

Oral steroids and doxycycline: Two different approaches to treat nasal polyps

Thibaut Van Zele, MD, PhD,^{a,*} Philippe Gevaert, MD, PhD,^{a,*} Gabriele Holtappels,^a Achim Beule, MD,^d Peter John Wormald, MD,^d Susanne Mayr, MD,^c Greet Hens, MD, PhD,^b Peter Hellings, MD, PhD,^b Fenna A. Ebbens, MD, PhD,^e Wytske Fokkens, MD, PhD,^e Paul Van Cauwenberge, MD, PhD,^a and Claus Bachert, MD, PhD^a Ghent and Leuven, Belgium, Erlangen-Nuremberg, Germany, Adelaide, Australia, and Amsterdam, The Netherlands

Background: There is little scientific evidence to support the current practice of using oral glucocorticosteroids and antibiotics to treat patients with chronic rhinosinusitis and nasal polyps.

Objective: We evaluated the effects of oral glucocorticoids and doxycycline on symptoms and objective clinical and biological parameters in patients with chronic rhinosinusitis and nasal polyps.

Methods: In a double-blind, placebo-controlled, multicenter trial, we randomly assigned 47 participants with bilateral nasal polyps to receive either methylprednisolone in decreasing doses (32–8 mg once daily), doxycycline (200 mg on the first day, followed by 100 mg once daily), or placebo for 20 days.

Participants were followed for 12 weeks. Patients were assessed for nasal peak inspiratory flow and symptoms and by nasal endoscopy. Markers of inflammation such as eosinophilic cationic protein (ECP), IL-5, myeloperoxidase, matrix metalloproteinase 9, and IgE were measured in nasal secretions. Concentrations of eosinophils, ECP, and soluble IL-5 receptor α were measured in peripheral blood samples.

Results: Methylprednisolone and doxycycline each significantly decreased nasal polyp size compared with placebo. The effect of methylprednisolone was maximal at week 3 and lasted until week 8, whereas the effect of doxycycline was moderate but present for 12 weeks. Methylprednisolone significantly reduced

levels of ECP, IL-5, and IgE in nasal secretions, whereas doxycycline significantly reduced levels of myeloperoxidase, ECP, and matrix metalloproteinase 9 in nasal secretions.

Conclusion: This is the first double-blind, placebo-controlled study to show a significant effect of oral methylprednisolone and doxycycline on size of nasal polyps, nasal symptoms, and mucosal and systemic markers of inflammation. (J Allergy Clin Immunol 2010;125:1069–76.)

Key words: Randomized controlled trial, placebo-controlled, double blind, methylprednisolone, doxycycline, *Staphylococcus aureus*, nasal polyposis, chronic rhinosinusitis, double-blind placebo-controlled, corticosteroids, antibiotics

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a disease of the sinuses characterized by mucosal thickening and polyp formation; it is frequently associated with asthma and aspirin intolerance.¹ The cause of nasal polyposis is not known, but 80% of Caucasian patients have major eosinophilic inflammation with a T_H2 cytokine profile, and bacterial superantigens might modulate disease severity.^{2–4}

Glucocorticosteroids have potent anti-inflammatory action and are the most common treatment for patients with CRSwNP. Placebo-controlled studies have shown that topical corticosteroid therapy reduces polyp size,^{5–7} nasal symptoms,^{8,9} and number of recurrences after polypectomy.^{10,11} However, topical corticosteroid therapy is not effective in all patients, leading to the use of systemic glucocorticosteroids and/or sinus surgery to control the disease. Although it is generally accepted that oral steroids are efficient for treatment of CRSwNP, only 1 placebo-controlled trial was conducted¹²; this short trial demonstrated the efficacy of a 2-week course of oral corticosteroids on symptoms and polyp size. However, the efficacy of a longer-term, single course of treatment and the local anti-inflammatory effects are unknown.

As a new approach, antibiotics are being used to treat CRSwNP—particularly in patients with disease exacerbated by the *Staphylococcus aureus* enterotoxin.² Antibiotics with anti-inflammatory effects can be used to treat patients with chronic rhinosinusitis without polyps, which might the precursor to CRSwNP. Several studies have shown the effect of macrolide antibiotics in patients with nasal symptoms^{13–15}; long-term treatment with these drugs, in selected cases, may be effective when corticosteroids fail.¹

We tested the effects of doxycycline in patients with CRSwNP. It was chosen because of its dual action: it has well described, broad-spectrum antibacterial activity against *S aureus* as well as

From ^athe Department of Otorhinolaryngology, University Hospital Ghent; ^bthe Department of Otorhinolaryngology, University Hospital St. Rafael, Leuven; ^cthe Department of Otorhinolaryngology, Head and Neck Surgery, Friedrich-Alexander University, Erlangen-Nuremberg; ^dthe Department of Surgery-Otorhinolaryngology, Adelaide University; and ^ethe Department of Otorhinolaryngology, Academic Medical Center, Amsterdam.

*These authors contributed equally to this work.

Supported by a grant from the Flemish Scientific Research Board, FWO Nr. A12/5-HB-KH 3 (holder of a Fundamenteel Klinisch Mandaat), by a postdoctoral grant from the Research Foundation Flanders (FWO), and by postdoctoral mandate from the Research Foundation Flanders (FWO).

Disclosure of potential conflict of interest: P. J. Wormald has received royalties from Medtronic ENT, is a consultant for NeilMed, and has received research support from the Garnett Passe and Rodney Williams Foundation. W. Fokkens has received research support from GlaxoSmithKline and Stallergenes. A. Beule has received research support from the European Union. The rest of the authors have declared that they have no conflict of interest.

Received for publication June 3, 2009; revised January 25, 2010; accepted for publication February 2, 2010.

Reprint requests: Thibaut Van Zele MD, PhD, Department of Otorhinolaryngology, Upper Airways Research Laboratory, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium. E-mail: thibaut.vanzele@ugent.be.

0091-6749/\$36.00

© 2010 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.02.020

Abbreviations used

CRSwNP: Chronic rhinosinusitis with nasal polyps
 ECP: Eosinophilic cationic protein
 IL-5R α : IL-5 receptor α
 MMP: Matrix metalloproteinase
 NPIF: Nasal peak inspiratory flow

anti-inflammatory properties. It appears to be effective in treatment of several chronic inflammatory airway diseases.¹⁶ Double-blind, randomized, placebo-controlled trials with long-term follow-up studies have not been conducted for treatment of CRSwNP with glucocorticosteroids and doxycycline; we evaluated the efficacy and anti-inflammatory effects of oral methylprednisolone and doxycycline in patients with CRSwNP.

