Benralizumab Effect on Severe Nasal Polyps: A Randomized Placebo Controlled Trial

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) can be a severe and debilitating disease associated with significant morbidity, complete anosmia, sinus pressure, and asthma exacerbations. Eosinophils play a role in the majority (85%) of patients. Benralizumab, an afucosylated monoclonal antibody directed against the IL-5 receptor has powerful apoptotic effects on eosinophils. Objective: We sought to investigate the therapeutic benefit of inhibiting the IL-5 receptor using benralizumab to treat severe nasal polyposis. Methods: Twenty-four patients (n = 24) with severe NP (grade 5 or more out of 8) with elevated eosinophils and a history of previous polypectomy were randomized in a double-blind fashion to receive 30mg benralizumab SC or placebo. Endoscopic NP score was assessed at baseline and at treatment week 20. CT scan, SNOT-22 survey, and UPSIT smell test score changes were also evaluated from baseline. Results: Compared to baseline, 8 out 12 patients receiving benralizumab had a significantly improved NP score versus 4 out of 12 placebo. 5 of 12 benralizumab treated patients had improvements in all major outcomes (polyp score, CT, SNOT-22 and smell test) versus 2 out of 12 placebo. The ratio of blood eosinophil count to allergen skin test positivity correlated with polyp reduction. Conclusion: Compared to baseline, benralizumab achieved a statistically significant reduction in polyp size by endoscopy and CT scan and was associated with both less symptoms and improved sensation of smell for most patients (10 of 12).

Key Words*: nasal polyps, benralizumab, eosinophils, chronic rhinosinusitis, smell test, skin test*

INTRODUCTION

Chronic rhinosinusitis (CRS) has a prevalence of more than 10% in the United States and Europe and is associated with several co-morbidities including asthma, acute infection, and obstructive sleep apnoea.(1-3) Total health care expenditure for CRS is more than $60 billion annually in the United States accounting for as much as 5% of the total US health care budget.(3-5) CRS with nasal polyps (CRSwNP) in particular, can be a severe and debilitating disease associated with significant morbidity, complete anosmia, sinus pressure, and acute asthma exacerbations. Not uncommonly, patients with CRSwNP often require multiple courses of oral corticosteroids and repeated surgical polypectomies to manage their disease.

CRSwNP is not exclusively related to immunoglobulin E (IgE) and interleukin-4 (IL-4) processes. As such, allergen immunotherapy is of limited value although, evidence suggests that immunotherapy improves innate immune function in addition to affecting the IL-4/IgE mediated immune axis.(6) Anti-IgE therapy such as omalizumab has also been shown to have some benefit in this population.(7-10) Dupilumab, an anti IL-4Rα antibody, has been shown to be efficacious in the CRSwNP patient population; however, it is worth noting that treatment resulted in a decrease in eosinophil-associated plasma eotaxin-3, indicating that other non-IL-4/IgE pathways are also impacted by this drug.(11) Similarly, the efficacy of dupilumab in eosinophilic asthmatics resulted in a reduction in eotaxin-3 and Fractional exhaled Nitric Oxide (FeNO) and

an increase in blood eosinophils, suggesting re-compartmentalization and other effects on this inflammatory cell cascade.(12)

In up to 90% of Caucasian patients with chronic nasal polyps, the disease exhibits pathology associated with eosinophils and interleukin-5 (IL-5).(13) CRSwNP patients with elevations in serum and mucosal eosinophils tend to have more severe NP disease and higher recurrence rates.(14) Eosinophilia is often so pronounced that patients with CRSwNP are sometimes evaluated for clonal hypereosinophilic processes, parasitic infections and autoimmune disorders.(15, 16) Despite chronic corticosteroid use, eosinophils may remain elevated. Indeed, high blood and tissue eosinophil counts are associated with increased disease severity and recurrence rates post surgery.(14) In addition, a number of proinflammatory genes that upregulate eosinophil recruitment and survival have been shown to be activated in nasal polyp tissue.(17)

A proof-of-concept study in Europe previously showed a reduction in polyp burden using mepolizumab, a monoclonal antibody that binds free IL-5 protein in circulation.(15) Benralizumab on the other hand, is an afucosylated monoclonal antibody that directly targets the α chain of the IL-5 receptor and has been shown to have powerful apoptotic effects on eosinophils. Benralizumab is efficacious treating severe asthmatics with eosinophilia(18, 19); however the potential for this drug to be used to treat patients with CRSwNP has not been previously evaluated. The unique mechanism of action of benralizumab targeting the IL-5 receptor on the surface of eosinophils leads to degradation of signalling, antibody-dependent cell-mediated cytotoxicity (ADCC), and apoptosis.(18) This direct effect on eosinophils leads to reduction of proinflammatory processes in the asthmatic airways but the effect on nasal polyp burden still needs to be determined.

We hypothesized that benralizumab 30mg SC given subcutaneously for twenty weeks would reduce endoscopic and radiographic nasal polyp size, as well as symptoms of nasal blockage and poor sense of smell in a double-blind randomized placebo-controlled study.

