Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma

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Background: Adult patients with nasal polyps often have comorbid asthma, adding to the serious effect on the quality of life of these patients. Nasal polyps and asthma might represent a therapeutic challenge; inflammation in both diseases shares many features, such as airway eosinophilia, local IgE formation, and a T_H2 cytokine profile. Omalizumab is a human anti-IgE mAb with proved efficacy in patients with severe allergic asthma. Omalizumab could be a treatment option for patients with nasal polyps and asthma.

Objective: The goal of this study was to investigate the clinical efficacy of omalizumab in patients with nasal polyps and comorbid asthma.

Methods: A randomized, double-blind, placebo-controlled study of allergic and nonallergic patients with nasal polyps and comorbid asthma (n = 24) was conducted. Subjects received 4 to 8 (subcutaneous) doses of omalizumab (n = 16) or placebo (n = 8). The primary end point was reduction in total nasal endoscopic polyp scores after 16 weeks. Secondary end points included a change in sinus computed tomographic scans, nasal and asthma symptoms, results of validated questionnaires (Short-Form Health Questionnaire, 31-item Rhinosinusitis Outcome Measuring Instrument, and Asthma Quality of Life Questionnaire), and serum/nasal secretion biomarker levels.

Results: There was a significant decrease in total nasal endoscopic polyp scores after 16 weeks in the omalizumab-treated group (−2.67, $P = .001$), which was confirmed by means of computed tomographic scanning (Lund-Mackay score). Omalizumab had a beneficial effect on airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and on quality-of-life scores, irrespective of the presence of allergy.

Conclusion: Omalizumab demonstrated clinical efficacy in the treatment of nasal polyps with comorbid asthma, supporting the importance and functionality of local IgE formation in the airways. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: *Omalizumab, anti-IgE, local IgE, nasal polyposis, asthma, quality of life*

Chronic rhinosinusitis with nasal polyposis (CRSwNP) and asthma are both complex inflammatory disorders and are a therapeutic challenge for health care. Among patients with CRSwNP, approximately 30% have asthma and 15% have aspirin intolerance.[1] Asthma is defined as a chronic inflammatory disorder of the airways characterized by chronic inflammation, airway hyperresponsiveness, and airflow obstruction, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The disease has a high prevalence, reported as 1 in 20 in the United States, and results in a chronic relapsing course.[2] Although some effective therapies exist for mild asthma, severe asthma remains difficult to treat, and the cost of the disease is substantial.[3]

Nasal polyps are benign edematous masses in the nasal cavities, paranasal cavities, or both with a probable overall prevalence of approximately 2% to 4% that can cause nasal obstruction, rhinorrhea, postnasal drip, and loss of smell.[4] Treatment options range from local or systemic corticosteroids to functional endoscopic sinus surgery. Especially patients with CRSwNP and comorbid asthma have a poor therapeutic response and a high recurrence rate, and their diseases are more difficult to treat. Both diseases have a serious effect on quality of life and cause a large financial burden for society.[4]

In 80% of white patients, the pathophysiology of CRSwNP is characterized by a prominent local eosinophilic inflammation with high production of eosinophil cationic protein, IL-5, and tissue IgE.[5,6] Moreover, the soluble IL-5 receptor α subunit, tryptase, and the soluble IL-2 receptor α subunit are important factors in the inflammation present in nasal polyps.[7,8] The level of tissue inflammation and local IgE formation in patients with CRSwNP is independent of the presence of allergy. However, the presence of asthma in patients with CRSwNP is associated with increased local IgE levels.[9] Recent evidence has accumulated suggesting that *Staphylococcus aureus* enterotoxins (SEs) act as superantigens and induce local polyclonal IgE formation combined with severe eosinophilic inflammation.[10,11] Moreover, formation of IgE against SEs in nasal polyp tissue is strongly associated with asthma in patients with CRSwNP.[12,13]

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Abbreviations used
AQLQ: Asthma Quality of Life Questionnaire
CRSwNP: Chronic rhinosinusitis with nasal polyposis
CT: Computed tomography
RSOM-31: 31-Item Rhinosinusitis Outcome Measuring Instrument
SEs: *Staphylococcus aureus* enterotoxins
SF-36: Short-Form Health Questionnaire
TPS: Total nasal endoscopic polyp score

