

REVIEW

Allergen-antibody complexes in the treatment of *Dermatophagoides pteronyssinus* hypersensitivity diseases

J.-M. R. SAINT-REMY and J. J. MACHIELS*

*Allergy and Clinical Immunology Unit, Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, Brussels, and *Chest Disease Unit, Internal Medicine Department, Clinique Saint-Pierre, Ottignies, Belgium*

Any prospective new therapy of allergic diseases should satisfy the following basic criteria: (i) to improve the patient's clinical status, which clearly implies that any proposed therapy should have a significant effect on the non-specific, inflammatory events occurring in any bronchi (or in the skin in the case of atopic dermatitis), and which affect the patient's daily life; (ii) to be at least as safe and efficient as current medications, including inhaled steroids and; (iii) to have an effect persisting for a significant length of time after the end of administration.

By virtue of the recently acquired understanding of the mechanisms by which IgE antibodies are produced and regulated, it is possible nowadays to envisage several strategies which could satisfy the above criteria. In broad terms, one can divide these strategies into several main categories. The first and more classical category includes methods by which the production of allergen-specific IgG antibodies is increased. This is still the hallmark of conventional desensitization, using allergens in native or modified forms. A second type of approach includes methods in which the aim is the down-regulation of the production of IgE antibodies, with or without effect on specific IgG. A recent review, which will not be developed here, summarizes these strategies [1].

Our choice was to develop a third approach, namely, to design a method by which tolerance to specific allergens could be induced. Several immunological mechanisms have indeed been described by which the production of antibodies can be reduced, but two properties of antibodies themselves attracted our interest. Firstly, antibodies can be used as inducers of anti-idiotypic antibodies which in turn can down-regulate the production of antibodies carrying the corresponding idio type, as it has been shown in animal models at least [2]. Secondly, an antibody has the capacity to alter the processing and presentation to specific T cells of the antigen it recognizes [3].

Both of these antibody regulatory properties could be significantly enhanced if the antibody is present in the

form of an immune complex, and so we decided to use allergen-specific antibody complexes for the treatment of allergic diseases. We prepared complexes in antibody excess since previous studies in other model systems had shown that such complexes can suppress antibody production. In addition, the complexes were prepared using autologous antibodies in order to favour an anti-idiotypic response without any risk of an anti-allotypic reaction. Antibodies were prepared by affinity chromatography from the serum of allergic donors and have been used over the past few years to treat a total of about 400 house dust mite-sensitive patients suffering from either bronchial asthma [4,5] or atopic dermatitis [6,7].

The results of these studies can be summarized as follows: (i) there is a drastic reduction in the level of parameters measuring specific reactivity, such as allergen skin tests or bronchial provocation tests. In a significant number of asthmatic patients, reactivity to inhaled allergen became undetectable; (ii) in bronchial asthma, there is a gradual reduction of bronchial reactivity to non-specific inhalants, such as acetyl-choline. In about 40% of the patients such reactivity became undetectable after the second year of treatment and was associated with an almost total abandon of concomitant medication that had been in daily use for years prior to the start of the therapy. Interestingly, these effects were maintained at least for a few years after completing the injection schedule (Fig. 1); (iii) in atopic dermatitis, the first signs of clinical improvement appeared after 3–4 months. After a longer period, about 85% of the patients responded to the treatment, with an average improvement of 80%. Forty per cent of the patients were completely free of disease several months after the end of the injection schedule (Fig. 2); (iv) no side-effects were observed when more than 3000 injections were administered. Several reasons could account for this. First, the amount of allergen present in the complexes is low, namely 500–1000 times lower than that which is used in conventional desensitization. It can be estimated that a cumulative amount of less than 0.5 µg allergen/kg body weight is enough to obtain clinical efficacy. Secondly, the allergen is administered in a form in which epitopes

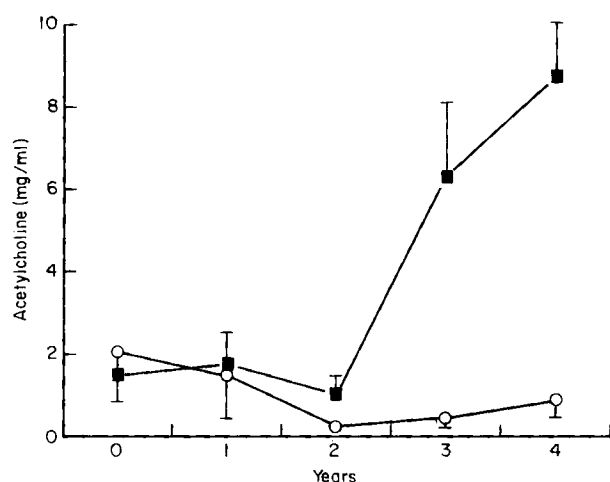


Fig. 1. Bronchial reactivity to acetylcholine. Variation with time of the mean concentration of acetylcholine whose inhalation resulted in a 35% reduction of specific airway conductance. Vertical bars represent SEM. Six of the seven patients in the treated (■) group did not react to the highest concentration (10 mg/ml) of acetylcholine. These results were obtained by injecting over 3 years a cumulative amount of 15 μ g autologous anti-*Der p* antibodies and 3 μ g *Der p* allergens. (—○—, placebo group).

recognizable by IgE antibodies are masked. Thirdly, injections are administered intradermally, thereby reducing the rate of allergen diffusion.

