Original Article

Factors Associated with Non-adherence to Specific Allergen Immunotherapy in Management of Respiratory Allergy

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ABSTRACT

Background. Non-adherence to specific allergen immunotherapy is a major hurdle faced by the allergist, contributing to poor clinical outcomes.

Objectives. To assess the independent association of various factors with non-adherence to specific allergen immunotherapy.

Methods. Fifty consecutive (non-adherent) and control (adherent) subjects receiving specific allergen immunotherapy were included in the study and various factors related to non-adherence including socio-demographic, clinical and immunotherapy related variables were compared between the two groups by univariate and multivariate analysis.

Results. On univariate analysis, gender, allergic conjunctivitis, family history, progression of disease, perception of immunotherapy, medicine requirement, and the pattern of missed doses greater than two in the last 10, 20 and 30 doses were found to be significantly associated with non-adherence. On multivariate analysis, independent association was observed with allergic conjunctivitis, family history, perception of immunotherapy, missed doses greater than two in the last 10 doses of immunotherapy and medicine requirement.

Conclusions. The independent factors associated with non-adherence may vary between different settings and countries. There is a need for developing individual case holding programmes to improve clinical outcomes in patients receiving specific allergen immunotherapy. **[Indian J Chest Dis and Allied Sci 2010; 52:91-95]**

Key words: Non-adherence, Adherence, Specific allergen immunotherapy, Asthma, Allergic rhinitis, Allergic conjunctivitis, Missed doses.

INTRODUCTION

Inadequate adherence of patients to prescribed treatment is a major cause of poor clinical outcome in the treatment of asthma.[1] Specific allergen immunotherapy is an important therapeutic option in the management of allergies where non-adherence is a major issue and is as crucial to the clinical outcome as the intrinsic effectiveness of the therapy.[2] Previous studies [3-5] have identified certain factors associated with non-adherence, but no attempt have been made to study the pattern of missed doses as a variable. Several studies[3-6] have observed a high percentage of non-adherence (12%-50%) in patients receiving allergen immunotherapy, and this is one of the major hurdles faced by an allergist. In the present study, various factors related to non-adherence were studied and the importance of the pattern of missed doses as an independent factor was evaluated.

MATERIAL AND METHODS

The study adopted a case-control design. The "case" was defined as a subject who had discontinued immunotherapy injections for at least six months within the last two years and placed in the group classified as 'non-adherent'. The "control" was defined as a subject who was continuing immunotherapy as scheduled for at least two years and this group was classified as 'adherent'.

One hundred subjects (50 cases and 50 controls) attending an allergy centre in India were included in the study to assess the factors associated with non-adherent behaviour. The subjects were identified by a retrospective chart review and were interviewed by a physician prospectively. The timeline for inclusion of the patients in the chart review was six months during the year 2003. A total of 140 subjects were initiated on immunotherapy. Patients who were

[Received: October 6, 2008; accepted after revision: March 26, 2009]

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adherent to immunotherapy for less than two years (n=29) and pediatric patients (n=3) were excluded. In the non-adherent, group as the objective was to study the pattern of missing doses with a minimum of 10 doses completed, those with less than 10 doses received (n=4) and those who could not be traced (n=4) were also excluded. Overall rate of non-adherence was found to be 41.4 percent.

The indications for immunotherapy in patients with allergic rhinitis and asthma were according to the guidelines of the World Health Organization.[6] The Institutional Review Board approved the study. All patients received at the allergist's office twice-weekly subcutaneous injections of increasing doses of the pre-mixed aqueous non-standardised allergen extracts until the maintenance concentration was reached. Immunotherapy was initiated with 1:50,000 or 1:5,000 wt/vol pre-mixed mixtures of allergen extracts and the final maintenance dose was 0.9mL of a 1:50 wt/vol allergen extract mixture every four weeks. The minimum number of allergens used for each patient was two and the maximum was four. The maintenance dose of each of the allergens used in the manufacturer's allergen extract mixture was 0.2mL to 0.4mL of 1:5 wt/vol of the selected allergens. The annual maintenance dose of each of the pollens used was 10,800 PNU, of house dust mite, 7200 PNU, and of cockroach, 3600 PNU. The maintenance phase was reached in all the patients between 24 to 28 weeks. The allergens used for immunotherapy included house dust mite, cockroach, weed pollens (*Parthenium hysterophorus*, *Artemisia tridenta* and *Amaranthus spinosus*), grass pollen (*Cynodon dactylon*) and tree pollen (*Prosopis julifora*). For all the patients, the attending allergist administered the injections after a clinical examination and peak flow measurement, which needed to be greater than 80% of their personal best values.

