

Accelerated Immunotherapy Schedules

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Published online: 1 June 2013
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Abstract Rush and cluster immunotherapy schedules are accelerated immunotherapy build-up schedules. A cluster immunotherapy schedule involves the patient receiving several allergen injections (generally 2–4) sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is generally reached in 4–8 weeks. In rush immunotherapy protocols, higher doses are administered at 15- to 60-min intervals over a 1- to 3-day period until the maintenance dose is achieved. This review will serve as an update for accelerated immunotherapy schedules. The review will include recent investigations demonstrating the safety of cluster schedules in atopic dermatitis, pediatric patients, and inhalant allergen mixtures and an accelerated protocol utilizing an infusion pump for allergen delivery. There has also been further elucidation on the immunological changes which occur during accelerated immunotherapy. Finally, new studies analyzing systemic reaction risk factors are discussed.

Keywords Accelerated immunotherapy schedules · Cluster immunotherapy · Rush immunotherapy · Subcutaneous immunotherapy · Pre-medication · Systemic reactions · Large local reactions

Introduction

Subcutaneous immunotherapy is divided into a build-up and a maintenance phase. With conventional immunotherapy schedules, the build-up phase generally involves 1–2 injections per week with a single dose each visit. The duration of the conventional build up phase varies but typically ranges

from 3 to 8 months. Accelerated immunotherapy build-up schedules allow the patient to achieve the benefits of immunotherapy more rapidly, as the maintenance dose is reached sooner. Additionally, it has the advantage of a reduced number of office visits, saving the patient time and possibly reducing costs (i.e., less office visit co-pays), which overall would increase the convenience of this treatment. Rush and cluster immunotherapy schedules are the two most common accelerated schedules used in the United States. A cluster immunotherapy schedule involves the patient receiving several allergen doses (generally 2–4) sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is generally reached in 4–8 weeks. In rush immunotherapy protocols (RIT), higher doses are administered at 15- to 60-min intervals over a 1- to 3-day period until the maintenance dose is achieved.

This review will serve as an update for accelerated immunotherapy schedules. New investigations have shown safety using cluster schedules in atopic dermatitis [1•] and in pediatric populations [2, 3], as well as several studies showing safety using inhalant allergen mixtures [4•, 5]. There has also been further elucidation on the immunological changes occurring during accelerated immunotherapy [6•, 7, 8]. Additionally, there is a new study using an infusion pump for allergen delivery [9•] and investigations analyzing systemic reaction (SR) risk factors [10, 11•].

Cluster Schedules

Efficacy and Safety

Controlled studies have demonstrated symptomatic improvement and immunologic changes shortly after reaching maintenance doses using cluster schedules [12–15]. While most studies found similar SR rates between cluster and conventional schedules [12–17], others noted an increased

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frequency [4•, 18–20]. *Cat A* randomized double-blind, placebo-controlled study of cat allergic subjects demonstrated symptomatic improvement in as soon as 5 weeks using an 8-visit cluster schedule over a 4-week period [12]. Response to titrated nasal challenge, skin prick testing and allergen-specific IgG4 at 5 weeks was predictive of the 1-year response. Four percent (1/26) of subjects had a SR.

Dust Mite. A controlled study of 239 dust mite (DM)-allergic patients demonstrated improved clinical and objective parameters in the sixth week using the cluster schedule, 6 weeks earlier than the 12-week conventional schedule [13]. There were no differences in SR per injection between groups (0.15 % in cluster group vs. 0.31 % conventional). A prospective randomized study of 96 DM-allergic patients found the 6-week cluster schedule reduced the time to reach maintenance by 57 % and had similar SR rates (1.0 % of injections, 6.7 % of patients) as the conventional schedule [16].

Two recent pediatric DM cluster studies confirm these findings. The first reported on 77 children <5 years who received a depigmented *D. pteronyssinus* extract polymerized with glutaraldehyde using a 2-week cluster schedule and found a 0.16 % SR rate per injection [2]. The second report analyzed 34 children undergoing a 6-week cluster schedule and found no differences in SR rates and earlier changes in specific IgG4 levels compared to the 14-week conventional schedule [3].

