

Systemic reactions from allergen immunotherapy

The purpose of this editorial is to examine the incidence of systemic reactions (SRs) to immunotherapy and to assess potential risk factors for SRs. Immunotherapy is used as part of the treatment for asthma and allergic diseases. Although many double-blind, placebo-controlled studies have established an effectiveness for treatment of allergic rhinitis, Hymenoptera hypersensitivity, and asthma,¹ a few studies of immunotherapy of asthma have not demonstrated efficacy.² Present-day concerns about the relative safety of this form of treatment still exist.

A fatal SR associated with immunotherapy was first reported by Lamson³ in 1924 after skin testing with milk, egg, oat protein, and rice in a 5-month-old child with chronic eczema. Eighteen years later, Vance and Strassman⁴ reviewed seven fatalities associated with the injection of a foreign protein. The risks associated with immunotherapy may not have been fully appreciated until 1985, when Lockey et al.⁵ made a preliminary report at the American Academy of Allergy and Immunology (AAAI) meeting of 15 fatalities associated with immunotherapy or skin testing occurring between 1973 to 1984 and reported by AAAI members in response to a questionnaire. In 1986 the British Committee on Safety of Medicines (the American Food and Drug Administration equivalent) reported 26 deaths associated with immunotherapy since 1957, five of which had occurred during the preceding 18 months. The committee recommended that immunotherapy be administered only in facilities having full cardiorespiratory resuscitation capabilities and that the patients receiving injections be observed ". . . for at least two hours after treatment."⁶

The following year Lockey et al.⁷ reported the completed analysis of the AAAI study, comprising 46 fatalities (the 15 above are included) from 1945 to 1984, 30 of which had sufficient data for analysis.

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Abbreviations used

AAAI: American Academy of Allergy and Immunology

SR: Systemic reaction

Six of these 30 deaths had been associated with skin tests and 24 with immunotherapy. Five of the six skin test fatalities had intracutaneous testing without preceding percutaneous testing. All six cases manifested symptoms within 20 minutes after their tests. Fifteen of 24 fatalities associated with immunotherapy had the onset of symptoms within 20 minutes after their injection(s). Three had onset of symptoms within 30 minutes and two after more than 30 minutes. The time of onset was unknown in four cases. Reid et al.⁸ cited nine immunotherapy-related fatalities in the United States during the period Jan. 1, 1985, through most of 1989. Eight additional cases, for a total of 17, have been reported for this same time span, of which all but two occurred within 20 minutes (Unpublished data). One unwitnessed fatality occurred more than 30 minutes after injections. Reid et al.⁹ reported 10 fatalities for 1990 through most of 1991.

The analysis of these data led to a position statement by the AAAI which recommended "The usual time interval of 20 minutes for allergen skin testing and immunotherapy is recommended to prevent serious and possibly fatal reactions. This may be extended for high-risk patients."¹⁰

Risk factors identified in these studies included errors in dosage, presence of symptomatic asthma, high degree of hypersensitivity (by skin tests or RAST), use of beta-blockers, injections from new vials, and injections made during seasons of exacerbation.¹¹

In the May 1992 issue of the JOURNAL (J ALLERGY CLIN IMMUNOL 1992;89:925-33), Hejjaoui et al.¹² report on the incidence of SRs during a prospective study of 454 subjects allergic to pollen receiving immunotherapy with standardized extracts administered by a rush protocol. The authors suggest that the use of potent standardized extracts may be associated with a higher risk for an SR than that associated with the use of a rush protocol alone. They also report a two-

