Original Article

Evaluation of a Guidelines-Based Approach to the Treatment of Chronic Spontaneous Urticaria

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What is already known about this topic? Considering scientific evidence of the treatment of chronic spontaneous urticaria in a rational manner, international scientific associations have made certain recommendations that are available to practitioners as clinical guidelines. However, these recommendations have not been evaluated in a step-by-step approach.

What does this article add to our knowledge? The sequential evaluation of treatment lines, recommended by urticaria guidelines, allows a more rational determination of control disease rates for each step and their clinical impact in an integrated manner.

How does this study impact current management guidelines? These results improve guideline recommendations by evaluating each line of treatment sequentially: use of H1 antihistamines in conventional doses (first line), up-dosing of antihistamines (second line), and use of omalizumab or cyclosporine in those with refractory response to H1 antihistamines.

BACKGROUND: International scientific associations have made recommendations for the management of chronic spontaneous urticaria (CSU) that have been summarized in clinical guidelines.
OBJECTIVE: To evaluate the clinical impact of guideline recommendations for CSU management.
METHODS: A multicenter, triple-blinded, prospective, randomized study (the Urticaria Research of Tropical Impact and Control Assessment project; ClinicalTrials.gov identifier: NCT01940393) was performed. Patients older than 12 years and diagnosed with CSU were recruited and treated according to the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guideline recommendations. The Dermatology Quality of Life Index (DLQI) was assessed every 2 weeks. As a first line of treatment, patients received a daily oral dose of antihistamine. After 4 weeks, in those patients without clinical response (DLQI ≤ 5), a higher dose (up to 4 times) of antihistamine was administered as a second line of therapy. After 2 months of follow-up, unresponsive patients received omalizumab or cyclosporine (as add-on therapy) for 4 months as a third line of treatment.
RESULTS: One hundred fifty patients were enrolled. After the first line of treatment, 88 patients (58.7%) reached a DLQI of 5 or less. With the second line of treatment, disease control rate was 76.7%. With the third line, 12 patients from the omalizumab group (8%) and 11 patients from the cyclosporine group (7.3%) reached a good clinical control (additional 15.3%). Control rate with line 1 treatment was superior at 1 month than at 2 weeks ($P < .0001$).
CONCLUSIONS: The application of these guideline recommendations for CSU led to a high rate of disease control, assessed by scoring severity and patients' perception of quality of life. These results support the usefulness of guideline recommendations. **(J Allergy Clin Immunol Pract 2018;6:177-82)**

Key words: *Urticaria; Guidelines; Antihistamines; Omalizumab; Cyclosporine*

Urticaria is a group of different clinical conditions and is a common disease that significantly impacts quality of life.[1] Among these conditions, it is estimated that chronic urticaria affects between 0.5% and 5% of the general population.[2,3] Avoidance of inducers (ie, physical, food, or others) may help to mitigate the frequency of symptoms in those cases in which a causal relationship with any of them has been identified; however, in a large number of patients, the symptoms appear spontaneously without a clear trigger, a clinical condition named as chronic spontaneous urticaria (CSU).[4-6] H1 antihistamines

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Abbreviations used
anti-H1- H1 antihistamines
CSU- Chronic spontaneous urticaria
DLQI- Dermatology Life Quality Index
EAACI- European Academy of Allergy and Clinical Immunology
UAS- Urticaria Activity Score
UAS7- Weekly Urticaria Activity Score

(anti-H1) are the cornerstone in the management of CSU. Some clinical studies support the usefulness of second-generation anti-H1, in a higher dose, to reduce the severity of symptoms in a proportion of patients without clinical control at a conventional dose.[7,8] When this treatment option is not successful, other pharmacological options, such as cyclosporine and omalizumab, are recommended.[9-11]

Considering scientific evidence of CSU treatment in a rational manner, international scientific associations have made certain recommendations that are available to practitioners as clinical guidelines.[3,12,13] However, these recommendations derive from merging independent investigations, which implies the inclusion of heterogeneous groups of patients and different study designs, which may bias comparison of therapeutics. To our knowledge, there are no reports that evaluate, as a sequential approach, treatment lines proposed in these guidelines. The application of each line of treatment as a stepwise protocol would allow to determine the impact of disease control achieved by each of them.