Pollen

A randomized, double-blind, placebo-controlled trial of 18 grass-allergic subjects demonstrated that immunologic changes occur early and at low doses in the active treatment group, with an increase in interleukin-10 at 2–4 weeks which was associated with late-phase skin test response inhibition [14]. Additionally, a placebo-controlled study using a glutaraldehyde-modified grass mixture showed improvements in nasal provocations tests in a mean of 2.3 months [21]. An open randomized parallel-group multicenter safety trial using allergoid grass pollen found a 3-week accelerated schedule as safe as a 6-week conventional schedule with similar changes in grass-specific IgG4 [22]. Furthermore, 395 pollen-allergic subjects undergoing a 5-week cluster schedule reaching 100,000 SQ-U of Alutard SQ had a 2.0 % SR rate per injection. Eighty percent of reactions were immediate and all were Grade 1 (84 %) or 2 (EAACI classification system; see Table 1) [5]. Finally, a double-blind placebo-controlled trial of 60 patients using cluster IT for Russian thistle demonstrated significant differences in symptom and medication scores with no moderate or severe SR [23].

Mold. A retrospective evaluation of 94 children receiving *Alternaria alternata* immunotherapy by either a cluster (55 %) or conventional (45 %) schedule revealed similar SR rates between regimens (5.8 % of cluster patients vs. 4.8 % conventional) [17].

Mixtures. In a retrospective observational multicenter European study of 1,147 patients undergoing cluster immunotherapy to inhalant allergens, thirty-nine patients (3.4 %) experienced 42 SR (0.6 %/injection). The majority of SR's were Grade 0, 1, and 2 (Table 1). Higher starting doses were associated with higher SR risk. The authors concluded cluster SR rates were similar to conventional SR rates [15]. A more recent United States (US) study evaluating inhalant allergen mixtures used an 8-week cluster schedule to reach maintenance, and 10.9 % of patients had SRs, with most SR being Grade 1 or 2 (WAO classification system; see Table 2) (87.2 %), though 10.6 % were grade 3 with one grade 4 SR. Most (87.5 %) SR occurred at the 1:10 v/v and 1:1 v/v concentrations. SR risk factors included asthma, age 21–40 years old, female gender, and the presence of weeds, grasses, cat, or dog in the extract [4•].

A pilot prospective observational study of 611 patients was undertaken to identify SR risk factors to cluster IT using aluminum-adsorbed extracts [10], and 10.6 % of patients (1.78 % of injections) experienced SR. They identified seven independent risk factors: age >14, previously on IT (was protective), sensitization to *Chenopodium album*, high sensitivity (specific IgE >20 % total IgE) to grass or olive pollen, olive pollen mono-therapy, and treatment schedule (2 vs. 4 visits: 22.2 vs. 5.9 % SR rate, OR 7.1) [10].

Several studies have noted higher SR utilizing cluster schedules [4•, 18–20]. Two groups noted higher SR rates in cluster regimens in birch- and grass-allergic patients. Nielsen et al. noted that 33 % of patients (7/21) experienced SR in the antihistamine premedication group versus 79 % in the placebo premedication group [18]. Winther et al. observed an increased SR rate during birch and grass cluster IT with the highest rates in grass-allergic subjects [19]. Overall, SR occurred after 0.7 % of birch injections and 3.3 % of grass injections ($P<.0001$) with more episodes of urticaria and asthma in the grass-allergic subjects. Finally, Møllerup et al. noted a 4.4 % SR rate per injection (39.1 % of patients) among 657 subjects (10,369 injections) undergoing cluster to a variety of allergens [20].

