

Advantages and disadvantages of accelerated immunotherapy schedules

Linda Cox, MD Fort Lauderdale, Fla

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Specific allergen immunotherapy (SIT) is currently the only US Federal Drug Administration–approved immune-modifying treatment for allergic asthma and rhinitis. In addition to its proven clinical efficacy, it can potentially alter the natural history of allergic disease and produce sustained clinical remission after discontinuation. Despite the clear benefits of SIT, only a small percentage of allergic patients subscribe to this treatment: 5% of the population with allergic rhinitis, asthma, or both in the United States (about 2.5 million persons). Inconvenience is one of the primary reasons for discontinuation of SIT¹ and likely one of the reasons for the low use of SIT. The inconvenience is likely due to the time involved because it is recommended that SIT be administered in a medical facility, with a wait period of 30 minutes after the injection.² In a conventional immunotherapy build-up schedule, the frequency of injections generally ranges from 1 to 2 times per week, with a single injection given each visit. The duration of the build-up phase depends on the frequency of the injections but generally ranges from 3 to 6 months. Accelerated immunotherapy build-up schedules offer the advantage of reduced office visits, which might decrease the patient's costs because of reduced travel time and office visit charges.

They might also allow patients to appreciate the benefits of SIT sooner because the effective therapeutic dose is reached in a shorter period of time, which can enhance compliance. The disadvantages of accelerated immunotherapy schedules include a potentially higher risk of systemic reactions (SRs) and the need for increased staff time and resources in the medical facility.

RUSH IMMUNOTHERAPY: INHALANT ALLERGENS

Rush immunotherapy (RIT) entails administering incremental doses of allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved. RIT schedules for inhalant allergens appear to be associated with a greater risk of SRs, particularly in high-risk patients.² The most accelerated aeroallergen protocol reaches the target maintenance dose in 7 injections over the course of 4 hours.³

One of the difficulties in evaluating the safety and efficacy of accelerated schedules is the heterogeneity of the study protocols

(eg, different target doses, schedules, and premedication regimens). There have been very few placebo-controlled trials or trials designed to compare accelerated schedules with conventional schedules.

Most aeroallergen RIT studies have been performed with single allergens, with dust mite and grass pollen being the 2 most extensively studied. Other allergens that have been studied with RIT include *Parietaria* species, birch, olive, plane tree pollen, ragweed, dog, cat, rat, and *Alternaria* species, with SR rates ranging from 14.7% of patients who received premedication to 100% of patients who did not receive premedication. A few RIT studies used mixtures of non-cross-reacting allergens with SR rates ranging from 55%⁴ to 73%⁵ of patients who did not receive premedication to 27%⁵ to 38%³ of patients who received premedication.

CLUSTER IMMUNOTHERAPY

Cluster immunotherapy entails administering several injections at increasing doses (generally 2 to 3 per visit) sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is generally achieved within 4 to 8 weeks. Few studies have been designed to compare the safety of cluster immunotherapy with a conventional schedule. One study of 239 patients with rhinitis and dust mite allergy with or without asthma specifically designed to compare the safety and efficacy of a 6-week cluster schedule compared with a 12-week conventional schedule found no differences between the 2 schedules in terms of adverse reactions and improved clinical and objective parameters in the cluster group 6 weeks before the conventional schedule group.⁶ In a recent review of accelerated SIT schedules, the SRs with cluster schedules ranged from 0% to 79% of patients.⁷ In a review article on cluster immunotherapy that analyzed 29 studies that included venom and aeroallergens, the authors concluded that the optimal tolerance of cluster schedules is associated with⁸ (1) use of premedication (antihistamine), (2) use of a depot preparation, (3) use of no more than 4 administrations per cluster, (4) use of a total of 4 to 6 clusters, and (5) administration of 1 to 2 clusters per week.