TABLE I. Conventional schedules

Ref (yr)	No. of patients	Diseases	Ages (yr) (mean)	Schedule of immunotherapy	Maintenance dose	No. of SRs (% pts w/SR)
28 (1992)	N/A	N/A	N/A	Conventional	N/A	143 (N/A)
29 (1991)	21	RW hayfever	N/A	Conventional	1.92 µg AgE	6 (28.6)
26 (1991)	70	Asthma (mite)	N/A	Conventional (std extract)	5000 AU	17 (19)
26 (1991)	71	Asthma (mite)	N/A	Placebo	0.25 - 0.5 ml	3 (3)
26 (1991)	45	Asthma (SRW)	N/A	Conventional (std extract)	10,000 AU	14 (16)
26 (1991)	44	Asthma (SRW)	N/A	Placebo	0.25 - 0.5 ml	7 (9)
20 (1990)	3536	N/A	N/A	Conventional	N/A	139 (3.9)
24 (1990)	3178	N/A	Median age w/SR = 29.5 No SR = 32.9	Conventional	N/A	166 (4.5)*
22 (1990)	615	N/A	N/A	N/A	N/A	N/A (6.7)
30 (1990)	141	N/A	N/A	Conventional (53 on VIT)	N/A	38 (15.6)
31 (1988)	11	Asthma (cat sensitive)	21-52	Conventional	See below†	2 (18.2)
32 (1988)	712	N/A	N/A	Conventional	Not >0.5 ml (1:10 wt/vol)	81 total SRs 33 late SRs (4.1)
23 (1987)	2989	N/A	N/A	Conventional	Up to 0.3 ml (1:50 wt/vol) each allergen	27 (0.8)
21 (1986)	416	Allergic rhinitis (grass ± tree ± weed)	N/A	Conventional	0.2 ml of 1:100 wt/vol or max tolerated dose	82 (16.8)
33 (1986)	628	N/A	N/A	Conventional	Not > 0.5 ml (1:10 wt/vol)	52 (7)
13 (1982)	52	RW, hayfever	N/A	Conventional	1 - 18.7 wg of AgE	13 (46.7)

RW, Ragweed; *std*, standardized; N/A, not available; Ag, antigen; AgE, antigen E; AU, allergy units; VIT, venom immunotherapy; SRW, short ragweed; RIT, rush immunotherapy; AIOH, aluminum hydroxide; *ophth*, ophthalmic; HEP, histamine equivalent prick; PNU, protein nitrogen units; AD, atopic dermatitis.

*Liberal criteria were used to define SR.

†Nine patients received median cumulative dose of 46.2 FDA units of *Fel d 1* equivalents over 12 months. Two remaining subjects received much lower doses that were considered to be inadequate treatment.

‡Authors suggested that a protocol with more injections over a longer time period might have produced fewer SRs.

§Two SRs involved "shock"; onset within "several minutes."

||Nineteen of 20 children (95%) had SR(s) during RIT. 5 of 14 (35.7%) children treated for cat allergen had SR(s) on maintenance. Two of seven adults (28.6%) who completed 3 years of treatment had a single episode of asthma.

Rate of SRs/injection	Onset of SRs	Comment
0.51%	103 ≤30 min 11 30-60 min 3 1-2 hr 12 >2 hr 14 not noted	
N/A	N/A	
N/A	N/A	
N/A	N/A	Five "severe" SRs occurred including one "severe" SR in the placebo group; authors concluded that SRs are caused by multiple factors including potent extracts, aggressive dosing, heightened patient surveillance, and placebo effect
N/A	N/A	
N/A	N/A	
N/A	N/A	65% of SRs occurred in females, 83% of SRs in young adults
0.30%	43 ≤15 min 45 15-30 min 41 30-60 min 37 >60 min	68 patients also on β-blockers (57 oral; 11 ophth); only 1 SR occurred in this subset
N/A	N/A	Asthma not assoc w/increased SRs; male SRs = female SRs
0.2%	N/A	This study was a chart audit of 18,993 total injections
0.6%	N/A	Low rate of SRs attributed to slow build-up period and lower peak doses
0.16% (late SRs)	48 ≤30 min 22 30-60 min 7 1-2 hr 4 2-6 min	Emphasis on late SRs (occurring 30 min to hours after injection); no late SRs involving hypotension noted
0.05%	18 ≤15 min 6 15-30 min 3 >30 min	Large local reactions usually did not precede SRs
0.3%	≤45 min	SRs more common among females than males
0.25%	32 ≤30 min 20 35 min to 6 hr	Late SRs more common in females than males (25:8)
3.2%	N/A	Patients highly sensitive to RW‡
0.1%	44 ≤1 hr§	Prospective survey of 43 French MDs; patients were an un-

fold reduction in SRs occurring in subjects treated with methylprednisolone, ketotifen (not available in the United States), and long-acting theophylline before their injections.

The summary of SRs reported in 38 studies (Tables I, II, and III) pays particular attention to the dosing schedule used in each study, the allergens used, and

the percent of subjects having one or more SRs, the percent of injections resulting in SRs, and the time of onset of the SR.

