
The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction

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Background: Even though no studies have shown that local reactions to immunotherapy injections predict subsequent systemic reactions, many protocols continue to call for dose adjustments after local reactions.

Objective: To determine whether the rate of systemic reactions to immunotherapy injections is affected by dose adjustment after local reactions.

Methods: In our clinic before March 1999, if a patient had a local reaction to an immunotherapy injection, an adjustment was made to repeat or reduce the next dose. From March 1999 on, no such adjustments were made. At our outlying clinics, the adjustment protocol continued. A retrospective review was conducted for shots given from March 1997 to February 2001, recording whether an immunotherapy visit resulted in a systemic reaction.

Results: In our clinic, there were 3,250 shot visits from March 1997 to February 1999 (adjustment protocol) and 4,692 visits from March 1999 to February 2001 (no adjustment protocol). The systemic reaction rate during the 2 periods was not different (1.11% vs 0.85%, $P = .29$). In the outlying clinics, there were 1,138 shot visits from March 1999 to February 2001 (adjustment protocol), and the systemic reaction rate was not different than in our clinic (no adjustment protocol) (0.88% vs 0.85%, $P = .86$).

Conclusions: The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is adjusted after a local reaction. These dose adjustments are thus unnecessary, and eliminating them lessens chances for errors and decreases the number of shots required to reach a therapeutic dose.

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INTRODUCTION

Allergen immunotherapy is an effective treatment for allergic rhinitis, allergic asthma, and allergic reactions to stinging insects.¹ Since the therapy involves the injection of substances to which the patient is allergic, there is a small risk of a systemic reaction (anaphylaxis) with each injection.² Another common adverse effect of the shots is local swelling at the injection site.^{3,4} It has been assumed that such a local reaction would increase the risk of a systemic reaction with a subsequent injection.^{5,6} However, data available from previous studies suggest that systemic reactions to immunotherapy injections are not predicted by previous local reactions.^{3,4} Current practice parameters for allergen immunotherapy state, “Published studies do not indicate that large local reactions are always predictive of subsequent systemic reactions. Nevertheless, in the experience of some experts, a correlation between large local reactions and subsequent systemic reactions can be made in some patients.”⁶ When an immunotherapy injection causes a local reaction, many shot

protocols have continued to call for a decrease in the next dose in an attempt to prevent a systemic reaction. Therefore, this study sought to determine whether the rate of systemic reactions to immunotherapy injections is affected by abandoning a protocol whereby the dose was repeated or reduced after a local reaction in favor of a protocol where no such dose adjustments were made.

METHODS

Some active duty service members, all dependents of active duty service members, and all military retirees undergoing allergen immunotherapy in our area receive their immunotherapy injections at the Allergy Clinic, San Diego, CA. Other active duty service members have their immunotherapy injections administered at outlying military medical clinics by personnel trained at the Allergy Clinic.

In February 1999, an unpublished abstract (later published by Tankersley et al⁴) was presented at the annual meeting of the Association of Uniformed Services Allergist-Immunologists. The abstract concluded that local reactions to immunotherapy injections do not predict systemic reactions. Based on this study, a change in the immunotherapy injection protocol was made at our Allergy Clinic. Before March 1999, if a patient had a local reaction to an immunotherapy injection, an adjustment was made to repeat or reduce the next dose according to an established protocol. Under this adjustment protocol, a local reaction with swelling of dime to nickel size called for the dose to be repeated, swelling nickel to quarter

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size called for a reduction in the next dose to the equivalent of the last dose that had caused no reaction, and swelling larger than quarter size called for the next dose to be reduced by 50%. From March 1999 on, a no adjustment protocol was instituted whereby no adjustment to the shot dose was made for local reactions. The outlying medical clinics continued to follow the adjustment protocol. Systemic reactions were defined throughout as any itching, redness, swelling, or frank hives distant from the injection site, any allergic rhinitis or asthma symptoms, any gastrointestinal symptoms, or any lightheadedness.