The marked local production of IgE antibodies in patients with CRSwNP appears to be functional and involved in the regulation of chronic inflammation.[14] Thus strategies to antagonize IgE antibodies could be of relevance. Omalizumab is a human anti-IgE mAb that has already been approved for the treatment of adults with moderate-to-severe (United States) or severe (Europe) allergic asthma whose symptoms remain uncontrolled after treatment with high-dose inhaled corticosteroids plus long-acting β-agonists.[15-17] Primarily, omalizumab binds free circulating IgE and inhibits the binding of IgE to the high-affinity IgE receptor, decreasing free IgE levels.[18] Second, omalizumab leads to a decrease in IgE receptors on mast cells, basophils, and dendritic cells.[19] The objective of this study was to evaluate the clinical efficacy and safety of anti-IgE treatment in adults with CRSwNP and comorbid asthma.

METHODS

Subjects

Twenty-four subjects 18 years or older with CRSwNP (according to the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines[4]) and comorbid asthma (based on Global Initiative for Asthma guidelines[20] and diagnosed by a respiratory physician) for more than 2 years were included. Total serum IgE levels were between 30 and 700 kU/mL. All patients received an allergy skin prick test; however, both allergic (n = 13) and nonallergic (n = 11) patients were allowed in this study. More detailed information can be found in the Methods section in this article's Online Repository at www.jacionline.org.

The study was conducted at the Department of Otorhinolaryngology of the University Hospitals of Ghent (n = 20 patients) and Leuven (n = 4 patients), Belgium. The study was approved by the ethics committee of the Ghent and Leuven University Hospitals, and all patients provided written informed consent before participation.

Study design, randomization, and masking

The study was an investigator-initiated, randomized, double-blind, placebo-controlled, 2-center (University hospitals of Ghent and Leuven) trial conducted from January 2007 through October 2008 (Fig 1). After a 2-week run-in period, subjects were randomized on a 2:1 basis (computer-generated randomization list) to receive subcutaneous treatment with anti-IgE (16 subjects) or placebo (8 subjects). Both the investigator and the subject were blind to study treatment. The dose (in milligrams) and dosing frequency (every 2 weeks/8 injections in total or every month/4 injections in total) of omalizumab (Xolair; Novartis, Basel, Switzerland) were based on total serum IgE levels (in international units per milliliter) and body weight (in kilograms), with a maximum dose of 375 mg. After screening, 10 visits were scheduled every 2 weeks over 20 weeks.

Outcome measures

Total nasal endoscopic polyp score. The primary end point of this study was the reduction in total nasal endoscopic polyp scores (TPSs) after 16 weeks of treatment. Polyps were evaluated on each side by means of nasal endoscopy at each visit and graded based on polyp size, resulting in scores of 0 to 4 (Table I). The sum of the left and right nostril scores, which is the TPS, was used for further analysis.

Secondary end points. Secondary end points included changes in Lund-Mackay computed tomographic (CT) scores, nasal and asthma symptoms, spirometric results, and quality-of-life questionnaire scores. For more detailed information, see the Methods section in this article's Online Repository.

For detailed information on statistical analysis, see the Methods section in this article's Online Repository.

RESULTS

Patient enrollment and baseline characteristics

Twenty-four patients were randomly assigned to a study group (Fig 1). One patient withdrew just before the first injection, and therefore 23 of the 24 subjects who were screened started treatment and constituted the intention-to-treat population. The baseline characteristics are summarized in Table II. Twelve of 24 patients were given a diagnosis of aspirin hypersensitivity based on history. Fifteen patients received omalizumab, and 8 patients received placebo. After the official medication leaflet and based on total serum IgE levels and body weight, 2 patients were assigned to receive an injection every 2 weeks, and the other 22 patients received the treatment every month.

Primary end point: TPS

The primary end point was the difference in TPSs after 16 weeks of treatment (Fig 2). After 16 weeks of treatment, a significant reduction in polyp size was observed compared with baseline size in the omalizumab group (−2.67, $P = .001$) but not in the placebo group (−0.12, $P = .99$). According to the linear mixed model, adjusting for baseline values, TPSs were significantly lower in patients from the omalizumab arm compared with patients in the placebo arm throughout the entire treatment period ($P = .02$). Differences between both groups reached statistical significance from 8 weeks onward (week 8, $P = .03$; week 12, $P = .04$; and week 16, $P = .005$).

Secondary end points

The Lund-Mackay score for CT images improved from 17.6 to 13.6 after 16 weeks ($P = .02$) in the omalizumab group and worsened from 17.8 to 18.3 ($P = .10$) in the placebo group. Comparing both treatment groups, CT images improved significantly in the omalizumab group ($P = .04$).

