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Original Article

The Effect of Immunotherapy on Nonspecific Bronchial Hyperresponsiveness in Bronchial Asthma and Allergic Rhinitis

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Allergen injection therapy may improve nonallergic bronchial hyperresponsiveness, but results at the moment are less than convincing. The present study was conducted to evaluate the effect of immunotherapy on the degree of nonspecific bronchial hyperresponsiveness in patients with allergic bronchial asthma (BA) and/or allergic rhinitis (AR). Methacholine challenge bronchial provocation test, allergic skin test, serum IgE and peripheral blood eosinophil counts were performed before and after 12 months or more of immunotherapy. The improved group, as determined by a shift of at least two doubling concentrations of methacholine, was 75% of AR (n=16), 41.7% of BA (n=24) and 53.8% of BA+AR (n=13). The geometric mean of the methacholine provocational concentration (PC_{20}) changed from 3.40 to 14.36 mg/ml ($P<0.05$) in AR, from 0.73 to 1.04 mg/ml in BA (not significant), and from 1.43 to 5.07 mg/ml ($P<0.05$) in BA+AR. In conclusion, nonspecific bronchial hyperresponsiveness was improved by immunotherapy in three quarters of the allergic rhinitis cases and in about a half of the allergic bronchial asthma patients, which suggests that immunotherapy might be helpful at preventing the development of bronchial hyperresponsiveness in allergic rhinitis patients, and that it does not improve bronchial hyperresponsiveness in about a half of allergic bronchial asthma patients.

Key Words: Bronchial hyperreactivity, bronchial provocation tests, immunotherapy, allergic bronchial asthma, allergic rhinitis

INTRODUCTION

Allergic rhinitis and asthma are closely related disorders that commonly co-occur. They are strongly related to family history, and are both associated with blood eosinophilia and elevated serum immunoglobulin (IgE) levels. Both be precipitated by exposure to aeroallergens, and are mediated by immediate hypersensitivity mechanisms. It has been suggested that allergic rhinitis patients hyperresponsive to methacholine are at greater risk of developing asthma than those with normal bronchial challenges.[1,2]

Controlled trials have shown that immunotherapy relieves the symptoms of allergic rhinoconjunctivitis with minimal side effects, provided that high-quality extracts are used in sufficiently large doses.[3] Studies using single allergen models of allergic asthma have also shown that immunotherapy reduces airway sensitivity to allergens, decreases signs and symptoms provoked by natural exposure, and in some cases improves basal pulmonary functions.[3-5]

Nonspecific bronchial hyperresponsiveness to methacholine and histamine are correlated with each other and with various aspects of the assessment of asthma severity. Measurement of airway responsiveness may provide some objective guidelines for assessing asthma severity, and serial methacholine inhalation tests may also be used to follow the patient and to monitor the results of treatment. Allergen injection therapy may also improve nonallergic bronchial responsiveness, but results at the moment are less than convincing.[6]

We performed repeated methacholine challenge bronchial provocation test in patients with allergic bronchial asthma and/or allergic rhinitis that had

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received immunotherapy with specific allergens to evaluate its effect on the degree of nonspecific bronchial hyperresponsiveness.

MATERIALS AND METHODS

Patients

We studied 16 patients with allergic rhinitis without symptoms of asthma (AR), 24 patients with allergic bronchial asthma (BA) and 13 patients with allergic bronchial asthma and allergic rhinitis (BA + AR). Their mean age (mean ± standard deviation) was 32.1 ± 10.3 years for the AR group, 37.0 ± 13.4 years for the BA group and 33.4 ± 9.1 years for the BA+AR group. All patients had typical clinical histories compatible with their diseases, manifested positive skin reactions to one or more inhalant allergens, and proved positive by the methacholine challenge bronchial provocation test. Patients were allowed to use a $beta_2$-adrenergic agonist metered dose inhaler as needed. Oral $beta_2$-adrenergic agonist and slow release theophylline tablets were prescribed to control asthma if needed, but these drugs were abstained from for at least 48 hours prior to the methacholine challenge bronchial provocation test. Systemic glucocorticoid may have been prescribed to control acute asthmatic attacks. Inhaled corticosteroids or other anti-inflammatory agents that might affect bronchial hyperresponsiveness were not prescribed. Tests were postponed for at least 8 weeks after respiratory infections, asthma flares, or systemic glucocorticoid treatment.

