

# Ultrarush versus semirush initiation of insect venom immunotherapy: A randomized controlled trial

Simon G. A. Brown, MBBS, PhD, FACEM,<sup>a,b,c</sup> Michael D. Wiese, BPharm, MCLinPharm, PhD,<sup>a,d</sup> Pauline van Eeden, PhD,<sup>c</sup> Shelley F. Stone, PhD,<sup>c</sup> Christine L. Chuter, MBBS, FRACGP,<sup>a</sup> Jareth Gunner, RN,<sup>a</sup> Troy Wanandy, BPharm, MSc,<sup>a,e,f</sup> Michael Phillips, MMedSci,<sup>g</sup> and Robert J. Heddle, MBBS, PhD, FRCPA, FRACP<sup>h,i</sup> Hobart, Perth, Adelaide, and Bedford Park, Australia

**Background:** Venom immunotherapy can be initiated by different schedules, but randomized comparisons have not been performed.

**Objective:** We aimed to compare the safety of 2 initiation schedules.

**Methods:** Patients of any age with prior immediate generalized reactions to jack jumper ant (*Myrmecia pilosula*) stings were randomized to venom immunotherapy initiation by a semirush schedule over 10 visits (9 weeks) or an ultrarush schedule over 3 visits (2 weeks). In a concurrent treatment efficacy study, the target maintenance dose was randomized to either 50 µg or 100 µg. The primary outcome was the occurrence of 1 or more objective systemic reactions during venom immunotherapy initiation. Analyses were by intention to treat. We also assessed outcomes in patients who declined randomization.

**Results:** Of 213 eligible patients, 93 were randomized to semirush (44 patients) or ultrarush (49 patients) initiation.

**Objective systemic reactions were more likely during ultrarush initiation (65% vs 29%;  $P < .001$ ), as were severe reactions (12% vs 0%;  $P = .029$ ). Times to maximal increases in venom-specific**

**IgG<sub>4</sub> were no different between treatments, whereas the maximal increase in venom-specific IgE occurred earlier with ultrarush treatment. Similar differences between methods were observed in patients who declined randomization. One hundred seventy-eight patients were randomized to maintenance doses of either 50 µg (90 patients) or 100 µg (88 patients). The target maintenance dose had no effect on the primary outcome, but multiple-failure-per-subject analysis found that the 50 µg dose reduced the likelihood of reactions.**

**Conclusion:** Ultrarush initiation increases the risk of systemic reactions. A lower maintenance dose reduces the risk of repeated reactions, but the effect on treatment efficacy is unknown. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

**Key words:** Insect sting allergy, anaphylaxis, immunotherapy, venom immunotherapy, randomized controlled trial

Insect stings account for up to one third of anaphylaxis episodes treated in suburban and rural emergency departments and a quarter of anaphylaxis deaths.<sup>1,2</sup> Insect venom anaphylaxis can be prevented by venom immunotherapy (VIT),<sup>3,4</sup> which also improves quality of life more than does the provision of an adrenaline autoinjector alone,<sup>5</sup> and when used in children also provides a significantly lower risk of sting reactions even up to 20 years after the treatment is stopped.<sup>6</sup>

VIT doses can be increased slowly, with weekly clinic visits over 15 weeks (traditional) or 8 weeks (modified or semirush), or rapidly, with dose increases over 1 to 3 days ("ultrarush" and "rush" protocols). Ultrarush treatment has been claimed to be as safe as slower techniques, with some authors even reporting greater safety and improved protection with faster initiation.<sup>7,8</sup> This has led to the widespread use of ultrarush protocols, despite a lack of direct comparison by randomized controlled trials.

We aimed to compare the safety of a commonly used ultrarush method with that of our established semirush initiation method for jack jumper ant (JJA, *Myrmecia pilosula*) VIT.<sup>4</sup> Our hypotheses were that (1) the risk of allergic reactions to treatment during initiation would not differ between these methods and (2) increases in serum concentrations of allergen-specific IgG<sub>4</sub> (sIgG<sub>4</sub>), a marker of allergen-specific regulatory T-cell response, would be earlier and more intense with ultrarush treatment.

## METHODS

### Participants

Between September 2006 and November 2008, we recruited volunteers of any age with a history of 1 or more immediate generalized allergic reactions to

From <sup>a</sup>the Jack Jumper Allergy Program and <sup>c</sup>the Department of Pharmacy, Royal Hobart Hospital, Hobart; <sup>b</sup>the Department of Emergency Medicine, Royal Perth Hospital, Perth; <sup>d</sup>the Centre for Clinical Research in Emergency Medicine and <sup>e</sup>the Clinical Trials WA, Western Australian Institute for Medical Research, University of Western Australia, Perth; <sup>f</sup>the Sansom Institute for Health Research, University of South Australia, Adelaide; <sup>g</sup>the Menzies Research Institute Tasmania, University of Tasmania, Hobart; <sup>h</sup>the Clinical Immunology Units, SA Pathology and Royal Adelaide Hospital, Adelaide; and <sup>i</sup>the School of Medicine, Flinders University, Bedford Park.