Methods

Patients and Selection Process

Twenty-four allergic and non-allergic adult subjects aged 18-75 with severe bilateral nasal polyps (average bilateral endoscopic nasal polyp total score of at least 5 out of 8 as defined below), eosinophil count of 300/µl or greater, refractory symptoms despite prior surgical polypectomy, and at least one oral steroid course over the previous twelve months were recruited. Potential subjects were excluded if they received immunosuppression or allergen immunotherapy build up in the past 3 months. Pregnant patients, those with cancer, immune deficiency, or helminth infection were also excluded as well as those receiving any type of anti-interleukin therapy. The study was performed at the Johns Hopkins University Asthma and Allergy Centre and was approved by the Johns Hopkins IRB. All participants provided written consent.

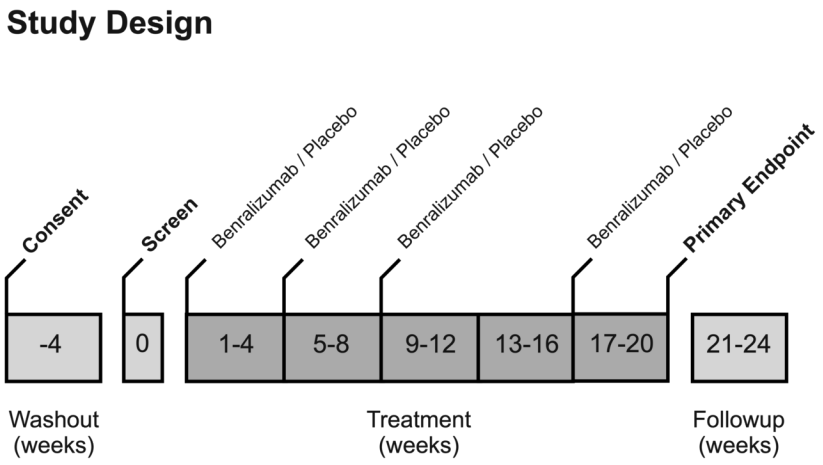


Figure 1 . Study Design

Study Design

We performed a randomized double-blind, placebo controlled study of benralizumab in patients with severe CRSwNP refractory to standard treatment, that minimally included the use of nasal steroids and at least one prior polypectomy. Subjects were instructed to abstain from taking oral or nasal corticosteroids and antihistamines for a period of one month before screening. Subjects meeting criteria for entry were randomized to receive benralizumab 30mg SC or placebo according to the schedule illustrated in Figure 1. During the study, subjects with inadequate control of symptoms were offered nasal steroids and/or oral corticosteroids according to a predetermined rescue protocol.

Outcome Measures

The primary outcome measure of this study was reduction in endoscopic nasal polyp score at 20 weeks after the first injection compared to baseline. The total bilateral polyp score (0-8) is the sum value from each nostril as used by others(15, 20) and 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. Endoscopy video scores were determined independently by two blinded investigators. Discrepancies were resolved with a third independent and blinded tiebreaking investigator.

Secondary endpoints included: 1) changes the Lund-Mackay (LMS) computed tomographic (CT) scan score, which determines the degree of sinus obstruction on a scale of zero to twelve (bilateral score 0-24)(21); 2) the Sino-Nasal Outcome Test (SNOT-22) clinical survey (measured from 0-110); 3)the nasal blockage score (NBS) (score 0-5); and 4) sensation of smell evaluated using the University of Pennsylvania Smell Identification Test (UPSIT) which includes 40 common smells imbedded on individual scratch and sniff testing cards. All outcomes were determined by a blinded investigator.

Other important outcomes included precise determination of allergic sensitization by skin prick testing, rescue medication use, laboratory evaluation of CBC, basic chemistry, electrolytes, LFTs and total serum IgE. The UniTest PC (Lincoln, Diagnostics, Decatur, IL) was used as a disposable skin test device.(22, 23) Allergens used for testing included several trees, grasses, weeds, molds, dust mite, cat, dog, mouse and cockroach (HollisterStier, Spokane, WA; Greer Laboratories, Lenoir, NC; ALK-Abello, Round Rock, TX). A short wave infrared camera (AllergyScope, Flare Diagnostics, Baltimore, MD) was used as a skin colour agnostic tool to determine the precise SPT wheal dimensions as per methods previously described.(24) A positive SPT was defined as a wheal of at least 3mm diameter and at least 2mm greater than the negative control.

Safety was evaluated by vital sign measurements, physical examination, laboratory assessment, and continuous adverse events reporting.

Statistical analysis

The primary outcome of this study was the change in the endoscopic nasal polyp score at 20 weeks treatment compared to baseline for both placebo and benralizumab treatment groups. This was analyzed using a two-tailed paired t-test and with 0.05 determined to be significant *a priori* . Lund-Mackay score as determined by CT scan, nasal blockage score (NBS), SNOT-22 and UPSIT smell test were evaluated by the same statistical methods. Baseline characteristics and laboratory values were compared by either an unpaired two-tailed t-test or Fisher's exact test when required. Among the benralizumab treated subjects, blood eosinophil count and skin prick test sensitivity were also compared against endoscopic NP score reduction or CT scan by using a one-tailed Spearman rank correlation and then plotted with a four-parameter logistic curve interpolation.

