escalation and at subsequent visit post-escalation are shown.

		Switched to omalizumab		No Switch		Total	
Visit	Escalation Status	n	UCT, mean ± SD	n	UCT, mean ± SD	N	UCT, mean ± SD
Baseline	Pre ^a	37	4.1 ± 3.1	296	6.0 ± 3.0	333	5.8 ± 3.1
	Post ^b	36	11.7 ± 3.3	243	9.1 ± 4.1	279	9.5 ± 4.1
Month 3	Pre ^a	2	6.0 ± 5.7	185	7.3 ± 2.9	187	7.3 ± 2.9
	Post ^b	2	9.0 ± 1.4	154	9.0 ± 3.8	156	9.0 ± 3.8
Month 6	Pre ^a	2	9.0 ± 1.4	130	7.6 ± 2.9	132	7.6 ± 2.9
	Post ^b	2	11.0 ± 0.0	110	9.0 ± 3.5	112	9.0 ± 3.5
Month 9	Pre ^a	2	5.0 ± 4.2	104	7.7 ± 2.7	106	7.7 ± 2.7
	Post ^b	2	14.0 ± 2.8	93	9.8 ± 3.4	95	9.9 ± 3.5
Month 12	Post ^b	2	14.0 ± 2.8	93	9.8 ± 3.4	95	9.9 ± 3.5

^aPatients were escalated to omalizumab at this visit; ^bPatients were escalated at the previous visit and have available data at this visit. H₁-AH, H₁-antihistamine; SD, standard deviation; UCT, urticaria control test