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Corresponding author: Simon G. A. Brown, MBBS, PhD, FACEM, Department of Emergency Medicine, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia. E-mail: [simon.brown@uwa.edu.au](mailto:simon.brown@uwa.edu.au).

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**Abbreviations used**

JJA: Jack jumper ant (*Myrmecia pilosula* species complex)  
 sIgE: Allergen-specific IgE  
 sIgG<sub>4</sub>: Allergen-specific IgG<sub>4</sub>  
 VIT: Venom immunotherapy

known or suspected JJA stings plus evidence of JJA venom-specific IgE (sIgE) by positive serology (Phadia CAP, Pharmacia Diagnostics, Uppsala, Sweden; positive cutoff 0.35 kU/L) or a positive intradermal skin test result, performed to a maximum concentration of 1.0  $\mu\text{g/mL}$ .<sup>4</sup> Exclusion criteria were negative serology for sIgE and a negative intradermal skin test result on 2 occasions 2 to 4 weeks apart; psychiatric illness rendering the patient unable to give informed consent; positive urine pregnancy test result in females of child-bearing age at the time of starting treatment; and poorly controlled cardiovascular or respiratory disease. Participants gave written informed consent and were enrolled by treating medical staff.

The Human Research Ethics Committee (Tasmanian) Network approved the study protocol, and it was registered with the Australian New Zealand Clinical Trials Registry (no. 12606000333516). Treatments were given at 2 hospital sites in Tasmania—the Royal Hobart Hospital and the North West Regional Hospital Burnie—and we collected data on all doses and reactions for a period of 12 months from starting treatment.

**Procedures**

Previous generalized sting reactions were graded mild, moderate, or severe according to our previously published system.<sup>1</sup> To screen for comorbidities, each participant had a clinical history, baseline spirometry, 12-lead electrocardiogram, full blood cell count, and biochemistry. If clinically indicated, we also conducted further investigations including formal lung function testing, exercise stress testing, and coronary angiography to assess and optimize chronic cardiovascular and respiratory disease prior to starting VIT. Baseline mast cell tryptase level was measured by Phadia CAP (normal <12  $\mu\text{g/L}$ ) to screen for mastocytosis.

We offered 1:1 open-label randomization to ultrarush or semirush initiation methods, with dosing schedule as per Table I. Patients who declined randomization of method were still monitored to determine whether the results would be generalizable to patients who chose their preferred initiation method. In a related study to determine the effect of the maintenance dose on protection from insect stings, we also offered 1:1 randomization to a target maintenance dose of either 50 or 100  $\mu\text{g}$ . Since reactions usually start to occur at lower doses, we did not expect this to influence the comparison of initiation methods. If there was an allergic reaction to treatment, subsequent doses were reduced to the last tolerated dose and gradually increased again as tolerated. Since these changes could become complex and varied considerably according to the target maintenance dose and because our venom extract had a short shelf life after reconstitution,<sup>9</sup> double blinding was considered impractical and unsafe and single blinding was used for all doses. To maintain allocation concealment, an investigator not involved in direct patient care (M. D. W.) generated and applied random number-based sequential treatment allocation after the receipt of a signed consent form.

Our venom production and formulation procedures have previously been described; these comply with the requirements of the European Pharmacopoeia.<sup>9,10</sup> The same standardized venom extract was used for laboratory investigations, skin testing, and immunotherapy.

Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers were withheld for 48 hours prior to each visit and recommenced no less than 2 hours after the last VIT injection of the day. A long-acting nonsedating H<sub>1</sub> antihistamine, loratadine (5 mg if <30 kg, 10 mg if  $\geq 30$  kg), was taken 1 hour before every visit. Children were offered a eutectic mixture of local anesthetic 5% cream (lignocaine + prilocaine), applied to the skin 1 hour before each dose.

Systemic reactions were defined by the presence of objective generalized features (erythema/urticarial, angioedema, wheeze, hypotension, and

