Mepolizumab, a humanized anti–IL-5 mAb, as a treatment option for severe nasal polyposis

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Background: Approximately 85% of nasal polyps (NPs) in white subjects are characterized by prominent eosinophilia. IL-5 is the key driver of eosinophilic differentiation and survival.
Objective: We sought to investigate the therapeutic potential of inhibiting IL-5 with a humanized mAb as treatment for severe nasal polyposis.
Methods: Thirty patients with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) refractory to corticosteroid therapy were randomized in a double-blind fashion to receive either 2 single intravenous injections (28 days apart) of 750 mg of mepolizumab (n = 20) or placebo (n = 10). Change from baseline in NP score was assessed monthly until 1 month after the last dose (week 8). Computed tomographic scans were also performed at week 8.
Results: Twelve of 20 patients receiving mepolizumab had a significantly improved NP score and computed tomographic scan score compared with 1 of 10 patients receiving placebo at week 8 versus baseline.
Conclusion: Mepolizumab achieved a statistically significant reduction in NP size for at least 1 month after dosing in 12 of 20 patients. IL-5 inhibition is a potential novel therapeutic approach in patients with severe eosinophilic nasal polyposis.
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Key words: *Anti–IL-5, mepolizumab, eosinophils, chronic rhinosinusitis, nasal polyposis*

Chronic sinus disease covers a multitude of different entities, such as chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). Although in the recent position paper for sinus disease of the European Academy of Allergy and Clinical Immunology the difference between CRSsNP and CRSwNP is made based on the results of clinical investigation and endoscopy,[1] other studies have suggested that these 2 entities have distinct pathways of inflammation.[2,3] CRSwNP in white patients is characterized by a T_H2 eosinophilic inflammation with high levels of IL-5 and IgE,[4-6] whereas CRSsNP shows a T_H1 milieu with high IFN-γ and TGF-β1 concentrations.[3]

In white patients 80% to 90% of the nasal polyps (NPs) are characterized by prominent eosinophilia.[1,7] It is assumed that through release of toxic products, eosinophils lead to tissue damage and growth of polyps.[8] The accumulation and activation of eosinophils is favored by low concentrations of TGF-β1 and by overproduction of IL-5 and eotaxin in NP tissue.[3] High amounts of IL-5 were detected in patients with NP, both at the mRNA and protein levels.[9,10] This cytokine seems to play a key role in the chemotaxis, activation, and survival of eosinophils.[11,12] Treatment of eosinophil-infiltrated polyp tissue with neutralizing anti–IL-5 mAb results in eosinophil apoptosis and decreases tissue eosinophilia *in vitro*.[10] Concerning the increased IgE level, there is increasing evidence that *Staphylococcus aureus*–derived enterotoxins stimulate eosinophilic inflammation through production of T_H2 cytokines and local IgE formation.[13]

Interestingly, NPs of Chinese patients are clinically indistinguishable from polyps of their white counterparts, but they lack IL-5 and eotaxin expression in the tissue, resulting in lower numbers of tissue eosinophils.[14,15] The direct comparison of polyps from Belgian and Chinese patients shows that there is a shared but still to be clarified pathway of mucosal edema formation, T-effector cell activation, and regulatory T-cell impairment.[16] Moreover, white patients had comorbid asthma more frequently than Chinese patients.[16] Inflammation in asthmatic patients shares many features with the eosinophilic inflammation seen in patients with NPs, such as an increased number of mucosal eosinophils, IgE formation, and a T_H2 profile with increased IL-5 and eotaxin levels.[17]

These findings suggest that different types of polyps might require different treatments based on the respective pathophysiology. Tailored medication schemes based on phenotyping have to be developed. In white patients IL-5 is a key driver of

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Abbreviations used

AC: Available case analysis
AUC: Area under the curve
CFB: Change from baseline
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps
CT: Computed tomography
ECP: Eosinophil cationic protein
IL-5Rα: IL-5 receptor α subunit
LDL: Lower detection limit
LOCF: Last-observation-carried-forward imputation
MPO: Myeloperoxidase
NP: Nasal polyp
nPIF: Nasal peak inspiratory flow
TPS: Total polyp score

maintaining polyps, namely eosinophilic differentiation and survival. The objective of the current study was to investigate the therapeutic potential of inhibiting IL-5 by using a humanized mAb as treatment for severe nasal polyposis. Our group has been able to demonstrate shrinkage of NPs in more than half of the patients treated with a single intravenous injection of an anti-human IL-5 mAb in the past.[18] Moreover, local IL-5 concentrations at baseline were significantly higher in responders in contrast to those seen in nonresponders. We suggested that nasal IL-5 levels could predict the response to anti–IL-5 treatment.[18] However, the primary end point of this study was safety, and efficacy was only studied by means of nasal endoscopy. In the current study we wanted to determine the efficacy of 2 injections of mepolizumab on NP volume in patients with severe CRSwNP using nasal endoscopy and computed tomographic (CT) scan imaging. In addition, markers of biological activity, such as IL-5 levels and nasal eosinophilia, were assessed over a period of 11 months after the last dose.

