



Accelerated Immunotherapy: Why Are We Going So Slow?

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Key points

- Cluster schedules are associated with a slightly increased risk of a SAR that can be reduced by taking an H1 antihistamine on the day of injections
- RIT is associated with a 27 to 38% risk of a SAR
- The risk of a SAR can be reduced with administration of corticosteroids, an H1 and H2 antihistamine and possibly a leukotriene blocker for 3 days prior to RIT
- Reactions during RIT tend to occur 1–2 h after the last injection so patients should be observed for that amount of time

Abstract

Purpose of review Accelerated schedules for administering subcutaneous aeroallergen immunotherapy have the potential to provide convenience, reduce the cost, and improve compliance over conventional (weekly) schedules. In this review, we describe studies of cluster and rush immunotherapy (RIT), the risk of systemic allergic reactions (SARs) for various schedules, and methods to reduce that risk.

Recent findings Cluster schedules are associated with a slightly increased risk of a SAR that can be reduced by taking an H1 antihistamine on the day of injections. The risk of a SAR can also be reduced with depo extracts, fewer injections per cluster, and administration of fewer than 3 clusters per week. RIT is associated with a 27 to 38% risk of a SAR that can be reduced with administration of corticosteroids, an H1 and H2 antihistamine and possibly a leukotriene blocker for 3 days prior to the procedure and by stopping at a lower dose. Reactions tend to occur 1–2 h after the last injection on the day of RIT, and there is an increased risk of a reaction if subsequent weekly doses are missed.

Summary Accelerated immunotherapy schedules can offer benefits over weekly schedules; however, the increased risk of a SAR needs to be considered when deciding to recommend such a schedule.

Introduction

Subcutaneous allergen immunotherapy for aeroallergens involves the subcutaneous administration of increasing amounts of an extract over time [1•]. While aeroallergen immunotherapy also can be given orally or sublingually, this review will focus on subcutaneous treatment. Initially the procedure induces a form of tolerance as the dose is increased. This phase of the process is generally referred to as the build-up phase. Traditionally, during the build-up phase, patients go to a healthcare facility weekly to receive an injection of increasing doses from 1 to 3 vials of extract. Depending on the initial dose and the anticipated maintenance dose, the build-up phase can take from 4 to 6 months to complete. The strategy during this phase is to increase the dose gradually so that a patient can develop tolerance without having a systemic allergic reaction (SAR) [2]. The process may need to be prolonged if the patient develops SARs since doses may need to be reduced temporarily and then increased again more gradually as tolerated. Once a patient reaches a maintenance dose, the frequency of injections is usually decreased to every 2 weeks and over time it can be reduced to as infrequently as every 4–6 weeks. Based on studies by Durham, the total duration of immunotherapy to aeroallergens generally is 3 to 5 years [3].

It is possible for patients to receive injections more frequently during the build-up phase [4••]. One strategy is to have the patient receive injections 2 or even 3 times

per week if their schedule permits it [5]. They can also receive 2 or 3 injections at 30-min intervals during each visit. This type of accelerated schedule is referred to as cluster immunotherapy. By receiving injections with this type of schedule, patients can reduce the time it takes to reach a maintenance dose to 4–8 weeks depending on how frequently they are seen and how many doses are given during each visit.

Though cluster schedules can reduce the time to reach a maintenance dose, even more rapid schedules have been studied. The most aggressive form of accelerated immunotherapy is referred to as rush immunotherapy (RIT). RIT schedules generally are designed to permit a patient to reach a maintenance dose in as little as 1 or 2 days [6]. While it is possible to administer a full maintenance dose using a RIT schedule, the high frequency of SARs associated with this usually prevents patients from doing so even with aggressive pretreatment with antihistamines and corticosteroids. In most cases, patients who receive RIT can tolerate a low-volume injection from their maintenance vial; however, the dose usually needs to be increased more slowly over the subsequent 4–8 weeks for the patient to reach a full maintenance dose [7]. Though a similar approach is used with immunotherapy using venoms to treat stinging insect allergy, this review will focus on treatment with aeroallergens.

