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

Philippe Gevaert, MD, PhD,[a]* Lien Calus, MD,[a]* Thibaut Van Zele, MD, PhD,[a] Katrien Blomme, MSc,[a] Natalie De Ruyck, MSc,[a] Wouter Bauters, MD, PhD,[b] Peter Hellings, MD, PhD,[c] Guy Brusselle, MD, PhD,[d] Dirk De Bacquer, MD, PhD,[e] Paul van Cauwenberge, MD, PhD,[a] and Claus Bachert, MD, PhD[a] *Ghent and Leuven, Belgium*

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 2013;131:110-6.)

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]

From [a]the Upper Airways Research Laboratory, Department of Otorhinolaryngology, [b]the Department of Radiology, and [d]the Department of Respiratory Medicine, Ghent University Hospital; [c]the Department of Otorhinolaryngology, University Hospital Leuven; and [e]the Department of Public Health, Ghent University.

*These authors contributed equally to this work.

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Corresponding author: Philippe Gevaert, MD, PhD, Upper Airways Research Laboratory, Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium. E-mail: philippe.gevaert@UGent.be.

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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 ($P = .03$)