Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment

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Background: Hypersensitivity to the sting of the imported fire ant (IFA) is a growing and significant cause of morbidity and mortality in the United States. Conventional immunotherapy with IFA whole body extract (WBE) has been shown to be effective; however, rush immunotherapy (RIT) with IFA WBE has not been studied.

Objective: In this study, we evaluated the safety and efficacy of RIT with IFA WBE and sought to determine whether prophylactic pretreatment with antihistamines and steroids reduces the systemic reaction rate associated with RIT.

Methods: Patients with IFA hypersensitivity were randomized to placebo or twice-daily terfenadine 60 mg, ranitidine 150 mg, and prednisone 30 mg initiated 2 days before RIT in a double-blinded study. The 2-day RIT protocol consisted of hourly injections to achieve a final dose of 0.3 mL 1:100 wt/vol. Patients returned on day 8 to receive 2 hourly injections of 0.25 mL 1:100 wt/vol (total, 0.5 mL) and again on day 15 for a single injection of 0.5 mL 1:100 wt/vol. Efficacy of the protocol was determined on day 22, a pair of IFA sting challenges being performed 2 hours apart.

Results: Fifty-nine patients were enrolled into the study; a total of 58 patients (age range, 18 to 49 years) initiated the 2-day RIT. Only 3 patients (5.2%) experienced a mild systemic reaction during the protocol. Among those experiencing a systemic reaction with RIT, there was no statistical difference between the 2 premedication groups (3.6% active and 6.7% placebo; $P = .87$). Sting challenges were performed on 56 patients for a total of 112+ stings; only 1 mild systemic reaction occurred (efficacy, 98.2%).

Conclusion: RIT with IFA WBE for IFA hypersensitivity is both safe and efficacious; the rate of mild systemic reactions is low. Premedication is not necessary, inasmuch as prophylactic pretreatment with antihistamines and steroids did not reduce the systemic reaction rate associated with RIT. (J Allergy Clin Immunol 2002;109:556-62.)

Key words: *Imported fire ant, whole body extract, Hymenoptera, immunotherapy*

Since their introduction into the United States in the 1920s at the port of Mobile, Ala, imported fire ants (IFA) have spread throughout the southern United States. *Solenopsis invicta* (red IFA) accounts for most of the colonization, *Solenopsis richtera* (black IFA) colonies being confined to northeastern Mississippi and northwestern Alabama. Currently, IFA populations can now be found throughout 16 of the southern United States—from as far west as Orange County, Calif, across the southern states, and up the eastern coast to Washington, DC.

With the spread of IFA across the entire southern United States, more individuals will encounter IFA in their environments and be at risk for a sting with subsequent anaphylactic reaction. Although IFA hypersensitivity remains a concern principally for those in endemic areas, it potentially has an impact on allergists worldwide, as patients in our mobile society with known hypersensitivity move out of endemic areas into other parts of the nation and the world.

On a national scale, the bulk of the attention given to insect venom hypersensitivity is given to bees and vespids. However, in endemic areas, IFA is the most frequent cause of Hymenoptera hypersensitivity, accounting for both the majority of referrals to a venom clinic and the majority of Hymenoptera immunotherapy treatments offered.[1]

Hypersensitivity to the sting of IFA is becoming a significant cause of morbidity and mortality in the United States. A 1989 report listed 32 deaths from IFA in the southeastern United States.[2] IFA are aggressive when disturbed, and multiple stings are the norm; in contrast, with the flying Hymenoptera, a single sting is most common. Unlike patients with flying Hymenoptera hypersensitivity, who might manage to avoid subsequent stings for many years or even decades, patients with IFA hypersensitivity are at daily risk of repeated stings. Tracy et al[3] reported a 51% attack rate in 107 patients who were followed for only a brief 3-week period. Although sting attacks most often occur outdoors, IFA sting attacks have also been reported indoors.[4-6]

Both conventional immunotherapy and rush immunotherapy (RIT) have been shown to be effective in

