Original article

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

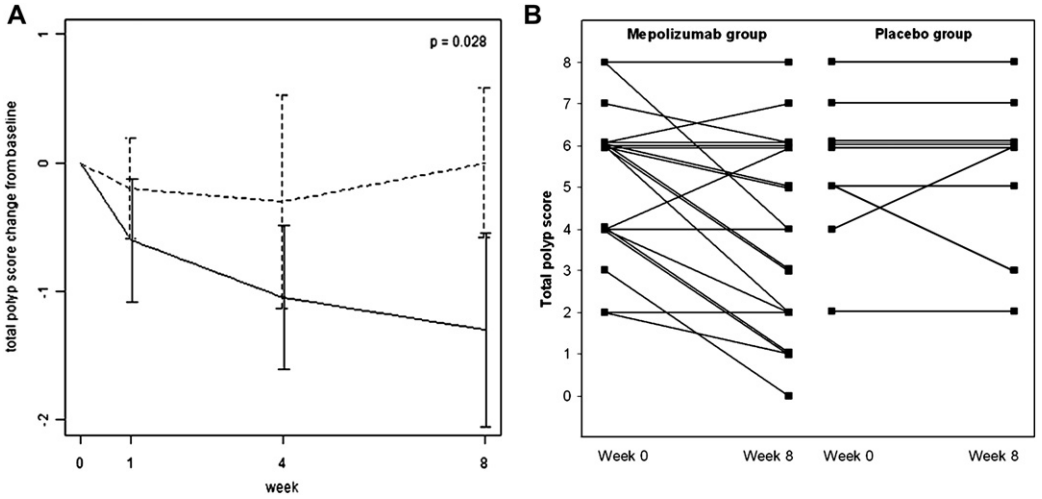

FIG 1. A, Mean CFB in TPS based on LOCF for the treated *(solid line)* and placebo *(dashed line)* groups starting at the moment of first administration. *Error bars* indicate 95% CIs of the mean based on normal approximation. **B,** Baseline and week 8 TPSs in absolute values based on LOCF for each subject and divided into the mepolizumab-treated and placebo groups.

a supporting analysis, improvement in TPS (defined as a negative CFB) was analyzed by using the Fisher exact test. Because of the large number of dropouts, we did not interpret any observations after week 8.

Regarding the CT scans, we checked interrater reliability by using the Fleiss κ coefficient. The Fisher exact test of CT score improvement in the treated versus placebo groups was performed for each rater. Symptom scores, blood eosinophil counts, serum ECP levels, and serum IL-5Rα levels were analyzed by using the exact Mann-Whitney *U* test, and nPIF was analyzed by using the area under the curve (AUC). For the markers in nasal secretions, there were a lot of observations below the LDL. Because of this, the Peto-Peto-Prentice test was used because it uses all data, acknowledging the unobserved values of less than the LDL, without imputing an exact value for them.[21] For nasal MPO levels, there was no LDL issue, and we have tested its CFB by using the exact Mann-Whitney *U* test.

Because of the large number of dropouts, the time to withdrawal was compared by using a Kaplan-Meier plot and the log-rank test. We also looked at the reasons for dropout and their implications in more detail. To deal with the missing data problem, we performed a last-observation-carried-forward imputation (LOCF) and an available case analysis (AC). Concerns exist regarding whether it is appropriate to use LOCF or AC.[22] For brevity, throughout the article, only the LOCF results are stated, but the AC results are also calculated (see Table E1 in this article's Online Repository at www.jacionline.org).

Within the treated group, a distinction could be made between responders (persons with an improved TPS of ≥1 unit at week 8 vs baseline values) and nonresponders. We investigated whether there were baseline differences between responders and nonresponders, again using the exact Mann-Whitney *U* test and the Peto-Peto-Prentice test, where appropriate.

We performed a *post hoc* power calculation for the Mann-Whitney *U* test of the primary end point (ie, TPS CFB at week 8) based on the present study using the O'Brien-Castelloe approximation. A *post hoc* power of 68% was obtained by using the LOCF paradigm.

Data analysis was performed with SAS version 9.1 software (http://www.sas.com/; SAS Institute, Inc, Cary, NC) and R version 2.11.1 software (http://cran.r-project.org/). Error bars in the figures represent 95% CIs of the mean based on normal approximation.