METHODS**Patients**

Forty-seven patients were recruited from January 2003 to March 2006 at 4 ear, nose, and throat departments in Europe (University Hospital Ghent, Belgium; University Hospital Leuven, Belgium; University Hospital Erlangen, Germany; the Academic Medical Center, Amsterdam, The Netherlands) and 1 in Australia (Queen Elizabeth Hospital, Adelaide, Australia). Patients were eligible to participate if they had recurrent bilateral nasal polyps after surgery or massive bilateral nasal polyps (grade 3 or 4; see this article's [Table E1](#) in the Online Repository at www.jacionline.org), were in good health, and were free of diseases that would interfere with the study. Patients were included only if none of the exclusion criteria were present (see this article's [Table E2](#) in the Online Repository at www.jacionline.org). The use of systemic or local corticosteroids or antibiotics was not allowed during the study; if necessary, patients were permitted to use nasal corticosteroids as rescue medication 2 months after dosing with the study medication. All patients provided written informed consent. The protocol was approved by the ethics committees of all participating sites. The trial was undertaken in compliance with Good Clinical Practice guidelines and the ethics principles set out in the Declaration of Helsinki.

Randomization and study scheme

Eligible patients were randomly assigned to 3 groups by individuals not involved in the study. Groups were given either oral methylprednisolone (32 mg/d on days 1-5; 16 mg/d on days 6-10; and 8 mg/d on days 11-20), oral doxycycline (200 mg on day 1, 100 mg/d on days 2-20), or placebo (lactose) in unlabeled capsules. The therapeutic regimen was selected on the basis of the doxycycline package information and evidence of tissue penetration.¹⁷ Follow-up visits were scheduled for 1, 2, 4, 8, and 12 weeks after dosing (see this article's [Fig E1](#) in the Online Repository at www.jacionline.org). Baseline assessments included collection of patients' full medical history and examinations; ear, nose, and throat inspections; skin prick testing; pregnancy testing; nasal endoscopy examinations; counts of eosinophils in peripheral blood samples; and analyses of nasal secretions. Study personnel and participants were blind for the duration of the study; randomization codes were revealed to researchers after recruitment, data collection, and data entry.

Outcome measures

The key outcome measure was nasal polyp score, determined from nasal endoscopy examination. Polyps were graded on the basis of a size grading system and given scores of 0 to 4 ([Table E1](#)). The total nasal polyp score is defined as the sum of the scores from the right and left nostrils. Nasal peak inspiratory flow (NPIF) measurements (Clement Clark International, Harlow,

United Kingdom) and symptoms (anterior rhinorrhea, nasal obstruction, post-nasal drip, and loss of sense of smell) were recorded. Eosinophil counts were measured with an automated system from a 4.5-mL heparinized blood sample. IL-5, IgE, matrix metalloproteinase (MMP)-9, and eosinophilic cationic protein (ECP) were quantified in nasal secretions. First, sinus packs (IVALON 4000 Plus 3.5 $\times$ 0.9 $\times$ 1.2 cm surgical products M-Pact, Eudora, Kan) were placed in both nasal cavities for exactly 5 minutes following previously described methods.¹⁸ Nasal secretions were collected, and IgE and ECP were measured by the UNICAP system (Pharmacia, Uppsala, Sweden). Serum and nasal secretions were assayed by using an ELISA for soluble IL-5 receptor α (IL-5R α ; Innogenetics, Ghent, Belgium), IL-5, MMP-9 (R&D Quantikine ELISA; Minneapolis, Minn), and myeloperoxidase (Oxis International, Portland, Ore). The values obtained by ELISA were corrected with a dilution factor.

Statistical analysis

The statistical analysis of efficacy was based on all randomized subjects in this study (intention-to-treat). Missing observations were replaced by the last nonmissing observation carried forward. Data are expressed as means and SEMs. The Student *t* test was used to compare baseline values between groups. The χ^2 method was used to compare the frequencies of rescue medication and early study termination between groups. Pairwise treatment comparisons were obtained from a 2-way ANOVA analysis by using data on treatment and site effects. Changes in clinical and biological parameters were evaluated by repeated-measures ANOVA analyses. Differences were considered to be statistically significant if *P* values were less than .05. All statistical analyses were performed by using SPSS 11.0 for Macintosh (Chicago, Ill).

RESULTS**Baseline characteristics and adverse events**

Forty-seven patients met the study eligibility criteria and were randomly assigned to study groups. The patient population consisted of patients with a mean total polyp score of 6.16 in the placebo group (*n* = 19), 5.86 in the methylprednisolone group (*n* = 14), and 5.93 in the doxycycline group (*n* = 14). Overall clinical characteristics did not differ significantly at baseline ([Table I](#)), although the placebo group included a nonsignificantly higher percentage of aspirin-intolerant patients. None of the patients in the groups given methylprednisolone or doxycycline left the study, but 7 patients in the placebo group withdrew from the study after week 4. Reasons for withdrawal included unsatisfactory therapeutic effects, withdrawal of consent, and serious adverse events (2 cases of asthma exacerbation that required treatment with oral steroids; see this article's [Table E3](#) in the Online Repository at www.jacionline.org); 48.5% of the subjects in the study reported at least 1 adverse event. There were no significant differences in the number or type of adverse events between treatment groups or between treatment and placebo groups.