This study aimed to evaluate, sequentially, current urticaria guideline recommendations for using anti-H1 in conventional doses (first-line treatment), up-dosing antihistamines (second-line treatment), and using omalizumab or cyclosporine in those with refractory response to anti-H1 (third-line treatment).

METHODS

Study population

A multicenter, prospective, triple-blinded study was conducted using as a starting point a previously formed cohort (Urticaria Research of Tropical Impact and Control Assessment; ClinicalTrials.gov identifier: NCT01940393).[7,14] Patients were recruited from 6 different centers in 2 Colombian cities (Bogotá and Medellín) with similar genetic and sociodemographical conditions.[15,16] Patients were older than 12 years, with a diagnosis of chronic urticaria defined as the recurrent of hives, with or without angioedema, on more than 3 days per week persisting for at least 6 weeks. An allergist or dermatologist made the diagnosis. Exclusion criteria were systemic disease presentation that could explain the hives and systemic steroids usage during the last 3 weeks before recruitment or any other therapy that could interfere with the evaluation of symptoms.

Quality of life and severity evaluation: Questionnaire tests

Because the Dermatology Life Quality Index (DLQI) was previously validated in Colombia, it was selected among different questionnaires to assess quality of life. In addition, we used the Urticaria Activity Score (UAS) and the weekly UAS (UAS7) to measure the disease severity.

Study design

We present the results base in the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guidelines. However, there were differences in the time of evaluation: the waiting time in the clinical response to antihistamines in the first and second lines was higher than recommended in the guide. As previously described,[7] participants were randomized (1:1:1:1:1) using Microsoft Excel 2010 (Microsoft Corp, Redmond, Wash) to receive 1 of 5 anti-H1 options frequently used in the 2 cities (Bogotá and Medellín). During the first month, participants received a daily oral dose of cetirizine (10 mg), fexofenadine (180 mg), bilastine (20 mg), desloratadine (5 mg), or ebastine (20 mg). All anti-H1 medications were supplied in a triple-blinded way every 2 weeks during the first 2 months of follow-up; they were then supplied monthly in identical capsules. A clinical evaluation was done every 2 weeks until the end of the follow-up.

After the first month, the anti-H1 dosage was adjusted according to its clinical effectiveness and adverse reactions. Patients whose disease was clinically controlled (DLQI $\leq$ 5) without adverse reactions continued with the same dose. The dose was increased in unresponsive patients (DLQI $\geq$ 5) according to the sedative effect of the treatment: if the participant reported mild or no sedative adverse effects with the conventional dose, it was quadrupled, whereas if a moderate or severe sedative effect was reported, it was doubled.

After 2 months, patients without clinical response with anti-H1 continued with an anti-H1 and were randomized to additionally receive omalizumab 300 mg/mo or cyclosporine 3 mg/kg/d (100-250 mg) for 4 months. The administration of these drugs was not blinded because of the difference in administration routes.

Safety and tolerability

Safety and tolerability were assessed according to the adverse events reported by participants during each clinical follow-up. Laboratory tests (blood cell count, aspartate aminotransferase, alanine aminotransferase, creatinine, ureic nitrogen, and electrocardiogram [EKG]) were performed at baseline and then monthly during follow-up. Sedation was evaluated with a questionnaire test as was described earlier.[7] The sedative effect was considered "strong" when patients had 3 points in 1 of the 3 questions or 6 to 9 points in total. When patients were included in the third line of treatment (omalizumab or cyclosporine), blood pressure was measured weekly and the aforementioned laboratory tests were performed every 2 weeks.