RESULTS

Patients

The baseline characteristics of the study patients are summarized in Table I. The history and symptoms of the mepolizumab and placebo groups were compared. Age and sex were similar. Almost half of the patients were atopic (based on skin prick test responses), and 43% had asthma. The number of patients who had undergone sinus surgery in the past was high. At baseline, our patient population consisted of 3 patients with grade 1, 6 patients with grade 2, 16 patients with grade 3, and 5 patients with grade 4 maximal unilateral NP size equally divided into the different groups. Consequently, the mean TPS in both groups was comparable.

Safety and adverse events

Sixteen (53%) of the 30 subjects reported at least 1 adverse event over 48 weeks of follow-up. One serious adverse event and 23 adverse events occurred. The serious adverse event was a diverticulitis caused by a preexisting condition and not considered to be related to the study drug. Of the adverse events, the common cold was the most frequent, as reported by 6 persons (5 episodes in the mepolizumab-treated group and 1 in the placebo group). Table E2 in this article's Online Repository at www.jacionline.org shows all the adverse events, comparing the mepolizumab-treated patients with the placebo group. None of them reached significance. We observed no meaningful changes in vital signs, physical examination results, and blood analysis.

Primary end point: TPS

The primary end point was the difference in TPS at week 8 (visit 5) versus baseline (visit 2). By using LOCF, the CFB with mepolizumab was −1.30 (SD, 1.72), and that with placebo was 0.00 (SD, 0.94), resulting in a treatment difference of −1.30 (SD, 1.51; $P = .028$, Mann-Whitney *U* test). Fig 1 shows the CFB at different time points and the baseline and week 8 TPSs for each subject.

Again, by using LOCF, the percentage improvement in TPS for mepolizumab was greater than that with placebo at 60% versus 10% (odds ratio, 13.5; $P = .018$, Fisher exact test).

Table E1 shows an overview of results obtained by using the LOCF and AC paradigms in the presence of missing data for

