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# Imported fire ant immunotherapy prescribing patterns in a large health care system during a 17-year period

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**Background:** No large evaluation has been performed of the maintenance vial concentration commonly used by physicians when prescribing imported fire ant (IFA) immunotherapy since the publication of the first Stinging Insect Hypersensitivity Practice Parameter 10 years ago.

**Objective:** To describe the prescribing patterns for IFA immunotherapy among practicing allergists in a large health care setting and the impact of published Practice Parameter recommendations.

**Methods:** Data from the US Army Centralized Allergen Extract Laboratory were analyzed to determine IFA immunotherapy prescribing patterns from 1990 to May 2007. This extract laboratory provides prescriptions for more than 320 US Department of Defense, US Department of Veterans Affairs, and US Public Health Service clinics.

**Results:** A total of 1,091 patients were given 1,437 new or revised prescriptions for IFA immunotherapy. Monotherapy for *Solenopsis invicta* and *Solenopsis richteri* was prescribed in 169 (11.8%) and 3 (0.1%) instances, respectively, with the remainder of patients given both IFA antigens. The most commonly prescribed maintenance vial dose was 0.5 mL of a 1:200 (wt/vol) dilution, accounting for 36.3% of prescriptions. A total of 17.3% of prescriptions had a maintenance vial dose of 0.5 mL of a 1:100 (wt/vol) dilution, 4.6% had a dilution of 1:10 (wt/vol), and 50.6% had a dilution between 1:10 and 1:100 (wt/vol). The mean starting dose was 4.4 10-fold dilutions below the maintenance dose (5.4 vials per treatment set).

**Conclusions:** The most commonly prescribed maintenance dose was 0.5 mL of a 1:200 (wt/vol) dilution, although most prescriptions used a maintenance dose consistent with recommended dosing in the Stinging Insect Practice Parameters. Both IFA antigens were used by most physicians. Further study evaluating the effective dose range for IFA immunotherapy is needed.

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## INTRODUCTION

Imported fire ant (IFA) stings are an important cause of hypersensitivity reactions in endemic areas.<sup>1,2</sup> IFA whole body extract (WBE) immunotherapy, although not a standardized extract, is the only currently available medical therapy that can modify the natural history of the disease and provide protection to patients from serious reactions on resting.

The efficacy of IFA WBE immunotherapy has not been demonstrated in randomized controlled trials as has been done for venom immunotherapy of the winged Hymenoptera.<sup>3,4</sup> However, in the studies that exist, IFA WBE appears to have an efficacy of approximately 97%,<sup>5–8</sup> which is similar to the efficacy of venom immunotherapy.

In the studies demonstrating the efficacy of IFA WBE, the maintenance vial concentration was in the range of 0.5 mL of a 1:10 to 1:100 (wt/vol) dilution.<sup>5–8</sup> On the basis of these studies, the Stinging Insect Hypersensitivity Practice Param-

eters have recommended this same range of dosing for IFA immunotherapy.<sup>9,10</sup> The update to the Stinging Insect Hypersensitivity Practice Parameters also indicated that physicians could treat patients with either *Solenopsis invicta* alone or a mix of both *S invicta* and *Solenopsis richteri*.<sup>10</sup>

No large systematic evaluation of IFA immunotherapy prescribing patterns has been performed since before the first Stinging Insect Hypersensitivity Parameter Parameter was published 10 years ago. This study evaluated prescribing patterns for IFA WBE in a large health care system.

## METHODS

The US Army Centralized Allergen Extract Laboratory (USACAEL) provides immunotherapy prescriptions for more than 300 US Department of Defense, US Department of Veterans Affairs, and US Public Health Service clinics. Approximately 20,000 new and refill prescriptions are filled via an electronic prescribing system each year (Extract Lab Management System).

The first prescriptions for IFA immunotherapy evaluated began in October 1990. At this time the stock vial concentration was 1:10 (wt/vol) aqueous product as a mix or individual IFA antigens (Hollister-Stier, Spokane Washington). In July 2002, the USACAEL changed to a stock vial of 1:20 (wt/vol) glycerin product in its inventory (Greer, Lenoir, North Carolina).