Ethical considerations

The Ethics Committee of IPS Universitaria Clinics (registry no. IN13-2013) and the University of Antioquia approved this study (registry no. BE-IIM 200910). All subjects signed an informed consent approving their voluntary participation in the study. In patients younger than 18 years, additional approval was asked from their legal representative.

Taking into consideration the recommendation of the ethics committee, we did not include a placebo group, because it would have provided little information on the primary outcome of the study and there is consistent evidence supporting the effectiveness of antihistamines as first-line treatment in patients with urticaria.

Statistical analyses

Most analyses were done using SPSS version 21.0 (SPSS Inc, Chicago, Ill). The total number and proportions were reported for categorical data. Frequency rates and their 95% CIs were obtained using Epidat 3.1 (Xunta de Galicia, PAO/World Health Organization). Mann-Whitney *U* test was used for comparison of continuous variables. Differences between proportions were analyzed by Pearson

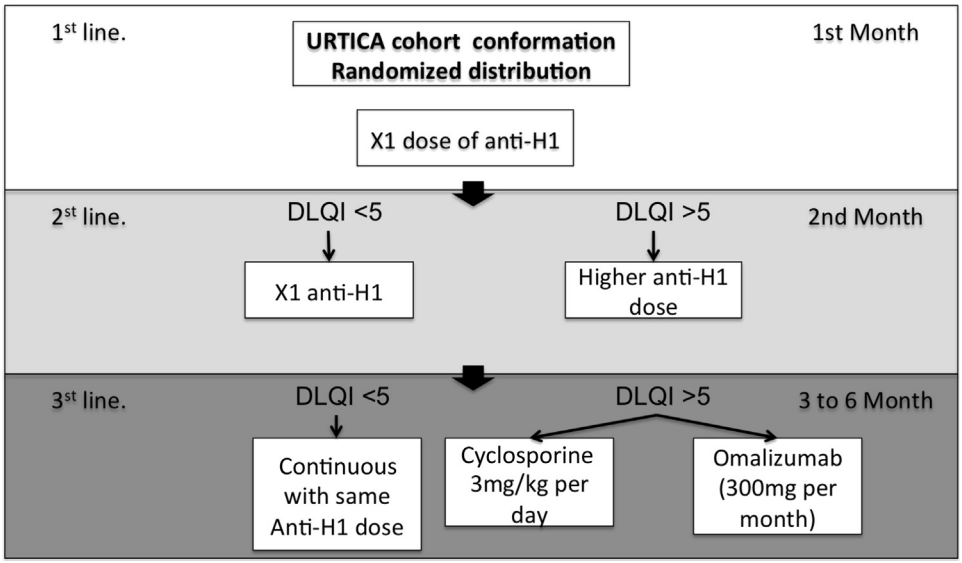

FIGURE 1. Study design. *URTICA*, Urticaria Research of Tropical Impact and Control Assessment.

chi-square test (or McNemar test when appropriate). Linear-by-linear association test was used for trend analysis. Multivariate binary logistic regression was used to analyze the relationships of exposures and outcomes.

RESULTS

A flowchart depicting the progress of subjects through the study is presented in Figure 1. Clinical and demographic features of patients involved in the study are presented in Table I. No significant differences were found between patients recruited from the 2 cities. Achievement of disease control during the 6-month follow-up is shown in Figure 2. According to DLQI results, the general success rate achieved with guideline recommendations was 92% (95% CI, 87.66%-96.34%). The 3 different control levels of the DLQI (none, moderate, and well-controlled) are shown in Figure 3. Twelve patients did not respond to any therapy and no significant predictors (age, sex, city of residence, onset age of urticaria, atopy, type of anti-H1, and basal DLQI) of treatment failure were identified (data not shown). In total, 88 patients (58.7%) were treated with line 1, 27 with line 2 (18%), and 35 with line 3 (23.3%). Rates of disease control (DLQI) increased gradually with every time point (P for a trend $<.0001$).