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Abbreviations used
IFA: Imported fire ant(s)
RIT: Rush immunotherapy
WBE: Whole body extract

treating flying Hymenoptera hypersensitivity.[7-8] Conventional immunotherapy with IFA whole body extract (WBE) has also been shown to be effective.[9-11] However, RIT with whole body IFA extract has not been studied. RIT can provide lifesaving protection within a very short time; in contrast, conventional immunotherapy can take as long as 6 to 12 months to reach a protective maintenance dose. Rapid protection is essential in the light of the high sting attack rate seen in endemic areas.[3] Furthermore, financial savings associated with RIT for the patient and facility could be substantial.[12]

In comparison with conventional protocols, however, RIT might be associated with an increased incidence of systemic reactions. Conventional venom immunotherapy has been reported to be associated with a systemic reaction rate of approximately 12%.[13] In contrast, RIT with flying Hymenoptera venom has variously been reported to have a systemic reaction rate of 0% to 85%.[12,14-16] The degree of interstudy variability and overlap of systemic reaction rates, however, complicates the interpretation of these data. Although prophylactic treatment has generally been accepted as decreasing the systemic reaction rate for aeroallergen immunotherapy, prophylactic treatment for venom immunotherapy with an H1 antihistamine or a combination of H1 and H2 antihistamines has shown conflicting results.[17-19]

In this study, we investigated both the safety and efficacy of RIT with IFA WBE and sought to determine whether prophylactic pretreatment with antihistamines and steroids reduced the systemic reaction rate associated with RIT.

METHODS

Patients

Male and female patients who were 18 to 65 years of age and had IFA hypersensitivity, as defined by a history of a systemic reaction (eg, diffuse urticaria, pruritus, and/or angioedema; upper airway obstruction; asthma/respiratory distress; cardiovascular decompensation; alteration of consciousness) to an IFA sting and the presence of a positive IFA skin test result were eligible for enrollment over a 35-month period from August 1996 to June 1999. The Investigation Review Board of Wilford Hall Medical Center approved the study protocol and the statement of informed consent, and a signed informed consent document was obtained from each patient before the study. Patients were excluded if they (a) were pregnant, (b) had any serious concurrent disease process, such as cardiopulmonary disease (including, but not limited to, coronary artery disease, a history of arrhythmias, chronic obstructive pulmonary disease, or asthma), that would place them at undue risk in the event of a systemic allergic reaction and its subsequent treatment, or (c) used a beta-blocker medication of any type. After the rush protocol and sting challenge, patients were continued on a conventional immunotherapy schedule with IFA WBE and were followed in the allergy clinic on a routine basis.

A patient was withdrawn from the study when any of the following occurred: the patient asked to withdraw; the patient became pregnant during the study; the patient developed a medical condition or required a medication that increased the risk of immunotherapy or the treatment of systemic reactions; the patient experienced a grade 6 reaction (definitions of grades are presented in Table I). Whenever the rush protocol was terminated early, the patient was offered a conventional IFA immunotherapy schedule. The conventional schedule used at our institution for IFA hypersensitivity begins at 0.1 mL 1:100,000 wt/vol and requires 23 injections to achieve the maintenance dose of 0.5 mL 1:100 wt/vol.

Each patient was initially evaluated in our venom clinic to confirm the referral history of IFA sting anaphylaxis. The severity of the historical systemic reaction was determined and graded according to the schedule shown in Table I. Only individuals with symptoms after suspected IFA sting of grades 3 to 6 were skin-tested.

Skin testing

Progressive skin testing was carried out on every prospective patient who had a history consistent with a systemic reaction to the sting of IFA. Positive and negative (saline) controls plus 1:1000 wt/vol WBE skin tests were performed through use of a prick method. A histamine base 1 mg/mL (histamine phosphate 2.75 mg/mL, Center Pharmaceuticals, Pompano Beach, Fla) in 50% glycerin and 0.4% phenol was used as the positive control for prick testing. If the WBE prick result was negative, the prick test was followed by intradermal testing, beginning with 1:1,000,000 wt/vol dilution IFA WBE and progressing in 10-fold increments to 1:1000 wt/vol, if needed. The skin test result was considered positive if the wheal diameter was 5 mm or greater with a flare of 11 mm or greater. A 0.1-mg/mL histamine base (histamine phosphate 0.275 mg/mL, Center Lab) in 0.4% phenol was used for the positive intradermal control; saline solution was used for the negative intradermal control. Skin testing and immunotherapy were performed through use of WBE (Bayer Corporation, West Haven, Conn) that consisted of an *S invicta*/*S richteri* mix from a 50-mL 1:10 wt/vol stock bottle in 0.4% phenol. Each patient with a positive skin test result was offered either a traditional immunotherapy schedule or the rush protocol. Those requesting to participate in the rush protocol study signed an informed consent document approved by our institutional review board. Each female patient was required to give a urine sample for a qualitative urine human chorionic gonadotropin test to confirm that she was not pregnant. Furthermore, every patient who was confirmed to have a history consistent with anaphylaxis and a positive skin test reaction to IFA was prescribed either auto-injectable epinephrine or an epinephrine kit.

