

REVIEW ARTICLE

Role of immunomodulators in allergen-specific immunotherapy

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Abstract

Allergen-specific immunotherapy (SIT) is the only causal treatment of allergic disorders and therefore a cornerstone in the management of respiratory allergy. SIT is effective in patients with allergic rhinitis and mild-to-moderate allergic asthma. Successful treatment is associated with decrease in allergic symptoms of the upper and lower airways. The most relevant limitation in the daily routine is the restricted use of SIT in patients with moderate-to-severe allergic asthma. A strategy to overcome this limitation is to combine SIT with immunomodulators. One example of a recently developed immunomodulator is Omalizumab, a humanized, monoclonal anti-IgE antibody that binds to circulating IgE molecules, thus interrupting the allergic cascade downstream the IgE production of B cells. Up to now, four clinical trials have been performed, which all showed that the combination of Omalizumab and SIT is safe and clinically more effective than SIT alone. Moreover, administration of Omalizumab prior to SIT reduces the risk of SIT-related systemic reactions. Omalizumab and SIT are also effective in patients with mild-moderate allergic asthma. In conclusion, the use of Omalizumab as an additive immunomodulator improves safety and efficacy and might be a useful approach to broaden the indication of specific immunotherapy in allergic patients.

Reviews, meta-analysis and comments about allergen-specific immunotherapy (SIT) enter the introduction frequently with comments like 'SIT is the most effective therapy for allergies' or 'SIT is the only currently available treatment that is proven to target the disease in a causative way'. However, there are several confinements which hamper the use of SIT. From the perspective of a practitioner, the most relevant limitation of specific immunotherapy in the daily routine is the restricted use in patients with moderate-to-severe allergic asthma. A recently published Cochrane analysis showed that the efficacy of SIT in asthmatic patients is clearly demonstrated: Immunotherapy reduces asthma symptoms, medication use, and improves bronchial hyperreactivity (1). Unfortunately, just in patients who might take major advantage of a disease-specific therapy, the concern about severe systemic side-effects and anaphylaxis gets in the way of SIT therapy (1–3).

An obvious strategy to overcome these limitations is to combine SIT with immunomodulators. The latter are defined as substances that alter the immune response by augmenting or reducing the ability of the immune system to produce antibodies that recognize and react with the antigen that initiated

their production. One example of a recently developed immunomodulator is Omalizumab, a humanized, monoclonal anti-IgE antibody that binds exclusively to circulating IgE molecules, thus interrupting the allergic cascade downstream the IgE production of B cells (4). Therefore, Omalizumab decreases the levels of circulating IgE regardless of allergen specificity by binding to the constant region of circulating IgE molecule, which prevent free IgE from interacting with the high- and low-affinity IgE receptors (FcεRI and FcεRII) on mast cells, basophiles, macrophages, dendritic cells, B lymphocytes, and other cells. Subsequently, the significantly reduced surface binding of IgE on the effector cells of the allergic immune response leads to a decrease in the release of the mediators of the allergic response, i.e., histamines, cytokines, and leukotirenes (4–7).

Basically, there are four major issues, which have to be addressed using Omalizumab in addition to specific immunotherapy: (i) Does the combination of SIT and Omalizumab result in amplified therapeutic effects? (ii) Does the combination of SIT and Omalizumab cause prolonged therapeutic effects? (iii) Is there a potential of pretreatment with Omalizumab in reducing systemic side-effects of SIT? (iv) Is