Methods

Allergic skin tests, methacholine challenge bronchial provocation tests, and measurements of serum IgE and peripheral blood eosinophil count were performed before and after the immunotherapy with specific allergens for 12 months or longer.

Allergy skin test and immunotherapy

Prick tests were performed on the backs of all patients with extracts of common inhalant allergens including *Dermatophagoides farinae*, house dust, various pollens and animal danders (Bencard Ltd., Betchworth, Surrey, U.K.) during the preliminary study. A follow up study was performed on the forearms with allergens that were administered for the immunotherapy. Skin reactions were read at 15 minutes. Wheal and erythema sizes were presented as the mean value of reaction diameters to the allergens used in the immunotherapy. Thirty-one patients received immunotherapy with house dust and mites and 22 patients were treated with these and additional pollens.

Methacholine challenge test

Nonspecific bronchial hyperresponsiveness was determined by the previously described standard method.[7] Aerosols of saline followed by doubled concentrations of methacholine (0.075 to 25.0 mg/ml) were inhaled. The forced expiratory volume in 1 second (FEV_1) was measured 5 minutes after each inhalation, and this was continued until the FEV_1 had fallen by 20% (calculated from the post-saline value). Provocational concentrations of methacholine used to produce a 20% decrease in FEV_1 from the baseline value (PC_{20}) were obtained by linear interpolation of the points on the graph of percentage reduction in FEV_1 plotted against the methacholine concentration in mg/ml. The result of the follow up methacholine challenge test was classified as improved if the methacholine threshold concentration, required for a positive response, had increased by more than 4 fold compared to that of the initial test, as no change if the change was within 4 fold; and as deteriorated if it had decreased more than 4 fold.[8]

Statistical analysis

Logarithmic transformation of PC_{20} was used for all calculations with statistical purpose to stabilize the variance, and normalize the distribution. The geometric mean of PC_{20} was calculated from the transformed values and presented as their original values (antilogarithms). Values of methacholine PC_{20}, baseline spirometry forced vital capacity

(FVC), FEV_1 and forced mid-expiratory flow ($FEF_{25\%-75\%}$), serum IgE, eosinophil count, and wheal size on the initial study were compared with values from the follow up study by using Student's t-test for paired values. Differences between methacholine PC_{20}s of the initial and follow up studies of the three groups were compared by MANOVA. Results are expressed as mean ± standard deviation, and the level of statistical significance was chosen at $P<0.05$.

RESULTS

Baseline spirometry, serum IgE and prick test wheal size

No significant difference was found between the baseline spirometry parameters, such as, FVC, FEV_1 and $FEF_{25\%-75\%}$ of the three groups, or between the initial and follow up tests, except BA + AR group (Table 1), and no significant changes of serum IgE follow up levels were found between groups. Wheal size significantly decreased on follow up in each group, but this finding was of limited value because the follow up prick test was conducted on the forearm and initial testing on the back (Table 2).

Methacholine challenge test after immunotherapy

Of the 16 patients with AR, 75% showed improvement, 12.5% no change and 12.5% a deterioration (Table 3). Although a half of the AR patients showed bronchial hyperresponsiveness in the asthmatic range (PC_{20} < 8 mg/ml) on initial testing, 10 patients had a negative methacholine challenge test on follow up (Fig. 1). Of 24 patients with BA, 41.7% were improved or showed no change, and 16.7% deteriorated (Table 3, Fig. 2). No negative conversions were found on follow up testing, and some patients showing minor changes after 12 months of immunotherapy revealed improvement after 24 months or longer (data not shown). Of 13 patients with BA + AR, 53.8% improved and 46.2% unchanged; no patient showed deterioration (Table 3, Fig. 3).