Clinical efficacy

After 1 week, a significant reduction of polyp size was observed in the group given methylprednisolone compared with the group given placebo (visit 2; *P* = .002), with a maximal reduction in polyp size after 2 weeks of treatment (*P* < .0001; cf [Fig 1](#)). The polyps began to recur after 2 weeks, but the methylprednisolone group still had a modest but significant reduction in polyp score compared with the placebo group (visit 5; *P* = .011) until month 2. After 3 months, no significant effect of methylprednisolone on polyp size was observed compared with placebo and baseline values. All nasal polyps initially responded with a reduction in

TABLE I. Baseline and clinical characteristics of subjects and need for rescue treatment after visit 4

	Placebo (n = 19)	Methylprednisolone (n = 14)	Doxycycline (n = 14)	P value
Baseline characteristics				
Male sex, n (%)	15 (78.9)	12 (85.7)	11 (78.6)	.672
Age (y), mean (SEM)	54.67 (3.07)	48.89 (3.23)	55.04 (4.28)	.208
Allergy, n (%)	11 (57.9)	5 (35.7)	2 (14.3)	.154
Asthma, n (%)	5 (26.3)	6 (42.9)	4 (28.6)	.465
Aspirin intolerance, n (%)	5 (26.3)	2 (14.3)	1 (7.1)	.426
Current smoker, n (%)	2 (10.5)	4 (28.6)	3 (21.4)	.365
Recurrence, n (%)	11 (57.9)	11 (78.6)	6 (42.9)	.446
Clinical characteristics				
Total polyp score, mean (SEM)	6.16 (0.29)	5.86 (0.27)	5.93 (0.37)	.470
Congestion, mean (SEM)	1.89 (0.23)	1.93 (0.30)	1.57 (0.31)	.928
Loss of smell, mean (SEM)	2.63 (0.14)	2.29 (0.29)	1.79 (0.30)	.245
Rhinorrhea, mean (SEM)	1.84 (0.20)	1.14 (0.23)	1.5 (0.31)	.071
Postnasal drip, mean (SEM)	1.58 (0.22)	1.36 (0.22)	1.64 (0.29)	.496
Nasal inspiratory flow, mean (SEM)	78.75 (13.16)	67.08 (14.95)	80.0 (18.2)	.564
Blood				
Eosinophils (%), mean (SEM)	5.7 (0.73)	5.9 (1.27)	5.09 (1.51)	.500
ECP (μg/L), mean (SEM)	20.96 (3.18)	19.77 (3.18)	14.36 (2.05)	.251
Soluble IL-5Rα (pg/mL), mean (SEM)	317.46 (37.04)	303.42 (21.82)	267.51 (30.73)	.522
Nasal secretion				
ECP (μg/L), mean (SEM)	362.87 (117.26)	515.62 (229.62)	853.56 (600.52)	.596
IgE (kU/L), mean (SEM)	158.23 (91.68)	84.38 (43.57)	23.84 (11.75)	.355
IL-5 (pg/mL), mean (SEM)	88.07 (41.95)	46.48 (20.78)	23.84 (11.76)	.518
MMP-9 (ng/mL), mean (SEM)	2,559.43 (1,056.03)	5,440.04 (2,811.37)	9,398.88 (6,283.58)	.421
Myeloperoxidase (ng/mL), mean (SEM)	6,808.53 (3,742.65)	18,539.36 (11,848.27)	22,001.33 (14,589.26)	.528
Need for rescue treatment after visit 4				
Rescue surgery, n/N	6/19	0/14	2/14	.15
Rescue nasal steroids, n/N	4/19	2/14	2/14	.88

size of at least 1 unit; however, after 3 months, nasal polyps recurred or grew back to their original size in all patients.

Administration of doxycycline for 20 days significantly reduced polyp size, starting at week 2, compared with placebo (visit 3; $P = .005$). The significant reduction of polyp size remained for up to 12 weeks after dosing (visit 4, $P = .001$; visit 5, $P = .002$; and visit 6, $P = .015$). Daily measurements of NPIF revealed significantly greater area under the curve values for methylprednisolone compared with placebo (2043 vs -154.3 ; $P = .023$). The area under the curve of for doxycycline (530) indicated a small but insignificant increase in NPIF over the entire study period (Fig 1).

Compared with placebo, subjects given methylprednisolone reported a decrease in nasal congestion after 1 week (visit 2; $P = .002$), 2 weeks (visit 3; $P = .007$), and 4 weeks (visit 4; $P = .001$). Congestion scores worsened progressively after week 4 and returned to baseline values. Similar trends were observed for postnasal drip symptoms (methylprednisolone vs placebo: $P = .031$ at visit 2, $P = .007$ at visit 3, and $P = .001$ at visit 4) and loss of smell (methylprednisolone vs placebo: $P = .006$ at visit 2; $P = .001$ at visit 3, and $P = .006$ at visit 4), whereas methylprednisolone treatment had no significant effect on rhinorrhea compared with placebo. Doxycycline treatment significantly reduced postnasal drip symptom scores at week 2 (visit 3; $P = .044$) and induced an almost significant reduction in rhinorrhea at week 8 (visit 5; $P = .058$; cf Fig 2).

Anti-inflammatory effects

Methylprednisolone treatment significantly decreased numbers of eosinophils in blood samples compared with placebo starting at

week 1 (visit 2; $P < .0001$), with a maximal decrease at 2 weeks (visit 3; $P < .0001$; cf Fig 3). Blood eosinophils counts returned to baseline levels at month 1 and were above baseline levels at month 2 and 3; this rebound eosinophilia was observed in 11 of 13 patients. Serum ECP and soluble IL-5Rα levels paralleled blood eosinophil counts and decreased significantly with methylprednisolone therapy for up to 4 weeks. In contrast, doxycycline had no effect on blood eosinophil counts and/or serum levels of ECP. However, serum levels of soluble IL-5Rα were significantly decreased at 1 month in patients given doxycycline (visit 4; $P = .01$) compared with those given placebo.

In nasal secretions, ECP levels decreased significantly in the methylprednisolone group at week 1 (visit 2; $P = .016$) and month 1 (visit 4; $P = .024$) and in the doxycycline group at 1 month (visit 4; $P = .032$), whereas they increased after 1 week in the placebo group. A small but significant reduction in IL-5 was observed in the methylprednisolone group at weeks 1, 2, and 4 compared with placebo (visit 2, $P = .037$; visit 3, $P = .027$; and visit 4, $P = .018$, respectively; Fig 4), whereas doxycycline treatment did not change IL-5 levels.

IgE levels in the treated groups were significantly lower compared with placebo at weeks 2 and 4 (visit 3, $P = .016$, and visit 4, $P = .003$, for methylprednisolone; $P = .043$ and $P = .003$, respectively, for doxycycline; Fig 4); however, these significances were mainly a result of an increase of IgE in the placebo group.