**TABLE I.** Immunotherapy initiation schedules (visits each 1 week apart)

| Ultrarush initiation |                                                                                                                                                                                                                                                                                                                      |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Visit 1              | At 30-min intervals: 0.1 $\mu\text{g}$ , 1 $\mu\text{g}$ , 3 $\mu\text{g}$ , 10 $\mu\text{g}$ , 20 $\mu\text{g}$ , 30 $\mu\text{g}$ , then:<br>For those allocated the 50- $\mu\text{g}$ target: no more doses on day 1<br>For those allocated the 100- $\mu\text{g}$ target: delay 60 min and give 40 $\mu\text{g}$ |
| Visit 2              | At 30-min intervals:<br>For those allocated the 50- $\mu\text{g}$ target: 25 $\mu\text{g}$ + 25 $\mu\text{g}$<br>For those allocated the 100- $\mu\text{g}$ target: 50 $\mu\text{g}$ + 50 $\mu\text{g}$                                                                                                              |
| Visit 3              | Maintenance dose: 50 $\mu\text{g}$ or 100 $\mu\text{g}$                                                                                                                                                                                                                                                              |
| Semirush initiation  |                                                                                                                                                                                                                                                                                                                      |
| Visit 1              | At 20-min intervals: 0.0001 $\mu\text{g}$ , 0.001 $\mu\text{g}$ , 0.01 $\mu\text{g}$                                                                                                                                                                                                                                 |
| Visit 2              | At 20-min intervals: 0.01 $\mu\text{g}$ , 0.1 $\mu\text{g}$ , 0.3 $\mu\text{g}$                                                                                                                                                                                                                                      |
| Visit 3              | At 20-min intervals: 0.3 $\mu\text{g}$ , 1.0 $\mu\text{g}$ , 3 $\mu\text{g}$                                                                                                                                                                                                                                         |
| Visit 4              | At 30-min interval: 3 $\mu\text{g}$ , 10 $\mu\text{g}$                                                                                                                                                                                                                                                               |
| Visit 5              | At 30-min interval: 10 $\mu\text{g}$ , 20 $\mu\text{g}$                                                                                                                                                                                                                                                              |
| Visit 6              | At 30-min interval: 20 $\mu\text{g}$ , 30 $\mu\text{g}$                                                                                                                                                                                                                                                              |
| Visit 7              | For those allocated the 50- $\mu\text{g}$ target (30-min interval): 25 $\mu\text{g}$ , 25 $\mu\text{g}$<br>For those allocated the 100- $\mu\text{g}$ target (30-min interval): 30 $\mu\text{g}$ , 40 $\mu\text{g}$                                                                                                  |
| Visit 8              | For those allocated the 50- $\mu\text{g}$ target: 50 $\mu\text{g}$<br>For those allocated the 100- $\mu\text{g}$ target (30-min interval): 50 $\mu\text{g}$ , 50 $\mu\text{g}$                                                                                                                                       |
| Visit 9              | For those allocated the 50- $\mu\text{g}$ target: 50 $\mu\text{g}$<br>For those allocated the 100- $\mu\text{g}$ target (30-min interval): 70 $\mu\text{g}$ , 30 $\mu\text{g}$                                                                                                                                       |
| Visit 10             | Maintenance dose: 50 $\mu\text{g}$ or 100 $\mu\text{g}$                                                                                                                                                                                                                                                              |

hypoxemia). Severe reactions were defined by either hypotension or hypoxemia ( $\text{SpO}_2 \leq 92\%$ ). Hypotension was defined as systolic blood pressure of less than 90 mm Hg for age 11 years and older, less than 70 mm Hg + (2  $\times$  age) for age 1 to 10 years, or less than 30% drop from baseline. If there was a reaction to treatment, subsequent doses were reduced to the last tolerated dose and gradually increased again as tolerated. All VIT doses and allergic reactions were recorded contemporaneously in a treatment database (Microsoft Access 2003) from which treatment summaries were printed, checked for accuracy, and filed as the medical treatment record.

**Venom-specific antibody studies (sIgE and sIgG<sub>4</sub>)**

Sera were taken on the first day of treatment and then 1, 3, 7, 12, and 26 weeks after this, immediately before treatment sessions. Samples were stored at  $-80^\circ\text{C}$  until analysis by dissociation-enhanced lanthanide fluorescence immunoassay optimized for measuring sIgE and sIgG<sub>4</sub> to both whole venom and the major allergen Myr p 2.<sup>11</sup>

**Analysis**

We estimated that 540 participants randomized between 2 groups would, with an alpha of .05 and a 2-tailed *P*, give more than 80% power to detect a 12% absolute difference in systemic reaction rate from the 34% observed during our first trial of semirush initiation.<sup>4</sup> We planned to perform an interim analysis as soon as the first 100 participants randomized to the initiation method completed this treatment phase, with the intention of stopping randomization if a statistically significant difference in the primary outcome was evident.

