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ALLERGY

Original article

Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR

Background: Anti-IgE therapy could be particularly beneficial for patients with concomitant disease as it targets a common factor in both diseases. The aim of this study was to evaluate the efficacy and safety of omalizumab in patients with concomitant moderate-to-severe asthma and persistent allergic rhinitis.
Methods: This multicentre, randomized, double-blind, parallel-group, placebo-controlled trial evaluated the safety and efficacy of omalizumab. A total of 405 patients (12–74 years) with a stable treatment (≥400 μg budesonide Turbuhaler®) and ≥2 unscheduled medical visits for asthma during the past year or ≥3 during the past 2 years were enrolled. Patients received omalizumab (≥0.016 mg/kg/IgE [IU/ml] per 4 weeks) or placebo for 28 weeks.
Results: Fewer patients treated with omalizumab experienced asthma exacerbations (20.6%) than placebo-treated patients (30.1%), $P = 0.02$. A clinically significant (≥1.0 point) improvement in both Asthma Quality of Life Questionnaire and Rhinitis Quality of Life Questionnaire occurred in 57.7% of omalizumab patients compared with 40.6% of placebo patients ($P < 0.001$). Omalizumab reduced Wasserfallen symptom scores for asthma ($P = 0.023$), rhinitis ($P < 0.001$) and the composite asthma/rhinitis scores ($P < 0.001$) compared with placebo. Serious adverse events were observed in 1.4% of omalizumab-treated patients and 1.5% of placebo-treated patients.
Conclusion: Omalizumab is well tolerated and effective in preventing asthma exacerbations and improving quality of life in patients with concomitant asthma and persistent allergic rhinitis.

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Epidemiological studies have shown that asthma and rhinitis frequently co-exist (1–3), with the majority of patients with allergic asthma experiencing concomitant rhinitis. Both diseases are associated with elevated serum immunoglobulin E (IgE) levels, and share similar inflammatory pathophysiologies (4, 5).

Concomitant rhinitis has a substantial impact on both healthcare costs and asthma outcomes (6). Additionally, the treatment outcomes in asthma and rhinitis have been linked (7, 8). In a retrospective study of 4944 patients, Crystal-Peters et al. demonstrated that patients with asthma treated for allergic rhinitis experienced a significantly lower risk of asthma-related events, including emergency department visits or hospitalizations, than those patients with untreated allergic rhinitis (7). Similar findings were also reported by Adams et al. (8). These findings suggest that patients may benefit from therapeutic approaches that target the common factors in both diseases (9). Strategies combining the treatment of both upper and lower airways disease are also recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop report (10).

Immunoglobulin E is a common factor in both allergic asthma and rhinitis, and clinical studies have found anti-IgE therapy with omalizumab to be efficacious in both diseases. Omalizumab binds to the high-affinity FcεRI domain of free circulating IgE, reducing the levels of serum-free IgE by 84–99% (11). In asthma, omalizumab treatment significantly reduces asthma exacerbations in addition to improving overall disease control and asthma-related quality of life (QoL) (12–16). Similar improvements in rhinitis control have also been seen with omalizumab treatment in patients with seasonal allergic rhinitis (SAR) and persistent allergic rhinitis (PAR) (17–19). One sub-study in patients with concomitant asthma and rhinitis found that omalizumab significantly improved combined asthma and rhinitis symptom scores (20). Given the link between rhinitis treatment and asthma control, the use of omalizumab in patients with both disorders could confer significant benefits.

The aim of study of omalizumab in comorbid asthma and rhinitis (SOLAR) was to evaluate the efficacy and safety of omalizumab in patients with concomitant asthma and PAR. The co-primary efficacy variables were the incidence of asthma exacerbations and the proportion of patients showing a response in both asthma and rhinitis QoL assessments.

Materials and methods

Patients

Eligible patients aged 12–75 years had a history of allergic asthma for at least 1 year with ≥ 12% increase in forced expiratory volume in 1 s (FEV_1) after 400 μg salbutamol. An IgE level from ≥ 30 to ≤1300 IU/ml was required, together with a positive skin-prick test to at least one indoor allergen. The positively testing allergen had to be one to which the patient would be exposed on a daily basis for the duration of the study, thus helping ensure that it was clinically relevant to the patient's disease. A history of moderate-to-severe PAR symptoms for ≥ 2 years was also necessary for inclusion. All patients were receiving ≥ 400 μg/day of inhaled corticosteroid (ICS) and had a history of ≥ 2 unscheduled medical visits for their asthma during the past year or ≥ 3 in the past 2 years. Participants were also required to have total scores of > 64/192 (32 items, amended to use a 0–6 scale) in the Asthma Quality of Life Questionnaire (AQLQ) and > 56/168 (28 items, 0–6 scale) in the Rhinitis Quality of Life Questionnaire (RQLQ) at baseline, which corresponds to a minimum QoL score worse than that of mild symptoms in both diseases (21, 22).