Doxycycline caused a significant decrease in levels of myeloperoxidase and MMP-9 in nasal secretions compared with placebo (Fig 4). MMP-9 levels decreased dramatically at week 1 (visit 2; $P = .025$) and week 2 (visit 3; $P = .028$) and myeloperoxidase

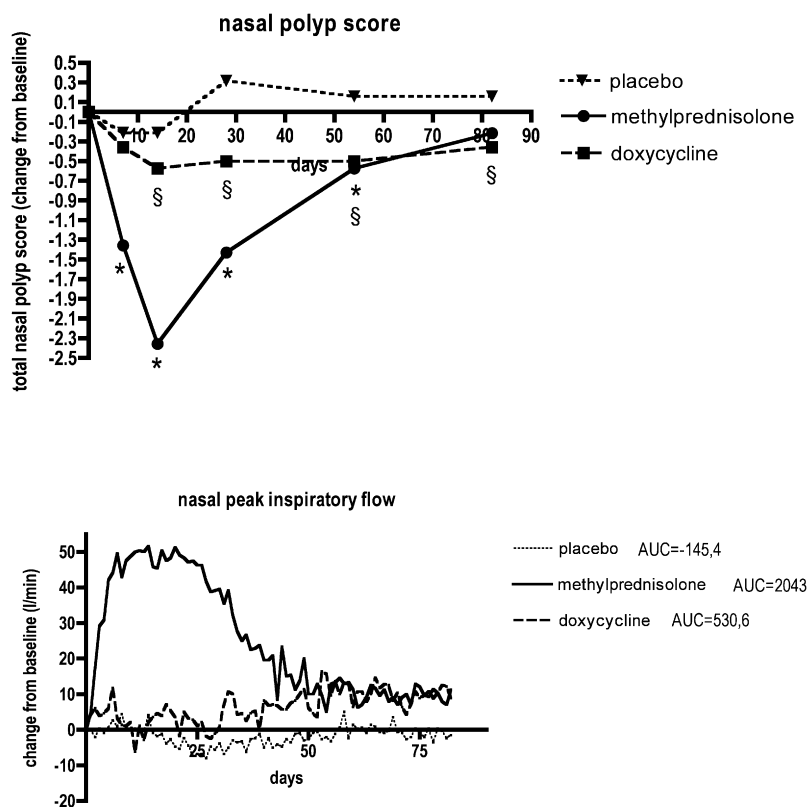


FIG 1. Polyp size after treatment with methylprednisolone (solid circles) vs placebo (solid triangles) or doxycycline (solid squares) vs placebo. The mean changes from baseline were significantly different between the methylprednisolone and placebo groups (* $P < .05$) and between the doxycycline and placebo groups (§ $P < .05$). NPIF values were affected by methylprednisolone (solid circles) compared with placebo (solid triangles) and doxycycline (solid squares) compared with placebo. Area under the curve (AUC) values were calculated for methylprednisolone, doxycycline, and placebo, including negative peaks.

levels were significantly reduced from week 1 until week 8 compared with placebo ($P = .006$ for visit 2, $P = .017$ for visit 3, $P = .016$ for visit 4, and $P = .022$ for visit 5). Methylprednisolone treatment did not change MMP-9 levels in nasal secretions but did tend to reduce myeloperoxidase production.

DISCUSSION

We investigated whether the antibiotic doxycycline could decrease nasal polyp size and improve symptoms and local inflammation in patients with CRSwNP. We also investigated the duration of symptomatic improvement and polyp size reduction after a short course of oral methylprednisolone. Doxycycline and methylprednisolone each significantly reduced the size of nasal polyps and local inflammation. However, polyps and symptoms recurred rapidly in the group given methylprednisolone; polyp size reached baseline values by 3 months after therapy with oral methylprednisolone began. Loss of smell and congestion were the major and most disabling complaints among patients with nasal polyposis¹⁹; we observed that although methylprednisolone significantly improved these symptoms, they rapidly worsened after the last dose.

Several uncontrolled studies have demonstrated the effects of oral corticosteroids on nasal polyps,²⁰⁻²⁴ but there have been no double-blind, placebo-controlled studies and only level III evidence for the effectiveness of oral corticosteroids.²⁵ A double-

blind, placebo-controlled study by Hissaria et al¹² reported a significant effect of 14 days of therapy with 50 mg prednisolone on nasal polyp size and symptoms (on the basis of a standardized patient questionnaire) compared with placebo. However, this study did not monitor subjects for recurrence of polyps and symptoms after dosing. The conclusion that oral corticosteroids have a significant effect on nasal symptoms and polyp size is therefore generally accepted—our study is the first to show a partial recurrence of polyps after a treatment period of 20 days and a total recurrence after 3 months in all the patients.

An open-label study by van Camp and Clement²⁰ showed that polyps tended to recur after 5 months of treatment with oral prednisolone. The longer durations of effects they observed might have resulted from the higher dose of glucocorticosteroids they gave to patients compared with this study. Our study shows that oral corticosteroids, given as single agents, have short-term effects on symptoms and polyp size, necessitating repeated treatments. Short-term therapy with corticosteroids is generally safe but has been associated with avascular necrosis on rare occasions.²⁶ Short-term therapy with oral steroids should not be given more than 3 or 4 times per year.¹ Prolonged topical treatment with intranasal corticosteroids is necessary to maintain the initial improvement in polyp size and symptoms.

Our study is also the first to show local and systemic, *in vivo* anti-inflammatory effects of oral corticosteroids on nasal polyps.

