
CME review article

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Accelerated immunotherapy schedules: review of efficacy and safety

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Objective: To provide a comprehensive evaluation of accelerated immunotherapy build-up schedules in terms of adverse reactions and clinical efficacy.

Data Sources: Peer-reviewed studies and review articles were selected from the PubMed database for articles published in the years 1976 to 2006 using the following keywords: *rush*, *cluster immunotherapy* in combination with *allergic rhinitis*, *asthma*, *Hymenoptera*, and *imported fire ant*.

Study Selection: Studies were selected if they provided safety and efficacy information on accelerated allergen immunotherapy schedules. Most of the studies reviewed were double-blind, placebo controlled, but some open-observational studies were included if they provided immunotherapy safety or other information the author thought was relevant.

Results: A wide range of systemic reactions were reported in the literature with inhalant allergens: ranging from 27% to 100% of the patients in rush immunotherapy studies and 0% to 79% of patients in the cluster studies. Predictors of systemic reactions with rush immunotherapy were forced expiratory volume in 1 second less than 80% of predicted and a high degree of skin test reactivity. Premedication clearly reduces the risk of systemic reactions with rush immunotherapy, but the effect on cluster schedules was not as clear.

Conclusion: Accelerated immunotherapy build-up schedules in selected patients may provide a rapid alternative to conventional build-up schedules without a significant increase in risk.

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INTRODUCTION

Specific allergen immunotherapy is currently the only immune-modifying treatment for allergic disease. In addition to its proven efficacy in the treatment of allergic rhinitis, asthma, and insect hypersensitivity, it may potentially alter the natural history of allergic disease, preventing the development of new allergen sensitizations and the progression from allergic rhinitis to asthma.^{1–5} Despite the clear beneficial effect of immunotherapy in allergic rhinitis and asthma, only a few allergic patients subscribe to this treatment.^{6–9} Inconvenience is likely the reason for not

choosing this treatment and one of the most frequent reasons for discontinuing it.^{10–12} The inconvenience is primarily due to the time involved, because it is recommended that specific allergen immunotherapy be administered in a medical facility. In addition to travel time, there is a recommended wait period of 20 to 30 minutes in the medical facility after the injection is administered.¹³ Immunotherapy involves 2 phases: a build-up phase (also known as up-dosing or induction) and a maintenance phase. The build-up phase involves administering increasing amounts of the allergen(s) until the maintenance dose is achieved. In a conventional immunotherapy build-up schedule, the frequency of injections ranges from 1 to 2 times a 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.

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Accelerated immunotherapy build-up schedules offer the advantage of reduced office visits, which saves patients time. Accelerated schedules may allow the patients to appreciate the benefits of immunotherapy more rapidly, because the effective maintenance dose is reached in a shorter period. Despite the fact that accelerated immunotherapy schedules have been successfully used in the treatment of allergic disease since the early 1900s,¹⁴ their use has been limited in the United States. This is likely due to the perception that accelerated immunotherapy schedules are associated with a greater risk of serious adverse reactions. Rush and cluster are the most commonly used accelerated immunotherapy schedules. A cluster immunotherapy build-up schedule entails administering several allergen injections (2 to 3) sequentially in a single day of treatment on nonconsecutive days, and maintenance dose is generally achieved within 4 to 8 weeks. In rush immunotherapy (RIT) protocols, incremental doses of allergen are administered at intervals that vary from 15 to 60 minutes over a period of 1 to 3 days until the target therapeutic dose is achieved. This review is intended to provide a comprehensive evaluation of accelerated immunotherapy schedules in terms of adverse reactions and clinical efficacy, which should enable the reader to better evaluate the risks and benefits of accelerated immunotherapy schedules in the treatment of allergic rhinitis, asthma, and venom hypersensitivity. Peer-reviewed studies and review articles were selected from the PubMed database for articles published in the years 1976 to 2006 using the following keywords: *rush*, *cluster immunotherapy* in combination with *allergic rhinitis*, *asthma*, *Hymenoptera*, and *imported fire ant*. Studies were selected if they provided safety and efficacy information on accelerated allergen immunotherapy schedules. Most of the studies reviewed were double-blind, placebo controlled, but some open-observational studies were included if they provided immunotherapy safety or other information the author thought was relevant.

ACCELERATED IMMUNOTHERAPY SCHEDULES: LEISURELY, INTENSIVE DESENSITIZATION, AND RUSH

The earliest treatment of allergic diseases with immunotherapy dates back to the early 1900s with the work of Noon and Freeman. Shortly after successful treatment of grass pollen allergic hay fever patients, with a conventional immunotherapy build-up schedule, which they referred to as “leisurely,” they began using accelerated schedules, which they referred to as “intensive desensitization” and rush. Freeman recounts their experience with leisurely and rush schedules in a 1930 *Lancet* article¹⁴: “In 1909, Noon and I began inoculating hay-fever patients with a grass pollen extract. . . . inoculations were given weekly merely because our out-patients at St. Mary’s Hospital were in the habit of coming every week. After we had arrived at what we believed to be an effective dose we made little or no attempt to increase it—being influenced by the routine practice for therapeutic immunization. I have called this older method ‘leisurely.’”

RUSH DESENSITIZATION

The article by Freeman also described the following: “A gymnastic instructress with hay fever previously inoculated (presumably with a conventional/‘leisurely’ schedule) but ‘owing to the pressures of work’ discontinued treatment. Early in June she arrived in a desperate state, a mental and physical wreck and quite unable to carry on her work. She was put through a four day ‘rush’ course and ‘went and rolled in a hayfield without being able to get a sneeze out of it’.” Freeman concluded that the advantages of the rush method were the saving of time, convenience, and patient compliance. These factors continue to play an important role in determining the success of immunotherapy treatment. Inconvenience was the most commonly cited reason for discontinuation of immunotherapy in 3 studies that evaluated compliance with immunotherapy through medical record review.^{10–12}

CONVENTIONAL IMMUNOTHERAPY SAFETY

The safety of accelerated immunotherapy schedules is generally compared with conventional schedules. To provide some perspective, one review reported that the incidence of systemic reactions (SRs) with conventional immunotherapy build-up schedules ranged from 0.05% to 3.2% of injections and 0.84% to 46.7% of patients (mean, 12.92%; SD, 10.8%).¹⁵ The 46.7% rate occurred in a study of patients highly sensitive to ragweed, who had positive intradermal skin test results of 1:312,500 wt/vol or greater concentration (≤ 0.01 $\mu\text{g/mL}$ of ragweed IgE).¹⁶ Excluding this study, the SR rates in this review were 0.6% per injection or less, and the percentage of patients experiencing SR rates ranged from 0.84% to 28.6% of patients. Fatal reactions with subcutaneous immunotherapy injections are relatively rare and occur at a rate of approximately 1 fatality per 2 million injections according to 3 surveys performed by the American Academy of Allergy, Asthma, and Immunology dating back to 1945.^{17–19}