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Data from the Extract Lab Management System were evaluated during the entire period of October 1990 through May 2007. The data were also evaluated with respect to dates of the Stinging Insect Hypersensitivity Practice Parameter publication and thus divided into 3 periods: (1) October 1990 through May 1999 (preparameter, period 1), (2) June 1999 through October 2004 (between parameters, period 2), and (3) November 2004 through May 2007 (postupdated parameter, period 3). The maintenance dose represents 0.5 mL of the maintenance concentration ordered. The study was performed under an approved institutional review board protocol.

Because of the nongaussian nature of the data, nonparametric methods were used to evaluate the data. The Kruskal-Wallis test was used for comparisons during the entire study period (all 3 intervals). The Mann-Whitney test was used for comparisons between periods. Prescriptions expressed in protein nitrogen units per milliliter ( $n = 3$ ) were excluded from analysis given the difficulty in comparing them to prescriptions expressed as weight/volume. The measures evaluated included the number of prescriptions, prescription order date, ordering facility, antigen(s) prescribed (*S invicta*, *S richteri*, or mix), concentration of maintenance vial, and number of vials in the treatment set.

## RESULTS

A total of 1,440 prescriptions for 1,092 patients were filled for IFA during the entire period studied. Prescriptions were filled from 121 sites, representing 28 states in the United States and 23 military facilities overseas. A total of 1,255 prescriptions (87%) were from states endemic for IFA. There were 139 unique prescriber numbers during the period evaluated, with a mean of 10 prescriptions per provider and a median of 3. A total of 1,265 prescriptions (88%) included both IFA antigens, and 169 (11.8%) contained *S invicta* alone. Three prescriptions were limited to *S richteri* antigen alone.

Among the prescriptions with both IFA antigens, 17 different maintenance concentrations were prescribed at least once, ranging from 1:10 (wt/vol) to 1:2,000 (wt/vol). Although 7 maintenance concentrations (1:10, 1:20, 1:40, 1:80, 1:100, 1:200, 1:400) represented 98% of prescriptions (Table 1), the prescriptions for *S invicta* monotherapy were more uniformly administered, with only 4 maintenance concentrations used, ranging from 1:20 (wt/vol) to 1:400 (wt/vol). The median and mode maintenance vial concentration was 1:100 (wt/vol), with a mean of 1:120 (wt/vol). Among the 3 periods, some changes in the maintenance concentration prescribed for *S invicta* monotherapy were observed (Table 2), although these were not evaluated statistically because of the relatively small number of prescriptions.

Among all prescriptions during the entire study period, the mean maintenance vial concentration was 1:160 (wt/vol), with a median of 1:100 (wt/vol) and a mode of 1:200 (wt/vol). From a previous study, 0.5 mL of a 1:10 (wt/vol) dilution has been estimated to contain 15 to 22  $\mu$ g of IFA

Table 1. Maintenance Vial Concentration of Imported Fire Ant Prescriptions During a 17-Year Period

| Maintenance vial concentration <sup>a</sup> | Pre-parameter | Between parameter | Post-updated parameter | Total        |
|---------------------------------------------|---------------|-------------------|------------------------|--------------|
| 1:10                                        | 66            | 0                 | 0                      | 66           |
| 1:20                                        | 122           | 23                | 0                      | 145          |
| 1:40                                        | 64            | 94                | 6                      | 164          |
| 1:80                                        | 0             | 62                | 30                     | 92           |
| 1:100                                       | 161           | 52                | 35                     | 248          |
| 1:200                                       | 98            | 300               | 123                    | 521          |
| 1:400                                       | 10            | 152               | 9                      | 171          |
| <b>Total</b>                                | <b>521</b>    | <b>683</b>        | <b>203</b>             | <b>1,407</b> |

<sup>a</sup> Maintenance vial concentration of the 7 most commonly prescribed concentrations, representing 1,407 of 1,440 prescriptions (98%).

