

Short communication

Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis

Background: Asthma and rhinitis are considered components of a single IgE-mediated inflammatory disorder. However, despite being shown to often co-exist, they are typically treated as independent conditions. Omalizumab, an anti-IgE antibody, has proven effective in the treatment of both asthma and rhinitis.

Aims: To examine whether a response to omalizumab in terms of asthma control predicts a higher likelihood of rhinitis response in patients with concomitant allergic asthma and rhinitis.

Methods: This *post hoc* analysis was conducted on efficacy results from the SOLAR trial in which patients with moderate-to-severe asthma and rhinitis were randomized to receive omalizumab or placebo for 28 weeks. Patients were classified as asthma responders based on the physician's overall assessment (complete control or marked improvement in a five-level evaluation). Rhinitis responders were identified using the Rhinitis Quality of Life Questionnaire (RQLQ) questionnaire (≥ 1.0 point improvement in overall score).

Results: Data were available for 207 omalizumab-treated patients and 192 placebo patients. According to the physicians overall assessment, 123 (59.4%) of omalizumab-treated patients were asthma responders, with the likelihood of a rhinitis response significantly ($P < 0.001$) greater in these patients than in the placebo group. The odds ratio for rhinitis response in omalizumab-treated asthma responders *vs* nonresponders was 3.56 (95% CI: 1.94–6.54).

Conclusions: A response in terms of asthma following omalizumab therapy is associated with a significantly increased probability of improvement in rhinitis.

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Allergic asthma and allergic rhinitis have shared pathogenic mechanisms and common triggers, and are considered to be components of a single IgE-mediated inflammatory condition (1). This is evidenced by the presence of similar inflammatory cells and mediators in both upper and lower airway inflammation, and communication of local inflammation to other areas (1). Asthma and rhinitis often co-exist. Epidemiological studies estimate that 60–80% of patients with asthma also have rhinitis, and 20–40% of those with rhinitis also have asthma (2). In patients with asthma, co-existing rhinitis leads to poorer asthma outcomes (3, 4).

Omalizumab, an anti-IgE antibody, is effective in the treatment of moderate-to-severe allergic (IgE-mediated) asthma, significantly reducing exacerbations and emergency visits and improving quality of life (QoL) (5–7). Omalizumab also significantly reduces nasal symptoms and significantly improves QoL in patients with allergic rhinitis (8, 9). Effective rhinitis management has been shown to improve asthma control among patients with

asthma and co-existing allergic rhinitis. In two studies, patients receiving treatment for rhinitis had a significantly lower risk of asthma-related emergency visits and hospitalizations compared with those not receiving rhinitis treatment (10, 11).

In a study of patients with concomitant moderate-to-severe allergic asthma and persistent allergic rhinitis (SOLAR) (6), omalizumab treatment was associated with significant benefits in individual and composite measures of asthma and allergic rhinitis control. Omalizumab-treated patients had significantly fewer exacerbations during the treatment period than placebo (0.25 *vs* 0.40 respectively, $P = 0.02$), and more omalizumab-treated patients achieved ≥ 1.0 -point improvement in both Rhinitis Quality of Life Questionnaire (12) (RQLQ) and Asthma Quality of Life Questionnaire (13) (AQLQ, 57.7% *vs* 40.6% respectively, $P < 0.001$).

Using data from the SOLAR trial, we examined whether a response to omalizumab in terms of asthma control predicted a rhinitis response in patients with co-morbid allergic asthma and rhinitis.

