

## REVIEW

# Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy

S. T. Holgate\*, R. Djukanović\*, T. Casale† and J. Bousquet‡

\*Southampton General Hospital, Southampton, UK, †Creighton University, Omaha, USA, and ‡Hôpital Arnaud de Villeneuve, Montpellier, France

### Summary

Omalizumab is a humanized monoclonal anti-IgE antibody developed for the treatment of allergic disease, with established efficacy in patients with moderate-to-severe allergic asthma and in patients with intermittent (seasonal) and persistent (perennial) allergic rhinitis (AR). Omalizumab is known to result in a marked reduction in serum levels of free IgE and down-regulation of IgE receptors on circulating basophils. Recent work has shed further light on its mechanism of action, showing significant and profound reductions in tissue (nasal and bronchial) eosinophils and in bronchial IgE<sup>+</sup> cells (mast cells), as well as T cells and B cells. Omalizumab treatment was also shown to be associated with down-regulation of IgE receptors on circulating (precursor) dendritic cells, suggesting that blocking IgE may inhibit more chronic aspects of allergic inflammation involving T cell activation. Further work with omalizumab demonstrated it to have important benefits in patients with poorly controlled asthma despite high-dose inhaled corticosteroid therapy, and analysis of clinical data suggests that the patients who are the best 'responders' to anti-IgE treatment are those with asthma at the more severe end of the spectrum. Notably, systemic anti-IgE therapy with omalizumab has been shown to improve symptoms, quality of life and disease control (asthma exacerbations) in patients with concomitant asthma and persistent AR. These impressive clinical data and the studies elucidating the anti-inflammatory profile of omalizumab also serve to emphasize the fundamental importance of IgE in the pathogenesis of allergic diseases.

### Immunoglobulin E and the allergic response

Elevated serum levels of specific IgE towards common environmental allergens characterize allergic diseases such as asthma and rhinitis. IgE plays a critical role in type I hypersensitivity reactions, binding to high-affinity IgE receptors (FcεRI) on mast cells via the Cε3 domain on its Fc fragment. Mast cells and their circulating counterpart, basophils, both express the FcεRI receptor, and it is well documented that basophil FcεRI expression correlates with serum IgE levels [1]. Recent work has confirmed that IgE itself appears to up-regulate the expression of FcεRI on human basophils, and it seems likely that this is mediated by IgE interacting through FcεRIα itself [2]. The finding that FcεRI expression on circulating basophils was significantly reduced by 99% in the presence of low serum levels of IgE during 90 days of treatment of ragweed-allergic individuals with the anti-IgE monoclonal antibody omalizumab [3] lends strong support to the role of IgE in controlling the expression of FcεRI. Furthermore, the responsiveness (histamine releasability) of these cells upon *ex vivo* allergen stimulation was significantly reduced by approximately 90% [3].

Dendritic cells (DCs) are important in T-helper (Th) cell differentiation, with type I DCs (DC1) enhancing Th1 differentiation and type II DC (DC2) being an important

factor for Th2 cell responses. DC2 cells are described as the gatekeepers of the immune response [4] and IgE occupancy of DC2 FcεRI receptors is associated with greater allergen uptake and an increase in the resulting immune response [5, 6]. In a group of 24 subjects with ragweed-induced rhinitis, Prussin et al. [7] studied the effect of omalizumab on DC and basophil FcεRI expression. Omalizumab treatment was associated with a significant decrease in basophil FcεRI expression at all time-points during the study (days 7, 14, 21, 28, 35, 42) compared with placebo ( $P < 0.001$ ). The level of FcεRI expression on both DC1 and DC2 cells was reduced in omalizumab-treated individuals, with a significant reduction observed as early as day 7 (Fig. 1). FcεRI expression on both DC1 and DC2 correlated with serum levels of free IgE in patients receiving omalizumab and there was a correlation between FcεRI expression on DC2 cells and that on DC1 cells and basophils. These results show that the anti-IgE effects of omalizumab regulate FcεRI expression in these cell types in parallel with similar kinetics of inhibition. Overall, the maximum decrease in FcεRI expression was 73% on basophils, 52% on DC1 cells and 83% on DC2 cells [7].

### Clinical studies of omalizumab

#### *Omalizumab in patients with allergic asthma*

Early studies in patients with mild allergic asthma showed that the anti-IgE concept translated into demonstrable clinical effects, as shown by inhibition of allergen-induced early and late bronchoconstrictor responses [8, 9]. A phase II

Correspondence: Stephen T. Holgate, IIR Division, Mailpoint 810, Level D, Centre Block, Southampton General Hospital, Southampton, SO16 6YD, UK.

E-mail: sth@soton.ac.uk

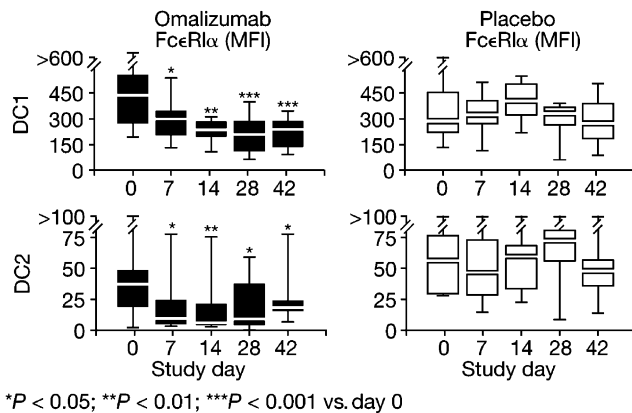


**Fig. 1.** Effect of omalizumab on Fc $\epsilon$ RI expression on precursor dendritic cells (DC1 and DC2). Patients were randomized to receive omalizumab ( $n = 16$ ) or placebo ( $n = 8$ ). Data show mean fluorescence intensity (MFI) representing Fc $\epsilon$ RI expression. The horizontal middle line is the median, the top and bottom of the boxes are quartiles and the T bars show maximum and minimum values. With permission [7].

