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The role of doxycycline in the management of chronic rhinosinusitis with nasal polyps☆,☆☆

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ABSTRACT

Introduction: Many theories on the pathophysiology of chronic rhinosinusitis with nasal polyposis (CRSwNP) exist. The most effective management of CRSwNP has not been elucidated. Doxycycline, which has anti-inflammatory and anti-bacterial properties, has shown durable effects; however, its efficacy in combination with standard therapy has not been examined. We hypothesized that its addition to the standard anti-inflammatory regimen would improve patient outcomes.

Methods: We performed a double-blind, placebo-controlled trial at a tertiary level institution. Patients with moderate or severe CRSwNP were randomized into two groups, each receiving a 20-day course of oral corticosteroids and doxycycline or placebo. The 22-item Sinonasal Outcome Test (SNOT-22), nasal polyp scores, and visual analog scale (VAS) scores were recorded at the initial, 3-, 8- and 12-week visits.

Results: 49 patients were enrolled, 24 in the experimental and 25 in the placebo group with 3 moderate disease patients in each group. There were 12 dropouts in the treatment group and 14 in the placebo group. The most common reasons for dropout were severe CRS and asthma exacerbations. There was no significant difference in SNOT-22 scores, nasal polyp scores, and VAS scores between the two arms.

Conclusions: Non-surgical management of patients with CRSwNP remains challenging. Our conclusions are limited given the high dropout rate and thus, limited sample size with inadequate power. This study is important, however, because a high dropout rate of mostly severe disease patients may illustrate that this patient population may not be optimally managed with medical therapy alone.

1. Introduction

Current standard medical treatment of chronic rhinosinusitis (CRS) includes the use of anti-microbial, anti-inflammatory and mechanical therapies. Per the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012) guidelines, treatment for mild and moderate disease is focused on topical steroid sprays and nasal saline irrigations, with culture-directed antibiotics for acute infection and consideration of doxycycline in moderate disease. In severe cases, a short course of oral steroids may be added [1].

Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have been shown to have higher rates of colonization with *Staphylococcus aureus* and increased immune responses to its enterotoxins. These activate inflammatory mediators and eosinophils that may contribute to nasal polyp growth [2]. Tetracycline antibiotics—such as doxycycline—have a separate anti-inflammatory effect, decreasing levels of myeloperoxidase and matrix metalloproteinase-9 (MMP-9) and possibly altering the eosinophil-associated expression of interleukin-5 (IL-5) and eotaxin-3 in CRS [3]. As a result, doxycycline could be an ideal therapeutic candidate for CRSwNP, as its dual anti-inflammatory and anti-microbial properties could affect multiple pathways in the underlying pathogenesis.

A recent trial comparing three weeks of doxycycline to oral steroids showed its effectiveness in reducing nasal polyp size and patient

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symptoms [4]. As a result of the supporting evidence, EPOS 2012 recommends considering doxycycline as a treatment option for patients with moderate CRSwNP [1]. Subsequently, Bezzera Soter et al. compared long-term doxycycline with nasal steroids to nasal steroids alone in difficult-to-control CRS and showed a significant improvement in patient symptoms and Lund-Kennedy scores in the treatment group [5].

Our clinical trial represents the first attempt to combine doxycycline with oral steroids in the management of moderate to severe CRSwNP. We hypothesize that the addition of doxycycline to the current standard of care will improve disease-specific quality of life, decrease symptoms, and reduce nasal polyp size. This study has the potential to have significant implications for adding to and improving the available treatment options for CRSwNP patients.