RIT FOR VENOM HYPERSENSITIVITY

Most published RIT studies are with venom allergic patients. The package insert of venom extracts provides a cluster schedule as an example of a recommended schedule. Most of the venom RIT studies have demonstrated both efficacy and safety comparable or superior to conventional schedules. In a 3-day venom RIT study of 9 high-risk patients, who previously had recurrent SRs with a conventional venom immunotherapy build-up schedule, 6 patients were able to achieve the therapeutic maintenance dose within 3 days, although 3 of 6 patients had mild cutaneous SRs.²⁰ Two patients were able to achieve the maintenance dose within 5 days, and 1 patient experienced anaphylaxis and treatment was discontinued. The patients had an intravenous line placed for the rush protocol. The study did not specify if the patients were premedicated before the RIT, but they had been premedicated with loratadine with the conventional schedule. Another

study of 101 “high-risk” venom allergic patients who were treated with 4-day RIT found that 100 patients (99%) were able to reach the maintenance dose with 8 injection-related SRs in 7 patients (6.9%).²¹ The patients were hospitalized during the 4-day RIT and premedicated with dimethindene maleate (first-generation H₁-receptor antagonist). Fifty-seven patients underwent an ultrarush desensitization that aimed at reaching a cumulative dose of 101.1 µg of Hymenoptera venom in 2.5 hours.²² The treatment was successfully completed by all except one, who had a hypertensive crisis unrelated to the RIT. Four patients (7%) had mild systemic reactions that required treatment (antihistamines and oral corticosteroids). A significant increase in venom-specific IgG4 was seen after 15 days ($P < .01$) and remained statistically significant after 1 year ($P < .001$). A similar safety profile of RIT has been demonstrated in patients with imported fire ant hypersensitivity. In a study that compared the safety of a 2-day RIT in 58 imported fire ant allergic patients randomized to placebo premedication or twice-daily terfenadine, 60 mg; ranitidine, 150 mg; and prednisone, 30 mg; initiated 2 days before RIT, 3 patients (5.2%) experienced a mild systemic reaction with no statistical difference between the 2 groups (3.6% active and 6.7% placebo).²³

INHALANT ALLERGENS

Dust Mite

Relatively few studies have evaluated RIT in patients with allergies to aeroallergens. Most studies have been performed with single inhalant allergens, with dust mite and grass pollen being the 2 most extensively studied. In a study of 125 mite allergic asthma patients aged 4 to 57 years (mean $\pm$ SD age, 25.3 $\pm$ 11.2 years) that used a 3-day RIT protocol with the target dose of 3,000 BU (4 µg of Der p 1) in patients older

than 10 years and 1,500 BU (2 µg of Der p 1) in children younger than 10 years, 43 patients (34.4%) had severe SRs that required antiasthma treatment or epinephrine.²⁴ The doses that elicited the SRs ranged from 30 to 3,000 BU (0.04 to 4 µg of Der p 1), but most asthma reactions occurred at 1,200 and 1,800 BU. The doses that caused anaphylaxis were fairly evenly distributed, ranging from 600 to 2,400 BU. The reaction rate per injection was 4.16%. All reactions occurred within 45 minutes after the last injection. The 2 predictors for SRs were skin prick end point titration ($P < .015$) and forced expiratory volume in 1 second (FEV₁) ($P < .001$) before RIT. Asthmatic reactions occurred in 73.3% of patients with an FEV₁ less than 80%, whereas only 12.6% of patients with an FEV₁ more than 80% had asthmatic reactions ($P < .0001$). The authors noted that if the patients with an FEV₁ less than 80% had been excluded from study, the SR rate would have reduced to 19.7% of patients. In a subsequent study of 1,152 dust mite allergic patients, the authors compared 4 RIT regimens with the same target maintenance dose and found a significant reduction in SR rate and severity with premedication and preventive measures.²⁵ The preventive measures were exclusion of patients with an FEV₁ less than 70% of predicted and modifying the schedule for large local reactions greater than 10 cm (Table 1). There was a very high SR rate in children younger than 5 years (45% of children). Similar results were seen in a study of 454 pollen allergic patients (orchard grass, *Parietaria*, plane tree, or olive) comparing the 4 different protocols (Table 1).²⁶ Premedication reduced the risk of SR 2-fold from 31.3% to 14.7% of patients (difference between groups A and B, $P < .015$). Premedication and preventive measures further reduced the SR rate to 7.5% (difference between groups A and C, $P < .005$). The SR rate

Table 1. Systemic Reactions According to Immunotherapy Schedule, Premedication, and Prevention Measures in Dust Mite and Pollen Allergic Patients With Allergic Rhinitis With or Without Asthma*

Treatment regimen	Allergen	SR per patient, %	SR per injection, %	Asthma reactions, %	Anaphylaxis, %
Group A: 3-day RIT, 290 patients	Dust mite, 290 patients	36	3.8	30.6	5.1
	Pollen, 74 patients	31.3	3.1	9.7	5.8
Group B: RIT plus premedication†	Dust mite, 160 patients	16.2	2.0	13.7	1.8
	Pollen, 102 patients	14.7	3.1	5.8	5.8
Group C: RIT plus premedication and preventive measure‡	Dust mites, 479 patients	7.3	0.8	6.9	0.2
	Pollen 200 patients	7.5	2.3	2.5	0.3
Group D: step protocol with premedication and preventive measure§	Dust mites, 223 patients	5.4	0.6	5.0	0.4
	Pollen, 78 patients	2.6	2	0	0

Abbreviations: RIT, rush immunotherapy; SR, systemic reaction.

* Data are from Hejjaoui et al.^{25,26} Target dose of 3,000 BU for patients older than 10 years and 1,500 BU for patients younger than 10 years (1,500 BU = 2 µg of Der p 1).

† For the premedication group, the protocol began on day 1 of RIT: methylprednisone (0.5 mg/kg) 9 AM only, ketotifen (1 mg) 9 AM and 7 PM, and a long-acting theophylline (5 mg/kg) 9 AM and 7 PM.

‡ Preventive measures included excluding patients with a forced expiratory volume in 1 second of less than 70% and slowing rate with large local reactions greater than 10 cm.

§ Step protocol with premedication and preventive measure maintenance achieved with 9 injections administered in 6 visits over 2 weeks.

with the step protocol was only slightly less than the premedication plus preventive measures group.

A study designed to investigate the effect of RIT on airway inflammation, airway responsiveness, and T-cell cytokine production in 8 dust mite allergic asthma patients demonstrated a significant improvement in clinical parameters 1 month after RIT: symptoms scores decreased from 16.63 ± 2.24 at baseline to 6.5 ± 3.35 , with progressive improvement during the 6-month period ($P < .03$). A similar pattern was seen in peak expiratory flow measurements ($P < .03$).²⁷ There was a significant change in all of the objective parameters studied 6 months after RIT: allergen and histamine-induced bronchoprovocation (both $P < .03$) and reduced total eosinophils ($P < .01$), EG2+ eosinophils ($P < .05$), and eosinophil cationic protein in induced sputum after allergen challenge ($P < .05$).