study in patients with moderate-to-severe allergic asthma reported reduced asthma exacerbations and corticosteroid requirements with the use of an intravenous formulation of omalizumab [10]. Subsequent phase III studies using the standard subcutaneous formulation of omalizumab were conducted in a total of 1405 children, adolescents and adults with moderate-to-severe allergic asthma and positive skin prick tests to one or more common environmental allergens [11–13]. Subcutaneous injections of 150–375 mg omalizumab were given every 2 or 4 weeks. The dose was based on the patient's baseline IgE and bodyweight, to provide a dose of at least 0.016 mg/kg of omalizumab per IU/mL of IgE per 4 weeks [14]. In these studies, omalizumab was added on to inhaled corticosteroid (ICS) therapy for 16 weeks (steroid-stable phase) and then, during a 12-week steroid-reduction phase, patients' doses of ICS were decreased to establish the optimal lowest dose required for an acceptable level of asthma control. The primary end-point for the studies in adults was reduction in asthma exacerbations.

In all three studies, both the incidence and frequency of exacerbations (defined as a worsening of asthma requiring treatment with oral or intravenous corticosteroids or doubling of baseline ICS dose) were significantly reduced in the omalizumab treatment group compared with placebo, although there was also a reduction in asthma exacerbation incidence and frequency in this treatment group. Patients significantly reduced their requirement for ICS, with a proportion totally withdrawing from this medication. Compared with the placebo group, a significantly greater reduction in ICS dose was achieved by the omalizumab-treated patients and a substantially greater percentage of omalizumab patients were able to withdraw from ICS treatment completely. Improvements in asthma symptoms and rescue bronchodilator use were observed. Improvements in asthma-related quality of life also occurred with omalizumab treatment for both the adults [15, 16] and children [17].

Exacerbation reduction is perhaps the most important goal of asthma management [18]. The data from the three phase III studies were pooled and analysed to determine the effect of omalizumab on serious exacerbations, which were measured by asthma-related emergency room visits and hospitalizations

[19]. Clearly, an improvement in potentially life-threatening episodes would provide significant benefits both for patients and in terms of reducing the overall cost of asthma care. Omalizumab-treated patients had significantly fewer unscheduled outpatient visits (21.3 vs. 35.5, rate ratio 0.60,  $P < 0.01$ ) and emergency room visits (1.8 vs. 3.8, rate ratio 0.47,  $P = 0.05$ ) per 100 patient-years compared with placebo-treated patients. Importantly, hospitalizations were markedly reduced from 3.42 events per 100 patient-years on placebo treatment to 0.26 on omalizumab treatment, a rate ratio of 0.08 ( $P < 0.01$ ).

Approximately 5% of asthma patients have severe asthma that is often inadequately controlled by ICS and long-acting  $\beta_2$ -agonists (LABA). These patients are at high risk of severe exacerbations and death and have the greatest medical need among the asthmatic population. A recent double-blind, parallel group, multicentre study (INNOVATE) was conducted in patients with severe persistent asthma that was inadequately controlled despite therapy with high-dose ICS and LABA (GINA step 4 treatment) [20]. Patients were randomized to receive omalizumab or placebo as add-on therapy for 28 weeks. Omalizumab significantly reduced ( $P = 0.042$ ) the clinically significant asthma exacerbation rate compared with the placebo group (after adjustment for imbalance in baseline exacerbation history). Omalizumab treatment also halved the severe exacerbation rate (0.24 vs. 0.48,  $P = 0.002$ ) and the incidence of emergency visits was significantly lower for omalizumab patients (0.24 vs. 0.43,  $P = 0.038$ ). The results of the INNOVATE study indicate that omalizumab is an effective add-on therapy for difficult-to-treat patients with inadequately controlled severe persistent asthma.

The efficacy of omalizumab treatment in patients with severe persistent asthma has also been demonstrated in a pooled analysis of data from seven studies [21]. Omalizumab treatment was added to current asthma therapy and compared with placebo (five double-blind studies) or with current asthma therapy alone (two open label studies). The studies included 4308 patients, 93% of whom had severe persistent asthma according to the GINA 2002 classification. Omalizumab treatment significantly reduced the rate of asthma exacerbations by 38% and the rate of total emergency visits by 47% ( $P < 0.001$  vs. control), suggesting that omalizumab may fulfil an important need in this difficult-to-treat asthma population.

### Studies of omalizumab in allergic rhinitis

Allergic rhinitis (AR) affects at least 10–25% of the population worldwide and is classified as intermittent (seasonal) or persistent (perennial) [22]. Both types are mediated by IgE. Although AR is not usually a severe disease, it can have a substantial impact on quality of life of patients [23]. Large phase III studies in AR have established the efficacy of omalizumab in both reducing symptoms and improving rhinitis-related quality of life for patients with intermittent and persistent AR [24–26].

### Onset of action of anti-immunoglobulin E effect

The onset of action of therapy is particularly important in seasonal AR, when patients need to respond quickly to changing pollen seasons. A recent study attempted to measure the onset of action of omalizumab by measuring the time taken

to inhibit the nasal responses to ragweed allergen [27]. In this single-centre, double-blind, placebo-controlled parallel group study, 24 patients (aged 19–50 years) with a 2-year history of ragweed-induced rhinitis were randomized to omalizumab ( $n = 16$ ) or placebo ( $n = 8$ ) and challenged with ragweed at intervals from days 7 to 42 of treatment. For the nasal challenge test, two sprays of nasal saline were administered to each nostril via nasal spray pump. This procedure was repeated three times at 10 min intervals. The acoustic rhinometry value after the third saline challenge was used as the baseline. Then, two sprays of ragweed solution (starting at 0.00054 AU concentration) were administered to each nostril and acoustic rhinometry was performed 10 min after administration of serial 10-fold ragweed concentrations to determine the dose eliciting a 30% decrease in nasal volume ( $PD_{30}$ ). On subsequent visits, patients received three nasal saline challenges followed by their  $PD_{30}$  dose of ragweed. Omalizumab (0.016 mg/kg/IgE (IU/mL)) was administered subcutaneously on days 0 and 28.