Potential Benefits of Accelerated Immunotherapy

Weekly schedules are the most common build-up strategy for aeroallergens; however, accelerated immunotherapy may offer several advantages over conventional weekly schedules [8]. These include patient convenience, the possibility of a more rapid improvement in symptoms, reduced risk of dosing errors and possibly reduced costs. Improved convenience is manifested as a shorter time that a patient needs to receive weekly injections [9]. This is important since the inconvenience associated with frequent visits is one reason for nonadherence with immunotherapy [10]. Accelerated schedules involve fewer weekly visits possibly leading to improved adherence with treatment. Since each injection is associated with a cost for administration, fewer weekly injections may also reduce the overall cost of immunotherapy.

One of the reasons for a SAR during the build-up phase is errors in administration [11••]. An error is more likely to occur during this phase because each patient has vials with 3 to 5 different dilutions in each extract series. Dosing

errors are more frequent during the build-up phase when it is possible to accidentally administer an incorrect dilution even when the vials have colored tops, and they are clearly labeled. Once a patient has completed the build-up phase, they receive injections from the 1 or 2 maintenance vials, reducing the risk of an administration error.

Since the efficacy of immunotherapy is related to the allergen dose, clinical improvement may not be appreciated until the patient has completed the build-up phase [12]. Accelerated schedules offer the advantage of achieving clinical efficacy earlier than conventional schedules. A double-blind study comparing cluster and conventional immunotherapy schedules for dust mite allergen by Tabar and colleagues showed that patients who were treated with cluster immunotherapy had decreased asthma and rhinitis symptoms 6 weeks sooner than those who were treated with a conventional weekly schedule [5]. Though earlier symptom improvement with accelerated schedules needs to be confirmed with other studies, the possibility of this benefit may be enough to encourage improved adherence.

Accelerated Schedules for Aeroallergens

Accelerated immunotherapy can be given using either a cluster, RIT or possibly a hybrid schedule. Tables 1 and 2 provide examples of schedules for cluster and

Table 1. A typical administration schedule for cluster immunotherapy

Visit number	Volume (mL)	Dilution	Vial color
1	0.1	1:1000	Green
	0.4	1:1000	Green
	0.1	1:100	Blue
2	0.2	1:100	Blue
	0.4	1:100	Blue
	0.05	1:10	Yellow
3	0.1	1:10	Yellow
	0.15	1:10	Yellow
	0.25	1:10	Yellow
4	0.35	1:10	Yellow
	0.5	1:10	Yellow
5	0.05	1:1	Red
	0.1	1:1	Red
6	0.15	1:1	Red
	0.2	1:1	Red
7	0.3	1:1	Red
	0.4	1:1	Red
8	0.5	1:1	Red

Table 2. Schedules for rush immunotherapy using aeroallergens

Time (min)	Cumulative dose	Volume (mL)	Dilution (v/v)	Vial color
Aggressive RIT schedule from Sharkey & Portnoy in which the patient received 2 injections from the 1:1 (v/v) vial [6].				
0	0.0003	0.30	1:1000	Green
30	0.0013	0.10	1:100	Blue
60	0.0043	0.30	1:100	Blue
90	0.0093	0.05	1:10	Yellow
180	0.0393	0.30	1:10	Yellow
240	0.0693	0.05	1:1	Red
300	0.1693	0.10	1:1	Red
Conservative RIT schedule from Smits et al. [25] that stopped at 0.1 mL of the 1:10 (v/v) vial.				
0	0.000025	0.025	1:10,000	Silver
15	0.000275	0.25	1:10,000	Silver
30	0.00053	0.025	1:1000	Green
45	0.00303	0.25	1:1000	Green
60	0.00553	0.025	1:100	Blue
75	0.03053	0.25	1:100	Blue
90	0.05553	0.025	1:10	Yellow
105	0.15553	0.1	1:10	Yellow
Day	Time	Dose (BU)	Cumulative dose (BU)	
1	9:00	30	30	
	9:30	150	180	
	10:00	300	480	
	11:00	600	1080	
	14:00	1200	2280	
2	9:00	1800	4080	
	11:00	2400	6480	
3	9:00	3000	9480	

A 3-day RIT schedule. BU = An arbitrary potency of 1000 BU was designated as the strength of *D. pteronyssinus* extract that elicited a median wheal size identical to wheal size provoked by the positive control solution when both solutions were tested in parallel in 30 highly allergic subjects. Maintenance dose (3000 BU) was given weekly for 6 weeks, then every 2 weeks for a year. Bousquet et al. [22].