Rush prophylaxis

Each patient was randomized in a double-blinded manner into one of 2 prophylaxis regimens: placebo or premedication. Premedications consisted of twice-daily terfenadine 60 mg, ranitidine 150 mg, and prednisone 30 mg. The prophylaxis regimen was initiated 2 days before the RIT and stopped on the evening when the rush protocol was completed. Randomization and 5 days of premedication or placebo were provided by our pharmacy. Premedications were crushed and placed within capsules identical to those used for the placebo preparations. The placebo preparations were distributed to patients within lactose-containing capsules to conceal the identity of the preparations. To allow the medication to be distributed in a double-blind manner, the pharmacy prepared the capsules, distributed them to the patients, and maintained the medication records.

Rush protocol

The rush protocol (Table II) was conducted in our allergy clinic, which has the appropriate equipment to treat an anaphylactic reac-

TABLE I. Reaction grading and dose modification

Grade	Symptoms	Dose modification
0	Wheal/swelling <3 cm	No modification of schedule
1	Wheal/swelling <3 cm	No modification of schedule
2	Wheal/swelling <6cm	No modification of schedule
3	Urticaria, pruritus, angioedema, itching, flushing	Repeat the dose
4	Nasal congestion, sneezing, rhinitis, oral pruritus, ocular tearing or pruritus	Return to the previous dose
5	Wheezing, dyspnea, chest tightness, abdominal cramping, nausea, vomiting	Decrease 2 doses and give injections every 2 h
6	Laryngeal edema, hypotension, syncope, dizziness, shock, arrhythmia, seizure	Terminate the RIT schedule

RIT, Rush immunotherapy.

TABLE II. Wilford Hall imported fire ant rush protocol

Day 1	Day 2*
0.1 mL 1:10,000,000	0.1 mL 1:1,000
0.3 mL 1:10,000,000	0.2 mL 1:1,000
0.1 mL 1:1,000,000	0.3 mL 1:1,000
0.3 mL 1:1,000,000	0.4 mL 1:1,000
0.1 mL 1:100,000	0.5 mL 1:1,000
0.3 mL 1:100,000	0.1 mL 1:100
0.1 mL 1:10,000	0.2 mL 1:100
0.3 mL 1:10,000	0.3 mL 1:100

*Day 2 cumulative dose: 0.75 mL 1:100 wt/vol

TABLE III. Post–rush immunotherapy schedule

Days 1-2	Rush protocol
Day 8	0.25 mL 1:100
	0.25 mL 1:100
Day 15	0.5 mL 1:100
Day 22	2 IFA sting challenges
Day 29	0.5 mL 1:100
Day 50	0.5 mL 1:100
Monthly	0.5 mL 1:100

IFA, Imported fire ant.

Environmental and occupational disorders

tion. The patient arrived in the morning and had intravenous access established. Baseline blood pressure, heart rate, respiratory rate, and peak flow data were obtained. Repeat vitals and peak flow were also recorded before each injection. Patients were monitored for 2 hours after the last injection of each day and then were allowed to return home for the evening; they were asked to have someone drive them home if possible. Patients were instructed to carry their epinephrine kits to and from the allergy clinic on each day of the rush protocol.