Two more recent studies have shown that this therapy can be applied to children with *D. pteronyssinus*-sensitive asthma (Lebrun *et al.* manuscript in preparation) and that complexes made of F(ab')₂ fragments of specific antibodies are at least as efficient as complexes made with whole antibody molecules [8]. The latter observation opens up new perspectives for treatment: since digestion of antibodies removes most allotypic determinants, a study in which multi-donor pools of gammaglobulins are used for the isolation of specific antibodies can be envisaged in which there is virtually no risk of allo-immune reaction. Such a study is now being carried out. For the same reason, it may become possible to use adjuvants to increase the idiotype immunogenicity, without risk of increasing the immunogenicity of determinants located on the constant parts of antibodies. Finally, the observation that the Fc part of the antibody molecule is not necessary for the efficacy of the complexes, suggests that so-called 'professional' antigen-presenting cells, which internalize antigen-antibody complexes after binding to cell surface Fc receptors, do not play a role in the mechanism of action of the administered complexes. Rather, as we have been able to confirm *in vitro*, specific B cells, or perhaps dendritic

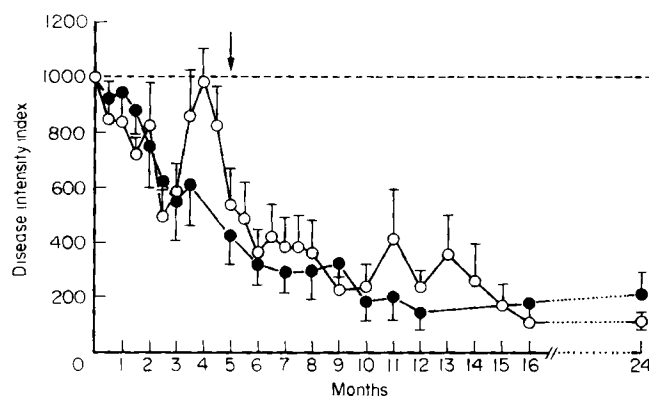


Fig. 2. Skin disease intensity index. Evolution of the disease intensity index for two groups of patients over 2 years. No injection of allergen-antibody complexes were administered during the second year. The index represents the sum of each symptom score (oedema, erythema, lichenification, desquamation, papules and excoriations) multiplied by the percentage of body surface area affected by dermatitis. Patients of Group A (●) were treated from day 0 while Group B patients (○) were first treated by injections of the carrier buffer. Active therapy for Group B patients was started on week 17 (arrow). Vertical bars represent SEM.

cells such as Langerhans' cells [9], are the primary cells interacting with allergen-antibody complexes.

Returning to complexes made from whole antibody molecules, what are then the biological alterations that result from injections of such complexes? Firstly, there is a rapid and sharp reduction in the level of specific anti-*Der p* antibodies, whether they belong to the IgE or IgG isotype [4, Jacquemin & Saint-Remy, manuscript submitted]. Interestingly enough, we found a close correlation between the reduction of IgG levels and clinical improvement, a finding which is in contrast with what is observed in conventional desensitization. The reduction in antibody titres is specific for the allergen under interest, as the level of total IgE or IgG antibodies is not modified [10 and Jacquemin & Saint-Remy, manuscript submitted]. Secondly, injections of allergen-antibody complexes boost the production of corresponding anti-idiotypic antibodies. We have, however, found only a loose correlation between levels of anti-idiotypic antibodies and clinical improvement, indicating that, although anti-idiotypic antibodies may play some role in the overall mechanism of the therapy, they do not fully explain the mode of action. Thirdly, we have recently observed that the suppression of anti-allergen antibody production is the result of an epitope-specific mechanism, i.e. antibodies whose production is down-regulated are of the same specificity as those administered in the form of complexes (Jacquemin & Saint-Remy, manuscript submitted). This could mean

that the further development of this therapy will necessitate polyclonal anti-allergen antibodies. An alternative could be to use antibodies towards immunodominant B cell epitopes of *Der p* allergens. The existence of such epitopes is, however, far from being clear, for at least two reasons. Firstly, their identification requires the use of monoclonal antibodies; those of murine origin may not recognize exactly the same epitopes as human antibodies (unpublished observations) and give only limited information on the specificity of human antibodies. To get round this problem, our approach has been to produce human monoclonal antibodies. The second reason stems from the observation that some, if not the majority, of allergen B cell epitopes are conformational rather than sequential, which renders their precise identification difficult.

