

High adherence to subcutaneous immunotherapy in a real-life study from a large tertiary medical center

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ABSTRACT

Background: Studies on real-life adherence to subcutaneous allergen immunotherapy (SCIT) for respiratory allergy are scarce. The aim of this study was to evaluate adherence to SCIT.

Methods: The patients prescribed SCIT for allergic rhinitis and/or asthma in 2009–2011 were contacted in 2014 and asked whether they completed at least the 3 years of SCIT and/or whether they suspended the treatment for at least 2 months. The Total Symptom Score–6, visual analog scale (VAS), asthma control test (ACT), medication scores, quality of life (QoL) scores, and immunotherapy satisfaction scores with VAS obtained before the initiation of SCIT in the first year and at the end of SCIT were compared.

Results: A total of 204 patients (136 female [66.7%]; mean age, 38.83 ± 12.02 years) were included; 73% (149/204) were both compliant and persistent; 14% (29/204) were only persistent; and, overall, 87.3% (178/204) were considered adherent. Adherence was more frequent in female patients (95% CI, 62.3–76.3%; $p = 0.018$). Medication, symptom, ACT, and QoL scores in the first year and at the end of the treatment were significantly lower than the initial scores, and the immunotherapy satisfaction scores at the end of treatment were higher than the scores in the first year in the patients who were adherent ($p < 0.001$ for each score).

Conclusion: The adherence rate to SCIT in our study was relatively high, in contrast to previous real-life data. Results of our study indicated that a close relationship between allergists and their patients during SCIT and the follow-up period in the same center improved the outcome of SCIT.

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Allergen immunotherapy has been used for >100 years as a treatment modality for respiratory allergies.¹ Subcutaneous immunotherapy (SCIT) has been one of the most acceptable routes because of its efficacy.² However, the length of therapy, its time-consuming procedure, painful injections, and some similar other reasons have the potential to affect adherence to this therapy. Since 1993, several studies on SCIT identified adherence rates that ranged between 13 and 89%.¹ This wide range may cause difficulty in drawing conclusions.

In addition, the definition of adherence in studies is not standardized.¹ Poor adherence is defined in different ways, such as suboptimal (taking a lower

dose than recommended), therapeutic gaps (inconsistent application of the therapy over time), nonpersistence (stopping therapy prematurely), and primary poor adherence (never starting the therapy).³ In some studies, patients who did not receive SCIT within a period of several months were considered as nonadherent, whereas, in one study, the number of injections received in a given time period was used to determine adherence.⁴ The follow-up period ranges as well, with a 3–4-year follow-up period in some studies and as short as 1 year in others.¹ Furthermore, adherence data from randomized controlled studies may not reflect the true compliance because participants are strictly observed and followed up. Therefore, data from real-life studies may provide a more realistic pattern.⁵

Studies on real-life compliance for SCIT are scarce.^{4,6–12} Recently, Kiel *et al.*⁶ analyzed the community pharmacy data base in the Netherlands for the years 1994–2009 and investigated the data of 2800 patients who were receiving SCIT for respiratory allergy. They found that only 23% completed the recommended duration of 3 years of immunotherapy and that the median duration for SCIT was 1.7 years.⁶ They concluded that real-life persistence is low and indicated that there is a need for identification of potential barriers and measures that will enhance persis-

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tence to SCIT.⁶ Another study searched a large number of patients who received SCIT with the “real life” sales data for different preparations and found that the compliance rates for unmodified SCIT preparations for at least three treatment years were 42% for pollen and 45% for mite preparations.¹³

The primary aim of this study was to evaluate the rate of adherence to SCIT in real-life practice. The secondary objective was to identify the factors that affect adherence. To improve the accuracy of the results, satisfaction scores that evaluated the efficacy of the treatment and quality of life (QoL) were prospectively applied during follow-up visits as a routine part of treatment. The questionnaire that concerned adherence data was retrospectively completed to prevent awareness of the adherence survey, which could have otherwise affected patient behavior.

