

CORRESPONDENCE

Comments on Balp et al

To the Editor

Few data are comparing chronic spontaneous urticaria (CSU) in children and adults. Balp et al¹ conducted an important online survey in five different European countries, with physicians that had seen at least one pediatric patient with CSU in the last 12 months. Their results suggest that the prevalence of chronic urticaria and CSU in children is similar to that observed in adults. On the other hand, they showed that there is a lower prevalence of angioedema in pediatric populations when compared to adults. They also highlight treatment patterns among this population indicating that a significant proportion of these patients are treated with H1-antihistamines, but around 1/3 of them are refractory to higher doses.

We conducted a retrospective analysis of medical records of patients treated at a center of excellence and reference in urticaria (UCARE) from April 2016 to June 2017. Disease characteristics and treatment patterns and response in children were compared to adults. The study was approved by the Ethics Committee, who waived the consent from patients, as it was a retrospective chart review.

A total of 113 patients with CSU between 4 and 76 years of age were evaluated, 31 of whom were children (aged 0-17 years). There was a higher prevalence in females in both groups, in a ratio of 5.8:1 in adults and 1.6:1 in children. In contrast to Balp et al,¹ most of our pediatric patients had angioedema (58%), and its presence was not related to disease duration or severity based on clinical criteria and urticaria activity score in 7 days (UAS7). Similar results were observed in adults. On the other hand, the length of the disease was on average longer in adults (310 weeks) than in children (170 weeks), but the more prolonged disease was associated with severity in neither group.

The presence of comorbidities such as atopy and autoimmunity was assessed, based on clinical history and the presence of laboratory markers (ANA and thyroid autoantibodies), respectively. Atopy was more prevalent in children (58%) than in adults (23%; $P < 0.05$), but there was no significant difference in autoimmunity prevalence between adults and children (21.9% and 29%, respectively).

Nonsteroidal antiinflammatory drugs (NSAIDs) is the leading cause of drug hypersensitivity reactions in our region,² and angioedema is the most frequent clinical manifestation. NSAIDs were associated with CSU exacerbations in up to 20% of patients, but more frequently in adults (25.6%) than in children (6.5%; $P < 0.05$). However, patients with angioedema were not at a higher risk of NSAID exacerbations.

Urticaria treatment aims total symptom control ($UAS7 \leq 6$).³ In our study, children achieved better disease control (64.5%) when compared to adults (37.8%; $P < 0.05$). H1-antihistamines are recommended as first- and second-line treatment for CSU.³ The majority of our pediatric patients (84%) are under treatment with an H1-antihistamine, but only 35% in licensed doses. Disease control was observed in 19% of children and 16% of the adults treated with these doses. Higher doses of H1-antihistamines were used by 52% of our pediatric patients (up to four times) and by 55% of adults and could control the symptoms in 35% and 14% of the patients, respectively.

Refractory CSU occurs in up to 40% of patients treated with H1-antihistamines.⁴ Balp et al¹ reported that 1/3 of the patients remained uncontrolled with H1-antihistamines at approved or higher doses. We observed a lower rate of nonresponders in children (23%). Omalizumab, cyclosporine, and leukotriene antagonists (LTRA) used to be recommended as add-on third-line treatment for patients with recalcitrant CSU.⁵ One of our pediatric patients was treated and controlled with LTRA associated with high doses of H1-antihistamine. Two of three patients were controlled with cyclosporine and 1 patient with omalizumab. In the adult's group, 30% of patients still had symptoms despite high doses of H1-antihistamines and required third-line treatment with LTRA (nine), cyclosporine (nine), and omalizumab (seven), with controlled disease in two, three, and five patients, respectively.

Our results showed some differences compared to Balp et al.¹ Despite the high number of patients evaluated, they used a methodology based on physician's recall, while we performed a medical record analysis. Moreover, patients seen in a center of reference tend to have more severe disease compared to those seen in private clinics and general hospitals. Even with a limited number of patients, clinical characteristics and treatment patterns of pediatric patients could be compared to adults, with some significant differences in our center. An increase in the number of patients analyzed and collaboration with other UCARE centers will allow us to understand better the similarities of CSU in these two populations.

