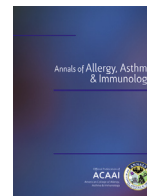




ELSEVIER

Contents lists available at ScienceDirect



A 1-day imported fire ant rush immunotherapy schedule with and without premedication

April M. Arseneau, MD; Teresa D. Nesselroad, MD; Jeffrey J. Dietrich, MD; Laura M. Moore, MD; and Michael S. Tankersley, MD

San Antonio Military Medical Center, San Antonio, Texas

ARTICLE INFO

Article history:

Received for publication April 8, 2013.

Received in revised form August 21, 2013.

Accepted for publication August 22, 2013.

ABSTRACT

Background: Rush immunotherapy (RIT) schedules can expedite protection in individuals sensitive to imported fire ant (IFA) stings.

Objectives: To evaluate the safety and efficacy of 1-day RIT with IFA whole body extract (WBE) and determine the benefit of premedication with antihistamines and prednisone.

Methods: Patients with systemic reactions to IFAs and evidence of specific IgE by skin test or serologic test started a 1-day RIT protocol without premedication. The 1-day RIT protocol consisted of a total of 10 injections every 30 to 60 minutes to achieve a 0.3-mL 1:100 (wt/vol) dose. A higher systemic reaction rate (SRR) prompted protocol revision to include a 3-day course of oral 20 mg of prednisone twice daily, 150 mg of ranitidine, and 10 mg of loratadine started 2 days before the 1-day RIT. Patients returned on days 8 and 15 to receive a 0.5 mL 1:100 (wt/vol) maintenance injection. The effectiveness of the RIT was evaluated with a sting challenge on approximately day 22.

Results: Eighty of the 96 patients enrolled initiated the 1-day RIT. The first nonpremedicated group exhibited a SRR of 24.3% (9 of 37 patients), whereas the revised premedicated group had a SRR of 9.5% (4 of 42 patients; $P = .07$). The most severe reaction during RIT included dizziness, angioedema, and urticaria. Sting challenges on 53 patients resulted in 1 mild rhinitis reaction (efficacy, 98.1%).

Conclusion: One-day RIT with IFA WBE for IFA hypersensitivity is efficacious. Although there was a trend with premedications to reduce SRRs during the RIT, safety data with premedication require confirmation in a larger trial.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Imported fire ants (IFAs), endemic to the southern United States, are a frequent cause of hypersensitivity reactions, encompassing 42% to 54% of insect hypersensitivity evaluations performed in these areas.^{1,2} Unique to the 2 species of IFA, *Solenopsis richteri* and *Solenopsis invicta*, is the difficulty practicing effective avoidance measures.³ An annual sting rate of 58% was reported from a population survey performed in a neighborhood in New Orleans, Louisiana.⁴ Furthermore, 51% of medical students completing a 3-week rotation in Texas experienced a sting during their visit, with 16% of those stung developing sensitization.⁵ Similar geographic regions have had sensitization rates of 25% to 29%^{6,7} when evaluated with IFA whole body extract (WBE) skin prick testing (SPT) and rates as

high as 65% by serum specific IgE detection (UniCAP method).⁸ Anaphylaxis and death are well known phenomena of IFA hypersensitivity in both indoor and outdoor settings.^{9–11}

Immunotherapy with IFA WBE has been found to be an effective and safe treatment for IFA hypersensitivity administered with a maintenance dose of 0.5 mL of 1:100 (wt/vol).^{12–15} For clarity, the 1:100 (wt/vol) dose is a 10-fold dilution of the 1:10 (wt/vol) manufacturer's extract. The 0.5-mL 1:100 (wt/vol) maintenance dose is also the most frequent maintenance dose prescribed by allergists.¹⁶ Conventional IFA WBE immunotherapy schedules recommend 25 to 28 injections to reach maintenance dose, raising concern for subtherapeutic treatment for up to 6 months.¹⁷ Patients sensitive to IFA are, therefore, at considerable risk of continued systemic reactions to stings during the months of immunotherapy build-up by conventional schedules. The high IFA sting attack rates in endemic areas make rush immunotherapy (RIT) particularly enticing.