The authors did suggest that the twice-a-week cluster might be associated with less adverse effects than the once-a-week cluster based on 2 separate grass pollen cluster studies with virtually identical protocols, except for the frequency of clusters: the SR rate was 33% with premedication/79% without premedication in the once-a-week cluster and 18% of premedicated patients in the twice-a-week cluster. The allergen immunotherapy practice parameter includes an example of a 5-week, 8-visit, 18-step cluster schedule.²

PREMEDICATION AND ACCELERATED IMMUNOTHERAPY

Few studies designed specifically to evaluate the effect of premedication on the SR rate with aeroallergen cluster or RIT have been published. The RIT premedication regimens varied,

From the Department of Medicine, Nova Southeastern College of Osteopathic Medicine. Disclosure of potential conflict of interest: L. Cox is on the speakers' bureau for Genentech/Novartis and is on the medical advisory board for Schering-Plough.

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Reprint requests: Linda Cox, MD, 5333 North Dixie Highway, Fort Lauderdale, FL 33334. E-mail: lindaswolfcox@msn.com.

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TABLE I. Comparison of different immunotherapy build-up schedules for aeroallergens

Schedule	Rush immunotherapy	Cluster immunotherapy	Conventional immunotherapy
No. of visits during build-up phase	1-3	8*	30*
No. of injections	8†	18*	30*
Time to reach maintenance dose	1-3 d	5 wk*	15 wk at a frequency of 2 times per week or 7.5 mo if injections administered once a week
Premedication‡	Recommended in the AIPP but no specific protocol provided. H1 antihistamine and corticosteroids were used in all protocols§ in addition to other medications (eg, H2 antihistamines, leukotriene antagonists, theophylline, and ketotifen).	Antihistamine recommended by AIPP with notation that 2 hours before has been shown to decrease SR and local reactions.	Not routinely recommended but rarely studied: one study found reduced frequency of severe SR and increased the proportion of patients who achieved the target dose with fexofenadine premedication.
Range of SRs‡			
Without premedication	15% to 100% of patients	3% to 79% of patients (100% in 1 study classified as cluster, but protocol had 5 injections per visit; allergen: <i>Cladosporium</i> species)	8.4% to 28.6% of patients; mean, 12.9%; SD, 10.8%§
With premedication	14.7% to 38% of patients	0 to 33% of patients	NA

NA, Not applicable.

*Based on examples in "Allergen immunotherapy: A practice parameter second update" (AIPP).²†Based on a 2-day rush protocol^{4,5} that was subsequently reduced to a 1-day protocol.¹¹‡Based on a review of accelerated immunotherapy schedules; marked heterogeneity in study protocols and target dose make comparison of reaction rates difficult.⁷§Based on a review of SRs to skin testing and immunotherapy.¹²

but most included corticosteroids. In the previously mentioned review of accelerated SIT schedules, the SR rates for RIT ranged from 15% to 100% of patients treated with RIT without premedication and 14.7% to 38% of patients treated with premedication.⁷ In a study specifically designed to study the effect of premedication with astemizole, ranitidine, and prednisone or placebo before and during RIT with non-cross-reacting allergen mixtures, 27% of patients who received premedication had SRs compared with 73% of the placebo-premedicated group.⁵

In another study that compared the effect of premedication (methylprednisone, ketotifen, and theophylline) and preventive measures (excluding patients with an FEV₁ of less than 70% of predicted value and modifying the schedule for large local reactions, which were defined as >10 cm), there was a significant reduction in SR rate and severity with both measures.⁹ The SR rate decreased from 36% of patients with RIT alone to 16% with premedication and 7.3% with premedication plus preventive measures. Another study that investigated the effect of 9 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) before ragweed RIT found a 5-fold decrease in anaphylaxis compared with that seen in the placebo-premedicated group. In a retrospective review of 65 patients treated with the most rapid accelerated aeroallergen RIT protocol (4 hours), which included premedication with prednisone, cetirizine, ranitidine, and zafirlukast or montelukast, 38% of the patients had SRs. The majority of SRs were classified as mild (76%), and most occurred (72%) after the final dose (0.05 mL of the maintenance concentrate).