Pollen

Several studies have been published on RIT with pollen allergens.^{26,28–35} These studies have used standardized extracts,^{28,30–32,34,35} depot preparations,^{31,36} and allergoids^{30,32,37} and include *Parietaria*,²⁶ birch,³⁴ olive,²⁶ plane tree pollen,²⁶ ragweed,³⁵ mixed grasses,^{30,32} orchard grass,^{30,32} timothy grass,³⁴ cocksfoot pollen,³¹ and Bermuda grass.²⁸ The reported SR rates in these studies ranged from 2.6%²⁶ to 36.8% (allergoid group)³² of patients. In a double-blind, placebo-controlled study that compared the safety of standardized orchard grass pollen extract with a grass pollen allergoid, SRs occurred in 36.8% of the patients treated with allergoid and 20% of the patients who received the standardized extract.³² The reactions observed with the standardized extract were more severe than the allergoid group.

In an open, longitudinal study designed to investigate the efficacy of a 3 injection per day 1-week RIT protocol with standardized aqueous extracts of birch or timothy pollen (Aquagen, ALK-Abello, Copenhagen, Denmark) without premedication, 4 (13%) of 30 patients experienced SRs (3 urticaria and 1 asthma attack) during RIT.³⁴ The target dose at the end of RIT was 10,000 SQ with a subsequent post-RIT build-up at every 3 weeks to a target dose of 100,000 SQ of standardized depot preparation (Alutard, ALK-Abello). The major allergen content was not given, but in subsequent studies 10,000 SQ corresponds to 2 μ g of Phl p 5.³⁸ Specific IgG and IgG4 increased continuously after the first week of RIT, and there was a significant change in symptoms and medication scores during the first pollen season compared with the untreated control group ($P < .05$ and $P < .001$, respectively).

In a double-blind, placebo-controlled study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on 159 adults with ragweed allergic rhinitis who were randomized into 4 treatment groups, omalizumab premedication followed by RIT or placebo RIT and placebo premedication followed by RIT or placebo RIT, there was a 5-fold decrease in the risk of anaphylaxis caused by RIT with omalizumab

premedication compared with the placebo premedication plus RIT group: 2 patients (5.6%) vs 10 patients (25.6%), respectively (odds ratio, 0.17; $P = .026$).³⁵ There was also a significantly greater improvement in disease severity scores in the omalizumab plus RIT group compared with the group that received RIT alone (0.69 vs 0.86; $P = .044$).

Animal

RIT protocols have been used to treat cat, dog,^{39–42} and rat allergic patients.⁴³ In a double-blind, placebo-controlled study, 39 cat and/or dog allergic adults and children were treated with a 1- to 2-week RIT protocol (15 cat, 17 placebo, and 7 dog) and followed up for 24 months.⁴² Adults were treated as outpatients with an aluminum-absorbed depot extract (Alutard SQ). The children were hospitalized for 1 to 2 weeks during the RIT, during which 5 to 7 injections (2 to 3 injections at higher concentrations) were administered daily. The target dose was 80,000 SQ (43 pg of Fel d 1 = 1 U subcutaneously; Aquagen SQ). After reaching the maintenance dose, they were switched to the depot extracts (Alutard SQ). All of the children developed mild SRs during RIT at doses ranging from 1,000 to 10,000 SQ. The character of the SRs was not provided, although it was stated that there were no asthma or urticaria reactions. Two children were unable to reach the dose of 10,000 SQ subcutaneously because of repeated SRs. The total number of SRs during RIT in the children was 44 per 557 injections (or 7.7% per injection). The frequency of SRs during the build-up and maintenance phases in the adult group was reported as 4% (18 of 443 injections), without specifying the frequency in each stage. Objective efficacy parameters were obtained after 12 and 24 months of treatment, and there was a significant change seen in the treatment group compared with the placebo group in skin prick test end point titration ($P < .001$), cat allergen bronchoprovocation ($P < .001$), histamine provocation ($P < .01$), and specific IgG4 and IgE (both increased, both $P < .001$).

Mold

There has been one published double-blind, placebo-controlled RIT study with an *Alternaria* extract standardized by laboratory assays, skin tests, and measurement of major allergen (Alt a 1).⁴⁴ Twenty-four patients with allergic rhinitis with or without asthma (ages 5–56 years) underwent a 7-injection 2-day RIT protocol administered in the hospital without premedication. All of the actively treated patients achieved the target maintenance dose of 2,000 BU, which was equivalent to 1.6 μ g of Alt a 1. Two (15%) of 13 actively treated patient experienced a SR on the first day (asthma). None of the placebo group had SRs. Efficacy parameters obtained after 1 year of treatment demonstrated significant changes in global symptom scores ($P < .005$), patient self-evaluation of treatment ($P < .001$), titrated skin prick tests ($P < .005$), nasal challenge ($P < .005$), and specific IgG ($P < .05$) in the actively treated group compared with the placebo group.

Allergen Mixtures

Few RIT studies that used mixtures of non-cross-reacting allergens have been published. A series of articles relayed the experience of a university hospital-based pediatric clinic with a 1- and 2-day RIT protocol with and without premedication in patients with allergic rhinitis and/or asthma using allergen extract mixtures.^{45–47} In the initial study, 11 patients (5 to 18 years), 4 classified as having steroid-dependent asthma, participated in a 9-injection 2-day RIT with no premedication.⁴⁶ The target dose was 0.1 mL of 1:100 wt/vol (1:100 wt/vol was the maintenance concentrate) of a non-standardized allergen extracts mixture and 1,500 to 2,400 AU/mL for dust mites. All except 1 patient, who experienced anaphylaxis associated with hypotension and respiratory distress, completed the RIT.

A total of 6 (55%) of 11 patients had SRs. Four patients had subsequent SRs within 4 weeks of completing the RIT. The grade of SRs ranged from 3 to 5, with grade 3 indicating generalized pruritus, sneezing, and mouth itchiness; grade 4, wheezing and shortness of breath; and grade 5, anaphylaxis. Three patients had grade 3, 1 patient had grade 3 to 4, 3 patients had grade 4, and 1 patient had grade 5 reactions. A significant correlation was found between severity of the SR and number of positive skin test results ($r = 0.60$, $P < .01$) and the cumulative size of skin reactions ($r = 0.75$, $P < .01$). Local reactions did not appear to predict SRs. A subsequent double-blind, placebo-controlled study of 22 children (5 to 18 years) was designed to investigate the effect of premedication on RIT.⁴⁵ Premedication with astemizole, ranitidine, and prednisone or placebo was begun the day before RIT and continued throughout the 2-day RIT.⁴⁵ Three (27%) of the 22 patients in the premedicated group and 8 (73%) of the 11 patients in the placebo group had SRs (Fisher exact test $P = .047$). The timing of the SRs ranged from 30 to 90 minutes after the previous injection, and all SR occurred at doses greater than 0.3 mL of 1:1,000 wt/vol. The mean time for SRs was 63 minutes after a previous injection (range, 30–120 minutes) at doses ranging from 0.5 mL of 1:1,000 to 0.1 mL of 1:100 wt/vol (average dose giving SR was 0.3 mL of 1:1,000 wt/vol). No subsequent SRs occurred during the 8 weekly maintenance injections after the RIT. The most important predictor for SRs was the initial wheal size on skin prick testing (ie, degree of allergen sensitivity). The authors observed that there was a notable increase in skin test reactivity in the placebo group just before the occurrence of their SR. The grade of severity of the SRs in the active group (one of each: grades 3, 4, and 5) was the same as the placebo group (2 grades 3 and 4 and 3 grade 5). In another study, the schedule was modified into an 8-injection 1-day RIT (total cumulative dose of 0.2 mL of the maintenance concentrate) with premedication.⁴⁷ SRs occurred in 5 (23%) of the 22 patients: 1 grade 3, 2 grade 4, and 1 grade 5. The time of SR in these 3 studies ranged from 30 to 120 minutes, and all SRs occurred at doses of 0.3 mL of 1:1,000 wt/vol or higher.