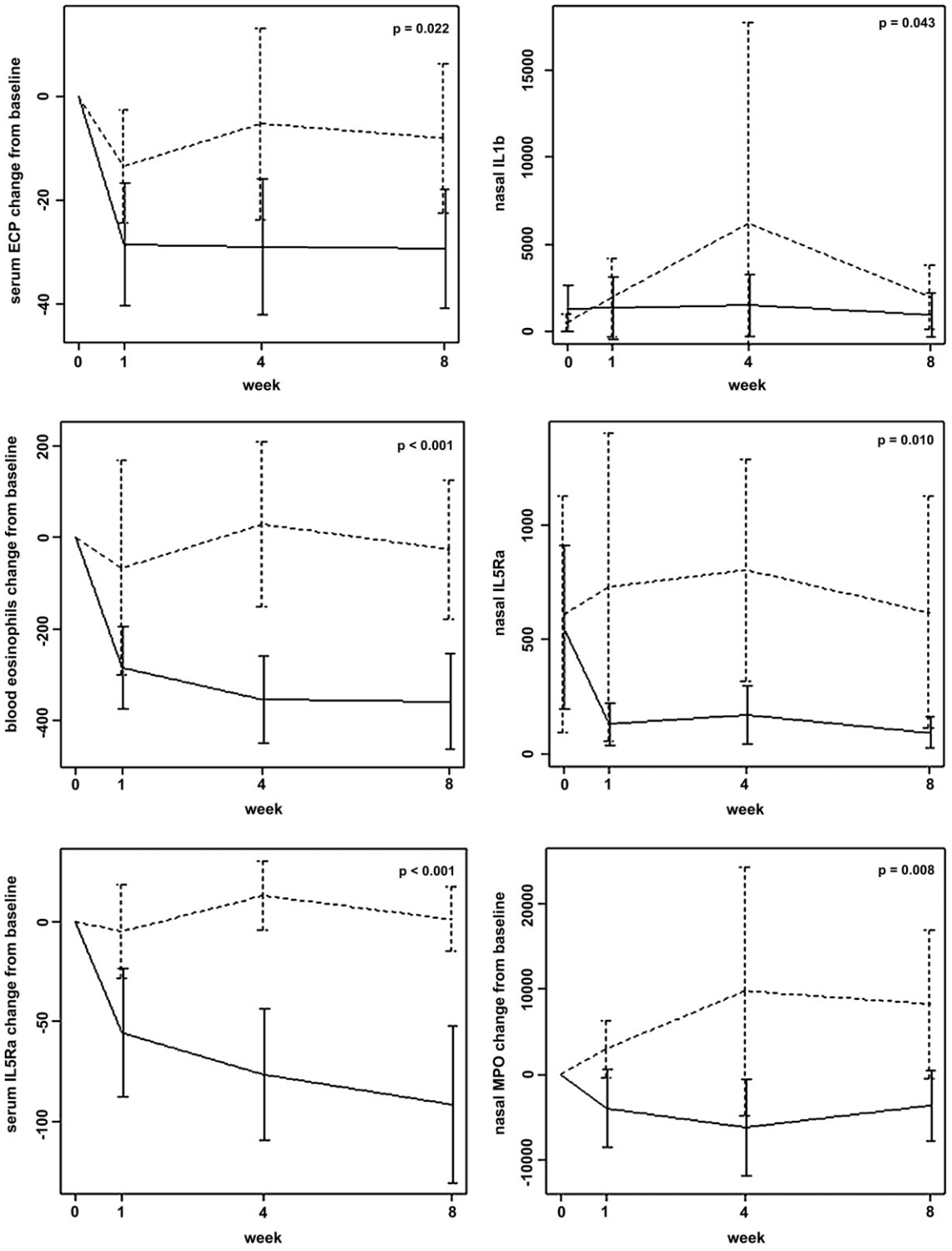

FIG 2. Mean CFB in serum ECP levels, blood eosinophil counts, serum IL-5Rα levels, and nasal MPO levels and mean nasal IL-1β and IL-5Rα levels (all in micrograms per liter), imputing 0 for observations of less than the LDL. These representations are based on LOCF and show the mepolizumab-treated *(solid line)* and placebo *(dashed line)* groups starting at the moment of first administration. *Error bars* indicate 95% CIs of the mean based on normal approximation.

both the difference in TPS versus baseline and percentage improvement. The LOCF and AC values of the comparisons below are also mentioned.

CT score improvement

The Fleiss κ coefficient of interrater reliability was 0.679 by using LOCF, indicating good agreement among the 3 raters of the

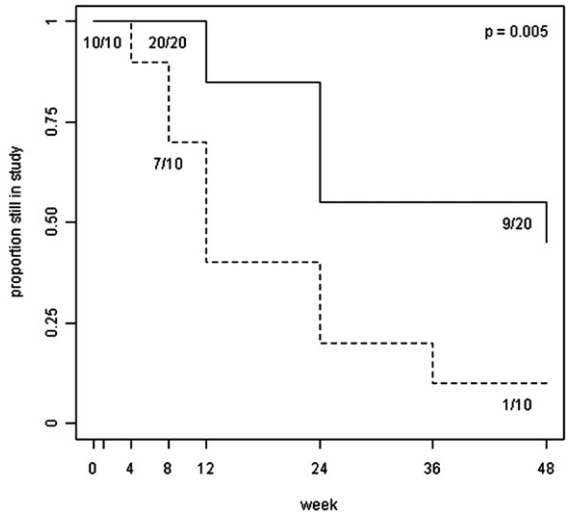

FIG 3. Proportion of patients still in the study in the mepolizumab-treated *(solid line)* and placebo *(dashed line)* groups starting at the moment of first administration.

CT scans. Fig E2 in this article's Online Repository at www.jacionline.org shows the percentage improvement in CT scan scores. An improvement was seen in more than half of the mepolizumab-treated patients and less than 20% of the placebo group compared with the baseline scans ($P = .058$, $P = .024$, and $P = .049$ for the different raters by using LOCF, Fisher exact test).

Symptom scores and nPIF

Reduction from baseline in loss of smell, postnasal drip, and congestion at week 8 was greater in the treated group than in the placebo group, but rhinorrhea stayed at the same level. Remarkably, the improvement in loss of smell stayed at the same level during the whole period of follow-up (11 months after the last dose), whereas the other symptoms normalized after a period of time. However, none of these differences were statistically significant. Fig E3 in this article's Online Repository at www.jacionline.org shows the mean CFB in nPIF, resulting in a different AUC. This suggests better values of nPIF in the mepolizumab-treated group than in the placebo group. The nPIF AUC values were also formally compared, resulting in a P value of .095 for LOCF.