The geometric mean value of the methacholine PC_{20} increased from 3.40 to 14.36 mg/ml (expressed in logarithmic values 0.53 ± 0.55 and 1.16 ± 0.39, respectively: $P<0.001$) in AR; from 0.73 to 1.04 mg/ml (expressed in logarithmic values -0.13 ± 0.61 and 0.02 ± 0.54 respectively: not significant) in BA; and from 1.43 to 5.07 mg/ml (expressed in logarithmic values 0.15 ± 0.68 and 0.70 ± 0.53, respectively: $P<0.05$) in BA + AR (Table 4). The improved PC_{20} geometric means in AR and BA + AR were significantly different from the corresponding BA values ($P<0.05$).

The comparison between the improved and the not-improved groups

In the case of AR, no difference of parameters examined during the initial test was apparent between the improved and the not improved groups. In BA, the improved group showed

Table 1. Comparison of Pulmonary Function Parameters between the Initial and the Follow up Tests

	FVC (L)		FEV1 (L)		FEF25% - 75% (L/sec)	
	Initial	Follow up	Initial	Follow up	Initial	Follow up
AR† (n=16)	3.46 ± 0.78 (88 ± 9)	3.47 ± 0.80 (87 ± 11)	3.00 ± 0.68 (95 ± 9)	3.04 ± 0.76 (95 ± 11)	3.77 ± 1.23 (106 ± 26)	3.76 ± 1.36 (104 ± 31)
BA‡ (n=24)	3.48 ± 0.95 (83 ± 14)	3.59 ± 0.92 (84 ± 9)	2.75 ± 0.94 (83 ± 16)	2.79 ± 0.92 (83 ± 16)	2.62 ± 1.60 (70 ± 31)	2.64 ± 1.70 (70 ± 34)
BA+AR§ (n=13)	3.15 ± 0.94 (81 ± 15)	3.50 ± 0.99* (88 ± 13)	2.72 ± 0.90 (86 ± 16)	2.86 ± 0.87 (92 ± 13)	2.98 ± 1.12 (84 ± 22)	2.93 ± 1.08 (82 ± 22)

Values are expressed as mean ± SD.
Predicted values are presented in the parentheses.
†allergic rhinitis; ‡bronchial asthma; §bronchial asthma with allergic rhinitis.
*$P<0.05$ when compared the follow up value with the initial one.

Table 2. Comparison of Serum IgE and Prick Test Wheal Size between the Initial and Follow up Tests

	IgE (IU/ml)		Wheal Size (mm)	
	Initial	Follow up	Initial	Follow up
AR† (n=16)	339 ± 265	413 ± 331	8.2 ± 3.4	6.2 ± 2.4*
BA‡ (n=24)	565 ± 385	557 ± 384	6.0 ± 3.3	4.4 ± 2.4*
BA + AR§ (n=13)	438 ± 364	347 ± 346	6.3 ± 4.3	4.6 ± 2.6*

Values are expressed as mean ± SD.
†allergic rhinitis; ‡bronchial asthma; §bronchial asthma with allergic rhinitis.
The initial prick test was performed on the back and the follow up test was performed on the forearm.
*$P<0.05$ when compared with the initial value.

Table 3. Result of Follow up Methacholine Challenge Test

Methacholine Bronchial Threshold	Improved	No change	Deteriorated
AR (n=16)	75.0%	12.5%	12.5%
BA (n=24)	41.7%	41.7%	16.7%
BA+AR (n=13)	53.8%	46.2%	–

Improved: more than 4 fold increase of methacholine threshold.
No change: within 4 fold change.
Deteriorated: more than 4 fold decrease.
AR, allergic rhinitis; BA, bronchial asthma; BA + AR, bronchial asthma with allergic rhinitis.