Safe and effective IFA rush schedules have been previously reported.^{18,19} Tankersley et al¹⁵ reported a successful 2-day IFA WBE RIT protocol that demonstrated no difference in systemic reaction rates (SRRs) between individuals with and without pretreatment medication regimens. In addition, dual sting challenges performed

Reprints: April M. Arseneau, MD, 1606 Marten St, Anchorage, AK 99504; E-mail: april.arseneau.1@us.af.mil.

Disclosures: Authors have nothing to disclose.

Disclaimer: The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Air Force, the US Department of Defense, or the US government.

Funding Sources: This study was funded by the US Air Force.

Table 1
Reaction classification system

Grade	Symptoms
0	Wheal/swelling <3 cm
1	Wheal/swelling 3–6 cm
2	Wheal/swelling >6 cm
3	Urticaria, pruritus, angioedema, flushing
4	Nasal congestion, sneezing, rhinitis, oral pruritus, ocular tearing or pruritus
5	Wheezing, dyspnea, chest tightness, abdominal cramping, nausea, vomiting
6	Laryngeal edema, hypotension, syncope, dizziness, shock, arrhythmia, seizure

on 56 patients resulted in only 1 mild reaction (efficacy, 98.2%).¹⁵ Initial data included in this study was previously published in 2009 and reported a reaction rate of 24% with 1-day RIT.²⁰ In this current study, we evaluated the safety and efficacy of 1-day RIT with IFA WBE and sought to determine whether premedication with antihistamines and prednisone would reduce the SRR associated with the 1-day RIT.

Methods

Study Participants

Inclusion criteria for enrollment into the study were patients 18 to 65 years of age with a history of systemic reaction to an IFA sting and positive IFA SPT result or IFA ImmunoCAP (Phadia, Uppsala, Sweden) specific IgE test result. Reaction severity was classified (Table 1), and only participants with grade 3 to 6 systemic reactions were eligible for enrollment. Patients were excluded for pregnancy, use of β -blocker medication, unstable coronary artery disease, chronic obstructive pulmonary disease, incompletely controlled moderate to severe persistent asthma, or forced expiratory volume in 1 second less than 80% predicted.

Testing

SPTs were performed using a WBE of 1:1,000 (wt/vol) of *S invicta/S richteri* mixture diluted from the manufacturer's extract of 1:10 (wt/vol) (Hollister-Stier Laboratories, Spokane, Washington). SPT results to both IFA WBE and a histamine control were considered positive if a wheal 3 mm or larger in diameter with surrounding erythema was produced. A negative control SPT result was concurrently performed with diluent and determined to be valid if the wheal was smaller than 3 mm. If the initial SPT result was negative then an intradermal skin test (IDT) was performed beginning with a 1:1,000,000 (wt/vol) concentration of the IFA mixture followed by sequential 10-fold increases to a maximal intradermal concentration of 1:1,000 (wt/vol). The IDT results were considered positive if a wheal 5 mm or larger in diameter with surrounding erythema was observed. IDT-positive and IDT-negative controls were used as well and determined to be valid if wheals of 5 mm or larger with surrounding erythema and less than 5 mm were observed, respectively. ImmunoCAP specific IgE test result was considered positive at a value 0.35 kU/L or higher.

Protocol

Patients with a history of a systemic reaction to IFA and evidence of specific IgE were offered IFA WBE immunotherapy. Patients were offered the option of this 1-day rush research protocol, the prior 2-day rush schedule,¹⁵ or a conventional schedule.¹⁷ This protocol was approved by the Wilford Hall Institutional Review Board, and all patients signed informed consent documents at the time of enrollment. Initially, the trial did not include premedications based on the finding of the study by Tankersley et al¹⁵ of no benefit in