METHODS

Patients ages ≥ 18 years who began SCIT between 2009 and 2011 for the diagnosis of allergic rhinitis (AR) and/or allergic asthma were included in the study. The patients who had previously received immunotherapy were not included. Premixed or single allergen extracts were used. Clustered, preseasonal, or conventional immunotherapy schedules were used. In the clustered schedule, two or three injections per visit per week were applied to reach the maintenance dose in 6 weeks. The conventional method consisted of one injection per visit every week to reach the maintenance dose in 25 weeks. Preseasonal immunotherapy was applied with pollen extracts before the pollen season with one or two injections every week for a total of 7 weeks. The mean of hunger and poverty thresholds, which were determined according to recent legal statements in Turkey, was used to determine the socioeconomic status of the patients. The mean threshold for monthly income was determined as \$806, and patients with higher or lower income than the population mean were assessed accordingly.¹⁴

The patients registered in our allergy outpatient clinic who were prescribed SCIT in 2009–2011 were contacted *via* telephone in 2014 and asked whether they completed the 3-year treatment period of pollen or mite immunotherapy and/or whether they had suspended the treatment for at least 2 months. The reasons for treatment interruption or termination were also questioned. The telephone questionnaire consisted of information about age, sex, education and employment status, place of birth, monthly household income, allergen sensitization, smoking habits, allergic disease diagnosis, type of allergen extract, immunotherapy regime, and date of initiation of immunotherapy. The number of patients who had missed doses that resulted in an interval of >2 months between subsequent injections

and any possible reasons for missed doses were identified through this questionnaire. The patients who stopped the treatment and the reasons for termination of the treatment were also recorded. The patients were verbally informed about the study during the telephone contact. Ethics approval from the ethics committee of Istanbul Medical Faculty was obtained before the study.

The efficacy of SCIT was identified with QoL, symptom, medication, and immunotherapy satisfaction scores. In addition, asthma control test (ACT) scores were determined in patients with asthma. These measures were routinely applied to these patients in their first visit before the initiation of immunotherapy and were repeated at the 1-year visit and, finally, at the end of 3 years of allergen immunotherapy. QoL scores were determined by a visual analog scale (VAS), with scores that ranged from “not at all bothersome” (0 mm) to “intolerable bothersome” (100 mm).¹⁵

The symptom scores were evaluated with both the Total Symptom Score–6 (TSS-6) and the VAS.^{15,16} The TSS-6 was assessed by the sum of six nasal, ocular, ear, and/or palate symptoms ratings, each ranging from 0 to 3, with a possible sum of 0 (absence of symptoms) to 18 (very severe).¹⁵ A VAS that ranges from “nasal symptoms in the last month/in the last pollen season, not at all bothersome” (0 mm) to “nasal symptoms in the last month, extremely bothersome” (100 mm) was also used to assess the severity of symptoms.^{16–18} SCIT treatment satisfaction was identified with the following instruction “please mark with an ‘X’ the point in the scale that best represents your current satisfaction with the allergy vaccine” and was assessed by means of a 100-mm horizontal VAS.¹⁹

The patients were instructed to use rescue medication as a stepwise regiment by stepping up when symptoms were not sufficiently alleviated. The regimen was adapted in our study from the document of the World Allergy Organization taskforce for patients with asthma and the common usage of leukotriene antagonists in Turkey as follows¹⁸:

Step 0: No rescue medication

Step 1: Antihistamine (oral/nasal/ocular) or leukotriene antagonists or bronchodilator

Step 2: Nasal corticosteroids, inhaled corticosteroids with or without step 1 drugs

Step 3: Antihistamine (oral/nasal/ocular) and leukotriene antagonists and/or nasal corticosteroids

Step 4: Oral corticosteroids

The medication scores were determined according to these steps, with a range from 0 to 6. The patients verbally consented to fill in the scores during their visits and also agreed to the use of these data in the study during the telephone contact.

Statistical Analysis

The patients who discontinued the recommended period of 3 years of immunotherapy were considered as “nonpersistent” and those who suspended the treatment for at least 2 months were grouped as “noncompliant.” The adherence rate, which consists of patients who were both persistent and compliant as well as patients who were solely persistent was summarized as a proportion with confidence interval of 95%. Medication, symptom, and ACT scores were nonparametric variables and, therefore, were analyzed with a Wilcoxon signed rank test and a Mann-Whitney *U* test, whereas symptom scores, SCIT satisfaction scores and QoL scores measured *via* VAS were all parametric variables and, therefore, were determined with a paired sample *t*-test. The results were evaluated at a $p < 0.05$ significance level.