Overall, cluster SR rates have ranged from 0.15 to 3.3 % of injections and 3 to 50 % of patients [24]. To provide perspective, a review of 38 studies using conventional build-up schedules found the SR rate between 0.05 and 3.2 % of injections and 0.8 and 46.7 % of patients (mean 12.9 %) [25]. In a review article on cluster immunotherapy analyzing 29 studies, the authors concluded that it was difficult to compare many aspects of the studies as 20 were not designed to specifically study

Table 1 2006 European Academy of Allergy And Clinical Immunology Grading of Severity for Systemic Side Effects

Classification of systemic reactions	
0 No symptoms	No symptoms or nonspecific symptoms.
I Mild systemic reactions.	Symptoms: Localized urticaria, rhinitis or mild asthma (PF<20 % decrease from baseline)
II Moderate systemic reactions:	Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF<40 % decrease from baseline).
III Severe (non-life-threatening) systemic reactions:	Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF>40 % decrease from baseline).
IV Anaphylactic shock	Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension, etc.

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cluster safety [26]. This review suggested the optimal tolerance of cluster schedules was associated with (1) use of premedication (antihistamine), (2) use of depot preparation, (3) no more than 4 injections/cluster, (4) use of 4–6 clusters, and (5) 1–2 clusters per week. The authors suggested the twice-a-week cluster might be associated with less adverse effects based on two separate grass pollen cluster studies with virtually identical protocols except for cluster frequency. The SR rate was 18 % of pre-medicated patients in the twice-a-week cluster [27] and 33 % with premedication/79 % without premedication in the once-a-week cluster [18].

Overall, cluster schedules demonstrate earlier onset of symptomatic improvement with similar or slightly increased risk of generally mild SR compared to conventional schedules, and may provide a balance between convenience and safety. Additionally, cluster dosing may provide cost savings: a recent European pharmacoeconomic study compared a 3-week cluster to a 13-week conventional build-up regimen and found the cluster up-dosing saved 244.95 euros per patient (\$318.88 in US dollars) [28]. The author has also noted low SR rates utilizing cluster to 0.4 mL 1:10 v/v. The first conventional injection given after the cluster at 0.05 mL 1:1 v/v has resulted in several SR, leading to pre-medication before that dose.

Rush Schedules

The most accelerated rush schedule for inhalant allergens entails the administration of 7 injections over 4 h. Ultra-rush stinging insect protocols achieve the maintenance dose in 3.5–4 h. The SR rates with RIT schedules ranges from 15 to 100 % of patients without premedication to 3–79 % of patients with premedication [24]. Most reactions are not severe, with flushing being the most common systemic symptom [29]. SR may occur up to 2 h after the final injection, necessitating a longer waiting period than for conventional schedules (1.5–3 h). While SR rates are high in inhalant allergy protocols and appear to be decreased with

premedication [30], flying Hymenoptera rush protocols have generally not been associated with a high SR incidence [31–34]. There have been conflicting data on the frequency of SR in imported fire ant (IFA) protocols [35, 36]. Selected RIT studies are detailed below by allergen type.

Dust Mite (DM)

A study of 125 DM allergic asthmatics aged 4–57 years (mean 25.3 years) utilizing a 3-day RIT protocol with a target dose of 4 ug Der p 1 (3,000 BU) in patients >10 years and 2 ug Der p 1 in those under 10 years resulted in an overall SR rate of 4.16 % per injection [37]. All SR occurred within 45 min after the last injection. Forty-three patients (34.4 %) had severe SRs requiring epinephrine or asthma treatment. The two predictors for SRs were skin prick test end point titration ($P<.15$) and pre-RIT FEV1 ($<.001$). If patients with an FEV1<80 % had been excluded, the SR rate would have decreased to 19.7 % of patients. Asthmatic reactions occurred in 73.3 % of patients with an FEV1<80 %, but only 12.6 % of patients with an FEV1>80 % ($P<.0001$).