According to the linear mixed model analysis, a significant decrease after treatment with anti-IgE was seen in the symptom scores for nasal congestion ($P = .002$; Fig 3, *A*), anterior rhinorrhea ($P = .003$; Fig 3, *B*), loss of sense of smell ($P = .004$; Fig 3, *C*), wheeze ($P = .02$; Fig 3, *D*), and dyspnea ($P = .02$; Fig 3, *E*). Cough (Fig 3, *F*) improved but did not reach statistical significance. Spirometric results also did not significantly improve after treatment with omalizumab.

After 16 weeks, the Short-Form Health Questionnaire (SF-36) of physical health was significantly improved in the omalizumab group ($P = .02$) but not in the placebo group ($P = .75$). Unlike physical health, mental health did not significantly improve in either treatment group. On the basis of the 31-item Rhinosinusitis Outcome Measuring Instrument (RSOM-31), sleep ($P = .03$)

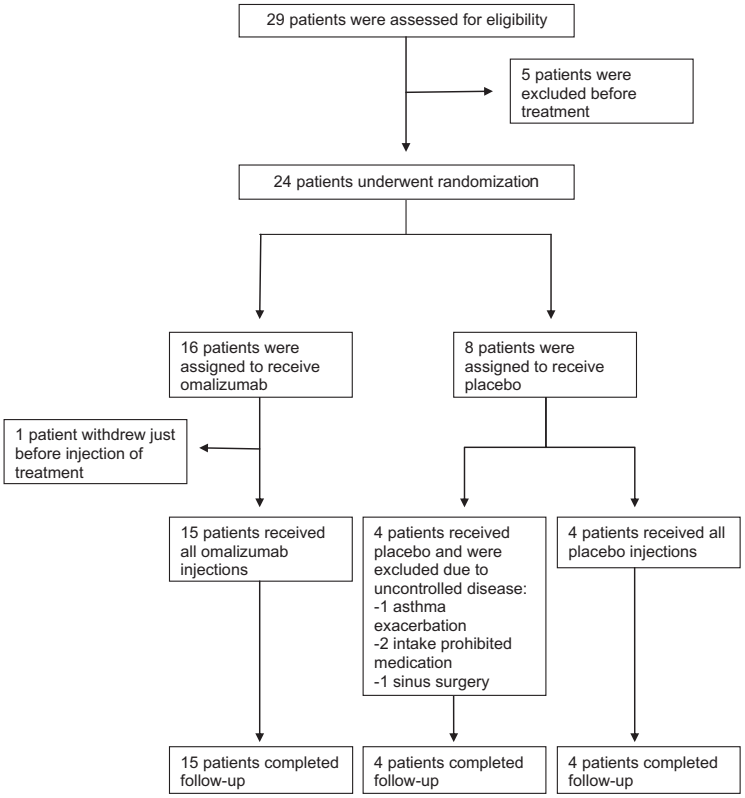

FIG 1. Number of patients who were screened, enrolled, and assigned to a study group and who completed the study.

TABLE I. The polyp scoring system used to evaluate polyp size in each nostril by means of nasal endoscopy

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

and general symptoms ($P = .01$) showed a significant improvement in the omalizumab group, whereas in the placebo group no significant changes were seen. The mean total Asthma Quality of Life Questionnaire (AQLQ) score (Fig 4) improved after treatment with 0.27 and 0.81 points, respectively, in the placebo and omalizumab groups. This change in the total AQLQ score after 16 weeks of treatment with omalizumab was significant ($P = .003$). Looking at the subcategories, there was a significant improvement during treatment in the omalizumab group in activity limitations ($P = .002$), symptoms ($P = .01$), and emotional function ($P = .02$).

Overall, 7 of 8 placebo-treated patients and 10 of 16 omalizumab-treated patients showed SE positivity in serum before treatment, and almost all showed positivity during treatment. No change in other serum and nasal secretion parameters was found to be significantly different after treatment.