Blood and serum markers

The CFB at week 8 in blood eosinophil counts ($P < .001$ for LOCF), serum ECP levels ($P = .022$ for LOCF), and serum IL-5Rα levels ($P < .001$ for LOCF) showed a significant reduction in the mepolizumab-treated versus placebo group. Evolution of serum ECP levels, blood eosinophil counts, and serum IL-5Rα levels is shown in Fig 2, whereas the individual values of week 0 and 8 are shown in Fig E4 in this article's Online Repository at www.jacionline.org.

Markers in nasal secretion

In contrast with nasal ECP ($P = .260$ using LOCF), nasal IL-5 ($P = .094$ using LOCF), and nasal total IgE ($P = .170$ using LOCF) levels at week 8, which were not significantly different between groups, nasal IL-5Rα ($P = .010$ for LOCF), nasal IL-6 ($P = .020$ for LOCF), and nasal IL-1β ($P = .043$ for LOCF) levels were significantly lower in the treated group. The CFB at week 8 in nasal MPO levels ($P = .008$ using LOCF) showed a significant reduction in the mepolizumab-treated group. Evolution of nasal IL-1β, IL-5Rα, and MPO levels is also shown in Fig 2, whereas the individual values of MPO are provided in Fig E4 as well.

Dropouts

The proportions of treated patients and patients receiving placebo still in the study at the different time points can be seen in Fig 3. There were 3 dropouts at the time of the primary end point (week 8), all of them in the placebo group. At the end of the study, there was a considerable dropout rate in both the mepolizumab and placebo arms. However, the time to dropout was significantly longer in the mepolizumab arm ($P = .005$, log-rank test vs placebo). The reasons for dropout were comparable (Table II). The most important were the need for rescue medication (5/20 in the mepolizumab-treated group and 3/10 in the placebo group) and nasal surgery with removal of NPs (4/20 in the mepolizumab-treated group and 3/10 in the placebo group), which were said to be exclusion criteria.

Responder analysis

The percentage of patients responding with an improvement in TPS at week 8 was 60% in the mepolizumab group (see Fig E5 in this article's Online Repository at www.jacionline.org). None of the baseline characteristics was significantly different between responders and nonresponders. In particular, we found no difference for baseline TPSs and local IL-5 levels ($P = .97$ and $P = .26$).

DISCUSSION

In this double-blind, randomized, placebo-controlled study we evaluated the effect of 2 intravenous injections of 750 mg of mepolizumab in patients with severe CRSwNP. This treatment produced a significant reduction in TPSs in 12 of 20 patients. These effects were confirmed by changes in CT scan evaluations. Together, the observations support a role for anti–IL-5 in a subgroup of patients with CRSwNP and confirm previous results achieved with a single injection of a different anti–IL-5 antibody, reslizumab.[18] It is possible that additional doses of mepolizumab could lead to a larger effect on nasal polyposis or even resolution of the disease in a still undefined subpopulation of patients with polyps. Moreover, the rebound eosinophilia seen with reslizumab was not observed with mepolizumab.

As previous studies showed, anti–IL-5 treatment is safe and well tolerated.[18,23,24] In our study we did not observe significant differences in adverse events between the treatment and placebo groups.

Both groups had a mean TPS of between 5 and 6 of a potential maximum of 8 points at baseline, reflecting the severity of the disease as determined by the inclusion criteria. A higher proportion of patients in the treated group improved compared with those in the placebo group at week 4, and this number increased after the second dosing. A beneficial effect was seen in more than half of the treated patients 1 month after the last dose. Because similar studies with anti–IL-5 treatment are lacking, we could

TABLE II. Overview of reasons for dropout in the mepolizumab-treated and placebo groups

	Week 8 (primary time point)		Week 48 (end of study)	
	Mepolizumab-treated group	Placebo group	Mepolizumab-treated group	Placebo group
Still in study	20/20	7/10	9/20	1/10
Rescue operation	0/20	1/10	4/20	3/10
Rescue medication	0/20	1/10	5/20	3/10
Accidental medication	0/20	1/10	1/20	1/10
Did not show up	0/20	0/10	1/20	2/10

only compare our results with those of our previous study.[18] This also showed a reduction in NP size in half of the patients. A meta-analysis testing the effect of intranasal steroids compared with placebo found a decrease in NP assessment (score of 0-3, which is comparable with our TPS without grade 4) of 0.43 to 0.63,[25] and we observed a mean decrease of 1.30 (with 4 grades instead of 3) with mepolizumab.