Patients receiving the following treatments were excluded: systemic corticosteroids, long-acting antihistamines, cromolyn sodium, nedocromil sodium, oral β_2-adrenoreceptor agonists, theophylline, leukotriene-receptor antagonists, inhaled anticholinergics, methotrexate, gold salts, cyclosporin and allergen-specific immunotherapy. Patients with active (in season) SAR at baseline, acute sinusitis, chest infection, persistent nonallergic rhinitis, pregnancy, or a platelet count of $\leq 130 \times 10^9$/l were also excluded.

Concomitant treatment with long-acting β_2-adrenoceptor agonists and nasal steroids was allowed if patients were on a stabilized regimen at screening. Asthma exacerbations could be treated with nebulized and/or inhaled β_2-adrenoceptor agonists, a short course (3–10 days) of systemic corticosteroids or doubling of the inhaled budesonide Turbuhaler® (AstraZeneca) dose in accordance with GINA guidelines (23). Rhinitis exacerbations could be treated with an oral antihistamine.

Study design

This multicentre, randomized, double-blind, parallel-group, placebo-controlled, 28-week trial evaluated the efficacy and safety of omalizumab in patients with concomitant moderate-to-severe allergic asthma (GINA) (24) and PAR. The study comprised a screening visit (week-5), followed by a 4-week run-in period and a 28-week double-blind treatment period when patients were randomized to receive either omalizumab or placebo. At the start of the run-in period, ICS medication was standardized by switching patients to an equivalent dose of commercially available budesonide Turbuhaler® (if they were not already taking this). In a conservative approach, 100 μg of budesonide Turbuhaler was assumed to be equivalent to 100 μg of budesonide via metered-dose inhaler and beclomethasone dipropionate, and 50 μg of fluticasone. During the 4-week run-in the dose was to remain unchanged; if any change in dose occurred the run-in was extended until the dose had remained stable for at least 4 weeks. Other asthma therapy and nasal steroid use were also to be stable during the run-in. At each scheduled evaluation visit after randomization, physicians used their clinical judgement to assess if the patient was receiving their optimal lowest dose of ICS and if the dose should be increased or reduced. Throughout the treatment period patients were closely monitored for signs of worsening asthma and had a predefined list of signs and symptoms that would prompt them to contact their physician.

The dose of omalizumab was dependent on body weight and serum IgE levels (at least 0.016 mg/kg/IgE [IU/ml] per 4 weeks) and was administered every 2 or 4 weeks. The 2-weekly schedule of administration was used for patients requiring higher doses owing to higher body weight and/or serum IgE levels, the larger volume of injection being more conveniently given in two divided doses.

Patients' asthma severity at baseline was classified according to the combination of clinical features and treatment classification set out in GINA (23). The treatment classification at step 3 was interpreted to include the option of higher doses of budesonide (> 800 μg) as single controller medication and combined therapy (up to 800 μg plus long-acting β_2-agonist).

The study was performed after an ethics committee approval and patients or their parents/guardians gave written informed consent.

Efficacy variables

The co-primary efficacy variables were the incidence of asthma exacerbations during the 28-week treatment period and the proportion of patients with improvement in both asthma and rhinitis QoL scores. An asthma exacerbation was defined as worsening of asthma requiring treatment with systemic corticosteroids or doubling of the baseline inhaled budesonide dose.

The AQLQ and RQLQ self-administered questionnaires were used. The AQLQ contains 32 items covering five domains (overall, symptoms, environment, emotions and activities) (21) using a 7-point scale, with a score of 1 representing the greatest impairment and a score of 7 representing no impairment in QoL, during the previous 2 weeks. The RQLQ contains 28 items, covering eight domains (overall, activity limitation, sleep impairment, non-nasal or nonocular symptoms, practical problems, nasal symptoms, eye symptoms, emotional function) (22) using a 0 to 6-point scale, with a score of 0 representing not troubled and 6 representing extremely troubled, over the previous 7 days (22). Data were collected using the 0–6 scale for both questionnaires to meet the inclusion criteria and were recoded to the 1–7 scale to provide consistency between questionnaires and with published results of the AQLQ (25).

Quality of life assessments were performed every 8 weeks, and the primary efficacy endpoint was the computed change from baseline in both the AQLQ and RQLQ at study end (week 28). The primary analysis compared the proportion of responders (a responder was defined as a patient with a ≥ 1.0-point improvement from baseline in both AQLQ and RQLQ). A secondary analysis assessed the number of patients achieving 0.5, 1.0 and 1.5-point improvements, which indicate the minimal important difference in QoL, a moderate change and a large change in QoL, respectively (26).

Secondary efficacy variables included rescue-medication use, separate AQLQ and RQLQ evaluations, Wasserfallen asthma and rhinitis clinical symptom scores (27), patient and investigator global evaluations of treatment effectiveness, pulmonary function tests [FEV_1, forced vital capacity (FVC), morning peak expiratory flow (PEF)] and ICS use.

