



Imported fire ant immunotherapy prescribing patterns in a large health care system during an 11-year period

Robert H. Wauters, MD^{*}; Daniel I. Brooks, PhD[†]; David J. Schwartz, MD^{*}

^{*} Department of Allergy and Immunology, Walter Reed National Military Medical Center, Bethesda, Maryland

[†] Department of Research Programs, Walter Reed National Military Medical Center, Bethesda, Maryland

ARTICLE INFO

Article history:

Received for publication April 1, 2020.

Received in revised form June 8, 2020.

Accepted for publication June 8, 2020.

ABSTRACT

Background: The first large-scale evaluation of prescribing patterns for imported fire ant (IFA) in a large US health care system was published by Haymore et al in 2009. In this first evaluation of prescriptions from 1990 to 2007, the most often prescribed maintenance IFA prescription was 0.5 mL of 1:200 wt/vol.

Objective: To provide an updated description of IFA prescribing patterns over the ensuing 11 years from same large health care system.

Methods: We reviewed 1349 new IFA prescriptions written from 2007 to 2018, from a large nationwide health care system, with primary end points being maintenance prescription strength and prescribing patterns.

Results: In comparison to the data published by Haymore et al in 2009, which reported that 17% of the prescriptions were written for 0.5 mL of 1:100 wt/vol maintenance, we found that 69% (95% CI: 66.4%–71.4%) of IFA prescriptions written in the past 11 years were for the maintenance concentration of 0.5 mL of 1:100 wt/vol. We further studied the linear trend over time of percentage of prescriptions written for individual concentrations and observed that the percentage of 1:100 wt/vol prescriptions increased 3.5% yearly ($R^2 = 0.68$, $P < .001$) from 2007 (40.0%, 95% CI: 24.6%–57.7%) to 2018 (84.4%, 95% CI: 77.4%–89.5%).

Conclusion: Our study shows significant improvement in the accuracy and precision of IFA immunotherapy dosing for patients with IFA hypersensitivity, with ascendancy of 0.5 mL 1:100 wt/vol as the predominant treatment dose. A total of 87% of patients within our study were treated within the parameter recommendations, a stark improvement from findings in the 2009 Haymore study.

Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

Introduction

The name imported fire ant (IFA) refers to *Solenopsis invicta* and *Solenopsis richteri*, the red and black fire ant, respectively. These species originated in South America and then were introduced to the United States through Mobile, Alabama, in the 1920s. Envenomation by IFA is the most frequent cause of hypersensitivity reactions in endemic areas.¹ As of January 2020, more than 367,000,000 square acres in 14 states (Alabama, Arkansas, California, Florida, Georgia, Louisiana, Mississippi, New Mexico, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia) and Puerto Rico have been determined to be endemic with IFA infestation by the United States Department of Agriculture.² Having specific immunoglobulin E to IFA is 1.7 times

more common in endemic areas than sensitization to other allergens associated with anaphylaxis in the same study population.³ Moreover, 35.7% of patients aged 2–5 years and 57.5% aged 11–20 years living in IFA endemic areas in the United States have sensitization to IFA, which is likely attributable to the IFA high attack rate of 30% to 60% per year in these regions.^{3,4} The avoidance of IFA in endemic areas is extremely difficult. As such, the management of patients with IFA hypersensitivity should center on whole-body extract (WBE) immunotherapy. Unlike immunotherapy for flying hymenoptera, IFA WBE is not standardized. However, it is the only treatment modality that is disease modifying and provides lasting protection to sensitized patients. There is a dearth of data from randomized controlled trials examining the efficacy of IFA WBE immunotherapy. However, the studies that have sought to evaluate efficacy report WBE to be up to 97% effective in reducing local reactions or preventing systemic symptoms after field stings and observed sting challenges.^{5,6}

The Stinging Insect Hypersensitivity Practice Parameter was first published in 1999, with updates in 2004, 2011, and 2016. All parameter iterations report 0.5 mL of 1:10 to 1:100 wt/vol as the

Reprints: Robert H. Wauters, MD, Department of Defense, Walter Reed National Military Medical Center, Allergy/Immunology Clinic BLD 19, 8901 Wisconsin Avenue, Bethesda, MD 20889-5600; E-mail: Robert.H.Wauters.mil@mail.mil.

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2020.06.013>

1081-1206/Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

most commonly used maintenance range for IFA WBE immunotherapy dosing.^{7–10} The most recent 2016 parameter update states that 0.5 mL of 1:200 wt/vol IFA WBE immunotherapy was the most commonly prescribed maintenance dose. This assertion is consistent with the findings in the only large systemic evaluation of IFA immunotherapy dosing by Haymore et al¹¹ which was published in 2009.