Omalizumab treatment reduced serum levels of free IgE from a median of 281 ng/mL on day 0, to 10.9 ng/mL on day 3, 28.1 ng/mL on day 28 and 17.5 ng/mL on day 42 ( $P < 0.001$ ). Omalizumab had a substantial impact on ragweed-induced reductions in nasal volume within the first 7 days of treatment. In a representative patient, the baseline 30% ragweed-induced nasal volume response was reduced to 12% on day 7 and further reduced to 6% on day 42. Similar significant reductions in the mean nasal challenge data occurred for the omalizumab-treated group as a whole. This suggests that omalizumab acts rapidly to significantly reduce serum free-IgE levels and significantly inhibits ragweed-induced reductions in nasal volume.

This study in patients with ragweed-induced rhinitis demonstrated that omalizumab rapidly reduces nasal symptoms and circulating free IgE, which (as described earlier) is paralleled by reductions in FcεRI expression on DC1 and DC2 cells and basophils. One might propose that administering omalizumab the week before the start of the pollen season, then again 4 weeks later, would protect patients from AR symptoms during the pollen season.

## Effect of anti-immunoglobulin E on airway inflammation

### Effect in patients with seasonal allergic rhinitis

Plewako et al. [28] conducted a placebo-controlled study on the anti-inflammatory effect of omalizumab in 30 patients with seasonal AR. Treatments were administered before or at the start of the birch pollen season and continued throughout the birch pollen season for up to 6 weeks. Eosinophil levels were determined from both blood and nasal biopsy samples (via the eosinophil-specific markers, eosinophil peroxidase and eosinophil granule proteins) and were significantly reduced with omalizumab treatment compared with placebo (Fig. 2). These reductions in eosinophils were also found to correlate with the levels of serum free IgE ( $P = 0.04$ ).

### Effects in patients with asthma

A number of studies have examined the effects of omalizumab on various inflammatory markers in patients with

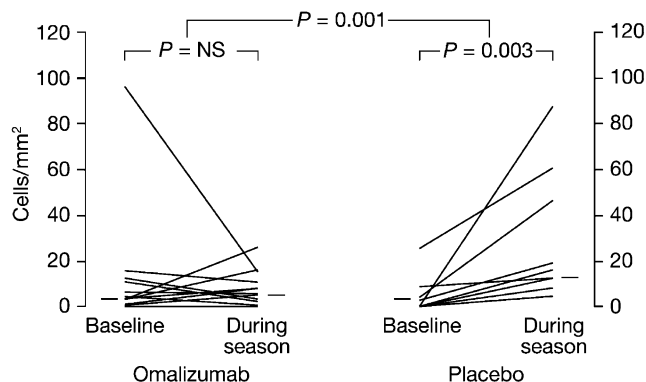


**Fig. 2.** Eosinophil peroxidase (EPO)<sup>+</sup> eosinophil counts in nasal biopsy specimens taken from patients with seasonal allergic rhinitis before (baseline) and during the birch pollen season. Patients received omalizumab (300 mg) ( $n = 19$ ) or placebo ( $n = 11$ ) for 4–6 weeks. With permission [28].

asthma [8, 29, 30]. In a pilot study, 19 patients with mild allergic asthma were randomized to receive either omalizumab or placebo for 11 weeks; eosinophils were measured in peripheral blood samples and in induced sputum [8]. Omalizumab significantly reduced both peripheral blood and induced sputum eosinophils compared with baseline values, but these reductions were not significantly greater than those in the placebo group.

Noga et al. [29] studied the levels of circulating mediators (IL-5, IL-6, IL-8, IL-10, IL-13 and s-ICAM) and eosinophils in 35 patients with moderate-to-severe asthma. Omalizumab was given in addition to ICS ( $\geq 500$  µg/day beclomethasone dipropionate (BDP)) and levels of inflammatory mediators were measured before and after 16 weeks of treatment. IL-13 levels decreased significantly from baseline ( $P < 0.001$ ) in the omalizumab group ( $n = 18$ ) compared with placebo ( $n = 17$ ). IL-5 (baseline median: 8.95 pg/mL [1.6–27.0], week 16 median: 6.3 pg/mL [0.48–24.7]) and IL-8 (baseline median: 3.74 pg/mL [0.8–20.1], week 16 median: 2.1 [0–5.1]) decreased, but did not reach statistical significance compared with placebo (IL-5 baseline median: 7.9 pg/mL [0.7–101.6], week 16 median: 6.76 pg/mL [0–130.9]; IL-8 baseline median: 2.6 pg/mL [0.65–14.6], week 16 median: 1.84 pg/mL [0–4.7]). IL-6, IL-10 and s-ICAM did not change over the course of the study.

IL-13 and IL-5 are produced by Th2 cells, eosinophils, mast cells and basophils [31], whereas IL-6 and IL-10 are produced by Th1/Th2 cells, macrophages and endothelial cells. The reduction in IL-5 and IL-13 therefore appears to reflect the proposed sites of action of omalizumab. This study also evaluated the effect of omalizumab on blood eosinophils after 16 and 52 weeks of omalizumab treatment. Compared with placebo, there was a significant decrease in eosinophils at both 16 and 52 weeks (Fig. 3). These findings suggest that omalizumab has significant additional anti-inflammatory effects when used as an add-on therapy to ICS.

While the effect of omalizumab on inflammatory markers was not the primary outcome measure of the studies described above, a 16-week randomized double-blind, placebo-controlled study in 45 patients with mild persistent asthma investigated sputum eosinophil counts as the primary variable [30]. All patients were treated with bronchodilators alone and had raised sputum eosinophil levels. The presence of

inflammatory markers was determined from both sputum induction and bronchial biopsies.