Safety variables

Adverse events were recorded at each treatment visit, and were classified by body system and severity. Haematology and

serum chemistry tests were also performed at baseline and study end.

Statistical analysis

The two co-primary variables were tested hierarchically, in that each comparison was performed using a 5% level of significance while maintaining the overall type-I error at 5% (28). The comparison of asthma exacerbations was tested first and, if significant, the QoL comparison was performed. The differences between treatment groups in the incidence of asthma exacerbation episodes and responders in the QoL assessment (≥1.0 improvement in overall score in both AQLQ and RQLQ) were compared using the Cochran Mantel Haenszel test stratified by centre. Patients who discontinued prematurely were included in the analysis using an imputed number of exacerbations, incorporating exacerbations experienced up to the point of discontinuation. All patients who discontinued prematurely had one asthma exacerbation added to their total if they had not already experienced an exacerbation within the week prior to discontinuation. As a secondary analysis, the asthma exacerbation rate per treatment period was calculated using Poisson regression adjusting for centre, where the proportion of days at risk from an exacerbation was offset against the number experienced. A sensitivity analysis was undertaken by assessing the effect of the imputation method on the primary analysis of asthma exacerbations. Secondary efficacy variables were analysed over the entire treatment period, using last observation carried forward where necessary. Rescue-medication use, ICS use and global evaluation of treatment effectiveness were analysed using the Cochran Mantel Haenszel test, stratified by center. Clinical symptom scores, QoL assessments and pulmonary function were analysed using an analysis of covariance model, with terms for treatment and centre and baseline as a covariate. Least square mean differences based on the model were also calculated.

It was determined that 405 randomized patients would provide in excess of 80% power to detect both of the co-primary comparisons of a 12% reduction in exacerbations and a 15% increase in QoL responders.

Three patient populations were defined for analysis: intent to treat (all randomized patients), per protocol (all patients who completed the study without major deviations from protocol procedures) and safety (all patients randomized who received at least one dose of study medication).

Results

A total of 405 patients were randomized, with 209 receiving omalizumab and 196 receiving placebo (intent-to-treat and safety populations). Demographic characteristics were similar in both groups (Table 1). The majority of patients (89% omalizumab, 91% placebo) had severe persistent asthma (24) at baseline and all patients had PAR. Seasonal allergies were balanced between treatment groups during the study, affecting more than half of all patients (Table 1). Twenty patients withdrew from the study (five from the omalizumab group and 15 from the placebo group), the main reasons being withdrawal of consent (3/209 omalizumab group, 6/196 placebo group) and loss to follow-up (1/209 omalizumab group, 3/196 placebo group). Approximately one-third of patients in each treatment group violated the protocol, but most violations were not considered significant (the majority were minor violations in the timing of drug administration). The per-protocol population comprised 192 patients on omalizumab and 174 on placebo.

Table 1. Baseline demographic and background characteristics

	Omalizumab ($n = 209$)	Placebo ($n = 196$)
Age, mean (SD)	38.3 (14.73)	38.5 (14.72)
Females, *n* (%)	109 (52.2)	114 (58.2)
Never smoked, *n* (%)	158 (75.6)	145 (74.0)
FEV_1 (% of predicted)*, mean (SD)	76.9 (15.72)	79.4 (17.46)
FEV_1 (ml), mean (SD)	2721.5 (833.41)	2782.1 (854.25)
Reversibility† (%), mean (SD)	17.8 (12.72)	17.2 (11.17)
Budesonide dose‡ (μg/day), mean (SD)	842.1 (430.28)	901.0 (474.80)
Asthma and rhinitis history		
Duration of allergic asthma, years [mean (SD)]	19.2 (13.27)	20.4 (13.17)
Duration of PAR, years [mean (SD)]	19.2 (13.46)	20.3 (13.15)
Patients with SAR, *n* (%)	112 (53.6)	115 (58.7)
Number of sensitivities to indoor allergens, *n* (%)		
None¶	1 (0.5)	1 (0.5)
1	14 (6.7)	16 (8.2)
2	42 (20.1)	46 (23.5)
≥3	152 (72.7)	133 (67.9)
Concomitant medications		
LABA, *n* (%)	86 (41.1)	71 (36.2)
Nasal steroids, *n* (%)	36 (17.2)	31 (15.8)
Asthma exacerbations requiring oral steroids in past year, mean (SD)	2.1 (1.26)	2.1 (1.35)
QoL scores		
Total AQLQ§, mean (SD)	4.0 (0.81)	4.0 (0.84)
Total RQLQ§, mean (SD)	3.8 (0.87)	3.7 (0.99)

* FEV_1 (% predicted) – calculated using patients predicted FEV_1 using the CRAPO formulae.

† Reversibility, % increase in FEV_1 upon β_2-agonist inhalation.

‡ Dose at baseline (stable dose during 4-week run-in), given via Turbuhaler®.

§ These are recoded means.

¶ Included in intent-to-treat population (all randomized patients).