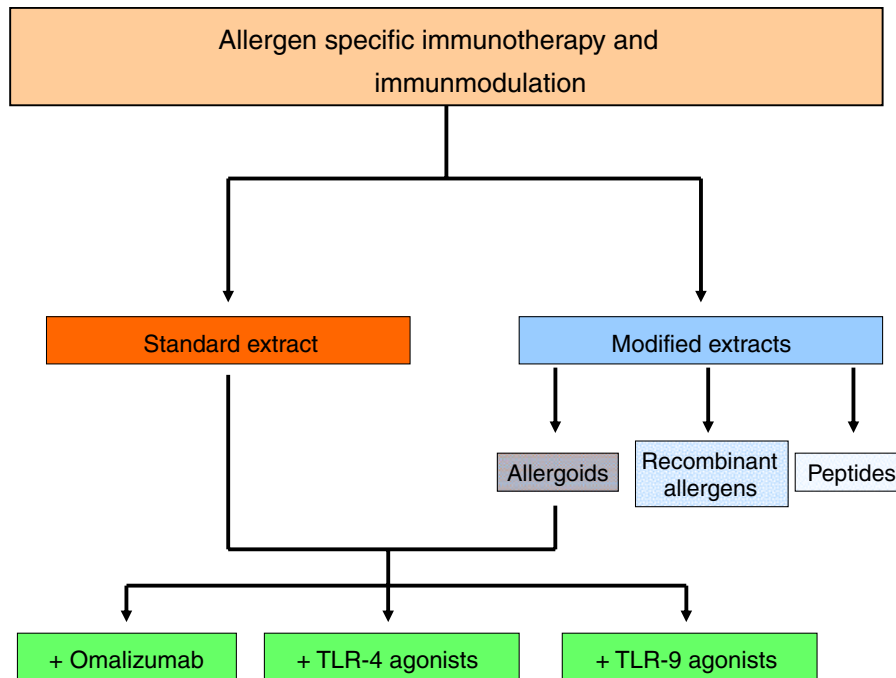


Figure 1 Immunotherapy and potential strategies of immunomodulation [adapted from Ref. (32)].

the combination of Omalizumab and SIT a safe and effective way to offer also patients with severe asthma a disease-specific treatment?

This article reviews the evidence for the use of Omalizumab and SIT therapy. Up to now, four clinical trials have been conducted. Additional clinical benefits of a combined therapy using Omalizumab and SIT have been shown in all clinical studies. Moreover, alternative strategies to improve the immunological responses and clinical outcomes in SIT-treated allergic patients, i.e., the activation of the innate immune system through Toll-like receptor (TLR) agonists, will be discussed (Fig. 1). This concept is realized in the development of Pollinex Quattro, an allergoid with the addition of the TLR-4 agonist monophosphoryl lipid A (MPL).

Omalizumab amplifies the therapeutic effects of SIT

The first clinical trial which looked at the clinical effects of a combined therapy of SIT and Omalizumab was performed in grass- and birch-pollen allergic children and adolescents in Germany (8, 9).

Children and adolescents ($n = 221$; age 6–17 years) with a clinical history of at least 2 years of birch- and grass-pollen-induced allergic rhinitis were included in this trial. All patients received subcutaneous specific immunotherapy (SIT) with either birch pollen (group A + B) or grass pollen (group C + D). After completion of the SIT titration phase (12 weeks), either placebo (group A + C) or Omalizumab (group B + D) was added 4 weeks before the start of the birch-pollen season and continued throughout the grass-pollen season. The initial aim of this intervention was to clarify,

if there might be an additional effect of Omalizumab treatment in patients already receiving SIT. At the beginning of this trial, there was a doubtful discussion about whether an anti-IgE-antibody might work or not. Quizzical reservation was based on the argument that anti-IgE intervene at the end of the allergic cascade. However, the results of the first clinical trial were overwhelming: Children in the Omalizumab group showed a reduction in their symptom load over the pollen seasons by 48% ($P < 0.001$) over SIT alone (Fig. 2).

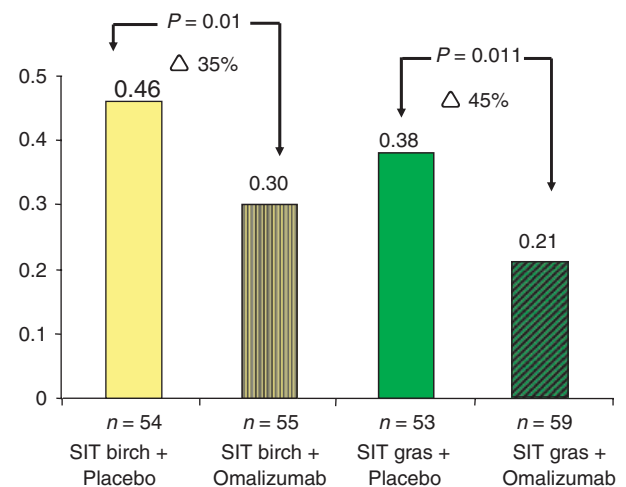


Figure 2 Symptom severity score in children and adolescents treated with specific immunotherapy to birch or grass pollen in combination with Omalizumab or placebo [adapted from Ref. (8)].