Table 2
Wilford Hall imported fire ant 1-day rush protocol

Time	Dose, mL ^a	Concentration, wt/vol
8:00 AM	0.3	1:100,000
8:30 AM	0.1	1:10,000
9:00 AM	0.3	1:10,000
9:30 AM	0.05	1:1,000
10:00 AM	0.15	1:1,000
10:30 AM	0.3	1:1,000
11:00 AM	0.05	1:100
12:00 PM	0.1	1:100
1:00 PM	0.2	1:100
2:00 PM	0.3	1:100
3:00 PM	End of office observation	

^aCumulative dose was 0.7 mL of 1:100 (wt/vol) concentration (1:100 wt/vol = 1:1 vol/vol).

a 2-day RIT procedure; however, a higher than expected SRR in this group (group 1) prompted revision of the protocol to include premedication with twice daily oral loratadine, 10 mg, ranitidine, 150 mg, and prednisone, 20 mg (group 2).²⁰ Treatment with these medications was started 2 days earlier and finished on the evening of the procedure once the patients returned home. As previously reported, group 1 data spanned May 2004 to January 2008.²⁰ Group 2 data included patients enrolled from February 2008 to October 2011.

The first day consisted of 10 injections administered during 8 hours (Table 2). A 30-minute wait period after the first 6 doses, 60 minutes after the next 3 doses, and 2 hours after the final dose was used. The dosing schedule began with an initial dose of 0.3 mL of a 1:100,000 (wt/vol) *S invicta/S richteri* WBE commercially available mixture. The mixture includes both species based on collection variability and possibility of hybridization. The final dose on day 1 was 0.3 mL of a 1:100 (wt/vol) maintenance concentrate. The 1:100 (wt/vol) maintenance vial was prepared by adding 1 mL of the 1:10 (wt/vol) manufacturer's extract to 9 mL of diluent in a 10-mL total volume vial. The total cumulative dosage of 1:100 (wt/vol) on day 1 was 0.7 mL. Patients returned on day 8 of the protocol for the full maintenance dose of 0.5 mL of 1:100 (wt/vol) split into 2 doses of 0.25 mL delivered in each arm. A single maintenance dose of 0.5 mL 1:100 (wt/vol) was delivered on day 15 (Table 3), and then the dosing interval was gradually spaced out to once monthly injections. On the rush day, intravenous access was obtained, and vital signs, including blood pressure, heart rate, respiratory rate, pulse oxygen, and peak flows, were obtained before each injection. Injections were only given to asthmatic patients if peak flows were 80% or more of personal best. The entire protocol was performed in the allergy clinic, which was hospital based and equipped to treat anaphylactic events. A physician provided direct oversight of each rush patient and determined whether cessation of the protocol was necessary due to systemic reactions (generally a grade 3–6 reaction, Table 1).

To establish efficacy, the protocol included an IFA sting challenge approximately 3 weeks after the rush procedure with a locally collected ant. Intravenous access was again obtained, and vital signs were measured at baseline and 15, 30, 60, and 120 minutes

Table 3
Postrush immunotherapy schedule

Protocol day	Dose	Concentration, wt/vol ^a
8	0.25 mL twice simultaneously in left and right arms	1:100
15	0.5 mL	1:100
22	IFA sting challenge	
29	0.5 mL	1:100
50	0.5 mL	1:100
Monthly	0.5 mL	1:100

Abbreviation: IFA, imported fire ant.

^a1:100 wt/vol = 1:1 vol/vol.