Of importance, the changes in the TPS were assessed objectively by using repetitive CT scans and evaluated by 3 independent observers. CT scan imaging confirmed that more than half of the patients objectively profited from this potentially new therapeutic approach.

The typical symptoms that are so characteristic of CRSwNP all showed trends toward improvement in the treated group, except rhinorrhea, but none of them reached statistical significance. Some of the effects were long lasting; the reduction in loss of smell in the treated group lasted for the whole period of follow-up. Nasal congestion seemed to improve temporarily, without reaching significance. Furthermore, nPIF changes compared with baseline values were superior in the mepolizumab-treated group, suggesting a decrease in nasal obstruction.

When analyzing systemic and local markers of eosinophilic inflammation, we found a significant decrease in blood eosinophil counts in the treated group compared with the placebo group, which was also reflected by ECP levels in sera. This is in line with the results of other studies in asthmatic patients and is considered the most important effect of the treatment in patients with hypereosinophilic syndrome.[26-28] The decrease in blood eosinophil counts was paralleled by a decrease in serum and nasal secretion IL-5Rα concentrations. Furthermore, nasal IL-6, MPO, and IL-1β levels were significantly decreased, suggesting effects of treatment also on the parameters of the neutrophilic inflammation present in patients with CRSwNP.

In contrast to reslizumab, there was no reactive eosinophilia with mepolizumab; this counterregulation clearly was of concern in former studies.[18,23] However, increasing blood eosinophil counts with associated deterioration of the clinical condition is also reported with mepolizumab.[29] The rebound eosinophilia after anti–IL-5 treatment is a result of a serum factor that enhances eosinophil survival. Reversal of this effect by the addition of anti–IL-5 suggests that this factor might be IL-5 itself.[30] We suggest that rebound eosinophilia could be avoided by the administration of multiple doses of anti–IL-5 treatment. This effect has also been seen in studies with more than 1 injection.[23,28,29] Monthly administration of this treatment is supposed to be most appropriate, stabilizing the clinical course and preventing rebound eosinophilia.[29] However, one study found that improvement in symptoms and eosinophilia lessened with each subsequent dose.[23] It remains unclear whether prolonged treatment with anti–IL-5 could be used and what the effect would be.

Because these patients have severe and disabling disease, we observed clearly more dropouts in the course of the study in the placebo group compared with the treatment group. Fig 3 shows that, at any point, the dropout rate was larger in the placebo group than in the mepolizumab-treated group. This difference was significant, indicating that dropout depends on treatment. In fact, the main reasons for exclusion were the need for systemic steroids and the need for surgery in the follow-up period, both of which were greater in the placebo group, although each reason for dropout was not statistically significant.

The comparison between responders and nonresponders did not provide the expected proof of the relationship between response to treatment and concentrations of IL-5 in nasal secretions at baseline, as seen in our previous study.[18] We also tested the effect of mepolizumab in the responder group (see the Methods and Results sections and Fig E5 in this article's Online Repository at www.jacionline.org). The decrease in TPSs in responders was significantly maintained until 36 weeks after treatment, implying a long-term effect.

One of the major study limitations is the small sample size (n = 30). This is probably the reason why we did not observe significant changes in symptom scores, although the NP and CT scan scores significantly improved. Another study limitation is the long-term dropout rate, which makes interpretation of long-term follow-up data difficult. Moreover, we only tested the administration of 2 injections of mepolizumab. More studies with a larger sample size and long-term treatment are required to determine the optimal treatment scheme for clinical use. Attention should be paid to parameters predicting treatment success because this will be of clinical relevance. We believe that anti–IL-5 treatment has great potential, especially when we succeed in predicting the patients who would respond to treatment.