Premedication also appears to reduce the incidence of SRs with cluster schedules. In one study designed to investigate the effect of premedication on cluster immunotherapy, SRs occurred in 79% of patients in the placebo premedication group compared with 33%

of patients in the loratadine premedication group ($P = .002$).¹⁰ However, several cluster studies demonstrated safety similar to that of conventional schedules without premedication.

PREDICTORS FOR RIT SRs

No fatalities were reported in any of the RIT studies, but severe SRs occurred in the single- and multiple-allergen studies in both the premedicated and nonpremedicated groups. A high degree of skin test reactivity was consistently identified as an RIT risk factor. Other risk factors identified in some of the studies include an FEV₁ of less than 80% of predicted value,⁹ increase in skin test reactivity before occurrence of SR (protocol included skin testing before injections),⁵ weed or dog allergen (study based in Texas),³ and age less than 5 years (45% in one study).⁹ One multiple-allergen RIT study found a significant correlation between severity of the SR and the number of positive skin test results and the cumulative size of skin reactions.⁵

Local reactions did not appear to predict SR in any of the RIT studies. Delayed SRs were reported in several studies, up to 120 minutes after the last injection (see Table I^{11,12} for a comparison of RIT, cluster, and conventional schedules).

VENOM

In general, most of the Hymenoptera venom RIT studies, including ultrarush schedules as short as 2.5 hours, have demonstrated both efficacy and safety comparable or superior with that of conventional schedules. The safety of venom RIT has been documented in "high-risk" patients, who were unable to achieve an effective dose with a conventional schedule.¹³

There was a relatively low incidence of SRs in a study of 57 patients who underwent a 2.5-hour ultrarush therapy resulting in a

cumulative dose of 101.1 μ g of Hymenoptera venom, with only 7% of the patients experiencing mild SRs.¹⁴

In a study of the safety of a 2-day RIT in 58 patients allergic to imported fire ant venom, there was no difference in SR rates between patients who received premedication (terfenadine, ranitidine, and prednisone) and those who received placebo.¹⁵ In general, rush protocols for Hymenoptera venom immunotherapy have not been associated with a higher incidence of SRs, as with aeroallergen RIT, and premedication is not routinely recommended.

TIMING OF CLINICAL AND OBJECTIVE RESPONSES WITH ACCELERATED IMMUNOTHERAPY SCHEDULES

The clear advantage of accelerated immunotherapy schedules is that they permit patients to attain a therapeutically effective dose more rapidly than with a conventional schedule. Symptomatic improvement has been demonstrated shortly after reaching the maintenance dose with cluster and rush schedules in several controlled trials. The immunologic changes associated with effective immunotherapy, such as an increase in allergen-specific IgG4 levels, have also been seen earlier with rush and cluster immunotherapy schedules. In one cluster study changes in nasal allergen challenge, titrated skin prick test, and allergen-specific IgG4 measurements seen after 5 weeks of cluster immunotherapy were predictive of the response at 1 year.¹⁶

Ultrarush venom immunotherapy schedules have demonstrated changes in IgG specificity (ie, changes in the wasp venom antigen epitopes recognized by IgG) that correlated with clinical tolerance as early as 12 hours after venom immunotherapy.¹⁷

CONCLUSION

Accelerated immunotherapy schedules offer the advantage of achieving clinical benefits of SIT sooner while requiring less patient time because of a reduced number of visits during the build-up phase. Changes in objective parameters associated with effective immunotherapy are also seen earlier with accelerated schedules. The disadvantage of accelerated immunotherapy schedules is that they can be associated with greater risk, particularly with aeroallergen RIT schedules. Premedication appears to reduce the risk with RIT to a level comparable with that of conventional immunotherapy schedules. Cluster schedules appear more promising in terms of the balance between safety and convenience but might also be associated with an increased incidence of SRs. Premedication also reduced the incidence of

local reactions and SRs with cluster immunotherapy. Accelerated schedules with venom immunotherapy do not appear to be associated with increased risk, and routine premedication is not recommended. In conclusion, accelerated immunotherapy schedules with premedication might offer allergic patients a more convenient alternative to the conventional immunotherapy schedule.

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