RESULTS

A total of 204 patients were included into the study; 138 patients (67.6%) were diagnosed as having AR, 61 patients (29.9%) had concomitant AR and allergic asthma, 3 patients (1.5%) had both AR and allergic conjunctivitis and 2 patients (1%) had allergic asthma. A total of 136 patients were women (66.7%); the mean age was 38.83 ± 12.02 years (min-max, 18–69 years), the mean duration of SCIT was 3.89 ± 1.20 years (min-max, 0.3–6 years), and the mean monthly household income was $\$786 \pm \$454$ (min-max, $\$256$ – $\$2840$). Seventy-three percent of the patients were both compliant and persistent, 14% (29) were persistent but noncompliant, and, overall, 87.3% were considered adherent, although some were noncompliant but persistent. The demographic features of the patients, the distribution of allergen extracts used for immunotherapy, and the immunotherapy schedules, depending on their adherence status to SCIT, are shown in Table 1. Adherence was more frequent in female patients (95% CI, 62.3–76.3%; $p = 0.018$). Age, occupation, level of education, place of birth and other demographic factors, diagnosis, the type of allergen extract, and the schedule used for immunotherapy did not have an effect on the adherence rate.

The symptom scores, medication scores, QoL scores, and satisfaction scores obtained at the beginning of SCIT were not different between the patients who were adherent and the patients who were not adherent (Table 2). Medication scores, symptom scores determined by VAS and TSS-6, and QoL scores in the first year and at the end of the treatment were lower than the initial scores in the patients who were adherent ($p < 0.001$ for each score). Also, the immunotherapy satisfaction scores at the end of treatment were higher than the first-year scores in the adherent group ($p < 0.001$). Similarly, in the nonadherent group, the decrease in

both TSS-6 and VAS symptom scores was significant at the end of the first year of treatment ($p = 0.001$ and $p < 0.001$, respectively) and at the end of treatment ($p = 0.009$ and $p < 0.001$, respectively). Also, the VAS QoL scores in the first year and at the end of the treatment decreased when compared with the initial scores ($p < 0.001$ for each score) in the nonadherent group. However, the medication and the immunotherapy satisfaction scores did not change when compared with the first scores in this group. The ACT scores were higher in the first year and at the end of the treatment when compared with the initial scores in both patients who were adherent and those who were not adherent ($p < 0.001$ for each score) (Table 2).

The reasons for interruption included change of residence (34%), delay in the importation of the vaccine (20.7%), familial problems (17.2%), lack of time (13.8%), pregnancy (3.4%), lack of efficacy (3.4%), and local or systemic reactions (3.4% each). The reasons for termination were lack of efficacy (66.7%), systemic reactions (8.3%), pregnancy (8.3%), familial problems (8.3%), efficacy before a year of SCIT (4.2%), and medical comorbidities (4.2%). There was a reverse correlation between the satisfaction scores and the termination of treatment ($p < 0.001$).

DISCUSSION

Our study, in contrast to previous studies, showed that the adherence rate to SCIT in respiratory allergy was relatively high in real-life settings of a tertiary center. Furthermore, the clinical efficacy measures showed that SCIT was an effective therapy for respiratory allergic diseases. An acceptable adherence rate for most treatments was defined as $>80\%$. However, in the majority of the adherence studies on SCIT, the rates were $<70\%$ ^{4,9,10,20,21} and, furthermore, even lower according to real-life data.^{6,13} The high adherence rate in our study may be due to the clinical efficacy of SCIT and, in addition, due to the close cooperation between the allergists and the patients in our allergy unit. In our clinic, the same allergy specialists observe the patients before and 30 minutes after each shot, and the same allergy nurses apply the injections throughout the therapy. We believe that this is the main factor that improves patients' confidence and adherence to the therapy.