During the second and subsequent visits, UAS was lower than 3 points in most patients (92.5%) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Hence, DLQI scoring was more sensitive to detect clinical changes during follow-up. Although the application of UAS7 to grade control disease was planned, the fact that only 48 patients (32%) kept a proper record of this questionnaire limited its analysis.

Lines 1 and 2: Antihistamines in conventional and higher doses

Because anti−H1-treated patients from the triple randomized controlled trial had similar control rates, they were considered as a single group for further analyses (n = 150). Disease control after 1 month of anti-H1 treatment at a conventional dose was observed in 88 patients (58.7%; 95% CI, 50.82%-66.58%); however, in 11 participants, it was reduced (0.5 times) because of reported strong sedation. Because the EAACI and the Global Allergy and Asthma European Network guidelines have proposed

TABLE I. Population characteristics

Characteristic	All (N = 150)	Medellín (n = 99)	Bogotá (n = 51)
Sex, female, n (%)	94 (62)	61 (61)	33 (64)
Age (y), mean (range)	28 (14-50)	28 (14-50)	28 (14-48)
Urticaria onset, mean (range)	26 (7-49)	26 (7-49)	26 (13-47)
Atopy, n (%)	66 (44)	44 (44)	22 (43)
Asthma, n (%)	21 (14)	11 (11)	10 (19)
Rhinitis, n (%)	63 (42)	40 (40)	23 (45)
DLQI, mean ± SD	15 ± 3	15 ± 3	15 ± 3
UAS, mean ± SD	3 ± 1	3 ± 1	3 ± 1

Note. There was no significant difference between patients from Medellin and Bogotá according to general characteristics.

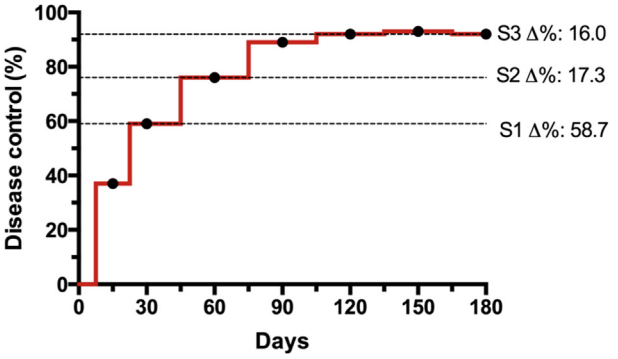

FIGURE 2. DLQI control (≤5 points) during 6 months of follow-up. S1: first month (anti-H1 1×); S2: second month (anti-H1 4×); and S3: sixth month (anti-H1 4× plus omalizumab or cyclosporine).

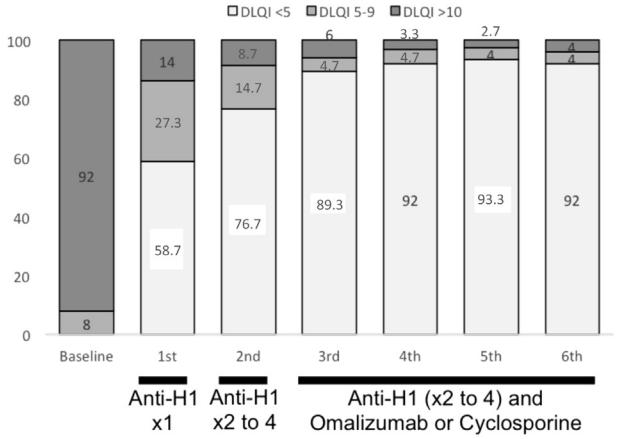

FIGURE 3. DLQI control degrees: none (black), moderate (gray), and well-controlled (white).