A double-blind, placebo-controlled study designed to compare the efficacy and safety of RIT with grass pollen or standardized mixed pollens demonstrated a similar incidence of SRs during RIT: 3 of 16 in the grass pollen group and 4 of 16 in the mixed pollens group.²⁹ However, clinical efficacy as measured by symptom medication scores and nasal challenge compared with placebo was only seen in the grass pollen group. There was a significant rise in grass specific IgG in both groups.

In a retrospective review of 65 patients who received RIT to multiple aeroallergens using a modification of the 1-day protocol previously discussed (7 injections instead of 8 and premedication with prednisone, cetirizine, ranitidine, and zafirlukast or montelukast), 25 patients (38%) experienced a SR.⁴⁸ All SRs occurred at doses equal to or greater than 0.1 mL of 1:10 vol/vol, and most occurred (72%) after the final dose (0.05 maintenance concentrate). Nineteen SRs (76%) were classified as mild, 5 (20%) as moderate, and 1 (4%) as severe. The SRs were associated with a higher degree of skin test reactivity and the presence of weed or dog allergen in the extract or vaccine.

CLUSTER IMMUNOTHERAPY SCHEDULES

Cluster immunotherapy is a build-up schedule wherein several allergen injections (2 to 3) are given sequentially in a single day of treatment, which results in the maintenance dose being achieved more rapidly than with a conventional schedule. Many different cluster schedules have been used in inhalant and venom immunotherapy. The injection visit frequency is 1 to 2 times a week, and the maintenance dose is usually achieved within 4 to 8 weeks. Many of the cluster studies were designed to study parameters such as efficacy or immunological changes, and few studies have directly compared the safety of the cluster immunotherapy with a conventional immunotherapy build-up schedule. A double-blind, placebo-controlled study of 239 patients with dust mite allergic rhinitis 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 using a standardized dust mite depot extract (ALK-Abello) extract found no differences between the cluster and conventional schedules in terms of adverse reactions (cluster group: 0.15% of injections, all grade 2).⁴⁹ The cluster schedule reduced the time to maintenance dose by 46% and led to decreases in asthma and rhinitis symptoms, reduced skin prick test reactivity, and increased specific IgE and IgG4 levels on reaching the maintenance dose in the sixth week, 6 weeks earlier than with the conventional schedule. The authors of the review presented similar findings in terms of the comparative safety of cluster immunotherapy in an earlier study of 63 dust mite allergic patients.⁵⁰

A review paper on cluster immunotherapy analyzed 29 studies that used a cluster build-up, 9 studies were designed to study the cluster schedule and 20 were designed to study other parameters (Table 2).^{16,37,51–69} The authors concluded that the optimal tolerance of cluster schedules is associated

Table 2. Summary of Studies Not Designed to Look at Cluster Schedule*

Allergens	Study	Extract	Visits in weeks	No. of injections Designed to Look at Cluster Schedule	Systemic reaction, No. (%) of patients
Summary of Studies Not Specifically Designed to Look at Cluster Schedule					
Dust mite	Van Bever et al ⁵¹	Aqueous	5	5/5/2/2/2	ND
	Garcia Ortega et al ⁵²	Aqueous	6	4/2/2/2/2/2	3 mild, 3 moderate
	Pichler et al ⁵³	Depot	8	2-3 per visit	0
	Tabar et al ⁵⁰	Aqueous then depot	7	4/3/2/2/2/2/1	1 moderate
Ragweed	Van Metre et al ¹⁶	Aqueous	7 every 3 weeks	3/2/2/2/2/1/1	10/18
	Norman et al ⁵⁴	Aqueous modified	5-6	11-13 injections total	5/16
Grass	Stevens et al ⁵⁵	Aqueous	9	5 × 2, 2 × 7	1 moderate
	Bousquet et al ^{33,37}	Aqueous modified	6	3/2/1/1/1/1	ND
	Fernandez-Tavora et al ⁵⁷	Aqueous then depot	3	5/5/5	10/20
	Walker et al ⁵⁹	Depot	7 (2 times a week)	3/2/2/1/1/1/1	4 (18%) active/5 (22%) placebo
Grass and Birch	Nielsen et al ^{59*}	Depot	7	3/2/2/2/2/2/1	33 % premedicated patients
		Depot	7	3/2/2/2/2/2/1	73% patients not premedicated
Molds	Dreberg et al ⁶⁰	Aqueous then depot	13	3/3/3/4/2/2/2/1	13/16 patients
	Malling et al ⁶¹	Aqueous	8	5 × visit	100% (anaphylaxis)
Epithelia	Bucur et al ⁶²	Aqueous then depot	13	5/3/2/2 and 1 × 9	58%
	Haugaard et al ⁶³	Aqueous then depot	8	2/2/2/2 and 1 × 4	6% per administration
Hymenoptera	Hunt et al ⁶⁴	Aqueous	7	3 and 1 × 6	ND
	Golden et al ⁶⁵	Aqueous	4 (fortnights)	3 and 1 × 3	16% patients
	Muller et al ⁶⁶	Aqueous	ND	ND	7/24
	Malling et al ⁶⁷	Aqueous then depot	4 (7 or 14 days)	5 × 4 × 44	5/21 (2 anaphylaxis)
Dust mite	Ewan et al ⁶⁸	ND	13	2 × 9 and 1 × 4	2/24
		Depot	4,	3/3/2/2	0.87% of injections
	Tabar et al ⁴⁹	Depot	6	4/3/2/2/2/1	0.15% of injections all grade 2
	Fernandez-Tavora et al ⁷⁵	Aqueous then depot	3	5/5/5	10/20 patients
Grasses	Moreno et al ⁷⁶	Aqueous	4	4/4/2/2	0.5 % of injections
	Mollerup et al ⁷⁷	Aqueous	6	4-2 per visit (18 total)	454 SFRs in 257 patients, 4.4% of injections and 39.1% of the patients, 93% grade 1 or 2
Mites, betula, grass, Hymenoptera		Aqueous then depot	7	2-4 per visit (18 total)	
		Depot	8	2-3 × visit (16 total)	
Birch or grass	Winther et al ⁷⁸	Birch depot	7	3/2/2/2/2/2/1	5/47 patients, 0.7% of injections
		Grass depot	7	3/2/2/2/2/2/1	21/44 patients, 3.3% of injections
Molds, <i>Alternaria</i>	Moreno et al ⁷⁹	Depot	4	10 total	2/60 patients, 0.3% of injections
		Depot	4	8 total	0
Summary of Studies Specifically Designed to Study the Cluster Protocol					

Abbreviation: ND, not declared.