METHODS

Patients

Thirty subjects with chronic rhinosinusitis with primary NPs (grade 3 or 4, see outcome measures) or NPs that are recurrent after surgery (grade 1-4) were included. The inclusion criteria specified that subjects must have had failure of standard care for CRSwNP, and the diagnosis of this condition was based on the European position paper on rhinosinusitis and NPs.[1] Use of systemic corticosteroids and surgical intervention was not allowed from 1 month before treatment until the end of the study, and subjects were not permitted to use nasal corticosteroids, nasal antihistamines, nasal atropine, nasal cromolyn, nasal saline, or antibiotic treatment for 2 months after first dosing. The study was conducted at the Department of Otorhinolaryngology of the University Hospital in Ghent, Belgium. The local ethics committee approved the study, and all volunteers provided written informed consent before participation in the study.

Study design

We performed a randomized, double-blind, placebo-controlled study of mepolizumab in patients with CRSwNP. After signing the informed consent form and a 4- to 12-week run-in period, subjects were randomized to receive 2 single intravenous injections (28 days apart) of 750 mg of mepolizumab (20 subjects) or placebo (10 subjects). Follow-up visits were scheduled 1, 4, 8, 12, 24, 36, and 48 weeks after first dosing. During the follow-up visit after 4 weeks, the second injection of mepolizumab was administered (see Fig E1 in this article's Online Repository at www.jacionline.org). All randomized patients were included in the analysis. The study was double blind up to 48 weeks.

TABLE I. Baseline characteristics of the study patients divided into the mepolizumab-treated and placebo groups

Baseline characteristic	Mepolizumab-treated group	Placebo group	*P* value
No.	20	10	
Age (y), mean (SD)	50.05 (8.86)	45.9 (11.43)	.37*
Female/male	6/14	2/8	.69†
Atopy (positive skin prick test response)	10/20	4/10	.71†
Asthma in history	10/20	3/10	.45†
Aspirin intolerance	5/20	0/10	.14†
Sinus surgery in history	15/20	8/10	1.00†
Duration of disease (y), mean (SD)	10.5 (5.61)	14.3 (8.23)	.25*
Tobacco use	5/20	1/10	.64†
TPS, mean (SD)	5.2 (1.74)	5.5 (1.65)	.70*
Total symptom score, mean (SD)	7.95 (1.79)	8.4 (1.71)	.48*
Loss of smell, mean (SD)	2.65 (0.59)	2.4 (0.84)	.50*
Congestion, mean (SD)	2.15 (0.75)	2.4 (0.70)	.41*
Anterior rhinorrhea, mean (SD)	1.5 (0.89)	1.8 (0.79)	.49*
Postnasal drip, mean (SD)	1.65 (0.99)	1.8 (0.63)	.77*

*Exact Mann-Whitney *U* test.
†Fisher exact test.

Outcome measures

The primary end point of this study was the reduction in NP score[19,20] at 8 weeks after the first dosing (1 month after the second dose). This total polyp score (TPS) is the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. CRSwNP was graded based on polyp size: 0, no polyps; 1, small polyps in the middle meatus not reaching below the inferior border of the middle concha; 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 concha; and 4, large polyps causing complete obstruction of the inferior meatus.

Secondary end points included changes in CT scan scores and assessments, such as nasal peak inspiratory flow (nPIF) or symptom score (sum of individual symptoms: anterior rhinorrhea, nasal obstruction, postnasal drip, and loss of sense of smell; 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms). CT scans were assessed for improvement versus worsening or no change after 8 weeks with respect to baseline values. This was done independently by 3 different observers. Biological activity was evaluated based on peripheral blood eosinophil counts and measurement of cytokines and mediators in sera and nasal secretions. Blood eosinophils were counted automatically by using a 2-mL heparinized blood sample. Nasal secretions were obtained by placing sinus packs (IVALON 4000 plus) in both nasal cavities for exactly 5 minutes, which were immediately processed as previously described.[12] Serum and nasal secretions were assayed by means of ELISA for IL-1β, IL-5 (R&D Systems, Minneapolis, Minn), myeloperoxidase (MPO; BioCheck, Foster City, Calif), and soluble IL-5 receptor α subunit (IL-5Rα; Innogenetics, Ghent, Belgium). Eosinophil cationic protein (ECP) concentrations were obtained by using the UniCAP system (Pharmacia & Upjohn, Uppsala, Sweden), whereas IL-6 concentrations were measured with a Fluorokine MAP cytokine multiplex kit (R&D Systems) using the Bio-Rad Bio-plex 200 (Bio-Rad Laboratories, Hercules, Calif). The lower detection limits (LDLs) before dilution were 2 μg/L for nasal ECP, 3.9 pg/mL for nasal IL-5, 7.8 pg/mL for nasal IL-5Rα, 1.8 pg/mL for nasal IL-6, 0.2 kU/L for nasal total IgE, and 0.1 kU/L for serum total IgE.

Safety was assessed based on adverse event reporting, vital signs measurement, symptom checks, physical examination, and blood analysis.

Statistical analysis

The primary end point of this study was the change from baseline (CFB) in TPS at week 8. This was analyzed by using the exact Mann-Whitney *U* test. As