

Factors affecting time required to reach maintenance dose during subcutaneous immunotherapy

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Background: Subcutaneous immunotherapy (SCIT) demands a significant time commitment on the part of the patient, especially during the escalation period when weekly visits are required. Many patients refuse or discontinue treatment in spite of the demonstrated clinical efficacy of SCIT. Understanding the factors that affect the length of the escalation phase would allow for counseling of patients, which may improve patient compliance. The aims of this study were to determine the mean time required to reach maintenance dose during conventional protocol SCIT and to identify factors that significantly affect the time required to reach maintenance dose.

Methods: We conducted a retrospective chart review of 55 patients (total of 79 treatment vials) who began SCIT between January 2007 and December 2010 and reached maintenance dose. The effect of demographic data, medical and social history, and SCIT allergen data on the time required to reach maintenance dose were examined using bivariate and multivariate analyses.

Results: The mean time to maintenance dose for the 79 treatment vials was 240.2 days (range, 76–720 days). Males

(mean 294.7 days) took significantly longer than females (mean 205.1 days) to reach maintenance dose ($p = 0.007$). Asthmatics (mean 285.5 days) took significantly longer than nonasthmatics (mean 218.0 days) to reach maintenance dose ($p = 0.008$). Age also significantly affected the length of the escalation phase; each additional year of age was associated with an increase in 3.9 days needed to reach maintenance dose ($p = 0.002$).

Conclusion: Gender, asthma, and age significantly impact the time required to reach maintenance dose during SCIT. © 2012 ARS-AAOA, LLC.

Key Words:

allergen immunotherapy; time; maintenance dose; conventional protocol; specific hyposensitization; subcutaneous immunotherapy

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Inhalant allergies affect an estimated 20% to 30% of adults in the United States, and up to 40% of young children.¹ Treatment options include allergen avoidance and environmental modification, pharmacotherapy, and immunotherapy. Pharmacotherapy includes the use of antihistamines, topical nasal steroids, antileukotriene receptor antagonists, mast cell stabilizers, and, in some cases, systemic steroids or decongestants. For patients whose

symptoms remain uncontrolled despite avoidance strategies and pharmacotherapy, antigen-specific immunotherapy is advised.^{2–4}

Immunotherapy is commonly delivered through the subcutaneous route. Although the mechanism of immunotherapy is not completely understood, in vitro analysis has demonstrated a myriad of immunological changes that occur during hyposensitization; this includes an eventual reduction in specific immunoglobulin (Ig) E and an increase in IgG.⁵ In addition, immunotherapy modifies the peripheral and mucosal T cell response to allergens, shifting from a T helper 2 (Th2)-dominated response to a Th1-dominated response.⁶ Regardless of the true mechanism of action, subcutaneous immunotherapy (SCIT) has been established as an effective treatment for allergic rhinoconjunctivitis and allergic asthma, as reflected in diminishing skin, nasal, and bronchial reactivity to treated allergens.^{17–9}

Conventional SCIT begins with escalating doses of allergen extract, usually given at weekly intervals. This is continued until the maximum-tolerated, or maintenance,

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dose is reached. The maintenance phase usually lasts between 2 to 3 years, and injections are given at increased intervals.⁵ In spite of the demonstrated clinical efficacy of SCIT, many patients refuse treatment due to the inconvenient time-commitment associated with conventional SCIT.^{10–14} Due to this factor, several accelerated cluster protocols have been introduced in an attempt to reach the maintenance dose in less time.¹⁵ However, these protocols have not been widely adopted in the United States and Europe, likely due to safety concerns, despite recent studies suggesting otherwise.^{12,16}

With the ultimate goal of increasing patient compliance for SCIT, we chose to study the SCIT protocol itself. It is well known that the time required to reach maintenance dose during the escalation phase varies greatly from one patient to another. However, little is known about which factors may influence the time it takes to reach the maintenance dose. The specific aims of this study were to determine the mean time required to reach maintenance dose during conventional protocol SCIT and to identify factors that significantly affect the time required to reach maintenance dose.

Patients and methods

Study design

This study was a retrospective chart review of all patients who began SCIT from January 1, 2007 through December 31, 2010, under the care of the senior author (WRR) at the Department of Otolaryngology–Head and Neck Surgery at Weill Cornell Medical College in New York City. All of the research was conducted with the approval of the New York Presbyterian Hospital–Weill Cornell Medical College Institutional Review Board. Only those patients who had reached maintenance dose for at least 1 of their treatment vials by December 31, 2010 were included in the study.

