Might Selective B-Cell Depletion have a Place in Targeted Allergy Therapy?

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Abstract: Allergic disease continues to extract a heavy burden of both patients and health care systems. Current treatment strategies cover a wide range of alternatives from allergen avoidance, to pharmacological and immunological intervention that attempt to produce short-term relief from symptoms. Immunization with allergens, available for some forms of allergy, aims to create long term tolerance but lack of standardization and problems with protocol compliance limit their success. Another approach is the use of pan anti-IgE antibodies such as Omalizumab which has shown success in moderate-to-severe allergy. This paper outlines a new strategy involving the specific ablation of allergen-specific B cells. One important advantage of this approach is that is does not interfere with the possible protective role of IgE antibodies or other components of the humoral immune response and should not suffer from non-specific toxicity.

Keywords: Targeted drug delivery, targeted therapy, peanut allergy, B-cell depletion, allergic immunotherapy.

INTRODUCTION

Allergic disease remains a significant burden for both patients and health care systems in developed countries. Here are just a few statistics. A recent survey reported that over the previous decade, the prevalence of asthma alone rose in the US from 7.3% to 8.3% [1] and in 2007, Barnett and Nurmagambetov [2] estimated that asthma cost the US economy up to $56 billion in direct and indirect costs. Allergic rhinitis is far more prevalent than asthma, with estimates running as high as 25% of Western populations [3] and attendant health costs in the US of over $11 billion [4].

Currently, allergy treatment strategies run the gamut from the ideal situation of complete allergen avoidance to not-so-ideal situations such as pharmacological attempts to neutralize allergoneic mediators secreted from activated mast cells, such as histamine. Allergen avoidance may only rarely be possible or practical, such as with some food allergies; pharmacological intervention is only effective in treating symptoms, but is not usually recommended for long term prophylaxis. Furthermore, some allergic conditions, such as allergic rhinitis, may be caused by sensitivity to several allergens whose concomitant presence in the environment may make allergen avoidance impossible and drug therapy an almost permanent feature of a patient's life. In contrast, immunological-based therapies aim to induce a state of allergen tolerance that is maintained long after cessation of therapy. Despite this perceived advantage, the clinical experience with current immune-base strategies shows there is need for novel approaches that can induce specific, long term benefit for patients without induction of side effects. This paper will outline one such approach, after a brief review of the more common strategies for allergic immunotherapy (AIT).

IMMUNE-BASED THERAPIES FOR ALLERGY

Immunization Therapy

Currently there are two main forms of AIT used clinically. The most developed approach consists of a protracted schedule of multiple immunization therapy (MIT) with specific allergens. While the mechanism of action of MIT is still not fully clarified, there is evidence that it may lead to a state of allergen tolerance either by inducing a Th2 to Th1 cytokine switch, expansion of T-regulatory cell populations, reduction of pro-inflammatory cytokines released from mast cells, eosinophils and T cells, and/or by the production of allergen-specific IgG4 blocking antibodies [5, 6]. MIT has indeed been correlated with long-term clinical benefit [7], particularly in patients with IgE-mediated disease. Interestingly, the levels of allergen-specific IgG4 induced following MIT have long been recognized not to correlate directly with the level of clinical improvement [8], even though follow up studies show that antibody persistence and long-term benefit are linked [9]. In the US, MIT is used mostly in the treatment of allergic rhinitis, asthma and venom-induced analphylaxis, although additional indications are also being pursued [5, 10].

A number of factors appear to influence the clinical efficacy of MIT, including the route of immunization, allergen extract composition and complexity, immunization schedule, effective dose and cost. These

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factors contribute to a low overall adherence to the protracted treatment protocols of about 20% after three years of therapy [11]. Side effects of MIT are not uncommon and may be caused by activation of local tissue mast cells or capillary basophils after unintentional vascular distribution of the allergen. The clinical efficacy of several forms of MIT has been demonstrated in multiple clinical trials, particularly with grass pollens. Overall the trials demonstrate a reduction in symptom-medication scores of between 20-28% [10].

MIT has been tested in a number of food allergies as well but with variable results. One reason for this inconsistency appears to be the route of administration, where in the case of cow milk allergy for instance, oral immunotherapy has emerged as being the more effective route of administration [12]. Safety and standardization issues are also limiting the use MIT for food allergy [13]. In peanut allergy, several open and double-blind trials demonstrated efficacy that was associated with an increased humoral immune response but side effects were a concern. Considering the potential severity of such side effects in peanut allergy and lack of long-term benefit from therapy, a recent review panel could not recommend the use of MIT for this condition [14]. For a comprehensive comparison of the common routes of MIT administration, the reader is referred to the review by Hochfelder and Ponda, [6].

There are a number of conditions in which MIT may be contraindicated. These include young children who generally find it difficult to comply with the protracted regimen, highly sensitive patients with allergy or cardiovascular disease who may develop severe adverse responses, patients receiving beta-blockers, patients with cancer or underlying autoimmune or immunodeficiency diseases and pregnant woman who are yet to begin therapy [5].

T Cell Epitope Immunotherapy

The control of IgE production is also dependent of T-cells, either in providing help to B-cell activation or in regulating it. Significant efforts have been invested over the years in identifying and employing allergen-derived peptides to induce specific T-cell tolerance. The results of these studies were recently reviewed by Cox *et al.* [10]. The use of peptide immunotherapy requires knowledge of well-defined allergens and to date the more important clinical trials have been carried out in cat and bee-venom allergy. In both cases, results have indicated that peptide immunotherapy reduced the levels of cytokines involved in both Th1 and Th2 responses. Clinical responses were overall encouraging. However the cohorts have not been large enough to allow definitive conclusions about efficacy.