A prospective study investigated the safety of aluminum hydroxide adsorbed DM RIT for atopic dermatitis (AD) and asthma: AD patients underwent either a 3-day rush or one of three 1-day ultrarush protocols (12 injections at 0.5-h intervals; 4 injections at 2-h intervals; 3 injections at 1-h intervals) to reach a goal dose of 5,000 therapeutic units/mL [1•]. They found similar SR rates between the rush (26.7 %) and ultrarush schedules (28.9 % overall) among AD patients though the 30-min interval ultra-rush group had the highest SR rate (36 %). Asthma patients underwent the 3-day rush protocol and had a 22 % SR rate. All SR in the study were EAACI grade 1 and 2 (Table 1) with nearly all SR involving urticaria; 95 % of SR occurred within 4 h of final dose [1•].

Pollen

Several pollen RIT studies have been published to include olive [38], plane tree [38], Parietaria [38], Bermuda grass [39], orchard grass [40, 41], mixed grasses [40, 41], timothy

Table 2 World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/ sign(s) of one organ system present^a Cutaneous	Symptom(s)/ sign(s) of more than one organ system present or Lower respiratory	Lower respiratory Asthma (e.g., 40 % PEF or FEV1 drop, NOT responding to an inhaled bronchodilator)	Lower or Upper respiratory Respiratory failure with or without loss of consciousness	Death
Generalized pruritus, urticaria, flushing or sensation of heat or warmth ^b	Asthma: cough, wheezing, shortness of breath (e.g., less than 40 % PEF or FEV1 drop, responding to an inhaled bronchodilator)	or	or	
or Angioedema (not laryngeal, tongue or uvular)	or Gastrointestinal	Upper respiratory Laryngeal, uvula or tongue edema with or without stridor	Cardiovascular Hypotension with or without loss of consciousness	
or Upper respiratory	Abdominal cramps, vomiting, or diarrhea			
Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion)	or			
or	Other			
Throat-clearing (itchy throat)	Uterine cramps			
or				
Cough perceived to come from the upper airway, not the lung, larynx, or trachea				
or Conjunctival				
Conjunctival erythema, pruritus, or tearing				
Other				
Nausea, metallic taste, or headache				
Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.				
Note: children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.				
Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to symptom(s)/sign(s) of the SR: a, ≤ 5 minutes; b, >5 minutes to ≤10 minutes; c, >10 to ≤20 minutes; d, >20 minutes; z, epinephrine not administered.				
The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection ^c and a suffix reflecting if and when epinephrine was or was not administered, e.g., Grade 2a; rhinitis:10 minutes.				
Final report: Grade a–d, or z _____ First symptom _____ Time of onset of first symptom _____				
Comments^d				

^a Each Grade is based on organ system involved and severity. Organ systems are defined as: cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a Grade 1. Symptom(s)/sign(s) from more than one organ system or asthma, gastrointestinal, or cardiovascular are classified as Grades 2 or 3. Respiratory failure or hypotension, with or without loss of consciousness, defines Grade 4 and death Grade 5. The Grade is determined by the physician's clinical judgment.

^b This constellation of symptoms may rapidly progress to a more severe reaction.

^c Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.

^d If signs or symptoms are not included in the Table or the differentiation between an SR and vasovagal (vasodepressor) reaction, which may occur with any medical intervention, is difficult, please include comment, as appropriate.

grass [42], and ragweed [43]. These studies have used standardized extracts [38–44], allergoids [40, 41, 46], and depot preparations [45, 47]. SR rates have ranged from 2.6 to 36.8 % (allergoid group) of patients.

In a study of 30 patients investigating a 1-week RIT protocol with standardized birth- or timothy-pollen extracts without premedication, 13 % (4/30) experienced SRs (3 urticaria, 1 asthma) [42]. Specific IgG and IgG4 increased continuously after the first week, and the RIT group had improved symptom and medication scores during the first pollen season. In a double-blind placebo-controlled study comparing the safety of standardized orchard grass extract with a grass pollen allergoid, 20 % of patients receiving the standardized extract experienced a SR versus 36.8 % of patients treated with allergoid. However, the SRs with the standardized extract were more severe [41].

