

Treatment With a Combination of anti-IgE and Specific Immunotherapy for Allergic Rhinitis and Asthma

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Abstract

Novel therapies that interfere specifically with immunological mechanisms underlying allergen-induced pathology are currently in clinical evaluation. Among these is *anti-IgE*, which directly targets IgE serum antibodies, thus inhibiting the central mechanism of immediate type hypersensitivity reactions. Application of anti-IgE antibodies effectively reduces IgE serum levels regardless of allergen specificity. It has been successfully tested in patients with allergic rhinitis, asthma and food allergy, showing significant efficacy in reducing symptom scores and use of rescue medications. Anti-IgE therapy is limited by high costs and the requirements for permanent or every-season treatment. The advantage of specific immune therapy (SIT) is the potential to alter the course of the disease, which has been demonstrated in patients with allergic rhinitis, insect venom allergy and, to a lesser degree, with asthma. The broader application of SIT is restricted by sometimes life-threatening side-effects. Here, we summarize the results of clinical trials investigating the effects of combination therapy with anti-IgE and SIT in patients with rhinitis and asthma. These studies show that combination of anti-IgE plus SIT may be beneficial for the treatment of allergic diseases by improving efficacy and limiting side effects.

Key words: Allergic rhinitis, allergic asthma, anti-allergic treatment, allergen specific immune therapy, anti-IgE therapy

Introduction

Despite the growing understanding of the development of allergic diseases, current treatment is unspecific and intervenes at a late stage of the allergic cascade (e.g., anti-histamines, beta-2-agonists, topical and systemic corticosteroids) [1,2]. New treatment options are therefore required that target the pathophysiological cascade of allergen-mediated immune reactions at an earlier stage or in a more *general* way [3,4]. Due to

the pivotal role of IgE, antagonizing or inhibiting IgE responses directly by anti-IgE antibodies provide such a novel and promising approach to treat allergic diseases [5]. Especially the combination of anti-IgE with specific immune therapy (SIT) bares great potential due to additive effects and increased safety. Here, we highlight the existing evidence by summarizing the results of clinical trials performed with a combination therapy of anti-IgE and SIT in allergic rhinitis and asthma patients.

I. Anti-IgE – mechanism of action

The binding site of IgE for the high-affinity IgE receptor (FcεRI) is located within the third domain of the heavy chain, Cε3 [6]. A monoclonal antibody was generated that recognizes the same residues in the Cε3 domain of IgE that are responsible for binding to FcεRI [7]. The humanized version named recombinant humanized monoclonal antibody (rhuMAb)-E25 or Omalizumab [8] has the following main *features* [9,10] (Fig. 1):

- (i) recognizing and binding IgE, but not IgG or IgA [11,12],
- (ii) inhibiting the binding of IgE to FcεRI [11,12],
- (iii) not binding IgE bound to mast cells or basophils, thus no induction of activation or degranulation (“non-anaphylactic antibody”) [11,12],
- (iv) blocking of mast cell degranulation following passive *in vitro* sensitization or *in vivo* allergen challenges,
- (v) reduction of the expression levels of FcεRI on mast cells and basophils [13],
- (vi) non-specific activity by binding to any kind of IgE molecule.

Single- and multi-dose trials in adults with and without allergic disease showed that anti-IgE was well tolerated and caused a decrease of IgE serum levels in a dose-dependent manner as soon as 5 min after iv and within 24 hrs after sc injections [14,15]. The decrease of IgE lasted, depending on the antibody dose, for about 4–6 weeks after a single injection of anti-IgE.