* Adapted from Parmiani et al.⁶⁹

† The premedicated group received loratadine, 10 mg, 120 minutes before the cluster. The premedicated group had significantly fewer systemic reactions compared with group who was not premedicated (33% vs 79% of patients, respectively).

with use of premedication (loratadine, 10 mg), use of a depot preparation, use of no more than 4 administrations per cluster, use of a total of 4 to 6 clusters, and administration of 1 to 2 clusters per week. The recommendation of twice a week clusters was based on the significant difference in SR rate seen in 2 separate grass cluster studies that had virtually identical protocols, except one study administered the clusters once a week,⁵⁹ whereas the other administered the clusters twice a week.⁵⁸ There was a 79% SR rate in the group without premedication in the once a week cluster study⁵⁹ compared with a 22%⁵⁸ rate in the patients without premedication in the study with a twice a week cluster. In addition to the cluster frequency, the authors speculated the differences in SR rate in the 2 studies could have also been due to the timing of the premedication, which was given at least 15 minutes before the cluster in the twice a week group and 120 minutes before in the once weekly group.

Two double-blind, placebo-controlled studies designed to investigate the dose response effect on the immunological changes associated with use of specific allergen immunotherapy that used US-licensed allergen in cat allergic patients have used a cluster schedule.^{70,71} Three doses (0.6, 3.0, or 15.0 μ g of Fel d 1) were compared, and the maintenance dose was achieved with 8 visits in 4 weeks. The first study examined the immunological changes at 5 weeks and used loratadine as a premedication.⁷⁰ There were no SRs in the 28 patients, and the 15.0- μ g dose of Fel d 1 produced the most consistent immunologic response, although the 3.0- μ g dose reduced skin prick test sensitivity and increased cat specific IgG4 (Table 3). The second study evaluated the immunological changes at 5 weeks and 1 year and found significant dose-dependent differences in symptom scores on nasal challenge ($P < .0001$), with titrated skin prick testing at 5 weeks ($P = .014$) and 1 year ($P < .0001$) and with cat specific IgG4 measurement at 5 weeks ($P = .004$) and 1 year ($P = .003$).⁷¹ Zafirlukast and loratadine were used as premedication, and 1 (3.8%) of 26 patients had an SR that consisted of generalized pruritus after administration of the first dose of the maintenance concentrate. The authors concluded that the response to titrated nasal allergen challenge, titrated skin prick testing, and allergen specific IgG4 measurement to cat immunotherapy at 5 weeks is predictive of the response at 1 year.

PREMEDICATION AND ACCELERATED IMMUNOTHERAPY SCHEDULES

Overall, few studies designed to specifically address the effect of premedication on the SR rate with allergen immunotherapy have been published (Table 4). Most studies that have investigated the effect of premedication have been with rush venom immunotherapy.^{72,73} The premedication regimen for the rush protocols varied, but all included an antihistamine and oral corticosteroids. The regimen for most of the cluster regimens was an antihistamine alone. To my knowledge, no double-blind, placebo-controlled studies specifically designed to investigate the effect of premedication with conventional build-up schedules with inhalant allergens have been published. One open-label, multicenter study that used a conventional build-up schedule compared the effect of fexofenadine (60 mg) administered 2 hours before the immunotherapy injection in preventing severe SRs in patients with cedar pollen or dust mite allergic rhinitis.⁸³ There was a significant reduction in the number of severe SRs in the patients who received premedication compared with the control group, who did not receive premedication before the injection ($P = .03$). One of the concerns with the use of premedication is that it may mask milder SRs, allowing the build-up to proceed to a subsequent more serious SR. To the contrary, the published literature on studies that have used accelerated schedules for inhalant allergen immunotherapy^{35,59} and venom immunotherapy have demonstrated less incidence of local and SRs⁷² and possibly greater efficacy of the RIT.⁷³ One study on venom RIT demonstrated greater efficacy in the premedicated group in terms of subsequent responses to field stings or sting challenge.⁷³ The study was designed to evaluate patients who had participated in a double-blind, placebo-controlled honeybee RIT trial premedicated with terfenadine or placebo 3 years earlier. Forty-one of the 47 patients available for reevaluation were reexposed by either a field sting or sting challenge.⁷³ Six patients in the placebo premedicated group had SRs, whereas none of the patients in the terfenadine group had SRs ($P = .012$). The authors speculated that the mechanism responsible for the significant difference seen in immunotherapy efficacy as manifested by response to reexposure through field sting or

Table 3. Dose Response Effect on Immunological Changes Associated With Cat Immunotherapy*^{70,71}

Immunotherapy dose of Fel d 1	Titration skin prick test, mean change (half-log dilutions)	Flow cytometry, mean decrease in CD4 ⁺ /IL-4 ⁺ PBMCs, %	Cat specific IgG4
Placebo	-0.35	-4.2	-4
0.6 μ g	0.03	1.86	144
3.0 μ g	0.84 ($P = .2$)	2.92	779 ($P = .01$)
15 μ g	1.7 ($P = .002$)	-11.4 ($P = .003$)	729 ($P = .006$)

* Twenty-eight cat allergic patients were randomized to receive placebo or 1 of 3 treatment dose groups (7 in each group): 0.6 μ g, 3.0 μ g, or 15 μ g of Fel d 1 with an 8-injection 4-week cluster protocol. Immunological evaluation was performed before immunotherapy and after the first weekly maintenance injection at 5 weeks.

Abbreviation: PBMCs, peripheral blood mononuclear cells.

Table 4. Summary of Results of Studies That Investigated or Provided Information on the Effect of Premedication