Allergic versus nonallergic patients

A comparison between allergic or nonallergic patients was made based on allergy skin prick test results. Within the omalizumab group who underwent treatment (n = 15), there were 7 allergic and 8 nonallergic patients (see Table III). After 16 weeks, the allergic and nonallergic patients both had a decrease in TPSs (-2.57 [$P = .03$] and -2.75 [$P = .06$], respectively). Changes in clinical symptoms and SF-36 and RSOM-31 scores were comparable between allergic and nonallergic patients. In allergic patients the Lund-Mackay CT scan score improved significantly (-2.61, $P = .04$) in contrast to that seen in nonallergic patients (-0.66, $P = .75$). Interestingly, the AQLQ demonstrated a significant amelioration in total AQLQ score in the nonallergic group (-59.4, $P = .03$), whereas allergic patients showed a nonsignificant amelioration (-12.3, $P = .12$). In contrast, the results for patients with aspirin hypersensitivity did not differ from those for patients without aspirin hypersensitivity.

Safety and adverse events

Safety was assessed based on vital signs, physical examination, blood analysis, and adverse event reports.

Twenty-two (95.7%) of 23 included patients reported at least 1 adverse event. There was 1 adverse event, the common cold, that appeared significantly more often in the omalizumab group compared with the placebo group ($P = .02$, Table IV). Most of

TABLE II. Baseline characteristics of subjects

	Omalizumab (n = 15)	Placebo (n = 8)	*P* value
Baseline characteristics			
Age (y), median (IQR)	50 (44-56)	45 (42-54)	.26
Men/women (n)	12/3	4/4	.18
BMI (kg/m^2), median (IQR)	2.55 (32.2-27.8)	22 (21.0-25.4)	.07
Allergy, no. (%)	7 (47)	6 (75)	.39
Asthma, no. (%)	15 (100)	8 (100)	.21
Aspirin hypersensitivity, no. (%)	8 (53)	4 (50)	.90
Previous sinus surgery, no. (%)	13 (87)	6 (75)	.59
Clinical characteristics			
TPS, median (IQR)	6 (4-6)	6 (6-8)	.05
Lund-Mackay CT scan score, median (IQR)	17.5 (14.5-21.0)	16.5 (15.3-21.3)	.95
UPSIT, median (IQR)	12 (10-23)	12 (10-13)	.57
FEV_1 (% predicted), median (IQR)	88.5 (71.0-114.8)	99.5 (73.5-110.3)	.68
PEF (% predicted), median (IQR)	97.5 (78.0-109.5)	100 (73.0-128.8)	.73
SF-36 physical health score, median (IQR)	48 (45-52)	50 (45.5-52.8)	.90
SF-36 mental health score, median (IQR)	41 (40-45)	42 (40.2-44.8)	.79
Total AQLQ score, median (IQR)	5.75 (5.41-6.38)	4.73 (4.92-6.28)	.14
Peripheral blood			
Eosinophils (/μL), median (IQR)	390 (313-698)	475 (365-630)	.67
Serum			
ECP (μg/L), median (IQR)	31 (14-56)	32 (20-91)	.56
sIL-2Rα (pg/mL), median (IQR)	901 (817-1224)	816 (692-1139)	.40
sCD23 (pg/mL), median (IQR)	2206 (1984-2852)	2331 (1797-2712)	.85
sIL-5Rα (pg/mL), median (IQR)	258 (207-332)	292 (249-413)	.32
Specific SE IgE (μg/L), median (IQR)	0.16 (0.03-0.46)	0.22 (0.12-0.62)	.37
Total IgE (kU/L), median (IQR)	108 (39-130)	84 (71-148)	.36
Tryptase (μg/L), median (IQR)	5.34 (3.96-7.45)	4.36 (3.27-5.55)	.33
Nasal secretion			
ECP (μg/L), median (IQR)	362 (176-653)	994 (591-1888)	.03
IL-5 (pg/mL), median (IQR)	66 (24-105)	90 (29-122)	.92
sCD23 (pg/mL), median (IQR)	536 (236-2047)	1479 (547-3451)	.16
sIL-5Rα (pg/mL), median (IQR)	494 (169-1128)	1199 (757-2771)	.06
Total IgE (kU/L), median (IQR)	20 (9-57)	89 (26-147)	.06
Tryptase (μg/L), median (IQR)	7.8 (7.5-25.2)	7.5 (7.5-25.2)	.79

BMI, Body mass index; *ECP*, eosinophil cationic protein; *IQR*, interquartile range; *PEF*, peak expiratory flow; *sCD23*, soluble low-affinity IgE receptor; *sIL2-Rα*, soluble IL-2 receptor, α subunit; *sIL-5Rα*, soluble IL-5 receptor, α subunit; *UPSIT*, The University of Pennsylvania Smell Inventory Test.