Finally, a recent prospective double-blind placebo-controlled study of 195 grass pollen allergic patients undergoing RIT with a depigmented polymerized grass extract showed improved symptom and medication scores in the second season, no EAACI grade 3 or 4 SR, and dose-dependent T cell proliferation and cytokine production[48].

Mold

There has been one double-blind, placebo-controlled RIT study with an *Alternaria* extract standardized by skin tests, laboratory assays, and major allergen Alt a 1 [49]. Twenty-four patients aged 5–56 years were administered a 7-injection 2-day RIT protocol without premedication in the hospital. All patients reached the target maintenance dose of 1.6 ug Alt a 1 (2,000 BU). Fifteen percent (2/13) of actively treated patients had a SR on the first day (asthma symptoms). At 1 year, the actively treated group had improvement in global symptom scores ($P<.001$), titrated skin prick tests ($P<.005$), nasal challenge ($P<.005$, and specific IgG ($P<.05$).

Animal

Several dog and cat RIT protocols have been published [50–53]. In a double-blind, placebo-controlled study, 39 cat-and/or dog-allergic children and adults were treated with a 1- to 2-week RIT protocol and followed for 24 months [53]. The target maintenance dose was 80,000 SQ(43 pg Fel d 1). After reaching maintenance they were switched to a depot extract (Alutard SQ). All children developed mild SR during RIT at doses ranging from 1,000 to 10,000 SQ. The overall RIT SR rate was 7.7 % per injection (44/557). The adult SR was 4 % per injection during build-up and maintenance combined (18/443). The treatment group had significant changes (vs. placebo) after 12 and 24 months in skin prick end point titration ($P<.001$), cat allergen bronchoprovocation

($P<.001$), histamine provocation ($P<.01$), and specific IgE and IgG4 ($P<.001$).

Inhalant Allergen Mixtures

A series of RIT studies reported the experience at a university hospital-based pediatric clinic with a 1- and 2-day RIT protocol using inhalant allergen mixtures [30, 54, 55]. In the initial study, 11 patients age 5–18 years underwent a 9-injection 2-day RIT protocol without premedication [54]. The target dose was 0.1 mL of 1:100 wt/vol (maintenance concentrate) of a non-standardized mixture and 1,500–2,400 AU/mL for dust mites. Fifty-five percent (6/11) of patients had SRs. Three patients had grade 3 reactions (Portnoy system: generalized pruritus, sneezing and mouth itchiness), three patients had grade 4 reactions (Portnoy system: wheezing and shortness of breath), and 1 had anaphylaxis. The severity of SR correlated with number of positive skin tests ($r=.60$, $P<.01$) and cumulative skin test reaction size ($r=.75$, $P<.01$). Subsequent RIT studies by the same group demonstrated lower SR rates utilizing premedication and are detailed in that section [30, 55].

A recent European study using Depigoid de-pigmented polymerized extracts (tree, grass and DM) found similar SR rates among 303 patients using a 1-day up-dosing versus a 3-week up-dosing (SR: 5.8 vs. 2.0 % per patient, respectively: NS) with 92 % reaching maintenance [56].

A recent intriguing study utilized a portable battery-operated infusion pump to deliver allergen subcutaneously to 81 AR subjects[9•]. A 1-mL syringe and an infusion line were adapted to the pump. Infusions lasted 30–45 minutes and were given once weekly to reach a maintenance dose in 2 weeks (pollen) or 3 weeks (pet epithelia, Hymenoptera). LLR>10 cm were all delayed and occurred in 17.3 % of patients. SR occurred in 13.6 % of patients and 4.0 % of doses, with all but one SR being delayed; there were two EAACI grade 3 SR (Table 1). SR per dose were 4.3 % for pollens, 3.8 % for epithelia, and none for Hymenoptera [9•].

While there are no reliable SR predictors, a recent study found higher baseline tryptase levels in SR patients (4.7 ug/L; range 2.9–6.9) compared to non-SR patients (2.7 ug/L; range <1–5.2) undergoing RIT to an inhalant mixture [11•]. Additionally, the post-SR tryptase level taken within hours after the SR (exact time not specified) among reactors was higher than the pre-SR level of this group (14.3 ug/L; range 9.0–23.0).

