

Review article

Effects of omalizumab on markers of inflammation in patients with allergic asthma

Asthma is a chronic inflammatory disease of the airways in which immunoglobulin E (IgE) plays a key role by activating a variety of inflammatory cells through interactions with FcεRI and FcεRII receptors. The role of IgE in allergic inflammation provided the rationale for developing omalizumab, a humanized monoclonal anti-IgE antibody, for patients with moderate-to-severe or severe allergic asthma. The reductions in circulating levels of IgE resulting from omalizumab treatment leads to reductions in FcεRI expression on mast cells, basophils and dendritic cells. This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia and levels of granulocyte macrophage colony stimulating factor, interleukin (IL)-2, IL-4, IL-5 and IL-13. By blocking IgE binding to its receptors and diminishing dendritic cell FcεRI receptor expression, omalizumab may also reduce allergen presentation to T cells and the production of Th2 cytokines. The anti-inflammatory effects of omalizumab may, therefore, explain the reductions in asthma exacerbations and symptoms seen in clinical trials in patients with moderate-to-severe or severe, persistent, inadequately controlled allergic asthma.

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Current management guidelines describe asthma as a chronic inflammatory disorder of the airways (1, 2). There is now considerable evidence to support its characterization as an allergic inflammatory disease in which immunoglobulin E (IgE) plays a key role (3, 4). IgE activates a variety of inflammatory cells, including mast cells and basophils, through interactions with receptors (FcεRI and FcεRII) on the cell surface (3). The activation of mast cells by IgE and the resulting mediator release is the first step in the allergic inflammatory cascade that ultimately leads to the development of asthma symptoms. Activated mast cells release a variety of pro-inflammatory mediators (such as prostaglandin D₂, leukotriene C₄, tumor necrosis factor-α, and a variety of Th-2 type cytokines, chemokines, and growth factors) that stimulate production of additional mediators. In turn, these promote adhesion and infiltration of circulating inflammatory cells (primarily eosinophils, basophils and Th2 cells) (5, 6) and initiate remodeling responses. In addition, activated mast cells are able to contribute to the maturation of dendritic cells that augment and maintain inflammatory responses (7).

The central role of IgE in allergic inflammatory asthma provided the rationale for the development of omalizumab, a humanized monoclonal anti-IgE antibody. In the US, omalizumab is indicated for adults and adolescents (age ≥12 years) with moderate-to-severe persistent

asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICS) (8). In Europe, omalizumab is indicated as add-on therapy to improve asthma control in adult and adolescent patients (age ≥12 years) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function [forced expiratory volume in 1 s (FEV₁) <80%] as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a long-acting inhaled β₂-agonist (LABA) (9).

The efficacy and safety of omalizumab has been demonstrated in a program of randomized controlled clinical trials. In the INNOVATE trial, 419 patients with inadequately controlled asthma despite high-dose ICS and LABAs received omalizumab or placebo for 28 weeks (10). The clinically significant asthma exacerbation rate was 0.68 with omalizumab and 0.91 with placebo (26% reduction). In addition, omalizumab significantly reduced the rate of severe asthma exacerbations (0.24 vs 0.48) and emergency visits (0.24 vs 0.43), compared with placebo. A pooled analysis of data from 4308 patients (93% with severe asthma) enrolled in seven studies provided further evidence of the efficacy and

safety of omalizumab (11). Omalizumab was shown to reduce the rate of asthma exacerbations by 38% and the rate of total emergency visits by 47%.

Real-life experience has also demonstrated the effectiveness of omalizumab. Omalizumab has been shown to reduce exacerbations requiring oral corticosteroids, emergency department visits and hospitalizations in a real-life setting in France (12). Since its approval in the US (2003) and Europe (2005), experience with omalizumab has yielded significant insights into its utility in treating allergic asthma. If omalizumab targets and interrupts multiple steps in the inflammatory cascade then the therapeutic advantages of anti-IgE therapy in allergic asthma would be clear.