Noteworthy, the protective effect of Omalizumab was independent of the type of allergen. This conclusion can be drawn looking at the symptom load during the grass-pollen season in the different groups: while children receiving 'unrelated' (birch)-SIT + placebo had a symptom load of 0.89 (reference value), children treated with 'unrelated' (birch)-SIT + Omalizumab had a symptom load of 0.49 (−45%) compared to SIT-grass + placebo 0.61 (−32%) and SIT-grass + Omalizumab 0.26 (−71%). Moreover, rescue medication use, number of days with symptoms, and symptom severity were significantly lower in the SIT plus Omalizumab groups compared with SIT alone (8, 9). The authors concluded that additional clinical benefit of Omalizumab was demonstrated in both pollen seasons, whether covered by SIT or not.

In addition, the association of IgE levels with symptom load during the pollen season in patients with or without anti-IgE therapy was assessed. Clinical results during the grass-pollen season were compared between reference group, who were treated with SIT with an irrelevant allergen (SIT birch + placebo), and children additionally receiving Omalizumab treatment (SIT birch + Omalizumab). Patients with high baseline-specific grass-pollen IgE (> 50 kU/l) had a significantly higher symptom load compared to those with low IgE levels (< 50 kU/l; $P = 0.015$). In patients who received Omalizumab, no association between baseline IgE levels and symptom load was observable (10).

As Omalizumab suppresses the IgE-mediated release of inflammatory mediators, the question arises whether the effect of Omalizumab can be quantified by measuring the leukotriene release. Therefore, the effect of Omalizumab in addition to SIT in children with seasonal allergic rhinitis on *in vitro* release of sulfido-leukotrienes (SLT) was studied. Combination of both, Omalizumab + SIT-grass and Omalizumab + SIT birch, resulted in significant lower SLT release after stimulation with the corresponding allergen compared to placebo + SIT ($P = 0.001$) (5). One year after Omalizumab therapy, there was no significant difference in SLT release between the groups (6). These results showed that parallel to the clinical effect, SLT release reflects the treatment effect of Omalizumab and might therefore be particularly attractive for monitoring Omalizumab therapy (5). Moreover, the combination of Omalizumab and SIT was associated with decreased eosinophilic cationic protein (ECP) and tryptase levels in nasal secretions in this population (11).

Long-term efficacy of Omalizumab and SIT

For subcutaneous SIT (SCIT), long-term efficacy even years after termination is documented (12, 13). Furthermore, clinical trials in children and adolescents revealed that SCIT may prevent new sensitization and reduce the development of asthma in patients with allergic rhinitis (14, 15). The rationale of potential long-term effects of SIT + Omalizumab treatment is that this combination might offer synergistic effects that neither method provides separately. The results of the clinical trial of Casale et al. (16) revealed that individuals receiving Omalizumab and SIT had reduced symptom scores

compared with those receiving SIT alone. Klunker et al. (17) studied in a subgroup of patients of this clinical trial whether the combination of SIT and Omalizumab has a cumulative effect on the inhibition of facilitated antigen presentation. They observed that ragweed immunotherapy induced serum regulatory antibodies that partially blocked binding of allergen-IgE complexes to B cells. Treatment with Omalizumab, which blocked IgE binding to the low-affinity IgE receptor FcεRII directly, inhibited allergen-IgE binding completely. Combined treatment resulted in prolonged inhibition of allergen-IgE binding compared with either treatment alone. This might be the immunological basis for enhanced clinical efficacy. However, up to now, there are no published data about long-term effects of a combined therapy of SIT and Omalizumab which support these immunological findings.