The initial immunotherapy dosage for the rush protocol was 0.1 mL 1:10,000,000 wt/vol. If there were signs or symptoms of either an allergic reaction, as defined by grades 3 to 6 (Table I), or (a) a fall in systolic blood pressure of >15 mm Hg, (b) an increase in pulse of >20 from baseline, or (c) a decrease in peak flow of > 15% from baseline, the patient was assessed for the presence of a systemic reaction by a physician before administration of the next injection. Patients remained in full view of an allergy technician at all times. Dose modification of the rush protocol was based on the criteria presented in Table I. Subcutaneous injections were administered in the triceps region, alternated arm to arm, and given on an hourly basis, the last injection being given no later than 3 PM. On completion of the rush protocol, the remainder of the injections were delivered according to the schedule shown in Table III. The injections on day 8 were given 1 hour apart; a 1-hour observation period followed the second injection. Neither vital signs nor intravenous access was used with the injections after the 2-day rush protocol.

Sting challenge

To ascertain effectiveness of the rush protocol, 2 sting challenges were conducted on day 22. IFA mounds were identified on the day of the challenges, and several fire ants were collected in a 50-mL plastic test tube. Patients had baseline vital signs and peak flow performed and intravenous access obtained before the sting challenge. A single IFA was removed from the 50-mL tube and placed on the ventral aspect of the patient's forearm and maintained in that location until a sting was initiated. The fire ant was allowed to remain in the stinging position until the sting was completed and was then removed and placed in a 10-mL test tube in a 10% ethanol preservative for transport to an entomologist for confirmation as *S invicta*. The patient was observed for a period of 2 hours after the sting for evidence of allergic or adverse symptoms. Repeat vital signs and peak flow were performed at 15, 30, 60, and 120 minutes after the sting. At the 120-minute post-sting mark, a second fire ant was selected and the sting challenge procedure was repeated. A physician was notified if any signs of a grade 3 to grade 6 systemic reaction (Table I) occurred or if any of the following occurred: a decrease in systolic blood pressure of >15 mm Hg; an elevation of pulse rate >20 beats/minute; a decrease in peak flow >15%. All sting challenges were performed by one of the study investigators.

Statistics

The correlation of historical sting reaction with skin test results was calculated through use of the Spearman correlation coefficient. The rate of reactions to RIT between the active and placebo prophylaxis groups were compared through use of χ^2 analysis. Results were considered statistically significant for P values less than .05.

RESULTS

All 59 patients enrolled in the study had histories of systemic reactions to IFA stings and positive skin test reactions to the WBE. The systemic reactions, according to the patients' historical reports of symptoms (Table I), were as follows: 14 patients (23.7%) had grade 3 reactions, 0 had grade 4 reactions, 12 (20.3%) had grade 5 reactions, and 33 (55.9%) had grade 6 reactions. The results of the initial cutaneous skin testing were as follows: 2 patients (3.4%) were positive at 1:1000 wt/vol prick; 29 (49.2%) were positive at 1:1,000,000 wt/vol

TABLE IV. Rush immunotherapy and sting challenge reactions

	Age (y)/sex	Initial reaction	Skin test	Study reaction	Premedication
Rush immunotherapy reactions					
	40/F	Grade 6	1:100,000	Grade 5	No
	20/F	Grade 6	1:100,000	Grade 5	Yes
	26/F	Grade 6	1:100,000	Grade 3	No
Sting challenge reaction					
	26/F	Grade 6	1:100,000	Grade 3	No

F, Female.

intradermal; 21 (35.6%) were positive at 1:100,000 wt/vol intradermal; 5 (8.5%) were positive at 1:10,000 wt/vol intradermal; and 2 (3.4%) were positive at 1:1,000 wt/vol intradermal. There was no statistical correlation between the severity of historical sting reaction and the dilution at which the skin test result was positive (r = –0.018; P = .894).

There was a wide range of positive responses—from 1:1,000 wt/vol by the skin prick method to 1:1,000 wt/vol by the intradermal method. The mean age of those enrolled in the study was 29.6 years, the range being 18 to 56 years. The male:female ratio in the study was 35:24 (59.3% male preponderance).