To expand upon our previous broad review of omalizumab and IgE in allergic inflammation (3), our aim in this review is to focus primarily on effects of omalizumab on a range of inflammatory markers in allergic asthma, thereby providing an updated comprehensive overview of current understanding on this topic. In addition, we briefly address the evidence describing the effects of omalizumab on markers of inflammation in other IgE-mediated allergic disease.

Omalizumab and IgE receptors

The potential for omalizumab to exert anti-inflammatory effects in patients with asthma arises from its ability to target the interaction between IgE and IgE receptors (FcεRI and FcεRII), thereby preventing inflammatory cell activation and interrupting a key step in the allergic inflammatory cascade. The effects of omalizumab on IgE receptors have been reviewed previously (3). In brief, omalizumab decreases levels of circulating IgE by binding to the constant region of the IgE molecule, preventing IgE from interacting with IgE receptors on inflammatory cells. Omalizumab does not bind to the variable allergen-specific region of IgE and therefore inhibits allergen-induced responses regardless of allergen specificity. Furthermore, omalizumab does not bind to cell-bound IgE thereby avoiding FcεRI cross-linking, which is one process that could increase the risk of anaphylaxis. The rapid reduction in free IgE levels that results from omalizumab administration leads to a downregulation of the FcεRI expression on inflammatory cells (3, 13–15). Following 3 months' omalizumab therapy, the density of FcεRI receptors decreased from approximately 220 000 to 8300 per basophil (13). Ultimately, a reduction in cells expressing FcεRI and IgE in the airways mucosa is achieved together with reductions in sputum and tissue eosinophilia (15).

Omalizumab and markers of inflammation in asthma

Eosinophils have a well characterized role in inflammation and release a variety of pro-inflammatory mediators, including granule-stored cationic proteins, newly synthe-

sized eicosanoids, and cytokines (16, 17). These pro-inflammatory effects of eosinophils underlie the observed correlation between eosinophilia and asthma severity and the risk of exacerbations (18, 19).

The effects of omalizumab on peripheral blood eosinophil counts were evaluated in two 28-week studies of patients with moderate-to-severe persistent IgE-mediated asthma (20, 21). In both of these placebo-controlled studies, patients receiving ICS (mean dose 672 µg/day beclomethasone dipropionate) were randomized to receive add-on omalizumab or placebo administered every 2 or 4 weeks depending on baseline total IgE and bodyweight. Circulating eosinophilia in patients receiving omalizumab or placebo ($n = 1071$) was evaluated in a pooled analysis of these two studies (22). Blood eosinophils, as absolute counts ($10^9/l$), were reported at the beginning of the treatment phase (baseline count), at the end of the corticosteroid-stable phase (week 16) and at the end of the corticosteroid-reduction phase (week 28). Mean ($\pm$ SD) baseline peripheral blood eosinophil counts were 0.304 ± 0.196 in patients randomized to omalizumab and 0.325 ± 0.218 in the placebo group. At the end of the corticosteroid-stable phase, least squares mean eosinophil counts had decreased significantly from baseline by 0.119 in omalizumab-treated patients ($P < 0.0001$), but the decrease from baseline in the placebo group (0.067) was not significant (Fig. 1). The difference in least squares mean reduction in eosinophil counts between the omalizumab and placebo groups was maintained at the end of the corticosteroid reduction phase (-0.078 vs -0.026 , $P < 0.0001$; Fig. 1), despite significantly greater reductions in ICS dose received by omalizumab-treated patients.

In addition to reducing peripheral blood eosinophils, omalizumab has also been shown to reduce eosinophilia in sputum and bronchial biopsies. A study of 45 patients

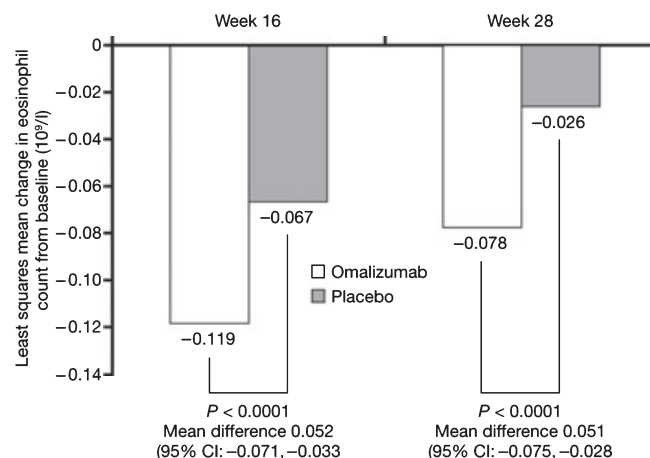


Figure 1. Least squares mean reductions in peripheral blood eosinophil counts from baseline to the end of the corticosteroid-stable phase (week 16) and corticosteroid-reduction phase (week 28).