2. Methods

An Investigational New Drug exemption was obtained from the U.S. Food and Drug Administration for the use of doxycycline for CRSwNP. The study was then approved by the Icahn School of Medicine Institutional Review Board. From September 2014 to April 2016 subjects were recruited from the Mount Sinai Department of Otolaryngology—Head and Neck Surgery Rhinology practice. All patients signed informed consent. Inclusion criteria were: diagnosis of CRS according to American Academy of Otolaryngology—Head and Neck Surgery diagnostic criteria [6]; nasal polyps on endoscopy; moderate (visual analog scale (VAS) score > 3, ≤ 7) or severe (VAS score > 7) disease as defined by EPOS2012 scored on a 10-cm VAS asking subjects, “How troublesome are your symptoms of rhinosinusitis?”; age 18 years or older and able to give informed consent. Exclusion criteria were: patients who had treatment with oral corticosteroids in the previous 4 weeks; cystic fibrosis or primary ciliary dyskinesia; diabetes mellitus; endoscopic sinus surgery (ESS) in the previous 3 months; allergy to doxycycline or glucocorticoids. Breastfeeding mothers and pregnant females were also excluded. Use of antibiotics or non-protocol corticosteroids (topical or systemic) during the study period resulted in withdrawal of the subject from the study.

2.1. Study protocol

Subjects were randomly assigned to one of two groups by the institution's Investigational Drug Service Pharmacy. Stratified randomization was used to maintain balanced distribution of moderate and severe disease patients. Subjects and investigators were blinded to the assignments. The treatment group received doxycycline (200 mg orally × 1 dose on Day 1, then 100 mg orally daily for Day 2–20) in addition to a standard treatment regimen used at our institution (oral methylprednisolone daily in a tapering dose: 32 mg × 5 days, 16 mg × 5 days, 8 mg × 10 days; and nasal saline sprays: 2 sprays each nostril three times a day) for a 20-day treatment course. The control arm received a placebo pill instead of doxycycline in addition to the standard regimen described above. After the 20-day treatment course, both groups received maintenance therapy, which included topical steroid sprays (fluticasone propionate, 2 sprays each nostril daily), nasal saline sprays, and saline irrigations performed 1–2 times a day. At the initial visit, subjects' history, nasal endoscopy, 22-item Sinonasal Outcome Test (SNOT-22) score, VAS score, polyp score (Table 1), middle meatus cultures and allergy tests were obtained. Allergy testing was performed via radioallergosorbent (RAST) or skin testing. At the 3-, 8-, and 12-week visits, interval histories, full examinations (including nasal endoscopy), SNOT-22, VAS, and polyp scores were obtained. At the 12-week visit, a middle meatus culture was repeated. Subjects that withdrew from the study but had completed the initial dosing regimen were called at or after the 12-week visit to obtain SNOT-22 scores over the phone. Those that withdrew because of severe CRS symptoms or asthma exacerbation requiring additional medical therapy were given a maximum 12-week SNOT-22 score.

Table 1
Nasal polyp scores. The score is determined for each nostril and the two scores added for a total nasal polyp score [12].

Score	Criteria
0	Absence of nasal polyps
1	Polyps confined to the middle meatus and not beyond the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps extending to the lower border of the inferior turbinate or medial to the middle turbinate
4	Large polyps causing almost complete obstruction of nasal cavity

2.2. Endpoints

The primary endpoint was the change in total SNOT-22 score at the 12-week visit. Secondary endpoints were changes in subjective sinusitis symptom scores from the SNOT-22, change in nasal polyp score, and change in VAS scores. The subjective symptom score was calculated by summation of the individual item scores from the SNOT-22 for “blockage/congestion of nose,” “runny nose,” “post nasal discharge,” “sense of taste/smell,” “facial pain/pressure.”

2.3. Statistical analysis

Statistical analysis was performed using SAS system software version 9.4 for Windows (SAS Institute Inc., Cary, NC). A power analysis was completed to detect a minimally important difference in SNOT-22 of 8.9 (standard deviation of 15) based on a validity study on SNOT-22 [7]. Forty-five experimental and 45 control subjects were needed to be able to reject the null hypothesis that the population means of the two groups were equal with probability (power) 0.8. The Type I error probability associated with this null hypothesis was 0.05. The analysis was performed with the use of linear mixed-effects models. Fixed effect factors include the treatment group, time (visit in weeks), and the interaction between treatment group and time. A p-value < 0.05 indicated statistical significance.