RIT types of accelerated immunotherapy. While cluster schedules take longer to complete than RIT, they are associated with fewer SARs. The decision regarding which to recommend should occur following a detailed discussion of the pros and cons of each with the patient.

Cluster Immunotherapy

Cluster immunotherapy involves administration of 1 to 3 injections from each extract series on 2–3 nonconsecutive days per week. Depending on the visit frequency and the number of injections per visit the build-up phase can take

from 4 to 8 weeks to complete. A typical cluster schedule is shown in Table 1. This schedule can be modified to accommodate a patient's schedule if desired and is fairly flexible.

Table 3 provides an overview of studies that evaluated various aspects of cluster schedules. In general, SARs associated with cluster immunotherapy have been reported in 1.5% to as high as 79% of patients receiving this schedule, though typical SAR rates are between 1.5 and 3.5%. The rate of SARs per injection ranged from 0.2 to 4.4%. Two studies found the frequency of SARs with cluster schedules to be comparable with that seen with conventional schedules [5, 13]. To put this into context, the reported SAR rate per injection for weekly subcutaneous immunotherapy based on a surveillance study of 28.9 million injection visits was 0.1% or 9.4 per 10,000 injections [14]. In addition, SARs occurred in 1.9% of patients, with 0.08% and 0.02% experiencing grade 3 and 4 SARs [11••].

Premedication may play a role in reducing SARs with cluster schedules. Premedication typically consists of an H1 antihistamine (typically diphenhydramine, loratadine, or cetirizine) given on the day of and at least 60 min prior to the first injection during any visit. One study found that premedication with loratadine reduced the SAR rate from 79 to 33% though this SAR rate is substantially higher than rates reported in other studies [15]. Another study found that premedication with omalizumab during the build-up phase reduced the SAR rate from 26.2 to 13.5% [16]. A review of 29 studies using a cluster schedule showed that, in addition to premedication, factors associated with a lower risk of SARs include use of a depot preparation, 4 or fewer injections per cluster, use of a total of 4 to 6 clusters, and administration of 2 clusters per week [17–19].

Given these observations, cluster immunotherapy may be an effective way to improve adherence and outcomes when compared with conventional immunotherapy schedules. We suggest that when discussing immunotherapy with patients and their families, the option of this type of schedule should be included [20].

Rush Immunotherapy

Though cluster schedules can permit a patient to reach a maintenance dose in as little as 2–4 weeks, more aggressive schedules have been studied that can do this in as little as 1 or 2 days Table 4. These schedules are referred to as rush or ultra-rush (depending on how many superlatives the author wishes to use) immunotherapy. While there clearly is an increased risk of a SAR with such schedules, the idea is to use extensive premedication with H1 and H2 blockers, corticosteroids and occasionally with leukotriene blockers to reduce that risk. Such treatment is not practical to use for cluster schedules due to potential side effects of the premedications such as corticosteroids when given over 2–4 weeks; however, for 1 or 2 days, they can be taken with minimal risk.

The most common RIT schedules rely on 1- or 2-day schedules. Typical RIT schedules are shown in Table 2. Initially, Bousquet described treatment with allergoids (formalin-denatured extracts) using 3 to 6-day schedules [21] [22]; however, with experience, this was reduced to 2 days [23]. One difficulty with interpreting the results of these studies is that the risk of a SAR with allergoids is