with mild-to-moderate persistent asthma with evidence of persistent airway inflammation ($\geq 2\%$ sputum eosinophilia) evaluated the inflammatory cells in induced sputum and bronchial biopsies following 16 weeks of treatment with omalizumab or placebo (15). Treatment with omalizumab resulted in significantly greater reduction in mean percentage sputum eosinophil counts (from 4.8% at baseline to 0.6% at week 16) than placebo (from 5.8% to 2.3%; $P = 0.05$). Omalizumab also led to a significantly greater reduction in eosinophil counts in the bronchial submucosa (from 8.0% at baseline to 1.5% at week 16) than placebo (from 6.3% to 6.4%; $P = 0.03$). Moreover, compared with placebo, omalizumab was associated with significantly greater reductions in cells staining positive for the high-affinity Fc ϵ RI for IgE in the epithelium ($P = 0.01$) and submucosa ($P < 0.001$). Reductions in CD3⁺ (epithelium, $P = 0.03$; submucosa, $P = 0.01$), CD4⁺ (submucosa, $P = 0.005$) and CD8⁺ (submucosa, $P = 0.05$) T lymphocytes were also significantly greater than those observed in the placebo group. Furthermore, omalizumab-treated patients had significantly greater reductions in submucosal B lymphocytes when compared with placebo ($P = 0.02$). Significantly greater reductions in cells immunostaining for interleukin (IL)-4 (cell surface) were also observed in the omalizumab group compared with placebo (epithelium, $P = 0.02$; submucosa, $P = 0.001$). In each of the epithelial and submucosal components, there were no significant differences between treatment groups in the number of mast cells, basophils, IL-5⁺ or IL-4⁺ cells (cytoplasmic), and low-affinity Fc ϵ RII receptor cells. The results of this study indicate that the beneficial effects of omalizumab on asthma exacerbations in patients with severe asthma may be a consequence of a reduction in airway eosinophilia (15). The reduction in IL-4⁺ cells is also important, as persistent IL-4 production has been identified as a characteristic of severe asthma and may play a key role in corticosteroid-resistant asthma (15, 23). It is therefore possible that omalizumab may provide some of its benefit in severe asthma by reducing airway mucosal levels of IL-4 (15).

Additional evidence of reductions in eosinophil infiltration in omalizumab-treated patients was provided by a randomized double-blind placebo-controlled study of 25 patients with mild allergic asthma (one of whom did not complete the study) (24). In this study, sputum was induced at baseline and following 8 and 12 weeks of treatment with omalizumab or placebo. Biopsy samples were collected 24 h after allergen challenge at baseline and 12 weeks after treatment, and the percentage of activated eosinophils (EG2⁺ cells) recorded. Median sputum eosinophils decreased from 4.0% at baseline to 0.8% after 8 weeks and to 0.5% after 12 weeks of treatment with omalizumab, compared with a reduction from 2.2% at baseline to 1.0% at 8 weeks and to 2.6% at 12 weeks in the placebo group. Median activated eosinophil counts in biopsies decreased from 15.0 cells/