Table 4
Description of reactions

Age, y/sex	Initial reaction grade	Positive skin test reactivity, wt/vol ^a	Rush reaction dose, wt/vol ^a	Rush reaction grade	Rush reaction symptoms
Group 1 (No Premedication)					
24/F	4	1:1,000 IDT ^b	0.15 mL 1:1,000	5	Nausea, tachycardia, chest tightness
33/F	6	1:1,000,000 IDT ^b	0.15 mL 1:1,000	5	SOB, throat scratchiness
26/M	6	1:1,000 IDT	0.05 mL 1:100	3	Pruritus
30/F	6	1:1,000,000 IDT	0.2 mL 1:100	3	Pruritus
29/M	3	SPT	0.3 mL 1:100	3	Pruritus
27/F	3	1:1,000,000 IDT	0.3 mL 1:100	3	Delayed urticaria
48/F	6	1:1,000,000 IDT	0.3 mL 1:100	3	Urticaria
32/M	3	SPT	0.3 mL 1:100	3	Urticaria
22/M	6	SPT	0.3 mL 1:100	3	Pruritus
43/F	5	1:10,000 IDT ^b	Sting challenge	4	Nasal and ear congestion
Group 2 (Premedication)					
32/F	5	1:1,000,000 IDT	0.15 mL 1:1,000	5	Chest pain, SOB, flushing
24/F	6	SPT	0.05 mL 1:100	5	Rhinorrhea, SOB
34/F	6	1:1,000,000 IDT	0.05 mL 1:100	6	Dizziness, urticaria, throat closing
37/F	3	SPT	0.2 mL 1:100	3	Pruritus

Abbreviations: IDT, intradermal test; SOB, shortness of breath; SPT, skin prick test.

^a1:100 wt/vol = 1:1 vol/vol.

^bReacted during skin testing.

after the sting. All patients demonstrated competency regarding indication and use of an epinephrine autoinjector (EpiPen) before discharge.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 17 (SPSS Inc, Cary, North Carolina). Reaction data were analyzed using χ^2 tests or Fisher exact tests, if appropriate, to determine significance of associations. Demographic characteristics were compared using either χ^2 tests or *t* tests.

Results

Thirty-eight patients began the 1-day rush protocol between May 2004 and January 2008 without premedication (group 1), and 42 patients began between February 2008 and October 2011 with premedication (group 2). In total, 96 patients were originally enrolled during this 7-year period. Several patients were lost to follow-up for a variety of reasons (eg, travel, military relocation, job change, changed their mind, and systemic reactions). One patient in group 1 had received the first 6 doses on the initial rush day without adverse reaction before having to leave because of a family emergency. He was later placed on a conventional schedule and was not included in any of the analyses. No patients withdrew from the study or had their dose adjusted as a result of large local reactions. The age range for the remaining 37 patients in group 1 was 18 to 49 years (mean age, 30.1 years), consisting of 13 women (35.1%) and 24 men (64.9%). The age range for the 42 patients in group 2 was 18 to 50 years (mean age, 34 years), and there were 26 women (61.9%) and 16 men (38.1%). The initial sting reaction for the 37 patients in group 1 was 11 with grade 3 reactions, 2 with grade 4 reactions, 8 with grade 5 reactions, and 16 with grade 6 reactions. The initial sting reaction for the 42 patients in group 2 was 18 with grade 3 reactions, 2 with grade 4 reactions, 9 with grade 5 reactions, and 13 with grade 6 reactions. For the 36 patients in group 1, the initial level of skin test positivity included 11 patients to the 1:1,000 (wt/vol) SPT, 9 to the 1:1,000,000 (wt/vol) IDT, 7 to the 1:100,000 (wt/vol) IDT, 4 to the 1:10,000 (wt/vol) IDT, and 5 to the 1:1,000 (wt/vol) IDT. For the 42 patients in group 2, the initial level of skin test positivity consisted of 13 patients to the 1:1,000 (wt/vol) SPT, 17 to the 1:1,000,000 (wt/vol) IDT, 6 to the 1:100,000 (wt/vol) IDT, 3 to the 1:10,000 (wt/vol) IDT, and 1 to the 1:1,000 (wt/vol) IDT. One additional patient in group 1 and 2 additional patients in group 2 had positive IFA WBE ImmunoCAP

results (13.2 kU/L in the group 1 patient and 18.2 kU/L and 8.03 kU/L in the group 2 patients).

