

# Systemic reaction rates to field stings among imported fire ant-sensitive patients receiving >3 years of immunotherapy versus <3 years of immunotherapy

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## ABSTRACT

As imported fire ants (IFAs) expand their range, hypersensitivity reactions to their stings are becoming a significant cause of morbidity and mortality in the United States. Currently, IFAs whole body extract (WBE) immunotherapy is the mainstay of treatment for IFA hypersensitivity but the optimal duration of treatment is unknown. A questionnaire was administered to patients diagnosed with IFA venom hypersensitivity based on history and the presence of IFA venom-specific IgE who had been offered immunotherapy. The patients were grouped into those who received  $\geq 3$  years of immunotherapy and those who received <3 years of immunotherapy. Forty of the 272 patients initially identified were successfully contacted (14%) with 6 patients being excluded. Of these patients, 19 reported having received <3 years of IFA immunotherapy (reduced course) and 15 stated they had been given >3 years of immunotherapy (complete course). Subsequent field stings were reported by 18 (95%) of the reduced course groups and 14 (93%) of the complete course group with 1 person from each group (6 and 7%, respectively) experiencing a systemic reaction. There were no significant differences between the two groups in the number of patients with subsequent field stings or systemic reactions after subsequent IFA stings. Less than 3 years of IFA immunotherapy may offer long-term protection against IFA hypersensitivity reactions although additional studies with more subjects and controls are necessary before definitive conclusions may be made.

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**Key words:** Allergen, desensitization, duration of immunotherapy, field sting, hypersensitivity reactions, immunotherapy, imported fire ant, long-term protection, venom, whole body extract

Imported fire ants (IFAs) were introduced into the United States through the port of Mobile, AL, in the early 1900s from South America.<sup>1</sup> *Solenopsis richteri* (black IFA) colonies have remained confined mostly to northeastern Mississippi and northwestern Alabama and *Solenopsis invicta* (red IFA) colonies have spread outside of the southern United States and now affect areas from Puerto Rico to as far west as California and as far east as Washington, D.C.<sup>2,3</sup> The attack rate in areas infested with IFAs has been reported at >50%.<sup>4</sup> With the continued spread of IFAs throughout a large part of the United States, the risk of IFA stings with subsequent anaphylactic or

systemic reactions becomes a significant health concern.

Along with the high rate of IFA stings in endemic regions, hypersensitivity reactions to the stings are becoming a significant cause of morbidity and mortality in the United States. In the United States, 14 million people are stung by IFAs annually and one-quarter of these people will develop some level of sensitivity to IFA venom.<sup>5</sup> A survey of 29,300 physicians in 1989 performed by the Fire Ant Subcommittee of the American Academy of Allergy and Immunology revealed 32 deaths secondary to reactions from IFA stings.<sup>6</sup> A more recent study found as many as 44 deaths from IFA stings reported in the literature over a 50-year period.<sup>7</sup>

Currently, aside from strict avoidance, the only available therapy to decrease the incidence of IFA hypersensitivity reactions is immunotherapy with IFA whole body extract (WBE). Immunotherapy with IFA WBE has been shown to be effective in both conventional immunotherapy<sup>8,9</sup> and rush immunotherapy regimens.<sup>3</sup> Currently, the optimal length of treatment with IFA immunotherapy is not known and no definitive recommendation about the duration of immunotherapy for fire ants was made in the "Stinging Insect Hypersensitivity: A Practice Param-

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Table 1 Results

|                                           | Mean Age at<br>Start of<br>Immunotherapy<br>(Range) | Mean Length<br>of<br>Immunotherapy | Mean Time<br>Since<br>Immunotherapy<br>Discontinuation | No. of Patients<br>with Subsequent<br>Field Stings (%) | No. of<br>Patients with<br>Subsequent<br>Systemic<br>Reactions (%) |
|-------------------------------------------|-----------------------------------------------------|------------------------------------|--------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------|
| Reduced course group<br>( <i>n</i> = 19)  | 34 years (5–75)                                     | 1.47 yr*                           | 7.21 yr                                                | 18 (95)                                                | 1 (6)                                                              |
| Complete course group<br>( <i>n</i> = 15) | 41 years (3–65)                                     | 5.53 yr*                           | 6.80 yr                                                | 14 (93)                                                | 1 (7)                                                              |

Reduced course group, <3 yr of IFA immunotherapy; complete course group, >3 yr of IFA immunotherapy.

\**p* < 0.05.

eter Update" from 2004.<sup>10</sup> However, the length of treatment with IFA immunotherapy commonly used often is 3–5 years based on extrapolation from flying Hymenoptera immunotherapy data. A 3- to 5-year course of flying Hymenoptera (e.g., honey bee, hornet, wasp, and yellow jacket) venom immunotherapy (VIT) has been shown to provide protection against systemic reactions to stings in 85–90% of cases for up to 13 years after stopping VIT.<sup>11–16</sup>

Large long-term studies regarding the efficacy of IFA immunotherapy after completion of a complete course are limited. The purpose of our study was to provide more information regarding the natural history of IFA hypersensitivity both with and without at least 3 years of IFA immunotherapy.