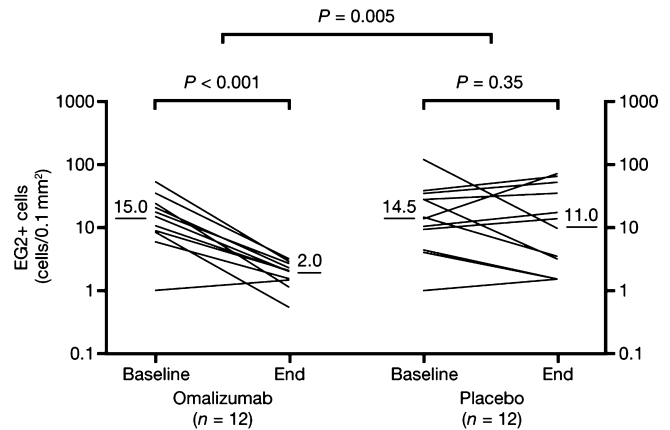


Figure 2. Individual eosinophil counts at baseline and after 12 weeks of treatment with omalizumab or placebo. Horizontal bars represent median values. Reproduced with permission from van Rensen et al. 2009 (24).

0.1 mm² at baseline to 2.0 cells/0.1 mm² at week 12 in omalizumab-treated patients, compared with a reduction from 14.5 cells/0.1 mm² at baseline to 11.0 cells/0.1 mm² at week 12 in the placebo group (Fig. 2). Omalizumab also significantly reduced the number of submucosal IgE⁺ cells compared with placebo. No significant differences in the number of mast cells, macrophages, neutrophil elastase or B lymphocytes were found between treatment groups. Of note, CD4⁺ T lymphocytes were significantly reduced after treatment with omalizumab ($P = 0.021$) but there were no significant between-group differences in the number of T lymphocytes.

The anti-inflammatory mechanisms underlying reductions in eosinophilia were also examined in a study of 19 patients with moderate-to-severe asthma and a history of allergic rhinitis (25). In this study, peripheral eosinophils were evaluated using fluorescence-activated cell sorting at baseline, following 12 weeks of treatment with omalizumab or placebo, and 12 weeks after cessation of treatment. After 12 weeks of treatment, eosinophil apoptosis was significantly higher in omalizumab recipients (mean percentage of eosinophils positive for Annexin 60.1%, range 26.6–95.5%), compared with the placebo group (45.6%, range 19.4–92.8%; $P = 0.004$) and compared with baseline (37.1, range 11.4–89.5%; $P = 0.0039$) (Fig. 3). Importantly, there was no significant change in the marker 7AAD, indicating that eosinophil apoptosis was not caused by necrosis. The number of peripheral T lymphocytes positive for granulocyte macrophage colony-stimulating factor (GM-CSF) was lower in the omalizumab group (mean 10.5%, range 5.0–26.0%) compared with the placebo group (12.1%, range 4.5–19.8%; $P = 0.018$) and compared with baseline (17.7%, range 10.8–27.4; $P = 0.0039$). The significant downregulation of peripheral GM-CSF⁺ T lymphocytes was predominantly attributable to a reduction in the number of GM-CSF⁺ CD4⁺ T lymphocytes;

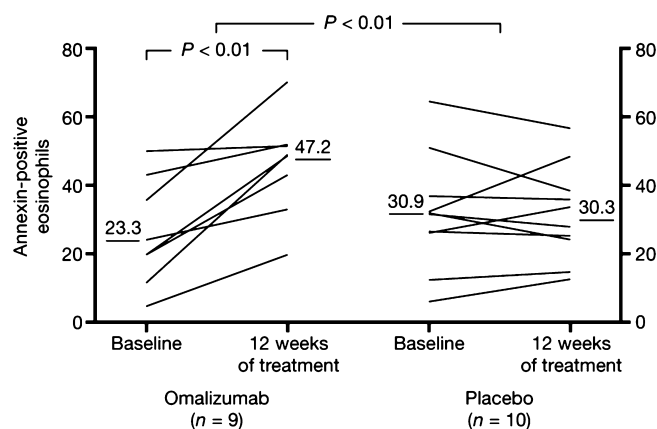


Figure 3. Change in eosinophil apoptosis (Annexin-positive cells) between baseline and week 12 in patients with allergic asthma receiving omalizumab or placebo. Individual values at baseline and week 12 of omalizumab therapy are presented. Horizontal bars represent medians. Reproduced with permission from Noga et al. 2006 (25).

no change was noted in the prevalence of GM-CSF⁺ CD8⁺ T lymphocytes. In addition, there were significant reductions in the number of IL-2⁺ and IL-13⁺ T lymphocytes in omalizumab-treated patients compared with placebo. There were no significant differences in IL-5⁺, IFN γ ⁺ or TNF- α ⁺ T lymphocytes between treatment groups.