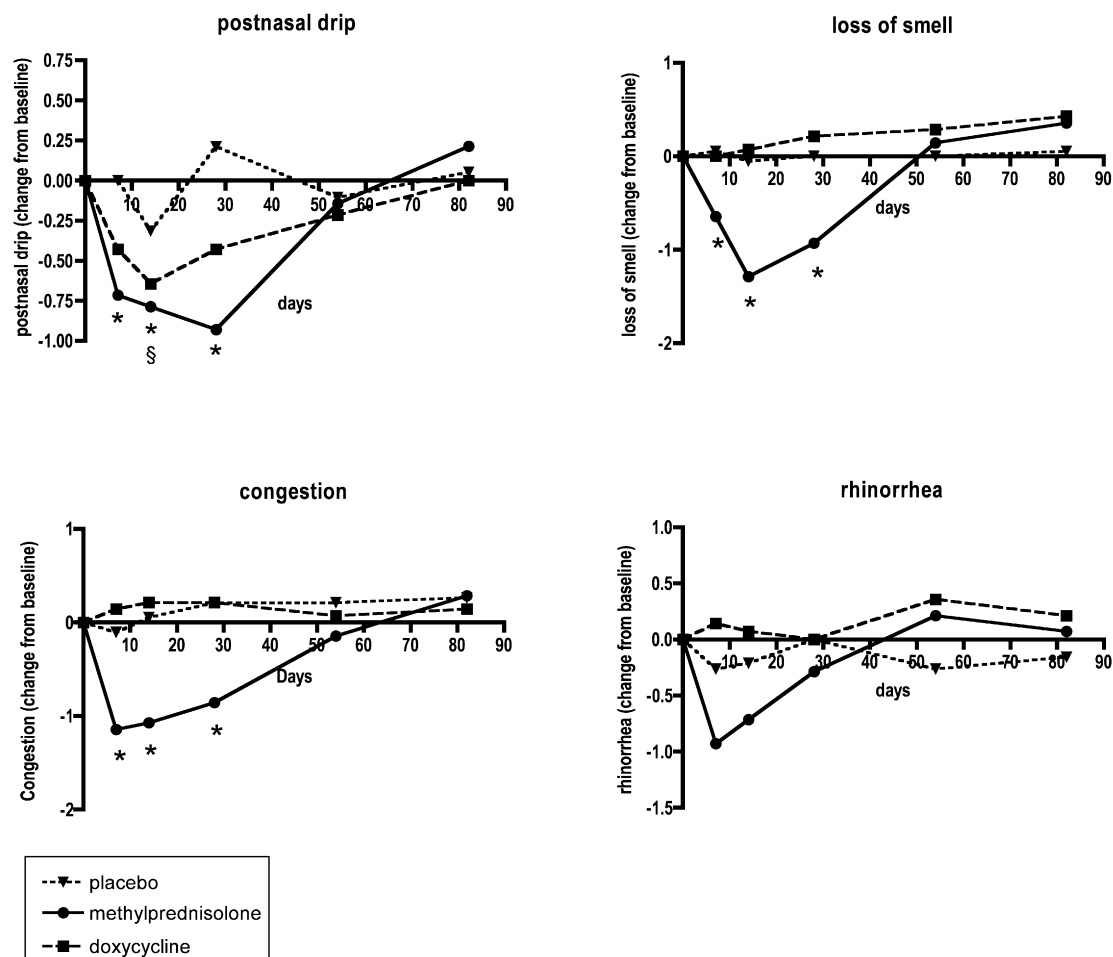


FIG 2. Nasal symptoms after treatment with methylprednisolone (solid circles) vs placebo (solid triangles) or doxycycline (solid squares) vs placebo. The mean changes from baseline were significantly different between the methylprednisolone and placebo groups (* $P < .05$) and between the doxycycline and placebo groups (§ $P < .05$).

Only small and temporarily significant decreases in IL-5, ECP, and IgE concentrations were observed in nasal secretions from patients treated with methylprednisolone compared with subjects given placebo. However, the significance of this difference was likely to result from increases of these mediators in the placebo group rather than a clear decrease in the methylprednisolone group. These data indicate that eosinophil-mediated inflammation worsens over time in untreated patients—all patients had to terminate the use of topical corticosteroids before the study began.

Oral corticosteroids were only capable of stabilizing IgE levels and preventing further increases, whereas levels of ECP and IL-5 tended to increase after visit 2. This finding is not in agreement with *in vitro* studies indicating that oral corticosteroids might significantly reduce ECP concentrations and shrink nasal polyps.²⁷ Oral corticosteroids have little effect on local anti-inflammatory responses, which might explain their short-term effects on polyp size and symptoms and the quick recurrence of polyps (within 2 months after treatment).

Oral corticosteroids have a potent effect on concentrations of eosinophils in the peripheral blood; levels were quickly reduced after the first week of methylprednisolone treatment but increased

rapidly after the last dose, reaching levels above baseline at visits 5 and 6. Almost all patients in the methylprednisolone group had this rebound effect, which paralleled the recurrence of polyps and symptoms. The exact mechanism of this rebound inflammation is unclear but these effects were also observed in trial of anti-IL-5 in patients with nasal polyps.²⁸

Another important aspect of this study is the clinical effect of doxycycline on bilateral nasal polyposis. Administration of doxycycline for 20 days significantly reduced polyp size at 1 month, which was maintained to the end of the follow-up period (week 12). This reduction in polyp size after 20 days of doxycycline treatment is similar to that observed after 4 weeks of therapy with mometasone furoate.²⁹ Doxycycline also significantly reduced postnasal drip but had no effect on other symptoms. This might have resulted from a small but progressive reduction in polyp size; we expect that longer-term treatment or higher doses would improve symptoms and outcomes.

The dose of doxycycline used in this study was selected on the basis of the antimicrobial effects of 100 mg, but inflammation and underlying tissue destruction were also dramatically reduced, even in patients given low doses of the drug (40 mg). The anti-inflammatory action of doxycycline is thought to be caused by