At the present stage, however, a number of questions remain unanswered. Firstly, we have to determine which patient categories might benefit from this therapy. All patients treated so far were severely affected by the disease. The very good tolerance to the injections, as exemplified in the recent paediatric study, suggests that allergen-antibody complexes might be worth considering for the vast majority of patients with sensitivity to house dust mites with, we think, two major advantages: long-term maintenance of the clinical improvement after administration of the treatment and, more importantly, the significant influence on non-specific inflammatory changes, both in the bronchi and in the skin. However, to broaden the scope of such therapy still requires a better determination of doses and injection frequency. The second question to be addressed is the need to simplify and automate the preparation of allergen-antibody complexes. The possibility of replacing autologous antibody preparations by pools of gammaglobulins and the identification of immunodominant allergen epitopes that would allow the use of monoclonal antibodies, are only two questions that remain to be evaluated and which could have a decisive effect on both the practical and experimental aspects of this therapy.

We believe that this approach of immunomodulation of the anti-*Der p* immune response is worth pursuing. Perhaps we should envisage studies in clinical conditions for which there is no current alternative, such as drug or food hypersensitivities. In this regard, it should be noted that the immune complex therapy is not limited to *Der p*, as indicated by the successful extension of the therapy to grass-pollen allergens [11]. Further, since allergen-antibody complexes suppress the production of IgG antibodies, applications may be envisaged for IgG-mediated diseases in which the relevant antigen is identified, such as some auto-immune diseases. In this context, we

recently reported a partial success in *Haemophilia A* patients producing anti-FVIII antibodies [12].

References

- 1 Saint-Remy JMR. Novel approaches in immunotherapy. In Bronchial asthma. Clin Rev All 1994; 12:23-42.
- 2 Blaser K, de Weck AL. Regulation of the IgE antibody response by idiotype-anti-idiotype network. Prog Allergy 1982; 32:203-64.
- 3 Manca F, Fenoglio D, Kunkl A et al. Differential activation of T cell clones stimulated by macrophages exposed to antigen complexed with monoclonal antibodies. J Immunol 1988; 140:2893-8.
- 4 Machiels JJ, Somville MA, Lebrun PM et al. Allergic bronchial asthma due to *D. pteronyssinus* hypersensitivity can be efficiently treated by inoculation of allergen-antibody complexes. J Clin Invest 1990; 85:1024-35.
- 5 Machiels JJ, Lebrun P, Jacquemin MG, Saint-Remy JMR. Significant reduction of nonspecific bronchial reactivity in patients with *Dermatophagoides pteronyssinus*-sensitive allergic asthma under therapy with allergen-antibody complexes. Am Rev Resp Disease 1993; 147:1407-12.
- 6 Jacquemin MG, Machiels JJ, Lebrun PM, Saint-Remy JMR. Successful treatment of atopic dermatitis by complexes of allergen and specific antibodies. Lancet 1990; 335:1468-9.
- 7 Leroy BP, Boden Griet, Lachapelle JM, Jacquemin MG, Saint-Remy JMR. A novel therapy for atopic dermatitis using antigen-antibody complexes: a double-blind placebo-controlled study. J Am Acad Dermatol 1993; 28:232-9.
- 8 Leroy BP, Jacquemin MG, Lachapelle JM, Saint-Remy JMR. Allergen-sensitive atopic dermatitis is improved by injections of allergen combined to F(ab')₂ fragments of specific antibodies. Br J Dermatol, in press.
- 9 Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and down regulated by tumour necrosis factor α . J Exp Med 1994; 179:1109-18.
- 10 Leroy BP, Lachapelle JM, Jacquemin M, Saint-Remy JMR. Treatment of atopic dermatitis by allergen-antibody complexes: long-term clinical results and evolution of IgE antibodies. Dermatology 1992; 184:271-4.
- 11 Machiels JJ, Somville MA, Lebrun PM, Jacquemin MG, Saint-Remy JMR. Allergen-antibody complexes can efficiently prevent seasonal rhinitis and asthma in grass pollen hypersensitive patients. Allergy 1991; 46:335-48.
- 12 Gilles JGG, Arnout J, Peerlinck K, Vermeylen J, Saint-Remy JMR. Antigen-antibody complexes made of FVIII and autologous specific antibodies down regulate the production of anti-Factor VIII antibodies. XXI International Congress of the World Federation of Hemophilia, April 1994, Mexico City, Mexico.