GM-CSF is an important factor in eosinophil growth and survival (26) that is released by CD4⁺ cells. GM-CSF also plays a key role in the late-phase allergic responses that are characterized by eosinophil influx to the airways (25). The reductions in IL-2⁺ and IL-13⁺ lymphocytes are important, given the documented influence of IL-2 on eosinophil activity (27, 28) and the relationship between IL-13 and bronchial hyper-reactivity, IgE production and asthma (29, 30). These data therefore indicate that omalizumab may exert anti-inflammatory effects by inducing eosinophil apoptosis through reductions in production of GM-CSF and by reducing numbers of peripheral IL-2⁺ and IL-13⁺ T lymphocytes (25).

The finding that omalizumab treatment was associated with a reduction in IL-13⁺ lymphocytes is consistent with previously observed reductions in circulating IL-13 in 35 patients with moderate-to-severe allergic asthma requiring daily administration of beclomethasone dipropionate (31). Omalizumab reduced circulating levels of IL-13, IL-5, and IL-8, in addition to reducing circulating eosinophil counts. There were no between group changes in levels of IL-6, IL-10 or soluble ICAM during the study.

Th2 cytokines (such as IL-4, IL-5 and IL-13) are produced by CD4⁺ T cells and are believed to play a key role in asthma pathogenesis by promoting recruitment and activation of mast cells and eosinophils, which are the primary effector cells in the allergic response (23).

Elevated levels of Th2 cytokines have been recorded in biopsies of the respiratory mucosa and in the sera of patients with asthma (23, 32–34). IL-4 has been shown to promote class switching to IgE in B cells (15, 35), is a key mediator of allergic inflammation, and has been shown to be associated with corticosteroid-resistant asthma (36).

There is also evidence that omalizumab attenuates the responses of basophils to allergen challenge in patients with asthma. Histamine release from basophils was evaluated in a study of 17 patients with allergic asthma (37). Maximal histamine release and cellular allergen sensitivity were significantly lower in the omalizumab group compared with placebo ($P < 0.01$ and $P < 0.05$ respectively). The reduced release of histamine from basophils was accompanied by significant changes in clinical markers of airway resistance, β -agonist usage, skin prick test, wheal area, and investigator global evaluation of treatment effectiveness.

Inhalation of adenosine 5'-monophosphate (AMP) by individuals with asthma leads to bronchoconstriction as a result of enhanced mast cell activation via stimulation of the adenosine A_{2B} receptor; therefore, AMP can be considered as an indirect measure of airway responsiveness (38). The effectiveness of omalizumab to reduce bronchoconstriction induced by AMP has been reported in patients with mild-to-moderate allergic asthma (39). Omalizumab has also been reported to reduce hyper-responsiveness to acetylcholine in patients with moderate-to-severe allergic asthma (37) and to methacholine in patients with mild allergic asthma (40, 41). Moreover, omalizumab was well tolerated and adverse events were similar in the omalizumab and placebo groups (31, 39–41). In contrast to these observations, omalizumab did not significantly affect airway hyper-responsiveness to methacholine in a study of patients with mild-to-moderate persistent asthma and sputum eosinophilia (15). This latter observation was surprising given the effects of omalizumab on IgE levels and eosinophils reported in the same study, thereby prompting the authors to suggest that IgE and eosinophils may not mediate methacholine hyper-responsiveness in mild-to-moderate persistent asthma.