A short report from Italy also demonstrated that improved relationships between allergists and their patients result in better compliance in real-life practice.²² Similarly, a previous study revealed that adherence to SCIT was significantly higher in patients who received their injections at their allergist's office as opposed to at an outside physician's office.¹⁰ Nearly all of the patients in this study had government-assisted health insurance that supported their immunotherapy

Table 1 Clinical and demographic data of the participants

	Patients		<i>p</i>
	Adherent (<i>n</i> = 178)	Nonadherent (<i>n</i> = 26)	
Age, mean	38.74 ± 12.04	39.46 ± 12.17	NS
Occupation, no. (%)			
Housewives	59 (33)	7 (27)	NS
White collar workers	53 (29)	11 (42)	NS
Students	24 (14)	1 (4)	NS
Tradesmen	14 (8)	5 (19)	NS
Retired	12 (7)	1 (4)	NS
Blue collar workers	10 (6)	0	NS
Health care personnel	6 (3)	1 (4)	NS
Sex, no. (%); 95% CI			
Women	124 (70); 62.3–76.3	12 (46)	0.018
Men	54 (30); 23.6–37.1	14 (54)	
Monthly household income of ≥\$806, no. (%)	76 (43)	6 (23)	NS
Cigarette, no. (%)			
User	28 (16)	4 (15)	NS
Nonuser	150 (84)	22 (85)	NS
Level of education, no. (%)			
Not educated	1 (1)	1 (1)	NS
Primary school	45 (25)	6 (22)	NS
Intermediate school	14 (8)	1 (4)	NS
High school	28 (16)	2 (8)	NS
University	5 (42)	15 (58)	NS
Postgraduate	15 (8)	1 (4)	NS
Place of birth, no. (%)			
Black Sea region	55 (31)	8 (31)	NS
Marmara region	44 (24)	6 (23)	NS
East Anatolia region	36 (20)	4 (15)	NS
Central Anatolia region	35 (20)	4 (15)	NS
Aegean region	3 (2)	2 (8)	NS
Mediterranean region	2 (1)	2 (8)	NS
Southeast Anatolia region	3 (2)	4 (15)	NS
Diagnosis of respiratory disease, no. (%)			
Allergic rhinitis	117 (66)	21 (81)	NS
Allergic asthma	2 (1)	0	NS
Allergic rhinitis and asthma	56 (31)	5 (19)	NS
Allergic rhinitis and conjunctivitis	3 (2)	0	NS
Type of allergen, no. (%)			
HDM	123 (69)	17 (65)	NS
Weed pollens	27 (15)	3 (12)	NS
Grass and cereal pollens	21 (12)	5 (19)	NS
Grass pollens	4 (2)	0	NS
Tree pollens	1 (1)	1 (4)	NS
Cat	2 (1)	0	NS
Immunotherapy schedules, no. (%)			
Clustered	149 (84)	23 (89)	NS
Conventional	22 (12)	1 (4)	NS
Preseasonal	7 (4)	2 (7)	NS

NS = nonsignificant; CI = confidence interval; HDM = house-dust mite.

Table 2 Measures of efficacy, quality of life and satisfaction scores in participants

Scores	Patients					
	Adherent			Nonadherent		
	Before Immunotherapy	At the End of the First Year of Immunotherapy	At the End of Immunotherapy	<i>p</i>	Before Immunotherapy	At the End of the First Year of Immunotherapy
TSS-6						
Median	15	10	4	<0.001*	13	10.5
Min-max	0–18	0–18	0–16	<0.001#	5–18	1–18
Medication						
Median	1	1	0	<0.001*	2	0.5
Min-max	0–4	0–3	0–3	<0.001#	0–3	0–3
ACT						
Median	11	17	24	<0.001*	14	20.5
Min-max	5–25	5–25	10–25	<0.001#	9–23	16–24
VAS symptom						
Mean	8.96 ± 1.30	6.30 ± 2.00	2.81 ± 2.33	<0.001*	8.79 ± 1.18	3.24 ± 2.73
Min-max	3–10	0–10	0–10	<0.001#	6–10	0–10
95% CI	8.43–9.49	5.49–7.11	1.87–3.75		8.59–8.97	2.84–3.64
VAS QoL						
Mean	8.63 ± 1.93	6.05 ± 2.27	2.98 ± 2.43	<0.001*	8.14 ± 1.98	3.74 ± 2.84
Min-max	0–10	0–10	0–10		0.5–10	0–9
95% CI	7.78–9.41	5.13–6.97	2.00–3.96	<0.001#	7.85–8.43	3.32–4.16
VAS satisfaction						
Mean	—	6.07 ± 2.87	7.81 ± 2.44	<0.001§	—	6.49 ± 3.44
Min-max		0–10	0–10			0–10
95% CI		4.91–7.23	6.82–8.80			5.98–7.00

TSS-6 = Total Symptom Score-6; min = minimum; max = maximum; NS = nonsignificant; ACT = asthma control test; VAS = visual analog scale; CI = confidence interval.