Pretreatment with Omalizumab reduces systemic side-effects of SIT

While the first clinical trial applied a study protocol which added Omalizumab after the up dosing phase of SIT, a second randomized double-blind, placebo-controlled (DBPC) trial in ragweed-allergic adults ($n = 159$) set the Omalizumab treatment prior to SIT (16). Four groups were enrolled (Fig. 3), who received either SIT or Omalizumab alone + placebo, or a combination of SIT and Omalizumab or Placebo combined with Placebo. A 9-week pretreatment period with Omalizumab was performed. Subsequently, a 1-day course of rush immunotherapy (RIT) was completed at least 3 weeks before the start of the ragweed season. RIT was performed by six injections of either placebo or aqueous allergen extract, starting with a diluted solution containing $0.012 \mu\text{g}$ of Amb a 1. Patients received over a 3-hour period a maximum $1.2 \mu\text{g}$ of Amb a 1, which is of 100-fold greater dose. This rush protocol intended a rapid increase in the administered allergen dosage, which might be chosen to provoke side-effects of SIT. Not surprisingly, a high number of side-effects and even systemic side-effects were noted in patients, who received SIT + placebo. Of note, pretreatment with Omalizumab resulted in a fivefold decrease in risk of anaphylaxis (odds ratio, 0.17; $P = 0.026$). Altogether, 20.5% of the patients in the immunotherapy-only group received epinephrine for allergic-like reactions during rush immunotherapy. Serious adverse events during rush immunotherapy were present in 2.6% for the Omalizumab plus immunotherapy patients, 0% for Omalizumab-only, 15% for immunotherapy-only, and 5% for the placebo-only patients. These data suggest that pretreatment of Omalizumab may be an effective option to apply higher doses of allergen immunotherapy more rapidly in a safe way to patients with allergic diseases. Moreover, Omalizumab might be also a treatment option in patients who failed to achieve the intended maintenance dose of SIT or who failed to be treated with SIT because of severe systemic side-effects. This might be of specific relevance in adult patients with hymenoptera venom anaphylaxis, where SIT is an established therapeutic option but adverse reactions and anaphylaxis may lead to withdrawal of treatment in some patients. Up to now, there is no

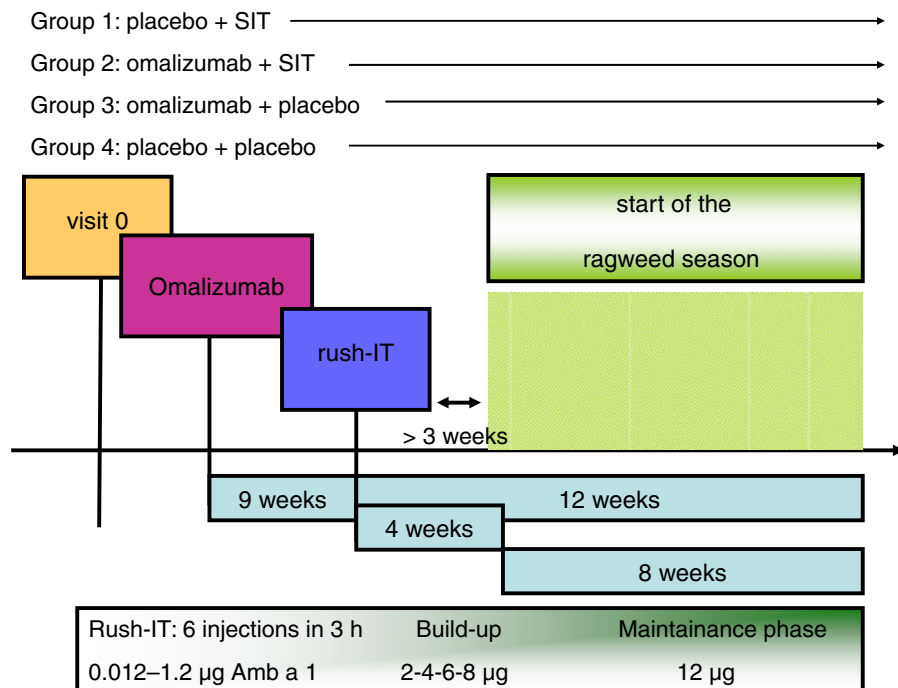


Figure 3 Study design of the clinical trial which demonstrated that Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis.

controlled clinical trial about the use of Omalizumab in patients receiving venom-specific immunotherapy. However, published case reports suggest that in patients, who experienced a systemic allergic reaction following a bee or vasp venom sting and who failed to tolerate specific immunotherapy, co-administration of Omalizumab was able to prevent anaphylaxis during venom-specific immunotherapy (18, 19). These observations need to be established in phase-3 clinical trials.