Knowing that previous studies have yielded a broad range of maintenance concentrations for IFA immunotherapy despite consistent parameter recommendations for 0.5 mL of 1:10 wt/vol to 1:100 wt/vol, we sought to evaluate if the maintenance dose of IFA immunotherapy has migrated toward parameter recommendations since the study by Haymore et al¹¹ was published. In addition, we analyzed IFA immunotherapy dosing trends in both endemic and nonendemic states over that same time to determine if significant differences in prescribing patterns exist between prescribers in the 2 areas.

Methods

The US Army Centralized Allergen Extract Laboratory (USACAEL) provides immunotherapy prescriptions for the Veteran's Administration, US Public Health Service, and Department of Defense, serving active-duty military service members, their family members, and military retirees. Approximately 30,000 new and refill immunotherapy prescriptions are processed each year by the USACAEL through the electronic extract lab management system. We reviewed 1349 new USACAEL IFA prescriptions written from 2007, picking up where the study by Haymore et al left off, through December 2018. Refills of preexisting prescriptions and refills of prescriptions initiated during the study period were excluded from this study so that each patient's treatment course was only counted once in our calculations. Our primary end points were maintenance prescription dose and the maintenance dose prescribed by physicians in endemic vs nonendemic areas.

The stock vial concentration of the IFA extract was 1:20 wt/vol (Greer Labs, Lenoir, North Carolina) throughout the entirety of our study. During the 2007–2018 time period being investigated in this study, updates to the stinging insect practice parameters were released in 2011 and 2016. These updates did not include significant changes to the reported maintenance dosing schedule for IFA immunotherapy.^{9,10} The maintenance dose is representative of a 0.5-mL injection of the maintenance concentration ordered in the extract lab management system. Concentration calculations included all prescriptions regardless of whether they were mixed IFA or monotherapy with 1 species of IFA. Our study was executed under an approved institutional review board protocol.

Data analysis was completed in R (R Core Team, Vienna, Austria). Alpha was set at 0.05 for all analyses. To analyze the increase in 1:100 prescriptions over time, we used a linear model because the trend was sufficiently linear over the studied period. To compare the distribution of prescriptions in endemic and nonendemic states, we used the Wilcoxon rank-sum test.

Results

A total of 1394 new prescriptions for IFA immunotherapy were reviewed. Prescriptions were filled by 156 unique providers from 95 locations representing 30 US states and 6 military treatment facilities outside the United States. During our study period, we identified 14 different maintenance concentration strengths ranging from 1:20 wt/vol to 1:400 wt/vol (Fig 1). The mean IFA immunotherapy concentration in our study was 1:87 wt/vol. Most prescriptions (89.6%) contained IFA for both *S. invicta* and *S. richteri*, but a small fraction received treatment for just *S. invicta* (10.2%). A negligible fraction (N = 3, 0.2%) received treatment for *S. richteri* alone.

The most common IFA maintenance concentration was 1:100 wt/vol, which occurred in 69% of the prescriptions (N = 930). Other

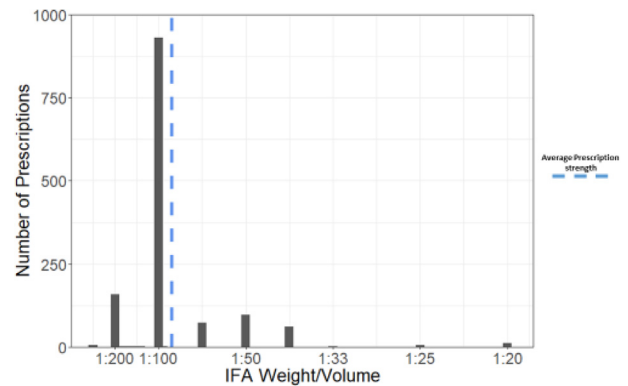


Figure 1. Number of prescriptions. IFA, imported fire ant.

notable, though less frequently prescribed, maintenance dose concentrations included 1:200 (12%, N = 158), 1:50 (7%, N = 97), 1:66 (5%, N = 74), and 1:40 (4.5%, N = 61). To evaluate the trend of this maintenance prescription over time, we calculated the percentage of prescriptions in each year that were written at 1:100 wt/vol and modeled the change in those prescriptions as a function of year (Fig 2). That analysis revealed a significant ($P < .001$) year-over-year increase in 1:100 wt/vol prescriptions of approximately 3.53% (95% CI: 1.94%–5.12%) per year across the 11 years. That model is not improved by an additional factor that delineates epochs into the dates of published practice patterns (2007–2011, 2012–2016, 2017–2018), though this is unsurprising given the small number of epochs and strong linear trend year over year.