Methods

Patients and study design

This *post hoc* analysis was conducted on efficacy results of the randomized, double-blind, placebo-controlled SOLAR study, the details of which have been reported previously (6). Briefly, patients included were 12–75 years of age with ≥ 1 year history of moderate-to-severe allergic asthma and ≥ 2 year history of moderate-to-severe persistent allergic rhinitis symptoms. An IgE level of 30–1300 IU/ml and positive skin-prick test to ≥ 1 indoor allergen were required. All patients were receiving ≥ 400 μ g/day of inhaled budesonide or equivalent, and had ≥ 2 asthma-related unscheduled medical visits in the past year or ≥ 3 visits in the past 2 years. Nasal steroids were allowed if patients were on a stabilized regimen at screening (17.2% omalizumab and 15.8% placebo). Patients receiving long-acting antihistamines were excluded. Patients were required to have baseline total scores of $> 56/168$ in the RQLQ (12) (further details are provided below) and $> 64/192$ in the AQLQ (13) (32 items, each scored on an amended 0–6 scale [0 = no impairment, 6 = greatest impairment], the scale having been amended to facilitate AQLQ administration alongside the RQLQ). The required baseline scores correspond to the minimum RQLQ and AQLQ scores worse than those of mild symptoms in both diseases (12, 14). The study comprised a screening visit, a 4 week run-in period and a 28 week treatment period. Patients received either omalizumab (at least 0.016 mg/kg/IgE [IU/ml] per 4 weeks, administered every 2 or 4 weeks depending on dose) or placebo, in addition to their current asthma therapy.

Outcome measures

The primary objective of this analysis was to examine whether a response to omalizumab in terms of asthma control predicted a higher likelihood of rhinitis response. The effect of omalizumab on rhinitis-related QoL was also assessed.

Asthma response classification. The physician's overall assessment has been shown to reliably evaluate response to omalizumab, compared with other response measures (15). This composite of several clinical measures grades asthma control in a five-level evaluation (complete control; marked improvement in control; discernable but limited control; no appreciable change; worsening in control). Patients were classified as asthma responders if they achieved complete control or marked improvement in control.

Rhinitis response classification. The RQLQ is a self-administered questionnaire containing 28 items and covers eight domains (overall, activity limitation, sleep impairment, nonnasal or nonocular symptoms, practical problems, nasal symptoms, eye symptoms, emotional function). Each item is scored using a 0–6-point scale, with a score of 0 representing not troubled and 6 representing extremely troubled, over the previous 7 days (12). Patients who achieved a moderate (≥ 1.0 -point) improvement in RQLQ overall score were classified as rhinitis responders. Data were also analyzed for patients achieving a large (≥ 1.5 -point) improvement in RQLQ overall score.

Statistical analysis

The statistical significance of differences in rhinitis response in asthma responders compared with asthma nonresponders and placebo were determined using the chi-square test. The odds ratio (95% CI) for rhinitis response in asthma responders vs asthma nonresponders was determined for both treatment groups and both RQLQ improvement thresholds.

Results

Of the 209 omalizumab patients and 196 placebo patients in the original study, data were available for 207 omalizumab patients and 192 placebo patients in this analysis. Ninety percent of patients met GINA 2002 criteria for severe persistent asthma (daily symptoms, frequent exacerbations and nocturnal symptoms, limitation of physical activities, FEV_1 or $PEF \leq 60\%$ predicted, PEF or FEV_1 variability $> 30\%$) (16). Baseline demographic and clinical characteristics of the omalizumab-treated asthma responder and nonresponder groups, and the placebo group were similar (Table 1). The presented baseline AQLQ overall score is recoded from the amended 0–6 scale used in the original study to the normal 1–7 scale (1 = greatest impairment, 7 = no impairment) for consistency with other published AQLQ results.

Asthma response

In total, 123 (59.4%) omalizumab-treated patients were asthma responders according to the physician's overall assessment.

