HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 3, 514–517
http://dx.doi.org/10.1080/21645515.2016.1243632

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

Compliance with allergen immunotherapy and factors affecting compliance among patients with respiratory allergies

Fardous Musa[a], Mona Al-Ahmad[a,b], Nermina Arifhodzic[a], and Waleed Al-Herz[c,d]

[a]Al-Rashid Allergy Center, Ministry of Health, Kuwait City, Kuwait; [b]Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait; [c]Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait; [d]Allergy and Clinical Immunology Unit, Department of Pediatrics, Al-Sabah Hospital, Kuwait City, Kuwait

ABSTRACT

Background: Allergen-specific immunotherapy (AIT) is safe and effective for the treatment of allergic rhinitis and allergic asthma. However, patient non-compliance is a major barrier to achieving optimal outcomes

Objective: To determine the level of compliance among patients using AIT and to identify factors associated with non-compliance

Methods: A retrospective analysis using questionnaires was conducted to study compliance among 236 patients with allergic rhinitis with or without asthma who began AIT in 2009 or 2010

Results: The compliance rates at 3 y were 58.7% among patients on subcutaneous immunotherapy (SCIT) and 11.6% among those on sublingual immunotherapy (SLIT). The mean durations of treatment with SCIT and SLIT were 31 (+/−18.3) and 15.9 (+/−14.7) months, respectively. The most common causes of non-compliance among patients on SCIT were the frequency of injections (82.2%), the duration of treatment (70.9%), and commuting to the Allergy Center (67.7%). Reasons for non-compliance among patients on SLIT were related to inconvenience (43.4%), improvement without treatment (30.2%) and perception of poor efficacy (25.0%) Conclusion: Compliance with AIT is low, but at 3 years, it was higher among patients on SCIT than among patients on SLIT. Reasons for non-compliance include difficulty adjusting to treatment protocols and a perception that the efficacy is low. Patient education regarding the treatment course and the slow effect, as well as the need for close follow up to effectively prevent and treat adverse reactions, are important factors for improving compliance and treatment outcomes.

ARTICLE HISTORY
Received 11 July 2016
Revised 11 September 2016
Accepted 28 September 2016

KEYWORDS
allergen-specific immunotherapy; adherence; compliance; subcutaneous; sublingual

Introduction

Allergen-specific immunotherapy (AIT) is both effective and safe for the treatment of allergic rhinitis and allergic asthma,[1] which are very common chronic conditions and are associated with significant morbidity and costs.[2] Allergen extracts are typically administered either by subcutaneous injections (SCIT) or as drops under the tongue (SLIT). The clinical effectiveness of AIT requires administration of standardized allergen extracts in adequate doses and for sufficient periods of time (3–5 years).[1,3] In general, poor compliance is a considerable problem for all long-term treatments.[4] Compliance with AIT is defined as the extent to which patients who received the first dose of AIT commit to the treatment schedule (dose, frequency/dosing schedule, and duration) recommended by the treating physician. Both the inconvenience of adhering to a long treatment duration using conventional dosing schedules and extracts, as well as the local and systemic reactions, present challenges to achieving successful outcomes.[5] Adherence is defined by the World Health Organization as the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed-upon recommendations from a health care provider.[4,6] According to the World Health Organization, 50% of patients suffering from chronic diseases do not follow treatment recommendations.[4] Non-adherence leads to an overall decrease in treatment benefits, as well as increases in hospitalizations, morbidity and mortality.[4]

The aim of this study was to determine the level of compliance and to determine the reasons for non-compliance among patients on AIT treated at Al-Rashid Allergy Center, which is a tertiary center in the State of Kuwait to which patients with allergic diseases are referred for evaluation and management.