SD, standard deviation; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; PAR, persistent allergic rhinitis; SAR, seasonal allergic rhinitis; LABA, long-acting β_2-agonist; AQLQ, Asthma Quality of Life Questionnaire; RQLQ, Rhinitis Quality of Life Questionnaire.

Primary efficacy outcomes

Both primary endpoints (asthma exacerbations and disease-related QoL) were significantly in favour of omalizumab. Fewer omalizumab-treated patients [20.6% (43/209)] experienced at least one exacerbation compared with placebo [30.1% (59/196)] ($P = 0.02$). The mean rate of exacerbations during the treatment period was lower with omalizumab than with placebo (0.25 and 0.40 respectively; $P = 0.02$). Analysis of the actual number of exacerbations (without imputed values) supported the primary analysis: 18.2% (38/209) of patients on omalizumab experienced at least one exacerbation compared with 25.5% (50/196) on placebo ($P = 0.0546$). In the per-protocol population, 18.8% (36/192) of omalizumab-treated patients and 28.2% (49/174) of

placebo-treated patients had at last one exacerbation ($P = 0.0225$).

Omalizumab treatment resulted in more responders (≥1.0-point improvement in both AQLQ and RQLQ) than placebo [57.7% (120/208) *vs* 40.6% (78/192); $P < 0.001$]. At baseline, there was no difference in QoL scores between groups (Table 1). At study end, omalizumab was more effective than placebo for all RQLQ domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional) and for the symptoms and environmental domains of the AQLQ (Fig. 1A,B). Despite a strong placebo effect, the number of responders on both QoL scales was significantly greater with omalizumab than placebo ($P \leq 0.001$). Table 2 gives the number of QoL responders to the AQLQ and RQLQ separately, using 0.5, 1.0 and 1.5-point thresholds. The responder rate for all three threshold categories was greater with omalizumab treatment than with placebo. For the per-protocol population, the proportion of patients who were defined as responders (AQLQ and RQOL) was greater with omalizumab treatment [58.1% (111/192)] than with placebo [43.3% (74/174)], $P = 0.0042$.

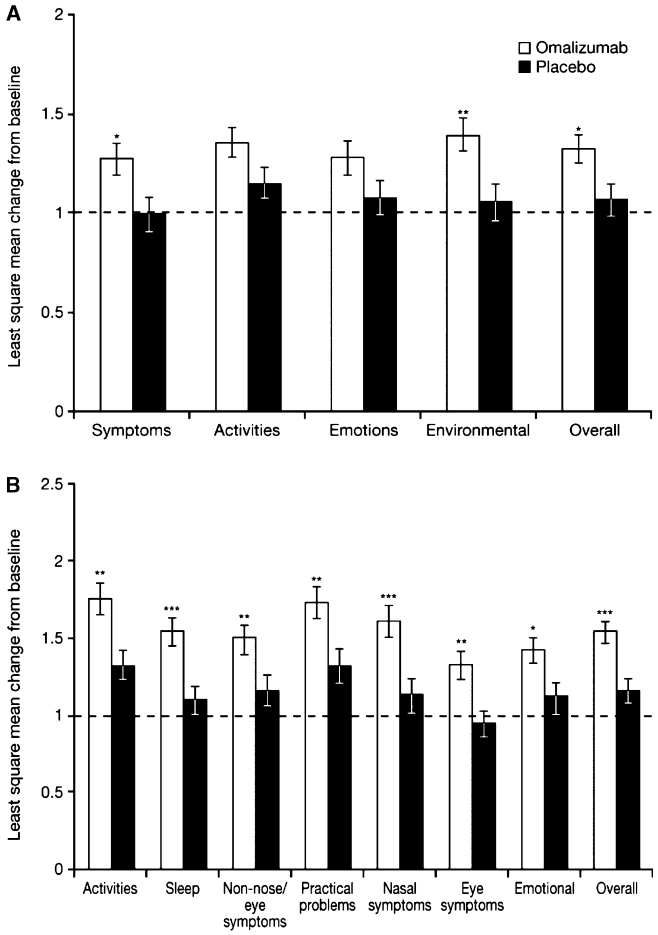

Figure 1. Effect of omalizumab on change from baseline in (A) AQLQ scores and (B) RQLQ scores (least square mean ± SEM) after 28 weeks treatment (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Secondary efficacy outcomes

Omalizumab treatment improved Wasserfallen asthma and rhinitis clinical symptom scores (Fig. 2). At study end, omalizumab significantly reduced both the total asthma symptom score (treatment difference −1.8, $P = 0.023$) and total rhinitis symptom score (treatment difference −3.53, $P < 0.001$) compared with placebo.