Treatment with omalizumab resulted in a significant reduction in mean percentage of eosinophils in induced sputum from 6.6% to 1.7% ( $P < 0.001$ ) compared with an 8.5% to 7.0% decrease in the placebo group (Fig. 4). Eosinophils in the epithelial and submucosal compartments were also reduced significantly with omalizumab, with one patient achieving submucosal levels equivalent to those of healthy individuals (Fig. 5).

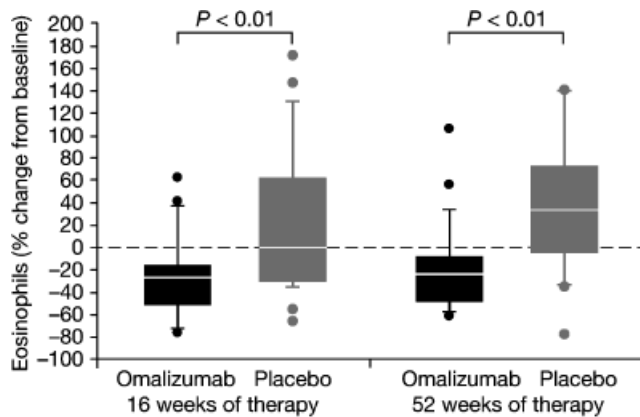


**Fig. 3.** Percentage change from baseline in peripheral blood eosinophils. Samples were taken before and after 16 weeks of treatment with omalizumab ( $n = 18$ ) or placebo ( $n = 15$ ). With permission [29].

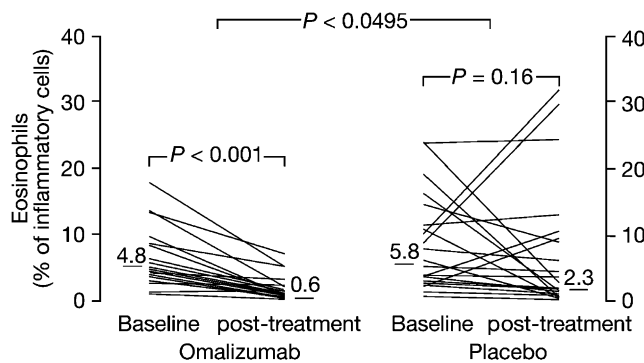


**Fig. 4.** Effect of omalizumab ( $n = 19$ ) or placebo ( $n = 22$ ) on airway eosinophil counts in induced sputum. Horizontal bars are medians. With permission [30].

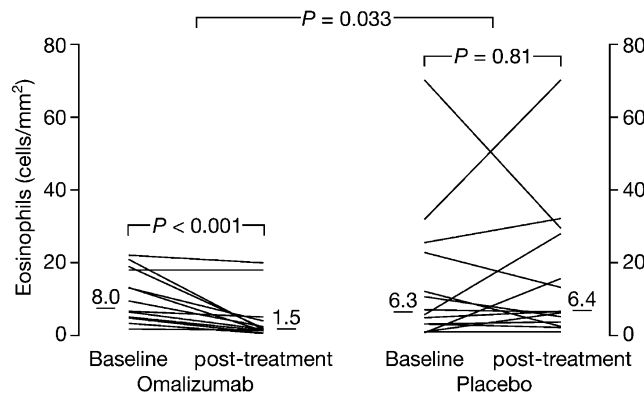


**Fig. 5.** Effect of omalizumab ( $n = 14$ ) or placebo ( $n = 14$ ) on airway eosinophil counts in the bronchial submucosa. Horizontal bars are medians. With permission [30].

Circulating free IgE was reduced to  $< 50$  ng/mL (21 IU/mL) in all omalizumab-treated subjects at study end. Staining with antibodies to IgE (indicated by the ring staining pattern) showed a striking reduction in the number of IgE<sup>+</sup> cells in the submucosa, with a 10-fold reduction in cell-associated IgE in the omalizumab group as a whole. This study did not specifically look at the type of cells associated with IgE but assumed that the majority were mast cells. Stained biopsy samples for FcεRI<sup>+</sup> cells in patients treated with omalizumab also showed marked reductions from baseline levels (by approximately 80%) and placebo (Fig. 6) ( $P < 0.001$ ), a finding that confirms previous studies investigating the effect of omalizumab on basophil FcεRI [3]. Consistent with current knowledge of the interaction between IgE and FcεRI, there was a significant correlation between the change in biopsy-expressed IgE and biopsy-expressed FcεRI ( $R_s = 0.92$ ,  $P < 0.001$ ).

This study also investigated the effect on other inflammatory markers as secondary outcomes. IL-4, produced by Th2 cells in response to allergen challenge, is of particular interest because it stimulates B cells to produce IgE and is known to up-regulate the expression of VCAM-1, a ligand that facilitates the endothelial adhesion of eosinophils [32]. Omalizumab substantially decreased cell surface IL-4 compared with placebo ( $P < 0.001$ ) (Fig. 7) and there was a positive correlation between the reduction in cell granule-associated IL-4 and submucosal eosinophils ( $R_s = 0.78$ ,

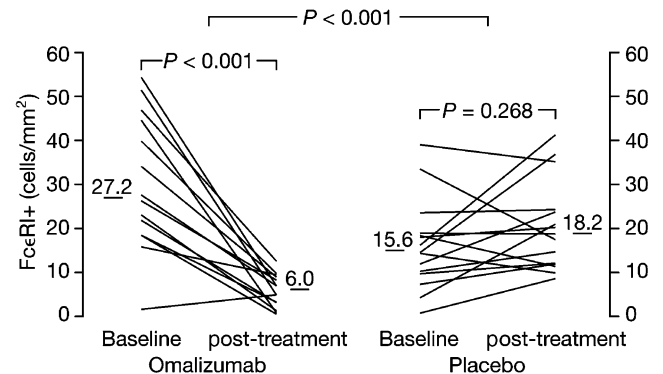


**Fig. 6.** Effect of omalizumab ( $n = 14$ ) or placebo ( $n = 14$ ) on the number of cells expressing FcεRI in the bronchial submucosa. Horizontal bars are medians. With permission [30].