Results

A total of 236 patients were included in the study (150 patients on SCIT and 86 patients on SLIT). The patients were, on average, in their fourth decade of life, and slightly more males than females were enrolled (Table 1). The mean duration of treatment was 31.0 months (SD ± 18.3) for SCIT and 15.9 months (SD ± 14.7) for SLIT ($P < 0.001$). The reported durations for which patients continued to take AIT are shown in Table 2. Eighty-eight patients on SCIT (58%) completed 3 y of treatment, while only 10 patients in the SLIT group (11.6%) did so. Table 3 shows the most common causes for non-compliance among patients on SCIT, which consisted of the frequency of

CONTACT Waleed Al-Herz, MD wemh@hotmail.com Department of Pediatrics, Faculty of Medicine, Kuwait University, 24923, Safat, Zip code 13110, Kuwait.

Table 1. Patient characteristics and duration of AIT.

Characteristic	Total (n=236) (100%)	SCIT (n=150) (63.5%)	SLIT (n=86) (36.4%)	P-value
Age (years) Mean ± SD	35.4 ± 13.2	37.4 ± 12.9	32.0 ± 13.0	0.003*
Gender, N (%)				
Male	142 (60.2)	94 (62.7)	48 (55.8)	0.301**
Female	94 (39.8)	56 (37.3)	38 (44.2)	0.301***
Duration (months) Mean ± SD	25.4 ± 18.5	31.0 ± 18.3	15.9 ± 14.7	< 0.001****

comparison between SCIT & SLIT patients in terms of
1-* Mean age of patients on SCIT vs Mean age of patients on SLIT
2-** the total number of male patients on SCIT vs those on SLIT
***the total number of female patients on SCIT vs those on SLIT
3-**** the total mean duration of treatment (in months) on SCIT vs SLIT
SD: standard deviation.

Table 2. Compliance according to duration of AIT treatment.

Duration (months)	SCIT n (%)	SLIT n (%)	P-value
0–12	39 (26.0)	44 (51.2)	< 0.001*
13–24	17 (11.3)	12 (14.0)	
25–35	6 (4.0)	20 (23.2)	
≥36	88 (58.7)	10 (11.6)	

*Comparison between the duration of treatment (in months) of SCIT vs SLIT

Table 3. Reasons for stopping SCIT (n = 62).

Variable	N (%)
Frequency of injections.	51 (82.2)
Duration of treatment	44 (70.9)
Commuting	42 (67.7)
Other commitments	32 (51.6)
Waiting time	14 (22.6)
Local side effects	13 (20.9)
Improvement	8 (12.9)
Pregnancy	4 (6.4)
Poor efficacy	4 (6.4)
Traveling	3 (4.8)
Other diagnosis	2 (3.2)
Other side effects	1 (1.6)
Misconceptions	1 (1.6)

injections (82.2%), the lengthy duration of treatment (70.9%), and problems related to commuting to the Allergy Centre (67.7%). In contrast, the most common causes for non-compliance among patients on SLIT were related to inconvenience (43.4%), improvement without treatment (30.2%) and poor perceived efficacy (25.0%) (Table 4).

Discussion

In the present study, we documented the overall compliance rate at the third year of treatment among patients receiving AIT and determined reasons for non-compliance. Only 58.7% of patients on SCIT and 11.6 % of patients on SLIT completed 3 y of treatment.

Similar previous studies showed large variability in compliance rates, which can be attributed to variability in the definition, the method of measurement and the treatment duration measured. A study conducted in the USA involving veterans treated with SCIT found a similar compliance rate (63.5%).[7] The authors attributed this finding to the fact that veterans older than 66 y are usually retired, and therefore, have fewer commitments. In contrast, a study conducted in the Netherlands showed low overall compliance to AIT.[8] Only 18% of patients completed 3 y of treatment (SCIT 23%; SLIT 7%), and the median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively. However, a high SLIT compliance rate (85%) was found in another study by Marogna et al,[9] which

Table 4. Reasons for stopping SLIT (n = 76).