These results were reflected in the patient assessments of treatment effectiveness. More omalizumab-treated patients described the control of their asthma symptoms as excellent or good [65.6%, (137/209)] compared with placebo-treated patients [53.1%, (104/196) $P = 0.009$]. Control of rhinitis symptoms was also rated as excellent or good by 60.8% (127/209) of omalizumab-treated patients compared with 36.2% (71/196) ($P < 0.001$) placebo-treated patients. Study investigators gave similar appraisals of omalizumab treatment. Investigators rated asthma control as excellent or good in 59.3% (124/209) of omalizumab-treated patients compared with 41.3% (81/196) ($P < 0.001$) placebo-treated patients. Investigators rated rhinitis control as excellent/good in 54.5% (114/209) omalizumab-treated patients compared with 26.5% (52/196) ($P < 0.001$) patients in the placebo group.

Treatment with omalizumab resulted in small increases from baseline in FEV_1 (treatment difference 73 ml, $P = 0.032$), FVC (treatment difference 84 ml, $P = 0.016$) and mean daily PEF (treatment difference 11 l/min, $P < 0.001$) by study end compared with placebo. Although the change from baseline for FEV_1 (% predic-

Table 2. Number of patients with 0.5, 1.0 and 1.5-point improvements in AQLQ or RQLQ scores*

	AQLQ			RQLQ		
Questionnaire	Omalizumab ($n = 209$)	Placebo ($n = 196$)	*P*-value	Omalizumab ($n = 209$)	Placebon ($n = 196$)	*P*-value
≥0.5-point imp	164 (78.8)	134 (69.8)	0.050	174 (83.7)	137 (71.4)	0.003
≥1.0-point imp	140 (67.3)	96 (50.0)	<0.001	140 (67.3)	100 (52.1)	0.001
≥1.5-point imp	100 (48.1)	64 (33.3)	0.003	106 (51.0)	68 (35.4)	0.002

* 0.5, 1.0 and 1.5-point improvements, indicate the minimal important difference in QoL, a moderate change and a large change in QoL respectively (37).
The values are represented as *n* (%).

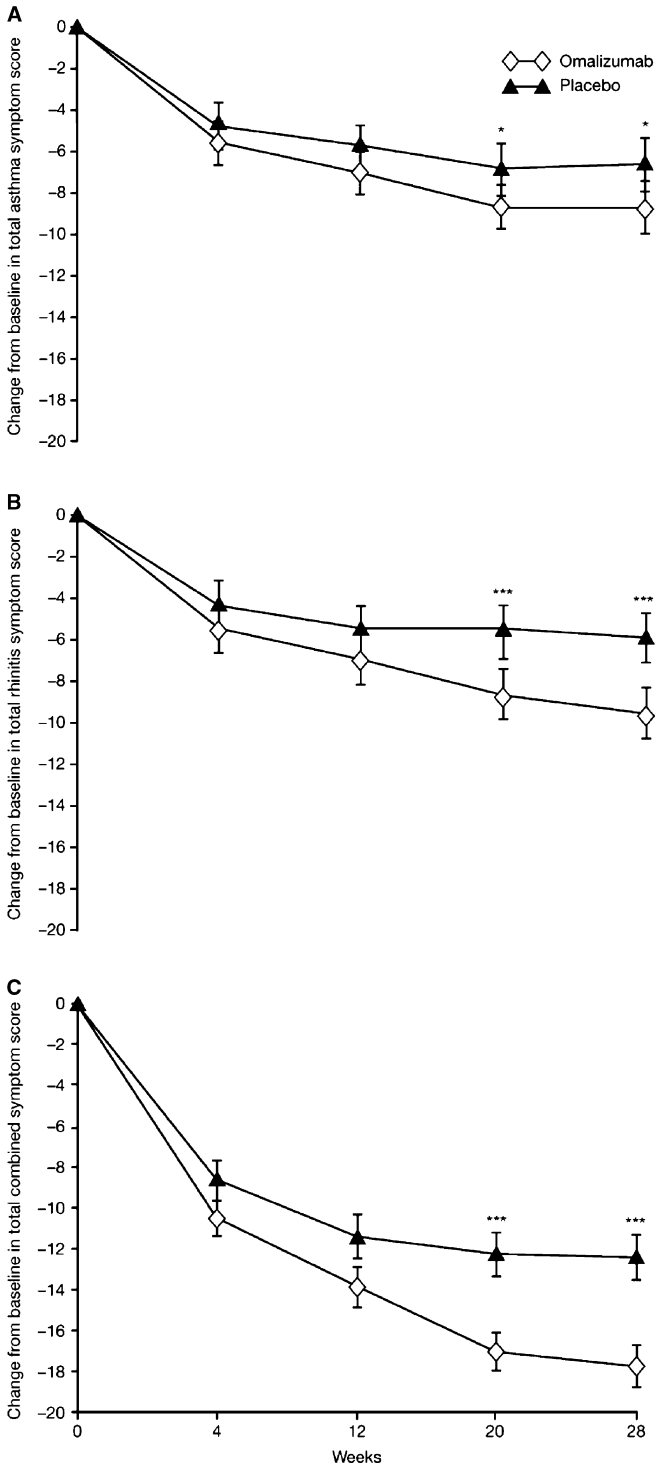

Figure 2. Effect of omalizumab on the change from baseline in (A) total asthma symptom score; (B) total rhinitis symptom score and (C) combined asthma and rhinitis symptom score (least square mean ± SEM) (*$P < 0.05$, ***$P < 0.001$).

ted) also increased with omalizumab, the difference between the groups did not reach statistical significance ($P = 0.065$).

