

Immunotherapy and systemic reactions

We read with interest the recent retrospective review by Winslow et al.¹ The authors reported systemic reaction (SR) rates lower than those previously published.² Of note, they use “standard build” for what is typically referred to as “conventional build-up”. The advantage of reporting SR rates within a single large practice is the assumed consistency and standardization of immunotherapy delivery.

The authors provide several possible explanations for their lower SR rates compared with conventional, cluster, and rush SR rates published in the literature: (1) their internal quality control for their immunotherapy protocols, (2) use of premedication regimens from previously published protocols, and (3) possible underreporting of SRs that occurred outside the supervised medical setting (eg, patient did not wait 30 minutes). In this brief communication, we discuss the rationale for why their protocols were associated with lower SRs than the published literature.²

The authors provide no perspective for the practice's historical SR rate with any of the 3 build-up schedules. Without this information, safety comparisons within or across different practice patterns or protocols cannot be made. Although an individual practice using a uniform practice build-up schedule offers a more optimum setting in which to study the effect of single changes,³ the reader must know a historical rate for comparison. There is also no comparative control group (eg, a cluster or rush group who received no premedication vs a premedication group to make conclusions on the regimens). Accelerated schedules comparing premedication and no premedication regimens are critical to make conclusions.⁴ In addition, the authors note that they could not account for SRs that occurred outside the office setting (eg, patients who did not wait the recommended 30 minutes). Some studies have reported as much as 50% of SRs may occur after the 30-minute wait.⁵ This may not only result in underreporting SRs but may also place the patient at risk for a SR in not dose adjusting the next injection. We recommend allergists enforce the wait time for patient safety.

Lastly, we would suggest the most likely reason for any allergy practice experiencing very low SRs may be secondary to using subtherapeutic maintenance doses. The authors report that their practice routinely administers maintenance doses below those recommended in the immunotherapy practice parameter for 3 allergens (Bermuda grass, dog, and ragweed).⁶ Therapeutic immunotherapy maintenance doses in the range of 5 to 20 μ g are effective,^{7,8} whereas low-dose immunotherapy is ineffective in double-blind, placebo-controlled trials.^{9,10} The authors do not

mention whether they mix molds and pollens. If so, the degradation of the other allergens by the proteolytic enzymes in mold extracts would also lead to subtherapeutic maintenance doses and lower SRs. Separation of mold extracts with their high proteolytic enzyme activities from other extracts is recommended in the practice parameter.⁶

In summary, we recommend US practices follow the practice parameter and use therapeutic maintenance doses for all their allergens. Patients invest a significant amount of time into an immunotherapy course and place their trust in the allergist to receive an optimum dose of each allergen.

Mike S. Tankersley, MD*

Linda S. Cox, MD†

*University of Tennessee Health Science Center
Memphis, Tennessee

†University of Miami Miller School of Medicine at Holy Cross Hospital
Ft Lauderdale, Florida
mtanker6@uthsc.edu

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Disclosures: Authors have nothing to disclose.

Author's response

Our primary hopes with the publication of this review¹ were 2-fold: (1) to add to the body of literature supporting the safety of subcutaneous aeroallergen immunotherapy and (2) to provide a template for allergists who might want to use cluster or rush schedules but have been dissuaded by historically high systemic reaction rates. We recognize that our retrospective analysis of more than 2.5 million injections was not designed to best determine why our systemic reaction rates were lower than those previously published.

Disclosures: Authors have nothing to disclose.

Because cluster and rush methods were implemented in our practice in 2010, the year our retrospective review began, there are no prior historical data. Our historical standard-build systemic reaction rate is similar to the published standard-build rate (0.01–0.02% per injection). Our study design did not allow for a comparative group to assess the premedication regimen, but we believe the rationale for providing premedication for rapid-build aeroallergen immunotherapy is well established.^{2,3} In accordance with clinical practice guidelines, we routinely split molds into a separate vial from pollens. We dutifully ascribe to the 30-minute wait rule, and each of our immunotherapy patients is required to sign a consent form explaining the rule. Known systemic