Early and late asthmatic responses. The early asthmatic response is mediated by the interaction of allergens with IgE bound to the surface of mast cells or basophils. The binding of allergens to IgE triggers cross-linking and aggregation of IgE receptors, which in turn promotes cell degranulation and the release of mediators such as histamine and tryptase and the synthesis and release of prostaglandins, leukotrienes, and cytokines (41). The late asthmatic response is associated with increased airway eosinophilic inflammation, heightened bronchovascular permeability, and increased bronchial hyper-responsiveness to nonspecific stimuli (41). Possible mechanisms underlying the late asthmatic response were investigated in a study of 24 individuals with cat allergy (42). In this study, challenge with inhaled Fel d 1-derived peptides

resulted in isolated late asthmatic reactions in 12 individuals, almost all of whom had marked increases in calcitonin gene-related peptide (a potent vasodilator) suggesting that vascular permeability and edema have an important role in mediating the bronchoconstriction.

The hypothesis that the effects of omalizumab on IgE receptors on mast cells and basophils and on eosinophilia would attenuate early and late asthmatic responses was investigated in 19 patients with stable, mild allergic asthma (41). The effects of omalizumab were evaluated by assessing reductions in FEV₁ during the early (0–1 h after allergen challenge) and late (2–7 h) responses during 70 days of treatment. During the early-phase response, the mean maximal fall in FEV₁ on allergen challenge was $30 \pm 10\%$ at baseline and $18.8 \pm 8\%$ at the end of treatment in the omalizumab-treated patients, compared with $33 \pm 8\%$ at baseline and $34 \pm 4\%$ at the end of treatment in the placebo group (omalizumab vs placebo, $P = 0.01$). For the late-phase response, mean maximal falls in FEV₁ were $24 \pm 20\%$ at baseline and $9 \pm 10\%$ at the end of treatment in the omalizumab-treated patients and $20 \pm 17\%$ at baseline and $18 \pm 17\%$ at the end of treatment in the placebo group (omalizumab vs placebo, $P = 0.047$).

Additional evidence that omalizumab attenuates both the early and the late asthmatic response was provided by a study in patients with mild allergic asthma (24). In this study, early (0–3 h after allergen challenge) and late (3–7 h) responses were evaluated by measuring the maximal percentage fall in FEV₁ from baseline. In patients receiving omalizumab, the change from baseline in early asthmatic response to allergen (28.9% at baseline; 15.3% at the end of treatment) was significantly different compared with placebo ($P = 0.002$) (Fig. 4). In addition, patients receiving omalizumab had a significant reduction in the late asthmatic response to allergen from 36.1% at baseline to 4.7% at the end of treatment, compared with 31.1% at baseline and 25.4% at the end of treatment in the placebo group (omalizumab vs placebo, $P < 0.001$) (Fig. 4).

Omalizumab and markers of inflammation in other IgE-mediated allergic diseases

Allergic rhinitis. Further evidence of the anti-inflammatory effects of omalizumab has been provided by studies in patients with seasonal allergic rhinitis treated before and during the pollen season (43, 44). In a study of 30 patients, peripheral and nasal eosinophil counts increased during the pollen season in patients receiving placebo but there was no change in the omalizumab group, which achieved a significant reduction in serum free IgE compared with baseline (43). Furthermore, treatment with omalizumab plus concomitant specific immunotherapy (SIT) has been shown to normalize the number of myeloid dendritic cells during the grass pollen season in children ($n = 48$; 6–17 years) with seasonal allergic