Of the 59 enrolled patients, 28 received active premedications and 31 received placebo premedications with their RIT. A total of 56 patients completed the rush protocol and sting challenges. Three patients were withdrawn from the study—2 because of a systemic reaction during the rush protocol and 1 who self-withdrew on the day before the rush protocol because of perceived side effects from the prophylaxis medications (after unblinding of the study, it became evident that this patient had been on placebo). Over the 35-month study period, most of the patients were seen in our venom clinic during the months of July, August, September, and October. A total of 913 injections were administered during the 2-day rush protocol among the 58 patients who initiated injections. No dose adjustments were required for large local reactions.

There were 3 systemic reactions during the rush protocol (Table IV) in this cohort of 58 patients; accordingly, the reaction rate was only 5.2% (3/58). With regard to these 3 reactions, 2 of the patients were on placebo premedications; the reaction rate in the placebo group was thus 6.7% (2/30). There was a reaction rate of 3.6% (1/28) in the active premedication group. There was no significant difference between the 2 groups (P = .867). The 95% upper confidence limit was 20.5% for the placebo group and 17.1% for the active premedication group. Historically, all 3 of these patients had grade 6 reactions that brought them to initial clinical attention, and all 3 had positive skin test results at the 1:100,000 wt/vol dilution.

The first of the 3 patients was a 40-year-old woman who received placebo premedications. She complained of chest heaviness and a subjective sensation of throat-tightening (though there was no objective angioedema) and had a decreased peak flow of 20%; this occurred after the first injection on day 2 of 0.1 mL 1:1,000 wt/vol. She was treated with subcutaneous epinephrine and had resolution of her signs and symptoms. She was subsequently changed to a traditional schedule and achieved maintenance without further difficulty.

The second of the 3 patients was a 20-year old woman who received active premedications. She complained of subjective throat-tightening and diffuse pruritus and had coughing that was noted at 1 hour after the first injection of 0.1 mL 1:10,000,000 wt/vol on day 1. She was treated with epinephrine and had resolution of her symptoms. She requested an opportunity to complete the rush protocol even though the protocol required us to stop the RIT. She was placed on once-daily oral loratadine 10 mg and prednisone 50 mg and removed from further data assessment, but she completed the same protocol, including a sting challenge, outside the research setting without further problems.

The third and final patient to experience a systemic reaction during the 2-day rush protocol was a 26-year old woman who received placebo premedications. She complained of intermittent diffuse pruritus and a transient 15-minute episode of lightheadedness without objective changes in vital signs. These symptoms resolved without intervention. Because of the lack of objective findings, no dose adjustment was made, and the patient completed the rush protocol with no further problems. However, this patient telephoned the following day, after completion of the 2-day rush protocol, and reported that she had awakened in the middle of the night, approximately 8 hours after her final injection, with a sensation of throat fullness, difficulty in breathing, and a diffuse pruritic rash. She did not seek medical attention, and the signs and symptoms resolved without further intervention.

Fifty-six patients completed sting challenges for a total of 112+ sting challenges (some patients received more than 2 stings; see below). During the challenges, several patients received multiple stings when the ant was not removed quickly enough; this was not the case with the single patient who reported a reaction. All of the IFA used in the sting challenges were identified by an entomologist as *S invicta*. Many field stings have also occurred in our cohort; no systemic reactions were associated with these stings. The single patient who reported a reaction (Table IV) was a 26-year old woman with a grade 6 historical reaction and a skin test result that was positive at 1:100,000. This patient was also reported as having a systemic reaction during the 2-day rush protocol. During the sting challenge she described a sensation of lightheadedness that occurred 15 minutes after her

sting but resolved without therapy and occurred with no objective evidence of hypotension or tachycardia. She was continued on maintenance immunotherapy and reported no field stings at a 2-year follow-up. The 1 systemic reaction gave us a treatment failure rate of 1.8% (1/56) and an efficacy rate of 98.2% (55/56). Of note, after the sting challenges, another patient reported having been on terfenadine for allergic rhinitis during the 5 consecutive days before her sting challenges.

DISCUSSION

The diagnosis and treatment of IFA hypersensitivity has advanced from that of 60 years ago, when patients who were IFA-hypersensitive were reported to be successfully treated with whole bee extract.[20] The specific and successful treatment of IFA hypersensitivity with IFA WBE was first reported by Triplett[10] in 1973 in a group of 18 patients followed over a 10-year period.