Table 3. Studies that used cluster schedules

Study	Allergen (s)	Patients	Schedule (s)	Systemic reactions
Fernandez-Tavora 1995 [30]	Grass	20 grass allergic patients	3 weekly visits, 5 injections per visit	10/20 patients
Massanari 2010 [16]	Cat, dog, or dust mite	248 patients with persistent asthma randomized to premedication with: • Omalizumab (<i>n</i> = 126) • Placebo (<i>n</i> = 122)	4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance	• Omalizumab: 17/126 [13.5%] • Placebo: 32/122 [26.2%] • Omalizumab fewer grade 3 SARs (6 vs 24). • Grade 4 reported in 2 patients in each group
Mellenup 2000 [31]	Birch, grass, dust mite	257 allergic patients	6 weekly visits, 2–4 per visit (18 injections total)	454 SARs in 257 patients 4.4% of injections and 39.1% of patients
Nielsen 1996 [15]	Birch, grass	45 pollen-allergic patients premedicated with • Loratadine (<i>n</i> = 21) • Placebo (<i>n</i> = 24)	7 visits (14 injections totals)	• Loratadine: 7 (33%) • Placebo: 19 (79%)
Quiralte 2013 [32]	Multiple aeroallergens (primarily dust mite and grass)	658 patients: • 339 cluster-SCIT • 319 weekly-SCIT	4-week cluster titration schedule (cluster-SCIT) or by an 8-week short conventional titration schedule (SC-SCIT),	• Cluster: 0.2% of doses and 1.5% of patients • Weekly: 0.7% of doses and 4.4% of patients Most reactions were mild. No grade 3 or 4 SARs. No life-threatening systemic reactions, anaphylactic shock, or adverse events leading to therapy discontinuation
Tabar 2005 [5]	Dust mite	239 patients with rhinitis, allergic bronchial asthma, or both	6-week cluster or weekly for 12 weeks	SARs all mild (0.15% of injections) No differences between schedules
Tabar 1999 [33]	Dust mite	63 patients: • Cluster (<i>n</i> = 29) • Weekly (<i>n</i> = 15) • No immunotherapy (<i>n</i> = 19)	7-week cluster	1/29 patients in cluster group, 3.4% of patients
Van Metre 1982 [13]	Ragweed	33 rhinitis patients allergic to ragweed: • Weekly (<i>n</i> = 15) • Cluster (<i>n</i> = 18)	weekly injections of ragweed extract or clustered at 3-wk intervals	SARs same in both groups ragweed IgE increased more in the cluster than conventional group
Walker 2001 [34]	Grass	44 patients: • Cluster (<i>n</i> = 22) • Placebo (<i>n</i> = 22)	rapid up dosing cluster regimen for 4 weeks, followed by monthly injections for 2 years	No significant local or SARs
Winther 2000 [35]	Birch, grass	91 patients • Birch (<i>n</i> = 47) • Grass (<i>n</i> = 44)	7 visits, 3/2/2/2/2/2/1	• 5/47 patients, 07% of injections for birch • 21/44 patients, 3.3% injections for grass

Table 4. Studies that used RIT schedules

Study	Allergen(s)	Patients	Schedule(s)	Results
Bousquet 1987 [21]	Group 1: placebo Group 2: 6-mix grass allergoid Group 3: standard orchard grass extract	Group 1: placebo. (N = 11) Group 2: 6-mix grass. (N = 19) Group 3: orchard grass. (N = 15)	RIT: 3 to 6 days build-up, maintenance administered weekly for 4 weeks, then every 2 weeks Total doses of allergoid ranged from 2350 to 13,500 PNU	Significant decrease in symptom days and medication scores vs placebo SARs: Allergoid: 36.8% Standard extract: 20%
Cardona 2012 [36]	Polymerized mite extract	575 patients	0.2 and 0.3 ml at first injection, and in single 0.5 ml doses in subsequent monthly injections	27 patients (4.6%) had 139 rxns (1.9% rxn/inject) 22 patients (3.8%) had 134 local rxns (1.8% LRs/inject) 8 patients (1.3%) had 8 SARs (0.1%) SARs/inject 5 SARs were grade 2 and 3 grade 1. 2 SARs during buildup.
Casale 2006 [37]	Ragweed	123 patients with rhinitis	1-day rush (maximal dose 1.2–4.0 mug Amb a 1) or placebo immunotherapy Groups (premedication) ● 9 weeks omalizumab (0.016 mg/kg/IgE [IU/mL]/mo) ● Placebo before and 12 weeks of omalizumab	5-fold decrease in risk of anaphylaxis caused by RIT (odds ratio, 0.17; $P = .026$).
Fajt 2017 [29**]	Mixture of aqueous extracts	362 adult patients with rhinitis	● Placebo after immunotherapy 1-day RIT- 8 injections at 1-h intervals 2 doses of 1:10,000(v/v), 2 doses of 1:1000(v/v), 4 doses of 1:100(v/v) 16 subsequent doses 1–2 times per week. Premedication (all patients): Prednisone, H1 and H2 antihistamine, leukotriene modifier	Predictors of SARs. Lower BMI; younger age; More allergens in the extract; allergy to cat, dust mite, and weed pollens ● 50 patients had 68 SARs (13.81%) ● 4.7% of SARs occurred on RIT day. ● Most SARs occurred > 30 min and were mild
Harvey 2004 [24]	Multiple aeroallergens	65 patients Premedication: Prednisone, 40 mg daily Cetirizine, 10 mg daily Ranitidine, 150 mg twice daily Zafirlukast, 20 mg twice daily, or Montelukast, 10 mg daily	1-day RIT protocol- 7 injections, 30 min apart (4 h) Der p1, Der f1 800 AU/dose Fel d 1837 BAU/dose Orchard (Dac g5) Timothy (Phl p5) grasses 6168 and 5824 BAU/dose Ragweed mix 3.7 antigen E units/dose	SARs in 25 patients (38%)