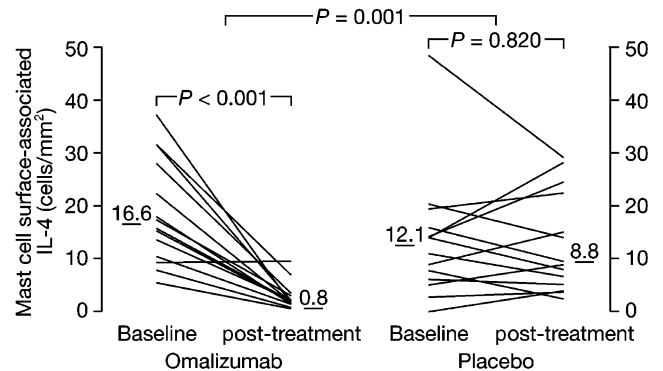


**Fig. 7.** Effect of omalizumab ( $n = 14$ ) or placebo ( $n = 14$ ) on the number of cells with cell-surface-associated IL-4 (median counts of submucosal cells staining positively with <sup>3</sup>H<sub>4</sub> monoclonal antibody against IL-4). With permission [30].

$P < 0.001$ ), suggesting that omalizumab may affect eosinophils levels via an IL-4-mediated effect. IL-4 is also produced by mast cells, basophils and eosinophils. Hence, the effects of omalizumab on eosinophils could result indirectly from omalizumab's action on Th2 cells (via altered antigen presentation from affected DCs, a process which is also enhanced by IL-4 [33, 34], or via inhibition of mast cell or basophil degranulation).

The studies in patients with allergic asthma or rhinitis showed omalizumab to have a pronounced anti-inflammatory effect in the airways. The omalizumab-associated reduction in eosinophils suggests that its actions may extend beyond IgE-bearing cells alone. Furthermore, while the reduction in eosinophils with omalizumab is comparable with that reported with ICS treatment, omalizumab appears to offer benefits when used as an add-on therapy to ICS. These findings provide useful evidence towards explaining the mechanistic basis for the efficacy of omalizumab in patients with allergic asthma and rhinitis.

### Clinical implications of anti-immunoglobulin E therapy

#### *Who will benefit most from anti-immunoglobulin E therapy?*

Omalizumab is currently approved for moderate-to-severe persistent allergic asthma in the USA, Canada and Brazil, for moderate persistent allergic asthma in Australia, and for severe persistent allergic asthma in New Zealand.

The evidence presented above shows that omalizumab has anti-inflammatory activity and attenuates both the early- and late-phase allergic responses, effects that may translate into clinical benefits for different categories of patient with allergic conditions. Recent clinical data suggest that omalizumab may be especially beneficial in patients with severe allergic asthma and in patients with concomitant allergic asthma and persistent AR.

Patients with severe asthma generally have greater unmet treatment needs than any other class of patient with asthma and may remain symptomatic despite high-dose ICS use, often experiencing frequent exacerbations of disease requiring emergency treatment [35, 36]. A new treatment that proved effective in this group of patients could reduce both indirect patient costs and direct healthcare costs and offer considerable socio-economic advantages. In severe persistent asthma, the treatment goal is to achieve the best possible improvements in symptom control, lung function and exacerbations. A multiple-step treatment regimen such as that recommended by the Global Initiative for Asthma [18] includes corticosteroid doses that are increased with increasing asthma severity and additional controller medications such as LABA, anti-leukotrienes and oral corticosteroids. However, in severe asthma, patients can remain symptomatic despite use of all available treatments. Additionally, patients receiving multiple therapies may not adhere to complicated regimens.

In the phase III clinical trials, add-on therapy with omalizumab was effective in improving disease control in patients with moderate-severe and severe allergic asthma [12, 13, 37]. To determine the potential clinical implications of its use in patients with severe disease, a meta-analysis from these

clinical trials was performed in a subgroup of individuals who were at high risk of serious asthma-related morbidity and mortality [38].

Of the 1412 patients enrolled in the phase III trials, 254 patients were identified as high risk (135 treated with omalizumab and 119 placebo) and suitable for inclusion in the meta-analysis. High-risk patients were defined as those who had been intubated at some time prior to screening, or who had visited an emergency room, experienced overnight hospitalization or received treatment in an intensive care unit (ICU) during the last year. Overall, the majority of the 254 high-risk patients had undergone emergency room admissions in the previous year (86.7% omalizumab, 86.6% placebo) and around one-third were hospitalized because of asthma over the same time period. Only a small proportion of patients had required ICU admission and/or intubation. The main outcome measure of this meta-analysis was the annualized rate of significant asthma exacerbation episodes (AEEs), defined as those requiring a doubling of baseline ICS dose or use of systemic steroids. Additional outcome measures included the proportion of patients who remained exacerbation free and the rate of asthma-related rehospitalizations. The study focused on the steroid-stable phase of the clinical trials for clarity of the results.

Analysis of the annualized AEEs showed a statistically significant difference between the treatment groups in favour of omalizumab; patients receiving placebo experienced a rate of 1.56 episodes per patient-year compared with a rate of 0.69 in those treated with omalizumab ( $P = 0.007$ ). By comparing the annualized rate of significant AEEs relative to the total patient population in these clinical trials, the absolute benefit of omalizumab was seen to be most apparent in high-risk patients. The rate of significant AEEs among placebo recipients was increased for high-risk patients relative to all patients combined yet, by contrast, the rate of significant AEEs in patients receiving omalizumab was independent of high-risk status. A greater number of omalizumab recipients were free of exacerbations during the steroid-stable phase of the studies compared with placebo recipients (82.2% vs. 64.7%, respectively), and fewer patients were rehospitalized because of asthma with omalizumab treatment compared with those receiving placebo (4.5% vs. 12.2%, respectively).