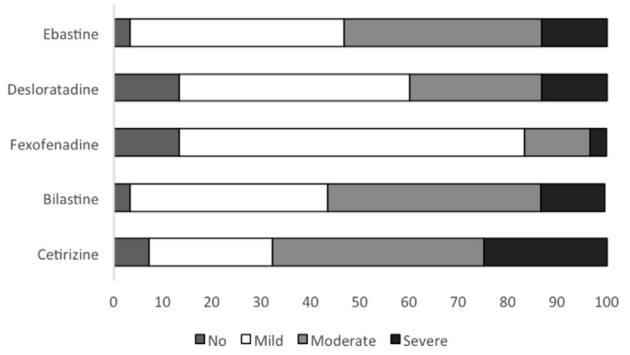

FIGURE 4. Antihistamines sedation effect. Sedation rate after 2 months with antihistamines in conventional and higher doses.

15 days, we tested whether 1 month of treatment could be a more useful time point. Control rates were higher at 1 month than at 2 weeks (McNemar test; $P < .0001$); 34.7% of patients who did not achieve disease control at day 15 were optimally controlled at day 30. Most patients who reached disease control at day 30 (26 out of 33; 78.7%) but not at day 15 showed DLQI scores between 5 and 10 (partially controlled) at that previous time point.

Line 2 was considered after 1 month of follow-up when disease control was not achieved with line 1 (Figure 2). Most uncontrolled patients were scaled up to 4 times anti-H1 dose (n = 60), except 2 who reported strong sedation. At the 2-month time point evaluation, 27 out of 60 (45%) patients had reached control by using line 2 recommendation. In conjunction, rate of disease control with line 1 and line 2 recommendations was 76% (95% CI, 69.17%-82.83%).

To evaluate sedation, results from the "sedation" questionnaire were considered in 2 different manners: the perception of the effect as well as its severity. This adverse effect was frequently reported with anti-H1 medications, being mild in most of the cases (Figure 4). Frequency of sedation with conventional dose at day 30 was high (103 patients out of 150; 68.6%). Sedation rates increased with up-dosing. In the group receiving higher doses of anti-H1 (line 2), sedation reports increased from 66.7% (20 out of 60) at day 30 when they were still treated with a conventional dose to 93.2% (55 out of 59) at 2 months ($P < .05$). The lowest mean sedation score was observed in the fexofenadine group (mean, 2.1 ± 1.6; 2-month time point). Post hoc comparisons among the different anti-H1 indicated that the sedation score of fexofenadine was significantly lower than that of cetirizine and bilastine and similar to that of desloratadine ($P = .53$) and ebastine ($P = .07$); 81% of sedation reports for this anti-H1 were categorized as mild. The 2 patients who discontinued anti-H1 (both receiving cetirizine) were also randomly allocated to any of the line 3 options, cyclosporine or omalizumab, together with those not achieving control with anti-H1 medications (n = 33).

Line 3: Antihistamines plus omalizumab or cyclosporine

From the 35 patients (23.3%) with DLQI of more than 5 at month 2, 18 patients were initially allocated to receive cyclosporine and 17 to receive omalizumab. After 2 weeks, 1 patient receiving cyclosporine presented with hypertension and was then given omalizumab. After 4 months, 12 subjects from the omalizumab group and 11 from the cyclosporine group reached a good clinical control (Figure 3). Similar efficacy rates were observed for the 2 line 3 drugs after 2 months ($P = .59$).

In the omalizumab group, 4 patients reported headache and 9 reported local pain after subcutaneous injection. In those receiving cyclosporine, 2 developed transitory hypertension: in one, blood pressure returned to normal values in less than 2 weeks, but in the other, it persisted over 2 weeks and treatment was replaced by omalizumab. Six patients reported mild abdominal pain at some moment but it disappeared during follow-up. There were no alterations during physical examination, EKG results, or clinical laboratory data after the 6 months of follow-up.