In summary, 2 injections of 750 mg of anti–IL-5 mAb (mepolizumab) showed a significant improvement over placebo in the endoscopic TPS. The TPS was decreased at week 8 in 12 of 20 patients receiving mepolizumab in contrast to 1 of 10 patients receiving placebo. In addition, 11 of 20 mepolizumab-treated patients showed an improvement in CT scan scores. Furthermore, the injection of 2 doses of mepolizumab was well tolerated, and no rebound eosinophilia was observed. IL-5 inhibition seems to be a promising novel therapeutic approach in patients with severe CRSwNP, but we require more long-term studies to assess its full possibilities and indications. Better phenotyping could help to select the patients who would benefit from this treatment.

Clinical implications: Two intravenous injections with mepolizumab (anti–IL-5) significantly reduce the size of NPs based on endoscopic scoring and blinded CT scan assessment.

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METHODS

A distinction was made between responders (persons with an improved TPS of ≥1 unit at week 8 vs baseline) and nonresponders within the treated group to investigate whether there were baseline differences between them. We kept the same classification to estimate the long-term effect of the treatment. Because there were fewer dropouts in the responder group, we could reliably interpret results up to week 36. We tested for a significant CFB in TPSs within the responders at different time points using the exact Wilcoxon signed-rank test. This test was also performed on the CFB of the symptom scores at week 8 within responders.

RESULTS

The percentage of patients responding with an improvement in TPS at week 8 was 60% in the mepolizumab-treated group. At week 36, 9 of 12 responders and 2 of 8 nonresponders were still in the study ($P = .045$, log-rank test of dropout responders vs nonresponders). Among the responders, the CFB in TPS was significantly different from 0 up to week 36. The CFB in TPS for responders and nonresponders is depicted in Fig E5. The CFB in symptom scores at week 8 among responders was significantly different from 0. In particular, we found a significant decrease at week 8 versus baseline for congestion ($P = .001$), rhinorrhea ($P = .012$), and postnasal drip ($P = .020$), whereas loss of smell was also reduced but did not reach significance ($P = .079$).

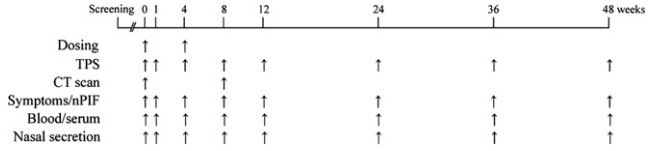

FIG E1. Study outline showing the different patient visits and the respective investigations.

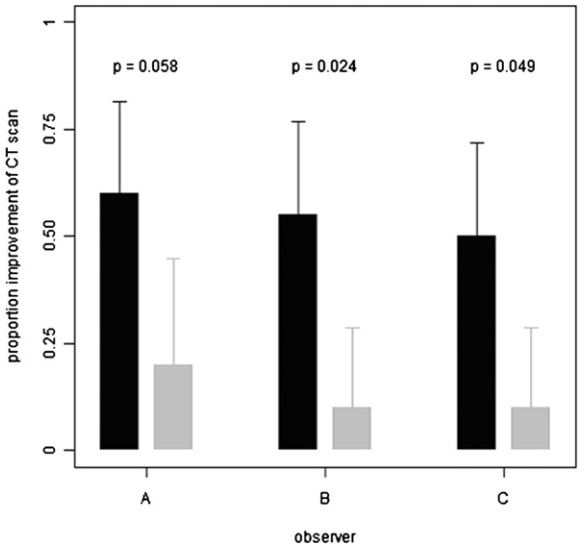

FIG E2. Proportional improvement in CT scan scores based on LOCF for the mepolizumab-treated *(black columns)* and placebo *(gray columns)* groups rated by 3 different observers (*A, B,* and *C*). *Error bars* indicate 95% CIs of the proportion based on normal approximation.