3. Results

Forty-nine subjects were enrolled and randomly assigned to study groups based on disease severity, 24 to the treatment group and 25 to the placebo group. (Fig. 1) There were 12 subject dropouts in the treatment group and 14 in the placebo group ($p = 0.67$). Of these, all had severe disease, except for one in each group with moderate disease. Five withdrawals occurred before the 3-week visit, 10 between the 3- and 8-week visit, and 11 between the 8- and 12-week visit. Because of our high drop-out rate due to severity of symptoms or asthma exacerbation, we terminated our study prior to enrolling our target number of subjects. Fifteen of our 26 dropouts (58%) were due to asthma or CRS symptom exacerbation requiring treatment. Twenty-one (80.8%) of the dropouts occurred after the 3-week treatment period. A total of 12 and 11 subjects in the treatment and placebo groups, respectively, completed the study protocol. An additional 8 subjects in the treatment group and 9 subjects in the placebo group completed SNOT-22 scores for the 12-week timepoint via phone calls or were given maximum SNOT-22 scores. Seven subjects were given a maximum SNOT-22 score because their reason for dropout was a CRS exacerbation; all other subjects were called to obtain SNOT-22 scores. If the subject declined to answer or was not reachable, no data was included for the 12-week timepoint.

3.1. Baseline characteristics

For the placebo and treatment groups, the baseline characteristics are shown in Table 2. No significant differences in demographics and

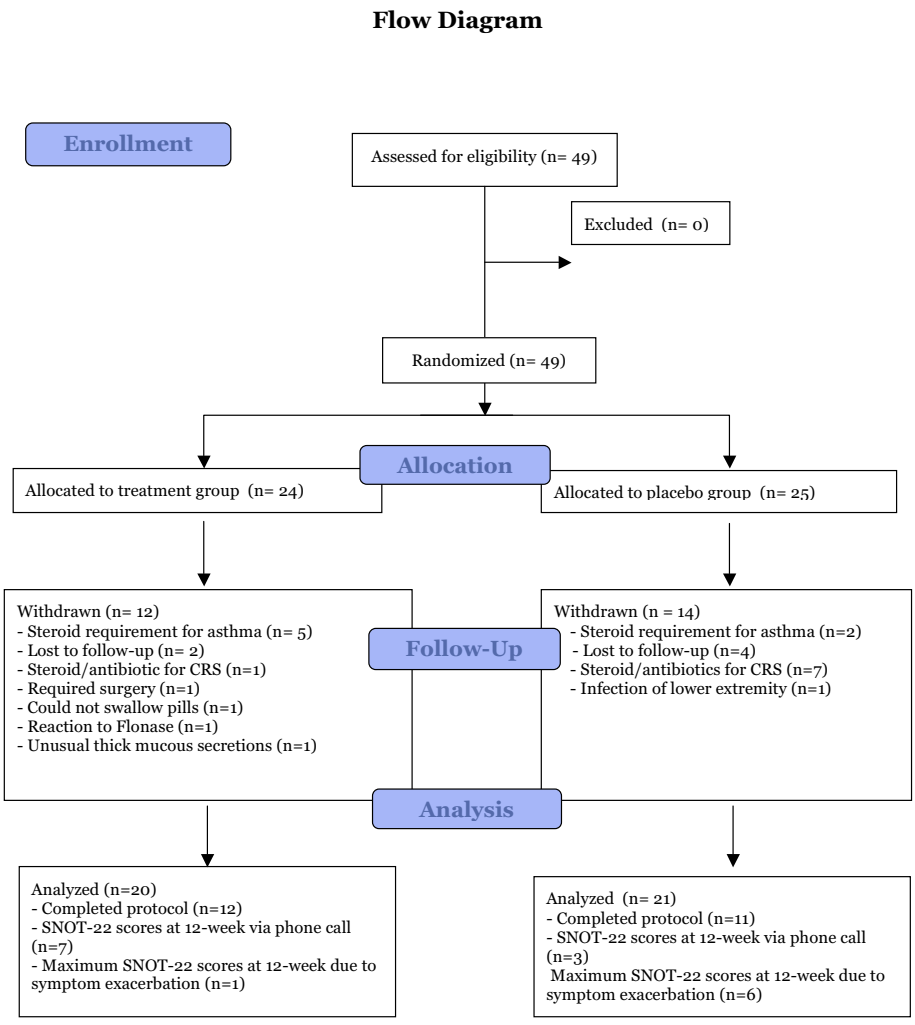

Fig. 1. Flow diagram illustrating the progress of patients through the trial. (SNOT-22 = 22-item Sinonasal Outcome Test.)