*Comparison of the beginning and end of the first year of treatment.

#Comparison of the beginning and the end of treatment.

§Comparison of the end of first year and the end of treatment.

expenses, which may have increased the adherence rate, which supported a recent study that revealed that inadequate health insurance coverage is the leading cause of nonadherence to SCIT.²³

In this study, the most frequent immunotherapy initiation schedule was the clustered method. In the latest studies with more optimal allergen extracts and less challenging schedules, the adherence to SCIT was better than previous investigations that demonstrated adherence rates to SCIT as 50%.^{7,24} Therefore, the use of accelerated schedules seems to improve adherence rates.¹⁰ However, More and Hagan²⁰ found that patients treated with rush or accelerated schedules of SCIT were less compliant; the researchers explained it was due to the higher frequency of adverse effects.

When we reviewed demographic factors associated with nonadherence to SCIT, younger and female patients appeared to be more frequently related to nonadherence^{6,23,25} whereas, in a few studies, sex did not have an impact on adherence.^{4,10,20,26} However, the men were found to be more prone to stopping their treatment prematurely in our study ($p = 0.018$). Similar to our finding, Rhodes²⁷ found that men ages 16–25 years were more prone to withdraw from their study. This may be explained by the fact that the majority of our female patients were housewives and, therefore, work-related inconvenience was not a factor for them. Also, younger people are possibly more mobile and, therefore, can be expected to be more nonadherent to SCIT. Although the mean age of patients who were adherent and patients who were not adherent in our study was not statistically different, larger number of subjects might allow for statistical analysis of these independent variables.

Patients with a higher socioeconomic status adhered better to SCIT according to a recent study.⁶ Although, all of our patients were considered to be in the modest or limited income category because nearly all of them had government-assisted health insurance, the effect of income can be obscured. As a supportive finding of this point in our study, there was no difference in the educational level and monthly household income data between the patients who were adherent and patients who were not adherent. Similarly, in a study from Germany, the social status did not seem to effect the adherence rate.²⁸ The type of allergic disease or the coexistence of AR and asthma was not an important factor that affected adherence to SCIT in our study, which is similar to other studies.^{10,20} However, in one study, patients diagnosed with both AR and asthma who were treated with an identified allergen were significantly more likely to be adherent than those diagnosed with either AR or asthma alone.⁴

The most significant reason for the termination of treatment in this study was the patients' perception of lack of efficacy; however, this did not seem to affect the

number of dropouts in the majority of the studies.⁵ When we compared the symptom scores obtained from the patients who were adherent and the patients who were not adherent, we clearly observed the improving efficacy scores in the follow-up of both groups, which may be seen as a result of the persistence of the effectiveness of the initial SCIT. Interestingly, in a few studies, symptom relief before completion of immunotherapy also worsens adherence.^{9,25} However, it was true only for one patient in our study. Senna *et al.*⁷ considered that the main reasons for discontinuation were inconvenience, which was defined as the need to go to the hospital to have the shots; a lack of efficacy; costs and loss of working hours; and adverse effects that were in line with our findings.⁷ Other SCIT studies revealed reasons for discontinuing SCIT as site inconvenience, high cost, systemic reactions, and medical comorbidities.^{1,9,25,27}

Our study should be viewed in light of its limitations. Personality traits that could affect adherence were not evaluated. The average combined symptom and medication scores proposed by the World Allergy Organization taskforce were not used because the medication scores were adapted according to the daily clinical practice in Turkey and the method of combined scores was not yet validated.^{18,29} In addition, the data from this study could not be generalized because it was performed at a single institution. Cost was not evaluated because all the patients had government-assisted health insurance, although it was clearly a noticeable factor that affected compliance in other real-life studies. Also, the small number of patients who were not adherent might have affected the statistical comparisons. Also, collecting data retrospectively with telephone interviews depended on patient understanding and recall, and, therefore, might have decreased the reliability of the results.

CONCLUSION

The adherence rate to SCIT in our study was relatively high, in contrast to previous real-life data. Results of our study indicated that a close relationship between allergists and their patients during SCIT and the follow-up period in the same center improved the outcome of SCIT; therefore, the organization of allergy units and the support of administrative staff had a strong potential to influence adherence rates for SCIT.