Use of both short-acting β_2-agonists and antihistamine rescue medications was similar between treatment groups. The mean number of puffs of short-acting β_2-agonists was 2.8 for both groups at baseline with mean daily puffs during the study period being 1.8 for omalizumab-treated patients and 2.4 for placebo-treated patients. The mean number of antihistamine tablets taken during the study period was 0.4 for both treatment groups.

A *post hoc* analysis of the incidence of asthma exacerbations in subgroups of patients receiving or not receiving a long-acting β_2-agonist was performed to investigate any differences in these populations. Exacerbation rates were similar to those in the overall population. In both groups (patients receiving and not receiving long-acting β_2-agonists), fewer patients experienced one or more exacerbations in the omalizumab group, although results did not reach statistical significance. The proportions of patients experiencing at least one asthma exacerbation, in the omalizumab *vs* placebo treatment groups, respectively, were 20.9% (18/86) *vs* 35.2% (25/71) in patients on long-acting β_2-agonists ($P = 0.128$) and 20.3% (25/123) *vs* 27.2% (34/125) in patients not on long-acting β_2-agonists ($P = 0.062$).

Adverse events

The overall incidence of adverse events was higher in the omalizumab group [78.5% (164/209)] than the placebo group [68.9% (135/196)], but there were no consistent differences between treatment groups in the body systems affected (Table 3). The majority of adverse events were of mild-to-moderate severity, with 6.2% (13/209) omalizumab and 9.2% (18/196) placebo-treated patients experiencing severe adverse events. The severe events were primarily infections (10 patients with nasopharyngitis, upper or lower respiratory tract infection, pneumonia, gastroenteritis or cystitis), nervous system disorders (seven patients with headache, migraine or torticollis), and musculoskeletal and connective tissue disorders (seven patients with back pain, arthralgia, myalgia, muscle spasms or tendonitis), with no clinically meaningful differences between treatments.

The incidence of adverse events suspected as study-drug related was 16.7% (35/209) of omalizumab-treated patients compared with 12.2% (24/196) of placebo-treated patients. The most frequent study drug-related adverse events were general and administration site reactions (18/209 omalizumab-treated patients and 8/196 placebo-treated patients). The incidence of urticaria and injection site reactions was higher in the omalizumab group than placebo (urticaria 1.9% [4/209] *vs* 0.5% [1/196], injection site reaction 7.7% [16/209] *vs* 4.6% [9/196]). None of the injection site reactions was severe.

The incidence of serious (as opposed to severe) adverse events was low and similar between treatments (1.4% [3/209] omalizumab; 1.5% [3/196] placebo). No serious

Table 3. Number (%) of patients with most frequent adverse events, ≥5% in either treatment group

Body system	AE preferred term	Omalizumab *n* (%)	Placebo *n* (%)
Infections and infestations	Nasopharyngitis	63 (30.1)	54 (27.6)
	Influenza	15 (7.2)	13 (6.6)
	Sinusitis NOS	12 (5.7)	7 (3.6)
	Upper respiratory tract infection NOS	10 (4.8)	13 (6.6)
Nervous system disorders	Headache NOS	20 (9.6)	20 (10.2)
Respiratory, thoracic and mediastinal disorders	Pharyngitis	11 (5.3)	14 (7.1)
Patients studied			
Total no. of patients		209	196
Total no. with adverse events		164 (78.5)	135 (68.9)

AE, adverse event; NOS, not otherwise specified.

adverse events led to discontinuation from the study and none was suspected as study-drug related. Three serious adverse events occurred in patients receiving omalizumab (acute appendicitis, mild chest pain, mild depression) and three in those receiving placebo (intestinal obstruction, atrial fibrillation, serious asthma exacerbation).

No clinically relevant changes from baseline in either haematology (including platelets) or biochemistry parameters occurred and no deaths were reported.

Discussion

This is the first study designed to evaluate the efficacy of omalizumab in patients with concomitant asthma and PAR. Most patients had severe persistent asthma as defined by GINA guidelines (24) and received treatment with standard asthma and rhinitis therapies. Omalizumab was used as an add-on treatment to these existing treatment regimens. In this comorbid population, treatment with omalizumab resulted in significantly fewer asthma exacerbations and significant improvements in both asthma and rhinitis-related QoL, compared with placebo. In addition, omalizumab significantly improved asthma and rhinitis clinical symptoms and lung function parameters compared with placebo.