Omalizumab and SIT is effective in patients with asthma

Recently, a randomized DBPC trial took a step forward involving patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal mild-moderate allergic asthma. A total of 140 patients (age 11–46 years) were randomized, of those 130 finished the study. In this trial, again treatment with Omalizumab prior to and during rush SIT resulted in more favorable results for the combination therapy when compared with SIT alone (20). A significant reduction of 39% in symptom load was observed in favor of SIT plus Omalizumab compared with SIT alone ($P = 0.04$). The combination therapy also reduced asthma-related impairments in the activities of daily living and improved lung function to a larger extent compared with SIT alone. Global evaluations of treatment effectiveness on asthma control by both investigators and patients were in favor of SIT plus Omalizumab compared with SIT alone. The clinical implication of these findings is that patients with moderate-to-severe allergic

asthma pretreated with Omalizumab might also benefit in the future from SIT as a causal treatment option (20).

Very recently, Casale et al. extended these findings and evaluated the tolerability of specific immunotherapy after pretreatment with Omalizumab or placebo in patients with symptomatic persistent asthma ($n = 248$) not adequately controlled with inhaled corticosteroids (21). After randomization to treatment with Omalizumab or placebo, patients received SIT to at least one of three perennial aeroallergens (cat, dog, and house-dust mite). The primary endpoint of this trial was a systemic allergic reaction after immunotherapy. Overall, 13.5% of patients treated with Omalizumab showed systemic allergic reactions to immunotherapy compared to 26.2% in those receiving placebo ($P = 0.017$). In addition, fewer respiratory-related systemic allergic reactions were observed (6 vs 24, respectively), and more patients were able to reach the target maintenance immunotherapy dose (87.3% vs 72.1%; $P = 0.004$) in the Omalizumab group compared to placebo (21).

These two clinical trials demonstrate that Omalizumab might be a safe and efficacious therapeutic option also in patients with allergic asthma.

Alternative immunomodulators

Alternative strategies to improve the immunological and clinical responses in SIT-treated allergic patients comprise the activation of the innate immune system through TLR agonists. Pollinex Quattro is a glutaraldehyde-modified allergoid with the addition of the TLR-4 agonist MPL, a nontoxic

derivate of the lipopolysaccharide (LPS) of *Salmonella* Minnesota R595 (22). TLRs are an important member of the family of pattern recognition receptors, which are crucial for the innate immune response. TLR is able to recognize conserved motifs which are predominantly found in microorganisms but not in vertebrates. In response to various pathogens, TLR activation induces predominantly a TH1 and regulatory T-cell response (23). Immunological studies showed a reduced B-cell activation, i.e. a decrease in CD23, CD54, and HLA-DR-II expression in isolated B cells of treated patients (24). In addition, Stuck et al. observed a significant decrease in IL-4 and IL-5 and increase in interferon-gamma release (reviewed in Ref. 22).

Up to now, one placebo-controlled, randomized, double-blind clinical trial was performed with grass-pollen extract containing MPL adjuvant. This study demonstrated a statistical significant advantage in favor of the active treatment for symptom and medication scores ($P = 0.013$) in patients ($n = 141$) with seasonal allergic rhinitis and sensitization to grass pollens (25). The clinical results were paralleled by an increase in grass-pollen-specific IgG antibody ($P < 0.01$). The authors concluded that this allergy vaccine containing MPL as a Th1-inducing adjuvant was safe and efficacious. Moreover, only four preseasonal injections produced significant changes grass-pollen-specific IgG levels normally associated with long injection schedules. A second placebo-controlled, randomized, double-blind clinical trial was recently finished and will be published soon (personal communication). Significant improvement of symptom and medication scores was additionally demonstrated in open-labeled clinical trials and postmarketing surveys in adults and children (26, 27). However, up to now, no head-to-head comparison between SIT + MPL adjuvant and SIT alone has been performed. Therefore, the significance of SIT + MPL adjuvant in comparison with standard SIT needs further evaluation.