Our primary outcome was the occurrence of 1 or more objective allergic reactions during treatment initiation. Secondary outcomes were the occurrence of 1 or more severe reactions and achievement of the target maintenance dose. Fisher's exact test was applied for dichotomous outcomes. CIs (95%) for proportions were calculated by using the binomial exact method. Exact

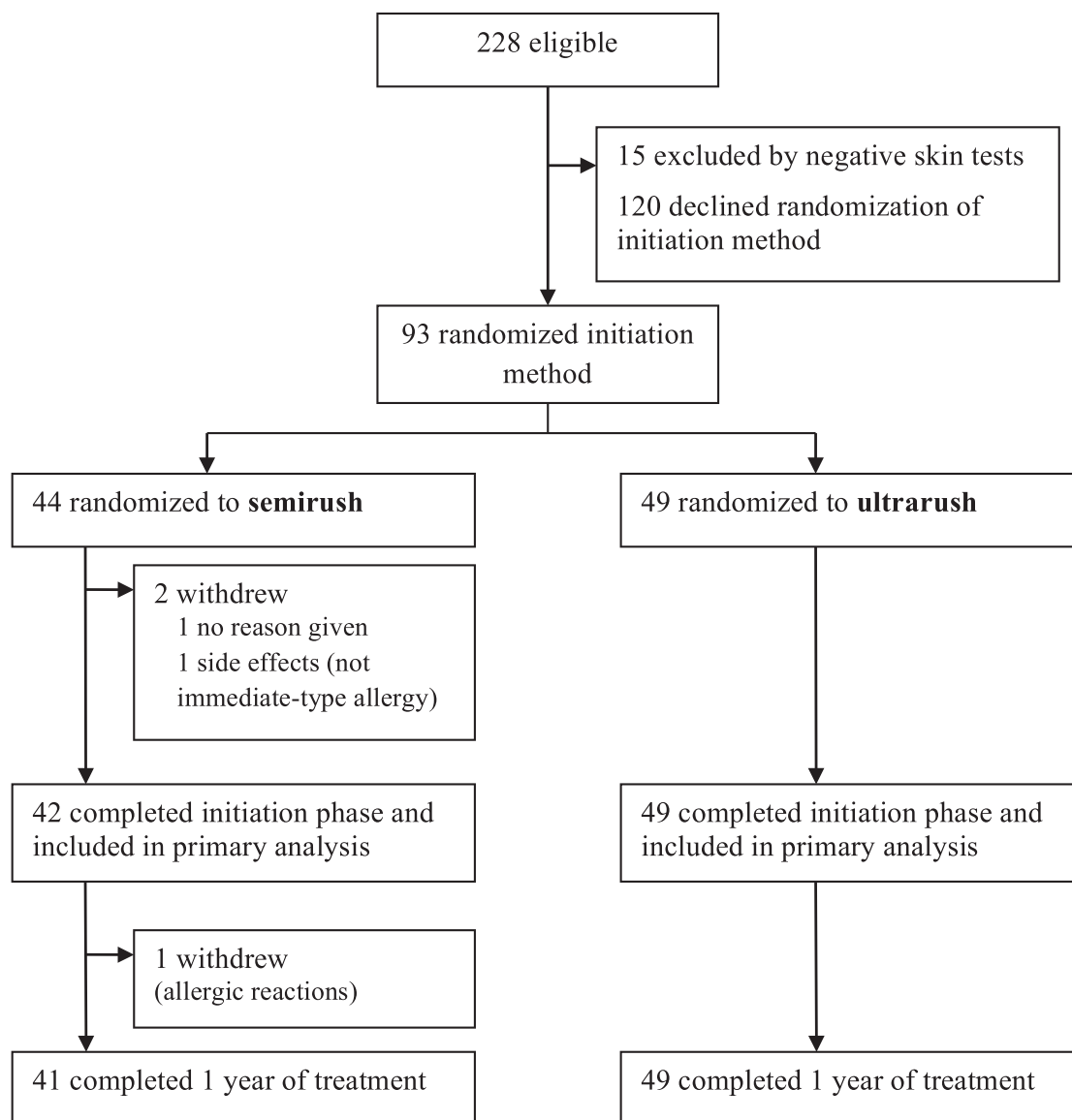


FIG 1. Trial profile.

logistic regression was used to identify any effect of the target maintenance dose on outcomes. Changes in sIgE and sIgG<sub>4</sub> from pretreatment values for each time point (“delta-sIgE” and “delta-sIgG<sub>4</sub>”) and times to maximum delta-values were compared by using the Wilcoxon rank-sum test. Statistical analyses were performed with Stata, version 12 (StataCorp, College Station, Tex). All analyses were by intention to treat.

Our predefined end points were problematic because some reactions occurred after the predefined initiation periods and dose escalation did not always proceed as planned. Therefore, to account for reactions after the predefined initiation periods, we performed a *post hoc* time-to-event analysis by using the logrank test with multiple failure-per-patient data, stratified by the target maintenance dose. This nonparametric approach was necessary because the effect of the initiation method on reaction hazard varied over time, violating the assumptions of the proportional hazards model.

