

Adherence and systemic reaction rates to allergy immunotherapy among veterans

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ABSTRACT

Background: Although allergen immunotherapy (AIT) is effective and safe, nonadherence is common. Limited data exist regarding adherence to AIT, factors that affect adherence, and systemic reactions associated with AIT among veteran populations.

Objective: To evaluate adherence to AIT and the prevalence of reactions secondary to AIT among patients at the Veterans Affairs Medical Center, Memphis, Tennessee.

Methods: A retrospective chart review was performed of veterans who received AIT at a single Veterans Affairs facility. Age, race, sex, the total number of shots, travel distance, a diagnosis of posttraumatic stress disorder (PTSD), and the number of severe adverse reactions were compared between the veterans who were adherent and veterans who were nonadherent.

Results: The overall adherence rate was 60.9%. Factors associated with adherence were a chart diagnosis of PTSD (29.3% [adherent group] versus 13.6% [nonadherent group]; $p = 0.03$) and home residence being a further distance from the facility (21.9 miles / 35.2 kilometers [adherent group] versus 18.0 miles / 28.9 kilometers [nonadherent group]; $p = 0.03$). Patients who were adherent received an average of more total injections compared with patients who were nonadherent. Age, sex, race, and history of systemic reactions during AIT displayed no statistically significant differences between the groups. There were a total of 20 systemic reactions, and the systemic reaction rate was 0.2% per AIT encounter and 0.1% per injection.

Conclusion: AIT adherence and systemic reaction rates among veterans at our facility was comparable with similar studies. Adherence was associated with a chart diagnosis of PTSD and home residence that was further away from the clinic.

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Allergy immunotherapy (AIT) is a safe, effective, and disease-modifying treatment modality for allergic rhinoconjunctivitis, allergic asthma, and atopic eczema; however, adherence is critical for success. Adherence difficulties to AIT have been well documented, with adherence rates that vary from 13% to 89%.¹ In addition, as many as 40% of patients fail to adhere to health care providers' recommended treatments when therapy is prophylactic or suppressive, or when dealing with chronic medical conditions, which thus provides a challenge to patients who undergo AIT for 3 to 5 years.^{2,3}

Previous studies identified younger age, inconvenience, residence change, adverse systemic reactions, and precluding medical conditions as reasons for AIT nonadherence.^{4–7} However, limited data exist regarding adherence to AIT, factors that affect adherence, and

adverse reactions associated with AIT among veteran populations. Our objective was to evaluate adherence rates to AIT, identify factors that affect adherence, and determine the systemic reaction rates and associated clinical manifestations among patients who receive AIT at the Memphis Tennessee Veterans Affairs Medical Center (MTVAMC).

METHODS

A retrospective chart review was performed of veterans for whom AIT was prescribed from 2009 to 2015 at MTVAMC. Inclusion criteria were veterans who received AIT at our facility. Excluded from the study were those who were scheduled to begin AIT but never received their first dose or veterans who received AIT at an outside facility. Adherence was defined as patients who received >50% of the recommended number of injections or completed at least 5 years of AIT. The recommended number of injections was defined as follows: ≥ 10 injections within the first 3 months of AIT initiation, ≥ 20 injections within the first 6 months of initiation, ≥ 30 injections within the first year of AIT, and ≥ 12 injections annually between years 1 and 5. Nonadherence was defined as patients who had received at least one injection and had stopped AIT without approval of their allergist or patients who received <50% of the recommended interval doses as mentioned above.

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Table 1 Descriptive statistics of veterans on allergen immunotherapy

	All Patients (N = 151)	Adherent Group (n = 92)	Nonadherent Group (n = 59)	p Value*
Age, mean (SD), y	53.4 ± 10.9	54.0 ± 11.2	52.6 ± 10.7	0.57#
Men, %	69.5	70.7	67.8	0.72§
Race, %				
White	35.8	35.9	35.6	1.00§
Black	61.6	61.9	61.0	
Other	2.6	2.2	3.4	
Injections, no. (IQR)	69 (30–142)	112 (60–171)	18 (8–60)	<0.001#
Systemic reaction, no. (%)	19 (12.6)	11 (12.0)	8 (13.6)	0.80§
PTSD diagnosis, no. (%)	35 (23.2)	27 (29.3)	8 (13.6)	0.03§
Distance to clinic, median (IQR), miles	21.1 or 33.9 km (14–38)	21.9 or 35.2 km (16–46)	18.0 or 28.9 km (10–29)	0.03#

SD = Standard deviation; IQR = interquartile range; PTSD = posttraumatic stress disorder.

*Compares adherent vs nonadherent groups.

#Mann-Whitney test.

§Fisher's exact test.