Variable	N (%)
Inconvenience	33 (43.4)
Improvement	23 (30.2)
Poor efficacy	19 (25.0)
Local side effects	17 (22.3)
Duration of Rx	10 (13.1)
Other side effects	10 (13.1)
Traveling	9 (11.8)
Pregnancy	3 (3.9)
Misconceptions	3 (3.9)

Table 5. The questionnaire design.

Sections	Questions
Demographics	1-Age (years) 2- Gender
Details of AIT & Causes of non compliance / poor compliance	3-When did you start receiving the allergy injections? 4-When did you stop receiving the injections? 5- If you stopped your injection treatment, Why? 1. Pain or reactions at injection site 2. Time needed to wait after injections 3. Frequent dosing schedule 4. Long duration of treatment 5. Distance from area of residence 6. Pregnancy 7. Doctors decision 8. Difficult to leave work 9. Others (please specify) Please answer the following questions if you were started on SLIT: 6- When did you start taking allergy treatment (SLIT)? 7-When did you stop taking allergy treatment drops under the tongue/SLIT 8- If you stopped your treatment what are the reasons? 1. Local reactions/ side effects (itching, pain, swelling under the tongue) 2. Difficult dose schedule 3. Long treatment duration 4. No improvement with this treatment 5. Improvement in symptoms, no need for treatment 6. Pregnancy 7. Doctor's decision 8. Others (please specify)

also showed a high adherence rate to the treatment protocol (72% of patients). Hsu et al.[10] studied attrition rates for SCIT and SLIT and found them to be 45% and 41%, respectively. SCIT patients reported inconvenience to be the main reason for discontinuation of treatment, whereas SLIT patients indicated concerns about efficacy.

There are several possible explanations for the low overall compliance to both SCIT and SLIT in the current study. Patients are usually more symptomatic at the beginning of any treatment, which makes them more motivated to commit to treatment. However, because allergic diseases are characterized by remissions and exacerbations, it is possible that patients become less motivated to take the recommended treatment when in remission. It is also possible to attribute poor compliance to the fact that patients may not experience immediate effects of treatment, or that they find treatment inconvenient due to work or other commitments. Another factor that may contribute to the low compliance rate is the long duration of treatment. For example, in patients on SLIT, 51.2 % completed up to 12 months of treatment, while only 11.6 % continued for the minimum required duration of 36 months or more. These data demonstrate a clear association between compliance and duration of treatment with SLIT; the longer the duration, the lower the compliance.

In the current study, compliance was found to be better among patients treated with SCIT than among those treated with SLIT. This can be explained by the fact that patients on SCIT visit the treating physician more often and therefore have more contact with the treating physician, which allows them to discuss their experience, expectations, concerns and side effects more closely and to receive timely and appropriate feedback and interventions. However, patients on SLIT take their medication at home; thus, they may not have the same opportunities to discuss side effects or concerns or misconceptions with their physicians, and they may decide to discontinue treatment on their own.

In analyzing reasons for non-compliance among our SCIT patients, inconvenience was a main factor, and it involved frequency of injections (82.2%), long duration of treatment (70.9%) and difficulties in commuting to the Allergy Centre (67.7%). Another 51.6% of patients mentioned time constraints, such as being busy with other activities such as studying, working and/or traveling, which may indicate that they prioritize other commitments over taking treatment. Inconvenience was also a main factor (50% of patients) for discontinuation of SCIT in a previous study.[11] In that study, 28 % of patients reported needle phobia as a factor for non-compliance. A study performed in China[12] showed a lower percentage of patients (7.9%) discontinuing SCIT due to adverse effects, while in our patients, 20.9% mentioned side effects as a cause of spontaneous discontinuation of SCIT.