Luis Felipe Ensina

Patricia Guerzet Ayres Bastos

Alex Eustaquio de Lacerda

Chayanne Andrade de Araujo

Inês Camelo-Nunes

Dirceu Solé

Department of Pediatrics, Division of Allergy, Clinical Immunology and Rheumatology, Federal University of São Paulo, São Paulo, Brazil

Correspondence: Luis Felipe Ensina, Department of Pediatrics, Division of Allergy, Clinical Immunology and Rheumatology, Federal University of São Paulo, Rua Barata Ribeiro, 490 - CJ. 67, São Paulo - SP 01308-000, Brazil (100alergia@gmail.com).

REFERENCES

1. Balp MM, Weller K, Carboni V, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018; <https://doi.org/10.1111/pai.12910>
2. Jares EJ, Sanchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol*. 2014;113:282-289.
3. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. *Allergy*. 2018;73:1393-1414.
4. Maurer M, Church MK, Gonçalo M, Sussman G, Sánchez-Borges M. Management and treatment of chronic urticaria (CU). *J Eur Acad Dermatol Venereol*. 2015;29(Suppl 3):16-32.
5. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.

DOI: 10.1111/pai.12963

Reply to Ensina et al

To the Editor,

Thank you for the opportunity to respond to the interesting letter of Ensina et al¹ sent in reference to our recent manuscript (Balp et al²). The two studies by Balp et al and Ensina et al had different objectives and were conducted in different geographical areas using different methodologies. Our study (Balp et al) reported diagnosed prevalence, clinical characteristics, and treatment patterns in pediatric patients (aged 0-17 years) with chronic spontaneous urticaria (CSU) in five European countries (United Kingdom, Germany, Italy, France, and Spain). It was a physician-based online survey with physicians recruited from a large and representative panel among these five European countries (conducted during September-October 2015). A total of 2074 physicians completed the screener questionnaire designed to estimate national prevalence of diagnosed CSU, and 1127 physicians completed the main questionnaire designed to collect data on CSU disease characteristics and treatments. The study included all relevant medical specialties that are likely to see, manage, and treat pediatric patients with CSU. The results reflect the real-world evidence and clinical practice across different specialties (GPs, pediatricians, dermatologists, and allergists) and not only specialized centers.

The study by Ensina et al aimed to describe and compare disease characteristics and treatment patterns in adults and children with CSU. The data were obtained from a retrospective analysis of medical records of patients treated at a GA²LEN Urticaria Center of Reference and Excellence (UCARE),³ Federal University of São Paulo, São Paulo, Brazil, from April 2016 to June 2017, and included a total of 113 CSU patients and among them 31 pediatric patients aged 0-17 years.

Both studies are valuable and contribute to the overall knowledge about CSU in the pediatric population, but are not directly comparable as outlined above. The small sample size of pediatric

CSU patients (N = 31) in the study by Ensina et al might limit the external validity. Nevertheless, Ensina et al provided important insights regarding gender-specific differences in disease prevalence, presence of comorbidities (atopy and autoimmunity), presence of angioedema, hypersensitivity associated with nonsteroidal anti-inflammatory drugs (NSAIDs), treatment patterns, and response to treatments in pediatric CSU patients in their UCARE center in Brazil. Particularly, differences between pediatric and adult patients were reported. There is limited comparative information available in the literature regarding clinical characteristics and disease management of CSU in pediatric patients.^{4,5} Therefore, the findings provided by Ensina et al are very relevant.

In our study, 5%-14% of pediatric CSU patients of the representative cohort had angioedema according to physician recall and report, whereas Ensina et al reported that 58% of patients seen in their center had angioedema. Another study by Volonakis et al, which investigated 226 pediatric urticaria patients aged 1-14 years, reported that wheals along with angioedema were present in 15% of patients.⁶ One major reason for these differences in angioedema prevalence could be that patients seen in a center of reference tend to have more severe disease compared to those seen in general practices by GPs, private clinics, and general hospitals. Ensina et al also highlighted this point. Moreover, the data reported by patients and physicians tend to be discrepant.⁷ Regarding angioedema, another study in CSU emphasized this difference in reporting between physicians and patients.⁸ In terms of prevalence of CSU, our study calculated diagnosed prevalence via extrapolating to the general pediatric population from a representative panel in five countries, whereas the study by Ensina et al presented the data relevant to the UCARE center.

The use of H1-antihistamines and response to treatment were reported in both studies. Ensina et al reported that the majority of pediatric patients received H1-antihistamine treatment, with 35% of