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Reply to "Don't put all your eggs (and milk) in one basket"



To the Editor:

We thank Kelleher et al¹ for their insightful comment regarding our rostrum on dietary advancement therapy (DAT). The title of the rostrum was intended to be posed as a question, not as a declarative statement.² We appreciate the success of their ladder studies³⁻⁵ and points made by Chua et al.⁶ Data regarding the use of ladders are evolving. Ladder products are not standardized and lack quality control, and we poorly understand the clinical significance of which labile proteins may remain intact at particular bake times and temperatures.²

No 2 store-bought or home-baked muffins are identical. If "baked" muffins have different heating times and allergen quantities, these seemingly equal products are, in fact, not allergenic equals, and this could pose more risk to a patient than may be recognized, especially among the higher-risk patients. Taking this a step further, one of the facets of the rostrum was to consider equipoise in deciding whether extensively heated milk and egg ingestion should be governed by the same rules we would apply to oral immunotherapy. For example, should we encourage a child to consume one of these products in the midst of a febrile viral respiratory infection versus waiting? Once again, the high-risk patient may be particularly sensitive to such co-factors; however, we lack the means to identify which DAT patients may be at higher risk. Lastly, is there any harm in having a documented discussion with a parent informing them that while most feel dietary

advancement therapy is safe, some risk exists? Therefore, the point of our rostrum was not to declare this process dangerous but to ponder what risk does exist and how to mitigate that risk. We do not suggest withholding DAT or cowering at potential risk but rather recognize that DATs in any form still represent some degree of allergenic challenge to a reactive immune system, and there may be potential safety issues that should be disclosed to parents so that they make a fully informed choice. Parents can then make their own decision if such risk can be managed.

There may be differences in acceptability in shared decision-making between countries and among clinicians, and some may have more paternalistic interactions with families than others. Time will tell if the published success of ladders is more the result of the ladder itself representing a safe, stepwise progression, or the result of subtle unrecognized heuristics in choosing patients more likely to have a transient egg or milk allergy phenotypes amenable to a ladder and who can progress through this with safety and efficacy. The rostrum is intended to open the field to considering if we fully understand the scope of safety in dietary advancement therapy and serve as a hypothesis-generating article. This has already evoked the intended response of academic discourse with our Irish colleagues and good friends.

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Does hydroxychloroquine work for chronic spontaneous urticaria?



To the Editor:

The December 2022 issue of *The Journal of Allergy and Clinical Immunology: In Practice* contains a real-world study of the effectiveness of hydroxychloroquine versus omalizumab as add-on therapy for patients with antihistamine-resistant chronic spontaneous urticaria (CSU).¹ This is based on a retrospective chart review of 265 patients in two centers over a 5-year interval. A complete response to omalizumab of 82% is noted at 3 months compared with 35% for hydroxychloroquine. The authors acknowledge that there is no placebo control, but if we assume a placebo effect of 25% to 30%, as documented in three prior double-blind controlled studies of omalizumab that included over 900 patients, it leaves an 8% to 13% success rate for hydroxychloroquine at 3 months. One included failures of H₁ and H₂ antihistamines and leukotriene antagonists.² In the current study at 1 year, the complete response rate was 82% for omalizumab versus 66% for hydroxychloroquine, with some hydroxychloroquine successes within the 18% who did not initially respond to omalizumab. That is the real-world part. However, a placebo control is still needed to estimate the spontaneous remission rate between 3 and 12 months of observation. My own experience with hydroxychloroquine is substantial (ie, as treatment for systemic lupus erythematosus and rheumatoid arthritis, as well as the hypocomplementemic urticarial vasculitis syndrome, with remarkable results in the latter entity within a few weeks).³ However, I have never seen a patient with antihistamine-resistant CSU in whom symptoms rapidly quieted with hydroxychloroquine, although I have never tried it beyond 1 month. For omalizumab, one to two injections often allow one to note an obvious response, even if incomplete, and for omalizumab failures (including up-dosing or more frequent administration), daily oral cyclosporine allows responses to be noted in 1 to 2 weeks.

The latest guideline does not recommend hydroxychloroquine as add-on therapy.⁴ What we are missing is a large, prospective, double-blind, placebo-controlled study by those who believe it to be an effective therapy for CSU, and in particular for antihistamine failures. A comparative time course of responsiveness with an approved assessment method to quantify severity is similarly required. Prior publications of hydroxychloroquine therapy for CSU had few patients. Some studies reported no significant effect on urticaria activity scores,⁵ and a study with no control group reported a success rate that is roughly the known placebo control improvement rate.⁶ The same is true for most publications involving methotrexate, sulfasalazine, H₂ antagonists, leukotriene antagonists, and dapsone.⁷ In fact, I could include references for each of these

(including some negative studies) and make the same argument that not one has efficacy in CSU. Even the only controlled study of dapsone had only a 33% to 41% improvement rate but no discernable placebo effect, which limits the interpretation of the findings. The authors¹ argue that considerations of cost and safety make hydroxychloroquine an attractive alternative add-on therapy for refractory CSU. That argument holds if efficacy has been shown, and I do not believe that the current evidence justifies that conclusion.

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Reply to "Does hydroxychloroquine work for chronic spontaneous urticaria?"



To the Editor:

We appreciate Kaplan's comments regarding our recently published retrospective study examining relative clinical effectiveness of hydroxychloroquine (HCQ) versus omalizumab in patients with chronic spontaneous urticaria (CSU) unresponsive to antihistamines.^{1,2} He identifies a modest complete response rate to HCQ of 35% in our study after 3 months of treatment, like placebo responses in published double-blind placebo-controlled trials of omalizumab. We agree that the effect size at 3 months is modest, but we found a compelling 66% complete response rate after 1 year of HCQ treatment. This 1-year complete response rate with HCQ far exceeds any possible improvement attributable to the small number of patients who might have experienced spontaneous resolution of CSU. We concur with Kaplan's experience that clinical responses are unlikely within the first 1