Table 2
Baseline characteristics of the study population. Values expressed as *n* (%) or *mean ± standard deviation.* (SNOT-22 = 22-item Sinonasal Outcome Test).

Characteristics	Treatment N = 24	Placebo N = 25	*p*-Value
Age (years)	51.5 ± 13.8	44.1 ± 12.2	0.052
Gender			0.47
Female	10 (42%)	13 (52%)	
Male	14 (58%)	12 (48%)	
Race			0.89
White	16 (67%)	19 (76%)	
Black or African American	5 (21%)	3 (12%)	
Asian	1 (4%)	1 (4%)	
Unknown/not reported	2 (8%)	2 (8%)	
Ethnicity			0.26
Hispanic or Latino	1 (4%)	5 (20%)	
NOT Hispanic or Latino	20 (83%)	18 (72%)	
Unknown/not reported	3 (13%)	2 (8%)	
Aspirin-exacerbated respiratory disease	6 (25%)	5 (20%)	
Prior endoscopic sinus surgery	13 (54%)	13 (52%)	0.88
SNOT-22 score	55.2 ± 24.3	54.4 ± 20.8	0.91
Subjective symptom score	16.3 ± 5.2	17.1 ± 4.4	0.55
Visual analog scale score	8.4 ± 1.5	8.1 ± 1.3	0.48
Disease severity			
Moderate	3 (13%)	3 (12%)	
Severe	21 (88%)	22 (88%)	
Nasal polyp score	6.0 ± 1.8	6.5 ± 1.3	0.33

clinical characteristics were found between the two groups. Overall, 43 (88%) of subjects had severe CRSwNP and 26 (53%) had recurrent disease after prior endoscopic sinus surgery. The overall positive allergy test rate was 63%. There was no significant difference between the two groups.

3.2. Primary endpoint

3.2.1. SNOT-22 scores

Based on the mixed-effects model, the interactive factor was not significant ($p = 0.44$) between the two groups' SNOT-22 scores. The interactive factor for all data is defined as the intervention, either treatment or placebo. Over the time period studied, there was no statistically significant difference in SNOT-22 scores between the two groups (Fig. 2). There was no significant difference in the change in SNOT-22 scores between each timepoint (initial visit to week 3, week 3 to 8, week 8 to 12, and week 3 to 12).

3.3. Secondary endpoints

3.3.1. Subjective symptom scores (SSS)

Based on the mixed-effects model, the interactive factor was not significant ($p = 0.87$). Over the time period studied, there was no statistically significant difference in SSS between the two groups (Fig. 3). There was no significant difference in the change in SSS between each timepoint between the two groups.