Table 4. (Continued)

Study	Allergen(s)	Patients	Schedule(s)	Results
Hejjaoui 1990 [23]	Dust mite	1152 mite-allergic patients age 3–63 Group 1: 290 patients Group 2: 160 patients Group 3: 479 patients Group 4: 223 patients	Group 1: RIT without pretreatment, Group 2: RIT with pretreatment, Group 3: RIT protocol with pretreatment and preventative measures, Group 4: Step protocol with pretreatment and preventative measures Premedication: methylprednisolone (0.5 mg/kg/day) ketotifen (2 mg/day) theophylline (10 mg/kg/day) Group 1: IT + omalizumab ($n = 8$) Group 2: IT alone ($n = 11$) Group 3: omalizumab alone ($n = 9$) Group 4: placebo ($n = 9$)	SARs per patient were 36.2% with RIT alone, 16.2% when the pretreatment was added, and 7.2% when pretreatment and preventive measures were used. Patients receiving the step protocol had 5.4% SARs. Children < 5 years of age had a significantly greater number of SAR
Klunker 2007 [38]	Ragweed	36 patients		Combined treatment resulted in the induction of long-lasting inhibitory antibody function for up to 42 weeks compared with either treatment alone
Morais-Almeida 2016 [39*]	Mite and/or pollen allergoids	100 children with rhinitis or asthma No premedication	1-day rush, maintenance dose 0.5 mL	21 LRs in 11 patients. 2 SARs.
Pfaar 2013 [40]	grass pollen	146 adult patients with rhinitis with or without mild asthma	Groups: • Accelerated (0.1–0.3–0.5 mL in weekly intervals), $n = 69$ • Weekly (0.05–0.1–0.2–0.3–0.4–0.5 mL in weekly intervals), $n = 75$	Increases in specific IgG and IgG4 after 4 months of treatment in both groups. Both groups (92.75 accelerated, 92.0% weekly) reached maintenance dose without SARs
Portnoy 1994 [41*]	Multiple aeroallergens	11 allergic children ages 6 to 18 years	8 injections over 1.5 days	9 of 11 (82%) patients experienced SARs
Sastre 2011 [27*]	Pollens, cat, dog, horse, and/or venom	81 patients with allergic rhinitis and/or asthma	SubQ infusion via an infusion pump. 2–3 doses lasting 30–45 min each for 3–4 sessions.	LRs occurred in 14% to 66% of patients and 4.7% to 9.2% of doses. SARs observed in 14–15% of patients and 3.8–5.7% of doses
Sharkey 1996 [6]	Multiple aeroallergens	22 allergic patients	8 injections over 6 h followed by 2 h of observation Premedication: astemizole, ranitidine, and prednisone for 3 days including the day of rush immunotherapy	Predictors of SARs: Skin sensitivity to the extract before and after premedication. Systemic reactions were observed in 3 (27%) active and 8 (73%) placebo
Smits 2007 [25]	Multiple aeroallergens	893 patients (1.5–77 years) Premedication: prednisone and H1-antihistamine for 3 days ($n = 568$). Or	2 separate half-day schedules with minor differences	18 (2.0%) experienced a mild systemic reaction. 1 (0.1%) experienced true anaphylaxis.