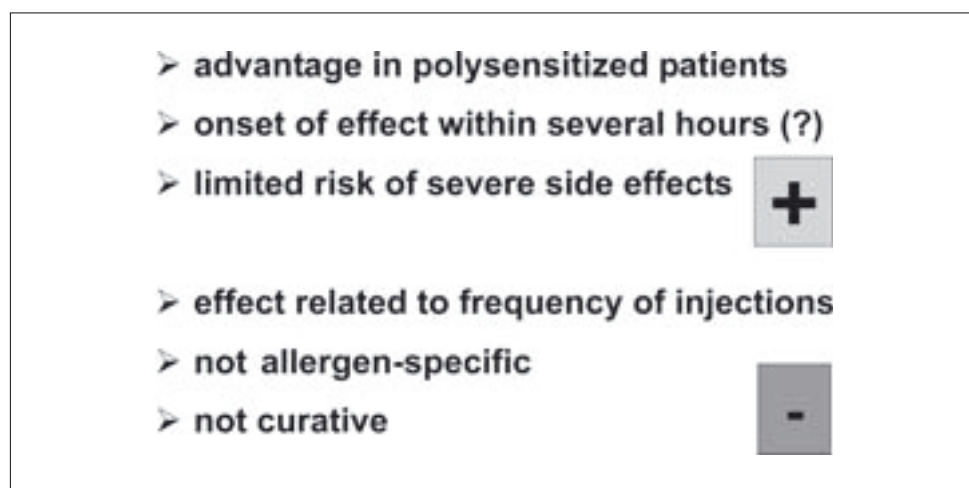


Fig. 1. Anti-IgE – Pro and Con. The advantages and disadvantages of treatment with anti-IgE.



Fig. 2. SIT – Pro and Con. The advantages and disadvantages of SIT.

In various clinical trials on adult (and in some trials adolescent) patients with allergic rhinitis [16–11], asthma [18–25] or food allergy [26], anti-IgE has been shown to be superior to placebo in reducing symptoms, inhibiting exacerbations, lowering rescue medication use and improving quality of life (reviewed in [27]). Anti-IgE (Xolair™) has now been approved for the treatment of adolescent (≥ 12 years) and adult patients with uncontrolled severe allergic asthma and used since several years [28].

II. Anti-IgE in combination with SIT

SIT is the only curative treatment for SAR and allergic asthma, and beneficial effects can be observed even years after discontinuation [29,30] (Fig. 2). Especially in children, administration of SIT may prevent the development of lower airway disease or asthma in subjects with upper airway disease or rhinitis. Application of SIT, however, is limited by the number of allergens which can be administered per injection, the lack of standardized vaccines for all important allergens and the limited ability to determine the optimal dose. In addition to these limitations, SIT carries the rare risk of serious side effects, such as anaphylactic reactions (5.4 severe events per million injections) and even death (1 per 2.5 million injections). Since anti-IgE reduces the serum concentration of IgE and thereby reduces IgE-mediated reactions, it was hypothesized that concomitant treatment of anti-IgE and SIT may improve the risk/benefit ratio of SIT in polysensitized patients during the consecutive pollen seasons and thereby may prove clinically superior to treatment with SIT alone.

1 Anti-IgE plus SIT for treatment of SAR in children and adolescents

A randomized, double-blind, parallel-group, multi-center phase III study in children with SAR investigated whether combined therapy with SIT and anti-IgE is superior to single treatment alone [31]. 221 patients (6–17 years) with moderate-to-severe SAR and sensitization to birch- and grass-pollen were started on SCIT-birch (2 groups) or SCIT-grass (2 groups) for 14 weeks prior to start of the

birch-pollen season. After SIT titration (12 weeks), placebo or anti-IgE was added for 24 weeks to one of the two groups of the respective SIT arms. When analyzed separately by season, the two groups receiving unrelated SIT (i.e. birch-SIT for grass season, and grass-SIT for birch season, respectively) were considered as placebo controls. Anti-IgE was administered sc at 2 or 4 week intervals at a dose equivalent to a minimum of 0.016 mg/kg/IU IgE /ml serum in 4 weeks. Primary endpoint was symptom load, the sum of mean daily symptom severity score plus mean daily rescue medication use.

Combination therapy of anti-IgE and SIT reduced symptom load (sum of mean daily symptom severity score plus mean daily rescue medication use) over the entire pollen seasons (birch and grass) by 48% compared to SIT alone ($p < 0.001$) (Fig. 3). Reduction of symptom load due to combination therapy was highly significant in allergen seasons, birch and grass, when compared to the SIT alone (Fig. 4).