Separate immunotherapy injection records, which indicate the date of each shot and any reaction the patient had to each shot, are maintained for immunotherapy patients. After approval by the Institutional Review Board of Naval Medical Center, San Diego, a retrospective immunotherapy injection record review was conducted for shots given from March 1, 1997, to February 28, 2001 (ie, from 2 years before the change in protocol was made until 2 years after). The number of shot visits was recorded. If more than 1 immunotherapy injection was given at a single visit, this was still counted as a single visit. Whether or not a given immunotherapy visit resulted in a systemic reaction was recorded.

All aeroallergen immunotherapy patients were following conventional as opposed to rush immunotherapy schedules. Typically, patients begin treatment with 1:100,000 (wt/vol) and progress through 1:10,000, 1:1,000, and 1:100 vials. The first dose from each vial is 0.05 mL, and the last dose from each vial is 0.5 mL. The increments of increasing doses between 0.05 and 0.5 mL are smaller, and thus the number of injections larger, as the strength increases. Most patients require a total of 23 weekly injections to reach a monthly maintenance dose of 0.5 mL (1:100). Most patients receive 2 shots per visit from 2 different vials, each containing approximately 10 different aeroallergens, including extracts of grass, tree and weed pollens, mold spores, cat, and house dust mites. Venom immunotherapy is given by a modified rush schedule, where patients achieve a maintenance dose of 100 µg in 6 weeks. Patients are not routinely given antihistamines or other treatment before injections. Patients are required to wait in the clinic for 30 minutes after injections. Patients who develop hives, itching, breathing difficulties, or lightheadedness are immediately evaluated and given epinephrine and

other treatment. Thus, reactions only rarely progress to hypotension or airway compromise.

The rate of systemic reactions was calculated for the Allergy Clinic from March 1, 1999, to February 28, 2001 (under the new no adjustment protocol), vs March 1, 1997, to February 28, 1999 (under the old adjustment protocol), and for the Allergy Clinic no adjustment protocol vs outlying clinics adjustment protocol during the same period from March 1, 1999, to February 28, 2001. The rate of systemic reactions was calculated as the number of shot visits that resulted in a systemic reaction divided by the total number of shot visits in a given period. The rates were compared using the Fisher exact test calculated by software available at <http://www.matforsk.no/ola/fisher.htm#INTRO> and <http://home.clara.net/sisa/fisher.htm>.

RESULTS

The rate of systemic reactions to immunotherapy injections for the Allergy Clinic from March 1, 1999, to February 28, 2001, under the new no adjustment protocol was not statistically different from the rate from March 1, 1997, to February 28, 1999, under the old adjustment protocol (0.85% vs 1.11%, $P = .29$) (Table 1). The rate of systemic reactions to immunotherapy injections for the Allergy Clinic under the no adjustment protocol was not statistically different from the rate at outlying clinics under the adjustment protocol during the same period from March 1, 1999, to February 28, 2001 (0.85% vs 0.88%, $P = .86$; Table 2).

Of the 76 total systemic reactions in the Allergy Clinic, 67 (88%) occurred during the buildup phase and 9 (12%) occurred at maintenance. Of the 76 total systemic reactions, 53 (70%) occurred in doses from the 1:100 (wt/vol) vial, 19 (25%) from the 1:1,000 vial, and 2 (3%) each from the 1:10,000 and 1:100,000 vials. A total of 405 (5%) of the overall 7,942 visits to the Allergy Clinic were for venom immunotherapy (197 of 3,250 visits under the adjustment protocol and 208 of 4,692 under the no adjustment protocol). Only 1 of the total 76 systemic reactions occurred in this group. The reaction occurred under the no adjustment protocol but was not preceded by a local reaction.