The study considered factors including age, gender, patient perception about the efficacy of the immunotherapy, cost, travel, adverse reactions, pain at the site of injection, interference with work schedule and job transfers. The perception of the patients about the efficacy of immunotherapy was recorded by asking the question "Do you feel that immunotherapy is helping you in the management of your allergies?" The information on cost referred only to the direct cost of immunotherapy and the response to the question "whether the cost influenced the continuation/discontinuation of immunotherapy?" Similar questions were asked to elicit information regarding pain, travel cost, adverse reaction of immunotherapy, interference with work schedule and job transfers.

The disease was classified as progressive or non-progressive based on the course of the disease since its inception. The disease was said to be progressive, if there was an increase in any of the following including the frequency of symptoms, duration of symptoms in each episode, increase in the severity of the symptoms or an increase in the medicine requirement. The patients were said to have missed a dose, when they did not receive it as scheduled, except if they had a medical illness. The study evaluated the pattern of missed doses as an independent factor for non-adherent behaviour. The pattern of missed doses was classified into three groups based on the number of missed doses in the last 10, 20 and 30 scheduled injections for each of the patients. In each of the groups, the missed doses were further categorised for analysis as those missing more than two doses or those missing less than two doses. The medication requirements of all the patients were documented at the time of interview and this was compared to their requirements at the initiation of immunotherapy recorded in their charts. A physician, not involved with the immunotherapy programme, interviewed all the patients to assess the various factors related to non-adherence according to a structured questionnaire. The adherent subjects were still continuing the immunotherapy and the non-adherent subjects had discontinued it at the time of the interview.

Statistical Analysis

Data was analysed using SPSS version 10 and EPIINFO. Univariate analysis was carried out to study the association of each factor and the odds ratio with 95% confidence interval was estimated for each of the factors. Multivariate step-wise logistic regression was adopted to study the independent association of these factors with non-adherence.

RESULTS

Data of a total of 50 adherent and 50 non-adherent patients were analysed. The patient population consisted of mostly young adults with a male preponderance in both the adherent and the non-adherent groups (Table 1). Most of the subjects had attended college in both the groups. The predominant indication for immunotherapy was allergic rhinitis followed by asthma. Most of the patients had progressive allergic disease. The most common sensitisation in both the groups was due to house dust mites, followed by cockroach and pollens.

It was observed in univariate analysis that age and education were not significantly different between the adherent and the non-adherent group (Table 2). Gender was found to have a significant association with females having higher risk odds ratio (OR 1.5) than males for the non-adherence. Among the clinical variables, the presence of allergic

Table 1. Demography and immunotherapy characteristics

Characteristics	Non-adherent Group (n=50)	Adherent Group (n=50)
Gender		
Male	24	34
Female	26	16
Education		
Primary	3	3
High school	11	6
Pre university	13	15
Graduate	18	21
Post graduate	5	5
Age distribution		
< 20 years	12	16
20-40 years	24	22
> 40 years	14	12
Mean age males (in years)	27.3±6.7	28.2±6.3
Mean age females (in years)	29.1±5.1	30.2±7.2
Disease		
Allergic rhinitis	48	46
Asthma	37	37
Allergic conjunctivitis	31	9
Disease behaviour		
Progressive	45	34
Non-progressive	5	16
Family history of allergies	29	13
Mean injections received	66.7±14.3	98.1±17.2
Mean duration of immunotherapy (weeks)	54.6±28.3	122.3±47.5
Time needed to reach maintenance dose (weeks)	25.8±1.4	25.9±1.3