Table I summarizes data from studies where conventional schedules of immunotherapy were evaluated. These reports did not distinguish between SRs occurring during the buildup or maintenance phases

TABLE I. Conventional schedules—Cont'd

Ref (yr)	No. of patients	Diseases	Ages (yr) (mean)	Schedule of immunotherapy	Maintenance dose	No. of SRs (% pts w/SR)
34 (1980)	19,739	N/A	N/A	Conventional	N/A	155 (N/A)
35 (1979)	N/A	Rhinitis ± asthma; 1 patient w/insect sens.	N/A	Conventional	N/A	94 (15)
36 (1957)	8706	Asthma &/or hayfever, rhinitis, AD, urticaria	N/A	Conventional	N/A	1774 (7.6)
36 (1990)	1410	Hymenoptera	N/A	Conventional VIT	100 µg each venom; 300 µg mixed venom	327 (12.1)
38 (1990)	26	Hymenoptera	N/A	Conventional VIT w/std Hymenoptera venom extracts	N/A	1 (3.8)
39 (1991)	21	Cat	9-47	Adults: conventional w/AIOH adsorbed Ag; Child: RIT w/water soluble Ag; depot Ag for maint	4.3 µg <i>Fel d 1</i>	10
39 (1991)	11	Dog	11-36	Adults: conventional w/AIOH adsorbed Ag; child: RIT w/water soluble Ag; depot Ag for maintenance	76 µg dog albumin	1 adult (20.0) See comment
40 (1985)	15	Seasonal rhinitis (100%), asthma (78.6%), conjunctivitis (10%)	11-53 (26.2)	Conventional w/alum precipitated extract	10,000 PNU	"Rare" (2 severe SRs reported)

of immunotherapy. The percent of subjects having one or more SRs ranged from 0.8% to 46.7% for conventional schedules (mean, 12.92%; SD, 10.8%; SE, 2.41%). Van Metre et al.¹³ reported SRs in 46.7% of subjects in a ragweed extract conventional immunotherapy study. It should be noted that the study population was highly sensitive to ragweed and had positive skin tests to ragweed pollen extract and ragweed antigen E at concentrations of 1:312,500 wt/vol and 0.01 µg/ml or less, respectively. Immunotherapy was initiated with 0.1 ml of 1:10,000 wt/vol dilution, and maintenance was achieved over 21 weeks. The authors stated that the unacceptable rate of reactions probably was related to the high degree of hypersensitivity in

the study population and proposed that giving many more injections over a longer time period before reaching maintenance might reduce the incidence of SRs.

The rate of SRs per injection during buildup and maintenance for studies in which conventional schedules were used ranged from 0.05% to 3.2% (mean, 0.5%; SD, 0.87%; SE, 0.25%), all studies but one reported rates of 0.6% or less. The exception was the report by Van Metre et al.¹³ These data include studies where standardized and nonstandardized extracts were used. No apparent differences were noted in the incidence of SRs.

Table II summarizes data from studies of seven treatment groups in which modified allergens were

Rate of SRs/injection	Onset of SRs	Comment
0.15%	65 1-12 hr 42 > 12 gr 4 — no info 42 ≤ 30 min 39 > 30 min	selected population 9 SRs w/pollen, 2 SRs w/dust, 1 SR w/Hymenoptera
0.14%	N/A	
N/A	N/A	Survey of 84 fellows and members of AAAI; 92% of patients achieved maint dose
N/A	N/A	Survey of physician fellows and members of AAAI; (25 respondents); all patients receiving VIT during pregnancy
N/A	N/A	1 adult had 4 SRs and withdrew from the study; 1 adult with 1 SR also withdrew from the study
N/A	N/A	19 of 20 children had 1-2 SRs on water soluble extracts during RIT; dog extract 50% as potent as cat as measured by HEP units, thus dog extract biologically less active
N/A	15 min to 6 hr	

used. Conventional schedules and modified-conventional schedules with increased intervals between maintenance injections (i.e., "allergoid boosters") are evaluated. No rush protocols are included.

The percent of subjects having one or more SRs in these studies of modified allergens ranged from 0% to 16.7% (mean, 8.44%; SD, 8.03%; SE, 3.59%). The rate of reaction per injection ranged from 0% to 5% (mean, 1.13%; SD, 1.82%; SE, 0.61%). The SRs occurred in groups using allergoids as well as in one group on placebo. No SRs were reported in either of the two studies using polymerized allergens.