SCIT

The initial concentration of each individual allergen to be included in the SCIT vial(s) was determined either through *in vitro* testing or a blended technique of epicutaneous and intradermal testing to a variety of allergens, including pollen, dust mites, epidermal proteins, and mold. Depending on the number of allergens being treated, it was decided whether or not to divide them into 2 separate treatment vials. The patients all received weekly injections of each treatment vial during the escalation phase, until the maintenance dose was reached, which was defined as the dose at which a 2.5-cm-diameter subcutaneous induration was seen at 20 minutes after the injection, or 0.5 mL from a 5 mL multidose vial containing 0.2 mL of all concentrated antigen was injected. This escalation phase began with a 0.05 mL injection of each vial, escalating by 0.05 mL each week. This process was continued for each vial until a maintenance

dose was reached, generally from a vial containing #1 dilution antigens (1:100 wt/vol) and concentrated antigen (1:20 wt/vol). Once the maintenance dose was reached, the interval between injections was increased to 2 weeks through the second year, then 3 to 4 weeks for the remainder of the treatment, for a total course of 3 to 5 years of SCIT.

Data collection

Each of the patients' charts was reviewed for the time that was required to reach maintenance dose for each individual treatment vial. Each individual treatment vial's characteristics were further analyzed for the number of allergens included, the number of antigen categories included (ie, trees, grasses, weeds), and the mean endpoint for antigens during intradermal testing. In addition, a comprehensive review of the charts was performed for the patients' demographic data (ie, gender, age), pertinent medical history (ie, asthma, chronic rhinosinusitis, polyposis), social history (ie, smoking and alcohol intake), a history of drug and food allergy, environmental factors (ie, pets at home), symptoms (conjunctivitis, nasal congestion, rhinorrhea, ear symptoms), a history of prior immunotherapy, and the use of topical or systemic pharmacotherapy during the escalation phase of SCIT.

Data analysis

All of the aforementioned factors were analyzed for their respective impact on the time required to reach maintenance dose for each individual vial. The null hypothesis was that each of the examined factors had no effect on the time required to reach the maintenance dose. Univariate analysis consisting of independent samples *t* test was performed for variables with ordinal values, whereas bivariate correlation analysis was performed for variables with nominal values; this was done initially to identify individual factors that potentially significantly influenced the time required to reach maintenance dose without controlling for the remaining variables being examined. These select significant factors were then used for a multivariate linear regression analysis to identify variables that significantly affected the time required to reach maintenance dose when controlling for the other factors being analyzed. Furthermore, univariate analysis consisting of independent samples *t* test was used to assess the effect of gaps in treatment and compliance for all significant variables. The *a priori* level of significance for the multivariate analysis was $p = 0.05$. All analyses were carried out in SPSS, version 19.0 (SPSS, Inc., Chicago, IL).

Results

A total of 55 patients were included in the study; 21 males and 34 females. The mean age was 35 years (range, 9–58 years of age) at the start of SCIT. Patient characteristics

TABLE 1. Patient characteristics

Characteristic	n	%
Total patients	55	100
Gender		
Female	34	61.8
Male	21	38.3
Asthma		
Yes	20	36.4
No	35	63.6
Chronic rhinosinusitis		
Yes	12	21.8
No	43	78.2
Polypsis		
Yes	8	14.5
No	47	85.5
Alcohol (≥ 1 drink/week)		
Yes	28	50.9
No	27	49.1
Smoking history		
Yes	15	27.3
No	40	72.7
Smoking during immunotherapy		
Yes	4	7.3
No	51	92.7
Drug allergies		
Yes	11	20.0
No	44	80.0
Food allergies		
Yes	15	27.3
No	40	72.7
Pets at home		
Yes	13	23.6
No	42	76.4
Prior immunotherapy		
Yes	16	29.1
No	39	70.9
Nasal congestion		
Yes	36	65.5
No	19	34.5
Rhinorrhea		
Yes	44	80.0
No	11	20.0
Eye symptoms		
Yes	20	36.4
No	35	63.6

(Continued)

TABLE 1. Continued

Characteristic	n	%
Ear symptoms		
Yes	9	16.4
No	46	83.6
Systemic treatment during immunotherapy		
Yes	28	50.9
No	27	49.1
Nasal steroids during immunotherapy		
Yes	28	50.9
No	27	49.1

are summarized in Table 1. Of the 55 patients included in the study, 31 patients (56.4%) were treated with a single vial of allergens and 24 patients (43.6%) required treatment with 2 allergen vials due to the number of allergens for which they were being treated. Thus, a total of 79 vials, all of which reached maintenance dose, were included in the study. None of the escalation phase injections were stopped prematurely due to systemic or local reactions.

