

in standard-risk children.⁵ The data on the fluid approach to prevention continue to evolve, and we agree that “starting low and going slow” is one of many practical ways of implementing primary prevention for some families. However, this discussion, although important, is not the primary focus of our rostrum.

Unfortunately, despite following whichever early introduction guidance a parent may choose, many children still develop clinical food allergies as a result. Therefore, our article was focused on the central issue of how to proceed when an infant reacts to a particular allergen during early intervention, irrespective of the prevention approach, and how to optimize that scenario. Our position is to advocate a seamless integration of failed primary prevention and infant OIT, as soon as possible after diagnosis, to reduce the time the infant lives with strict avoidance as a primary management strategy and immerse the family in an active management approach. We feel this can be both empowering for the family and immunologically protective for the infant, as this maximizes the potential that the allergenic food can be integrated into the diet in the desensitized child, with minimal risk of developing the well-documented adverse psychological effects that are often associated with allergen avoidance.

Our larger point in the rostrum was to emphasize that even “the best-laid plans of mice and men often go awry,” and that despite best intentions in adhering to any early introduction strategy (including attempts at starting low and going slow), there will always be infants who fail this approach. These infants can be helped by providing the option of early OIT.²

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honorarium for lectures from ImSci and MedLearningGroup, and multiple state/local allergy societies. M. Shaker has participated in research funded by DBV, serves on the Joint Task Force on Practice Parameters, is an associate editor for the *Annals of Allergy, Asthma, and Immunology*, and is a member of the editorial boards for the *Journal of Allergy and Clinical Immunology In Practice* and the *Journal of Food Allergy*. E. M. Abrams is a collaborator with the Institute for Health Metrics and Evaluation. She is an employee of Public Health Agency of Canada (PHAC), but the views expressed are her own and not those of PHAC. S. B. Cameron has been a member of advisory boards for Medexus, Sanofi, Bausch Health, and Pfizer, and was a committee member of the Canadian Society of Allergy Clinical Immunology (CSACI) oral immunotherapy guidelines. V. E. Cook has been a member of advisory boards for Sanofi Genzyme, Bausch Health, and ALK, and has received honoraria from Aralez Pharmaceuticals and CSL Behring. D. M. Fleischer has received research support from Aimmune Therapeutics and DBV Technologies; has been a member of advisory boards for DBV Technologies, Genentech, Novartis, Nasus Pharma, and DOTS Technologies; has been a member of the Medical Advisory Board for the Food Allergy & Anaphylaxis Connection Team (FAACT) and Medical Advisory Council for the National Peanut Board; and has received royalties from UpToDate. R. Mak is the advisory board member of ALK and Sanofi, and has received speaker honoraria from Novartis, Padiapharm, and AstraZeneca. T. K. Vander Leek has served on advisory boards for and received honoraria from Aralez/Miravos, Bausch Health, and Covis Pharma. E. S. Chan has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Padiapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, and Avir Pharma; is a member of the healthcare advisory board for Food Allergy Canada; and was co-lead of the CSACI oral immunotherapy guidelines. The rest of the authors declare that they have no relevant conflicts of interest.

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Have we reached our final destination with biologics in severe uncontrolled asthma?



To the Editor:

Portacci et al¹ eloquently proposed a comprehensive assessment model for defining super-responders to biologics in patients with type 2 (T2)-high severe uncontrolled asthma (SUA). This in turn begs the pertinent question as to whether it is preferable to block upstream epithelial alarmins such as thymic stromal lymphopoietin (TSLP) or downstream cytokines such as IL4, IL5, and IL13 (Figure 1) in order to achieve the best response in a given patient.²

In this regard, the recent 2-year DESTINATION study³ with the anti-TSLP agent tezepelumab in SUA provided some important clues in showing significant reductions in annualized asthma

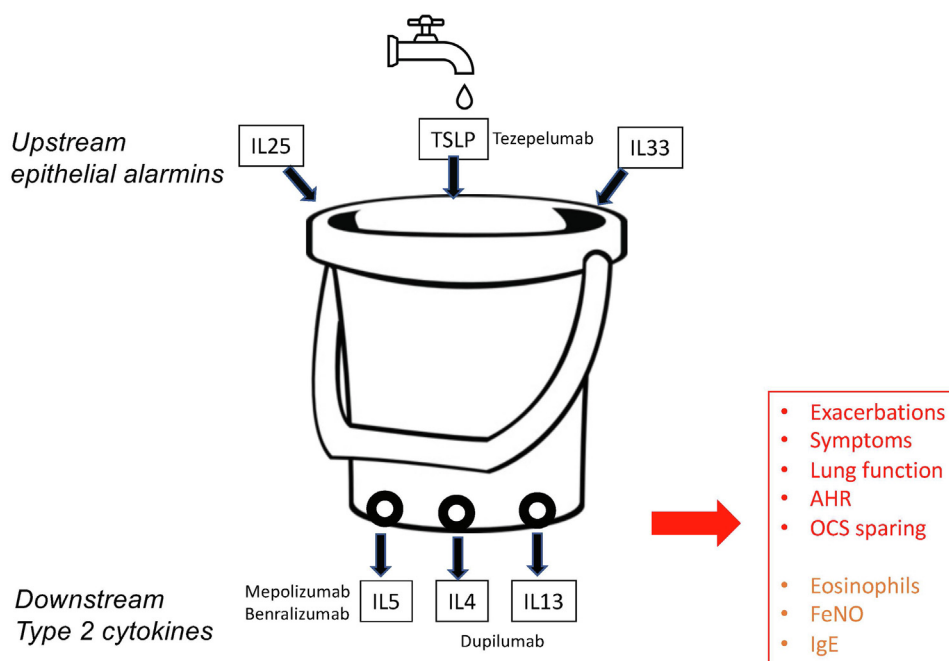


FIGURE 1. The type 2 bucket analogy depicting the effect of blocking upstream alarmins such as thymic stromal lymphopoietin (TSLP) in terms of attenuating downstream expression of cytokines including IL4, IL5, and IL13. *AHR*, Airway hyper-responsiveness; *FeNO*, fractional exhaled nitric oxide; *OCS*, oral corticosteroids.

exacerbation rates (AAER) in both T2-high and -low patient phenotypes characterized by cutoffs according to blood eosinophils (Eos) of 300 cells/ μ L or fractional exhaled nitric oxide (FeNO) of 25 parts per billion (ppb). It was evident that the respective 95% confidence intervals for AAER did not overlap, in turn indicating that the relative efficacy was significantly superior in T2-high patients amounting to a 25% difference for Eos $\geq$ 300 cells/ μ L versus <300 cells/ μ L and a 32% difference for FeNO $\geq$ 25 ppb versus <25 ppb. This is perhaps unsurprising given that tezepelumab attenuates downstream expression of T2 cytokines including IL4, IL5, and IL13.

Because tezepelumab only partially suppresses Eos compared with depletion by benralizumab, we would therefore be interested in a pragmatic head-to-head comparison in SUA to look at super-responders, especially for patients who present with high levels of Eos $\geq$ 1000 cells/ μ L. In addition, it would be informative to directly compare both biologics in patients who are dependent on maintenance oral corticosteroids (OCS), where tezepelumab was found to be ineffective overall in the SOURCE study and given the proven OCS sparing efficacy of benralizumab in the PONENTE study.^{4,5} Then we may have reached our final destination.

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