Besides the use of MPL as adjuvant, there are several additional strategies to use TLR agonists to meliorate the efficacy of SIT. One of these concepts comprises the combination of SIT with a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA containing a CpG motif. The immunostimulatory sequence interacts with the toll-like receptor 9 (TLR9) and inhibits the type 2 helper T (Th2) immune response. Recently, a small, placebo-controlled clinical trial was performed, and ragweed allergic patients ($n = 25$) were immunized with a six-injection regimen with Amb a 1 in combination with immunostimulatory oligodeoxyribonucleotide conjugate (AIC) (28). Compared to placebo, the AIC group had lower peak-season daily nasal symptom diary scores ($P = 0.02$), and better midseason overall quality-of-life scores ($P = 0.05$). The clinical improvements in the AIC group when compared with the placebo group were maintained through the subsequent ragweed season. However, a recently initiated clinical trial was discontinued after interim analysis, which revealed no significant differences between verum- and placebo-treated patients, presumably because of only minimal ragweed-induced symptoms in both, the placebo and the verum group (29).

A single centre, open-label phase I/IIa study evaluated the safety, tolerability, and clinical efficacy of CpG immunostimulatory sequence (A-type CpG ODN) included into virus-like particles as an adjuvant to SIT with a house-dust mite extract (29). This regime was well tolerated ($n = 20$ patients), and symptoms of rhinitis and allergic asthma were significantly reduced. All patients achieved almost complete alleviation of allergy symptoms after 10 weeks of SIT. Large-scale phase 3 studies will be needed to determine the role of house-dust mite allergen together with A-type CpG ODN packaged into virus-like particles (30).

Summary and conclusion

With increased understanding of the pathogenesis of respiratory allergies at a molecular and immunological level, a number of immunomodulatory treatments have been identified and tested for their ability to provide long-term control and medication-sparing effects. Apart from the alternate routes of immunotherapy, additional approaches to SIT include the use of allergoids, recombinant allergens, and the use of peptide fragments of corresponding T-cell epitopes of the specific allergen. Immunomodulators in addition to standard immunotherapy aim to achieve an increase in regulatory T cells and/or a reduction of TH2 cytokine production and/or a reduction of mediators of the allergic immune response. However, the guideline of all new approaches is enhanced efficacy and safety demonstrated in properly performed clinical trials. Several new immunomodulatory techniques targeting specific immunological mechanisms of respiratory allergies are currently under clinical evaluation, i.e., strategies to use TLR agonists to upgrade the efficacy of SIT. The TLR-4 agonist MPL as adjuvants to allergoids has been shown to improve symptom and medication scores significantly over placebo. However, up to now, no head-to-head comparison between SIT + MPL adjuvant and SIT alone has been performed. The most advanced of the new immunomodulatory techniques is the addition of Omalizumab to standard SIT therapy. The results of four double-blind, placebo-controlled clinical trials showed that the combination of Omalizumab and SIT is safe and clinically more effective than SIT alone during the first year of treatment (8, 16, 20, 21, 31). Moreover, administration of Omalizumab prior to SIT reduces the risk of SIT-induced systemic IgE-mediated reactions. Omalizumab and SIT is also effective in patients with mild-to-moderate allergic asthma. The results of this proof of concept trials must now be broadened in subsequent studies to patients with severe asthma. Moreover, potential long-term effects of Omalizumab and SIT need further clarifications.

Conflict of interest

MVK has consultant arrangements and has received grants as head of a clinical trial from Novartis Pharma, Nuernberg, Germany. He has consultant arrangements for Bencard, Muenchen, Germany. He has received speaker's fees from Novartis Pharma, Roche Pharma, Infectopharm and Glaxo SmithKline GmbH.