## RESULTS

Between September 4, 2006, and November 11, 2008, 228 people were judged eligible for the trial on the basis of clinical

histories and physical health. We excluded 15 because of negative skin test results and negative serology for sIgE to JJA venom. Ninety-three agreed to randomization of the initiation method—44 to semirush and 49 to ultrarush (Fig 1). Table II shows baseline characteristics including allocated target maintenance doses. Of the 120 who declined randomization, 31 selected initiation with semirush and 89 selected ultrarush. One hundred seventy-eight patients (84%) were randomized to either 50 µg (90 patients) or 100 µg (88 patients) maintenance dose.

A safety review was held in December 2007 in response to a series of severe reactions in ultrarush patients necessitating hospital admission. This review noted that severe reactions were occurring only in the ultrarush group. However, many semirush patients had not started and/or completed initiation, preventing definitive analysis. The planned interim analysis was therefore brought forward to November 2008 to include complete data from the initiation phase from all individuals who had been randomized at the time of the safety review. This found that

TABLE II. Baseline characteristics

|                                         | Semirush<br>(n = 44) | Ultrarush<br>(n = 49) |
|-----------------------------------------|----------------------|-----------------------|
| Age (y)                                 | 48 (26-61)           | 49 (34-60)            |
| Male sex                                | 21 (48%)             | 24 (49%)              |
| Airways disease                         | 6 (14%)              | 7 (14%)               |
| Diabetes                                | 2 (4.6%)             | 2 (4.1%)              |
| Hypertension                            | 6 (14%)              | 10 (20%)              |
| Heart disease                           | 1 (2.3%)             | 1 (2.0%)              |
| Beta-blocker treatment                  | 1 (2.3%)             | 2 (4.1%)              |
| ACEI and/or ARB treatment               | 1 (2.3%)             | 5 (10%)               |
| Age at first sting reaction (y)         | 38 (13-53)           | 43 (18-52)            |
| No. of sting reactions                  | 2 (1-3)              | 2 (1-2)               |
| Years since last reaction               | 2 (0-7)              | 1 (0-4)               |
| Prior worst sting reaction              |                      |                       |
| Mild                                    | 1 (2.3%)             | 2 (4.1%)              |
| Moderate                                | 31 (71%)             | 30 (61%)              |
| Severe                                  | 12 (27%)             | 17 (35%)              |
| + Documented hypotension                | 4 (9.1%)             | 4 (8.2%)              |
| + Documented hypoxemia                  | 2 (4.6%)             | 3 (6.1%)              |
| Intradermal venom skin test sensitivity |                      |                       |
| 0.01 µg/mL                              | 24 (55%)             | 30 (61%)              |
| 0.1 µg/mL                               | 10 (23%)             | 8 (16%)               |
| 1.0 µg/mL                               | 10 (23%)             | 11 (22%)              |
| Serum sIgE positive                     | 28 (64%)             | 34 (69%)              |
| Randomization of target dose            | 43 (98%)             | 46 (94%)              |
| Target dose 100 µg                      | 18 (41%)             | 28 (57%)              |
| Mast cell tryptase                      | 4.2 (3.0-5.9)        | 3.5 (3.0-5.3)         |

Data are number (%) or median (interquartile range).

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

systemic reactions were more common with ultrarush treatment and randomization was stopped. Additional patients had been randomized and commenced treatment prior to this analysis because we needed to wait for these participants to start and complete initiation. Therefore, the final analysis included 93 participants randomized to the initiation method.

In the randomized semirush group, 2 withdrew before completing the 10-visit initiation phase without experiencing an objective allergic reaction to VIT, leaving 42 for the primary analysis. In 1 case, no reason was given, and in the other, generalized aches and pains, vomiting, and diarrhea 11 hours after the first treatment were attributed to VIT by the patient, who was unwilling to continue. In the patient-select semirush group, 1 patient moved house and was unable to complete the initiation phase. Patients who withdrew during the initiation phase after having immediate-type allergic reactions (our primary end point) were included in the analysis.

### Primary analysis

Table III shows the main results of treatment. Compared with randomized semirush, randomized ultrarush initiation had a higher risk of 1 or more objective systemic (65% vs 29%;  $P < .001$ ) and severe (12% vs 0%;  $P = .029$ ) reactions during the initiation phase. All severe reactions were characterized by systolic hypotension, but not hypoxemia. Ultrarush patients were less likely to achieve the target maintenance dose (20% vs 60%;  $P < .001$ ) by the end of the initiation phase, but the proportion of subjects achieving the intended target dose in the first year of treatment was the same in all groups (90%-94%). Logistic

regression analysis found that the target maintenance dose had no effect on any of these outcomes.

### Outcomes in patients who chose their initiation method

In patients who chose the initiation method, 1 semirush patient withdrew prior to the completion of initiation because of a change of residence. Reactions during treatment initiation occurred in 9 of the 30 semirush patients (30%, 15%-49%) who completed this phase and 54 of the 89 patients (61%, 50%-71%) who chose ultrarush ( $P = .003$ ). No severe reactions occurred in semirush patients, whereas 9 ultrarush patients (10%, 4.7%-18%) had 1 or more severe reaction ( $P = .110$ ).