Time to reach maintenance

The mean endpoint for allergens in each individual vial during intradermal testing (IDT) (prior to initiation of SCIT) was 3.69 (range, 1–5.5). The mean number of total allergens each patient was treated for was 7.6 (range, 1–15 total allergens). The mean number of allergens in each of the 79 treatment vials examined in the study was 5.30 (range, 1–9 total allergens). When the allergens were grouped into 1 of 7 categories (trees, grasses, weeds, molds, animal dander, dust mites, and cockroaches), the mean number of allergen categories included in each allergen vial was 3.1 (range, 1–5 total categories). The mean time to maintenance dose for the 79 treatment vials was 240.23 days (range, 76–720 days). An analysis of variance comparing the mean vial strength at maintenance for each vial and the time required to reach maintenance, was not significant ($p = 0.175$).

Analysis of patient factors

Univariate analysis consisting of independent samples t test and bivariate correlation analysis results are summarized in Tables 2 and 3. Gender ($p = 0.007$), a history of asthma ($p = 0.049$), a history of chronic rhinosinusitis ($p = 0.025$), smoking during SCIT ($p = 0.045$), age ($p = 0.004$), the mean endpoint of allergens in each vial ($p = 0.039$), and the number of SCIT vials per patient ($p = 0.006$) appeared to significantly affect the time required to reach maintenance dose on this initial analysis.

The results of the multivariate linear regression analysis using these variables are shown in Table 4. Age ($p = 0.002$, $\beta = 3.840$), gender ($p = 0.007$, $\beta = 82.157$), and a history of asthma ($p = 0.008$, $\beta = 80.673$) were each found to significantly affect time required to reach maintenance

TABLE 2. Univariate analysis for variables predictive of time required to reach maintenance dose

Variable	<i>p</i>
Gender	0.007 ^a
Asthma	0.049 ^a
Chronic rhinosinusitis	0.025 ^a
Polyposis	0.491
Alcohol (≥ 1 drink/week)	0.458
Smoking history	0.833
Smoking during immunotherapy	0.045 ^a
Drug allergies	0.832
Food allergies	0.948
Pets at home	0.065
Prior immunotherapy	0.756
Nasal congestion	0.202
Rhinorrhea	0.605
Eye symptoms	0.586
Ear symptoms	0.425
Systemic treatment during immunotherapy	0.705
Nasal steroids during immunotherapy	0.482

^aDenotes significant variables used for multivariate analysis.

TABLE 3. Bivariate correlation analysis for variables predictive of time required to reach the maintenance dose

Variable	<i>p</i>
Age	0.004 ^a
Number of total antigens	0.620
Mean endpoint for allergens per vial	0.039 ^a
Number of antigen categories per vial	0.097
Number of immunotherapy vials	0.006 ^a

^aDenotes significant variables used for multivariate analysis.

dose. There was a positive correlation between age and time required to reach maintenance dose with each additional year of age, corresponding to an increase in approximately 4 days required for maintenance dose. Meanwhile, the male gender correlated to an increase in approximately 82 days to reach maintenance dose and a history of asthma correlated to approximately 81 days longer to reach maintenance dose during conventional protocol SCIT.

Patient compliance

An independent samples *t* test comparing the mean time required to reach maintenance in patients, with the longest gap between escalation phase injections being <2 weeks and ≥ 2 weeks, was significant ($p = 0.010$), as expected. However, an independent samples *t* test comparing the longest gap in treatment per patient between males and

females ($p = 0.342$), and between asthmatics and nonasthmatics ($p = 0.085$), were both not significant. Furthermore, bivariate correlation analysis showed no correlation between age and the longest gap in treatment per patient ($p = 0.825$).

Discussion

SCIT demands a significant time commitment on the part of the patient, especially during the escalation period when weekly visits are required. Due to this inconvenience, many patients refuse or discontinue treatment in spite of the demonstrated clinical efficacy of SCIT.^{12,13,17} Cohn and Pizzi¹³ studied 217 patients undergoing allergen immunotherapy and found that nearly one-half of the 109 patients who stopped receiving treatment did so because of the inconvenience of the treatment schedule. Sublingual immunotherapy (SLIT), which is administered at home by the patient, offers a convenient alternative to SCIT. Studies have demonstrated that sublingual immunotherapy elicits a similar immunological response as SCIT, with similar improvements seen in symptom and medication scores. Furthermore, it has demonstrated a very good safety profile with the majority of adverse reactions occurring locally in the oral cavity.^{18,19} However, successful SLIT requires that the patient remembers to place the drops under the tongue daily, and the treating physician loses a great deal of monitoring ability.