Study	Allergen	Protocol	Target dose	Premedication regimen	Control group	Results
Hejjaoui et al ²⁵	Dust mite (Dpt)	One-day rush followed by 5 singly injection visits over 14 days	3,000 BU if > 10 years, 1,500 BU if < 10 years, 3000 BU = 4 µg of Der p 1	Methylprednisone and ketotifen long-acting theophylline	Historical control from earlier trials	36% SR rate in group without premedication, 16% in group with premedication and further reduced SR rate to 7.3% of patients by excluding patients with FEV ₁ <70% predicted and modifying regimen for large local reactions
Portnoy et al, ^{45,46} Sharkey and Portnoy ⁴⁷	Multiple allergens	1- and 2-day rush	Target dose was 0.1 mL of maintenance concentrate, which contained 1:100 wt/vol to 1:400 wt/vol of nonstandardized extracts or mites at 1,500–2,400 AU/mL	Astemizole, ranitidine and prednisone	Historical and placebo premedicated controls	55%–73% of patients not premedicated had SR vs 27% and 23% of premedicated groups
Walker et al ⁵⁸	Grass	Cluster 7 visits over 4 weeks	Target dose 20 µg of Ph p 5	Loratadine, 10 mg, at least 15 min before cluster	Placebo group	All SR delayed; essentially no difference in SR rate between placebo (22%) and premedicated group (18%)
Ewbank et al ⁷⁰	Cat	Cluster 8 visits over 4 weeks	3 Target doses: 0.6, 3.0, and 15 µg of Fel d 1	Loratadine, 10 mg, 2 hours before procedure	No group without premedication to compare	No SRs
Muller et al ⁷³	Venom	4-day rush	Target dose: 100 µg of honeybee venom	Terfenadine, 120 mg twice daily	Placebo premedication	4 patients (15%) in premedication group had SR vs 10 (38%) in placebo group
Nielsen et al ⁵⁹	Timothy and birch	Cluster 7 weekly visits	Target dose: 23 µg of Bet v 1 23 and 25 µg of Phl p 5	Loratadine 2 hours before injections	Placebo premedication	Significant difference between groups in SR rate: 7 (33.3%) in loratadine group and 19 (79.2%) in placebo group
Brockow et al ⁷²	Venom	Rush	Target dose, 100 µg of venom	Terfenadine, 120 mg, ± ranitidine, 300 mg	Placebo premedication	SR causing discontinuation of immunotherapy: 15% placebo vs 2 % premedication
Casale et al ³⁵	Ragweed	Rush	4 µ g initially then changed to 2 µg of Amb b1	Fexofenadine and omalizumab for 9 wk	Compared with placebo premedication	33.3% omalizumab and placebo vs 56.4% placebo; omalizumab plus RIT; anaphylaxis decreased from 25.6% in the placebo plus RIT to 5.6% in the omalizumab plus RIT (<i>P</i> = .026)
Nanda et al ⁷¹	Cat	Cluster 8 visits over 4 weeks	3 Target doses: 0.6, 3.0, and 15 µg of Fel d 1	Zafirlukast and loratadine	No placebo premedication	1/26 SR

Abbreviations: FEV₁, forced expiratory volume in 1 second; RIT, rush immunotherapy; SR, systemic reaction.

challenge in the 2 groups was related to the immunomodulatory role of histamine.

IMMUNOLOGICAL CHANGES AND ACCELERATED IMMUNOTHERAPY

Most RIT studies have been designed to evaluate efficacy and safety, and few have studied the early immunological changes associated with RIT. It is likely that the early mechanisms behind the tolerance induced during the RIT protocol are different from the mechanisms seen over time with conventional immunotherapy (ie, rise in specific IgG4 levels, induction of T-regulatory cells and IL-10 production). It is likely that the early mechanism behind the tolerance during RIT is similar to that seen with drug desensitization. Immunological changes seen with conventional immunotherapy have been reported earlier in some RIT studies. In a venom ultrarush immunotherapy study, no significant change was found in IgG titers until 15 days after the therapy, but a rapid change occurred in the capacity of the individual sera to prevent antigen binding of pooled pretreatment sera, with mean percentage inhibitions falling from $80\% \pm 15\%$ before venom immunotherapy to $26\% \pm 14\%$, $35 \pm 15\%$, and $34\% \pm 5\%$ after 12 hours, 24 hours and 15 days, respectively ($P < .001$ by 1-way analysis of variance).⁸⁴ The early changes in IgG specificity (ie, changes in the wasp-venom antigen epitopes recognized by IgG) correlated with clinical tolerance. Another study specifically designed to study the immunological changes associated with 2- to 4-week RIT in 10 dust mite allergic asthmatic children demonstrated a significant reduction in skin and nasal reactivity to mite allergen, accompanied by a rise in serum allergen specific IgE and specific IgG4 levels 1 to 2 days after the maintenance dose was reached.⁸⁵ T-cell proliferative responses to mite antigen were suppressed, and the numbers of CD8⁺ T cells were increased in frequency. A marked increase occurred in interferon- γ production, and the correlation between the increase in interferon- γ production and the changes in cutaneous reactivity was highly significant.

In the 2-day RIT study that used mixed allergen extracts, a significant rise occurred in specific IgG levels 2 weeks after RIT, with a continued rise through the 8-week follow-up period.⁴⁵ In the study that investigated the effect of omalizumab on RIT, a 10-fold rise occurred in ragweed specific IgG 1 to 4 weeks into the ragweed season (the RIT was completed at least 3 weeks before season).³⁵ Der f 1 stimulation of peripheral blood mononuclear cells from 9 dust mite allergic asthma patients treated with RIT resulted in significantly higher production of interleukin-12 and interferon- γ and lower production of interleukin-4 compared with untreated atopic control patients.⁸⁶ Significant increases also occurred in the expression of interleukin-12 receptor β 2-chain before and after stimulation of CD4⁺ T cells with interleukin-12 or interferon- γ . In the cat cluster studies previously discussed, the dose-dependent immunological changes in titrated nasal allergen challenge, titrated skin prick testing, and allergen specific IgG4 seen after 5 weeks of

treatment were predictive of the 1-year response.⁷¹ These studies indicate that the immunological changes associated with immunotherapy may occur more rapidly with the accelerated immunotherapy schedules.

CONCLUSIONS

In summary, accelerated immunotherapy schedules have been used in the treatment of allergic disease for many years. They offer the advantage of convenience by reducing patient time and allow for rapid appreciation of the clinical benefits of immunotherapy. The major deterrent to the use of accelerated immunotherapy schedules is concern about the safety of these rapid protocols. Review of the published studies that used accelerated immunotherapy schedules with aeroallergens strongly suggests that RIT schedules without premedication carry a greater risk of SRs. In the studies reviewed, the SR rates for RIT ranged from 27%³³ to 100%⁴² for patients treated with RIT without premedication and 7.2%²⁵ to 27%⁴⁵ for patients treated with premedication. Premedication appears to reduce the SR rate to a range that is comparable to conventional build-up schedules, which is in the range of SRs reported with conventional schedules (0.84% to 28.6% of patients; mean, 12.92%; SD, 10.8%).¹⁵

Cluster schedules appear more promising in terms of the balance between safety and convenience. However, there was also a considerable range in reported SRs in the cluster studies reviewed in this article from 0 patients in a cat study with loratadine premedication⁷⁰ to 79% of the patients in the group without premedication in a grass pollen study comparing the effect of loratadine premedication.⁵⁹ As with RIT, premedication appears to reduce the incidence of SRs with cluster schedules.⁵⁸ However, some cluster studies demonstrated safety similar to conventional schedules without premedication.^{50,87} In addition to premedication, a review article on cluster immunotherapy schedules suggested the following factors are associated with optimal tolerance of cluster immunotherapy schedules: use of a depot preparation, use of no more than 4 administrations per cluster, use of a total of 4 to 6 clusters, and administration of 1 to 2 clusters per week. However, the authors suggested the best results were seen in studies with twice a week clusters.⁶⁹ The degree of skin test reactivity and FEV₁ less than 70% of predicted were identified as predictors of SRs during RIT.

In conclusion, accelerated immunotherapy schedules with premedication may offer allergic patients, particularly patients without the identified risk factors for SRs, a more convenient alternate to conventional immunotherapy schedules without significantly increasing the risk compared with conventional schedules.