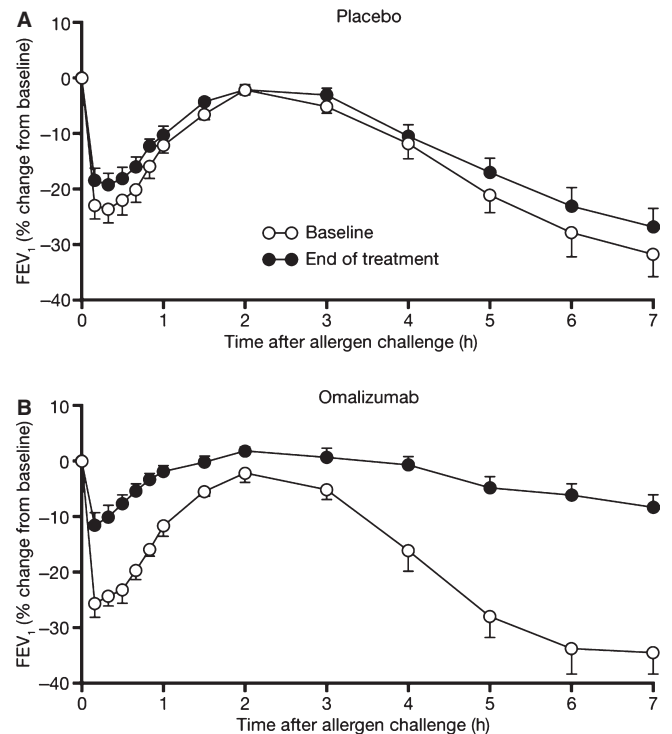


Figure 4. Forced expiratory volume in 1 s as a percentage of baseline in the first 3 h after allergen challenge (early phase response) and from 3 to 7 h after allergen challenge (late phase response) in the placebo (A) and omalizumab (B) groups. Reproduced with permission from van Rensen et al. 2009 (24).

rhinitis (44). Despite sensitization to grass and birch pollen, reductions were found during the grass season.

The effects of SIT and omalizumab on release of eosinophilic cationic protein (ECP), tryptase, IL-6, and IL-8 in nasal secretion were also evaluated in a study of 225 children with a history of seasonal allergic rhinoconjunctivitis induced by birch and grass pollen (45). Patients in the placebo plus SIT group showed significantly elevated ECP levels (during the grass pollen season and after the pollen season) compared with baseline and had stable levels of tryptase, IL-6, and IL-8 during the pollen season. Omalizumab plus SIT was associated with stable ECP levels and had significant reductions from baseline in tryptase (during the birch pollen season and after the pollen season). Levels of tryptase in nasal secretions in the omalizumab plus SIT group were significantly reduced compared with placebo plus SIT levels during the birch pollen season and after the pollen season. A decrease in IL-6 was observed after the pollen season in both treatment groups. An additional analysis investigated the effect of omalizumab and SIT on the leukotriene pathway in 92 children with sensitization to birch and grass pollens and seasonal allergic rhinitis (46). At the end of treatment, the combination of omalizumab and SIT resulted in significantly lower leukotriene release after allergen stimulation compared with placebo plus SIT ($P = 0.001$).

These findings in patients with allergic rhinitis add to the evidence for anti-inflammatory effects of omalizumab already described in patients with asthma. Each of these investigations were conducted in sub-populations from larger studies in which omalizumab was well tolerated and omalizumab-treated patients with allergic rhinitis had a similar adverse event profile to that observed in placebo-treated patients (47, 48).

It should be noted that omalizumab is not currently indicated for the treatment of patients with allergic rhinitis.

Skin allergic responses. Studies of cutaneous responses to allergens have also provided evidence of the anti-inflammatory effects of omalizumab. A study of 24 atopic allergic volunteers evaluated the effects of omalizumab or placebo for 12 weeks on early- and late-phase skin reactions and cellular infiltration in skin biopsies after intradermal allergen challenges (49). Omalizumab recipients had a progressive reduction in the late-phase reaction that was significantly larger than the reduction in the early-phase reaction (median -63% vs -24% respectively). A significant reduction of the late-phase reaction was achieved within 2 weeks of initiating treatment, compared with 8 weeks for the early-phase reaction. Skin biopsy results revealed increased levels of CD3⁺ (total) T cells and eosinophils in the placebo group compared with omalizumab, indicating that omalizumab prevented eosinophil influx and T-cell priming responses. Of note, a lower proportion of patients in the omalizumab group experienced at least one adverse event (33% vs 67%) and all events were considered mild. Further evidence of the effects of omalizumab on skin allergic responses was provided by a study of patients with moderate-to-severe allergic asthma, which evaluated immediate hypersensitivity skin test reactions to tree,

grass and weed pollens, moulds, dust mites, cat and dog allergens, mouse antigen, and cockroaches (50). There were marked reductions in skin test reactivity after the administration of omalizumab, with some reductions becoming more pronounced 20 min after administration. One of seven patients with a positive skin test to mouse antigen experienced a mild urticarial reaction following omalizumab administration; however, subsequent treatment with omalizumab led to no further adverse events. Other studies in patients with asthma and atopic dermatitis have also shown that omalizumab may attenuate responses to skin allergen challenge (31, 51), although the effects in skin appeared to be less pronounced than those seen in the airway, possibly due to differences in antibody penetration, cellular environment or mast cells (3).