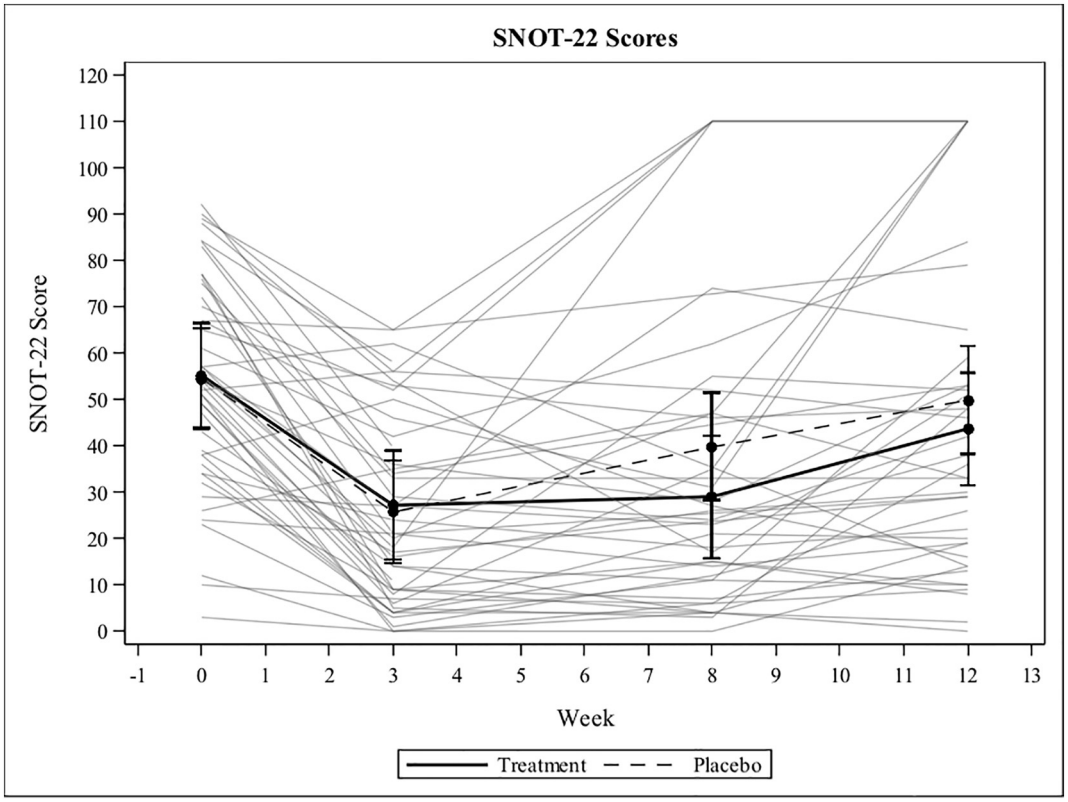

Fig. 2. Mean SNOT-22 scores at each timepoint. Gray lines are subject-level scores, solid and dotted lines are means. (SNOT-22 = 22-item Sinonasal Outcome Test.)

3.3.2. VAS scores

Based on the mixed-effects model, the interactive factor was not significant ($p = 0.82$). Over the time period studied, there was no statistically significant difference in VAS scores between the two groups (Fig. 4). There was no significant difference in the change in VAS scores between each timepoint.