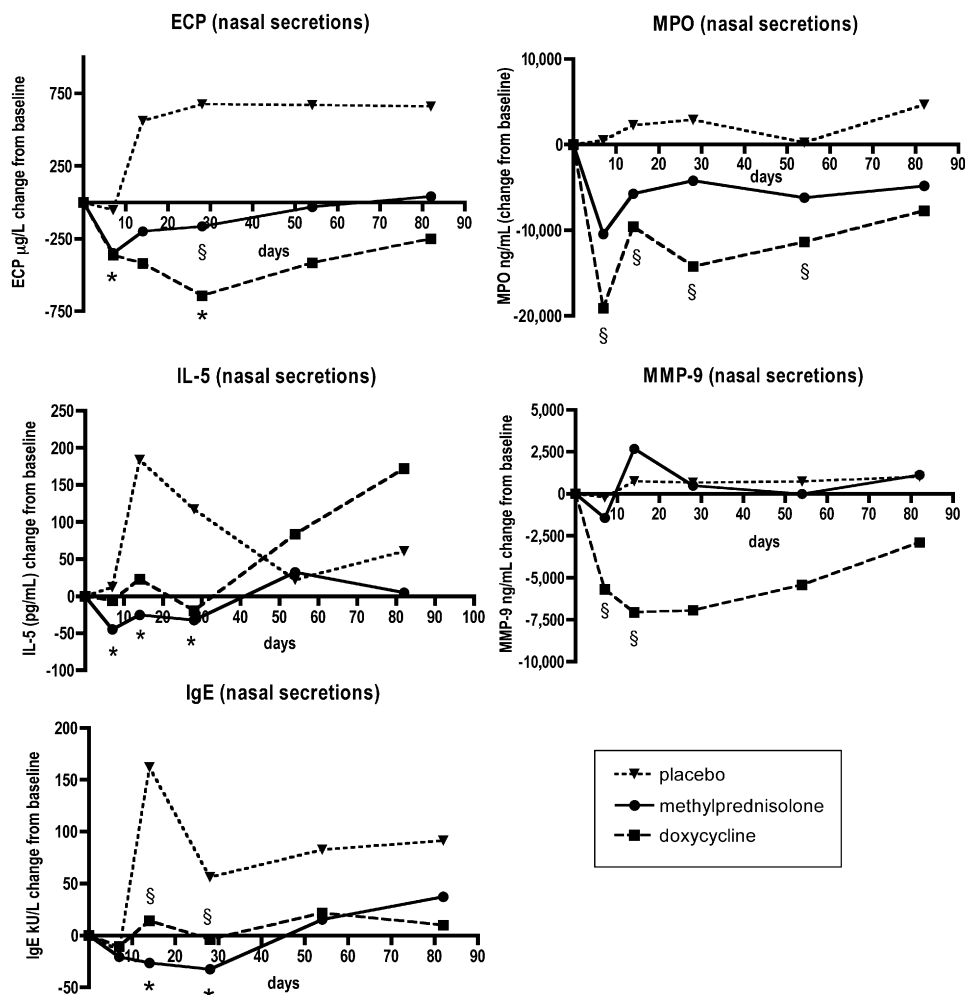


FIG 3. Serum inflammatory parameters, blood eosinophilia, serum soluble IL-5R α , and serum ECP levels after treatment with methylprednisolone (solid circles) vs placebo (solid triangles) or doxycycline (solid squares) vs placebo. The mean changes from baseline were significantly different between the methylprednisolone and placebo groups (* $P < .05$) and between the doxycycline and placebo groups (§ $P < .05$). MPO, Myeloperoxidase.

inhibition of the collagenase activity of 1 or more MMPs.¹⁶ In nasal polyps, the ratio of MMP-9 to its inhibitor (tissue inhibitor of metalloproteinase 1) TIMP-1 is higher than in normal tissues, leading to matrix degradation, edema, and chronic inflammation.³⁰ In this study, doxycycline significantly reduced levels of MMP-9 in nasal secretions, reducing the damage to nasal polyp tissue and eventually polyp size. The ability of doxycycline to reduce ECP reflects the downregulation of eosinophil degranulation, whereas the reduction of myeloperoxidase reflects reduced neutrophilic activity. These events could be related to antimicrobial activity against pathogens such as *S aureus*. However, collection of multiple nasal swabs would have been required to confirm this relationship, which would have reduced the patient compliance.

Doxycycline was administered by aerosols to a mouse model of asthma; it decreased allergen-induced airway inflammation and hyperresponsiveness and inhibited the development of bronchial remodeling by downregulating production of IL-5 and IL-13 and activity of MMPs.³¹ Interestingly, doxycycline also inhibits immunoglobulin production by reducing terminal B-cell differentiation and class switching.³² Given the increased levels of local IgG, IgE, and IgA levels in nasal polyps,³³ doxycycline inhibition

might mediate the low levels of IgE observed in nasal secretions from patients given doxycycline compared with the steady increase in IgE levels observed in controls. These antimicrobial and anti-inflammatory effects might cause a decrease in size of nasal polyps.

Doxycycline has great potential for extended use—its long half-life permits once-daily dosing, it has excellent bioavailability, and blood and tissue levels are equal in patients given oral or intravenous doses of the drug. Long-term treatment with doxycycline alone, or in combination with intranasal corticosteroids, might be required for greater improvement of symptoms. Because this was a proof-of-concept study for doxycycline, patients did not receive nasal corticosteroids during treatment, which would have influenced the nasal polyp score, symptoms, and the local release of cytokines and mediators. Further studies should mimic current clinical practices as much as possible.

Even though the patients in this study were randomly assigned to groups, the placebo group included a higher percentage of aspirin-intolerant patients. However, statistical analyses that excluded all aspirin-intolerant patients yielded essentially similar results to the overall study. Therefore, the disproportionate