References

- Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;**8**:CD001186.
- Bousquet J, Michel FB. Safety considerations in assessing the role of immunotherapy in allergic disorders. *Drug Saf* 1994;**10**:5–17.
- Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 2004;**113**:1129–1136.
- Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy* 2009;**64**:1728–1736.
- Kopp MV, Brauburger J, Riedinger F, Beischer D, Ihorst G, Kamin W et al. The effect of anti-IgE treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;**110**:728–735.
- Kopp MV, Stenglein S, Kamin W, Friedrichs F, von Berg A, Zielen S et al. Omalizumab (Xolair) in children with seasonal allergic rhinitis: leukotriene release as a potential in vitro parameter to monitor therapeutic effects. *Pediatr Allergy Immunol* 2007;**18**:523–527.
- Eckman JA, Sterba PM, Kelly D, Alexander V, Liu MC, Bochner BS et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 2010;**125**:889–895.
- Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, von Berg A et al. 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.
- Rolinck-Werninghaus C, Hamelmann E, Keil T, Kulig M, Koetz K, Gerstner B et al; Omalizumab Rhinitis Study Group. The co-seasonal application of anti-IgE after pre-seasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. *Allergy* 2004;**59**:973–979.
- Rolinck-Werninghaus C, Keil T, Kopp M, Zielen S, Schauer U, von Berg A et al; Omalizumab Rhinitis Study Group. Specific IgE serum concentration is associated with symptom severity in children with seasonal allergic rhinitis. *Allergy* 2008;**63**:1339–1344.
- Bez C, Schubert R, Kopp M, Ersfeld Y, Rosewich M, Kuehr J et al. Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy* 2004;**34**:1079–1085.
- Des Roches A, Paradis L, Knani J et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;**51**:430–433.
- Durham SR, Walker SM, Varga EM et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–475.
- Moller C, Dreborg S, Ferdousi HA et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J Allergy Clin Immunol* 2002;**109**:251–256.
- Jacobsen L, Niggemann B, Dreborg S et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;**62**:943–948.
- Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG et al; Immune Tolerance Network Group. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;**117**:134–140.
- Klunker S, Saggar LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR et al; Immune Tolerance Network Group. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007;**120**:688–695.
- Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pre-treatment and concurrent treatment with omalizumab. *J Investig Allergol Clin Immunol* 2009;**19**:225–229.
- Kontou-Fili K, Filis CI. Prolonged high-dose omalizumab is required to control reactions to venom immunotherapy in mastocytosis. *Allergy* 2009;**64**:1384–1385.
- Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C et al; DUAL Study Group. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy* 2009;**39**:271–279.
- Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;**125**:383–389.
- Gawchik SM, Saccar CL. Pollinex Quattro Tree: allergy vaccine. *Expert Opin Biol Ther* 2009;**9**:377–382.
- Jain VV, Kitagaki K, Kline JN. CpG DNA and immunotherapy of allergic airway diseases. *Clin Exp Allergy* 2003;**33**:1330–1335.
- Rover AC, Reimann S, Zuberbier T, Worm M. Immunophenotypic characterization of peripheral B cells. During short-term immunotherapy with tree pollen allergoid and the immunoadjuvant monophosphoryl lipid A. *J Investig Allergol Clin Immunol* 2002;**12**:227–234.
- Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four pre-seasonal injections. *Allergy* 2001;**56**:498–505.
- Drachenberg KJ, Prohl S, Urban E, Woroniecki SR. Single-course specific immunotherapy with mixed pollen allergoids: results of a multi-centre study. *Allergol Immunopathol* 2003;**31**:77–82.
- Drachenberg KJ, Heinzkill M, Urban E, Woroniecki SR. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A (MPL) for children and adolescents. *Allergol Immunopathol* 2003;**31**:270–277.
- Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R et al; Immune Tolerance Network Group. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;**355**:1445–1455.
- Dynavax Reports Interim TOLAMBA Ragweed Allergy Results from DARTT Trial [press release January 8, 2007]. Berkeley, CA: Dynavax Technologies, 2007.
- Senti G, Johansen P, Haug S, Bull C, Gottschaller C, Muller P et al. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/II a clinical trial. *Clin Exp Allergy* 2009;**39**:562–570.
- Kamin W, Kopp MV, Erdnuess F, Schauer U, Zielen S, Wahn U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010;**21**:e160–e165.
- Casale TB, Stokes JR. Future forms of immunotherapy. *J Allergy Clin Immunol* 2011;**127**:8–15.