The probability of a patient responding to omalizumab treatment was calculated using results from two phase III trials conducted in adults and adolescents with moderate-to-severe allergic asthma [12, 13]. Response was defined as a response in at least one of the following four aspects: reduced symptom scores, reduced usage of rescue medication, improved lung function and/or improved quality of life, with no asthma exacerbation during the 6 weeks' treatment. The analysis [39] involved data from 1070 patients with allergic asthma who were symptomatic despite moderate-to-high doses of inhaled BDP and showed that omalizumab had the greatest effect in those who had the most severe disease. When compared against baseline ICS dose and forced expiratory volume in 1 s (FEV<sub>1</sub>) (both predictors of severity of illness), the patients who benefited most from omalizumab treatment were those receiving the highest ICS dose and those with the poorest lung function. In patients receiving a dose of  $\geq 800 \mu\text{g/day}$  BDP the probability of response to omalizumab was estimated at 65% compared with only 40% on placebo

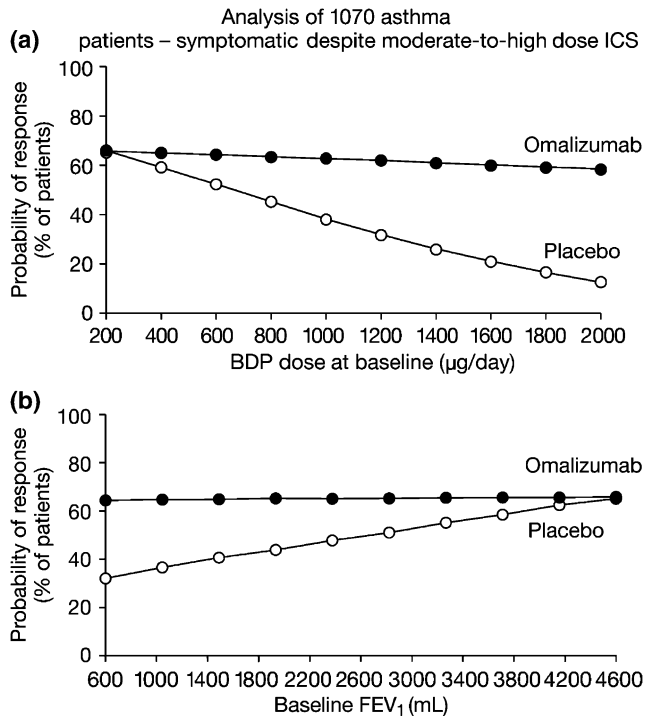


**Fig. 8.** Probability of response to omalizumab treatment in relation to (a) baseline dose of beclomethasone dipropionate (BDP) and (b) baseline forced expiratory volume in 1 s ( $FEV_1$ ). With permission [39].

( $P = 0.037$ ) (Fig. 8a). In patients with an  $FEV_1$  of  $\leq 65\%$  predicted, the response rate was 60% for omalizumab recipients compared, again, with only 40% for placebo ( $P = 0.072$ ) (Fig. 8b).

The efficacy of omalizumab was recently investigated in a clinical trial of patients with poorly controlled moderate-to-severe asthma despite treatment according to best current practice, which included the use of concomitant anti-leukotrienes, LABA and oral corticosteroids [40]. Compared with current asthma therapies alone, omalizumab-treated patients experienced significantly fewer asthma deterioration-related incidents. Results from this study may provide further evidence of the benefit of add-on omalizumab treatment in the most severe asthma population who, despite all available asthma therapies, continue to be poorly controlled and experience frequent asthma exacerbations. These analyses show that omalizumab has the greatest benefit in patients with severe asthma, which is in contrast with ICS treatments that may become less effective with increasing asthma severity.

These data, when taken together with the results of INNOVATE [20] and the pooled efficacy analysis [21], indicate that omalizumab promises to be a particularly useful add-on treatment option for patients with severe asthma.

#### Safety of omalizumab – pooled safety analysis

A large number of patients have received treatment with omalizumab in controlled clinical studies with 3285 patients receiving more than 12 weeks' omalizumab treatment, 2484 receiving more than 24 weeks, 690 more than 36 weeks and 555 more than 52 weeks (Novartis, Horsham Research Centre, UK, data on file). Overall, the frequencies of adverse

**Table 1.** Adverse events (occurring in  $\geq 5\%$  of patients) in all controlled studies

| Preferred term                    | Omalizumab (%),<br>$n = 3678$ | Control (%),<br>$n = 2452^*$ |
|-----------------------------------|-------------------------------|------------------------------|
| Any adverse event                 | 74.8                          | 75.2                         |
| Upper respiratory tract infection | 15.7                          | 15.7                         |
| Headache                          | 15.5                          | 15.6                         |
| Nasopharyngitis                   | 14.4                          | 15.9                         |
| Sinusitis                         | 10.1                          | 12.0                         |
| Pharyngolaryngeal pain            | 6.4                           | 6.0                          |
| Cough                             | 5.9                           | 7.1                          |
| Bronchitis                        | 5.2                           | 5.6                          |
| Influenza                         | 5.0                           | 6.6                          |

\*Placebo or standard-therapy control.

events were similar between the omalizumab and control groups (Table 1) and there were no more events in patients with severe asthma than in those with mild asthma. No pattern or cluster of adverse events has emerged; the majority of adverse events were of short duration and mild to moderate in severity.

There has been some recent interest in neoplasia adverse events with omalizumab. Malignant neoplasms were reported in 25 (0.5%) omalizumab-treated patients compared with five (0.2%) control patients across all completed studies (all but one were solid tumours). A panel of blinded, independent oncologists determined that none of the cases was related to study treatment. The onset of most of the tumours preceded treatment with omalizumab, and 60% of tumours presented within less than 6 months of treatment. Overall, the clinical data do not suggest a causal relationship between omalizumab and cancer.

There was no increase in the frequency of type I hypersensitivity adverse events. The overall incidence of urticaria was 1.2% in both omalizumab and control groups. Anaphylactic and anaphylactoid reactions were rare and were not accompanied by systemic manifestations such as hypotension. There is no evidence of any immune complex nephropathy or any anti-omalizumab antibodies.