Table 4. (Continued)

Study	Allergen(s)	Patients	Schedule(s)	Results
Stevens 1985 [42]	Grass pollen	prednisone and H1- and H2-blockade for 3 days (<i>n</i> =325) 43 total patients semi-rush <i>n</i> = 20; weekly- <i>n</i> = 23	–	SARs not different between the two groups
Temino 2013 [26]	Multiple aeroallergens	138 patients Premedicated on the same day of RIT with prednisone and histamine 1 and 2 receptor blockers	1-day rush: eight injections over 5 h, and stopped at one 10-fold dilution below the maintenance vial	Predictors of SARs: - Well-controlled asthmatic patients had same risk as non-asthmatic patients. - Ending RIT at 10-fold dilution below the maintenance vial did not decrease the SAR rate. - The post-RIT SAR rate was similar to that seen with weekly schedule. SARs: 38 patients (28%). 1.3% SARs per injection. 82% of SARs occurred after the last dose of the protocol. No severe anaphylaxis requiring ED/hospital.
Uriarte Obando 2015 [28]	Multiple aeroallergens	112 patients: 94.6% had allergic rhinitis 74% had asthma 5% Hymenoptera allergy	Use of an infusion pump during the up-dosing phase of SCTT according to a rush schedule	SARs 26 injections (4.8%) in 13 patients (11.6%).
Xie 2015 [9]	HDM	33 patients with mite allergic rhinitis	Incremental dose phase in a week instead of 15 weeks	Symptom scores and medication usage was significantly reduced Cutaneous reactions to mite allergen were significantly decreased SARs in 4 patients

likely to differ from that of aqueous extracts that are used in the USA. In addition, the biologic potency of the extracts was defined in arbitrary units (BUs) that cannot be easily converted into potency units that are used today for many standardized extracts. Since the likelihood of a SAR is dose-dependent, this limits the ability to compare early results with more recent observations.

Given the success of 3- and then 2-day RIT schedules using allergoids, the next step was to test the feasibility of a 1 1/2-day schedule using aqueous extracts. [7] In one study, 11 patients were treated with aqueous extracts containing a mixture of antigens to which they were prick-sensitive. These patients were not systematically premedicated; however, 4 required oral steroids for 7 days prior to RIT to get their asthma stable enough to qualify for the procedure. A series of 8 subcutaneous injections were given starting with 0.3 mL of 1:1000 (*v/v*) and ending with 0.10 mL of 1:1 (*v/v*) 1.5 days later. Increasing doses starting with 0.15 mL of 1:1 (*v/v*) and ending with 0.5 mL were given weekly for 8 weeks after that. All patients but one completed the RIT. Four had sore arms, four had pruritus and/or sneezing, four developed wheezing, and one experienced anaphylaxis with hypotension. Systemic reactions on the day of RIT tended to occur at higher doses and usually started more than 30 min after a previous injection. Subsequent weekly injections were tolerated without reactions by seven of the patients. Since 9 of 11 (82%) patients experienced SARs, the risk of this schedule was considered to be too high for the procedure to be feasible in practice.

That was followed by a study by Sharkey in which 22 patients were randomized to receive either premedication with astemizole, ranitidine, and prednisone for 3 days including the day of RIT or with placebo. The patients were next given RIT with 8 injections over 6 h followed by 2 h of observation according to the schedule in Table 2. This was followed by 8 weekly injections. During the RIT day, SARs were observed in 3 (27%) patients in the active group and 8 (73%) patients in the placebo group which was a statistically significant difference. The best predictor of a SAR was skin sensitivity to the extract both before and after premedication. In other words, patients who still reacted strongly to their extract by prick skin test despite taking the premedication were at increased risk of a SAR during the procedure. Such patients presumably failed to respond to the premedication and remained at increased risk leading the authors to suggest that this could be a marker for increased risk of a SAR during RIT.

A subsequent study by Harvey [24] used a 1-day RIT protocol consisting of 7 injections, 30 min apart (a total of 4 h) following premedication with prednisone, 40 mg daily, cetirizine, 10 mg daily, ranitidine, 150 mg twice daily, and either zafirlukast 20 mg twice daily or montelukast 10 mg daily. SARs were observed in 25 of 65 patients (38%) which are similar to the rate observed by Sharkey. Since then, Smits published a study of 893 patients that underwent rapid desensitization using a 2.5-h RIT protocol consisting of 8 injections, 15 min apart, followed by 30 min of observation after the last injection [25]. As seen in Table 2, this protocol had a much lower targeted end-point dosage. Premedication consisted of either prednisone or an H1 antihistamine was given to 568 patients for 3 days, and the same treatment along with an H2 antihistamine was given to an additional 325 patients. Eighteen patients (2%) were reported to have a mild SAR, and only one patient (0.1%) had a severe SAR. The lower target dosage was likely to be a key factor in the considerably lower rate of SARs seen in this study.