IgE Targeted Immunotherapies

The second main form of AIT, and which has entered the clinic in recent years, is the use of monoclonal antibodies to block the activity of IgE. The most developed and currently the only FDA approved such antibody is Omalizumab (Xolair®, Roche/ Genentech) a recombinant, humanized monoclonal with specificity for the IgE constant region. Omalizumab successfully inhibits the binding of free, circulating IgE to the high affinity $IgFc_{\varepsilon}$ receptor found on mast cells and basophils, thereby blocking allergen induced cell degranulation and secretion of allergoneic mediators. It does not compete with the receptor for cell-bound IgE because the recognized epitope, CH3ε, is not exposed under such conditions. While this means that cell-bound IgE is still available to bind allergen if the latter is present, the antibody itself does not cross-link adjacent IgE's to induce mast cell degranulation [15]. Omalizumab is currently indicated for the treatment of moderate-to-severe allergic asthma where, after individual dosing, circulating IgE can fall by up to 99% [15]. Additional clinical trials indicate its efficacy in the treatment of allergic rhinitis [16], other respiratory, skin and food allergies and possibly anaphylaxis [18-21]). The drug however is expensive and anaphylactic reactions to it have been reported [22]. Also, oral or inhaled formulations have not yet been developed so this drug, although effective, may suffer similar limitations in compliance as does MIT.

A series of other anti-IgE antibodies have been developed and were reviewed recently by Catley [15]. While some of these seem to present a biological advantage, such as higher affinity of IgE, in clinical trials they have yet to deliver clinical benefit beyond that of Omalizumab.

Another approach to regulating IgE levels is to ablate B cells. This includes the use of anti-B cell antibodies such as Rituxin that targets the CD20 membrane protein present on most mature B cells. In one study Rituxin was used in sequential switch therapy with Xolair to treat 6 cases of severe AD refractory to conventional therapy. Overall, the protocol resulted in decreased serum IgE level and B-cell counts during the treatment period. B cells counts returned to baseline levels only 10 to 11 months after

treatment [23]. What is the consequence of such prolonged B cell depletion on the health of the patient? This question was addressed in a study by Pescovitz and colleagues [24] in patients with Type 1 diabetes. While pre-existing antibody levels were not affected, they concluded that during the time of B-lymphocyte depletion, Rituximab recipients had a decreased antibody response to neoantigens and significantly lower titers after recall immunization with diphtheria and tetanus toxoid. However with B cell recovery, immune responses returned toward normal. They also noted that while naïve B cell recovery took about 12 months, memory B cell recovery remained depleted. The authors did not report on the influence of prolonged anti-B cell therapy on the rate on infection, although it has been reported that under some circumstances, this therapy may significantly increase the risk of infection, especially in the presence of other immunomadulatory drugs [25].

Ablation of IgE-producing B cells is also being approached by using antibodies that target a unique segment present in the membrane-binding region of IgE but which is absent in other immunoglobulin isotypes. Several such antibodies are being developed [26, 27] but clinical data on their efficacy is not yet available.

What might be the long-term consequences of the total ablation of IgE-producing B cells? This question begs a more basic one as to the role of IgE in homeostasis and immune regulation, a topic reviewed recently by others [28, 29]. IgE production is tightly regulated and associated with crosstalk with the cytokine network [29], which might suggest that local, regulated tissue IgE responses could form a component of a wider immune-directed elimination of specific environmental antigens. In this regard, one would view clinically relevant allergic reactions as an aberration of IgE homeostasis. IgE levels are known to be elevated in helminth infection [30] and studies with $IgE^{-/-}$ mice implicate their role in the immune clearance of worms [31]. In addition, work over the last decade has elucidated antigen-independent roles for IgE, particularly in the survival, growth and maturation of mast cells [28, 32]. The full physiological role of IgE is not yet understood, but clearly, its natural function cannot be to induce allergic reactions. Given this assumption, the strategy of total ablation of IgE-producing B-cells may produce relief from symptoms, but the long term effects of this type of therapy are unknown.

Allergen-Specific IgE Elimination

An alternative and more holistic approach would be to develop therapies that explicitly target B-cells producing allergen-specific IgE. In this way, the pathological clone or clones of B-cells would be ablated without the potential harmful consequences of eliminating an otherwise physiological system. The ability to target specific B-cell clones was demonstrated over 30 years ago [33]. We have reported on several targeted delivery systems in which small molecule or peptide haptens, when linked to toxins or drugs, can be used to specifically eliminate specific IgG-producing B-cells [34, 35]. There is no reason to doubt that similar approaches could not be used for IgE.

To demonstrate proof-of-principle, if would be useful to begin with allergic diseases in which the range of potent allergens is limited and for which defined molecular information is available. An example would be peanut allergy. The presence of IgE antibodies to several proteins in peanut legumes can produce severe allergic responses in about 1.5% of children under 5 years of age [14, 36] and they can be fatal. Of the eight peanut proteins allergens that have been identified, Ara h1 and Ara h2 are the most important, with over 90% of patients possessing IgE antibodies to them [37]. Management of peanut allergy currently focuses on allergen avoidance, with educating both patients and their families about peanut-containing products. This can be difficult to achieve, especially with young children. Immunotherapy-based methods are being considered, but due the potential serious side effects, oral immunization with full protein allergens is not one of them [14]. Instead, some studies are testing the use of allergenic peptides from Ara h2 [38]. These peptides, or others derived from technologies such as phage display peptide libraries [39] could be used as initial candidates antigen fragments to specifically carry cytotoxic drugs to the target B-cell clones. In most patients, sensitivity to peanut allergens is also life-long, so the ability to swiftly knock out pathogenic B-cell clones, could allow significant clinical benefit.

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