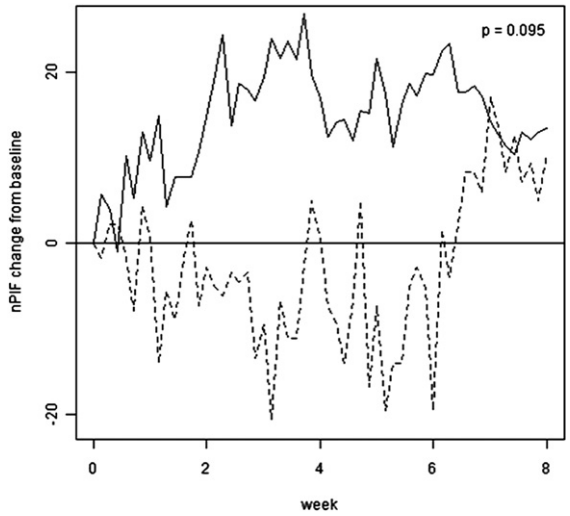

FIG E3. Mean CFB in nPIF based on LOCF for the treated *(solid line)* and placebo *(dashed line)* groups starting at the moment of first administration.

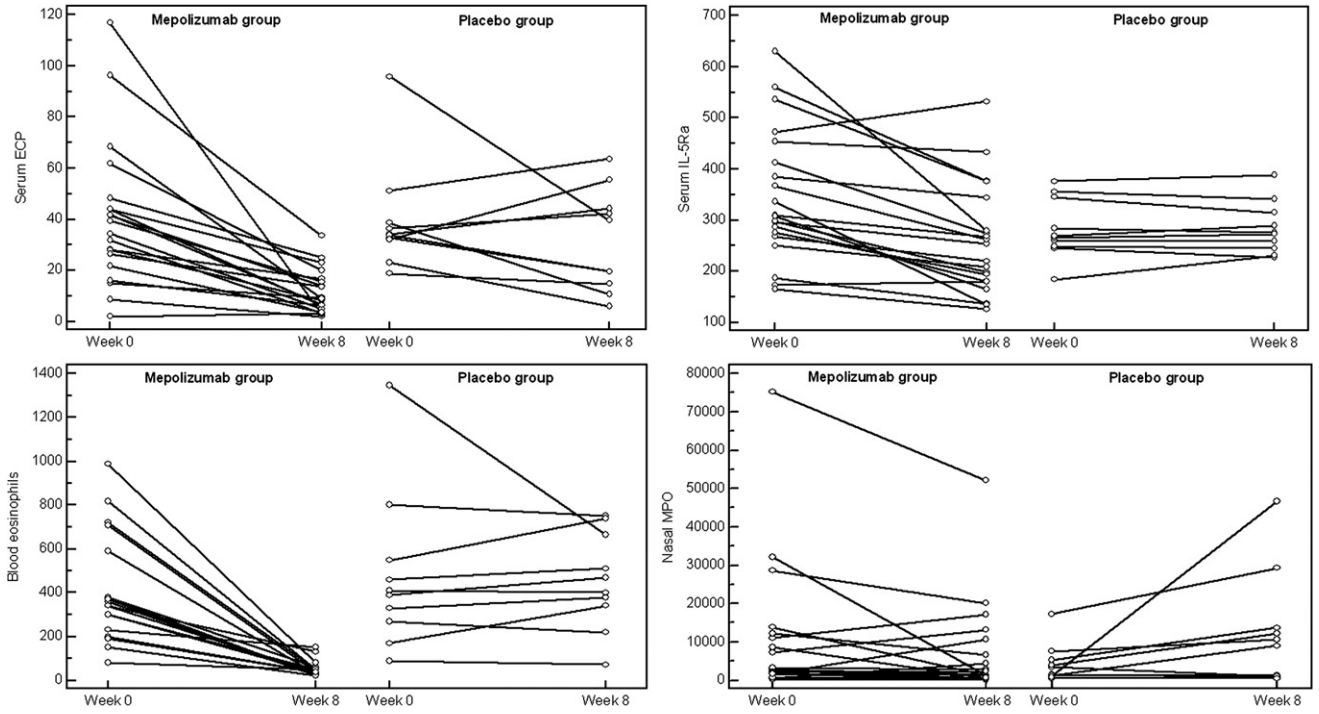

FIG E4. Individual values of serum ECP levels, blood eosinophil counts, serum IL-5Rα levels, and nasal MPO levels (all in micrograms per liter) at weeks 0 and 8 based on LOCF for the mepolizumab-treated and placebo groups.