Differentiating the two components adding to symptom load revealed that rescue medication reduction was a major contributing factor to the observed improvements. Over both pollen seasons, addition of omalizumab resulted in reduction of the median rescue medication score of about 80% compared to the two SIT groups. OCS as the last rescue medication to be used was reported by 15 patients receiving SIT + placebo compared to 5 patients on SIT + anti-IgE. Symptom severity, the second component of symptom load, was significantly reduced by the combination

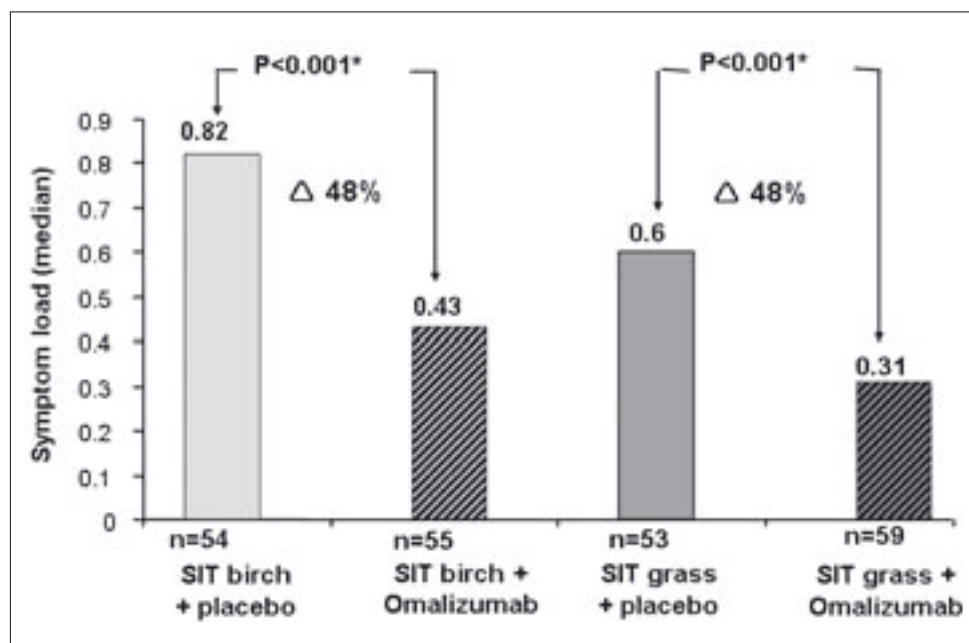


Fig. 3. Anti-IgE & SIT reduces Symptom Load in rhinitis patients. Symptom load (sum of symptom score + rescue medication score) during entire pollen season (birch and grass) after treatment with allergen-specific immunotherapy with birch (SIT-birch) or grass allergen (SIT-grass) combined with anti-IgE or placebo. Reproduced from Kuehr et al. [31].