Allergic rhinitis is common among patients with asthma, and appears to be increasing in prevalence (29). Concomitant rhinitis adds to a patient's burden of symptoms and is also linked with more severe asthma (7, 8). Treatment with omalizumab targets an underlying cause of both diseases and, on the basis of the present study, appears to provide significant clinical benefits for the growing population of comorbid patients.

At the time of this study, there was no standard combined assessment for treatment response in patients with both asthma and rhinitis. The main hurdle in assessing response in concomitant disease is to be able to determine whether one or both diseases respond to treatment. Baiardini et al. recently addressed these issues with their Rhinasthma questionnaire (30). In this study, however, we used asthma exacerbations and asthma and rhinitis-related QoL as co-primary endpoints. Asthma exacerbations are an important indicator of asthma control and affect a large number of asthma patients despite treatment in accordance with the guidelines (31). Omalizumab treatment significantly reduced the number of patients experiencing asthma exacerbations, and reducing the overall exacerbation rate by 38% compared with placebo. This confirms results from previous clinical studies in asthma in which omalizumab has consistently reduced asthma exacerbations by up to 58% (12, 13, 15). In a recent study (32), omalizumab significantly reduced the frequency and incidence of asthma exacerbations in patients with severe allergic asthma who were being maintained, at the investigator's discretion, on the lowest effective dose of ICS. The background level of exacerbations was higher than in the present study, possibly because patients in that study had previously undergone a period of controlled ICS reduction. With omalizumab treatment, however, their ICS requirement remained lower than in patients on placebo and lower than prior to the period of controlled steroid reduction. The clinical significance of the ability of omalizumab to reduce asthma exacerbations was underlined in a recent report demonstrating that omalizumab-treated patients experienced a significant reduction in serious exacerbations resulting in unscheduled outpatient visits, emergency room treatment or hospitalization (33).

Disease-related QoL is particularly important from the patient's perspective because poor QoL frequently occurs in both asthma and rhinitis (34, 35). Allergic rhinitis is often overshadowed by the patient's asthma (36, 37), so assessment of QoL in both diseases is particularly important. This study assessed both asthma and rhinitis-related QoL, thus providing a means of assessing the response to treatment in both diseases. The interpretation of QoL data should account for the fact that significant changes in scores may not relate to clinically meaningful effects. Juniper identified a change of 0.5 points as being the minimal important difference and a 1.5-point change as being a large improvement (26). We selected a ≥1.0-point improvement in both QoL assessments to define a 'responder' in the primary analysis, as this level of response indicates a full category improvement. However, we also

assessed response to each QoL assessment at 0.5 and 1.5-point thresholds. One limitation of our analysis was that all patients (aged 12–74 years) used adult versions of the AQLQ and RQLQ. However, as reported previously, no bias of the QoL analyses resulted when adolescents used the adult version of the questionnaire (14, 16).

There was a strong placebo response in the QoL responder assessment with 40.6% (78/196) of placebo patients achieving a ≥1.0-point improvement. This level of placebo effect, however, is well documented in both asthma and rhinitis studies (38, 39) and may have resulted from improved treatment compliance with concomitant medications. All patients received moderate-to-high doses of concomitant inhaled budesonide Turbuhaler® (400–2400 μg/day). Additionally, 39% of all patients received long-acting β_2-agonists and 17% received concomitant nasal steroids at baseline (Table 1) although half had used them in the past, which suggests a reluctance in patients to sustain nasal corticosteroid treatment for perennial symptoms. Despite the placebo response, significantly more omalizumab-treated patients (57.7%, 120/209) were (≥1.0-point) responders in the combined QoL assessment. The improvements were consistent at each threshold level, with more omalizumab-treated patients also responding at the 0.5-point and 1.5-point thresholds. These results confirm findings from previous studies in asthma (14, 16) and rhinitis (17–19).

Omalizumab showed other efficacy benefits beyond placebo in terms of symptoms and lung function. Omalizumab treatment improved clinical symptoms for asthma, rhinitis, or the combination of the two when compared with placebo. Clinical symptoms were assessed at 4, 12, 20 and 28 weeks. Improvements in asthma and rhinitis symptoms, either alone or in combination, reached significance after 20 and 28 weeks' treatment. These improvements confirm findings from a previous comorbid sub-study of a large asthma trial in patients with poorly controlled asthma despite treatment according to current best practice. They reported similar improvements in total asthma and rhinitis symptom scores with omalizumab treatment compared with current asthma therapies alone (20).

In terms of lung function, omalizumab significantly improved absolute FEV_1, absolute FVC and mean daily PEF. While modest, these improvements are important when seen in the context of an add-on therapy to moderate-to-high doses of ICS, in patients with long-standing respiratory disease. Although rescue medication use was not significantly affected by omalizumab treatment, this may be a reflection of the low level of asthma and rhinitis rescue-medication use at baseline. Significant effects were evident for a proportion of study days, but the overall change in rescue medication use was not significant.