The main reason for non-compliance with SLIT in our patients was the inconvenience of taking daily sublingual drops (43.4%). The drops must be retained under the tongue for at least 2 minutes and swallowed thereafter, and the treatment must be kept refrigerated at all times. Poor perception of efficacy (25.0%) and the presence of side effects (22.3%) also contributed to patient discontinuation of SLIT. More than 10% of our patients mentioned other side effects such as facial numbness and swelling, nausea, vomiting, and abdominal cramps after taking the drops, and they justified stopping SLIT due to these side effects. These reasons are similar to ones found in a previous study.[9]

The validity of a questionnaire is the degree to which it accurately measures what it is supposed to measure, to help improve the quality and credibility of data. A valid questionnaire must be simple, reliable, precise, adequate for the problem intended to be measured, reflective of the underlying theory or concept to be measured and capable of measuring change. These features apply to our questionnaire. It is also considered reliable since reliability is a measure of reproducibility of data and results, in case of reassessment using the same questionnaire. Hence, the nature and circumstances related to AIT haven't changed. Another aspect of reliability concerns internal consistency among the questions, which is the fact that similar questions give rise to similar answers and this applies to our questionnaire based on the results obtained.

We are aware of some limitations in our study. This is a retrospective study that includes patients who were started on AIT since 2009 and data were collected based on questionnaires. There is a recall bias, which is seen, in all retrospective studies of this design. Moreover, there is a limitation of data using a questionnaire. Patients who have discontinued treatment early in the course of treatment were contacted by phone and the total duration was taken into consideration. Those who never took treatment were not included in the study. The total duration included all months on treatment, whether patients discontinued early or late during therapy. The small number of patients recruited also limits us to draw a meaningful conclusion. We are in need for further similar studies.

In general, it can be stated that patients' attitudes and understanding, as well as convictions and expectations, play a major role in compliance with treatment.

Conclusion

Compliance with SCIT is better than compliance with SLIT, although compliance is low for both treatments. Compliance is influenced by the complex interaction of factors related to the treatment protocol, the patient, the physician, the patient-physician relationship and the disease itself. Improved patient-physician communication, simplicity of the treatment regimen and regular contact and follow-up visits are the primary means of enhancing compliance. Pharmaceutical companies working on AIT are also required to improve allergen extracts to ensure a quick response to treatment and to minimize the occurrence of side effects related to treatment. Our study support an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance of AIT, especially SLIT which is extremely low. An adequate education, good selection of patients, and a strict follow-up can significantly reduce AIT discontinuations.

Methods

The study population consisted of patients diagnosed with allergic rhinitis with or without allergic asthma who began AIT in 2009 or 2010 at the Al-Rashid Allergy Center. Allergic

sensitization was confirmed based on skin prick testing using standardized extracts (Stallergenes, France). We have used Alyostal allergen extracts (Stallergens, France). The following common inhalant allergen extracts at a dose of 100 Index of Reactivity per milliliter (IR/ml) were used: DP, DF, Cat, Dog, 5 Grasses, Bermuda, Artemisia, Salsola, at a dose of 100 Index of Concentration per milliliter (IC/ml) included the following: Date palm, Chenopodium, Plantago, and at a dose of 1000 Index of Concentration per milliliter (IC/ml) included Mixed Feathers, Alternaria, and Cladosporum. Allergen-specific immunoglobulin E (IgE) was tested using HYTEC Enzyme Immunoassay (HYCOR Europe Bio Crest B.V. Lohfelden, Germany) according to the standard procedures. All patients were educated about both types of AIT and were given the option of receiving either SCIT or SLIT. Patients were first seen and counseled by the treating physician who would give them a briefing about AIT treatment. The physician would discuss the objectives, treatment's options, and answer all patients' questions. Patients would then spend about 30 minutes with a nurse, who's been trained in the immunotherapy unit for a long time, and would discuss in more detail the specific type of treatment the patient is to receive (SCIT vs SLIT). All patients would receive a demonstration of how to use the vaccine and spent some time answering their questions. Finally, all patients would be given brochures with written basic information related to AIT for further reference. Moreover, they are given contact numbers of the AIT unit, in case they have any other questions or comments. Commercial aero-allergen extracts/vaccines (Stallergenes, France) were administered according to the manufacturer's recommendations for both build-up and maintenance phases. Non-compliance was defined in this study as discontinuing AIT, after receiving at least one dose, without the approval of the treating doctor and without reaching the minimum recommended treatment duration of 3 y. Data collection was performed using a questionnaire (Table 5). The patients were able to choose more than one option as the reason for discontinuation of AIT without their physician's approval. All patients signed an informed consent to participate in the study, which was approved by the Ethics Committee of the Ministry of Health in Kuwait.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 21, IBM Corp., Armonk, NY, USA). The Pearson chi-square test was used to determine the association between categorical variables, and the Mann-Whitney test was used for continuous variables. P-values < 0.05 were considered significant.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, Nelson M, Weber R, Bernstein D, Khan D, et al. Allergen immunotherapy: A practice parameter third update. J Allergy Clin Immuno 2011; 127(1 Suppl):S1-S55; http://dx.doi.org/10.1016/j.jaci.2010.09.034