Summary and conclusions

Patients with persistent asthma require anti-inflammatory therapy to maintain control of the disease and prevent exacerbations (1, 2). Inhaled corticosteroids have long been central to the control of persistent asthma (1, 2), although some patients continue to have asthma that is inadequately controlled despite intensive treatment (52). The introduction of omalizumab as an add-on therapy for inadequately controlled moderate-to-severe or severe, persistent, allergic asthma provided a valuable new treatment option for these patients. Given the importance of anti-inflammatory therapy for control of severe persistent asthma, it is important to determine the effects of omalizumab on markers of inflammation.

The interaction between omalizumab and free IgE interrupts a key step in the allergic inflammatory cascade, preventing IgE from binding to mast cells, basophils, and dendritic cells, and down-regulating IgE receptor expres-

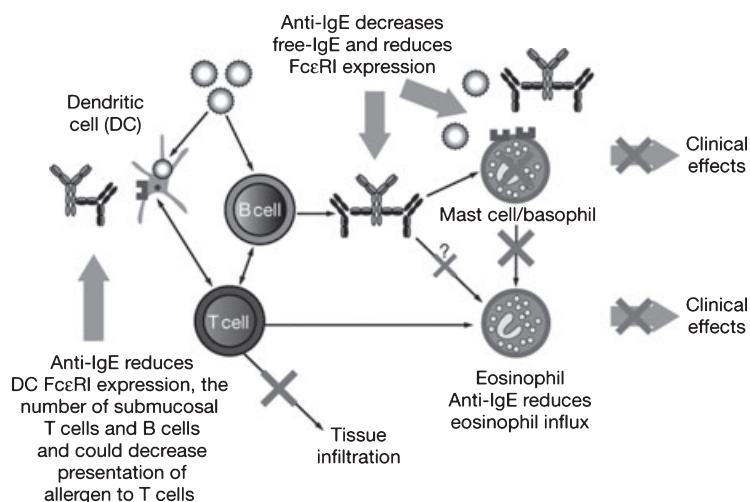


Figure 5. Proposed mechanisms of action of omalizumab. Reproduced with permission from Holgate et al. 2005 (3).

sion on these inflammatory cells thereby inhibiting degranulation and the release of inflammatory mediators. Several studies have shown that treatment with omalizumab reduces both peripheral and bronchial tissue eosinophil counts, as well as reducing the release of a variety of pro-inflammatory mediators such as GM-CSF, IL-2, IL-4, IL-5, and IL-13. As omalizumab reduces both mast cell degranulation and eosinophil infiltration, this results in attenuation of both the early- and late-asthmatic responses. Overall, these findings are consistent with the previously proposed mechanism of action of omalizumab (Fig. 5) (3). Omalizumab reduces free IgE levels and reduces FcεRI-receptor expression on mast cells and basophils leading to decreased mast-cell activation and sensitivity and a reduction in eosinophil infiltration and activation. In addition, omalizumab also reduces dendritic cell FcεRI receptor expression, which may lead to a reduction in allergen presentation to T cells, followed by a reduction in differentiation of Th2 cells, inhibition of Th2-cell activation and a consequent decrease in the release of Th2 cytokines (such as IL-4, IL-5 and IL-13) involved in the recruitment and activa-

tion of mast cells and eosinophils (3). The interruption of these steps in the inflammatory response may underlie the reductions in asthma exacerbations reported in clinical trials of omalizumab in patients with severe, persistent, inadequately controlled, allergic asthma, and it could possibly contribute to decreased airway remodeling in patients with asthma (53).

In conclusion, there is now a strong body of evidence demonstrating that omalizumab inhibits multiple key components of the allergic inflammatory cascade. Omalizumab substantially reduces the activity of IgE, eosinophils, basophils, mast cells, and dendritic cells thereby targeting allergen sensitization and the acute and chronic effector phases of allergic inflammation.

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