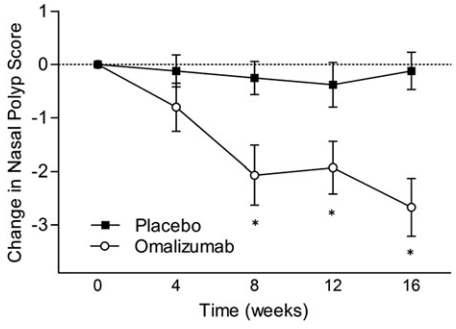

FIG 2. TPS: change from baseline over weeks based on last-observation-carried-forward imputation in the placebo-treated *(solid squares)* and omalizumab-treated *(open circle)* groups. *Error bars* indicate 95% CIs of the mean based on normal approximation.

the adverse events were mild. Only 1 patient of the placebo group dropped out because of an adverse event (asthma attack). One patient in the omalizumab group had a fatal lymphoblastic lymphoma 1 year after finishing the study. Furthermore, no meaningful changes in vital signs, physical examination and blood analysis results were observed.

DISCUSSION

Both CRSwNP and asthma have a serious effect on quality of life and represent a large financial burden for society.[21,22] Previous case reports and case series suggested the beneficial effect of omalizumab in patients with CRSwNP and comorbid allergic asthma.[23-25] This is the first double-blind, randomized controlled trial investigating the clinical efficacy of a new treatment option, omalizumab, in patients with CRSwNP and comorbid asthma.

Our study shows, for the first time, a significant decrease in TPSs after treatment with omalizumab. Moreover, omalizumab (but not placebo) caused improvement in nasal and asthma symptom scores compared with baseline scores. Furthermore, omalizumab causes a beneficial effect on SF-36 physical health, RSOM-31, and AQLQ scores. The improvement in quality of life is an important outcome in the evaluation of disease severity because its measurements reflect the effect that symptoms and disease have on the patient's daily life.

It is important to understand the difference between total serum IgE and specific local tissue IgE levels to elucidate the mechanism of action of omalizumab in patients with CRSwNP. In patients with CRSwNP, total serum IgE levels are only partially correlated to local tissue IgE levels and local eosinophilic inflammation.[5] The highly increased local tissue IgE levels