Age (measured as a continuous variable), race, sex, total number of injections, travel distance (measured *via* a continuous variable in miles from their home to MT-VAMC *via* Google Maps), chart diagnosis of posttraumatic stress disorder (PTSD), and the number of severe adverse reactions were compared between the veterans who were adherent and veterans who were nonadherent. Systemic reactions and their clinical manifestation after AIT were recorded and classified per the World Allergy Organization 2010 grading system (grade 1–5).⁸ The number of emergency epinephrine injection requirements also was recorded. The study was approved by the institutional review board at MTVAMC. Statistical analysis was done by using GraphPad Prism software version 6 (GraphPad Software, Inc., La Jolla, CA). Dichotomous variables were compared by using Fisher's exact test, and continuous variables were compared by using the Mann-Whitney test.

RESULTS

A total of 198 charts of veterans who were prescribed AIT were identified. Forty-seven veterans were excluded because they never received their first AIT shot or because their AIT administration took place at another medical facility. A total of 151 veterans who received AIT from our facility were analyzed. Overall, the adherence rate among the 151 patients in AIT was 60.9%. The median age of those who received AIT was 54 years, and 69.5% were men. The majority were African American (61%), and 35.8% were white. Thirty-five patients (23.2%) were found to have a chart diagnosis of PTSD. Statistically significant factors associated with adherence were a chart diagnosis of PTSD (29.3% [adherent group] versus 13.6% [nonadherent

group]; $p = 0.03$), living at further distances from our facility (21.9 miles / 35.2 kilometers [adherent group] versus 18.0 miles / 28.9 kilometers [nonadherent group]; $p = 0.03$), and received more injections (median of 112 injections [adherent group] compared with median of 18 injections [nonadherent group]; $p < 0.001$). Age, sex, race, and history of systemic reactions during AIT displayed no statistically significant differences between the adherent and nonadherent groups. (Table 1)

There were a total of 20 systemic reactions among 19 patients of a total of 7485 AIT visit encounters and 13,063 injections. Systemic reaction rates were 0.2% per encounter and 0.1% per injection. Epinephrine was administered on 12 occasions among the 20 systemic reactions. Per the World Allergy Organization 2010 grading system there were five grade 1 reactions, fourteen grade 2 reactions, one grade 3 reaction, and no grade 4 or grade 5 reactions. (Fig. 1) The most observed clinical manifestations in those who experienced a systemic reaction were generalized cutaneous findings (75%) (pruritus, urticaria, flushing) and respiratory symptoms (55%) (cough, dyspnea, wheeze). Twenty percent of the systemic reactions were associated with angioedema, 15% were associated with upper airway pruritus and throat clearing, 10% were associated nausea, and 5% were associated with speech difficulty and oropharyngeal edema. (Fig. 2)

DISCUSSION

In this retrospective study, we analyzed adherence to AIT in a single veteran population. Our adherence rate of 60.9% among these veterans who received AIT in the Memphis area was comparable with the only other study that looked specifically at patients who received

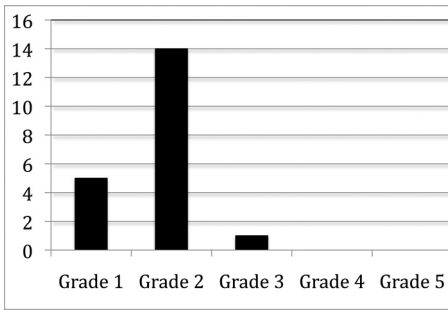


Figure 1. Allergen immunotherapy (AIT) systemic reactions. The AIT systemic reactions per the World Allergy Organization Grading System (Ref. 8) in our veteran population. The number of patients is on the y-axis and World Allergy Organization grade is on the x-axis.

AIT in a Veterans Affairs facility.⁷ In that study, which examined adherence at the West Los Angeles Veterans Affairs Medical Center, Guenechea-Sola *et al.*⁷ reported a 63.5% adherence rate to AIT.

Despite the clinical value of immunotherapy, patient adherence is often very low, and adherence rates vary greatly, which likely reflects varying methodologies used to define adherence as well as the diverse and undefined populations that have been studied. For example, a review of 12 studies (6 subcutaneous immunotherapy, 5 sublingual immunotherapy, and 1 nasal immunotherapy) reported adherence rates that ranged from 27 to 97%.⁹ More and Hagan⁵ described an overall AIT compliance rate of 77% at a military medical center and deemed adherence rates on whether the patient had received at least one AIT injection over a 3-month period. Another study that compared both subcutaneous immunotherapy and sublingual immunotherapy showed overall attrition rates of both forms to approach 50%.¹⁰ Our study defined adherence similarly to Guenechea-Sola *et al.*⁷ because that study also examined a Veterans Affairs population. Thus, we aimed to provide some level of consistency in defining and measuring adherence in the veteran population.