This study is the first to evaluate 3 issues pertaining to therapy with WBE for IFA hypersensitivity: the safety of a rush protocol, the efficacy of a rush protocol, and the influence of prophylactic treatment on systemic reactions. With respect to mean age, the 29.6 years reported in our study is similar to the 30.5 years and the 36 years reported in 2 previous demographic studies in IFA hypersensitive populations.[1,21] The male predominance noted in this report (59.3%) is comparable to what was reported in 3 prior studies in IFA hypersensitive populations (range, 50.2% to 61.6% male preponderance).[1,21,22] The seasonal trend seen in patient enrollment—69.5% (41/59) of our patients were enrolled during the 4-month period from July through October—reflects both the fact that IFA are most active in the warm summer months and the fact that patients are most likely to be engaged in outdoor activities at that time. Although there was no correlation between skin test results and historical reaction, a majority (55.9%) of the 59 patients enrolled had severe grade 6 historical reactions that prompted their referral to our venom clinic for evaluation.

Of the 59 patients enrolled in the study, 56 successfully completed both the 2-day rush protocol and the sting challenges. Our data strongly support the safety of the 2-day protocol; only 3 of the 58 patients who initiated injections had mild reactions, for a reaction rate of 5.2% among the cohort. This reaction rate compares favorably with those seen in rush protocols for the flying Hymenoptera, in which reaction rates of 0% to 85% have been reported.[12,14-16] The reaction rate reported in this study falls within the range of systemic reaction rates—3% to 12%—that are often cited for flying Hymenoptera venom injections.[13,23-25]

Among those experiencing a systemic reaction with RIT, there was no statistical difference between the 2 premedication groups (3.6% active and 6.7% placebo; $P = .87$). Our results are consistent with 2 prior flying Hymenoptera venom RIT studies that showed similar systemic reaction rates with and without prophylactic treatment with terfenadine/fexofenadine.[18-19] In one of these, a study by Berchtold et al,[18] a comparable number of patients were evaluated; however, in this placebo group, treatment with prednisone and clemastine was permitted, and this might have masked significant differences.

To our knowledge, the only investigation in the literature to show a decrease in systemic reaction rates with prophylactic treatment in flying Hymenoptera venom RIT is a study by Brockow et al.[17] However, when subjective systemic complaints are included in the data analysis of the study by Brockow et al, there are no differences between the group with and the group without prophylactic treatment.

All 3 of the studies showed a significant decrease in large local reactions with the prophylactic treatment. Although we did not look specifically at the incidence of large local reactions in our study, no dose adjustments were required and no patients withdrew from the study because of large local reactions. Of interest, 1 patient withdrew from the study before initiation of the RIT protocol because of perceived side effects from the prophylactic treatment, but when the study was unblinded, it was found that she had been on placebo. This might have been related to a steroid phobia that is not infrequently seen in our clinic.

Of the 56 patients who received sting challenges, the single reaction gave us an efficacy rate of 98.2%, which correlates with the efficacy rates reported for venom immunotherapy for flying Hymenoptera. Despite the subjective nature of this single reaction, we chose to classify it conservatively as a treatment failure. The decision to do 2 separate sting challenges was based on the premise that those with flying Hymenoptera hypersensitivity are at a ~60% risk of repeat anaphylaxis on subsequent sting before immunotherapy.[26] Although surveys of individuals with anaphylactic episodes to IFA stings have shown that patients stung by IFA usually have received multiple stings, most of the reported deaths attributed to anaphylaxis to IFA stings resulted from fewer than 5 stings.[2] It is possible that the results of our 2 separate sting challenges reflect a still inadequate testing dose. The exact number of stings that are appropriate for an adequate challenge remains unknown. Several of our patients did receive 2 or more stings per individual challenge—when the ant was not removed quickly enough after completion of the first sting, or when it was unclear to the investigator whether the fire ant had actually delivered the first sting and was now delivering a second sting. The latter situation was evident when 2 pustules (rather than a single pustule) appeared at the sting site. Another fact that might support the contention that our challenges were appropriate is that we allowed each ant to remain on the patient until the sting was completed. This was evidenced by the ant's removing its stinger from the stinging position and changing its body position from the characteristic arched position that is assumed during a sting. Some ants remained in this arched position up to approximately 30 to 45 seconds—far longer than would have been allowed if the patient had received a field sting. Although it is unknown whether more venom is delivered as the sting progresses in time, theoretically this

could be the case, and our sting challenges might thus have been similar to field stings of 3 to 5 stings.