To the best of our knowledge, this is the first study to study to examine the time required to reach maintenance therapy during SCIT. This is important information because patients often anticipate the arrival of the maintenance phase as a sign of their progress, and they may become discouraged when the escalation phase continues longer than expected. While inconvenience remains an obstacle for SCIT, we feel that accurate counseling will produce realistic expectations and help maximize compliance to the therapy.

We have identified, for the first time, that male gender, higher age, and the presence of asthma are associated with increased time to reach maintenance. As noted previously, injections were given on a weekly basis during the escalation phase; however, given the demanding nature of this schedule, patients often had longer gaps in treatment between escalation phase injections (most commonly due to travel, vacation, or illness unrelated to immunotherapy). Although the longest gap between injections was found to significantly affect the time required to reach maintenance dose, there was no significant difference in the longest treatment gaps between males and females, and between asthmatics and nonasthmatics. Furthermore, there was no correlation between age and the longest gap in treatment. These results suggest that patient compliance likely did not influence the finding that age, gender, and asthma significantly affected the time required to reach maintenance dose.

TABLE 4. Multivariate analysis for variables predictive of time required to reach maintenance dose

Variable	Number of vials	Mean time to maintenance dose (days)	Univariate or bivariate correlation <i>p</i> value	Multivariate analysis	
				β	<i>p</i>
Gender			0.007 ^a	82.157	0.007 ^a
Male	31	294.7			
Female	48	205.1			
Asthma			0.049 ^a	80.673	0.008 ^a
Yes	26	285.46			
No	53	218.04			
Chronic rhinosinusitis			0.025 ^a	−59.069	0.079
Yes	18	173.2			
No	61	260.0			
Smoking during immunotherapy			0.045 ^a	96.791	0.141
Yes	4	430.0			
No	75	232.7			
Age			0.004 ^a	3.840	0.002 ^a
Mean endpoint for allergens per vial			0.039 ^a	20.917	0.171
Number of immunotherapy vials			0.006 ^a	−50.40	0.094

^aDenotes variables with significant effect.

The results of this study are helpful to know when counseling patients who are about to begin SCIT, but they also raise some important questions. Does a prolonged escalation period have an impact on the efficacy of the therapy, both short-term and long-term? Do age, gender, and presence of asthma affect the overall outcome of therapy? Future studies will be required to help answer these important questions. Additionally it is unknown why these factors would delay the time required to reach maintenance. It is well-known that asthma is a manifestation of a predominant Th2-type response in the airway, and this imbalance between the Th1-type and Th2-type cytokine responses in asthmatics may be so severe that it takes longer for the biochemical effects of SCIT to take place.²⁰

A variety of immunotherapy approaches have been implemented in an attempt to reduce the time required to achieve the maintenance dose. One such approach is that of the accelerated cluster schedule, the principles of which were first described by Freeman as far back as 1930.¹⁵ Accelerated cluster protocols involve the administration of multiple injections sequentially per treatment day in weekly intervals, whereas rush protocols entail administering incremental doses of allergen at intervals varying between 15 and 60 minutes, over 1 to 3 days, until the target therapeutic dose is achieved.^{10,14,21} The evaluation of the safety and efficacy of these accelerated schedules has been difficult due to the diversity of the study protocols with regard to factors such as target doses, schedules, and premedication regimens. As such, these schedules have not been widely adopted in Europe and in the

United States, likely due to safety concerns.¹² However, an increasing number of recent clinical studies have demonstrated a safety profile similar to that of conventional SCIT protocols.^{14,22–28}

Currently, all patients generally undergo the same basic protocol when beginning SCIT. This study has demonstrated that not every patient experiences this therapy in the same way, and this raises the question of whether adjustments need to be made in immunotherapy protocols based on the patient's age, gender, or asthma status. Other factors affecting the course of immunotherapy, such as the presence of local reactions or systemic side effects during the escalation period, need to be more closely examined as well. Furthermore, it remains to be seen whether age, gender, and asthma affect the time required to reach maintenance during accelerated SCIT protocols, and whether these accelerated schedules have an impact on patient compliance and therapeutic outcome vs conventional SCIT escalation schedules.

Conclusions

The escalation phase for SCIT lasted approximately 8 months, although a wide range was seen. Increased age, male gender, and a history of asthma significantly increased the time required to reach maintenance dose during conventional SCIT. Considering the inconvenient nature of this therapy, accurate counseling of patients may be helpful in improving patient compliance. Further work

is needed to determine whether or not these factors have an impact on the outcome of therapy, and whether or not SCIT protocols need to be adjusted based on these findings. ❹

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