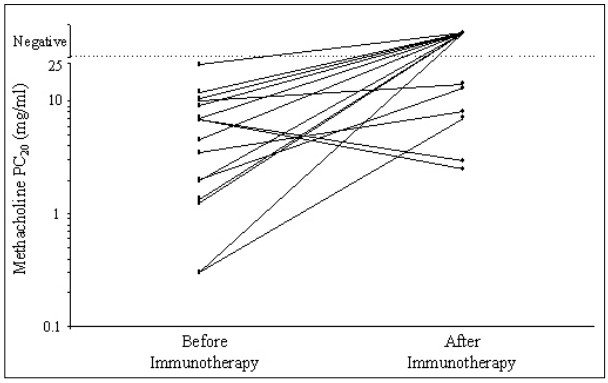

Fig. 1. The effect of immunotherapy evaluated by methacholine challenge test in 16 patients with allergic rhinitis (PC_{20} : Provocation concentration causing a fall of 20% of a control FEV_1 measurement).

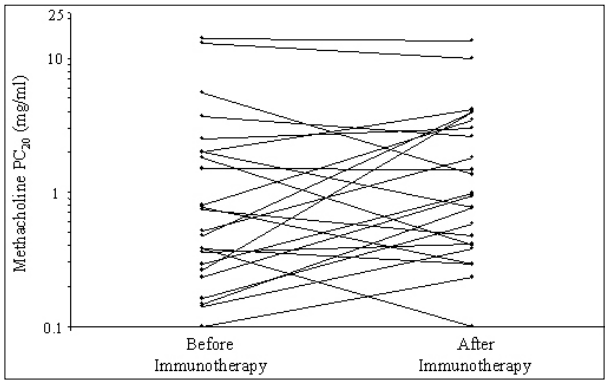

Fig. 2. The effect of immunotherapy evaluated by methacholine challenge test in 24 patients with bronchial asthma (PC_{20}: Provocation concentration causing a fall of 20% of a control FEV_1 measurement).

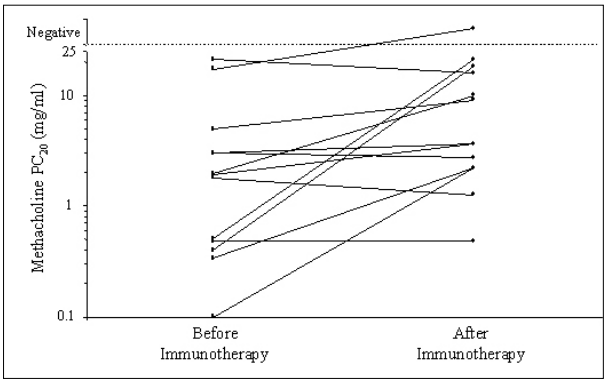

Fig. 3. The effect of immunotherapy evaluated by methacholine challenge test in 13 patients with bronchial asthma and allergic rhinitis (PC_{20} : Provocation concentration causing a fall of 20% of a control FEV_1 measurement).

Table 4. The Comparison of the Geometric Means of Methacholine PC_{20} between the Initial and Follow up Tests

	Initial	Follow up	P value
	Methacholine PC_{20} (mg/ml)	Methacholine PC_{20} (mg/ml)	
AR (n=16)	3.40 (0.53 ± 0.55)	14.36 (1.16 ± 0.39)	< 0.001
BA (n=24)	0.73 (-0.13 ± 0.61)	1.04 (0.02 ± 0.54)	NS
BA+AR (n=13)	1.43 (0.15 ± 0.68)	5.07 (0.70 ± 0.53)	< 0.05

Mean ± SD values of Log PC_{20} are expressed in parentheses.
NS, Not significant.
AR, allergic rhinitis; BA, bronchial asthma; BA + AR, bronchial asthma with allergic rhinitis.

