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Using National Registries to Identify Targeted Therapies for Refractory Urticaria

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Dear Editor,

We agree with the commentary by Murat Türk and İnsu Yılmaz about the need for head-to-head trials of omalizumab and ligelizumab in chronic spontaneous urticaria (CSU) [1], as such trials may provide clinicians with invaluable datasets regarding the possible dose-response relationship.

The most pressing need is to understand both the failure of responses to biologic therapies and the optimal duration of such therapies. Developing disease stratification models that could reliably predict non-responders, partial responders, and those requiring multiple treatment courses would help clinicians to a great extent. Given that the resistance to omalizumab in CSU is estimated at 23% in children and up to a third in adults [2, 3], and that only 42% were found to have a complete response at week 12 (even with the highest dose of 240 mg of ligelizumab) [4], there is clearly a real need to understand the factors that contribute to anti-IgE resistance in CSU.

When biologics fail, patients look for more acceptable options than continuous oral corticosteroids or restarting medications that previously failed to control their urticaria. Prior to the licensing of omalizumab, low-dose ciclosporin, and mycophenolate were the "go to" drugs for treating "difficult urticaria." Designing randomized, placebo-controlled, cross-over trials of low-dose ciclosporin or mycophenolate in conjunction with omalizumab might pave the way for better treatment options for CSU and help to delineate disease clusters. However, such trials would most likely have to be self-funded by centres dedicated to CSU research. These factors lead to a paucity of good-quality data on the long-term efficacy or induction of remission by biologic therapy for CSU.

Generating prospective longitudinal "real world" datasets via national registries, i.e., that include demographics, clinical and laboratory parameters, therapeutic response including quality-of-life (QoL), patient-reported outcome measures (PROM), and disease activity scores (UAS7) at various time points, could aid the development of disease

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stratification models. This may then help to identify targeted therapies that are difficult to capture in clinical trials.

Well-maintained registries provide a temporal profile of how chronic conditions are being managed, e.g., the Finnish National Anaphylaxis Registry and the European Anaphylaxis Registry (refractory anaphylaxis data) [5, 6]. However, such data is only effective in leading to policy change if it remains highly accurate from the primary point of entry to the methodologies used to interpret and analyse it. A case in point is the recent publication by Francuzik et al. [7] that made use of the European Anaphylaxis Registry to analyse data from 3,612 patients. They concluded that patients receiving beta-blockers and ACE-inhibitors had a higher risk of developing severe cardiovascular problems (including cardiac arrest) with venom-induced reactions. Incorvaia et al. [8] point out that this conclusion is too generic and not universally supported. Beta-blockers and ACE-inhibitor drugs are prescribed for arterial hypertension that is usually considered a cardiovascular condition, but not all cardiac conditions have arterial hypertension, and therefore each patient will have their own individual risk.

Even with all these caveats, national registries that maintain long-term data on immunotherapy remain excellent sources of information for analysing data from patients with refractory urticaria, paediatric patients who required immunosuppressants, and urticaria disease activity during pregnancy/breastfeeding, as these groups of patients are routinely excluded from clinical trials. Clinical trials in CSU have mainly involved the Caucasian White population, and national registries could also enable investigation into ethnicity-based disparities, as has been conducted in the case of allergic and autoimmune diseases [9]. Obtaining sustained remission in resistant CSU remains a distant goal at present, but one that is achievable.

Conflict of Interest Statement

S.K. is a member of the Steering Committee of the BSACI British Registry for Immunotherapy. L.J.M. reports that she is the Paediatric Secretary of the BSACI British Registry for Immunotherapy; is principal investigator for and receives educational grants from Danone Nutricia and Regeneron, and previously received educational grants from Allergy Therapeutics, Mead Johnson, and ALK-Abellò. T.C.D. reports receiving educational grants from Allergy Therapeutics, Danone Nutricia, and ALK-Abellò. M.T.K. received funds from ALK-Abellò to attend an international conference; is the clinical lead of the national allergy accreditation programme (IQAS) and chair of the BSACI Equality Diversity and Inclusivity Working Group; has received grants from NIHR, MRC CiC, FSA, and UK R&I (unrelated to this work); and his department received funds from ALK-Abellò, Thermo Fisher, MEDA, and other pharmaceutical companies for the PracticAllergy course. M.E.-L. reports that he is chair of the BSACI British Registry for Immunotherapy and that the Registry has received unrestricted educational grants from Allergy Therapeutics, ALK-Abellò, and Stallergenes Greer.

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