Flying Hymenoptera

Many venom RIT studies have been published, and most have demonstrated efficacy and safety comparable or superior to conventional schedules. Venom extract package inserts provide a cluster schedule as an example of a

recommended schedule. In a 3-day RIT protocol of 9 high-risk patients who had prior SR during conventional build-up, 6 were able to reach maintenance in 3 days (despite mild cutaneous SRs), 2 reached maintenance in 5 days, and 1 patient had anaphylaxis and discontinued treatment [33]. In a study of 101 “high-risk” venom allergic patients treated with a 4-day RIT protocol, 99 % were able to reach the maintenance dose with a SR rate of 6.9 % [57]. Furthermore, 57 patients underwent an ultra-rush desensitization over 2.5 h reaching a cumulative dose of 101.1 ug of Hymenoptera venom [34]. Four patients (7 %) had mild SRs which were treated with antihistamines and corticosteroids. Venom-specific IgG4 increased significantly after 15 days ($P<.01$) and remained higher at 1 year ($P<.001$). Finally, a recent study using an ultra-rush protocol found fewer SR in the 3-h ultrarush protocol compared to a 5-day RIT protocol and 15-week conventional schedule [58].

IFA

An initial prospective controlled 2-day RIT protocol suggested no significant difference between the pre-medicated (antihistamine and steroids) and placebo-treated patients (3.6 vs. 6.7 %) [35]. However, a prospective 1-day RIT protocol (37 patients) at the same center found a higher SR rate (24 %) without premedication; SR generally involved urticaria and/or pruritus [36].

Immunological Changes

Several new investigations have shown immunological changes occur early during accelerated immunotherapy schedules. A recent study utilized whole genome expression profiling to identify changes in mRNA expression of peripheral blood mononuclear cells (PBMC) from allergic patients undergoing RIT [6•]. They identified 44 transcripts (28 up-regulated, 16 down-regulated) which had a 2-fold change in expression change from pre-RIT to 7 weeks and 4 months post-RIT. These included up-regulation in genes for IL-1 β , IL-8, CD40L, BTK, and BCL6. There was also a downward trend in Fc ϵ R1 expression at the 4-month timepoint, and increased allergen-specific IgG4 levels [6•]. Two prospective randomized studies of cluster DM IT found increased levels of IL-10-secreting Tr1 cells, IgG4, and allergen-induced IL-10 synthesis from PBMC cultures versus controls at the end of the first year [7, 8]. However, the levels of CD4+CD25+Foxp3+T cells, allergen-specific Th1 and Th2 cells, production of IL-4 and IFN- γ , and function of CD4+CD25(high)T cells were not altered, suggesting the up-regulation of Tr1 cells may be a useful marker for IT success [8].

Four recent accelerated VIT studies demonstrated various immunological changes: decreases in cytotoxic-T-lymphocyte-associated-antigen-4 (CTLA-4) and increases in IL-10 in as early as 24 h [59], reduction in basophil threshold sensitivity to anti-Fc ϵ R1 stimulation and decreases in Fc ϵ R1 gene and cell surface expression as early as day 5 [60], decreases in intercellular-adhesion-molecule-1 (ICAM-1) levels immediately after an ultra-rush protocol [61], and decreases in 9 α ,11 β -PGF2 plasma levels by day 40 [62]. All studies illustrated that immunological changes occur early after RIT initiation.

Premedication

Oral Antihistamines for Venom Immunotherapy

Oral antihistamines have been effective in decreasing LLR and SR during rush VIT protocols (Table 3) [63–65]. While rush VIT SR are generally low, some rush VIT studies have shown that antihistamines decrease the SR frequency compared with placebo [64]. Antihistamines also decreased the LLR frequency during the first 4 weeks compared with placebo, although the addition of ranitidine to terfenadine did not provide additional benefit compared to terfenadine alone [64]. Two additional rush VIT studies demonstrated that antihistamine pretreatment decreased LLRs and cutaneous systemic symptoms of pruritus, urticaria and angioedema, but did not decrease the frequency of respiratory, cardiovascular or gastrointestinal reactions [63, 65].