Temino and colleagues published a study of 138 patients who underwent RIT using a protocol consisting of 8 injections over 5 h with an end dose that was 10-fold lower than the final targeted maintenance dose. [26] Premedication in this study included same-day administration of prednisone and H1 and H2 antihistamines. Thirty-eight patients (28%) had SARs with most reactions (82%) occurring after the last dose.

Perhaps one of the most interesting methods for administering RIT with an infusion pump in 81 patients with allergic rhinitis and/or asthma sensitized to pollens, cat, dog, horse, and/or venom. [27•] A 1-mL syringe with an infusion line was adapted to deliver extract subcutaneously over 30–45 min. Patients received 2–3 doses every 2 weeks for 3–4 doses to reach a maintenance dose. Local reactions (LRs) occurred in 14 to 66% of patients and 4.7 to 9.2% of doses. SARs were observed in 14–15% of patients and 3.8–5.7% of doses. In a subsequent report describing maintenance doses given by infusion pump, LR were found in 7.5% of doses and 17.8% of patients. SARs were observed in 4.8% of doses and 11.6% of patients [28].

Managing the Risks Associated with RIT

While one of the goals of RIT is to achieve maintenance dosing in a matter of days as opposed to months, the primary objective is to achieve this safely. In certain situations, it may be prudent to modify the end-point dosage of the RIT protocol, given that most SARs occur with the last few doses of more standard RIT protocols. Though this may delay the time to maintenance dosing, the notable reduction in SARs with this method may offer a way for allergists to feel more comfortable offering patients accelerated immunotherapy schedules in the office. As with conventional schedules, careful selection of patients and recognition of known risk factors remains an integral part of the decision-making when considering accelerated immunotherapy schedules.

Since the rate of SARs is substantially higher with RIT, and less so with cluster schedules, the judicious use of premedication is important. The consensus appears to be that for cluster schedules, an H1 antihistamine (e.g., cetirizine) should be given the day of the injection and at least 60 min before the first injection is given. For RIT the evidence supports administration of an oral corticosteroid for 3 days prior to, and on the day of the procedure and on the next day if a 2-day schedule is used. At the same time, patients should be treated with an H1 and H2 antihistamine, though the evidence for inclusion of the H2 antihistamine is weak at best. There is no evidence supporting the use of a leukotriene blocker prior to RIT; however, this treatment has been used without obvious harm in at least 1 study so a decision to recommend it should be based on clinical judgment and patient preference.

SARs associated with RIT usually occur 60 or more minutes after the last injection is given which is longer than the 30 min which is typical of conventional schedules [29••]. For that reason, we recommend that patients should be kept for at least 2 and possibly for 3 h after the last dose is given. While there is no evidence indicating an increased risk of anaphylaxis 3 h after the last injection, it is reasonable to consider providing patients with an epinephrine autoinjector to use if a SAR occurs after they leave.

Most studies describe giving increasing doses at weekly intervals for at least 8 weeks following RIT. In an observational study of 885 patients who received 1-day RIT, Cook found that there was a higher risk of a SAR with the first 1 or 2 weekly injections. That risk was reduced by having patients take an H1 antihistamine prior to those injections. There was also a slightly increased risk of a SAR as the patient reached their maintenance dose. Anecdotally, we have noticed that there is an increased risk of a SAR if the patient misses a dose 1 or 2 weeks after the RIT procedure, so we believe that it is important that those doses be given as planned. It is not known whether there is an increased risk of a SAR if doses are missed later in the 8-week schedule. We routinely reduce the frequency of injections to every 2 weeks following 8 weeks and have not noticed an increased rate of SARs in those patients.

Conclusion

Accelerated immunotherapy schedules offer a way for patients to achieve relief of their allergy symptoms in a more convenient, cost-effective, and timely manner. As demonstrated by multiple studies, with the proper precautions taken, these schedules can be followed while offering similar SAR rates to those of conventional schedules. The decision about which type of schedule to pursue should be made carefully with input from the allergist, patient, and their family. In many instances, the possibility of an accelerated build-up phase may allow a patient to more seriously consider, benefit sooner from, and subsequently adhere to their immunotherapy injections.

Compliance with ethical standards

Conflict of Interest

Jessica Van Mason declares that she has no conflict of interest.

Jay M. Portnoy declares that he has no conflict of interest.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
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