Table 1. Rate of Systemic Reactions to Immunotherapy Injections for the Allergy Clinic under the No Adjustment Protocol vs the Adjustment Protocol*

	Systemic reaction this shot visit	No systemic reaction this shot visit	Total shot visits	Systemic reaction rate per visit, %
No adjustment protocol	40	4,652	4,692	0.85†
Adjustment protocol	36	3,214	3,250	1.11†
Total study period	76	7,866	7,942	0.96

* The no adjustment protocol period was March 1, 1999, to February 28, 2001. The adjustment protocol period was March 1, 1997, to February 28, 1999. The total study period was March 1, 1997, to February 28, 2001.

† $P = .29$.

Table 2. Rate of Systemic Reactions to Immunotherapy Injections for the Allergy Clinic No Adjustment Protocol vs Outlying Clinics Adjustment Protocol during the Same Period (March 1, 1999, to February 28, 2001)

	Systemic reaction this shot visit	No systemic reaction this shot visit	Total shot visits	Systemic reaction rate per visit, %
Allergy clinic	40	4,652	4,692	0.85*
Outlying clinics	10	1,128	1,138	0.88*

* $P = .86$.

DISCUSSION

A 1986 study examined the incidence of local and systemic reactions at any time during immunotherapy.³ The timing of the local reactions relative to systemic reactions was not stated, so the study more addressed the issue of whether patients who tend to have local reactions to immunotherapy injections are the same ones who tend to have systemic reactions. The investigators found that 36% of patients who had a systemic reaction had never had a local reaction at any time and concluded that "prior local reaction may not be a useful guide to determine subsequent systemic reactions."

In 1996, the Joint Task Force Practice Parameters for Allergen Immunotherapy were published.⁵ The document referenced the 1986 study³ but nonetheless stated that efforts to "prevent anaphylactic reactions caused by allergen immunotherapy" should include "possible adjustment of extract dosage if large local reactions occur." A 2000 study examined the incidence of systemic reactions during a 9-month period when dosage adjustments were made for local reactions and a similar period when no such adjustments were made.⁴ The investigators found no difference in the rate of systemic reactions during these 2 periods and concluded that "local reactions during allergen immunotherapy do not require dose adjustment." A revision of the Joint Task Force Practice Parameters for Allergen Immunotherapy was published in 2003.⁶ This document references the 2000 study⁴ and states, "Published studies do not indicate that large local reactions are always predictive of subsequent systemic reactions. Nevertheless, in the experience of some experts, a correlation between large local reactions and subsequent systemic reactions can be made in some patients." When an immunotherapy injection causes a local reaction, many shot protocols have continued to call for a decrease in the next dose in an attempt to prevent a systemic reaction.

The current study has investigated the issue even more thoroughly. The bottom line for any protocol designed to minimize systemic reactions to immunotherapy injections must be the rate of such systemic reactions. When we abandoned our protocol whereby an immunotherapy injection dose was repeated or reduced after a local reaction in favor of a protocol where no such dose adjustments were made, the rate of systemic reactions remained unchanged. We had the additional advantage of examining the adjustment protocol vs no adjustment protocol during the same (simultaneous) period in the Allergy Clinic vs our outlying clinics and again

found no difference in the rate of systemic reactions whether or not dosage adjustments were made after local reactions.

A lingering concern expressed in the current Practice Parameters for Allergen Immunotherapy⁶ seems to indicate particular worry about "large" local reactions relative to subsequent systemic reactions. In the present study, although most systemic reactions (67 [88%] of 76) were not preceded by any local reaction at all, of the 9 that were, 2 of the local reactions were dime to nickel size, 5 were nickel to quarter size, and only 2 were larger than quarter size. Another lingering concern seems to indicate particular worry about "local reactions" (plural).⁶ In the present study, in the 9 cases where systemic reactions were preceded by local reactions, the 5 shot visits before the systemic reaction were also reviewed. In only 1 case had there been recurrent local reactions.

Based on the current study, we conclude that the rate of systemic reactions to immunotherapy injections is the same whether or not the dose is adjusted (repeated or reduced) after a local reaction. Eliminating these dose adjustments lessens chances for dosage errors and decreases the number of shots required to reach a therapeutic maintenance dose.

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