A total of 1086 (81%) IFA immunotherapy prescriptions were written in states listed as endemic by the United States Department of Agriculture for IFA (Fig 3). Average prescription strengths in the nonendemic states were significantly ($P < .001$) less concentrated (1:99 wt/vol) than those in endemic states (1:84.45 wt/vol) (Fig 3). Although this trend was consistent throughout the entire study period, it was significantly attenuated during the later years of the study (2017–2019) after the most recent practice parameter update, as prescription strengths in both endemic (1:94.97) and non-endemic (1:105.8) states migrated toward 0.5 mL of 1:100 wt/vol.

Discussion

The Stinging Insect Hypersensitivity Practice Parameter was first published in 1999, with updates in 2004, 2011, and 2016. All iterations of the parameters suggest a maintenance IFA immunotherapy concentration of 0.5 mL of 1:10 wt/vol to 1:100 wt/vol.

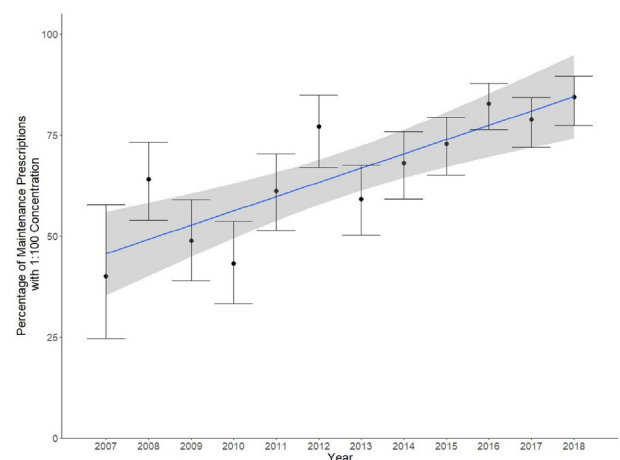


Figure 2. Percentage of maintenance prescriptions with 1:100 concentration.

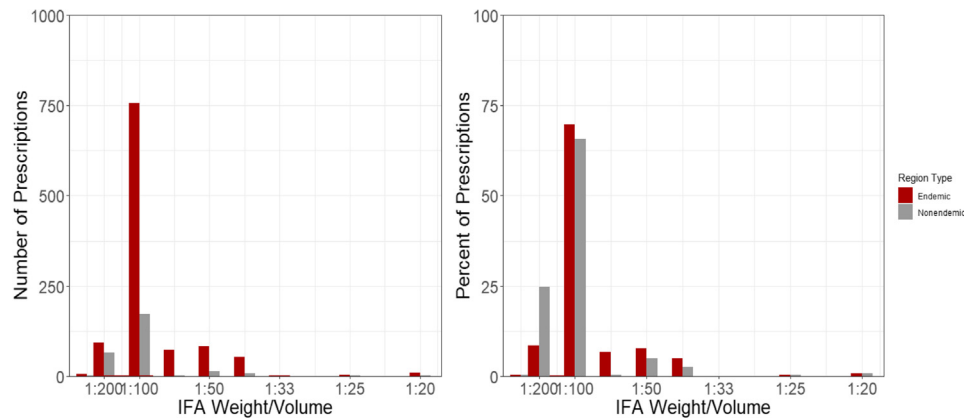


Figure 3. Number of prescriptions. IFA, imported fire ant.

Despite this, the most recent Stinging Insect Hypersensitivity Practice Parameter, published in 2016, states that 0.5 mL of 1:200 wt/vol is the most commonly prescribed maintenance concentration in a survey of practicing allergists, which is consistent with the findings of the study by Haymore et al.^{10,11} Our study sought to evaluate if change in the prescribing practices in the same large nationwide health care system occurred from 2007 to 2018 and if changes were more consistent with the published practice parameter guidelines. Our research demonstrates ascendancy of 0.5 mL 1:100 wt/vol maintenance IFA immunotherapy as the predominant treatment for IFA hypersensitivity. The most common IFA maintenance concentration in our study was 1:100 wt/vol, which occurred in 69% of prescriptions (N = 930), as compared with only 17% (N = 248) in the study by Haymore et al.¹¹ This observed migration toward the parameter recommended dosing is an encouraging finding in our large systematic observational study. Over the 20 years since the first Stinging Insect Hypersensitivity Practice Parameter was published, a vast array of different IFA immunotherapy prescriptions has been noted.¹¹ Our study identified 14 different maintenance concentration strengths ranging from 1:20 wt/vol to 1:400 wt/vol, a narrower range than was identified in the study by Haymore et al.¹¹ which reported a range of 1:10 wt/vol to 1:2000 wt/vol. The mean IFA immunotherapy concentration in our study was 1:87 wt/vol vs the more dilute 1:160 wt/vol noted in the study by Haymore et al.¹¹ During our study period, 87% (N = 1180) of the patients were being treated with IFA prescriptions written within parameter recommendations, vs 51% (N = 715) in the study by Haymore et al.¹¹