#### Concomitant allergic disease

Asthma and rhinitis frequently coexist, with the majority of patients with allergic asthma also suffering with AR [22, 41]. Both conditions are associated with elevated levels of serum IgE and share similar pathophysiologies [22, 42]. Patients who have asthma and concomitant rhinitis experience more severe asthma symptoms and higher disease-associated costs than those with asthma alone [43, 44]. Anti-IgE therapy could be especially suitable for patients with concomitant disease. The World Health Organization-sponsored Allergic Rhinitis and its Impact on Asthma (ARIA) workshop report [22] recommended that patients with persistent rhinitis be evaluated for asthma and vice versa and, importantly, that strategies that combine the treatment of upper and lower airways be used where possible. To this end, the Study of Omalizumab in comorbid Asthma and Rhinitis (SOLAR) study has shown encouraging results [45].

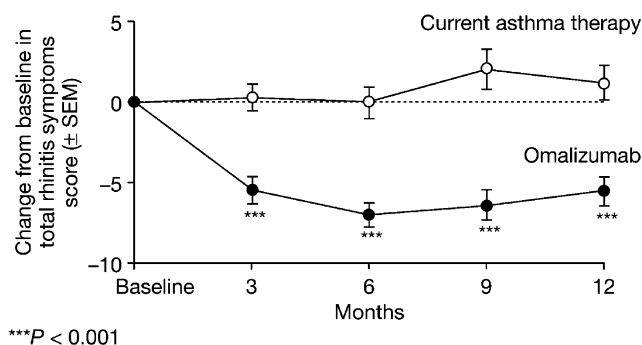
The SOLAR study was a randomized double-blind, placebo-controlled multicentre parallel-group 28-week trial.

It included both adolescents and adults with moderate-to-severe allergic asthma (requiring moderate-to-high doses of ICS and with a history of  $\geq 2$  unscheduled medical visits for allergic asthma and/or asthma exacerbations during the past year) and concomitant moderate-to-severe persistent AR (symptoms for  $\geq 2$  years). In total, 405 patients were randomized to receive omalizumab add-on therapy (at least 0.016 mg/kg/IgE (IU/mL) every 4 weeks) or placebo and were assessed by means of two primary outcome measures. The first was the number of AEEs experienced during the 28-week treatment period and the second was a combined asthma and rhinitis quality-of-life assessment where patients were evaluated by both the Asthma Quality-of-Life Questionnaire (AQLQ) [46] and the Rhinitis Quality-of-Life Questionnaire (RQLQ) [23]. Clinical responders were defined as having a  $\geq 1.0$  improvement in both questionnaires. Significantly fewer omalizumab-treated patients (20.6%) experienced at least one exacerbation compared with placebo (30.1%) ( $P = 0.02$ ). Patients treated with omalizumab also achieved clinically significant improvements in both quality-of-life assessments. At the end of the study, 57.7% of omalizumab-treated patients achieved a  $\geq 1.0$ -point improvement in both AQLQ and RQLQ compared with 40.6% of placebo-treated patients ( $P < 0.001$ ). When the AQLQ and RQLQ were considered individually, the difference between scores for each treatment group remained significant, with 67.3% of omalizumab recipients achieving a clinically significant response in the AQLQ compared with 50% of placebo recipients ( $P = 0.0004$ ), and 67.3% of omalizumab recipients achieving a clinically significant response in the RQLQ compared with 52.1% of placebo recipients ( $P = 0.0013$ ). Omalizumab may be the first drug that improves quality of life associated with both nasal and bronchial allergic disease in the same patients.

In another recent clinical trial [40], a subgroup analysis of patients with co-morbid asthma and rhinitis found omalizumab to be beneficial when administered as add-on treatment in patients with concomitant disease. This was an open-label study where patients were randomized to receive best standard care, with or without the addition of omalizumab (at least 0.016 mg/kg/IgE (IU/mL) every 4 weeks) for 12 months. The trial involved 312 adolescent and adult patients with persistent moderate-to-severe allergic asthma whose disease was poorly controlled, as defined by  $\geq 1$  emergency room visit and  $\geq 1$  additional course of oral corticosteroids because of asthma in the last year. A subgroup of 205 patients had concomitant asthma and rhinitis. Asthma and rhinitis symptoms were evaluated using the Wasserfallen symptom score and results showed that omalizumab add-on treatment significantly improved asthma, rhinitis and combined asthma and rhinitis Wasserfallen symptom scores at each visit throughout the study ( $P < 0.001$  for all treatment comparisons) (Fig. 9).

### Future studies

A study evaluating the use of omalizumab therapy prior to immunotherapy is currently under way. As omalizumab is known to reduce DC Fc $\epsilon$ RI expression, some researchers theorize that this may alter the mode of antigen presentation, and allow greater doses of antigen (given as immunotherapy)



\*\*\* $P < 0.001$

**Fig. 9.** Effect of current asthma therapy alone ( $n = 70$ ) or with addition of omalizumab ( $n = 135$ ) on combined Wasserfallen asthma and rhinitis symptom scores in patients with concomitant asthma and rhinitis. With permission [45].

to be tolerated. The primary objective in this study is to determine whether omalizumab given prior to rush immunotherapy, followed by 12 weeks of dual omalizumab and immunotherapy, is more effective than rush immunotherapy followed by immunotherapy alone. The secondary objective considers both the efficacy and safety of dual omalizumab and immunotherapy compared with omalizumab alone or placebo. Clinical tolerance and the immunological mechanisms involved are also assessed. Results from this study should improve the understanding of the role of IgE and potential benefits of anti-IgE therapy with omalizumab.

### Conclusions

The development of a selective anti-IgE humanized monoclonal antibody that binds to IgE and prevents its association with IgE receptors was a major breakthrough in the treatment of allergic disease. As such, omalizumab interrupts the allergic cascade by preventing allergen from activating mast cells or basophils. Omalizumab has been assessed in multiple clinical trials in both children and adults, demonstrating a high level of efficacy in allergic asthma and rhinitis. However, the mechanisms whereby omalizumab influences the pathophysiological responses in the airways were, until recently, largely unknown.