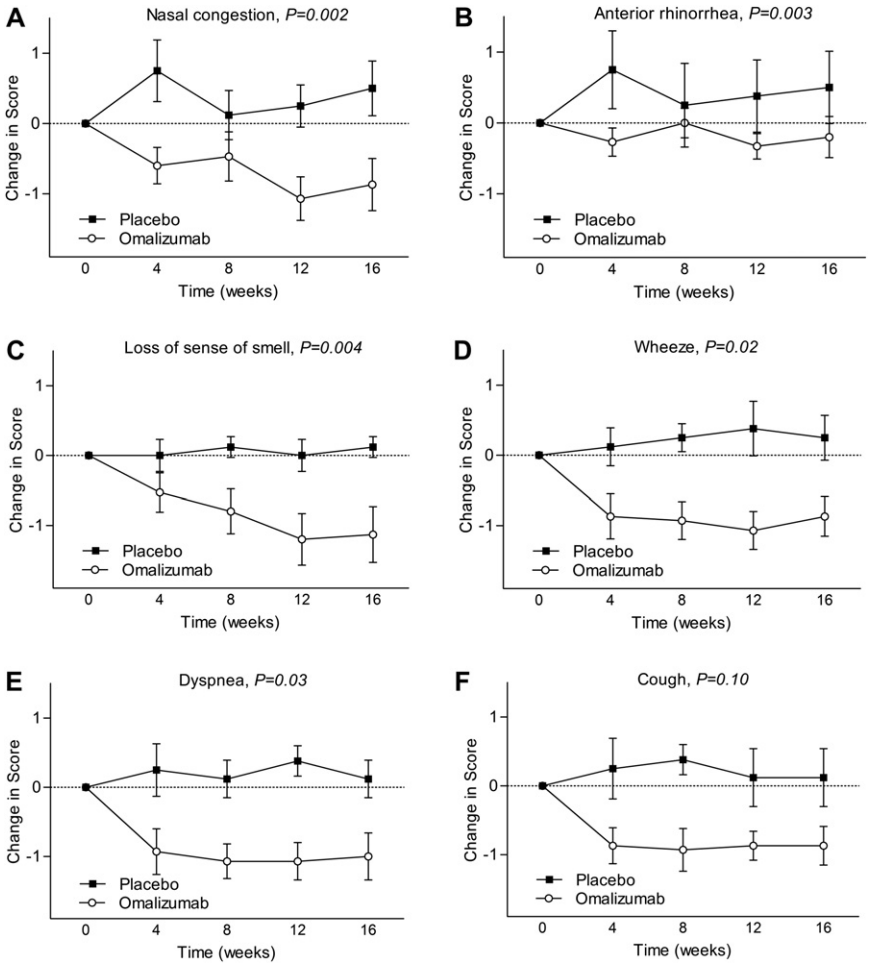

FIG 3. Change from baseline in nasal congestion **(A)**, anterior rhinorrhea **(B)**, sense of smell **(C)**, wheezing **(D)**, dyspnea **(E)**, and cough **(F)** in the omalizumab-treated *(open circles)* and placebo-treated *(solid squares)* groups. *P* values represent the change from baseline after 16 weeks of treatment. *Error bars* indicate 95% CIs of the mean based on normal approximation.

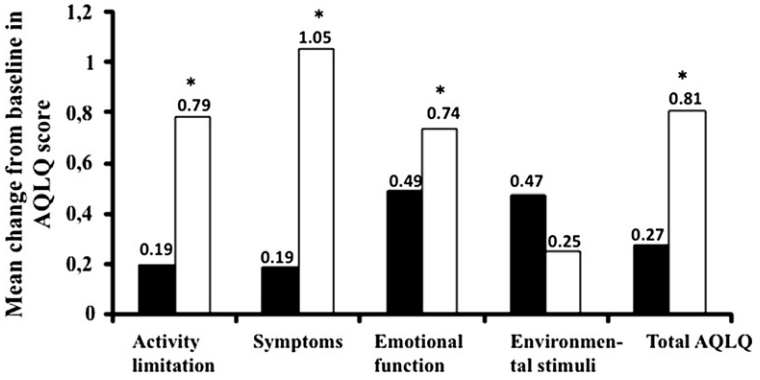

FIG 4. Improvement in AQLQ scores after treatment with omalizumab *(open columns)* or placebo *(solid columns)*. Changes from baseline in the different domains of the AQLQ and the total AQLQ score after 16 weeks of treatment are shown. *Significant improvement for activity limitation ($P = .002$), symptoms ($P = .01$), emotional function ($P = .02$), and total AQLQ ($P = .003$) scores.

in nasal polyps are often polyclonal, associated with SE activity, and independent of total serum IgE levels or allergy skin prick test responses.[10] We recently demonstrated that mucosal polyclonal IgE is functional by inducing mast cell degranulation independent of serum IgE levels.[14] Moreover, in patients with CRSwNP, tissue IgE levels are related to the severity of disease and the presence of comorbid asthma.[12,13] Conducting this study and seeing an improvement in clinical markers and quality of life support the importance of local IgE levels in the pathophysiology of CRSwNP and asthma.

TABLE III. Mean change from baseline in primary and secondary end points after 16 weeks of treatment with omalizumab in allergic and nonallergic patients

	Omalizumab (n = 15)			
	Allergic (n = 7)	*P* value	Nonallergic (n = 8)	*P* value
TPS	−2.57	.03	−2.75	.06
Lund-Mackay CT scan score	−2.61	.04	−0.66	.75
Symptom score				
Nasal congestion	−0.86	.25	−0.88	.19
Anterior rhinorrhea	−0.43	.50	0.00	.99
Loss of sense of smell	−1.75	.06	−0.75	.39
Wheezing	−0.71	.12	−1.00	.09
Dyspnea	−1.00	.06	−1.00	.11
Cough	−0.43	.25	−1.25	.06
SF-36				
Mental health score	8.76	.11	5.96	.06
Physical health score	−0.30	.89	−2.21	.04
RSOM				
Nasal symptoms	−2.81	.06	−0.88	.73
Ocular symptoms	−0.57	.72	−0.33	.10
Sleep	−2.75	.09	−4.18	.14
Ear symptoms	−1.14	.30	−0.55	.46
General	−2.55	.11	−2.49	.09
Practical problems	−1.11	.64	−0.75	.78
Emotional consequences	−1.10	.44	−2.10	.13
AQLQ				
Activity limitations	5.00	.03	12.86	.02
Symptoms	5.14	.17	23.00	.02
Emotional function	1.71	.07	6.33	.06
Environmental stimuli	0.43	.70	2.67	.06
Total score	12.29	.09	59.43	.02