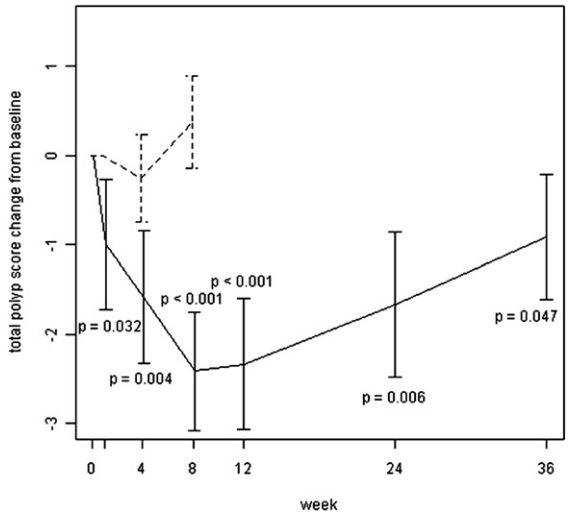

FIG E5. Mean CFB in TPS based on LOCF for responders *(solid line)* and nonresponders *(dashed line)* starting at the moment of first administration. *Error bars* indicate 95% CIs of the mean based on normal approximation.

TABLE E1. Comparison of results obtained by using the LOCF and AC paradigms in the presence of missing data

Quantity	LOCF paradigm		AC paradigm	
	Effect size	*P* value	Effect size	*P* value
TPS CFB at week 8*	−1.3 (1.51)	.028	−1.3 (1.50)	.037
Power for TPS CFB at week 8†	0.68	—	0.66	—
TPS improvement vs baseline at week 8‡	13.50	.018	26.05	.009
CT improvement, interrater reliability§	0.68	—	0.65	—
CT improvement, rater A‡	6.00	.06	3.75	.21
CT improvement, rater B‡	11.00	.024	7.33	.10
CT improvement, rater C‡	9.00	.049	6.00	.19
nPIF AUC*	1,047 (1,602)	.10	NA#	NA#
Blood eosinophil count, CFB at week 8*	−332 (241)	<.001	−413 (213)	<.001
Serum ECP level, CFB at week 8*	−2,124 (2,514)	.022	−2,425 (2,622)	.025
Serum IL-5Rα level, CFB at week 8*	−9,255 (7,520)	<.001	−9,829 (7,913)	<.001
Nasal ECP level at week 8¶	0.77	.26	0.82	.42
Nasal IL-5 level at week 8¶	0.39	.10	0.50	.31
Nasal total IgE level at week 8¶	0.61	.17	0.60	.23
Nasal IL-5Rα level at week 8¶	0.30	.010	0.38	.06
Nasal IL-6 level at week 8¶	0.44	.020	0.32	.026
Nasal IL-1β level at week 8¶	0.45	.043	0.38	.038
Nasal MPO level, CFB at week 8*	−11,891 (11,150)	.009	−12,970 (12,102)	.041
TPS, CFB within responders at week 24‖	−1.67 (1.44)	.006	−2.33 (1.30)	<.001
TPS, CFB within responders at week 36‖	−0.92 (1.24)	.047	−1.89 (1.62)	.024

*Values are presented as means (SDs), according to the exact Mann-Whitney *U* test.
†O'Brien-Castelloe approximation of *post hoc* power of Mann-Whitney *U* test.
‡Odds ratio, Fisher exact test.
§Fleiss κ coefficient.
¶Hazard ratio, Peto-Peto-Prentice test.
‖Values are presented as means (SDs), exact Wilcoxon signed-rank test.
#Not possible because of small sample remaining.

TABLE E2. Comparison of reported serious adverse events and adverse events between the mepolizumab-treated and placebo groups

	Mepolizumab-treated group (n = 20)	Placebo group (n = 10)
Serious adverse events:		
diverticulitis (preexisting)	1	0
Adverse events:		
Allergic reaction: amoxicillin–clavulanic acid	1	0
Allergic reaction: mosquito	1	0
Bronchitis	3	0
Common cold	5	1
Disc herniation (preexisting)	1	0
Fracture (arm)	1	0
Headache (3 d after injection)	1	0
Mild increased thyroid hormones (T3 and T4)	1	0
Otitis	1	0
Pain on 3 left fingers (nervus medianus)	1	0
Pharyngitis	1	0
Red swollen eyes	0	1
Short of breath	1	0
Sinusitis	2	1

Each number represents how many episodes of the event occurred in the respective group.