The 23 groups in which rush or accelerated schedules were used are summarized in Table III. The per-

cent of subjects having one or more SRs during the maintenance phase of immunotherapy ranged from 0% to 21.1% (mean, 4.77%; SD, 6.47%; SE, 2.05%). However, the number of SRs was higher during buildup when the interval between injections was reduced ("rush" or "semirush" protocols). Subjects having one or more SRs ranged from 0% to 66.7%, with accelerated (i.e., "rush," "semirush," or "clustered") schedules (mean, 21.33%; SD, 17.86%; SE, 3.72%). These protocols were associated with rates of SRs per injection ranging from 0% to 6.4% (mean, 2.36%; SD, 1.7%; SE, 0.38%). Grammer et al.¹⁴ reported no SRs among 35 subjects with grass-sensitive hayfever when polymerized grass extracts, which were indi-

TABLE II. Modified allergens

Ref (yr)	No. of patients	Diseases	Ages (yr) (mean)	Schedule of immunotherapy	Maintenance dose	No. of SRs (% pts w/SR)
19 (1990)	20	Orchard-grass rhinitis (100%), asthma (55%), conjunctivitis (85%)	N/A (28.2)	High-dose protocol with HMW-GOID	10,000 PNU	3 (15.0)
19 (1990)	19	Orchard-grass rhinitis (100%), asthma (53%), conjunctivitis (80%)	N/A (24.7)	Low-dose protocol with HMW-GOID	2000 PNU	2 (10.5)
19 (1990)	18	Orchard-grass rhinitis (100%), asthma (50%), conjunctivitis (60%)	N/A (21.5)	Placebo	N/A	3 (16.7)
41 (1990)	22	N/A	N/A	Allergoid boosters; 6-wk intervals	N/A	N/A
41 (1990)	21	N/A	N/A	Allergoid boosters; 3-mo intervals	N/A	N/A
15 (1989)	23	Grass pollinosis (Bermuda, orchard, and timothy) and RW allergic rhinitis	24-61	Polymerized RW (11-wk regimen), IPG (9-wk regimen)	Total dose of PRW = 2,955 AU, total dose of IPG = 71,950 PNU	None (0)
16 (1986)	16	Tree + RW pollinosis &/or grass pollinosis	N/A	12-wk schedule polymerized allergens	Total doses: 48,850 PNU IPT, 48,850 PNU IPG	None (0)

HMW-GOID, High-molecular-weight allergoid; PRW, polymerized ragweed; IPG, individually polymerized grasses; IPT, individually polymerized trees

vidualized for each patient, were administered by means of an accelerated schedule. The two other studies cited in which polymerized extracts were used also reported no SRs among 39 subjects.^{15, 16} This suggests that this particular modification of extract material may be responsible for the lower incidence of SRs reported in these studies. Van Bever et al.¹⁷ reported no SRs in 19 asthmatic subjects sensitive to mites treated with a semirush protocol. The subjects achieved maintenance within a month as contrasted with most other rush programs where maintenance was achieved in 1 to 3 days.

A review of the time of onset of SRs indicates that most reactions begin within 15 to 20 minutes, regardless of the schedule used. Most SRs are mild and are successfully managed with conventional measures. No fatalities are recorded in these 38 reports. Bousquet et al.¹⁸ and Hejjaoui et al.¹² noted, in separate studies, that the time of onset of the SR could be inversely correlated with severity of the reaction.

Other factors may increase the likelihood of an SR. These include incorrect injection technique as cited by Bousquet et al.,¹⁹ a higher risk for females versus males (two studies reported this trend,^{20, 21} whereas one did not²²), and asthmatic subjects with a previous SR. However, one study of 615 subjects (303 with asthma) did not find an increased incidence of SRs among asthmatic subjects.²²

Hepner et al.²³ studied 2989 subjects and reported that most SRs occurred in the absence of previous large local reactions. A later study by Hepner et al.²⁴ did not find an increased incidence of systemic reactions in subjects on beta-blockers. Hejjaoui et al.,^{12, 25} in two separate reports, described five treatment groups, each of which received premedication with a combination of methylprednisolone, ketotifen, and long-acting theophylline as a part of their rush immunotherapy regimen. All five premedicated groups had a decreased incidence in SRs compared with rush immunotherapy without premedication.

Rate of SRs/injection	Onset of SRs	Comment
N/A	15 min to 6 hr	No "moderate" or "severe" SRs
N/A	15 min to 6 hr	Authors state 1 "moderate" SR possibly caused by inadvertent intra-vascular injection of extract
N/A	All ≤ 30 min	All SRs "minor"
0.2% (1982) 3% (1983) None (1984-85)	All ≤ 30 min	No treatment other than antihistamine required
None (1982) 5% (1983) 2% (1984) None (1985)	N/A	
0%	N/A	PRW and IPG given as separate injections
0%	N/A	

Two studies reported SRs in three different placebo groups,^{19, 26} including one "severe" reaction, thus underscoring the potential for adverse events even with placebo.

