

Anti-IgE Therapy Combined with SIT: Contra

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In attempting to present a cogent "contra" argument in this debate examining the use of a combination of anti-IgE and specific immunotherapy (SIT), I intend to address issues from a basic science (immunology) point of view rather than a clinical perspective. A number of scenarios are presented to address some questions that, I believe, require answers before moving forward with combination therapy.

The rationale for combining these therapeutic approaches needs to be defined in the context of the strengths and weaknesses of each.

Specific Immunotherapy

Strengths

- Potentially "curative" and antigen-specific

Weaknesses

- High incidence of adverse events, time consuming and inconvenient

Anti-IgE

Strengths

- Markedly reduces IgE-mediated symptoms of allergy, effective for all allergens

Weaknesses

- Palliative and costly

The potential benefits of combination therapy are considered below;

- Fewer IgE-mediated adverse events with SIT leading to improved safety
- Potential for a shorter course of treatment in SIT
- Potential for delivery of higher doses of allergen, leading perhaps to improved efficacy
- Prospect of curative treatment of life-threatening allergic sensitisations i.e. peanut allergy

Some of the questions arising from considerations of the possible benefits of combination therapy are as follows;

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- Does the use of anti-IgE improve the safety of SIT?
- Can synergism be demonstrated?
- Will improved safety allow shorter periods of treatment with higher, more efficacious doses of allergen?
- Will improved safety allow SIT to be effectively and safely used in life-threatening disease?

Improving the safety of SIT

The first issue then, is one of safety. The concept of combining anti-IgE and immunotherapy to improve safety is sound and difficult to argue against. Thus far, anti-IgE has demonstrated an impressive safety profile, despite the fact that immune complexes between IgE and anti-IgE remain in the peripheral circulation for prolonged periods of time in the form of trimers and hexamers. The complexes appear not to create any problems, no doubt due at least in part to the fact that the anti-IgE monoclonal does not fix complement.

Unlike earlier studies with murine monoclonal antibodies in tumour therapy, there do not appear to be any documented cases in which individuals have developed anti-anti-IgE antibodies. This is the result of the "humanised" nature of the anti-IgE antibody known as "E25". Anecdotally, pre-clinical studies with a higher affinity version of the anti-IgE antibody have generated concerns about the induction of thrombocytopenia. However, little information is currently available. Interestingly, transient thrombocytopenia was observed in the study presented by Professor Wahn [1] and this appeared to be more frequent in the active treatment group. However, this resolved in all subjects.

Anti-IgE and skin prick tests

A commonly employed objective method of evaluating allergenicity of a substance is the skin prick test (SPT). The expectation that arises from the use of anti-IgE in combination with SIT is that "allergic" reactions will be reduced following depletion of circulating IgE by 95% or more. Interestingly, a study from Togias and colleagues presented in abstract form (Togias A. et al. J Allergy Clin Immunol 1998; 101: S171) showed that anti-IgE, despite impressive reductions in circulating levels of free IgE, only reduced the magnitude of the weal and flare reaction in the skin by one half to two thirds. Whether the residual reaction is actually due to IgE or not perhaps does not matter as it may still be considered to have potential to contribute to symptoms. Thus, the failure of anti-IgE to abrogate the early-phase reactions to allergen may ultimately compromise the safety of this potentially promising approach.

Monosensitised versus polysensitised subjects

Another issue to be borne in mind when considering which patients may benefit from the combined approach is that of sensitisation to one allergen or multiple aller-

gens. When an individual is sensitised to one allergen it may be expected that the concentration of IgE (specific for that particular allergen) bound to the surface of mast cells and basophils would be high, relative to an individual with multiple sensitisations. In the case of the latter, IgE directed at each individual allergen effectively dilutes each of the other specificities in terms of numbers of molecules per mast cell/basophil. Thus, in the case of a polysensitised individual, a reduction of circulating and cell bound IgE may reduce mast cell numbers below the triggering threshold of the cell. This is clearly less likely to be achieved when much of the IgE on the cell surface has a single specificity.

Demonstration of improved safety in clinical trials

Although conventional immunotherapy has a relatively high rate of adverse events, the size of clinical trials required to demonstrate a significant reduction in incidence with combined SIT and anti-IgE is surprisingly large. If a rate of adverse events of 1% is assumed and one analyses the confidence interval around 1%, it is apparent that only a study with approximately 500 individuals in each arm (active and placebo) would be required to generate sufficient power. This is clearly not a trivial study as it would require substantial resource. An alternative would be to adopt an immunotherapy approach in which adverse events occur at a much higher rate. RUSH immunotherapy is associated with high rates of adverse events. If one adopts a notional rate of 36%, demonstration of a significant reduction in adverse events by concomitant use of anti-IgE could be demonstrated with as few as 8 or 10 patients in each group. The question is: Would such a study be viewed as ethical?