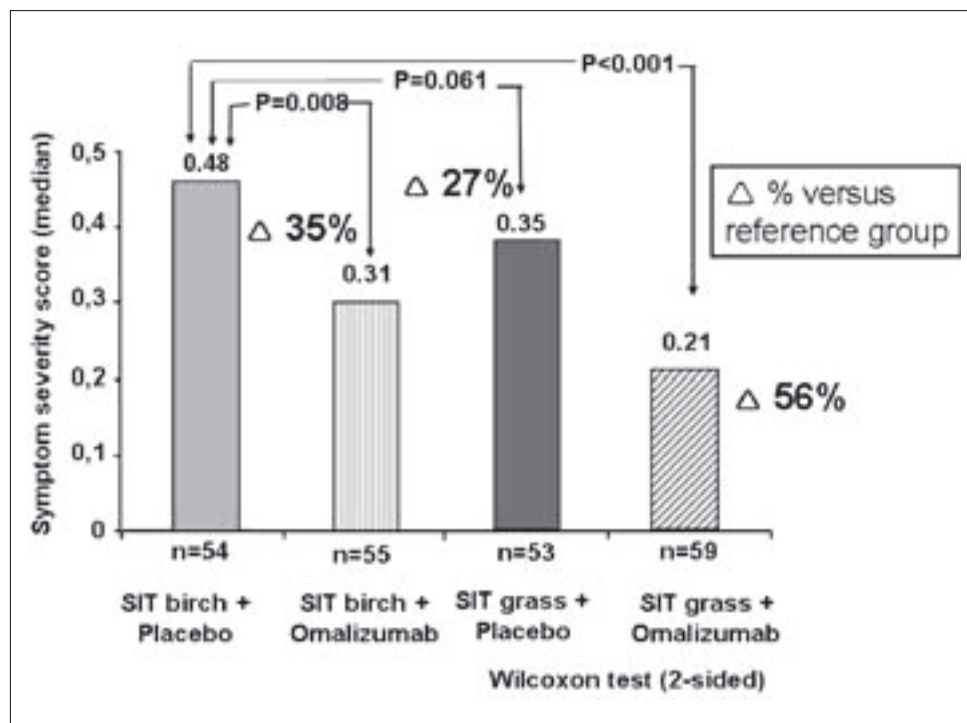


Fig. 4. Anti-IgE & SIT reduces Symptom severity during specific season. Symptom severity during specific grass pollen season after treatment with allergen-specific immunotherapy with birch (SIT-birch) or grass allergen (SIT-grass) combined with anti-IgE or placebo. Reproduced from Rolinck-Werninghaus et al. [32].

of anti-IgE with SIT in the separate groups. Sub analysis of the effects in the specific season showed reduction of symptom severity scores after combination treatment by 56% compared to control (unrelated SIT plus placebo), versus 28% in the group receiving only SIT [32]. The effect of anti-IgE was best explained by and correlated with the decrease of allergen-specific IgE, whereas levels of total IgE at baseline were not associated with seasonal symptom severity [33]. Moreover, experimental support for the clinical benefit was provided by the relationship of serum IgE and *in vitro* mediator release. The decline of serum IgE levels accomplished by anti-IgE treatment correlated with decreased leukotriene release after specific stimulation of mast cells *in vitro* [34] and reduced production of pro-inflammatory mediators in nasal lavage fluids [35].

In conclusion, combination therapy with anti-IgE plus SIT in patients with SAR showed

- improved efficacy for the primary outcome parameter (symptom load) over SIT alone,
- prevention of nasal inflammation and leukotriene release during treatment (year 1),
- but no lasting modification of inflammation or mediator release (year 2 and 3).

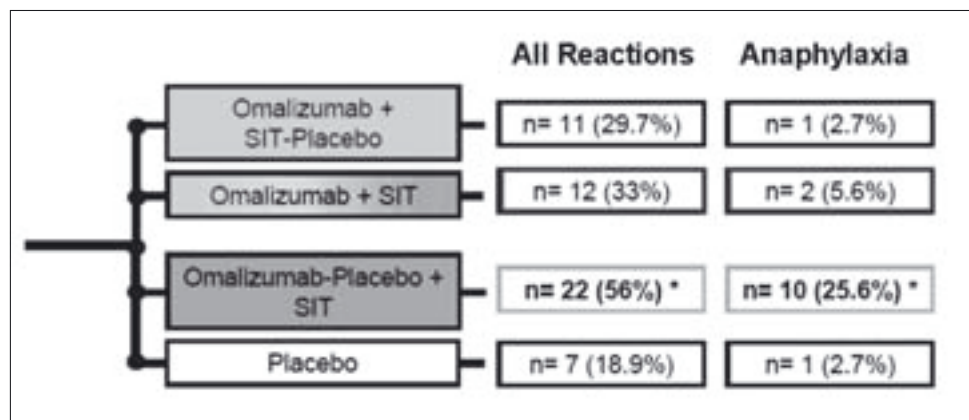


Fig. 5. Anti-IgE reduces allergic side-effects upon rush SIT. Frequency of adverse events in patients receiving rush SIT or placebo SIT plus Omalizumab or placebo. Reproduced from Casale et al. [37].

2. Anti-IgE plus rush-SIT for treatment of SAR in adults

Rush immunotherapy (RIT) is a method of accelerated desensitization with aeroallergens and offers an attractive alternative since it potentially provides better compliance, faster response and lower costs compared to conventional SIT. However, RIT is accompanied by a higher risk of systemic anaphylactic reactions due to IgE-mediated type-I hypersensitivity [36]. In a 2006 trial, the outcome in safety and efficacy of the combination of RIT and anti-IgE for SAR were analyzed [37]. Patients with ragweed-induced SAR were included in a 3-center, double-blind, placebo-controlled phase III trial. The objective was to examine whether omalizumab, given 9 weeks before and 12 weeks together with RIT, increases safety and efficacy compared to SIT alone. A total of 159 patients between the ages of 18 and 50 years, with a minimum 2-year history of ragweed SAR and no recent immunotherapy, were randomized into 4 treatment groups: (i) RIT + anti-IgE; (ii) Placebo-RIT + anti-IgE; (iii) RIT + Placebo anti-IgE; (iv) Placebo-RIT + Placebo anti-IgE.