### Venom and peptide allergen-specific antibody changes during treatment

Fig 3 shows the changes in sIgE and sIgG<sub>4</sub> to whole venom during the first 6 months of VIT. Delta values were significantly higher in the ultrarush group up to and including 3 weeks for sIgE and 7 weeks for sIgG<sub>4</sub>, after which differences were not statistically significant. Although sIgG<sub>4</sub> started to rise earlier in the ultrarush group, the median time to peak delta values was the same (12 weeks) for both semirush and ultrarush patients ( $P = .680$ ). In comparison, the median time to peak delta-sIgE was 3 weeks for ultrarush treatment compared with 7 weeks for semirush treatment ( $P = .004$ ). During the first 6 months of VIT, the maintenance dose did not have a statistically significant effect on the magnitude or timing of peaks. Similar results were found for sIgE and sIgG<sub>4</sub> for the major allergen Myr p 2.

### Post hoc analysis

Logrank tests including reactions beyond the initiation phase using multiple failure-per-patient data confirmed the difference in reaction risks between randomized ultrarush and semirush treatments, with 45 reactions (1 severe) in 13 people for semirush versus 84 reactions (9 severe) in 35 people for ultrarush ( $P = .032$  for any reaction;  $P = .025$  for severe reactions). However, in this analysis, the higher target maintenance dose was associated with a greater risk of systemic reactions. To further explore this effect, we examined the 178 patients in whom the target maintenance dose had been randomized. Stratified logrank tests of significance for differences in multiple failure-per-subject data between randomized 50 µg and randomized 100 µg target maintenance groups gave  $P < .001$  and  $P = .007$  for semirush and ultrarush treatments, respectively.

Fig 2 explores the target maintenance dose effect, displaying reaction hazards per visit. Cumulative failure curves (Fig 2, A) show that the vast majority of patients who reacted did so during treatment initiation and that the main determinant of whether a patient would experience 1 or more reactions was the initiation method. Smoothed hazard estimates (multiple failure-per-subject data, Fig 2, B) show that the higher target maintenance dose was associated with higher hazards for reactions throughout the first year of therapy. The corresponding stability in cumulative failure rates (single failure-per-subject data) indicates that this ongoing hazard was from recurrent reactions in the same individuals who started reacting during initiation. Semirush treatment to a

TABLE III. Outcomes

|                                                                                     | Semirush (n = 42) | Ultrarush (n = 49) |
|-------------------------------------------------------------------------------------|-------------------|--------------------|
| One or more objective reactions during the initiation phase                         | 12 (29%, 16%-45%) | 32 (65%, 50%-78%)  |
|                                                                                     | $P < .001$        |                    |
| One or more severe reactions during the initiation phase                            | 0 (0%)            | 6 (12%, 4.6%-25%)  |
|                                                                                     | $P = .029$        |                    |
| Achieved target dose by the end of the initiation phase                             | 25 (60%, 43%-74%) | 10 (20%, 10%-34%)  |
|                                                                                     | $P < .001$        |                    |
| Achieved target dose either during initiation or during the first year of treatment | 41 (93%, 81%-99%) | 48 (94%, 83%-99%)  |
|                                                                                     | $P = 1.000$       |                    |

Data are number (percentage, 95% CI for the percentage).