Six patients experienced reactions during skin testing (SPT and IDT) with only 1 (group 2) proceeding through RIT and sting challenge without incident. Two of these patients developed systemic reactions during RIT (group 1), 1 reacted to the sting challenge (group 1), and 2 (both in group 2) refused to continue the study after their SPT reaction. Overall, 28 of 37 (75.7%) of the patients in group 1 and 38 of 42 (90.5%) of the patients in group 2 completed the RIT protocol without systemic reaction. As seen in Table 4, 9 of the 37 patients in group 1 (24.3%; 95% confidence interval, 10.5%–38.1%) and 4 of the 42 patients in group 2 (9.5%; 95% confidence interval, 6.9%–12.1%) experienced a systemic reaction during RIT. All reactions occurred the day of the rush protocol and, more specifically, were subdivided into the following groups: group 1 consisted of 7 grade 3 reactions and 2 grade 5 reactions, and group 2 included 1 grade 3, 2 grade 5, and 1 grade 6 reactions. Antihistamines, epinephrine, inhaled β -agonist, and oral steroids were administered for some but not all reactions as determined to be medically appropriate by the caregiver.

Of the 66 patients who completed the 1-day RIT without a systemic reaction, 54 consented to a sting challenge on day 22 of the protocol. Only 1 of these patients experienced a reaction after the sting challenge, which consisted of only nasal and ear congestion. This was similar to her reaction after her positive IDT result at 1:10,000 (wt/vol). Her immunotherapy maintenance dose was subsequently doubled to 1 mL of 1:100 wt/vol IFA WBE, and she has had no additional field stings. Fifty-two sting challenges resulted in immediate cutaneous wheal-and-flare responses only followed by a characteristic pustule, suggesting adequate sting and development of tolerance (efficacy, 98%). All ants were later reviewed by an entomologist and confirmed to be *S. invicta*. In addition, multiple patients who successfully completed the protocol later reported IFA stings without evidence of additional systemic effects. One individual presented for a sting challenge; however, the collected ant would not sting and was later confirmed to be *Crematogaster laeviuscula*. This patient, however, received several field stings at a later date without sequelae.

Discussion

This 1-day RIT protocol using IFA WBE was efficacious (1 of 53 confirmed IFA sting challenges [1.9%] resulted in a reaction) and had a low rate of systemic reactions. Premedication with antihistamines and prednisone reduced the SRR from 24.3% to 9.5%. Although this

reduction did not reach statistical significance ($P = .07$), we believe this finding to be clinically significant. The use of premedication has been supported by prior studies with both aeroallergen^{21–23} and flying Hymenoptera RIT.^{24–26} Particularly, oral antihistamines used before venom RIT produced a significant reduction in urticaria, angioedema, and pruritis,^{24–26} which constituted most reactions (7 of 9 [77.8%]), causing cessation of the protocol in group 1.

The efficacy of this study mirrors that of a prior 2-day IFA RIT protocol that resulted in 98.2% clinically negative sting challenge results,¹⁵ as well as a conventional build-up schedule that resulted in a reaction in only 1 of the 47 patients (97.9% efficacy) assessed.¹² Safety is an obvious concern with RIT protocols; however, the SRR of 9.5% using antihistamines and prednisone prophylactically appears to reduce the SRR to that near the prior 2-day IFA RIT protocol. This previously published 2-day protocol revealed a SRR of 3.6% (1 of 28 patients) in those who received pretreatment, and 6.7% (2 of 30 patients) in those who did not ($P = .87$).¹⁵ The SRR in the group 2 premedication cohort surprisingly appears to mimic that seen with conventional IFA immunotherapy schedules, recently reported in the Imported Fire Ant Field Reaction and Immunotherapy Safety Characteristics study to be 9.1%.¹³ All reactions responded to treatment, with only 1 of the 13 reactions classified as grade 6 (group 2). Furthermore, the reaction graded as the most severe did not include any respiratory symptoms and consisted of urticaria, dizziness, and angioedema. One reaction in group 2 required 4 doses of epinephrine to treat nasal congestion, rhinorrhea, globus, dyspnea, and flushing; however, most reactions that required epinephrine responded to a single dose. Several patients reported subjective symptoms only and did not require epinephrine, yet they were still included in the SRR data report and transitioned to a conventional build-up. Protocol cessation was managed extremely conservative in an effort to provide a schedule that would be both feasible and comfortable for practicing allergists in an office setting.