TABLE IV. Adverse events in the omalizumab- and placebo-treated groups recorded during the study

Adverse events	Omalizumab (n = 15)	Placebo (n = 8)
Asthma exacerbation	0	1
Frontal headache	4	1
Nasal obstruction	3	3
Shortness of breath	2	1
Allergy	1	0
Common cold	8	0
Jaundice	0	1
Gastroenteritis	1	0
Acute sinusitis	0	1
Shoulder pain	1	0
Otitis media	2	0
Left ulnar hypoesthesia	1	0
General myalgia	1	0

This clearly defined study population with nasal polyps and asthma is characterized by T_H2 inflammation with tissue eosinophilia and polyclonal local IgE production. SEs have been identified as inducers and amplifiers of this local polyclonal IgE formation.[11] Recent work has demonstrated that SEs are able to induce T-cell activation and a T_H2 bias, to increase tissue eosinophilia, and to induce B-cell activation, leading to the production of polyclonal IgE.[14] In this study, on the basis of the selection of patients with nasal polyps with comorbid asthma, 70% of subjects were SE-IgE positive before treatment, and almost 100% were SE-IgE positive during treatment.

Omalizumab has a proven beneficial effect on moderate-to-severe allergic asthma. It does not change spirometric results but decreases asthma exacerbations and the need for rescue medication.[15-17] Except for some case reports, there is no proof of efficacy in nonallergic asthma.[26] However, there are many similarities between allergic and nonallergic asthma, including the eosinophilic inflammation and increased levels of IL-5, IL-4, and IL-13.[27,28] Similarly to patients with CRSwNP, several studies have suggested a role for local tissue IgE in patients with nonallergic "intrinsic" asthma. In this study patients with nasal polyps with asthma were not selected for atopy or skin prick test response positivity. Both the allergic and nonallergic patients treated with omalizumab experienced a significant beneficial effect on upper and lower airway symptoms and quality-of-life scores, irrespective of their allergic status. This observation strongly supports the findings of a functional role of local polyclonal IgE in airway mucosal tissue and might serve as the final proof of concept that local IgE mediates airway symptoms in allergic but also nonallergic airways.

This might broaden the use of omalizumab to the most difficult-to-treat group of patients with severe CRSwNP and asthma, irrespective of allergy. However, mainly because of the costs, the use of omalizumab should be restricted to patients with CRSwNP and asthma when previous endoscopic sinus surgery is not able to control upper airways symptoms. Recently, severe chronic upper airway disease was defined as the condition in which the patient's symptoms are inadequately controlled despite adequate pharmacologic treatment, as in asthmatic patients with CRSwNP.[29] It needs to be stressed that the finding of high local IgE levels is especially frequent in airway tissue of asthmatic patients with nasal polyps compared with levels seen in nonasthmatic patients with nasal polyps.[12] Therefore the use of omalizumab might be restricted to carefully selected patients with moderate-to-severe combined disease (ie, CRSwNP with concomitant asthma).

For revealing the underlying mechanism, we measured inflammatory parameters in sera and nasal secretions before and after treatment. In contrast to previously published anti–IL-5 studies, inflammatory parameters were not influenced by omalizumab.[30] This finding suggests that the beneficial effect is not mediated through an influence on the eosinophilic inflammation but rather directly through IgE or its receptor.[31]

This study has potential limitations, such as the limited sample size of 24 patients, which was estimated before the start of the study. Despite randomization, the placebo-treated subjects had higher parameters of nasal eosinophilic inflammation at baseline. Importantly, there was a high dropout rate (4/8 subjects) in the placebo arm of the study. These limitations should be taken into account when designing future studies.

Because anti-IgE treatment targets the immune system, there is special interest in the safety of the product. In patients with severe asthma, omalizumab has an acceptable safety profile; however, the long-term safety study for omalizumab is still ongoing.[32,33] During this study, adverse events were comparable between both groups. However, 1 patient in the omalizumab group experienced a fatal lymphoblastic lymphoma 1 year after finishing the study; the relationship to the study medication and the event is unlikely. In the literature neoplasia was reported more frequently in omalizumab-treated patients (0.50%) than in control subjects (0.18%) across all completed studies.[34] This overall evaluation

of studies could not draw any conclusion on the causal relationship between the use of omalizumab and the development of cancer.