REFERENCES

1. Reisacher WR, and Visaya JM. Patient adherence to allergy immunotherapy. *Curr Opin Otolaryngol Head Neck Surg* 21: 256–262, 2013.
2. Nelson HS. Advances in upper airway disease and allergen immunotherapy. *J Allergy Clin Immunol* 111(suppl. 3):S793–S798, 2003.
3. Bourdin A, Halimi L, Vachier I, et al. Adherence in severe asthma. *Clin Exp Allergy* 42:1566–1574, 2012.

4. Donahue JG, Greineder DK, Connor-Lacke L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 82:339–347, 1999.
5. Makatsori M, Senna G, Pitsios C, et al. Prospective adherence to specific immunotherapy in Europe (PASTE) survey protocol. *Clin Transl Allergy* 5:17, 2015.
6. Kiel MA, Röder E, Gerth van Wijk R, et al. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol* 132:353–360.e2, 2013.
7. Senna G, Ridolo E, Calderon M, et al. Evidence of adherence to allergen-specific immunotherapy. *Curr Opin Allergy Clin Immunol* 9:544–548, 2009.
8. Vita D, Caminiti L, Ruggeri P, and Pajno G. Sublingual immunotherapy: Adherence based on timing and monitoring control visits. *Allergy* 65:668–669, 2010.
9. Cohn JR, and Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 91:734–737, 1993.
10. Tinkelman D, Smith F, Cole WQ III, and Silk HJ. Compliance with an allergen immunotherapy regime. *Ann Allergy Asthma Immunol* 74:241–246, 1995.
11. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: Patterns of care, resource use, and costs. *J Allergy Clin Immunol* 121:227–232, 2008.
12. Sieber J, De Geest S, Shah-Hosseini K, and Mosges R. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. *Curr Med Res Opin* 27:855–861, 2011.
13. Egert-Schmidt AM, Kolbe JM, Mussler S, and Thum-Oltmer S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. *Patient Prefer Adherence* 8:1475–1481, 2014.
14. Turkish Labor Union Considerations, 1952. Available at: www.turkis.org.tr/Aclik-Yoksulluk-k91.
15. Demoly P, Bousquet PJ, Mesbah K, et al. Visual analogue scale in patients treated for allergic rhinitis: An observational prospective study in primary care. *Clin Exp Allergy* 43:881–888, 2013.
16. Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 62:367–372, 2007.
17. Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: An EAACI position paper. *Allergy* 69:854–867, 2014.
18. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 62:317–324, 2007.
19. Justicia JL, Cardona V, Guardia P, et al. Validation of the first treatment specific questionnaire for the assessment of patient satisfaction with allergen-specific immunotherapy in allergic patients: The ESPIA. *J Allergy Clin Immunol* 131:1539–1546, 2013.
20. More DR, and Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol* 88:391–394, 2002.
21. Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol* 116:1380–1381, 2005.
22. Lombardi C. What is the factor that improves adherence to allergen-specific immunotherapy? A secretary. *Ann Allergy Asthma Immunol* 114:530–531, 2015.
23. Vaswani R, Garg A, Parikh L, and Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: Inadequate health insurance coverage is the leading cause. *Ann Allergy Asthma Immunol* 115:241–243, 2015.
24. Incorvaia C, Mauro M, Ridolo E, et al. Patient's compliance with allergen immunotherapy. *Patient Prefer Adherence* 2:247–251, 2008.
25. Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. *Ann Allergy* 70:480–482, 1993.
26. Mahesh PA, Vedanthan PK, Amrutha DH, et al. Factors associated with non-adherence to specific allergen immunotherapy in management of respiratory allergy. *Indian J Chest Dis Allied Sci* 52:91–95, 2010.
27. Rhodes BJ. Patient dropouts before completion of optimal dose, multiple allergen immunotherapy. *Ann Allergy Asthma Immunol* 82:281–286, 1999.
28. Hommers L, Ellert U, Scheidt-Nave C, and Langen U. Factors contributing to conductance and outcome of specific immunotherapy: Data from the German National Health Interview and Examination Survey 1998. *Eur J Public Health* 17:278–284, 2007.
29. Clark J, and Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. *Allergy* 62:1023–1028, 2007. □

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