Rhinitis response

Rhinitis-related QoL significantly improved in omalizumab-treated asthma responders for all individual domains and overall RQLQ score compared with placebo (Table 2). More omalizumab-treated asthma responders had a rhinitis response (≥ 1.0 -point improvement in RQLQ overall score) than placebo-treated patients (78.9% vs 52.1%, $P < 0.001$; Fig. 1). The number of omalizumab-treated asthma nonresponders who responded in terms of their rhinitis (51.2%) was similar

Table 1. Baseline demographic and clinical characteristics

	Omalizumab asthma responders* (n = 123)	Omalizumab asthma nonresponders† (n = 84)	Placebo (n = 192)
Age, mean (SD)	36.4 (14.7)	40 (14.6)	37.6 (14.7)
Females, n (%)	65 (52.8)	43 (51.2)	112 (58.3)
Serum total IgE, IU/ml, mean (SD)	252.6 (194.4)	212.9 (155.7)	227.5 (175.0)
% predicted FEV_1 (SD)	77.7 (15.0)	75.6 (16.9)	79.6 (17.5)
ICS dose, μ g/day (SD)	984 (536)	1161 (529)	1,119 (593)
AQLQ overall score (SD)	4.0 (0.8)	3.9 (0.8)	4.0 (0.8)
Total asthma symptoms score (SD)	16.2 (8.0)	16.9 (7.6)	16.2 (7.9)

AQLQ, Asthma Quality of Life Questionnaire; FEV_1 , forced expiratory volume in 1 s; ICS, inhaled corticosteroids (budesonide equivalent); IgE, immunoglobulin E; SD, standard deviation.

*Complete asthma control or marked improvement in asthma control, according to the physician's overall assessment.

†Discernable but limited improvement in asthma control, no appreciable change or worsening of asthma control, according to the physician's overall assessment.

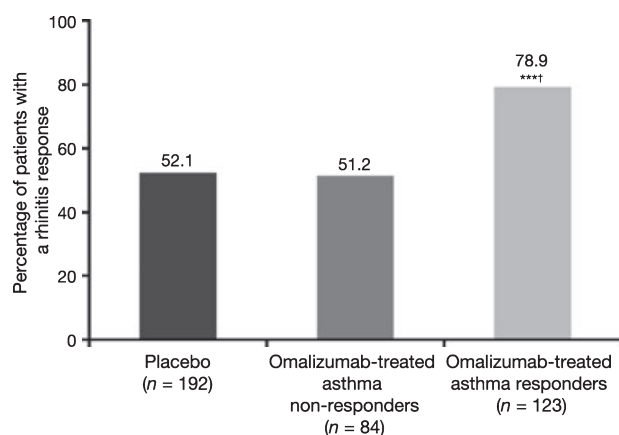
Table 2. Change from baseline in RQLQ scores in asthma responders vs placebo

	Omalizumab asthma responders		Placebo		Omalizumab asthma responders vs placebo
	<i>n</i>	LSM*	<i>n</i>	LSM*	LSM difference (95% CI)***
Activities	120	1.99	191	1.33	0.66 (0.35, 0.97)
Sleep	123	1.89	192	1.14	0.75 (0.47, 1.03)
Nonnose/eye symptoms	123	1.79	192	1.20	0.60 (0.32, 0.87)
Practical problems	123	2.05	192	1.35	0.69 (0.38, 1.01)
Nasal symptoms	123	1.92	192	1.16	0.76 (0.45, 1.07)
Eye symptoms	121	1.48	191	0.94	0.54 (0.26, 0.82)
Emotional	122	1.76	192	1.15	0.62 (0.36, 0.88)
Overall	123	1.83	192	1.18	0.65 (0.41, 0.89)

CI, confidence interval; LSM, least squares mean.

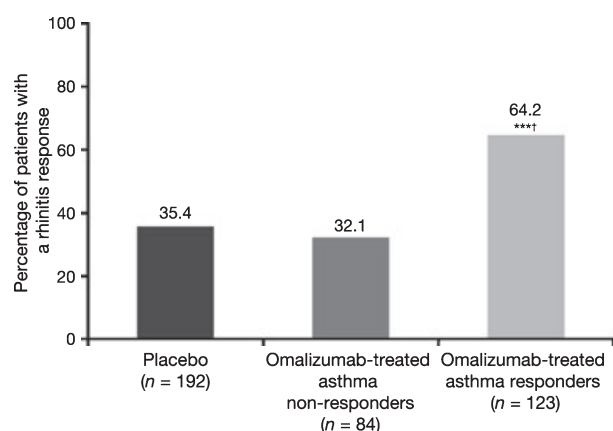
*Week 28 or discontinuation.