Finally, a retrospective study reported that terfenadine premedication during rush VIT might improve efficacy as the terfenadine group had fewer SR to sting challenges and field stings [66]. However, this finding was not confirmed by prospective study [67].

Oral Antihistamines for Inhalant Immunotherapy

Most premedication studies for accelerated inhalant schedules utilized combination premedication; however, several cluster IT studies with antihistamines alone have been performed. A controlled study demonstrated that Loratadine premedication reduced the SR frequency during cluster IT with grass or birch pollen extract when taken 2 h before the first injection (33 % of patients in Loratadine group, 79 % placebo group) [18]. A cat cluster IT study using Loratadine pretreatment for all 28 subjects (no placebo premedication) demonstrated no SR [68]. A 4-week grass cluster IT study using Loratadine pretreatment for all subjects resulted in no immediate large local or SR, but 18 % of patients experienced a delayed SR [27].

Table 3 Selected studies investigating the effect of premedication on accelerated immunotherapy schedules

Study	Allergen	Protocol	Target dose	Premedication regimen	Results (SR are % of Patients)
Cluster studies					
Walker et al. [27]	Grass	7 visits, 4 weeks	20 ug Phl p 5	Loratadine 10 mg >15 min before cluster or placebo	All AR delayed; SR rate 18 Loratadine vs. 22 placebo
Ewbank et al. [68]	Cat	8 visits, 4 weeks	0.6, 3.0, and 15 ug Fel d 1	Loratadine 10 mg 2 h before, no placebo group	No SR
Nielsen et al. [18]	Timothy and birch	7 weekly visits	23 ug Bet v 1 25 ug Phl p 5	Loratadine 10 mg 2 h before or placebo	Fewer SR in Loratadine group (33) vs. placebo (79.2)
Nanda et al. [12]	Cat	8 visits, 4 weeks	0.6, 3.0, and 15 ug Fel d 1	Zafirlukast and loratadine, no placebo group	1/26 SR
Rush studies					
Heijaoi et al. [70]	Dust mite	1-day rush	3,000 BU (4 ug Der p 1) if >10 years; 1,500 BU if <10 years old	Methylprednisolone, ketotifen, theophylline vs. historical control from earlier trials	36 nonpremedicated group vs. 16 premedicated group vs. 7.3 if excluding FEV1 <70 and modifying for LLR
Portnoy et al. [30], Sharkey and Portnoy [55]	Multiple inhalant allergens	1-day and 2-day rush	0.1 mL maint concentrate (1:100–1:400 wt/vol)	Astemizole, ranitidine, prednisone	55–73 nonpremedicated group vs. 23–27 premedicated group
Casale et al. [43]	Ragweed	Rush	4 ug initially then 2 ug Amb a 1	Fexofenadine and omalizumab for 9 weeks before rush	Any SR: 56.4 placebo vs. 33.3 omalizumab. Anaphylaxis: 25.6 placebo vs. 5.6 omalizumab
Brockow et al. [64]	Venom	Rush	100 ug of venom	Terfenadine 120 mg±/– ranitidine 300 mg	SR causing immunotherapy discontinuation: 15 placebo vs. 2 premedication

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Leukotriene Antagonists

A pilot study demonstrated montelukast premedication taken 2 h pre-injection decreases the size and delays the onset of LLR during rush VIT [69]. No controlled studies have investigated the effect of leukotriene antagonists on SR incidence.

Combination Pretreatment

Two studies demonstrated that combination pretreatment with ketotifen, methylprednisolone, and theophylline during 3-day RIT with either pollen [38] or DM [70] decreased SR frequency.