Patient and investigator assessments of treatment effectiveness also rated omalizumab treatment better than placebo. Interestingly, the proportion of patients and investigator assessments judged to be good or excellent at the end of the study was very similar to the proportion of patients evaluated as being responders with the QoL endpoint.

Omalizumab was well tolerated during the study, with no serious or study treatment-related adverse events leading to discontinuation. Most adverse events were of a mild-to-moderate nature, with the overall incidence being marginally higher in the omalizumab group. Subcutaneous injection of omalizumab was well tolerated, with infrequent and generally mild local reactions.

In conclusion, this study of patients with concomitant asthma and PAR found that omalizumab is significantly more efficacious than placebo in preventing asthma exacerbations and in improving disease-related QoL when added to standard asthma and rhinitis therapies. This supports previous observations showing that coordinated management of asthma and rhinitis results in optimal disease control.

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References

1. 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**:54–59.
2. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000; **106**(Suppl. 5):S201–S205.
3. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol 2003;**111**: 1171–1183.
4. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003;**58**:691–706.
5. Schmidt D, Watson N, Ruehlmann E, Magnussen H, Rabe KF. Serum immunoglobulin E levels predict human airway reactivity *in vitro*. Clin Exp Allergy 2000;**30**:233–241.
6. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. Eur Respir J 2003;**21**:116–122.
7. 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.

8. Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. J Allergy Clin Immunol 2002;**109**:636–642.
9. Passalacqua G, Canonica GW. Treating the allergic patient: think globally, treat globally. Allergy 2002;**57**: 876–883.
10. Bousquet J, Van Cauwenberge P, Khaltaey N. Allergic rhinitis and its impact on asthma (ARIA) Workshop Report. J Allergy Clin Immunol 2001;**108**(Suppl. 5):S147–S334.
11. MacGlashan DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J 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**:1438–1445.
12. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;**108**:184–190.
13. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;**18**: 254–261.
14. Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F et al. The anti-IgE antibody omalizumab improves asthma related quality of life in patients with allergic asthma. Eur Respir J 2002;**20**:1088–1094.
15. Holgate S, 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**:233–240.
16. Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. J Allergy Clin Immunol 2003;**111**:278–284.
17. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;**286**:2956–2967.
18. Ädelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000;**106**: 253–259.
19. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A et al. Omalizumab, an anti-immunoglobulin E antibody, is effective and well tolerated in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2003;**91**:160–167.
20. Bousquet J, Harnest U, Chung KF, Oshinyemi K, Blogg M. Omalizumab improves symptom control in patients with poorly controlled allergic asthma and concomitant rhinitis. J Allergy Clin Immunol 2003;**111**:A295.
21. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;**147**:828–832.
22. 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.
23. National asthma education and prevention programme. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health 1997. Pub. no. 98–4051: Bethesda, MD.
24. National Institutes of Health. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2002. No. 02–3659. Bethesda, MD.
25. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the asthma quality of life questionnaire. Chest 1999;**115**: 1265–1270.
26. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;**47**:81–87.
27. Wasserfallen JB, Gold K, Schulman KA, Baraniuk JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. J Allergy Clin Immunol 1997;**100**: 16–22.
28. Maurer W, Hothorn L, Lehmacher W. Multiple comparisons in drug trials and pre-clinical assays a-priori ordered hypothesis. In: Vollmar J, editor. Biometrie in der chemisch-pharmazeutischen Industrie 6. Testing principles in clinical and preclinical trials. Stuttgart: Gustav Fischer, 1995:3–15.
29. Verlato G, Corsico A, Villani S, Cerveri I, Migliore E, Accordini S et al. Is the prevalence of adult asthma and allergic rhinitis increasing? Results of an Italian study. J Allergy Clin Immunol 2003;**111**:1232–1238.
30. Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. Allergy 2003;**58**:289–294.
31. Green RH, Brightling CE, Pavord ID, Wardlaw AJ. Management of asthma in adults: current therapy and future directions. Postgrad Med J 2003;**79**:259–267.
32. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. Ann Allergy Asthma Immunol 2003;**91**: 154–159.
33. 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.
34. Juniper EF. Effect of asthma on quality of life. Can Respir J 1998;**5**(Suppl. A): 77A–84A.
35. Meltzer EO, Nathan RA, Selner JC, Storms W. Quality of life and rhinitic symptoms: Results of a nationwide survey with the SF-36 and RQLQ questionnaires. J Allergy Clin Immunol 1997;**99**:S815–S819.
36. Leynart BJ, Neukirch F, Liard R, Bousquet J, Neukirch C. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. Am J Respir Crit Care Med 2000;**162**: 1391–1396.
37. Gerth van Wijk R. Allergy: a global problem. Quality of life. Allergy 2002;**57**:1097–1110.
38. Joyce DP, Jackevicius C, Chapman KR, McIvor RA, Kesten S. The placebo effect in asthma drug therapy trials: a meta-analysis. J Asthma 2000;**37**:303–318.
39. Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996;**98**:724–731.

Appendix

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