Immune complexes

The issue of immune complex-mediated complications of anti-IgE therapy has been the subject of much debate and as discussed earlier, no evidence of any immune complex-related pathology has been reported in studies with anti-IgE. However, when treating patients with allergic rhinitis or asthma (with anti-IgE) their challenge with allergen on a daily basis is primarily via the respiratory route. So they inhale very, very low doses and the vast majority of immune complexes are simply formed between allergen-specific IgE and the anti-IgE therapy. These are small, soluble and appear to be relatively inert. However, high dose solid-phase allergen, such as that employed in depot allergen immunotherapy, may have potential to cause some problems. This needs to be investigated before any kind of depot immunization is used widely, because in contrast to inhaling very low doses of aeroallergens SIT involves administration of a large dose of allergen adsorbed onto the solid phase (aluminium hydroxide for example). In this scenario there is potential for sequestration of specific IgE at the site of allergen injection where complexes are bound to form on a larger scale. Thus, there is the potential, at least from the theoretical point of view, that immune complex lattice formation may occur as a result.

Taking the concept a step further, the adjuvant effect of the aluminium hydroxide itself must also be considered. It has always been argued that because anti-IgE antibodies are humanized and have only 5% mouse sequence remaining, they will not gen-

erate an immune response. However, an inert excipient with adjuvant effect. The question then is whether an immune response

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erate an immune response. This is all very well if they are simply injected in saline or an inert excipient. However, this can not be assumed if the antibodies are co-localised with adjuvant. So there will again be the potential for complex formation, but with relatively large quantities of aluminium hydroxide (or whatever the adjuvant is). The question then is: Will this have an adjuvanting effect on the anti-IgE therapy leading to an immune response?

Potential for synergy

The issue of whether combination therapy offers the prospect of synergic action as opposed to additive effect is potentially important in relation to improved efficacy and the desire to reduce treatment duration and increase allergen dose. The issue of reduced duration of treatment is beyond the scope of this debate as we only have a single study to focus on. However, the study of Kuehr and Ulrich Wahn does allow us to investigate the issue of synergism of effects [1]. To present this data again, anti-IgE treatment resulted in, depending on the group, 40 to 60% improvement in symptom load and the allergen immunotherapy resulted in a reduction of symptom load about 30%. This was only in the case of grass pollen SIT as the birch pollen treatment was not particularly effective in this study. The conclusion from this data is that these effects are additive and there is no demonstrable synergy.

Non-IgE mechanisms in allergic reactions

It is a popular misconception that allergic disorders are solely related to the interaction of IgE with allergen. It must be considered that in addition to IgE-mediated mechanisms there are also contributions from other sources. This issue has apparently been discussed previously in relation to the combination of anti-histamines and conventional immunotherapy. Will anti-IgE allow the use of higher doses of allergen in a safer format? But the question then is: Will there be non-IgE-mediated adverse events as a result of increased allergen?

To provide a working example of the potential problems that may be associated with delivery of large doses of allergen under the cover of anti-IgE, I refer to our own studies with T cell epitopes from the major cat allergen Fel d 1 [2]. We were able to take cat-allergic asthmatic individuals and challenge them with a relatively high molar dose of peptides containing T cell epitopes. Such a challenge triggered isolated late-phase bronchospasm in some individuals. This occurred as a result of T cell recognition of the allergen epitopes. The magnitude of the reduction in FEV1 in these subjects was completely unrelated to the level of specific IgE. Thus, although an individual has high levels of IgE and moderately severe disease, the level of IgE bears no relationship to the potential for non-IgE-mediated side effects. A patient with very low IgE could have a very large T cell-dependent late-phase response with increased allergen dose in SIT.

Conclusions

Having considered some of the issues from an immunological perspective, my conclusions are that there are too many unanswered (and in fact even "unaddressed") questions surrounding the use of anti-IgE and SIT as combination therapy. Taking issues such as cost versus improved safety into account, my personal view is that the only likely indications for anti-IgE therapy and SIT will be in the treatment of food allergy and other life-threatening conditions such as peanut allergy and hymenoptera venom allergy.

References

1. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, von Berg A, Leupold W, Bergmann KC, Rolinck-Werninghaus C, Grave M, Hultsch T, and Wahn U. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109: 274-280.
2. Haselden BM, Kay AB, and Larché M. Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J Exp Med* 1999; 189: 1885-1894.

Discussion

Falagiani: First, I would like to touch a non-medical aspect. Behind the therapies are the allergy doctors and the pharmaceutical companies. Companies marketing anti-IgE therapy are very big multinational pharmaceutical companies whereas companies producing therapeutics for allergen-specific immunotherapy are small. Do you really think that an alliance between David and Goliath could be possible? Second, what about the risk of the use of anti-IgE antibodies in patients with parasitic infections or for tourists travelling to exotic countries who are running a risk of a parasitic infection?

Larché: If I can start with my own perceptions of the second question. I think the issue of concomitant parasitic infection is akin to the one that I showed with the potential problems with immune complexes. During immunotherapy you have a depot of high-density allergen, whereas with parasitic infection you will going to have a systemic or at least an organ-based high load of antigen. This is going to potentially give you an enormous amount of immune complexes. I think we simply do not know what the outcome of that will be. So again, I would rather err on the side of safety, when you are thinking about therapy in those people.

Wahn: The question of David and Goliath, what was the outcome of this fight? As far as I know, David did not do so badly and if I could give you some political advice, I would say well, why don't you get in touch with these people? In regard to the question of parasitic infections: Most of the studies I presented here were not done in developing countries but in the US or in Europe. So far the patients have been more or less carefully followed during these studies and there has been no incidence that can be contributed to parasitic infection or parasite-specific IgE. But in order to answer these questions, you should study populations that have higher parasite exposure than Europe or the US.

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