Table 5. The Comparison of Initial Pulmonary Function Parameters and Methacholine Threshold between the Improved and the Not Improved Groups

	FVC (L)	FEV_1 (L)	$FEF_{25\%-75\%}$ (L/sec)	Methacholine PC_{20} (mg/ml)
AR†				
Improved(n=12)‖	3.60 ± 0.81 (90 ± 9)	3.13 ± 0.69 (97 ± 9)	3.86 ± 1.21 (107 ± 26)	2.90 (0.46 ± 0.62)
Not improved(n= 4)¶	3.05 ± 0.60 (82 ± 8)	2.64 ± 0.56 (90 ± 4)	3.50 ± 1.42 (102 ± 32)	5.76 (0.76 ± 0.22)
BA‡				
Improved(n=10)‖	3.13 ± 0.89 (79 ± 17)	2.25 ± 0.65 (74 ± 18)	1.72 ± 0.62 (51 ± 17)	0.24 (-0.63 ± 0.32)
Not improved(n= 14)¶	3.72 ± 0.95 (86 ± 11)	3.10 ± 0.97* (89 ± 12*)	3.26 ± 1.79* (83 ± 31*)	1.64 (0.22 ± 0.52)*
BA+AR§				
Improved(n= 7)‖	2.75 ± 0.46 (74 ± 15)	2.34 ± 0.38 (80 ± 15)	2.73 ± 0.75 (80 ± 20)	0.80 (-0.10 ± 0.73)
Not improved(n= 6)¶	3.62 ± 1.18 (90 ± 11*)	3.06 ± 1.12 (94 ± 15)	3.27 ± 1.47 (87 ± 26)	2.83 (0.45 ± 0.54)

Values are expressed as mean ± SD; predicted values or Log PC_{20} are presented in the parentheses.
*$P<0.05$ comparing the improved group with the not improved group.
‖more than 4 fold increase of methacholine threshold.
¶within 4-fold change or more than 4 fold decrease of methacholine threshold.
†allergic rhinitis; ‡bronchial asthma; §bronchial asthma with allergic rhinitis.

significantly lower values of initial baseline FEV_1, $FEF_{25\%-75\%}$ and methacholine PC_{20} than those of the not-improved group. In BA + AR, the improved group showed significantly lower values of initial FVC than that of the not-improved group. The improved group showed a tendency towards lower initial methacholine PC_{20} (Table 5). No differences in initial serum IgE, eosinophil counts and prick test wheal size were found between the improved and the not-improved groups (data not shown).

DISCUSSION

Asthma and allergies are among the most common chronic diseases. Although the role of inhalant allergens has been clearly demonstrated in the pathogenesis of asthma, the importance of specific immunotherapy remains controversial.[5] In the management of asthma, clinical history and physical examination are the indices most often used to evaluate severity and guide therapy, however, an accurate history is not always available. Spirometry or peak flow measurement

also proved of limited value. The effects of any particular type of therapy remain difficult to evaluate objectively.

It has been suggested that airway hyperresponsiveness is an important determinant of asthma severity and treatment requirement.[9] Cockcroft mentioned that the regular monitoring of nonallergic bronchial responsiveness would provide objective evidence to document improvement and might provide a clue regarding the adequacy of treatment, particularly with respect to environmental control. Furthermore, it was suggested that new treatments for asthma should also be monitored with regard to their effects, both short-term and long-term on nonallergic bronchial responsiveness.[6] Results of studies examining the evolution of bronchial hyperresponsiveness in patients undergoing mite specific immunotherapy are unclear.[5] Some studies have demonstrated bronchial hyperresponsiveness improvements, whereas others have not.[5]

A recent meta-analysis of randomized controlled trials of allergen specific immunotherapy in asthma revealed improved bronchial hyperresponsiveness.[4] But, it is well recognized that studies showing negative findings are less likely to be published than those showing statistically significant positive findings. This would have biased the meta-analysis towards finding a benefit from allergen immunotherapy.[4] Recently, a double-blind, controlled trial of multiple allergen immunotherapy in 121 children with moderate-to-severe perennial asthma reported no discernable benefits.[3] In particular, no changes of methacholine challenge bronchial hyperresponsiveness were evident with immunotherapy. Our study involved upon milder bronchial asthma patients and was conducted upon adults.