The strengths of our study include a large study population of 1349 new IFA VIT prescriptions. In addition, the high number of prescribing allergists from medical centers inside and out of endemic areas in diverse geographic regions across the United States and abroad, which are accounted for in our study, makes this one of the largest and diverse studies to look at IFA immunotherapy prescribing to our knowledge.

The weaknesses of our study include our data being deidentified, which precludes evaluation of demographic information in our patient population. All refill prescriptions were eliminated from our study, but it is not possible to know if a new prescription being evaluated in our study was written to mitigate an ineffective first prescription based on field sting experience, which could skew data toward a more concentrated average. It is impossible to tell from our data whether the trend we are observing is due to consistently published parameter recommendations, simply a product of time, or a combination of the two. Finally, we must acknowledge that these are observational data, and it may be too soon to recommend other allergists change their prescribing patterns based on our research.

Our study shows significant improvement in both the accuracy and precision of IFA immunotherapy maintenance dosing for patients with IFA hypersensitivity, with ascendancy of 0.5 mL 1:100 wt/vol maintenance IFA immunotherapy as the predominant treatment dose. When all prescription strengths are considered, we found that 87% (N = 1180) of patients within our study period were being treated within the consistently recommended dosing range based on practice parameters, which is a stark improvement from the previous study of this same population.¹¹ It remains unclear whether the consistent recommendations on dosing ranges in the practice parameters or time are the driving factors of this observation. Regardless of a causal relationship, the authors found these trends encouraging. Despite these promising findings, it must be noted that prescription concentrations did remain on the dilute end of the reported dosing range. Our institutional review board–approved protocol plans to look at outcomes associated with different final maintenance concentrations for IFA immunotherapy as far as both field stings and treatment reactions during buildup and at maintenance. This is an area wherein there is an extreme paucity of data to guide clinical care decisions, and further research is warranted. The authors believe that our findings are extrapolatable to practicing allergists in the civilian community. We suggest that all allergists prescribing WBE for the treatment of IFA hypersensitivity evaluate their prescribing practices to ensure that they are falling within current practice parameter recommendations. We are encouraged and optimistic that outcomes data in our cohort may help guide future dosing parameter recommendations.

Acknowledgments

We thank Sue Kosisky, Lorne McCoy, and Dr Michael Nelson for their expertise and support on this project.

References

- Freeman TM. Hymenoptera hypersensitivity in an imported fire ant endemic area. *Ann Allergy Asthma Immunol*. 1997;78(4):369–372.
- United States Department of Agriculture. Imported fire ants. Available at: https://www.aphis.usda.gov/aphis/ourfocus/planthealth/plant-pest-and-disease-programs/pests-and-diseases/imported-fire-ants/ct_imported_fire_ants. Accessed March 3, 2020.
- Caplan EL, Ford JL, Young PF, Ownby DR. Fire ants represent an important risk for anaphylaxis among residents of an endemic region. *J Allergy Clin Immunol*. 2003;111(6):1274–1277.
- Partridge ME, Blackwood W, Hamilton RG, Ford J, Young P, Ownby DR. Prevalence of allergic sensitization to imported fire ants in children living in an endemic region of the southeastern United States. *Ann Allergy Asthma Immunol*. 2008;100(1):54–58.
- 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(3):556–562.

6. Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol*. 1992;90(2):210–215.
7. Portnoy JM, Moffitt JE, Golden DB, et al. Stinging insect hypersensitivity: a practice parameter. The Joint Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):963–980.
8. Moffitt JE, Golden DBK, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol*. 2004;114(4):869–886.
9. Golden DBK, Moffitt JE, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol*. 2011;127(4):852–854.e23.
10. Golden DBK, Demain J, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol*. 2017;118(1):28–54.
11. Haymore BR, McCoy RL, Nelson MR. Imported fire ant immunotherapy prescribing patterns in a large healthcare system during a 17-year period. *Ann Allergy Asthma Immunol*. 2009;102(5):422–425.