The number, scope, and severity of adverse events (AEs) associated with RIT were highest in those patients receiving RIT with placebo anti-IgE, a 5-fold increase in the risk to develop AE compared with placebo SIT ($p=0.001$) (Fig. 5). Only small differences in AEs were noted between study groups receiving omalizumab plus RIT (33.3%), omalizumab plus Placebo-RIT (29.7%), or placebo omalizumab plus Placebo-RIT (18.9%). AE increased in a dose-dependent correlation with the total amount of allergen administered. The percentages of patients with SAE during RIT were 2.6 for omalizumab plus RIT, 0 for omalizumab-only, and 15.0 for RIT-only, compared to 5.0 for placebo-only group. Patients receiving omalizumab in combination with rush-SIT showed a significant improvement in severity scores during the ragweed season compared to patients on rush-SIT alone (0.69 vs. 0.86, $p=0.044$).

In summary, treatment with omalizumab prior to and during RIT offers substantial protection from serious IgE-mediated allergic reactions due to SIT. The data

of the discussed studies show that omalizumab treatment results in safer and more effective use of SIT, even with accelerated treatment programs.

3 Anti-IgE plus SIT for treatment of comorbid SAR and asthma in children and adolescents

Allergic diseases such as SAR and seasonal allergic asthma (SAA) frequently coexist in the same patients [38], and prospective studies suggested that SAR may predispose the development of asthma. The physical condition of comorbid patients at peak pollen season is significantly worse compared to patients with SAR alone, and an impairment of quality of life is incremental if comorbid patients are compared to patients with either asthma or rhinitis alone [39,40]. Unfortunately, SIT is burdened with the risk of inducing systemic side-effects particularly for patients with SAA [41,42]. It was therefore tempting to speculate that application of anti-IgE in combination with SIT may also provide faster symptom relief and better safety compared to SIT alone in patients with comorbid SAR together with SAA.

A randomized, double-blind, placebo-controlled, multicenter trial on 140 patients (age 11–46 years) was performed to assess efficacy and safety of omalizumab versus placebo in combination with SIT during the grass pollen season [43]. Omalizumab or placebo was started 2 weeks prior to SIT; total treatment lasted 18 weeks. Primary endpoint again was daily “symptom load”.

Combination therapy reduced symptom load by 39% ($p=0.0464$ Wilcoxon test) over SIT monotherapy. This difference was mainly due to reduced symptom severity ($p=0.0044$), while rescue medication use did not change significantly. Combination therapy also improved asthma control (ACQ, $p=0.0295$) and quality of life in the

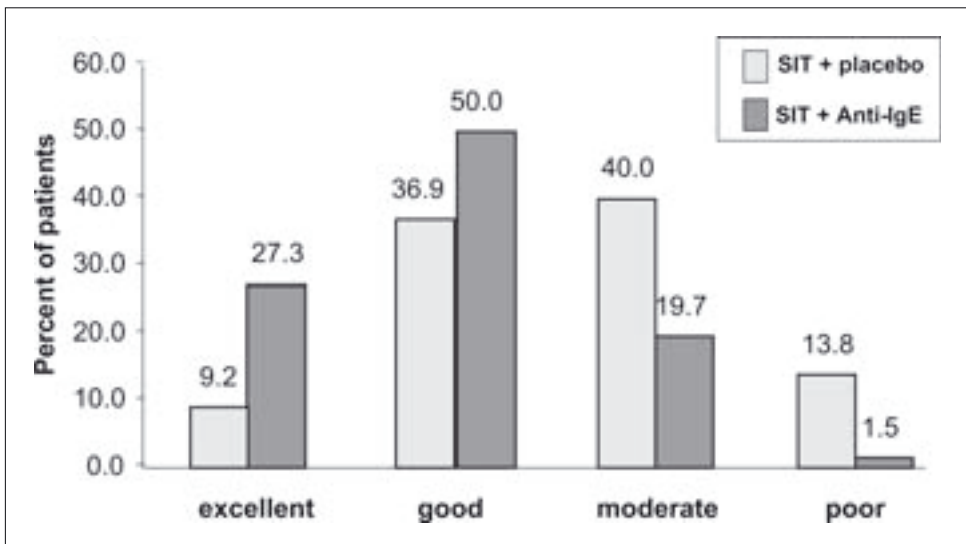


Fig. 6. Anti-IgE & SIT improves estimation of treatment efficacy. Global evaluation of treatment effectiveness (GETE) by patients with comorbid SAR and allergic asthma receiving SIT plus anti-IgE or placebo. Reproduced from Kopp et al. [43].