Juniper et al followed bronchial hyperresponsiveness in patients with asthma for up to 30 months.[10] The main conclusion of their study was that bronchial hyperresponsiveness remains stable over long periods when there are no exacerbating factors. These authors also found that in a subgroup of their patients, bronchial hyperresponsiveness to histamine tended to improve after prolonged treatment with inhaled corticosteroids. Theophylline and bronchodilator aerosols alone were found not to change the severity of bronchial hyperresponsiveness.[11,12]

In general, most subjects reached a "best" value for PD_{20} after 5 to 12 months of immunotherapy and did not improve further.[13] The reproducibility of the bronchial challenge tests is only to within one to two times the concentrations or doses, and clinically significant improvement or deterioration is reflected only by a shift of at least two doubling concentrations or doses in either direction.[8]

Our study demonstrates that 53.8% of BA + AR and 41.7% of BA patients became less reactive to methacholine after immunotherapy. Immunotherapy improved bronchial hyperresponsiveness in 17 (45.9%) of 37 patients with allergic bronchial asthma (Table 3). In terms of the geometric mean of PC_{20}, a significant improvement was found in AR and BA + AR (Table 4). This suggests the possibility that immunotherapy might be more effective in asthma associated with allergic rhinitis than asthma not associated with allergic rhinitis. The improved group in BA showed lower baseline FEV_1 at 74 ± 18% of the predicted value, which was compatible with moderate persistent asthma. It suggests the possibility that immunotherapy might also be effective in moderate persistent bronchial asthma. However, these remain only possibilities and conclusions should not be drawn. There were some limitations to our study that should be mentioned in the context of immunotherapy evaluation. Our study was of limited sample size, and not randomized in design, and immunotherapy did not improve bronchial hyperresponsiveness in about a half of the allergic bronchial asthma patients.

The relationship between baseline FEV_1 and airway responsiveness to histamine or methacholine, differs in asthmatics and patients with chronic airflow limitations. Airway hyperresponsiveness to histamine or methacholine is not diagnostic of asthma when chronic airflow limitations are present.[14] A significant correlation was obtained between baseline lung function and the reactivity of airways.[15] In our study no chronic airflow limitations or differences in baseline spirometry measurements were detected between the initial and the follow up tests in any intra- or inter-group comparison (Table 1).

Population studies have established that symptomatic asthmatic patients have a $PC_{20} < 8$ mg/ml,

and most normal subjects with no symptoms or history of asthma have a $PC_{20} > 8$ mg/ml.[16-18] We previously reported the asthmatic range of methacholine PC_{20} was less than 4.66 mg/ml in Korean allergic bronchial asthma.[19] An appreciable number of subjects with allergic rhinitis demonstrate physiologic evidence of peripheral airway obstruction, which may occur spontaneously during the symptomatic stages or in response to the inhalation of a cholinergic agent. Although the dose of methacholine producing a 20% decrease in FEV_1 was greater in rhinitis than asthmatics, there was considerable overlap between the methacholine PC_{20}s of the two groups.[20,21]

In Korea, 69% of AR patients responded to methacholine inhalation (% decrease of FEV_1 > 15%).[22] The persistence of bronchial hyperresponsiveness to methacholine, as measured by S. Gaw, was present throughout the year in patients of seasonal AR, although no abnormalities were found in the spirometric variables.[23] In the present study 75% of the AR group showed improved methacholine PC_{20}, although about a half of the AR group had PC_{20} values lower than the asthmatic range on the initial test. Ten patients (63%) of the AR group receiving immunotherapy became normal by the methacholine challenge test on the follow up. We suggest that immunotherapy might be effective for the management of AR patients with nonspecific bronchial hyperresponsiveness and might be helpful at preventing the onset of bronchial asthma.

In conclusion, nonspecific bronchial hyperresponsiveness was improved by immunotherapy in three-quarters of the allergic rhinitis patients and in about a half of the allergic bronchial asthma patients with allergic rhinitis. These results suggest that immunotherapy might be helpful at preventing the development of bronchial hyperresponsiveness in allergic rhinitis patients, and that it does not improve bronchial hyperresponsiveness in about a half of allergic bronchial asthma patients.

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