DISCUSSION

Although different therapeutic agents have been proposed for the management of CSU, second-generation anti-H1, omalizumab, and cyclosporine are among the narrow group of pharmaceutical approaches recommended in clinical guidelines with enough scientific support of their safety and effectiveness. In the Joint Task Force on Practice Parameters,[13] representing the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology, other drugs, such as first-generation anti-H1, doxepin, anti-inflammatory agents, some immunosuppressants, and biologics, have been recommended, but only for certain groups of patients. In this study, using the European urticaria guideline as a benchmark, which shares similarities with the American proposal, we evaluated their most frequent pharmaceutical recommendations in a cohort of patients with CSU, administering, in a step-by-step manner, second-generation anti-H1 at a conventional dose or higher and omalizumab or cyclosporine as add-ons in refractory cases to assess their efficacy and safety.

After avoidance of possible triggers, first line of treatment for CSU is a second-generation anti-H1. The physiopathology of urticaria is mostly associated with histamine release. In spite of this, by using UAS7 to grade symptom severity, some reports have informed that clinical improvement after anti-H1 treatment is within the range of 5% to 50%.[17] This low response rate may be due to the co-release of other proinflammatory substances

during urticaria exacerbations as well as the occurrence of urticaria reactions, which are caused by non—histamine-mediated mechanisms.[18,19] According to our data, there was a significant proportion of patients whose symptoms were reduced with anti-H1 treatment: 76% of them achieved good clinical control with anti-H1 medications (measured by the DLQI), 58% with conventional doses, and 18% with higher doses. These findings support the use of anti-H1 medications as the first line of treatment in patients with CSU. Superior rates of efficacy observed with our results with regard to those found in other studies[20,21] may be due to the application of different scoring systems. Because most of the patients did not properly register information for UAS7 scoring, we decided to use DLQI results, which rather reflect patients' perception of illness and its impact on daily activities, even though this questionnaire is not intended to objectively assess disease severity. Despite the moderate correlation between the DLQI and the UAS (data not shown), sometimes severity score systems do not reflect the high impact perceived for patients. For example, most of the patients in our study had severe symptoms at baseline with significant improvement after anti-H1 treatment but with occasional relapses; nevertheless, they considered that these exacerbations were less severe and/or frequent than before and that they may realize their daily activities without limitations. Another important aspect to be considered is that in real-life studies (as well as in others with open design), a lower adherence could affect clinical response. This was a controlled study with a regulated delivery of medication, which helps to improve adherence to treatment.

EAACI guidelines recommend evaluating the efficacy of anti-H1 at conventional doses after 2 weeks of starting treatment. Although a placebo control group is necessary to better define a time point to evaluate the clinical effects of a treatment, it should be considered that in our findings disease control was achieved in a great proportion of patients as early as in 15 days, but also that a significant additional number of them (18%) reached it after 1 month. In a pilot study ($n = 54$), we observed that a 2-month therapy with conventional doses did not significantly increase disease control rates (data not shown), but a 2-week therapy was significantly better than a 1-week therapy.

It was observed that all anti-H1 drugs had a significant clinical improving effect on disease symptoms, according to DLQI and UAS scoring systems. With regard to safety, no alterations in laboratory tests or EKG results were observed in this sample; however, more than half the patients (91.8%) reported sedation as a side effect. Among anti-H1, fexofenadine was the least sedative. Although second-generation anti-H1 are considered nonsedating drugs, this adverse effect is reported in some cases. In this study, its frequency was higher than expected; thus, alternative explanations to objective drug-related sedation should be considered. Perhaps the high sedation rate in this Colombian population is due to a placebo-like effect; although the type of anti-H1 was blinded for patients, they did know they were receiving antihistamines. Even though this has not been formally addressed, there is a general belief in our country that these medications cause sedation. Another reason could be that the "sedation" questionnaire has good sensitivity, but low specificity. Even in those patients who reported a "severe" sedation effect, only 2 (7.2%) from the cetirizine group dropped out and 72% scored with "little or no impact" when they were asked for "treatment impact" through the DLQI questionnaire. In this sense, objective psychometric assessments are essential to determine the extent of sedation impairment.