conjunctivitis (OR 8.8), non-progression of disease (OR 2.3) and negative family history (OR 4.6) had significant association with non-adherence. Some of the factors related to immunotherapy including cost (case n=0, control n=0), pain (case n=1, control n=1), difficulty in travel to the medical facility (case n=2, control n=2), interference of the immunotherapy schedule with the patient's work schedule (case n=2, control n=1), job transfers (case n=1, control n=0) and presence of significant adverse effects related to immunotherapy (case n=3, control n=2) were not considered for univariate analysis due to low cell frequency. Of the factors related to immunotherapy, subjects having a negative perception of immunotherapy had a very high risk (OR 27.6) for non-adherence. A non-decrease in medicine requirement (OR 6.6), the pattern of missed doses greater than two in the last 10 (OR 13.5), 20 (OR 6.0) and 30 (OR 5.0) doses had a significant association with non-adherence.

Table 2. Factors related to non-adherence: results of univariate analysis

Factors	Non-adherent (n=50)	Adherent (n=50)	Odds Ratio (95%CI)	Significance p Value
Gender				
Male	24	34	1.0	0.042
Female	26	16	1.5(1.0–2.4)	
Age				
<20 years	12	16	1.0	
20-40 years	24	22	0.7 (0.3–1.9)	>0.05 (NS)
>40 years	14	12	0.7 (0.2–2.3)	
Education				
College	36	41	1.0	>0.05 (NS)
School	14	9	0.56 (0.2–1.6)	
Disease				
Allergic rhinitis absent	2	4	1.0	
Allergic rhinitis present	48	46	0.6 (0.2–2.1)	>0.05 (NS)
Asthma absent	13	13	1.00	>0.05 (NS)
Asthma present	37	37	1.9 (0.8–1.8)	
Allergic conjunctivitis absent	19	41	1.0	<0.01
Allergic conjunctivitis present	31	9	8.8 (3.4–22.7)	
Progression of disease				
Non-progressive	5	16	1.0	<0.01
Progressive	45	34	2.4 (1.1–5.3)	
Family history of allergic disease				
Family history present	29	13	1.0	<0.01
Family history absent	21	37	4.6 (1.9–11.2)	
Allergens used for immunotherapy				
House dust mite + cockroach	12	14	1.0	
House dust mite + pollens	24	25	1.0 (0.6–1.6)	>0.05 (NS)
Hosue dust mite + pollens + cockroach	14	11	0.8 (0.5–1.4)	
Factors related to immunotherapy				
Positive perception	32	49	1.0	<0.01
Negative perception	18	1	27.6 (3.5–216.8)	
Medicine requirement				
Decreased	23	43	1.0	<0.01
Not decreased	27	7	6.6 (2.3–19.9)	
Missing doses in last 10 doses				
Less than 2 doses	25	46	1.0	<0.01
2 or more doses	25	4	13.5 (3.8–52.1)	
Missing doses in last 20 doses				
Less than 2 doses	14	35	1.0	<0.01
2 or more doses	36	15	6.0 (2.3–15.7)	
Missing doses in last 30 doses				
Less than 2 doses	11	30	1.00	<0.01
2 or more doses	39	20	5.0 (1.9–13.0)	

On multivariate step-wise logistic regression analysis, it was observed that the presence of allergic conjunctivitis, family history, perception of immunotherapy, missed doses greater than two in the last ten doses of immunotherapy and a non-decrease

in medicine requirements were significantly associated with non-adherence (Table 3). The total agreement of the model with five independent variables was 81 percent with sensitivity to detect non-adherence of 76 percent.

