Immunotherapy and Its Role in Asthma and Allergic Diseases

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Introduction :

Immunotherapy can be defined as an attempt to provide some protection from natural exposure to external allergens by the prophylactic administration of antigens which have been shown to induces allergic symptoms[1].

Immunotherapy was first described by Robert Cooke in 1918[2]. Mr. Noon an English Physician was showed that immunotherapy produced improvements in patients with hay fever (allergic rhinitis)[3]. Most workers successively established that patients with IgE mediated disease improve with allergen specific immunotherapy. The importance of allergen - induced inflamation in asthma has recently becomes more widely appreciated. In different study it was found that prevalence of asthma increased as serum IgE increased for all age groups. In fact no asthma was present in subjects with the lowest IgE levels for age & sex. Conclusion was that asthma is almost always associated with some types of IgE related reaction and therefore has an allergic basis. Another way to assess the role of allergy in asthma is to examine the link between allergic factor and the rate of emergency room visits of asthma.

An obvious goal of immunotherapy is to demonstrably reduce that portion of a patients symptoms of asthma that can be attributed to the allergen in question. An additional but perhaps more difficult aim is to reduce the patients comprehensive asthma severity[4,5].

One of the most intriguing outcomes of immunotherapy as it applies to asthma is a decrease in allergen specific bronchial reactivity.

There is an impression that immunotherapy is more effective in patients whose asthma is related to contact with domestic animals, but has not yet been objectively confirmed.

The immunological basis of immunotherapy now being actively investigated in many centres. One of the earlier theories that it stimulates the production of blocking antibodies IgG, specific for the injected allergen still remains general support but there is now strong circumstrantial evidence that IgG antibody ablates the late but not the early IgE mediated response. This postulate has potentially important implications because it suggests that experimental studies on the efficacy of imunotherapy should be targeted on the late response, which in clinical terms is probably more important than the early response inthe type of asthmatic for whom this form of treatment is likely to be of value[6,7].

Another possible mechanism by which immunotherapy may influence the resposne to allergic challenge is by generating the productin of IgG and IgA blocking antibodies in respiratory secretions. If it should prove to have any substance, perhaps we shall one day be treating allergic asthma by the inhalation of a specific 'blocking' IgG or IgA aerosol8.

Possible mechanism of action of immunotherapy[9]

1. Decrease in allergen-specific IgE over time.
2. Ablation of expectant postseasonal rise in allergen - specific IgE.
3. Increase in allergen-specific IgG-blocking antibodies.
4. Increase in allergen-specific IgG and IGA antibodies in respiratory secretions.
5. Decrease in allergen-induced basophil histamine release in some patients.
6. Decrease in antigen induced proliferation of lymphocyte mediators.
7. Generation of antigen-specific suppressor cells.

When to consider immunotherapy for asthma[10,11].

1. Allergens are demosntrated to be the essential basis for the majority of asthma symptoms.
2. Avoidance measures and medication have not yielded acceptable results.
3. Clinical trials have demonstrated efficacy (pollens, mite mold ? animal danders ?)
4. Risks and benefits of immunotherapy with the allergen in question favor its use.

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Results of Immunotherapy Trials with Allergen Extract in Different Centres in the World[12,13].

Immunotherapy trials with dust extract -

Allergen	Author(s)	Year	Length of Treatment	Age Group	Clinical Parameters (no. improved/Total)		Significant Improvement	Decreased Bronchial allergen sensitivity	Decreased Nonspecific bronchial sensitivity
					Extract	Placebo			
Dust	Bruun	1949	2 yrs	A	74/95	28/82	Yes	–	–
	British Tuberculosis Association	1968	4 mo	A	18/30	19/35	No.	–	–
	Aas	1971	3 yrs	C	43/51	16/28	yes	yes	–

A = adult; C= children

House dust mite immunotherapy trials-

Allergen	Author(s)	Year	Length of Treatment	Age Group	Clinical Parameters (no. improved/Total)		Significant Improvement	Decreased Bronchial allergen sensitivity	Decreased Nonspecific bronchial sensitivity
					Extract	Placebo			
Mite	Maunsel et al.	1971	6-9 mo	C,A	14/18	10/16	No	–	–
(Der f)	Newton et al.	1978	1 yr	A	2/7	2/7	No	–	–
	Formgren et al.	1984	1 yr				–	Yes	No
	Murry et al.	1985	1 yr	C	4/7	2/4	No	No	No(↑)
Mite	Smith	1971	13 wk	C, A	10/11	8/11	No	–	–
(Der p)	D'Souza	1973	12 Kw	C, A	25/40	24/43	No	–	–
	Pauli et al.	1984	12 mo	A	3/9	4/9	Yes (limited)	–	–
	Gaddie et al	1976	$13^1/_2$ mo	C,A	–	–	No	–	–
	Marques and Avila	1978	$7^1/_2$ mo	C, A	13/16	8/12	No	–	–
	Warner et al.	1978	12 mo	C	23/27	22/24	No	Yes (late)	
	British Thoracic Society	1979	12-18 mo	C, A	19/33	9/18	No	–	–
	Bousquel et al.	1985	7 wk	A	-/20*	-/10	–	Yes	–
	Bousquet et al	1988	1 yr	A,C	Asthma Severity score Improved from 3.2 to 1.1 in 171 patients	Asthma Severity score worsened slightly from 3.0 to 3.2 in 44 patients	Yes	–	–
	Van Bever and Stevens	1989	1 yr	C	13/15	0/8	Yes	Yes (late)	–