## METHODS

A retrospective chart review identified patients that had been evaluated for a reaction to an IFA sting between 1984 and 2000 at a military medical center located in San Antonio, TX. Patients that were diagnosed with IFA venom hypersensitivity based on a history of anaphylaxis to IFA sting and the presence of IFA-specific IgE on skin testing or *in vitro* serum testing who had been offered immunotherapy were contacted *via* telephone. Questions/topics answered by patients during the telephone survey included description and date of IFA sting reaction that prompted allergy evaluation, recommendations made by Allergist, immunotherapy history, and field sting history after immunotherapy.

Patients were grouped into those who received <3 years (reduced course) and those who received ≥3 years (complete course) of IFA immunotherapy. All subjects on IFA immunotherapy received a maintenance dose of 0.5 mL of a 1:100 w/v concentration of IFA WBE. Those patients who were still receiving IFA immunotherapy or had never received IFA im-

munotheapy were excluded. The responses to the telephone survey of the two groups were compared using standard univariant analyses. The local Institutional Review Board approved this study.

## RESULTS

Successful contact was made with 40 (14%) of the 272 patients that were offered IFA immunotherapy. The reduced and complete course groups contained 19 and 15 patients, respectively. Six patients, who were contacted, were excluded from the comparison (three patients were still receiving immunotherapy and three patients had never received immunotherapy). Reduced course group patients received an average of 1.47 years of immunotherapy versus 5.53 years in the complete course group (*p* < 0.05). The average length of time since discontinuing immunotherapy was 7.2 years for the reduced course group compared with 6.8 years in the complete course group (*p* > 0.05). Subsequent stings were experienced by all but one patient from each group after the discontinuation of immunotherapy. One patient from each group (6% of reduced and 7% of complete course) reported a systemic reaction after subsequent sting. The reactions were described as respiratory distress by the reduced course patient and angioedema by the complete course patient and both patients reported them as being not as severe as their initial reaction. There were no significant differences in any of the groups' characteristics or outcomes studied other than the length of treatment (Table 1). The two groups were similar in the type and severity of their reported initial reactions. In the reduced course group, 9 of the 19 patients reported a multi-system reaction and 8 of the 15 patients from the complete course group reported a multisystem reaction during their initial event.

## DISCUSSION

Very little is known about the natural history of IFA venom hypersensitivity and the long-term effectiveness of IFA immunotherapy. An abstract by Motta *et al.* evaluated 17 subjects who had received IFA immunotherapy for 2–19 years with a sting challenge performed at least 3 months after the discontinuation of IFA immunotherapy and found that 16 of the 17 subjects (94%) had no reaction.<sup>17</sup> Additionally, an abstract by Quinn *et al.* evaluated nine subjects who had received IFA immunotherapy for 15 months to 20 years with a sting challenge performed a mean of 57 months after the discontinuation of IFA immunotherapy and found that none of the nine subjects had a systemic reaction.<sup>18</sup> Although these studies did establish the long-term efficacy of IFA immunotherapy, they did not evaluate the effects of duration of treatment on long-term efficacy.

More is known about winged Hymenoptera VIT. A study conducted by Reisman and Lantner<sup>14</sup> found that 2 years of VIT may be as effective at preventing resting systemic reactions as >2 years of VIT. In contrast, Lerch and Müller<sup>12</sup> reported that VIT duration of at least 5 years gives improved long-term protection compared with a 3-year course. However, given that the optimal length of IFA immunotherapy for IFA venom hypersensitivity is not known, our questionnaire-based investigation attempted to compare outcomes among patients that received a complete course of IFA immunotherapy to patients that received <3 years of immunotherapy.

Our observational study was conducted among U.S. military personnel and their family members. This is a highly mobile population and the ability to contact them was limited, which resulted in a very low contact rate (14%) and small sample size ( $n = 34$ ). Obviously, the small number of subjects is a significant limitation in this study. The mobility of this group explains why some of the patients surveyed (reduced group,  $n = 19$ ) received <3 years of immunotherapy. Other reasons cited for not receiving a complete course of immunotherapy include retirement/separation from the military, noncompliance with schedule, other illness, and pain associated with injections. A selection bias may have occurred for those patients that tolerated future stings and were comfortable with staying in an IFA endemic area whereas patients who were not able to be contacted may have moved to avoid future stings. The study is also limited by recall bias as well as reliance on patient history both of which are inherent in studies using patient survey evaluations. We only recorded whether patients had experienced a field sting after immunotherapy and did not quantify the number or assess timing of the stings.

We found no difference in the incidence or severity of systemic reactions to field stings after immunotherapy discontinuation for the two groups studied. In fact, the systemic reaction rate was low for both the complete and the reduced course groups (7 and 6%, respectively) after discontinuation of IFA immunotherapy. This study does reinforce that IFA resting rate is high (over 93% in study population) and that avoidance is difficult and unreliable even in patients that have had a prior systemic reaction.

Because our population has been followed for ~7 years after treatment with IFA immunotherapy longer-term protection outcomes remain unknown. Although no recommendations on treatment can be made based on our findings because of the small number of subjects, these results do add to the uncertainty regarding the optimal duration of IFA immunotherapy. This study highlights the need for more evidence to support current practices and that additional prospective studies with larger numbers of patients and controls are needed to determine if <3 years of IFA immunotherapy should be considered.

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