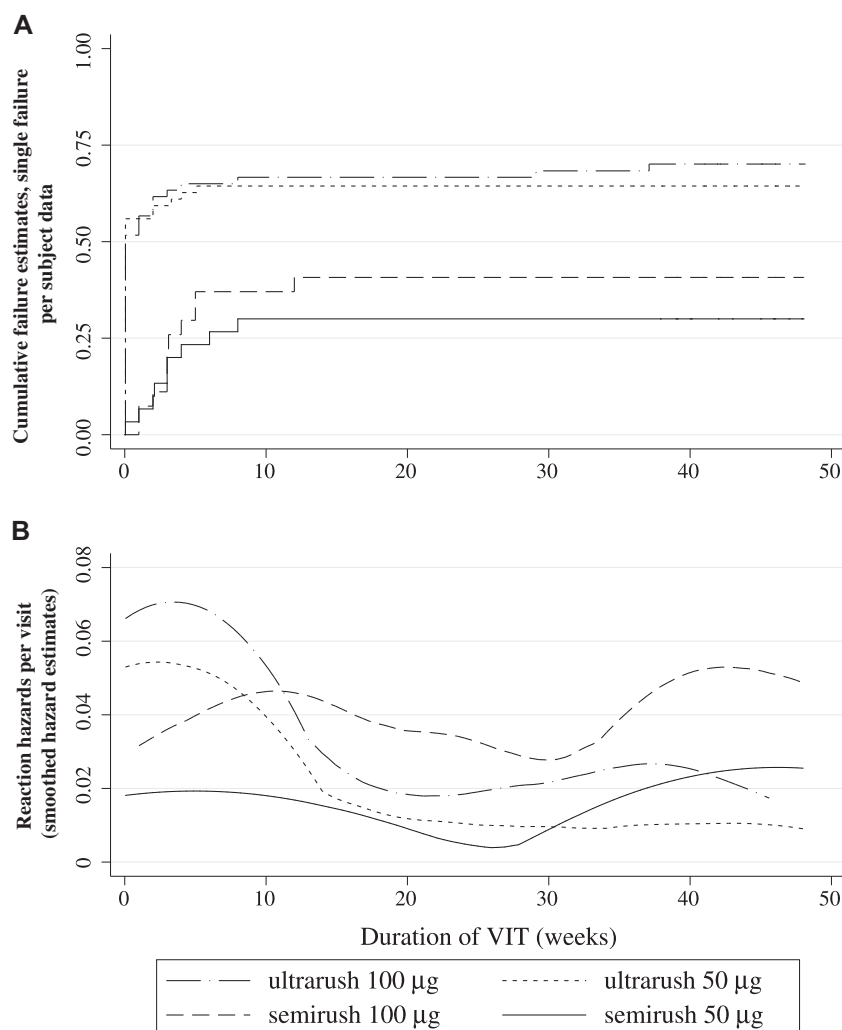


**FIG 2.** A and B, Time-to-event analysis for systemic reactions in 178 participants for whom the target maintenance dose was randomly allocated to either 50 µg or 100 µg.

target maintenance dose of 50 µg was associated with the lowest risk of reactions overall.

## DISCUSSION

We confirmed our previous findings that semirush VIT has an excellent safety profile with severe reactions being rare and found that systemic allergic reactions, including hypotensive anaphylaxis, were more likely with ultrarush treatment. A lower maintenance target dose reduced reaction risk after the initiation phase,

but the efficacy of this lower dose is not yet known. Maximal increases in sIgE also occurred earlier and were more intense with ultrarush VIT, suggesting enhanced sensitization to allergens with ultrarush treatment. In comparison, the timing of maximal sIgG<sub>4</sub> change did not differ between groups. The increased risk of reactions persists for about 10 weeks during ultrarush (Fig 2), corresponding with the time to peak sIgG<sub>4</sub> (Fig 3).

This is the first randomized trial of VIT initiation methods to be reported. Strengths of this study include its prospective design

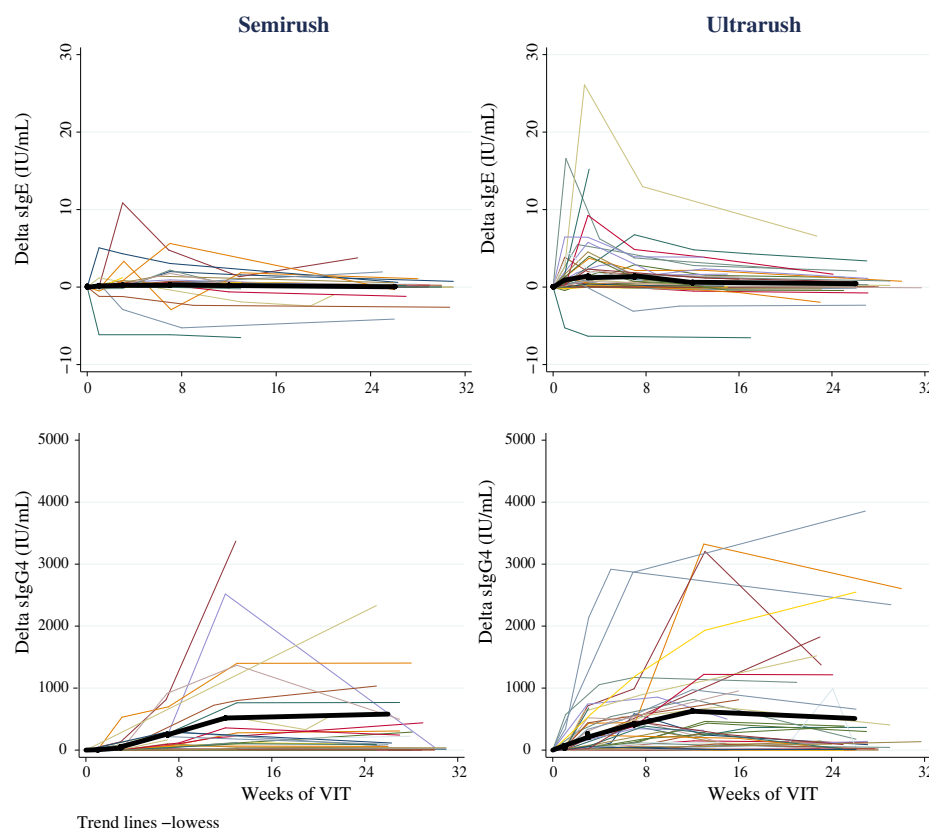


**FIG 3.** Changes in whole venom sIgE and sIgG<sub>4</sub> during treatment in randomized semirush and randomized ultrarush patients.