A = adult; = children

• This study did not examine clincial improvement - it examined changes in bronchial sensitivity to allergen.

Pollen extract immunotherapy trisls :

Allergen	Author(s)	Year	Length of Treatment	Age Group	Clinical Parameters (no. improved/Total)		Significant Improve-ment	Decreased Bronchial allergen sensitivity	Decreased Nonspecific bronchial sensitivity
					Extract	Placebo			
Grass	Frankland and Augustin	1954	4 mo	C, A	29/31	8/26	Yes	–	–
Pollen	McAllen	1969	3 mo	C, A	17/27	2/8	Yes	–	–
	Hill et al.	1982	6 mo	C	In 1st session, symptom scores increased in both groups; in 2nd season, only placebo scores increased		No	–	–
	Ortolani et al.	1984	10 mo	A	Lower symptoms scores in 8 treated vs. 7 placebo patients		Yes	No	–
	Bousquet et al.	1985	4 mo	C, A	23 patients; average symptom/ Medication score=0.9	10 patients; average symptom/m medication score = 2.7	Yes	–	–
	Reid et al.	1986	8 mo	A	9 patients; symptom/ medication score = 47	9 patients/ symptom medication score = 178	Yes	–	–
	Bousquet et al.	1989	4 mo		39 patients average symptom score - 15.1	18 patients average symptom score 54.8	Yes	–	–
Ragweed polled	Brucce et al.	1977	8 mo	A	15 patients mean physcan asthma score = 4.4	17 patients; mean physcan asthma score = 4.1	No	No	–
Birch pollen	Rak et al.	1988	4 mo	A	20 patient average medication score = 2.8	20 patietnts; average medication score = 18.1	Yes	–	Yes (trend)

A = adult; C = children

Mold extract immunotherapy trials-

Allergen	Author(s)	Year	Length of Treatment	Age Group	Clinical Parameters (no. improved/Total)		Significant Improve-ment	Decreased Bronchial allergen sensitivity	Decreased Nonspecific bronchial sensitivity
					Extract	Placebo			
Mold Clados-porium	Dreborg et al.	1986	10 mo	C	Median medication scores in 16 extract patients lower than in 11 placebo patients		Yes	Yes	–
Alternaria	Cantani et al.	1988	3 yr	C	31/39	0/40	Yes	–	–
Cladosporium	Malling et al	1986	5-7 mo	A	5/11	1/11	Yes	–	–
Alternaria	Horst et al.	1990	1 yr	C, A	0.84* in 13 patients	3.55*in 11 patients	Yes	–	–

* Global symptom medication scores
A = adult; C= Children

Animal "dander" immunotherapy trials –

Allergen	Author(s)	Year	Length of Treatment	Age Group	Clinical Parameters (no. improved/Total)		Significant Improve-ment	Decreased Bronchial allergen sensitivity	Decreased Nonspecific bronchial sensitivity
					Extract	Placebo			
Animal	Taylor et al.	1978	4 mo	A	-/5*	-/5	–	Yes	No
Cat	Ohman et al.	1984	4 mo	A	6/9	2/9	Yes	Yes	No
	Van Metre et al.	1988	1 yr	A	11/11	4/11	–	Yes	No
Cat and	Sundin et al.	1986	1 yr	C, A	13/22	5/17	Yes	Yes (cat)	yes
dog	Bertelsen et al.	1989	9 mo	C	-/14*	-/13	–	yes	Yes (cat)
Dog	Valovirta et al.	1986	1 yr	C	8/15	2/12	Yes	Yes	–

A = adult; C = children

* This study did not examine clinical improvement - it examined changes in bronchial sensitivity to allergen. Denomniator = number of patients

At present the efficacy of immunotherapy is fairly well-documented in allergic rhinitis and in allergy to insect venoms. In contrast, the complexity of the asthmatic process seems to have made it particularly difficult to reach unequivocal results with respect to the usefulness or otherwise of immunotherapy in this disease.