Surprisingly, IFA immunotherapy, despite its life-saving capability, is often disrupted by patient adherence. Logistical challenges are reported as inhibitory reasons for not initiating immunotherapy or reaching therapeutic maintenance immunotherapy doses. In addition to reaching a maintenance dose far more rapidly, RIT provides a convenient and cost-effective option for many patients. Most patients given the choice between conventional (3–6 months), 2-day, or 1-day schedules chose the latter based on reduced time away from work and travel costs. Although our patients do not require copayments, this might also be a reason for a patient to choose a 1-day RIT schedule for IFA hypersensitivity.

A unique characteristic of IFAs in endemic areas, compared with flying Hymenoptera, is how difficult it is to effectively maintain sting avoidance.⁵ Reducing the time to reach protective IFA immunotherapy dosing offers much needed patient reassurance and potentially reduces the morbidity and mortality associated with future field stings. Participants who reacted during the 1-day RIT protocol were able to advance to maintenance considerably faster even when compared with the alternative of a conventional schedule. This finding was due to the observation that 7 of 9 reactions (77.8%) in group 1 and 3 of 4 reactions (75%) in group 2 occurred in the final 1:100 (wt/vol) maintenance vial. Convenient and rapid IFA immunotherapy advancement may be particularly important given that recent research indicates only 71% of patients follow recommendations to start and at 1 year only 35% remain adherent, with logistical constraints reported as a significant impediment.²⁷ Although not used in this study, a prospective RIT study has demonstrated a significant decrease in the occurrence of local reactions (>3 cm) being significantly delayed by montelukast but not by desloratadine.²⁸ For patient comfort during RIT, premedication with montelukast might be considered.

In conclusion, a 1-day IFA WBE RIT protocol is effective and, when accompanied with premedications, demonstrates similar

safety to conventional build-up. This study addresses practice parameter recommendations for further studies to clarify the risk of fire ant RIT and a consideration for premedication.²⁹ As with all immunotherapy, the risks, benefits, and alternative therapy options should be discussed and individualized to the patient and practice. This study, spanning a period of 7½ years, is the longest and largest prospective IFA immunotherapy study to date. Given high sting rates in endemic areas and ecosystem-driven territorial expansion,³⁰ IFA RIT protocols are a valuable means to provide efficient morbidity reduction.

Acknowledgments

We thank Anneke C. Bush, ScD, MHS, for assistance with statistical analysis of the data. In addition, great appreciation goes to Chad P. McHugh, MPH, PhD, and Keith W. Blount, PhD, for their entomology expertise. We acknowledge the contributions made by and the dedication of Steven Nguyen, MD, to this study and also to the US Air Force for many years, and we dedicate this article to his memory.