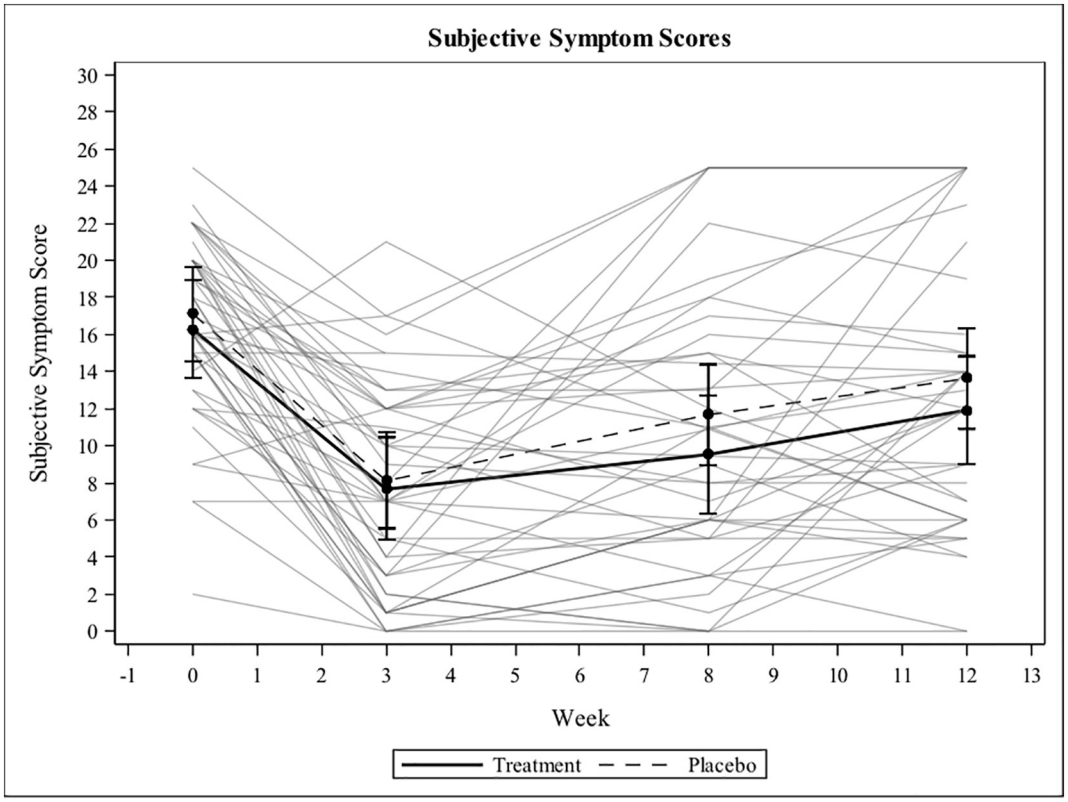

Fig. 3. Subjective symptom scores at each timepoint. Gray lines are subject-level scores, solid and dotted lines are means.

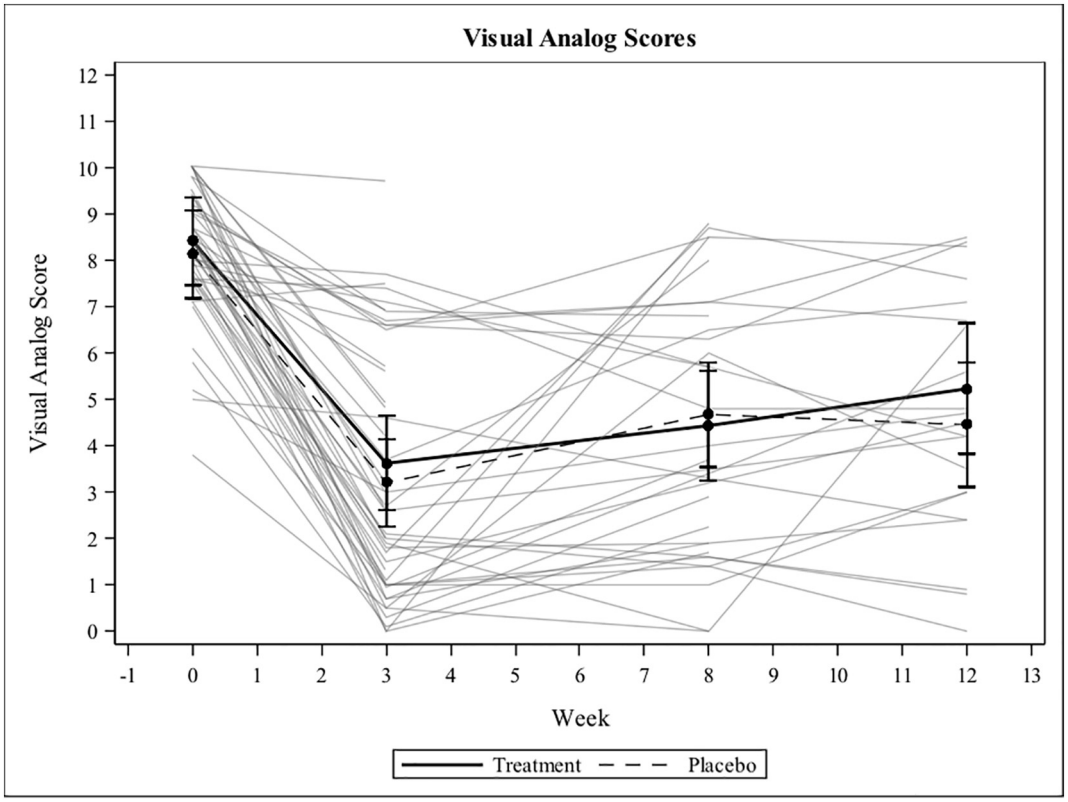

Fig. 4. VAS scores at each timepoint. Gray lines are subject-level scores, solid and dotted lines are means. (VAS = Visual analog scale.)