Table 3. Factors related to non-adherence: results of step-wise logistic regression analysis

Factors	Odds Ratio (95% CI)	Significance P Value
Clinical		
Family history	3.7 (1.1–12.5)	0.04
Allergic conjunctivitis	6.3 (1.8–22.6)	<0.01
Immunotherapy related factors		
Negative perception	19.5 (2.0–191.9)	0.01
Non-decrease in medicine requirement	7.43 (1.9–29.0)	<0.01
Missing more than 2 doses in last 10 doses	8.1 (1.9–34.9)	<0.01

DISCUSSION

Adherence is defined as the extent to which a patient's behaviour or action coincides with the advice received.[7] Non-adherence is common among patients with asthma, significantly affecting its control.[8] It is expensive and accounts for a significant economic burden.[9] Inadequate patient adherence to prescribed treatment is a major cause of poor clinical outcome in the treatment of asthma.[10] Adherence to pharmacotherapy has been reported to be around 50% in both adults [11] and children.[8] Several published studies[3-5] have observed a high percentage of non-adherence (12% to 50%) in patients receiving allergen immunotherapy, and it is one of the major hurdles faced by an allergist.

A previous study by Tinkelman *et al*[3] identified receiving allergy injection outside the allergist's office as a major factor for non-adherence. The study also identified younger patients at higher risk for non-adherence while gender and diagnostic category did not influence adherence. Rhodes[12] identified factors associated with non-adherence, including medical issues especially psychiatric, inconvenience, relocation, systemic allergic reaction to immunotherapy, lack of insurance coverage, and prior track record of non-adherence in pharmacotherapy and poor patient perception as important. A study at a military medical center by More and Hagan[13] identified that active military duty, rush immunotherapy and age between 18-45 were important predictors of non-adherence.

In the present study, out of the nine factors associated with non-adherence in univariate analysis, five were found to be significantly associated with non-adherence on multivariate step-wise logistic regression analysis. Gender was associated with non-adherence in our population, but not age or educational status in the univariate analysis. However in the multivariate analysis, gender was not seen to be associated with non-adherence. A negative family history of atopy was associated with non-adherence probably due to the fact that subjects with a positive family history may have been better informed about allergic diseases, including the need for long term treatment. Allergic conjunctivitis was another clinical factor associated with non-adherence, probably due to a poor clinical response and may contribute to a negative perception about immunotherapy. A non-decrease in medicine requirements may not satisfy patient expectations and may also contribute to non-adherence. It was observed that patients who had a positive perception regarding immunotherapy were more likely to be adherent while patients who felt that immunotherapy was not helping them were likely to be non-adherent. We evaluated the role of missed doses and the pattern of missed doses in our population and observed on multivariate analysis that missing more than two doses in the last ten doses' stood as an independent factor and had a significant association with non-adherence.

Unlike in the earlier studies[3,13] where the type of allergen disease was not observed as important, patients with allergic conjunctivitis in the present study were at a higher risk of non-adherence. Age of the patient that was an important predictor of non-adherence in two of the earlier studies[3,13] was not found to be associated with non-adherence in our study. Relocation and job transfers were not found to be important. Perception of immunotherapy identified in an earlier study[4] was found to be significantly associated with non-adherence in our study too. None of the subjects receiving immunotherapy in our study were covered by insurance. Since most of the patients were young adults, there were no significant medical co-morbidities, that could affect adherence in our study. There were no anaphylactic reactions noted in any of the patients and all the patients reached maintenance dose between 24 to 28 weeks. Present study additionally evaluated family history, progression of the disease, and change in medicine requirements during the course of immunotherapy and the pattern of missed doses, which were not studied earlier. Progression of the disease, significantly associated with non-adherence on univariate analysis, was not found to be important on multivariate analysis.

In conclusion, independent factors associated with non-adherence may vary between different settings and countries. Therefore, it is felt that a number of studies need to be conducted in different practice

settings in different countries to assess variables that are associated with non-adherence. The most important independent factor found in the present study was the perception whether immunotherapy was useful for them or not. More time may be needed to counsel patients receiving immunotherapy on its likely outcomes. More studies are, therefore, required to further identify ideal practices of case-holding in patients receiving immunotherapy.

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