In the series of studies described in this article, omalizumab was shown not only to inhibit mast cell and basophil responses but also to have a profound effect on the numbers of inflammatory cells, such as eosinophils, T lymphocytes and B lymphocytes. These cells are fundamental to the chronic inflammatory response in allergic diseases such as asthma and rhinitis. This increased understanding places anti-IgE therapy firmly in the domain of an anti-inflammatory treatment for chronic allergic disease, with effects on multiple cell types. While bronchial and nasal biopsy studies have been carried out in patients with relatively mild disease, results from clinical studies suggest that the anti-inflammatory effect of omalizumab also extends to more chronic and severe allergic asthma.

The introduction of omalizumab appears likely to have a major impact in the therapy of difficult-to-treat asthma. The fact that allergic diseases frequently occur at more than one anatomical locality, especially the upper respiratory tract and sinuses, means that patients receiving this therapy should see

improvements in the multiple manifestations of allergy. Eighty years after the discovery of reagin, the first anti-IgE treatment, omalizumab, is now a promising new therapeutic option for patients with allergic diseases.

## References

- Malveaux FJ, Conroy MC, Adkinson NF Jr, Lichtensterin LM. IgE receptors on human basophils. Relationship to serum IgE concentration. *J Clin Invest* 1978; 62:176–81.
- MacGlashan D, McKenzie-White J, Chichester K et al. In vitro regulation of FcεRIα expression on human basophils by IgE antibody. *Blood* 1998; 91:1633–43.
- MacGlashan DW Jr, Bochner BS, Adelman DC et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; 158:1438–45.
- Upham JW. The role of dendritic cells in immune regulation and allergic airway inflammation. *Respirology* 2003; 8:140–8.
- Stingl G, Maurer D. IgE-mediated allergen presentation via FcεRI on antigen-presenting cells. *Int Arch Allergy Immunol* 1997; 113:24–9.
- Maurer D, Ebner C, Reininger B et al. The high affinity IgE receptor (FcεRI) mediates IgE-dependent allergen presentation. *J Immunol* 1995; 154:6285–90.
- Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεRI expression. *J Allergy Clin Immunol* 2003; 112:1147–54.
- Fahy JV, Fleming HE, Wong HH et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828–34.
- Boulet LP, Chapman KR, Côté J et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997; 155:1835–40.
- Milgrom H, Fick RB Jr, Su JQ et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999; 341:1966–73.
- Milgrom H, Berger W, Nayak A et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108:E36.
- Busse W, Corren J, Lanier BQ et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108:184–90.
- Solèr M, Matz J, Townley R et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18:254–61.
- Hochhaus G, Brookman L, Fox H et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003; 19:491–8.
- Finn A, Gross G, van Bavel J et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol* 2003; 111:278–84.
- Buhl R, Hant G, Solèr M et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. *Eur Respir J* 2002; 20:1088–94.
- Lemanske RF, Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics* 2002; 110:E55.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. NIH publication number 02-3659, Issued January 1995 (updated 2002, 2003). Available at: [www.ginasthma.com](http://www.ginasthma.com)
- Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol* 2003; 111:87–90.
- Humbert M, Beasley R, Ayres J et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60:309–16.
- Bousquet J, Cabrera P, Berkman N et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005; 60:302–8.
- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma (ARIA) workshop report. *J Allergy Clin Immunol* 2001; 108 (Suppl.):S147–334.
- Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991; 21:77–83.
- Ådelroth E, Rak S, Haahtela T et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 106:253–9.
- Casale TB, Condemi J, LaForce C et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis. *JAMA* 2001; 286:2956–67.
- Chervinsky P, Casale T, Townley R et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 91:160–7.
- Lin H, Boesel KM, Griffith DT et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. *J Allergy Clin Immunol* 2004; 113:297–302.
- Plewako H, Arvidsson M, Petruson K et al. The effect of omalizumab on nasal allergic inflammation. *J Allergy Clin Immunol* 2002; 110:68–71.
- Noga O, Hanf G, Kunkel G. Immunological changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol* 2003; 131:46–52.
- Djukanović R, Wilson S, Kraft M et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004; 170:583–93.
- Larché M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. *J Allergy Clin Immunol* 2003; 111:449–61.
- Rajakulasingam K, Till S, Ying S et al. Increased expression of high affinity IgE (FcεRI) receptor-α chain mRNA and protein-bearing eosinophils in human allergen-induced atopic asthma. *Am J Respir Crit Care Med* 1998; 158:233–40.
- Vercelli D, Jabara HH, Lee BW, Woodland N, Geha RS, Leung DY. Human recombinant interleukin 4 induces FcεRI on normal human monocytes. *J Exp Med* 1988; 167:1406–16.
- Bieber T, Rieger A, Neuchrist C et al. Induction of FcεRI on human epidermal Langerhans cells by human recombinant interleukin 4 and gamma interferon. *J Exp Med* 1989; 170:309–14.
- Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998; 12:1209–18.
- Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, Silverman S. Risk factors and costs associated with an asthma attack. *Thorax* 2000; 55:19–24.
- Holgate ST, Chuchalin AG, Hebert J et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34:632–8.
- Holgate ST, Bousquet J, Wenzel S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab, an anti-immunoglobulin E antibody in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin* 2001; 17:233–40.

- 39 Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma. *Chest* 2004; 125:1378–86.
- 40 Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004; 59:701–8.
- 41 Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999; 103:54–9.
- 42 Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003; 58:691–706.
- 43 Paramore C, Leidy N, Watrous M, Doyle J, Zeiger R. Impact of disease severity and co-morbid allergic rhinitis on costs of care for patients with asthma. *Am J Respir Crit Care Med* 2000; 161:A789.
- 44 Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109:57–62.
- 45 Vignola AM, Humbert M, Bousquet J et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59:709–17.
- 46 Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993; 147:828–32.