based on well-accepted VIT regimes developed over the last 30 years,<sup>8,12,13</sup> randomization to control for known and unknown confounders, use of a standardized venom extract from 1 insect species with 1 major allergen,<sup>14</sup> inclusion of potentially high-risk individuals including older patients with comorbidities, and use of a prospectively defined, objective definition of systemic reaction occurrence and severity. We also measured outcomes in patients who declined randomization and chose their treatment, thus confirming the applicability of our results to a routine clinical setting. Antihistamine premedication was used for all participants because this is common practice to reduce reaction rates<sup>15</sup> and to remove antihistamine treatment as a potential confounding variable. Weaknesses include that we could not blind the initiation method, that we used single blinding rather than double blinding of doses, and that we did not use observers blinded to treatment protocol to grade reaction severity. We also could not fully apply an intention-to-treat analysis because it was impossible to determine outcomes in the 2 patients who withdrew. However, if both had reactions, the primary analysis would have been similar, with reaction rates of 14 of 44 (33%) versus 32 of 49 (65%),  $P = .002$ .

Reported systemic reaction rates during VIT vary between 0% and 67% and are difficult to interpret because of a lack of standardized definitions and reporting, variable use of antihistamine premedication, variable baseline allergy severity of subjects (and reporting of same), variations in age, gender balance, and comorbidities of the populations being treated, and variations in treatment schedules and insect species to which patients were allergic. A review of 26 published reports of mainly honeybee and

vespid (yellow jacket) VIT in 2002 found that the overall reaction rate for slower traditional outpatient regimes given at weekly visits over 2 to 3 months was 11.2% compared with a reaction rate of 11.3% for 1-day (ultrarush) regimes.<sup>16</sup> In these studies, however, the number of ultrarush cases was relatively small, with the majority coming from 1 study reporting a remarkably low reaction rate,<sup>7</sup> in whom more than 90% were treated with vespids (yellow jacket) venom, which has a much lower risk of reactions compared with honeybee.<sup>8</sup> A recent prospective multicenter observational European Academy of Allergy and Clinical Immunology study of honeybee and vespids VIT confirmed that the main predictor of reactions was the venom used (higher rate of emergency intervention during honeybee VIT) and also found that faster initiation methods were associated with increased rates of emergency intervention, irrespective of the venom species used. Furthermore, there appeared to be a progressive increase in the risk of needing emergency treatment for a reaction with increasingly rapid dose escalation (conventional 4.3%, rush 7.2%, and ultrarush 11.4%).<sup>17</sup>

The mechanisms by which VIT reduces clinical reactivity are complex, and no laboratory parameter has been shown to accurately predict the outcome of VIT. Allergen-specific regulatory T cells are thought to play a pivotal role in the development of tolerance and modulation of B-cell activity to suppress sIgE and to produce blocking sIgG antibodies, with the IgG<sub>4</sub> subclass thought to be particularly important.<sup>18</sup> However, clinical protection does not correlate well with titers of sIgE, sIgG, or intradermal skin test reactivity,<sup>19</sup> and sIgE is known to rise during VIT despite achieving clinical protection.<sup>3</sup> Multiple effector pathways

may be involved in providing protection during VIT and changes in the specificity and affinity of antibodies produced may also be important.<sup>20</sup> Therefore, the measurement of sIgE and sIgG<sub>4</sub> is, at best, only an approximate marker of T<sub>H</sub>2-type (“allergic”) and regulatory T-cell (“suppressive/protective”) responses, respectively.

This randomized controlled trial confirms that ultrarush treatment increases the risk of adverse reactions to VIT and is consistent with findings from the European Academy of Allergy and Clinical Immunology safety study. Patients should be informed of these risks before a regime is chosen on the basis of perceived benefits. This is particularly important if there are significant comorbidities and/or advanced age, when a severe reaction could be life threatening. These and other factors may also influence the likelihood of a reaction, and further studies are required to define risk factors for severe reactions. A lower maintenance dose reduces the risk of reactions after the initiation phase, but whether this provides acceptable protection from accidental stings requires further study.

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**Clinical implications: The greater risk of allergic reactions, including severe hypotensive reactions, with ultrarush immunotherapy may be particularly important if there are comorbidities or advanced age, when a severe reaction could be life threatening.**

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