In conclusion, this study is the proof of concept that omalizumab is an effective treatment option in patients with CRSwNP and comorbid asthma. In this study patients were selected based on the presence of nasal polyps and asthma, irrespective of the presence of allergy. Nevertheless, omalizumab was equally efficacious in both allergic and nonallergic patients with nasal polyps and asthma. The treatment dose was based on total serum IgE levels. However, because this and other studies suggest the determining role of local tissue IgE production, further research is needed to understand the role of local tissue IgE levels in patient selection and adequate dosing regimens in patients with severe airway diseases, such as CRSwNP and asthma.[35]

Clinical implications: Omalizumab is a treatment option in patients with nasal polyps and comorbid asthma.

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METHODS

Subjects

All subjects were in otherwise good health. Maintenance treatment for asthma was standardized and controlled by a respiratory physician. During the study, subjects were not permitted to use systemic corticosteroids, an inhaled corticosteroid (doses of greater than 1000 μg/d beclomethasone dipropionate or equivalent), antibiotic treatment, leukotriene receptor antagonists, or nasal decongestants.

Secondary end points

A CT scan of the nose and paranasal sinuses was performed at baseline and after 16 weeks of treatment. The CT scans were evaluated by using the Lund-Mackay score, a quantitative comparative score, performed by 2 independent blinded examiners, an otorhinolaryngologist and a radiologist.[E1] The inter-rater agreement in Lund-Mackay scores proved to be acceptable, with an intra-class correlation of 0.77.

Subjects were asked to score their nasal (nasal congestion/obstruction, anterior rhinorrhea, and loss of sense of smell) and asthma (cough, wheezing, and shortness of breath) symptoms daily as absent, mild, moderate, or severe (scores of 0, 1, 2, or 3, respectively). Adverse events and use of concomitant medications were recorded on the diary card, which was distributed at each visit.

Spirometry was performed at baseline and at 16 weeks to evaluate the lower airways. On the basis of age, sex, and height, percent predicted FEV_1 and peak expiratory flow values were measured.

Furthermore, 3 questionnaires were self-administered at baseline and at 16 weeks: the SF-36,[E2] the RSOM-31, and the AQLQ.[E3]

Biological activity was evaluated based on peripheral blood eosinophil counts, serum total IgE levels and measurement of cytokines and mediators in sera and nasal secretions at baseline and every 4 weeks.[E4] Sera and nasal secretions were assayed for the soluble low-affinity IgE receptor (sCD23), IL-5, the soluble IL-2 receptor α subunit (sIL-2Rα, a marker of T-cell activity; R&D Systems, Minneapolis, Minn), and the soluble IL-5 receptor α subunit (sIL-5Rα; Innogenetics, Ghent, Belgium) by using ELISA. Eosinophil cationic protein, tryptase, and total and SE IgE concentrations were measured by using the UniCAP system (Pharmacia & Upjohn, Uppsala, Sweden). SE positivity was present if patients had an SE IgE level at baseline in serum of 0.1 kU/L or greater.

Statistical analysis

Data were analyzed according to the intention-to-treat principle with last-observation-carried-forward imputation. One patient had discontinued anti-IgE treatment (at 14 weeks); 4 patients in the placebo group had stopped their study medication at several moments during the study period. All patients completed all study visits. The distributions of baseline characteristics in both study arms were compared according to the Fisher exact test for dichotomous data and the Mann-Whitney *U* test for continuous data. Changes in TPSs, CT scores, symptom and quality-of-life scores, and blood and nasal secretion measurements at 4, 6, 8, and 10 weeks compared with their baseline values (baseline = week 0) were statistically evaluated according to the Wilcoxon signed-rank test in both treatment groups. The effect of anti-IgE treatment on changes in these variables throughout the entire study period after baseline was analyzed according to a linear mixed-effects model including treatment, time, and the treatment-by-time interaction as fixed effects and using patients as a random effect (with unstructured covariance structure). In these models adjustment was done for values obtained at baseline (visit 2). A type I error rate of .05 was adopted *a priori* to indicate statistical significance. All analyses were carried out with SAS software, version 9.1 (SAS Institute, Cary, NC). The initial power analysis was calculated based on similar and previous studies at our department with a primary end point of the TPS (power of 80% and 5% significance level). A *post hoc* power calculation revealed that our study sample achieves 92% power to detect a 50% difference in the average TPS at 16 weeks.

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