REFERENCES

1. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. *Ann Allergy Asthma Immunol.* 2001;87(1 suppl 1):43–6.
2. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal

- rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251–256.
3. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, VI: specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. 1997;99:450–453.
 4. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children mono-sensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy*. 2001;31:1392–1397.
 5. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy*. 2001;31:1295–1302.
 6. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? a meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med*. 1995;151:969–974.
 7. Abramson MJ. Allergen immunotherapy for asthma (Cochrane Review). *Cochrane Database Sys Rev*. 2005.
 8. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis. *Clin Ther*. 2000;22:342–350.
 9. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther*. 2000;22:329–241.
 10. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol*. 1993;91:734–737.
 11. Lower T, Henry J, Mandik L, Janosky J, Friday GA Jr. Compliance with allergen immunotherapy. *Ann Allergy*. 1993;70:480–482.
 12. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol*. 2002;88:391–394.
 13. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter. *Ann Allergy Asthma Immunol*. 2003;90(1 suppl 1):1–40.
 14. Freeman J. "Rush inoculation," with special reference to hay fever treatment. *Lancet*. 1930;744–747.
 15. Stewart GE I, Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol*. 1992;90(4 pt 1):567–78.
 16. Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J Allergy Clin Immunol*. 1982;69:181–193.
 17. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol*. 2004;113:1129–1136.
 18. Lockey RF, Turkeltaub P, Bukantz SC. Fatalities associated with skin testing and immunotherapy: a retrospective study by questionnaire. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankfurt A M*. 1988;82:153–162.
 19. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol*. 1993;92(1 pt 1):6–15.
 20. Goldberg A, Confino-Cohen R. Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy. *Ann Allergy Asthma Immunol*. 2003;91:405–410.
 21. Sturm G, Kranke B, Rudolph C, Aberer W. Rush Hymenoptera venom immunotherapy: a safe and practical protocol for high-risk patients. *J Allergy Clin Immunol*. 2002;110:928–933.
 22. Schiavino D, Nucera E, Pollastrini E, et al. Specific ultrarush desensitization in Hymenoptera venom-allergic patients. *Ann Allergy Asthma Immunol*. 2004;92:409–413.
 23. Tankersley MS, Walker RL, Butler WK, Hagan LL, Napoli DC, Freeman TM. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. *J Allergy Clin Immunol*. 2002;109:556–562.
 24. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract: systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol*. 1989;83:797–802.
 25. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, IV: systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol*. 1990;85:473–479.
 26. Hejjaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol*. 1992;89:925–933.
 27. Kohno Y, Minoguchi K, Oda N, et al. Effect of rush immunotherapy on airway inflammation and airway hyperresponsiveness after bronchoprovocation with allergen in asthma. *J Allergy Clin Immunol*. 1998;102(6 pt 1):927–34.
 28. Armentia-Medina A, Blanco-Quiros A, Martin-Santos JM, et al. Rush immunotherapy with a standardized Bermuda grass pollen extract. *Ann Allergy*. 1989;63:127–135.
 29. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species, II: efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol*. 1991;88:43–53.
 30. Bousquet J, Braquemon P, Feinberg J, Guerin B, Maasch H, Michel FB. Specific IgE response before and after rush immunotherapy with a standardized allergen or allergoid in grass pollen allergy. *Ann Allergy*. 1986;56:456–459.
 31. Bousquet J, Guerin B, Dotte A, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuvanted pyridine extracted material in grass pollen allergy. *Clin Allergy*. 1985;15:179–193.
 32. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids, I: rush immunotherapy with allergoids and standardized orchard grass-pollen extract. *J Allergy Clin Immunol*. 1987;80:591–598.
 33. Bousquet J, Hejjaoui A, Soussana M, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids, IV: comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol*. 1990;85:490–497.
 34. Moverare R, Vesterinen E, Metso T, Sorva R, Elfman L, Haah-tela T. Pollen-specific rush immunotherapy: clinical efficacy and effects on antibody concentrations. *Ann Allergy Asthma Immunol*. 2001;86:337–342.
 35. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for

- ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2006;117:134–140.
36. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy.* 1996;51:489–500.
37. Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids, III: efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol.* 1989;84(4 pt 1):546–56.
38. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2006;117:319–325.
39. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts, V: effects of 3 years of treatment. *J Allergy Clin Immunol.* 1991;87:955–964.
40. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts, II: in vivo and in vitro immunologic effects observed in a 1-year double-blind placebo study. *J Allergy Clin Immunol.* 1986;77(3):488–96.
41. Hedlin G, Heilborn H, Lilja G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol.* 1995;96(6 pt 1):879–85.
42. Lilja G, Sundin B, Graff-Lonnevig V, et al. Immunotherapy with cat- and dog-dander extracts, IV: effects of 2 years of treatment. *J Allergy Clin Immunol.* 1989;83:37–44.
43. Hansen I, Hormann K, Klimek L. Specific immunotherapy in inhalative allergy to rat epithelium [in French]. *Laryngorhinootologie.* 2004;83:512–515.
44. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. *J Allergy Clin Immunol.* 1990;85:460–472.
45. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy.* 1994;73:409–418.
46. Portnoy J, King K, Kanarek H, Horner S. Incidence of systemic reactions during rush immunotherapy. *Ann Allergy.* 1992;68:493–498.
47. Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. *Ann Allergy Asthma Immunol.* 1996;76:175–180.
48. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. *Ann Allergy Asthma Immunol.* 2004;92:414–419.
49. Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol.* 2005;116:109–118.
50. Tabar AI, Muro MD, Garcia BE, et al. *Dermatophagoides pteronyssinus* cluster immunotherapy: a controlled trial of safety and clinical efficacy. *J Investig Allergol Clin Immunol.* 1999;9:155–164.
51. Van Bever HP, Stevens WJ. Suppression of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mite (*Dermatophagoides pteronyssinus*). *Clin Exp Allergy.* 1989;19:399–404.
52. Garcia-Ortega P, Merelo A, Marrugat J, Richart C. Decrease of skin and bronchial sensitization following short-intensive scheduled immunotherapy in mite-allergic asthma. *Chest.* 1993;103:183–187.
53. Pichler CE, Marquardsen A, Sparholt S, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D. farinae* results in decreased bronchial hyperreactivity. *Allergy.* 1997;52:274–283.
54. Norman PS, Lichtenstein LM, Kagey-Sobotka A, Marsh DG. Controlled evaluation of allergoid in the immunotherapy of ragweed hay fever. *J Allergy Clin Immunol.* 1982;70:248–260.
55. Stevens WJ, Verhelst JA, van den Bogaert W, Bridts CH. Clinical and biological evaluation of semi-rush and ordinary immunotherapy schemes in type I allergic respiratory diseases. *Allergy.* 1985;40:447–452.
56. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids, II: comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol.* 1988;82(3 pt 1):439–46.
57. Fernandez-Tavora L. Inmoterapia cluster con extractos de polenes: estudio de tolerancia, cambios inmunologicos y eficacia clinica. *Rev Esp Alergol Clin Immunol.* 1991;6:68–74.
58. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol.* 2001;107:87–93.
59. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol.* 1996;97:1207–1213.
60. Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation, I: clinical results. *Allergy.* 1986;41:131–140.
61. Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy, V: clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. *Allergy.* 1986;41:507–519.
62. Bucur J, Dreborg S, Einarsson R, Ljungstedt-Pahlman I, Nilsson JE, Persson G. Immunotherapy with dog and cat allergen preparations in dog-sensitive and cat-sensitive asthmatics. *Ann Allergy.* 1989;62:355–361.
63. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander, I: clinical results. *Allergy.* 1992;47:249–254.
64. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med.* 1978;299:157–161.
65. Golden DB, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med.* 1980;92:620–624.
66. Muller U, Lanner A, Schmid P, Bischof M, Dreborg S, Hoigne R. A double blind study on immunotherapy with chemically modified honey bee venom: monomethoxy polyethylene glycol-coupled versus crude honey bee venom. *Int Arch Allergy Appl Immunol.* 1985;77:201–203.
67. Malling HJ, Djurup R, Sondergaard I, Weeke B. Clustered immunotherapy with Yellow Jacket venom: evaluation of the influence of time interval on in vivo and in vitro parameters. *Allergy.* 1985;40:373–383.
68. Ewan PW, Deighton J, Wilson AB, Lachmann PJ. Venom-