The following conclusions can be made:

1. The percent of subjects who have an SR from immunotherapy is small but appears to increase as
 - a. the immunotherapy schedule is accelerated;
 - b. high-dose regimens are used in highly sensitive subjects.
2. Maintenance immunotherapy appears to be associated with fewer SRs than the build-up period of rush and accelerated schedules of immunotherapy.
3. Premedication with a combination of methylprednisolone, ketotifen (not available in the United States), and long-acting theophylline appears to decrease the incidence of SRs associated with rush protocols. Such studies have not been done with conventional protocols. Premedication has not been an accepted practice because of concerns
 - a. about masking a mild reaction, which, with a future injection, could become a more serious reaction or delay the onset of a reaction beyond the waiting period. Additional data are needed.
4. The 20-minute waiting period, as recommended by the AAAI, is adequate for conventional immunotherapy. However, a longer waiting period is necessary for high-risk subjects. Such high-risk factors include the following:
 - a. rush immunotherapy;
 - b. unstable asthma (perhaps asthma itself);
 - c. seasonal exacerbation;
 - d. high degree of hypersensitivity;
 - e. beta-blockers (they should be discontinued, where possible).

Seven to 10 million immunotherapy injections are administered annually in the United States.²⁷ The risk of a fatal SR from such therapy is extremely small. However, any SR is unacceptable, and all physicians prescribing and/or administering such therapy must

TABLE III. Accelerated schedules

Ref (yr)	No. of patients	Diseases	Ages (yr) (mean)	Schedule of immunotherapy	Maintenance dose	No. of SRs (% pts w/SR)
13 (1982)	18	RW hayfever	N/A	Clustered	1-18.7 µg of AgE	19 (55.6)
42 (1991)	120	N/A	N/A	4-visit modified rush VIT protocol	1 ml of 100 µg/ml	16 (10)
17 (1990)	19	Asthma (mite)	8-15.7 (12.2)	Semirush (maintenance achieved at 1 mo)	1000 BU	None (0)
14 (1986)	35	Grass hayfever	21-65	Accelerated IT w/IPG extracts	3,300 to 9,900 PNU, total up to 72,000 PNU IPG	None (0)
12 (1992)	74	Rhinitis (100%), asthma (39.2%)	N/A (24.6)	RIT (3 days)	1608 BU (mean)	31.1% RIT 8.1% maint
12 (1992)	102	Rhinitis (100%), asthma (44.1%)	N/A (23.6)	RIT (3 days) w/premedication	1488 BU (mean)	14.7% RIT 5.9% maint
12 (1992)	200	Rhinitis (100%), asthma (34.8%)	N/A (29.6)	RIT (3 days) w/pre-medication + preventative measures	1130 BU (mean)	7.5% RIT 6.0% maint
43 (1992)	9	Asthma (88.9%)	N/A	RIT (1.5 days) Weekly maintenance injections	N/A	6 (66.7) RIT 0 maint
25 (1990)	290	Asthma (78%) and/or rhinitis (92%)	4-63 (24.1)	RIT (3 days)	2064 BU (mean)	105 (36.2)
25 (1990)	160	Asthma (85%) and/or rhinitis (90%)	4-63 (26.2)	RIT (3 days)	1954 BU (mean)	26 (16.2)
25 (1990)	479	Asthma (80%) and/or rhinitis (82%)	4-63 (29.1)	RIT (3 days) w/pre-medication & preventative measures	1254 BU (mean)	35 (7.3)
44 (1990)	13	Rhinitis (100%), asthma (38.5%), conjunctivitis (69.2%)	7-23 (12.15)	RIT (2 days) w/standardized <i>Alternaria</i> extract	2000 BU	2 (15.4)
45 (1990)	106	Hymenoptera	N/A	Rush VIT	100 µg cumulative dose given over 3 hr 30 min	8 (7.5) rush VIT 0 w/booster inj day 15
46 (1990)	59	Hymenoptera	N/A	4-day rush VIT	N/A	18 (30.5)
46 (1990)	27	Hymenoptera	N/A	6-hr rush VIT	N/A	6 (22.2)

BU, Biologic unit; IR, index of reactivity; *Dp*, *Dermatophagoides pteronyssinus*.

*Authors suggested that a protocol with more injections over a longer time period might have produced fewer SRs.

†Two subjects with no SRs had received premedication with H₁ & H₂ blockers plus glucocorticoid before RIT.