Table 2. Maintenance Vial Concentration of *Solenopsis invicta* Monotherapy Prescriptions

| Maintenance vial concentration | Pre-parameter | Between parameter | Post-updated parameter | Total      |
|--------------------------------|---------------|-------------------|------------------------|------------|
| 1:20                           | 7             | 0                 | 0                      | 7          |
| 1:40                           | 1             | 0                 | 0                      | 1          |
| 1:100                          | 63            | 35                | 22                     | 120        |
| 1:200                          | 0             | 28                | 13                     | 41         |
| <b>Total</b>                   | <b>71</b>     | <b>63</b>         | <b>35</b>              | <b>169</b> |

protein.<sup>11</sup> A total of 50.6% of prescriptions had a maintenance concentration in the range of 1:10 to 1:100 (wt/vol). A total of 521 prescriptions (36%) had a maintenance vial concentration of 1:200 (wt/vol), 248 (17%) had a concentration of 1:100 (wt/vol), and 66 (5%) had a concentration of 1:10 (wt/vol). There were 5 prescriptions in which the maintenance vial concentration was less than 1:400 (wt/vol).

During the entire period, the mean starting concentration prescribed was 4.4 10-fold dilutions below maintenance. Thus, the mean number of vials per treatment set was 5.4, with a median of 5. For the preparameter interval (period 1), there were 534 prescriptions, representing 37% of the total. For the period between insect parameters (period 2), there were 696 prescriptions (48%), and for the postupdated parameter period (period 3), there were 207 prescriptions (15%).

Statistically significant differences were found in the mean maintenance concentration during the entire period ( $P < .001$ , Kruskal-Wallis test) and between each period (Fig 1):  $P < .001$  for period 1 vs 2,  $P < .001$  for period 1 vs 3, and  $P = .04$  for period 2 vs 3 (Mann-Whitney test). The mean, median, and 95% confidence interval for each period are included in Figure 1. The mode for the maintenance concentration was 1:100 (wt/vol) for period 1 and 1:200 (wt/vol) for periods 2 and 3.

In evaluating prescribing patterns during the 3 periods of interest, all the 1:10 (wt/vol) maintenance vial prescriptions were prescribed in period 1, before 1998. The 1:20 (wt/vol)

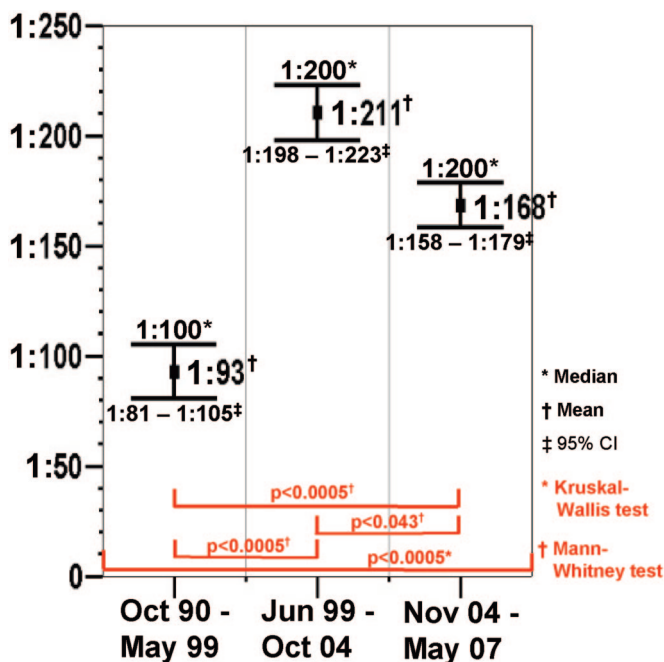


Figure 1. Maintenance vial doses during the 3 periods: (1) October 1990 through May 1999 (preparameter, period 1), (2) June 1999 through October 2004 (between parameter, period 2), and (3) November 2004 through May 2007 (postupdated parameter, period 3). Doses are all 0.5 mL and in weight/volume. Statistically significant differences were found during the entire period ( $P < .001$ , Kruskal-Wallis test) and between each period:  $P < .001$  for period 1 vs 2,  $P < .001$  for period 1 vs 3, and  $P = .04$  for period 2 vs 3 (Mann-Whitney test). Error bars indicate 95% confidence intervals (CIs).

maintenance vial was not prescribed after 2002, so that beginning in 2003 the highest maintenance vial concentration prescribed was 1:40 (wt/vol). The 1:100 (wt/vol) maintenance vial concentration was the only dilution used in each year of the study, although it represented a more significant proportion of prescriptions during period 1 compared with later periods. Beginning in 1998 (period 1), the frequency of 1:200 (wt/vol) maintenance concentration prescriptions increased significantly and became the most common concentration in periods 2 and 3.