A study of 1,152 DM-allergic subjects examined the effects of 4 different RIT regimens with the same maintenance dose and found significant SR reduction with preventive measures and pre-medication [70]. Preventive measures included modifying the schedule for LLR >10 cm and excluding patients with FEV1 <70 %. Premedication with methylprednisolone, ketotifen, and long-acting theophylline reduced the SR rate from 36–16.2 % of patients ($P<.015$), and premedication plus preventive measures reduced the rate further to 7.3 % ($P<.005$).

The same group found similar results in 454 pollen allergic subjects [38]. Premedication reduced the risk of

SR from 31.3 to 14.7 % ($P<.015$), and premedication plus preventive measures reduced the SR to 7.5 % ($P<.005$).

After an initial RIT study without premedication resulted in a 55 % SR rate [54], a university-based pediatric group investigated the effect of premedication on RIT with allergen mixtures in subsequent studies. The first of these two studies was a double-blind, placebo-controlled 9-injection 2-day RIT study of 22 children [30]. Premedication with astemizole, ranitidine, and prednisone or placebo was begun the day before RIT and continued through the rush. Premedication reduced the SR rate to 27 % compared to 73 % in the placebo group ($P=.047$). The number of local reactions was also decreased.

In a subsequent study, the schedule was modified into an 8-injection 1-day RIT (cumulative dose 0.2 mL maintenance concentrate) with similar premedication [55]. SR occurred in 23 % of patients: one patient had urticaria, three had wheezing or respiratory symptoms, and one had hypotension plus respiratory symptoms. All SRs occurred at doses of 0.3 mL 1:1,000 wt/vol or higher.

In one of few cluster protocols utilizing combination premedication, a cat cluster regimen using Loratadine 10 mg and Zafirlukast 20 mg taken 2 h before dosing resulted in SR rates in 3.8 % of patients [12].

Finally, a retrospective review of 65 patients undergoing RIT to inhalant allergen mixtures reported 38 % of

patients had SR [29]. They utilized a modification of the 1-day protocol noted above and gave 7 injections over 4 h, reaching a dose of 0.05 mL of the undiluted concentrate. All patients were pre-medicated with prednisone, cetirizine, ranitidine, and zafirlukast or montelukast. Most SRs (72 %) occurred after the final dose of the protocol. Nineteen (76 %) were mild, 5 (20 %) were moderate, and 1 (4 %) were severe. SR were associated with higher skin test sensitivity and the presence of weed or dog allergen.

Omalizumab in Combination with Immunotherapy

Omalizumab has also been shown to reduce SR to RIT. The use of omalizumab 9 weeks before and in conjunction with ragweed RIT improved symptom severity scores compared with immunotherapy alone and resulted in a 5-fold decrease in the risk of anaphylaxis [43]. Additionally, a prospective study examined the effect of 16 weeks of treatment with omalizumab or placebo on the incidence of SR during cluster immunotherapy in 248 asthmatic subjects [71•]. Eligible subjects were required to have perennial asthma not well controlled despite inhaled corticosteroids and to be sensitive to DM, cat and/or dog. After 13 weeks of pretreatment with omalizumab or placebo, subjects received a 4-week cluster regimen, which overlapped with continued omalizumab/placebo treatment for 3 weeks. Compared with placebo, omalizumab pretreatment reduced the rate of SR from 26.2 to 13.5 % of subjects. The cluster regimen was followed by 7 weeks of maintenance injections during which no omalizumab or placebo were given; there were no SR during this phase.

Conclusions

Accelerated IT schedules provide earlier clinical improvement and improved convenience, though they introduce increased SR risk. However, many cluster IT schedules have similar SR rates to conventional schedules, and pre-medication significantly decreases SR rates. Additionally, there may be cost savings by reduced patient visits and medication requirements. New concepts include using accelerated IT in children, utilizing an infusion pump to deliver allergen, and measuring tryptase levels pre-rush to help identify systemic reactors. As more accelerated IT studies are done and more Allergists gain clinical experience using accelerated schedules, more patients will have another up-dosing option for IT.

Compliance with Ethics Guidelines

Conflict of Interest Christopher W. Calabria declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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