case of asthma (AQLQ, $p=0.0293$) and rhinoconjunctivitis (RQLQ, $p=0.0537$). Numbers of patients with “excellent or good” treatment efficacy according to ratings of investigators (75.0% *versus* 36.9%) or patients (78.5% *versus* 46.1%) were markedly higher in the combination group than under SIT alone (Fig. 6).

In summary, combination of anti-IgE with SIT for treatment of patients with SAR and comorbid seasonal allergic asthma was safe and reduced symptom load in a statistically significant and clinically meaningful manner.

III. Benefits and limitations of anti-IgE in combination with SIT for treatment of SAR

Anti-IgE therapy and SIT are two powerful and effective, yet very different approaches for the treatment of allergic diseases. Anti-IgE is one of the first of several new immunological methods for anti-allergic therapy with a disease-specific approach. Targeting IgE aims at the common and most distinct phenotype obvious in all patients suffering from allergic diseases: increased IgE serum levels. The findings of several clinical trials showed that anti-IgE is an effective therapy for pediatric and adult patients with allergic rhinitis and moderate to severe allergic asthma, and is safe and well tolerated.

These considerable benefits of anti-IgE therapy are counterbalanced by some disadvantages: anti-IgE is not a curative approach since it does not aim to inhibit the induction phase of an allergic immune reaction or to induce allergen-specific (immune) tolerance. Therefore, treatment with anti-IgE has to be repeated or sustained whenever allergen-mediated responses may be elicited, e.g. during the pollen season or prior to consumption of food allergens. Moreover, anti-IgE targets just one of many mediators released during an allergen-mediated immune cascade, therefore potentially missing other pathways that are independent of IgE.

In comparison, SIT is a truly disease modifying approach aiming to cure an allergic disease by implementing allergen-specific (clinical) tolerance. This strategy is limited by several facts: SIT shows highest efficacy when thorough diagnosis has clearly identified a responsible allergen and a highly purified or recombinant allergen is available. SIT, of course, is allergen-specific, and thus may be less effective for many of the poly-sensitized patients often greatly suffering under the disease. Most importantly, SIT bears the risk of severe anaphylactic side-effects, limiting its application especially for patients with severe asthma.

Due to the above-mentioned characteristics of both strategies, combination of SIT with anti-IgE therapy may be a successful treatment option. Anti-IgE antibodies are not allergen-specific and thus may add to the beneficial effects of SIT, a significant improvement for the often multi-sensitized SAR patients, who suffer under long pollen seasons and frequent co-morbidity of the lower airways. Thus, treatment with anti-IgE antibodies may support SIT in preventing the development of allergen-mediated airway diseases such as allergic asthma, in patients with predisposing SAR. Effective control of SAR thus may provide preventive and/or

therapeutic treatment of concomitant respiratory diseases. The simultaneous treatment with anti-IgE plus SIT definitely will lower the risks of anaphylactic reactions to SIT, allowing a broader application as well as more rapid dosing and higher allergen doses for SIT.

Concluding remarks

For the future, cost-benefit analysis of the advantages of the addition of anti-IgE to SIT should be performed. New areas of potential indications for this combination have to be investigated, especially those where IgE plays a major role for development of the disease:

- (i) Food allergies in infancy that currently can not be treated by SIT and thus require expensive diets,
- (ii) insect venom allergies with high risk of anaphylactic reactions under SIT,
- (iii) pediatric asthma that is often associated with high (allergen-specific) IgE serum levels.

Especially here, the combination of anti-IgE therapy with SIT may be a very valuable and even cost-reducing treatment option with a curative approach and limited risk. Future trials thus need to delineate the optimal target group of patients that may ideally benefit from anti-IgE plus SIT.

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Discussion

Jacobsen: What product and what kind of immunotherapy did you use in the last study you showed? And what was the dose that was used because that is relevant in the combination therapy.

Hamelmann: This is one of the weak spots of this last study, the DUAL study, because it was Depigoid®; the company is Novartis, I think I can say this, it is not a secret. It is a depigmented allergoid in the regular concentration. It is on the market, so it is regular product.