## DISCUSSION

In this single large health care system, a wide variety of maintenance concentrations were used for IFA immunotherapy during the 17 years evaluated. During the period studied, there was a shift to more dilute maintenance concentrations. The changes in maintenance concentration were statistically different for all periods. During the preparameter period (period 1), the mean and median maintenance concentrations were within the current Practice Parameter recommendations of 1:10 to 1:100 (wt/vol). For periods 2 and 3, however, the mean and median maintenance concentrations fell outside current Practice Parameter recommendations.

No large systematic evaluation has been performed of IFA immunotherapy prescribing patterns since the first Stinging Insect Hypersensitivity Practice Parameter was published 10 years ago. There were 2 surveys of IFA prescribing patterns before the Stinging Insect Hypersensitivity Practice Parameter publications.<sup>12,13</sup>

The first survey,<sup>12</sup> published in abstract form, had a response rate of 42% (42/100). Thirty-six respondents reported treating a total of 231 IFA allergic patients. The authors extrapolated total protein content from the survey data to determine the maintenance dose reported by physicians. The average maintenance dose was reported as 5.9  $\mu$ g (approximately 0.5 mL of a 1:30 [wt/vol] dilution). The median was not reported. The authors reported that 37 of 231 patients (16%) were receiving a maintenance dose of at least 22  $\mu$ g, although 59 of the 231 patients (26%) were receiving less than 2  $\mu$ g (approximately 0.5 mL of a <1:100 [wt/vol] dilution). Thus, approximately 58% of patients in this survey received between 2 and 22  $\mu$ g as their maintenance dose.

In the second survey<sup>13</sup> the response rate was 37% (329/879), with 268 respondents (82%) having evaluated IFA patients. The mean maintenance dose was 5.7  $\mu$ g. The most common (mode) and median maintenance concentration was 1:100 (wt/vol) (approximately 1.85  $\mu$ g). The next most commonly prescribed maintenance concentration was 1:10 (wt/vol). There were also a number of prescriptions for a maintenance concentration as dilute as 1:1,000 (wt/vol), so a significant range of dosing was also apparent in this survey.

Our data from the same period (period 1), before the Practice Parameter publication, are comparable to the data published in these 2 surveys. Because there is of paucity of information regarding IFA prescribing patterns since the Stinging Insect Hypersensitivity Practice Parameters were published, it is unclear if the trends seen in the current study are unique to our health care system. However, the results may provide some important insights regarding the maintenance doses commonly prescribed by practicing allergists since the Stinging Insect Hypersensitivity Practice Parameter publication.

Given the wide variation in maintenance concentrations prescribed for IFA immunotherapy evident in this and other surveys of practicing allergists, prospective studies are needed to better delineate the effective dosing range for patients with IFA hypersensitivity. In this regard, there is evidence of significant amounts of IFA venom in WBE, such that 0.5 mL of a 1:10 (wt/vol) concentration contains approximately 15 to 22  $\mu$ g of total venom protein.<sup>11</sup> A typical fire ant sting is thought to contain less than 1  $\mu$ g of venom protein.<sup>14</sup> One report indicated that the average number of stings from IFA is approximately 9,<sup>15</sup> and in another survey most cases of anaphylaxis occurred with fewer than 5 stings.<sup>16</sup> It would also be useful to standardize IFA WBE extracts, as is the case for other Hymenoptera. Thus, dosing recommendations could more reliably be given in micrograms rather than in maintenance vial concentration. From the available information,<sup>11</sup> if a maintenance dose for total

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IFA protein was extrapolated from the current recommendations in the Stinging Insect Hypersensitivity Practice Parameters, it would be in the range of 1.5 to 22  $\mu$ g.

Further study is also needed to evaluate differences in individual prescribing patterns, which may have contributed to the observed patterns. For example, where and when specialty training was performed, the number of years in practice, and other such factors may be important influences.

In conclusion, this is the first large systematic evaluation of IFA immunotherapy prescribing patterns since either of the Stinging Insect Hypersensitivity Practice Parameters was published. In this large health care system, the most commonly prescribed maintenance concentration for IFA immunotherapy was 1:200 (wt/vol). Further study is needed to confirm that this maintenance concentration is efficacious in IFA allergic patients.

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