[2] Brozek J, Bousquet J, Baena-Cagnani C, Bonini S, Canonica G, Casale T, van Wijk R, Ohta K, Zuberbier T, Schünemann H. Allergic rhinitis and its impact on asthma (ARIA guidelines): 2010 Revision. J Allergy Clin Immunol 2010; 126(3):466-76; PMID:20816182; http://dx.doi.org/10.1016/j.jaci.2010.06.047

[3] Zuberbier T, Bachert C, Bousquet P, Passalacqua G, Canonica G, Merk H, Worm M, Wahn U, Bousquet J. GA^{2}LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy 2010; 65(12):1525-30; PMID:21039596; http://dx.doi.org/10.1111/j.1398-9995.2010.02474.x

[4] Sabaté E. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: WHO 2003; 35(3):207

[5] Reisacher W, Visaya J. Patient adherence to allergy immunotherapy. Curr Opin Otolaryngol Head Neck Surg 2013; 21(3):256-62; PMID:23549440; http://dx.doi.org/10.1097/MOO.0b013e32835f8048

[6] Vrijens B, De Geest S, Hughes D, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012; 73(5):691-705; PMID:22486599; http://dx.doi.org/10.1111/j.1365-2125.2012.04167.x

[7] Guenechea-Sola M, Hariri S, Galoosian A, Yusin J. A retrospective review of veterans' adherence to allergen immunotherapy over 10 years. Ann Allergy Asthma Immunol 2014; 112(1):79-81; PMID:24331403; http://dx.doi.org/10.1016/j.anai.2013.10.018

[8] Kiel M, Röder E, Gerth van Wijk R, Al M, Hop W, Rutten-van Mölken M. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013; 132(2):353-60; PMID:23651609; http://dx.doi.org/10.1016/j.jaci.2013.03.013

[9] Marogna M, Spadolini I, Massolo A, Canonica G, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: Clinical efficacy and more. Allergy 2004; 59(11):1205-10; PMID:15461603; http://dx.doi.org/10.1111/j.1398-9995.2004.00508.x

[10] Hsu N, Reisacher W. A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy. Int Forum Allergy Rhinol 2012; 2(4):280-4; PMID:22434716; http://dx.doi.org/10.1002/alr.21037

[11] Stokes S, Quinn J, Sacha J, White K. Adherence to imported fire ant subcutaneous immunotherapy. Ann Allergy Asthma Immunol 2013; 110(3):165-7; PMID:23548525; http://dx.doi.org/10.1016/j.anai.2012.11.010

[12] Huang YN, Huang Y, Dai J, Yang F. Causes of stopping subcutaneous specific immunotherapy in asthmatic children. Zhongguo Dang Dai Er Ke Za Zhi 2012; 14(9):671-4; PMID:22989436