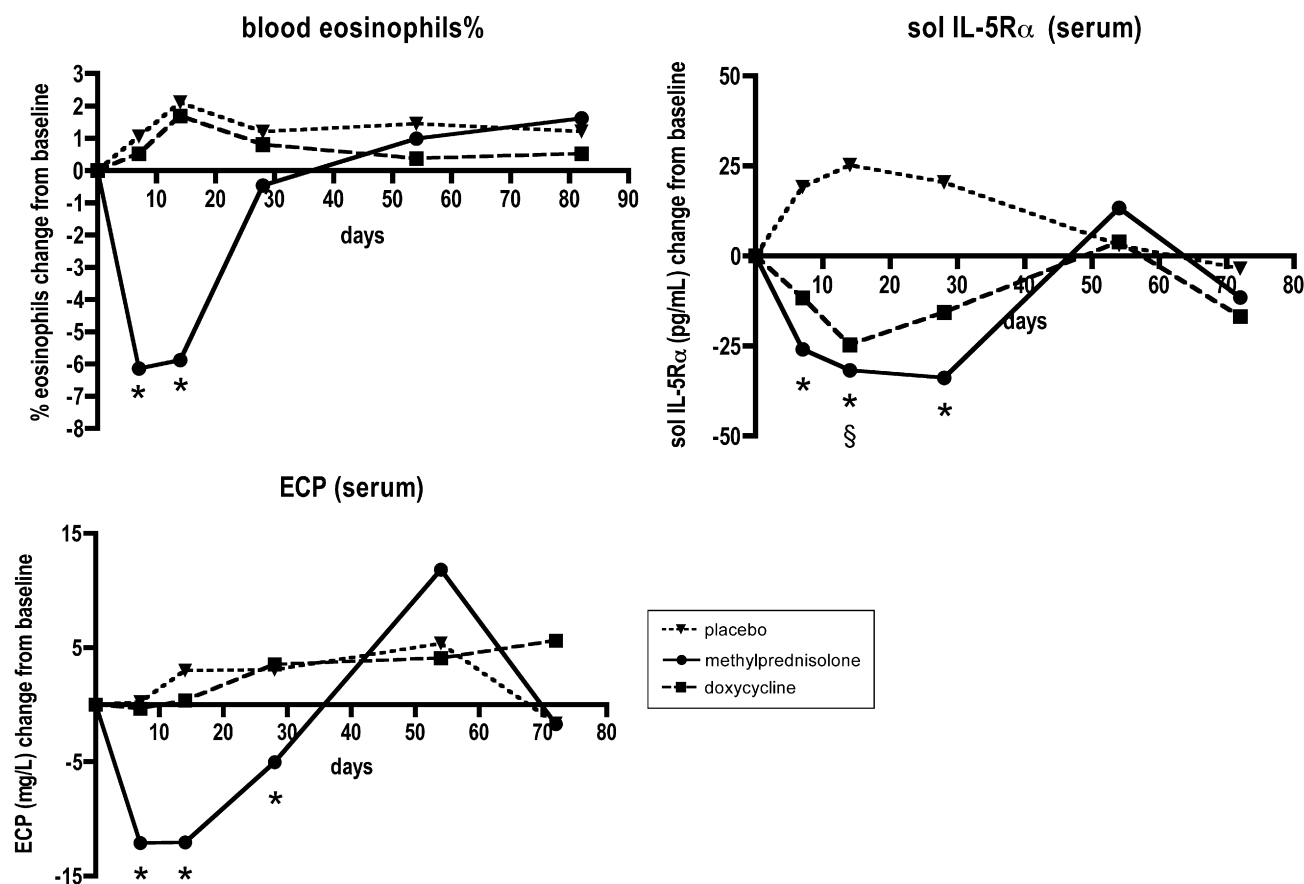


FIG 4. Inflammatory markers in nasal secretions after treatment with methylprednisolone (solid circles) vs placebo (solid triangles) or doxycycline (solid squares) vs placebo. The mean changes from baseline were significantly different between the methylprednisolone and placebo groups (* $P < .05$) and between the doxycycline and placebo groups (§ $P < .05$). sol, Soluble.

number of aspirin-intolerant patients in the placebo group did not affect the conclusions.

This study highlights the need for long-term studies with doxycycline to establish their therapeutic role in the treatment of nasal polyposis and to improve treatment standards. Treatment of nasal polyps with oral corticosteroids is of limited value unless it is associated with surgery or therapy with intranasal corticosteroids.

Clinical implications: Oral doxycycline causes a long-term reduction in nasal polyp size, whereas methylprednisolone causes an initial reduction in polyp size but complete recurrence after 2 months.

REFERENCES

1. Fokkens W, Lund V, Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007: a summary for otorhinolaryngologists. *Rhinology* 2007;45:97-101.
2. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. *J Allergy Clin Immunol* 2004;114:981-3.
3. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* 2006;61:1280-9.
4. Bachert C, Gevaert P, van Cauwenberge P. Staphylococcus aureus superantigens and airway disease. *Curr Allergy Asthma Rep* 2002;2:252-8.
5. Vendelo Johansen L, Illum P, Kristensen S, Winther L, Vang Petersen S, et al. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. *Clin Otolaryngol Allied Sci* 1993;18:524-7.
6. Tos M, Svendstrup F, Arndal H, Orntoft S, Jakobsen J, Borum P, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. *Am J Rhinol* 1998;12:183-9.
7. Holopainen E, Grahne B, Malmberg H, Makinen J, Lindqvist N. Budesonide in the treatment of nasal polyposis. *Eur J Respir Dis Suppl* 1982;122:221-8.
8. Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin Allergy* 1975;5:159-64.
9. Deuschl H, Drettner B. Nasal polyps treated by beclomethasone nasal aerosol. *Rhinology* 1977;15:17-23.
10. Dingsor G, Kramer J, Olsholt R, Soderstrom T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy: a randomized, double blind, parallel, placebo controlled study. *Rhinology* 1985;23:49-58.
11. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. *Rhinology* 1980;18:9-18.
12. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol* 2006;118:128-33.
13. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl* 1996;525:73-8.
14. Legent F, Bordine P, Beauvillain C, Berche P. A double-blind comparison of ciprofloxacin and amoxicillin/clavulanic acid in the treatment of chronic sinusitis. *Chemotherapy* 1994;40(suppl 1):8-15.
15. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. *Am J Rhinol* 2002;16:303-12.

16. Rempe S, Hayden JM, Robbins RA, Hoyt JC. Tetracyclines and pulmonary inflammation. *Endocr Metab Immune Disord Drug Targets* 2007;7:232-6.
17. Sundberg L, Eden T, Ernstson S. Penetration of doxycycline in respiratory mucosa. *Acta Otolaryngol* 1983;96:501-8.
18. Watelet JB, Gevaert P, Holtappels G, Van Cauwenberge P, Bachert C. Collection of nasal secretions for immunological analysis. *Eur Arch Otorhinolaryngol* 2004;261:242-6.
19. Alobid I, Benitez P, Bernal-Sprekelsen M, Roca J, Alonso J, Picado C, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. *Allergy* 2005;60:452-8.
20. van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. *Rhinology* 1994;32:5-9.
21. Lildholdt T. Surgical versus medical treatment of nasal polyps. *Rhinol Suppl* 1989;8:31-3.
22. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps: the use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. *Arch Otolaryngol Head Neck Surg* 1997;123:595-600.
23. Benitez P, Alobid I, de Haro J, Berenguer J, Bernal-Sprekelsen M, Pujols L, et al. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. *Laryngoscope* 2006;116:770-5.
24. Alobid I, Benitez P, Pujols L, Maldonado M, Bernal-Sprekelsen M, Morello A, et al. Severe nasal polyposis and its impact on quality of life: the effect of a short course of oral steroids followed by long-term intranasal steroid treatment. *Rhinology* 2006;44:8-13.
25. Patiar S, Reece P. Oral steroids for nasal polyps. *Cochrane Database Syst Rev* 2007(1): CD005232.
26. Richards RN. Side effects of short-term oral corticosteroids. *J Cutan Med Surg* 2008;12:77-81.
27. Bachert C, Gevaert P, Holtappels G, Cuvelier C, van Cauwenberge P. Nasal polypsis: from cytokines to growth. *Am J Rhinol* 2000;14:279-90.
28. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol* 2006;118:1133-41.
29. Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryszak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol* 2005;116:1275-81.
30. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. *Allergy* 2004;59:54-60.
31. Gueders MM, Bertholet P, Perin F, Rocks N, Maree R, Botta V, et al. A novel formulation of inhaled doxycycline reduces allergen-induced inflammation, hyperresponsiveness and remodeling by matrix metalloproteinases and cytokines modulation in a mouse model of asthma. *Biochem Pharmacol* 2008;75:514-26.
32. Kuzin II, Snyder JE, Uguine GD, Wu D, Lee S, Bushnell T Jr, et al. Tetracyclines inhibit activated B cell function. *Int Immunol* 2001;13:921-31.
33. Van Zele T, Gevaert P, Holtappels G, van Cauwenberge P, Bachert C. Local immunoglobulin production in nasal polyposis is modulated by superantigens. *Clin Exp Allergy* 2007;37:1840-7.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Elsevier Periodicals Customer Service
3251 Riverport Lane
Maryland Heights, MO 63043