- specific IgG antibodies in bee and wasp allergy: lack of correlation with protection from stings. *Clin Exp Allergy*. 1993;23:647–660.
69. Parmiani S, Fernandez Tavora L, Moreno C, Guardia P, Rico P. Clustered schedules in allergen-specific immunotherapy. *Allergol Immunopathol (Madr)*. 2002;30:283–291.
 70. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. *J Allergy Clin Immunol*. 2003;111:155–161.
 71. Nanda A, O'Connor M, Anand M, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. *J Allergy Clin Immunol*. 2004;114:1339–1344.
 72. Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 1997;100:458–463.
 73. Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol*. 2001;107:81–86.
 74. Vidal-Trecan G, Moreno C, Guardia P. Immunoterapia cluster con un extracto depot de *Dermatophagoides pteronyssinus*: estudio prospectivo de tolerancia. *Rev Esp Alergol Immunol Clin*. 1997;12:351–355.
 75. Fernandez-Tavora L. Aqueous extracts and cluster schedule: a good approach for immunotherapy buildup phase *Allergy*. 1995;50(26):P-0592.
 76. Moreno C, Fernandez-Tavora L, Vidal C, Justicia JL, Guerra F. Estudio prospectivo de seguridad de una pauta agrupada con extractos acuosos de polenes. *Alergol Immunol Clin*. 2001;16:95–101.
 77. Møllerup MT, Hahn GW, Poulsen LK, Malling H. Safety of allergen-specific immunotherapy. Relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. *Clin Exp Allergy*. 2000;30:1423–1429.
 78. Winther L, Malling HJ, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis, II: side-effects. *Allergy*. 2000;55:827–835.
 79. Moreno C, Fernandez-Tavora L, Justicia JL, Guerra F, Vidal C. Busqueda de una pauta idonea para iniciacion de inmunoterapia con un extracto de *Alternaria tenuis*. *Alergol Immunol Clin*. 2001;16:133–137.
 80. Tarhini H, Knani J, Michel FB, Bousquet J. Safety of venom immunotherapy administered by a cluster schedule. *J Allergy Clin Immunol*. 1992;89:1198–1199.
 81. Moreno C. Immunoterapia con veneno de himenopteros: seguridad de una pauta agrupada *Alergol Immunol Clin*. 1999;14:315–321.
 82. Quercia O, Rafanelli S, Puccinelli P, Stefanini GF. The safety of cluster immunotherapy with aluminium hydroxide-adsorbed honey bee venom extract. *J Investig Allergol Clin Immunol*. 2001;11:27–33.
 83. Ohashi Y, Nakai Y, Murata K. Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis. *Ann Allergy Asthma Immunol*. 2006;96:600–605.
 84. Michils A, Baldassarre S, Ledent C, Mairesse M, Gossart B, Duchateau J. Early effect of ultrarush venom immunotherapy on the IgG antibody response. *Allergy*. 2000;55:455–462.
 85. Lack G, Nelson HS, Amran D, et al. Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-gamma production in CD4+ T cells. *J Allergy Clin Immunol*. 1997;99:530–538.
 86. Tazaki T, Minoguchi K, Yokoe T, et al. Allergen rush immunotherapy increases interleukin (IL)-12 production and IL-12 receptor beta2 chain expression in patients with allergic asthma. *Cell Immunol*. 2004;228:20–26.
 87. Tabar AI, Fernandez-Tavora L, Alonso R, et al. Olerance of a cluster schedule with a house dust mite extract quantified in mass units: multicentre study. *J Investig Allergol Clin Immunol*. 2004;14:193–197.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Cox L. 2006;97:126–138.

CME Test Questions

1. All of the following were associated with a greater risk of systemic reactions during rush immunotherapy except:
 - a. forced expiratory volume in 1 second (FEV₁) less than 80% of predicted
 - b. female sex
 - c. high degree of skin test reactivity
 - d. children younger than 5 years
2. All of the following were found to be associated with the reduced incidence of systemic reactions with cluster immunotherapy schedules except:

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- a. clusters administered twice a week
 - b. no more than 4 injections per cluster
 - c. aqueous extracts
 - d. premedication
3. Premedication with accelerated immunotherapy schedules (best answer)
- a. decreases the incidence of systemic reaction but increases the severity of the reactions
 - b. decreases the incidence of systemic reactions with rush immunotherapy but not with cluster immunotherapy schedules
 - c. is only effective in preventing systemic reactions with accelerated schedules if begun 7 days before treatment
 - d. has been shown to decrease systemic reactions frequency with rush and cluster schedules without a concomitant increase severity of the systemic reaction
4. All of the following immunological changes have associated with rush immunotherapy except:
- a. increase in allergen specific IgG4 demonstrated within 2 weeks of completing rush immunotherapy
 - b. increased interferon- γ production that correlated with decreased skin test reactivity within 1 to 2 days of completion of rush immunotherapy
 - c. increase in interleukin-13 production
 - d. lower production of interleukin-4 in allergen stimulated and higher production of interleukin-12 and peripheral blood mononuclear cells from rush immunotherapy patients
5. The following are true about rush immunotherapy in venom-allergic patients except:
- a. Rush immunotherapy should not be considered in patients who have had recurrent systemic reactions with a conventional schedule.
 - b. Ultrarush schedules have been used that achieve a cumulative dose of 101 μ g in 2.5 hours.
 - c. Significant increase in venom specific IgG4 has been demonstrated 15 days after rush immunotherapy.
 - d. No difference occurs in the incidence of systemic reactions during rush immunotherapy imported fire ant allergic patients treated with or without premedication.
- Answers found on page 202.**
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