

Shooting for a faster approach to the immunotherapy target: will cluster become conventional?

The use of accelerated subcutaneous immunotherapy (SCIT) build-up schedules dates back to the early 1900s with the work of Noon and Freeman.¹ Approximately 15 years after starting to inoculate hay fever patients using a weekly schedule called “leisurely,” Freeman began using more rapid-build protocols. In a 1930 article, Freeman recounts successful cases treated with “rush” desensitization, describing a gymnastics instructress who had previously discontinued immunotherapy because of the “pressures of work,” who was able to roll in a hayfield without being able to “get a sneeze out of it” after rush immunotherapy (RIT) and a young girl with horse-induced asthma who probably had the first RIT-related systemic reaction (SR). Although this article recounts events nearly 100 years ago, the pertinent issues continue to be important factors in allergen immunotherapy today (ie, patient time and safety). Inconvenience, the reason the busy gymnastics instructress discontinued SCIT, is still the primary reason for discontinuation^{2,3} and is likely the most common reason for not beginning SCIT. The time required to receive this treatment in a supervised medical facility is probably the major cause of the inconvenience. A common feature of many novel immunotherapy approaches currently under investigation is that they reduce the time required to receive this treatment. Sublingual immunotherapy is associated with less frequent and severe SRs than SCIT, and home administration is the standard of care. Allergen vaccines mixed with adjuvants have produced significant clinical improvement in the first season after a single course of 4 to 6 injections.

Accelerated immunotherapy schedules offer another means to reduce time by decreasing the number of visits during the build-up phase. In general, they have not been widely used in the United States, likely because of safety concerns.

Rush immunotherapy appears to be associated with a greater risk of SRs compared with conventional build-up schedules. One review found the SR rate with RIT ranged from 15% to 38% of patients with premedication and up to 100% of patients without premedication.⁴

In contrast, cluster immunotherapy may be associated with the same or slightly increased frequency of SRs. Although there have been few studies designed to compare the safety of

cluster immunotherapy, cluster regimens have been used in numerous immunotherapy studies designed to evaluate factors such as dose response and immunological changes. One study demonstrated that the immunological changes associated with SCIT during cluster immunotherapy occurred early and at low doses, with an increase in interleukin-10 at 2 to 4 weeks, which was associated with inhibition of the late-phase skin test response.⁵ Other studies have demonstrated that the immunological changes with SCIT after a 5-week cluster immunotherapy protocol are predictive of the response at 1 year.⁶

One study comparing a 6-week cluster immunotherapy protocol with a 12-week conventional schedule found no differences in terms of SRs and improved clinical and objective parameters in the cluster immunotherapy group 6 weeks sooner than in the conventional group.⁷

In this issue of the journal, the tolerability of cluster immunotherapy is examined in a retrospective, observational, multicenter study of 1,147 patients. There were 42 SRs (0.6% of doses) in 39 patients (3.4%), who received a total of 6982 doses. Most reactions were classified as grade 0 or 1, and there were no grade 4 (anaphylactic shock) reactions. This reaction rate is similar to rates reported with conventional immunotherapy schedules. To provide some perspective, one review of 38 studies that used conventional build-up schedules found that the SR rate ranged between 0.05% and 3.2% of injections and between 0.8% and 46.7% of patients (mean, 12.92%).⁸

In summary, as we go into the 21st century and allergen immunotherapy’s second century, the focus continues to be on developing safer and more effective formulations and/or protocols. However, this disease-modifying treatment continues to be much underused, with only an estimated 2.5 million (approximately 5%) of the allergic population receiving SCIT in the United States. Inconvenience related to time is very likely the primary barrier.

Many novel immunotherapy approaches show much promise in terms of overcoming this barrier, but they are still under investigation and not currently available in the United States. Accelerated immunotherapy schedules, with allergen extracts currently available in the United States, is another means to reduce the inconvenience of SCIT. Concerns about safety have likely limited the use of these schedules. However,

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recent studies have suggested that cluster immunotherapy may be associated with a similar incidence of SRs as conventional schedules. Cluster immunotherapy may provide a risk-benefit balance that is acceptable to the prescribing allergist and considerably more convenient and attractive to the busy allergic patient than the conventional schedule described nearly 100 years ago as leisurely—and maybe cluster will become “conventional” in the United States.

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