References

- Freeman TM. Hymenoptera hypersensitivity in an imported fire ant endemic area. *Ann Allergy Asthma Immunol*. 1997;78:369–372.
- Dietrich JJ, Quinn JM, England RW. Reasons for outpatient consultation in allergy/immunology. *Allergy Asthma Proc*. 2009;30:69–74.
- Letz AG, Quinn JM. Frequency of imported fire ant stings in patients receiving immunotherapy. *Ann Allergy Asthma Immunol*. 2009;102:303–307.
- deShazo RD, Griffing C, Kwan TH, Banks WA, Dvorak HF. Dermal hypersensitivity reactions to imported fire ants. *J Allergy Clin Immunol*. 1984;74:841–847.
- Tracy JM, Demain JG, Quinn JM, Hoffman DR, Goetz DW, Freeman TM. The natural history of exposure to the imported fire ant (*Solenopsis invicta*). *J Allergy Clin Immunol*. 1995;95:824–828.
- Strom GB, Boswell RN, Jacobs RL. In vivo and in vitro comparison of fire ant venom and fire ant whole body extract. *J Allergy Clin Immunol*. 1983;72:46–53.
- Stafford CT, Moffitt JE, Bunker-Soler A, Hoffman DR, Thompson WO. Comparison of in vivo and in vitro tests in the diagnosis of imported fire ant sting allergy. *Ann Allergy*. 1990;64:368–372.
- Partridge ME, Blackwood W, Hamilton RG, Ford J, Young P, Ownby DR. Prevalence of allergic sensitization to imported fire ants in children living in and endemic region of the southeastern United States. *Ann Allergy Asthma Immunol*. 2008;100:54–58.
- Rhoades RB, Stafford CT, James FK. Survey of fatal anaphylactic reactions to imported fire ant stings. *J Allergy Clin Immunol*. 1989;84:159–162.
- Rupp MR, deShazo RD. Indoor fire ant sting attacks: a risk for frail elders. *Am J Med Sci*. 2006;331:134–138.
- More DR, Kohlmeier RE, Hoffman DR. Fatal anaphylaxis to indoor native fire ant stings in an infant. *Am J Forensic Med Pathol*. 2008;29:62–63.
- Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol*. 1992;90:210–215.
- La Shell MS, Calabria CW, Quinn JM. Imported fire ant field reaction and immunotherapy safety characteristics: the IFACS study. *J Allergy Clin Immunol*. 2010;125:1294–1299.
- Forester JP, Johnson TL, Arora R, Quinn JM. Systemic reaction rates to field stings among imported fire ant-sensitive patients receiving >3 years of immunotherapy versus <3 years of immunotherapy. *Allergy Asthma Proc*. 2007;28:485–488.
- Tankersley MS, Walker RL, Butler WK, Hagan LL, Napoli DC, Freeman TM. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. *J Allergy Clin Immunol*. 2002;109:556–562.
- Moffitt JE, Barker JR, Stafford CT. Management of imported fire ant allergy: results of a survey. *Ann Allergy Asthma Immunol*. 1997;79:125–130.
- Golden DBK, Moffitt JE, Nicklas R, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol*. 2011;127:852–854.
- Duplantier JE, Freeman TM, Bahna SL, Good RA, Sher MR. Successful rush immunotherapy for anaphylaxis to imported fire ants. *J Allergy Clin Immunol*. 1998;101:855–856.
- Judd CA, Parker AL, Meier EA, Tankersley MS. Successful administration of a 1-day imported fire ant rush immunotherapy protocol. *Ann Allergy Asthma Immunol*. 2008;101:311–315.
- Dietrich JJ, Moore LM, Nguyen S, Hagan L, Tankersley MS. Imported fire ant hypersensitivity: a 1-day rush immunotherapy schedule without premedication. *Ann Allergy Asthma Immunol*. 2009;103:535–536.
- Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush

- immunotherapy with mixtures of allergenic extracts. *Ann Allergy Asthma Immunol*. 1994;73:409–418.
- [22] Hejjaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol*. 1992;89:925–933.
- [23] Nielsen L, Johnson CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 1996;97:1207–1213.
- [24] Brockow K, Kiehn M, Riethmüller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 1997;100:458–463.
- [25] Berchtold E, Maibach R, Müller U. Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy*. 1992;22:59–65.
- [26] Reimers A, Hari Y, Müller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy*. 2000;55:484–488.
- [27] Stokes SC, Quinn JM, Sacha JJ, White KM. Adherence to imported fire ant subcutaneous immunotherapy. *Ann Allergy Asthma Immunol*. 2013;110:165–167.
- [28] Wohrl S, Gamper S, Hemmer W, Heinze G, Stingl G, Kinaciyan T. Premedication with montelukast reduces local reactions of allergen immunotherapy. *Int Arch Allergy Immunol*. 2007;144:137–142.
- [29] Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1–S55.
- [30] Kemp S, deShazo R, Moffitt J, Williams D, Buhner W. Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern. *J Allergy Clin Immunol*. 2000;105:683–691.