OR FAX TO:

314-447-8029

OR PHONE:

800-654-2452
Outside the U.S.:
314-447-8871

OR E-MAIL:

Journals Customer Service-
usa@elsevier.com

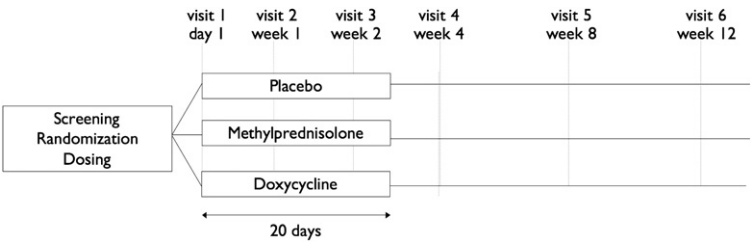


FIG E1. Study design. At visit 1, randomized allocation to 1 of the 3 treatment groups took place. Follow-up visits were scheduled at 1, 2, 4, 8, and 12 weeks after randomization.

TABLE E1. Polyp scoring system

Polyp score	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.
4	Large polyps causing almost complete congestion/obstruction of the inferior meatus

TABLE E2. Inclusion and exclusion criteria

Inclusion criteria	Subjects must be at least 18 years of age, of either sex, and of any race.
	Subjects must have a diagnosis of bilateral nasal polyps at screening and baseline that have recurred after surgical resection or nasal polyps that are grades 3 or 4 in both nares using the polyp scoring system.
	Subjects must be in good health and free of any clinically significant disease that would interfere with the study schedule or procedures or compromise the subjects' safety.
	Subjects must be willing to give informed consent and adhere to visit schedules and medication restrictions and agree to perform daily diary entries.
	Subjects with concurrent asthma must be maintained on no more than 1000 mcg/d beclomethasone dipropionate or the equivalent.
Exclusion Criteria	Nonpregnant women of childbearing potential must use a medically acceptable, adequate form of birth control. This includes: (1) hormonal contraceptive as prescribed by a physician (eg, oral combined, hormonal implant, depot injectable); (2) medically prescribed intra uterine device (IUD); (3) condom in combination with a spermicide; (4) monogamous relationship with a male partner who has had a vasectomy or is using a condom plus spermicide during the study. They must have started this birth control method at least 3 months before screening (with the exception of condom in combination with a spermicide), and they must agree to continue its use for the duration of the study. Women of childbearing potential who are not currently sexually active must agree and consent to using a double-barrier method should they become sexually active during the course of this study. Women who are surgically sterilized or are at least 1 year postmenopausal are considered not to be of childbearing potential. However, all female subjects must have a urine pregnancy test before treatment, which must be negative.
	Male subjects must agree to use an adequate form of birth control for the duration of the study. They must either agree to use a condom with spermicide or agree to have sexual relations only with women using medically acceptable forms of birth control as described.
	Women must not be pregnant, breast-feeding, or premenarcheal.
	Subjects who have required a burst of oral corticosteroids within the 3 months before screening are excluded from the study.
	Subjects with systemic fungoid infections, known allergic reaction on methylprednisolone or tetracyclines, hypertension, diabetes (type 1 and 2), glaucoma, tuberculosis, herpes infection, or zona ophtalmica are excluded, and children are excluded.
	Patients with antineutrophil cytoplasmic antibodies such as patients with Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis are excluded on the basis of the systemic involvement, nasal crusting, vasculitis, and septal perforation.
	Subjects with acute sinusitis or concurrent nasal infection or subjects who have had a nasal or upper respiratory tract infection within 2 weeks of the screening visit are excluded.
	Subjects with cystic fibrosis, primary ciliary dysfunction or Kartagener syndrome by history are excluded.
	Subjects must not have been diagnosed with a parasitic infection.
	Subjects must not be known to be HIV-positive or positive to hepatitis B surface antigen or C antibodies. Testing will not be done at screening.
	Subjects must not have had an acute asthmatic attack requiring admission to a hospital (excluding emergency department visits that resulted in direct discharge without hospitalization) within the 4 weeks before screening.
	Subjects must not have received immunotherapy within the previous 3 months.

TABLE E3. Adverse events

Adverse events (n)*	Placebo (n = 19)	Methylprednisolone (n = 14)	Doxycycline (n = 14)
Headache	0	1	1
Common cold	0	1	1
Earache and/or fullness	1	0	0
Asthma exacerbation	2	0	0
Dyspnea	0	1	1
Chest pain	1	0	0
Reflux and/or gastric pain	2	2	2
Fungal and/or yeast infection skin	0	1	0
Skin rash	0	1	2
Back pain	1	0	0
Muscle ache	1	0	0
Insomnia	0	1	1
Diarrhea	0	1	1
Eye hematoma	0	1	0
Constipation	0	1	0
Toothache	1	0	0
Knee surgery	1	0	0
Herpes skin infection	1	0	0

*Some patients reported multiple adverse events.