Since even the best extracts and regimens at present cannot help all patients and because an individual patients response to treatment is unpredictable, immunotherapy should generally not be the first choice of treatment for patients with allergic asthma. A reasonably clear association between the asthmatic symptoms and the offending allergen must by established to ensure optimal results[14,15].

The pharmacologic advances of recent years have resulted in a change in the use of immunotherapy. Sustained-released medications, inhaled symathomimetics with prolonged durations of action, wider use of cromolyn in pediatric asthma, and most importantly, a growing trend toward the use of inhaled steroids at doses capable of reducing airway inflammation and bronchial hyper-responsiveness have reduced the need for allergen immunotherapy. The benefits and risks of the various treatment modalities (avoidance, medications, and immunotherapy) need to be examined for each patient. Immunotherapy is a potentially dangerous, tedious treatment. Recurrent visits to the physician's office can be time-consuming, but may allow better "fine-tuning" of the patient's pharmacologic regimen and enhance compliance. What are the dangers of many years of oral theophylline or inhaled steroid use ? Dose a standard immunotherapy treatment course, for example, 5 years, have an effect into the future on what would have been the natural history of the process ? If so, this would affect the cost-benefit comparison for drug versus injection therapy. Refinements in immunotherapy may improve results and decrease risks. It has not been as easy to demonstrate efficacy of immunotherapeutic treatment in asthma as in allergic rhinitis. Nevertheless, well controlled trials of immunotherapy in mite, pollen, animal dander, and more recently mold allergy have been promising. In practice, allergy injections are generally adminstered to patients who have significant allergic rhinitis. If a patients also has some degree of asthma, immunotherapy may produce a beneficial response for the problem as well. Whether immunotherapy should be considered for asthma alone depends on the clinical situation, and the parameters governing that decision require further refinement[15].

Untoward effects of immunotherapy[4,16]

Untoward reactions following therapy are of several types. Local swelling at the injection site occurs in about 20% of patients and are a source of discomfort, not danger. Systemic or generalized reactions consist of urticaria, breathing difficulties attributable to laryngeal edema or bronchospasm, and hypovolemic shock which can be life-threatening.

Conclusion :

In summary, allergy is now generally considered to be important in the pathogenesis of asthma in children and adults. Avoidance measures and

medications are frequently recommended. Immunotherapy is commonly employed, although its precise role is still undefined[17]. There is mounting evidence that immunotherapy induces clinical improvement in allergic asthmatic. But most specialists agree that if the improvement gained through immunotherapy can be had through pharmacologic means and manipulation of enviromental triggers, then immunotherapy may not be necessary.

References :

1. Bacal E et al. Polymerized whole ragweed. An improved method of immunotherapy. J. Allergy Clin. Immunol 1979; 62 : 289.
2. Bousquet J et al. Eosinophilic inflammation in asthma N Engl J Med 1990; 323 : 1033.
3. Cockcoroft DW. Mechanism of perennial allergic asthma Lancet 1983; 2 : 253.
4. Committee or Safety of Medicines. Desensitizing vaccines Br. Med. J 1986; 293 : 948.
5. Grant, IWB, Mosbech H, Weeke B. Does immunotherapy have a role in the treatment of asthma ? Clin Allergy 1986; 16 : 7.
6. Levine MI. Systemic reactions to immunotherapy (abstract). J Allergy Clin Immunol 1979; 63 : 209.
7. Lichtenstein LM. An evaluation of the role of immunotherapy in asthma. Am Rev Respir Dis 1978; 117 : 191.
8. Lichtenstein, LM, Valentine MD, Norman PS. A reevaluation of immunotherapy for asthma. Amj Rev. Respir Dis, 1984; 129 : 657.
9. Lockey RF et al. Fatalities from immuniotherapy (IT) and skin testing J Allergy Clin. Immunol 1987; 79 : 660.
10. Moss RB. Allergic etiology and immunology of ashtma. Ann. Allergy 1989; 63 : 566.
11. Norman PS. Fatal misadventures (editorial). J. Allergy Clin Immutol 1987; 79 : 572.
12. Norman PS, Lichtenstein LM. The clinical and immunologic specificity of immunotherapy J Allergy Clin Immunol 1978; 61 : 370.
13. Position Statement. Personnel and equipment to treat systemic reactions caused by immunotheray with allergic extracts. J. Allergy Clin Immunol 1986; 77 : 271.
14. Reid KN et al. Fatalities (F) from immunotherapy (IT) and skin testing (ST) (abstract). J Allergy Clin. Immunol 1990; 85 : 180.
15. Tuchinda M, and Chai H. Effect of immunotherapy in chronic asthmatic children. Allertgy 1973; 51 : 131.
16. WHO/IVIS Working group report. Current status of allergen immunotherapy. Lancet 1989; 1 : 259.
17. Editorial. Systemic reactions from allergen immunotherapy. J Allergy Clin. Immunol. 1992; 90 : 567.