Three randomized, double-blind, placebo-controlled studies (ASTERIA I, ASTERIA II, and GLACIAL) support, with more than 900 subjects, the efficacy and safety of omalizumab as an add-on therapy for patients with CSU who remained symptomatic despite anti-H1 treatment at licensed or higher doses.[13] Kessel and Toubi[22] showed that long-term use of cyclosporine is effective and safe, even after a 10-year administration in patients with severe CSU. All these studies demonstrated that both drugs are useful for treating anti-H1 refractory patients; however, they do not permit to conclude in which exact rate add-on therapy is required to achieve disease control because study participants were selected on the basis of being "nonresponders" to anti-H1 treatment. This has been discussed further by Kaplan.[23] The high response rate to antihistamines in our population could be due to the placebo effect; however, even after 3 months, most patients reported adequate control according to the DLQI and few patients required the third line of management; according to the quality-of-life measure used, 23% of patients with CSU (8.7% with DLQI > 10 and 14.7% with DLQI of 6-10) required omalizumab or cyclosporine, and both therapies had a good clinical impact in patients without anti-H1 response. There are few retrospective studies comparing therapies recommended as third line in guidelines or other alternative therapies.[24] In these studies, subjective evaluation parameters were used. Their use makes comparisons difficult. In general, omalizumab is preferred to cyclosporine because of its less toxic profile. We observed that both therapies (omalizumab and cyclosporine) had a similar effectiveness in patients with CSU with refractory response to anti-H1, and in general both were safe options. However, 1 patient receiving cyclosporine presented with a significant increase in blood pressure and was thus given omalizumab; once cyclosporine was suspended, the pressure returned to baseline values in a few days. Although previous studies have shown that response to cyclosporine could be observed within 1 or 2 weeks of treatment, in our study, omalizumab showed a faster effect.

CONCLUSIONS

A total of 92% patients reached a DLQI of 5 or less with EAACI guideline recommendations after 6 months of treatment, 58% with conventional doses of anti-H1 (line 1), an additional 18% with higher doses (line 2), and 15% with omalizumab or cyclosporine (line 3). This rate of clinical control and severity reduction supports the clinical usefulness of urticaria guideline recommendations. Our results could also contribute to improve guidelines for the treatment of CSU. One-month therapy with conventional doses of anti-H1 was superior to the 2-week time point (proposed in the current recommendations) to evaluate the efficacy of a drug dose. Also, the low rate of adverse effects within a 4-month period of administering omalizumab or cyclosporine indicates that both drugs are well tolerated. It is recommendable to perform similar studies in patients with inducible urticaria.

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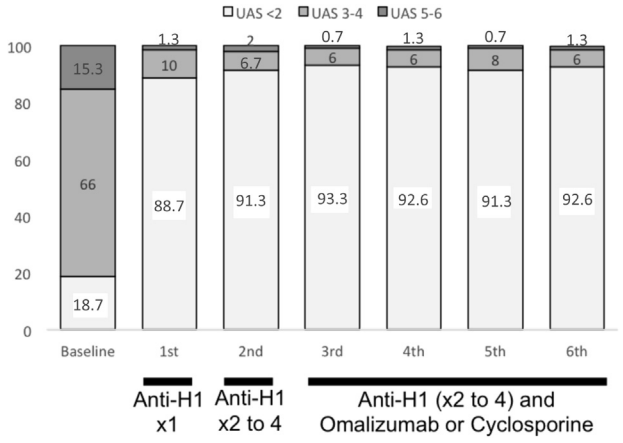

FIGURE E1. Urticaria Activity Score (UAS) control degrees: none (black), moderate (gray), and well-controlled (white).