This 2-day rush protocol offers several advantages for those patients with IFA hypersensitivity who live in IFA-endemic areas. In contrast to patients hypersensitive to the flying Hymenoptera, who can avoid subsequent stings for years and even decades, those with IFA hypersensitivity in endemic areas are at a very high daily risk of another sting. Tracy et al[3] reported a sting attack rate of 51% over a brief 3-week period in San Antonio, Tex, among a group of first-year medical students. Potentially lifesaving treatment can be offered in a very brief period with the 2-day rush protocol used in this study, and it is associated with a low rate of mild systemic reactions. Another advantage of the 2-day rush protocol is the convenience in achieving a maintenance dose. Our institution currently uses a traditional 23-injection schedule to achieve maintenance for those not desiring the rush protocol for IFA hypersensitivity. Accordingly, rather than having to make 23 separate visits, each with a 20 to 30 minute wait following the injection, patients can achieve maintenance in only 2 days. This rush protocol might also offer additional financial savings to the both the patient and the physician.[12] A final advantage of the rush protocol is unique to our population, which included active-duty pilots. Normally, a military pilot is required by regulations to be grounded and prohibited from flying until he or she is at a maintenance dose of immunotherapy; this would typically mean a minimum of 3 to 6 months of lost flying time, which would have a major impact on the pilot as well as on the mission of the pilot's squadron. The rush protocol avoids this loss of flying time; the pilot can be back in the cockpit in a matter of days. The rush protocol also allows an active-duty military member in basic training to return to duty, and it avoids the loss of financial resources associated with having to discharge such an individual should a rush protocol be unavailable.

Although this is the fourth study to date supporting the efficacy of WBE in the treatment of IFA hypersensitivity, several questions still remain.[9-11] There has been no double-blinded, placebo-controlled study that evaluated the effectiveness of this current standard of care treatment for IFA hypersensitivity. The rush protocol in this study might offer the groundwork needed to complete a controlled prospective trial of WBE versus venom versus placebo. If such an investigation were to be conducted, patients could be unblinded after the sting challenges and those who had been on placebo could be placed on WBE immunotherapy.

Venom appears to be superior to WBE for skin testing, but the financial constraints associated with obtaining venom from IFA have thus far made it prohibitive for routine use in skin testing and immunotherapy.[27] Recent literature has recommended that the US Food and Drug Administration consider IFA venom vaccines for orphan drug status.[28] Perhaps a recombinant peptide form of IFA immunotherapy could be marketed in the future, given that Sol i 2 protein, one of the 4 important allergens for *S invicta*, has recently been produced in high yield with the native protein conformation.[29]

On the basis of the favorable results of this study and the fact that we started at a 1:10,000,000 wt/vol dilution rather than at the 1:100,000 wt/vol dilution used in our traditional schedule, a goal of future investigation might be to evaluate a 1-day rush protocol. In addition, a modified rush protocol, such as is commonly used for other Hymenoptera venom schedules, could provide an easier way for physicians in practice to administer extracts. Utilization of skin test reactions to guide the starting dose might be appropriate in these areas.

In conclusion, a 2-day RIT protocol with IFA WBE appears to be safe; the rate of mild systemic reactions was low. Premedication is not necessary, inasmuch as our study revealed no statistical difference in systemic reaction rates associated with IFA RIT between active and placebo premedication groups. A maintenance dose of 0.5 mL 1:100 wt/vol of a mixed *S invicta*/*S richtera* WBE, achieved through use of this rush protocol, offers a 98.2% efficacy against 2 separate IFA sting challenges. This level is comparable to the currently accepted level of protection achieved with venom immunotherapy for flying Hymenoptera. Current patients will complete a minimum of 3 to 5 years of total immunotherapy before consideration is given to discontinuation.

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