3.3.3. Nasal polyp scores

Based on the mixed-effects model, the interactive factor was not significant ($p = 0.72$). Over the time period studied, there was no statistically significant difference in nasal polyp scores between the two groups (Fig. 5). There was no significant difference in the change in nasal polyp scores between each timepoint.

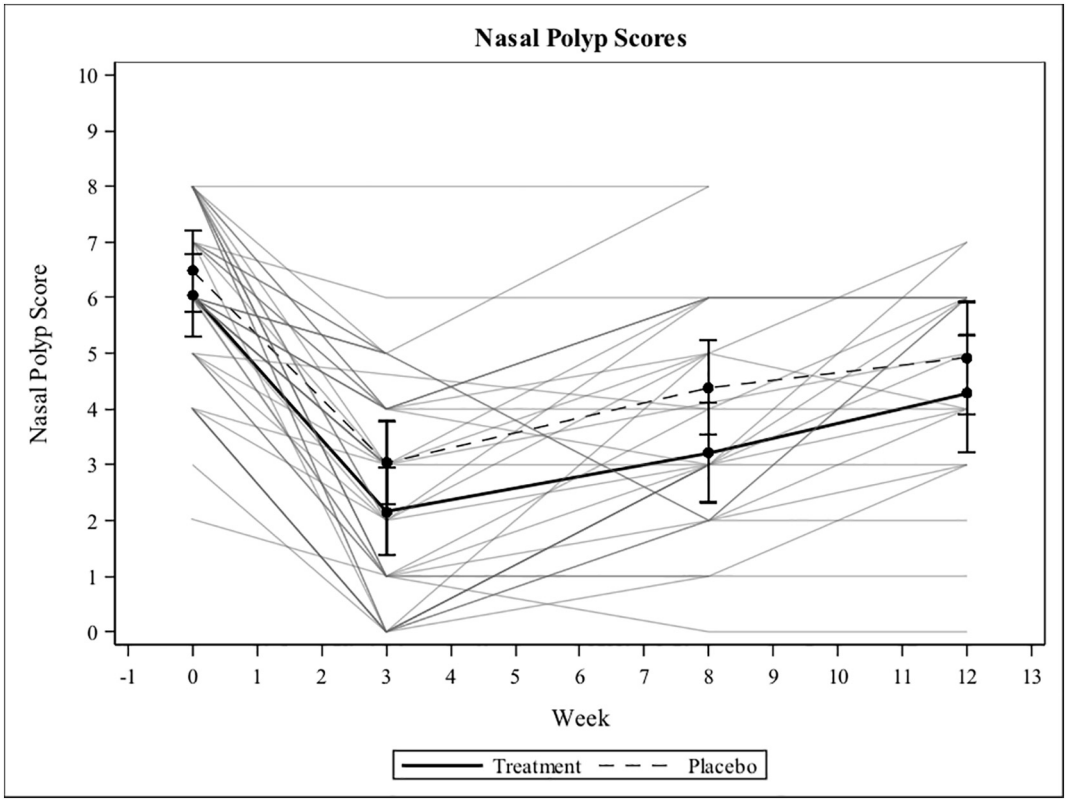

Fig. 5. Nasal polyp scores at each timepoint. Gray lines are subject-level scores, solid and dotted lines are means.

3.3.4. Middle meatus cultures

Forty-four subjects had initial visit middle meatus culture swabs. Of the 23 subjects that completed the study, 17 had 12-week middle meatus culture swabs. Seven subjects had growth at the initial and 12-week visit. Three subjects had growth at the initial visit but no growth at the 12-week visit. Three subjects had no growth at the initial visit but growth at the 12-week visit. None of these results were statistically different between the two groups. At the initial visit, 8 patients had cultures positive for *S. aureus*, while only one culture obtained at the 12-week visit was positive for *S. aureus*.

