DOI: 10.1111/jdv.17659 JEADV

COMMENTARY

Chronic urticaria – From 'Cinderella' to a 'Rock star' in 30 years

JEADV is now on its 30th anniversary, and the new era of chronic urticaria has the same age. Although Hippocrates already recognized urticaria, until the 1980s/1990s, chronic urticaria (CU) or chronic idiopathic urticaria, further renamed chronic spontaneous urticaria (CSU), was considered an orphan disease,[1] the 'Cinderella' disease.[2] There was no significant investigation apart from the effect of histamine on weals and H1 antihistaminics were the mainstay of treatment, with a considerable unsatisfaction by patients and their doctors. In the last 30 years, the panorama has significantly changed, and nowadays, scientific sessions on chronic urticaria in dermatology or allergology congresses, as a 'rock star', attract many attendees and fill up large congress rooms.

Precisely 30 years ago, in 1991, Clive Grattan published the results confirming that the circulating factor he had identified in CSU patients that caused a positive autologous serum skin test (ASST) was actually an autoantibody with functional properties anti-IgE.[3] Working in London, integrated in the team of Malcom Greaves and with the collaboration of Michiro Hide and Naomasa Niimi, Clive Grattan and collaborators further identified this autoantibody as an IgG anti-FcεRI or anti-IgE, which exhibited the capacity to degranulate mast cells or basophils.[4,5] Evidence that 30–50% of CSU cases were dependent on this autoantibody and, therefore, CSU was an autoimmune disease, was reinforced by the team of Alan Kaplan in the United States in the following years.[6] A new era began in the treatment of CSU with the use of ciclosporin and other immunosuppressants, but results were irregular, and the ASST was not a sufficient predictor of response.

The other big step forward occurred in 2011 when, after a few isolated reports and exploratory proof of concept studies in the United States,[7] the Berlin team, led by Marcus Maurer, showed that 70% of CSU patients who exhibited IgE antibodies to thyroperoxidase responded well to the anti-IgE monoclonal antibody, omalizumab.[8] These results were further strengthened by the clinical trial published in the New England Journal of Medicine in 2013[9] and reproduced in many other clinical trials and real-life studies. This very safe and effective 'shot in the arm' treatment[1] was really a new breakthrough for patients, but it was also like a starting shot for investigation on pathophysiology and other treatment options for CSU, with a steep rise in publications on this subject (>7500 in the last 10 years). It also raised new awareness on this disease within the medical community and the public.

But omalizumab was not yet the final answer, as some CSU patients did not respond and, whereas some responded completely in days, others took weeks to months to respond, suggesting different types of CSU. Many studies conducted mainly in Berlin but in collaboration with many other centres, like Barcelona, Hiroshima, Milan, and the Unites States, now united under the UCARE 'umbrella' (GA^{2}LEN Urticaria Center of Reference and Excellence), have partially answered this question, identifying at least two subphenotypes of CSU. Autoallergic or type I autoimmune CSU is associated with the presence of IgE autoantibodies (anti-IL-24, anti-thyroperoxidase, anti-dsDNA and other autoallergens), and as these autoantibodies are quickly complexed by omalizumab, these patients respond very rapidly to the treatment. This form of CSU is mostly associated with negative ASST and negative basophil histamine releasing assay/basophil activation test, and patients have total serum IgE values on the upper limit of normal or above it. On the contrary, type IIb autoimmune CSU has circulating functional pathogenic IgG antibodies to the patient's own IgE or its high affinity receptor (FcεRI) on mast cells and basophils, which are responsible for a positive ASST, basophil activation tests and basophil releasing assays. This subtype is frequently associated with basopenia, eosinopenia, low or very low total serum IgE, which responds slowly to omalizumab (only after the secondary reduction of FcεRI on mast cells and basophils) but may respond well to short courses of cyclosporin. Unhappily, this difference is not always so straightforward, and there are many mixed or unclassified CSU cases.[10] Moreover, there are still no widely available commercial kits to detect either IgE to autoallergens or IgG to FcεRI, and there are no definitive biomarkers to predict treatment response or disease duration and severity. There is still much to learn within the field of CSU and also within the different forms of chronic inducible urticaria and different types of angioedema.

Regularly updated guidelines on the diagnosis and management of urticaria have contributed to improve the care of patients worldwide,[11] but apart from licensed recommended treatments, many new promising drugs are being tested with very encouraging results, such as the new anti-IgE monoclonal antibody (ligelizumab) or the Bruton tyrosine kinase (BTK) inhibitors (fenebrutinib and remibrutinib). Still, many other drugs with different targets, namely cytokines (IL-4, IL-5, IL-17, TSLP) and mast cell receptors (siglec-8, C5aR1, MRGPRX2,

cKIT), are being studied[12] and will certainly benefit our patients and improve our understanding of this puzzling disease that is still carrying a high burden for the patient and the society.[13]

M. Gonçalo*
Department of Dermatology, Coimbra University Hospital Center, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
*Correspondence: M. Gonçalo. E-mail: mgoncalo@fmed.uc.pt

References

1 Greaves MW. Chronic urticaria: an orphan disease for 125 years. *Brit J Dermatol* 2014; **170**: 1211–1213.
2 Yosipovitch G, Greaves M. Chronic idiopathic urticaria. A "Cinderella" disease with a negative impact on quality of life and health care costs. *Arch Dermatol* 2008; **144**: 102–103.
3 Grattan CEH, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991; **21**: 695–704.
4 Hide M, Francis D, Grattan C, Hakimi J, Kochan J, Greaves M. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *New Engl J Med* 1993; **29**: 1230–1235.
5 Niimi N, Francis DM, Kermani F *et al*. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Investig Dermatol* 1996; **106**: 1001–1006.
6 Ferrer M, Kinét JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-FcεRIα (α-subunit) in chronic urticaria. *J Allergy Clin Immunol* 1998; **101**: 672–676.
7 Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; **122**: 569–573.
8 Maurer M, Altrichter S, Bieber T *et al*. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011; **128**: 202–209.
9 Maurer M, Rosen K, Hsieh H *et al*. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; **368**: 924–935.
10 Schoepke N, Asero R, Ellrich A *et al*. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria (aiCSU): results of the PURIST Study. *Allergy* 2019; **74**: 2427–2436.
11 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.
12 Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. *Ann Allergy Asthma Immunol* 2020; **124**: 2–12.
13 Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M *et al*. The global burden of chronic urticaria for the patient and the society. *Br J Dermatol* 2021.**184**:226–236.

DOI: 10.1111/jdv.17659