Saxon: I want to take exception to the term “rapid answer”. The studies of anti-IgE show that at eight weeks and i.v. doses of ten mg per kick you get a 20% decrease in skin test reactivity. So that is not rapid. That is why these studies are designed with at least two months of run-in of anti-IgE before you start with allergen; because you do not really change anything. You are not taking anything off mast cells. I did not want anyone to go away with the idea you give allergen and anti-IgE together at the start of the therapy. You need to get that that run-in just to take that allergen out of the serum. And my question then is: when you block the leukotriene inhibition at one year, were the patients still on anti-IgE?

Hamelmann: This was during the first year of treatment. They were at the end of the anti-IgE treatment...

Saxon: Taken the half-life of that drug, it is still in there and it is going to make the test meaningless. It is going to be what is driving the test.

Vieths: A comment regarding the last trial you mentioned and also your summarizing statement. First of all, some of the people who had some problems with the study

work at the Paul-Ehrlich-Institut, you are right, because one problem was that you used an extract that had no marketing authorization. So you compared something with...

Hamelmann: I totally agree – I am not happy with that protocol.

Vieths: The second point I would like to make is that I do not share your general statement on improved efficacy. Because I think this is only true if you define efficacy by reduction of symptoms during the first season or during treatment, which is not what you want to achieve by immunotherapy, in my view.

Hamelmann: Okay, but I think the nice thing about this concept is that you already have improved efficacy in the first year. And the same holds true for the rapid action. Of course it is not a rapid action within hours, but it is an action that is measurable within the first year of treatment and, compared to the subcutaneous immunotherapy, you have a significant improvement in clinical efficacy due to this combination. So it does not help you after three or four years, but it helps you at the moment.

Vieths: But I think we should be precise in this. What you have shown is that you have a reduced rescue medication and you have a very nice symptomatic treatment. But it is not an improved immunotherapy, from my point of view. Because what you want to improve is the effect of immunotherapy.

Hamelmann: It is improved efficacy of a combination therapy with regard to the parameters of symptom severity. Of course not if you are looking at immunotherapy effect on the long term, that is true.

Bousquet: I would like to come back to asthma. Did you measure pulmonary function in the study and was there a change?

Hamelmann: Yes, we measured it and there was no significant change.

Bousquet: It is a problem for me, because if you have symptoms of asthma without impairment of pulmonary function this is probably bronchial symptoms or perhaps dermatitis, but it is not true asthma. And this is the major problem with seasonal asthma, because after the great analysis I checked I was struck by two things. First of all, I mention the inconsistency of results in perennial rhinitis because in perennial rhinitis you have everything, whereas in seasonal rhinitis it is quite homogenous. And then the studies in seasonal asthma – there is one from ALK that was meant to be in seasonal asthma and the patients did not have asthma. So I think that we need to better think about what seasonal asthma is, before doing studies and think that it is asthma.

Hamelmann: I can explain that. Of course, the diagnosis asthma was a clinical diagnosis and of course we did not include patients that already had impaired lung function, because this would be outside of the indication for immunotherapy of asthma.

We had symptoms, we had bad asthma control, but in this kind of patient population you do not see FEV1 under 80%. In pediatric patients this is not the best parameter you should choose if you looked for asthma symptoms. Lung function is not necessarily changing.

Bousquet: I am sorry to say, but for me asthma is an air flow obstruction. So an air flow obstruction should be measurable. If you have asthma without impairment of lung function I do not know what it is.

Robinson: I guess even in their wildest most optimistic mood Novartis cannot really expect health care system to support the dual cost of anti-IgE treatment and immunotherapy for rhinitis. It seems to me the only feasible indication for this would be if it were to make immunotherapy save in severe asthma patients. And I just wondered if you comment on that and also comment on whether any studies are planned on that.

Hamelmann: I am very happy that you say this, this is what I meant with the perspectives. Of course, it is not a good treatment for the overall allergic rhinitis patient and we should now move on to the new indications and use the tool anti-IgE – maybe not to improve efficacy, but to improve safety of rush immunotherapy protocols or immunotherapy in patients that have a high risk of severe side-effects. Definitely, food-allergic patients, insect venom allergics and severe asthma patients are among them. And yes, there are studies in the planning but it is not so easy.