In our patient population, patients who were adherent were more likely to have had a chart diagnosis of PTSD, lived a further distance from the clinic, and

received a higher number of total injections. Factors of age, race, sex, or history of systemic reactions were not associated with better AIT adherence. These findings were somewhat unique because multiple studies demonstrated an association between AIT nonadherence and patient characteristics that include younger age,^{5,7,11} government insurance,¹² minority race,¹³ systemic reactions, cost, and lack of insurance.¹⁴

To our knowledge, this was the first study to display statistically significant data on AIT adherence and a chart diagnosis of PTSD (29.3% [adherent group] compared with 13.6% [nonadherent]) and the second study to provide correlation between mental health disorders and adherence rates. The other comparable veterans' adherence study found a trend toward better adherence rates in patients with PTSD and/or general psychiatric disorders, but results were not statistically significant.⁷ Better AIT adherence rates among patients with PTSD may be explained by the fact that these individuals were followed up closely by our mental health colleagues and already have more frequent follow-up, which thus promotes better AIT adherence.

As expected, patients who were adherent received an average of more total injections (median, 112 total injections) than patients who were nonadherent (median, 18 injections), which reiterated that fewer injections were a direct result of patient nonadherence. However, contrary to logical thought, patients who were adherent actually lived farther from the clinic (21.9 miles / 35.2 kilometers) on average than patients who were nonadherent (18.0 miles / 28.9 kilometers), which could be attributable to these individuals having a greater allergic disease burden versus greater treatment commitment. However, one could argue that the 4-mile (6.4 kilometer) difference is not "real-world" relevant.

Understanding risk factors for nonadherence to AIT is a first step in improving patient care. Bender and Lockey,¹⁵ recently reported that communication models, including patient-centered care, shared decision making, and motivation interviewing, can be used to help improve immunotherapy adherence. Thus, perhaps focusing these efforts on patients at "high risk" for nonadherence can better use resources.

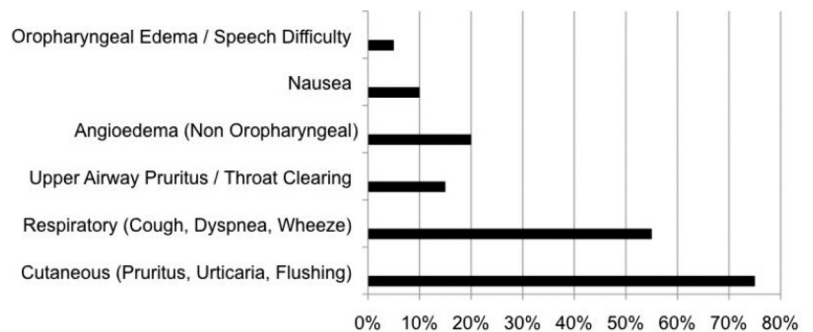


Figure 2. Clinical manifestations observed in systemic reactions after allergen immunotherapy (AIT); the clinical manifestation percentages among the veterans who experienced systemic reactions after AIT.

A total of 20 systemic reactions among 19 patients, 7485 AIT visit encounters, and 13,063 injections occurred from 2009 to 2015 at our Veterans Affairs facility. Our systemic reaction rates of 0.1% per injection and 0.2% per AIT visit encounter were comparable with previous AIT systemic reaction surveillance studies.^{16,17} The majority of systemic reactions in our veteran population were mild, and epinephrine was only given on 12 occasions over 20 systemic reactions. No fatalities or intubations occurred, and, per the World Allergy Organization 2010 grading system, most reactions were grade 1 or 2.⁸ Generalized cutaneous findings and respiratory symptoms were the most observed clinical manifestations in those patients who experienced severe adverse reactions, followed by angioedema, nausea, and oropharyngeal edema with speech difficulty. These results continue to demonstrate that, although systemic reactions are always a possibility, subcutaneous AIT is a safe treatment modality used to combat atopic diseases states.

Several limitations to our retrospective study that examined veterans who received AIT and who experienced systemic reaction rates exist. It would have been beneficial to parse out veterans with a diagnosis of asthma who received AIT because this has been associated with previous AIT systemic reaction rates.¹⁸ Moreover, it would have been noteworthy to evaluate the veteran's perception of AIT efficacy on symptom improvement with a comparison of adherence rates because one would expect a greater adherence rate with efficacy of therapy.

CONCLUSION

AIT continues to be an effective therapy that is disease modifying, but its success relies heavily on adherence and avoidance of systemic reactions. In our veteran patient population, patients who were adherent were more likely to have a chart diagnosis of PTSD and to live a further distance from the clinic. We stand a greater chance for AIT treatment success if we can better identify factors that affect adherence and embrace better communication models with our patients. Further larger veteran population studies are needed to evaluate trends observed in this study.

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