4. Discussion

The goal of our study was to investigate the role of doxycycline in combination with standard therapy for the treatment of CRSwNP. We hypothesized that the addition of doxycycline to maximal medical therapy could improve quality of life and decrease disease burden. We elected to terminate our study prematurely because of a high dropout rate. We believe this was due to the high percentage of our study population with severe, difficult-to-treat CRSwNP (as evidenced by their high VAS and nasal polyp scores, high prevalence of aspirin-exacerbated respiratory disease (AERD), and prior ESS) who had frequent symptom exacerbations requiring steroids or antibiotics. In addition, many patients with severe CRSwNP concomitantly have severe asthma symptoms, which was illustrated by the high percentage of subjects that withdrew because of asthma exacerbations requiring steroids. Multiple studies highlight the correlation between severe asthma and severe CRS, mainly because of inflammation of both the upper and lower airway [8–10].

While we were not able to draw any conclusions from our data because of limited power due to sample size, our study does highlight some key points. Firstly, most of our study population had severe disease, and was unable to be adequately managed with doxycycline or placebo and oral steroids. This suggests that such severe disease patients may not be able to be managed with medical therapy alone, and perhaps the limited role of doxycycline in this population. These patients may require surgery followed by medical therapy. Second, while patients in both groups displayed an improvement in their SNOT-22 and symptom scores at the 3-week evaluation, these scores regressed at both the 8- and 12- week evaluation for both groups. This evidence combined with the fact that the majority of dropouts (80.7%) occurred after the three-week period perhaps indicates a maintenance regimen of topical nasal steroid spray, nasal saline spray and nasal saline irrigation, as indicated by treatment guidelines, is not effective for patient with severe disease. These patients may benefit from more aggressive maintenance regimens including steroid nasal irrigations to avoid symptom exacerbations. Many recent studies have demonstrated the utility of budesonide irrigations as maintenance therapy after ESS for CRS [11].

Our study also has some key differences when comparing to previous clinical trials, which may explain the differences in results. A key difference is the inclusion criteria. The inclusion criteria for the Van Zele study was an objective measure of a polyp score of 3 or 4, or recurrent polyposis after surgery. The inclusion criteria for our study, on the other hand, was a subjective measure of moderate or severe disease as defined by the EPOS guidelines. We chose this as an inclusion criteria because we believe it more accurately reflects the effect of the disease on the patients' quality of life. As many studies have illustrated, subjective outcomes do not always correlate to objective outcomes in CRS. This difference in inclusion criteria may explain why we selected for a more difficult-to-treat population in our trial, thus resulting in a higher dropout rate. In addition, our study combined doxycycline with oral steroids, whereas the previous clinical trials combined doxycycline with topical steroids. Oral steroids may have such a significant systemic anti-inflammatory effect that they minimize a detectable benefit of doxycycline in our sample size.

A limitation of this study is the inadequate power due to our dropout rate and the risk for a Type II error. In addition, we recruited a high percentage of severe and recurrent disease patients from a tertiary-care center. We see a higher percentage of patients with severe disease and refractory polyps that are often referred because of multiple failed attempts at disease control via medical therapy. Thus, our study did not accurately represent moderate disease patients. As proposed in the EPOS2012 guidelines, doxycycline may be more effective for these patients.

5. Conclusion

Our study is the first study to test the efficacy of doxycycline and oral steroids as a medical management strategy for CRSwNP. We were unable to completely evaluate the impact of doxycycline on the primary endpoint, limited by our high dropout rate due to severity of disease and inadequate maintenance therapy. Our study is important, however, because it highlights the deficit in knowledge of the pathophysiology of moderate and severe disease, and the need for new treatment and maintenance guidelines. Such studies are important in the literature. Severe disease patients may not be adequately maintained on medical therapy alone, and doxycycline may only be suitable for patients with moderate disease; however, further studies are needed to elucidate the role of doxycycline. In addition futures studies may demonstrate that patients with severe disease are better candidates for early surgery, and medical management reserved for those with mild or moderate disease.

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