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.** © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

***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