*** $P < 0.001$ analysis of covariance.



*** $P < 0.001$ vs placebo; † $P < 0.05$ vs asthma non-responders, chi-square test

Figure 1. The likelihood of a rhinitis response (≥ 1.0 -point improvement in RQLQ overall score) is significantly increased in omalizumab-treated asthma responders.



*** $P < 0.001$ vs placebo; † $P < 0.078$ vs asthma non-responders, chi-square test

Figure 2. The likelihood of a rhinitis response (≥ 1.5 -point improvement in RQLQ overall score) is significantly increased in omalizumab-treated asthma responders.

to placebo (Fig. 1). The odds ratio (95% CI) for rhinitis response in asthma responders vs asthma nonresponders was 3.56 (95% CI: 1.94–6.54) in the omalizumab group and 2.15 (95% CI: 1.20–3.87) in the placebo group.

Using a ≥ 1.5 -point improvement in RQLQ overall score, 64.2% of omalizumab-treated asthma responders were also rhinitis responders compared with 35.4% of placebo-treated patients and 32.1% of omalizumab-treated asthma nonresponders (Fig. 2, Table 2). The odds ratio (95% CI) for rhinitis response in asthma responders vs asthma nonresponders was 3.79 (95% CI: 2.11–6.82) in the omalizumab group and 3.52 (95% CI: 2.56–5.95) in the placebo group.

Discussion

In patients with co-morbid allergic asthma and rhinitis, these data indicate that rhinitis-related QoL is significantly improved in asthma responders to omalizumab therapy, and that this asthma response is associated with a significantly increased probability of improvement in rhinitis. At the ≥ 1.0 -point improvement RQLQ threshold, omalizumab-treated asthma responders had 3.5 times higher odds than omalizumab-treated asthma nonresponders of a rhinitis response. In the placebo group, asthma responders had twice the odds than asthma nonresponders of a rhinitis response. Taken together, these data further suggest that rhinitis and asthma share a common etiology. The higher odds ratio observed in omalizumab-treated asthma responders may reflect an additional treatment effect of systemic anti-IgE therapy above that which may be attributed to underlying variability in asthma control or a placebo response. As in the original study, the placebo group rhinitis response in this analysis was sizeable and, as Vignola et al. noted, may be attributable to the placebo effect observed in asthma and rhinitis studies due to increased compliance with

concomitant medications (6). This may be particularly relevant in omalizumab double-blind studies, as patients visit physicians every 2 or 4 weeks for placebo administration.

Asthma and rhinitis frequently co-exist and are associated with similar epidemiological, pathological and physiological features (1, 2). The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines suggest that proper management of allergic rhinitis may help to optimize the management of co-existing asthma (17). Allergic diseases of the upper and lower airways are typically treated as independent conditions: current guidelines recommend that rhinitis is managed by allergen avoidance, pharmacotherapy and immunotherapy (17), whereas daily controller medication and preferably inhaled corticosteroids (ICS) are recommended for mild persistent asthma, with regular ICS and long-acting β_2 -agonists for moderate and severe persistent disease (16). With increasing evidence that rhinitis and asthma are components of a single, persistent, inflammatory condition affecting the whole respiratory tract with shared pathogenic mechanisms and common triggers, there is strong rationale for

managing these allergic diseases in a combined strategy (17). Considering the central role that IgE plays in the inflammatory processes of rhinitis and asthma (1, 2), systemic omalizumab could play an important role in a unified management approach.

In conclusion, this study demonstrates that a response in terms of asthma following omalizumab therapy is associated with a significantly increased probability of rhinitis improvement. Although anti-IgE therapy is not indicated for the treatment of patients with rhinitis in the absence of other allergic conditions, patients with concurrent allergic asthma and rhinitis may gain particular benefits for both asthma and rhinitis from this therapy.

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