‡Dose reached after first 2 days of step protocol.

§Dose reached at the end of step protocol.

Rate of SRs/injection	Onset of SRs	Comment
6.4%	N/A	Patients highly sensitive to RW*
1.5%	N/A	No severe SRs; no “late” SRs reported
0%	N/A	
0%	N/A	
5.5%	Most ≤15 min None >45 min	Quicker onset of SRs associated with more severe reaction; all anaphylactic reactions began within 15 min
3.1%	Most ≤15 min None >45	
2.3%	Most ≤15 min None >45 min	
N/A	“Usually >60 min after previous injection	
3.8%	≤45 min	All SRs occurred during rush protocol; all subjects had his- tory of IT intolerance as a result of SRs†
2.0%	≤45 min	
0.8%	≤45 min	Premedication w/methylprednisolone, ketotifen, and long- acting theophylline reduced SRs by half and decreased their severity
2.6%	N/A	All SRs occurred on first day of RIT protocol; no SRs on maintenance
N/A	N/A	All SRs w/honeybee; none w/yellow jacket; no SRs either group after booster injections given 2 weeks after rush protocol
1.3%	N/A	
1.7%	N/A	

be aware of these risks and institute appropriate office
procedures to minimize them. Reassessment of the
“optimal dose” of standardized extracts may be nec-
essary to adjust for the increased potency of stan-

dardized extracts. This may improve the overall
safety of immunotherapy by limiting the incidence of
SRs while providing more predictable therapeutic
results.

TABLE III. Accelerated schedules—Cont'd

Ref (yr)	No. of patients	Diseases	Ages (yr) (mean)	Schedule of immunotherapy	Maintenance dose	No. of SRs (% pts w/SR)
46 (1990)	208	N/A	N/A	3.5-hr rush VIT	N/A	15 (7.2)
18 (1989)	125	Asthma (mite)	4-57 (25.3)	RIT (3 days) w/std extract	3000 BU age >10 yr 1500 BU age ≤10 yr	47 (37.6) RIT 5 (4.0) maint 5 patients had from 1-3 reactions
47 (1987)	19	Rhinitis (grass) ± asthma (74%) ± conjunctivitis (53%)	N/A (26.2)	3-day RIT w/6 mixed grass pollen allergoid	1000 PNU	7 (36.8) RIT 4 (21.1) on maint
47 (1987)	15	Rhinitis (grass) ± asthma (73%) ± conjunctivitis (73%)	N/A (20.7)	4-day RIT w/std orchard grass pollen extract	2 IR (0.2 ml 10 ⁻³ wt/vol)	3 (20%) during RIT, 0 on maint
48 (1985)	20	Asthma ± perennial rhinitis (mite)	18-41 (29.1)	RIT (3-4 day) w/std Dp extract	3000 BU	4 (20) RIT 0 maint
40 (1985)	23	Seasonal rhinitis (100%), asthma (82.6%), conjunctivitis (21.7%)	12-43 (23.2)	RIT (3-6 day) w/std extracts	1000 BU	N/A (40) RIT 0 maint
12 (1992)	78	Rhinitis (100%), asthma (34.6%)	N/A (23.8)	Step protocol w/pre-medication + preventative measures	660 BU‡ (mean) 1518 BU§ (mean)	N/A (2.6) step N/A (2.6) maint
25 (1990)	223	Asthma (76%) and/or rhinitis (95%)	4-63 (22.5)	Step protocol w/pre-medication + preventative measures	726 BU‡ 1662 BU§	12 (5.4)

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- Executive Committee, American Academy of Allergy and Immunology. The waiting period after allergen skin testing and

Rate of SRs/injection	Onset of SRs	Comment
1.0%	N/A	Authors concluded that rate of SRs during RIT decreases as treatment duration decreases
4.16% (RIT) 0.17% (maint)	Most ≤ 15 min None >45 min (RIT) ≤ 20 min (maint)	43 subjects (34.4%) had a "severe" SR requiring antiasthma treatment or epinephrine; the quicker the onset, the greater the severity of the reaction
3.7% (RIT)	N/A	
2.2% (RIT)	N/A	
2.5% (RIT)	N/A	Adrenalin required in 3 of 4 SRs
N/A	67% ≤ 15 min 18% 15-30 min 15% >30 min	All SRs "mild" and "easily controlled"
2.0%	Most ≤ 15 min None >45 min	
0.6%	≤ 45 min	Premedication w/ methylprednisolone and long-acting theophylline associated with decreased incidence and severity of SRs

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