An *a priori* power analysis was performed based on prior studies using anti-IL5 monoclonal antibody therapy where there was an average of 32% reduction in nasal polyp score yielding an effect size of 0.535 and standard

deviation of 1.5. To achieve 80% power (alpha 0.05) using the same effect size, a total sample size of 22 was determined to be adequate for our study (11 per arm). To accommodate for potential dropout, we randomized 24 total subjects. An intention to treat analysis was performed.

Randomization and data monitoring was performed by an independent team. An independent and blinded group was also responsible for data monitoring and receipt of locked study data prior to unblinding. Two separate groups then analyzed the data. Data analysis was performed using Prism version 8.4.1 for Mac (GraphPad Software, San Diego, CA).

Results

Baseline Characteristics

The baseline characteristics are summarized in Table I. A comparison was made between the placebo and benralizumab treatment groups at baseline. There was no significant difference in age, gender, BMI, history of asthma, number of prior surgical polypectomies, or the number of years since the patient was first diagnosed with NP. All but two patients reported a current or prior history of mild to moderate asthma and at least half of the participants skin tested positive to at least one aeroallergen tested. The number of patients that described sensitivity to aspirin was greater in the placebo group (P=0.049) however, this was not determined by a challenge procedure. In many cases the history of aspirin sensitivity was vague and often listed because a health care provider had previously and appropriately warned of this possibility. All patients were required to have been treated with at least one course of oral corticosteroids within the year preceding enrolment.

The baseline bilateral endoscopic score was at least 5 or more out of 8 to be enrolled and was similar in both groups (P=0.195). Most patients had a score of either 5 or 6, however three patients had a score of 7 or more. One patient in the benralizumab treatment group was enrolled with a polyp score of 5 but upon repeat measurement at the end of study by an independent investigator, the baseline score was corrected to 4.

CT scan Lund-Mackay (LMS) score was similar in both groups (P=0.104) and was well correlated with the endoscopic polyp score (P=0.028). Baseline smell test scores determined by UPSIT were similar among both groups with most patients (80%) scoring 12 points or less indicating that their answers were likely guesses.

About half of the patients that had at least one SPT positive out of 30 aeroallergens tested and this was similar among both groups (P=0.341). There was no statistical difference in the total number of positive SPT between the two groups (P=0.562).

Benralizumab (n=12) Placebo (n=12) P value

History

Age [yrs] 49.8 50.8 0.861

Male gender [n (%)] 7 (58) 7 (58) 1.0 ++

BMI [kg/m^2] 32.4 29.1 0.199

Asthma history [n (%)] 10 (83) 12 (100) 0.239 ++

Years with polyps [yrs] 10.0 11.1 0.793

Polypectomy number [n] 3 2.3 0.427

Aspirin sensitive [n (%)] 3 (25) 8 (67) 0.049 ++ *

Prednisone in past yr [n (%)] 12 (100) 12 (100) 1.0 ++

Clinical Assessments

Endoscopic polyp score (0-8) 5.7 6.2 0.195

CT Lund-Mackay score (0-24) 18.0 20.6 0.104

UPSIT smell test (0-40) 12.2 10.7 0.459

Atopic by any SPT [n (%)] 6 (50%) 8 (75%) 0.341 ++

Number of SPT positives [mean] 8/30 10/30 0.562

Laboratory Tests

Eosinophils (/μl) 698 846 0.484

IgE, Total serum (kU/L) 208 470 0.271

Table I . Baseline Characteristics. Historical information, clinical assessments and laboratory values are indicated at baseline for both benralizumab and placebo group. Total number of participant (n) is 24 with values expressed as mean. P values are calculated with unpaired two-tailed t-test unless otherwise indicated. ++ symbol indicates a one-tailed Fisher's exact test was performed. P value of 0.05 or less indicates significance by * symbol.

Primary Outcome

Benralizumab improved both the endoscopic nasal polyp score and corresponding CT score (LMS) by week 20 (SD=1.03; P=0.004, and SD=4.31; P=0.012 respectively) compared to baseline. The change in polyp score and CT score compared to placebo was -0.5 and -2.6 respectively, however this did not reach statistical significance. Eight out of twelve benralizumab treated subjects (66%) improved by endoscopy and nine of twelve (75%) improved by CT scan. The mean change in endoscopic polyp score was -0.9 with treated subjects improving from 0 to -3 points. No subject worsened in the benralizumab treatment group.

There was no significant change from baseline in NP score (P=0.166) or CT score (P=0.233) among placebo treated subjects at week 20. As shown in Figure 2, there was a modest and non-significant improvement in mean NP score among the placebo group of -0.3, a change that was 3-fold less than the benralizumab treated group.

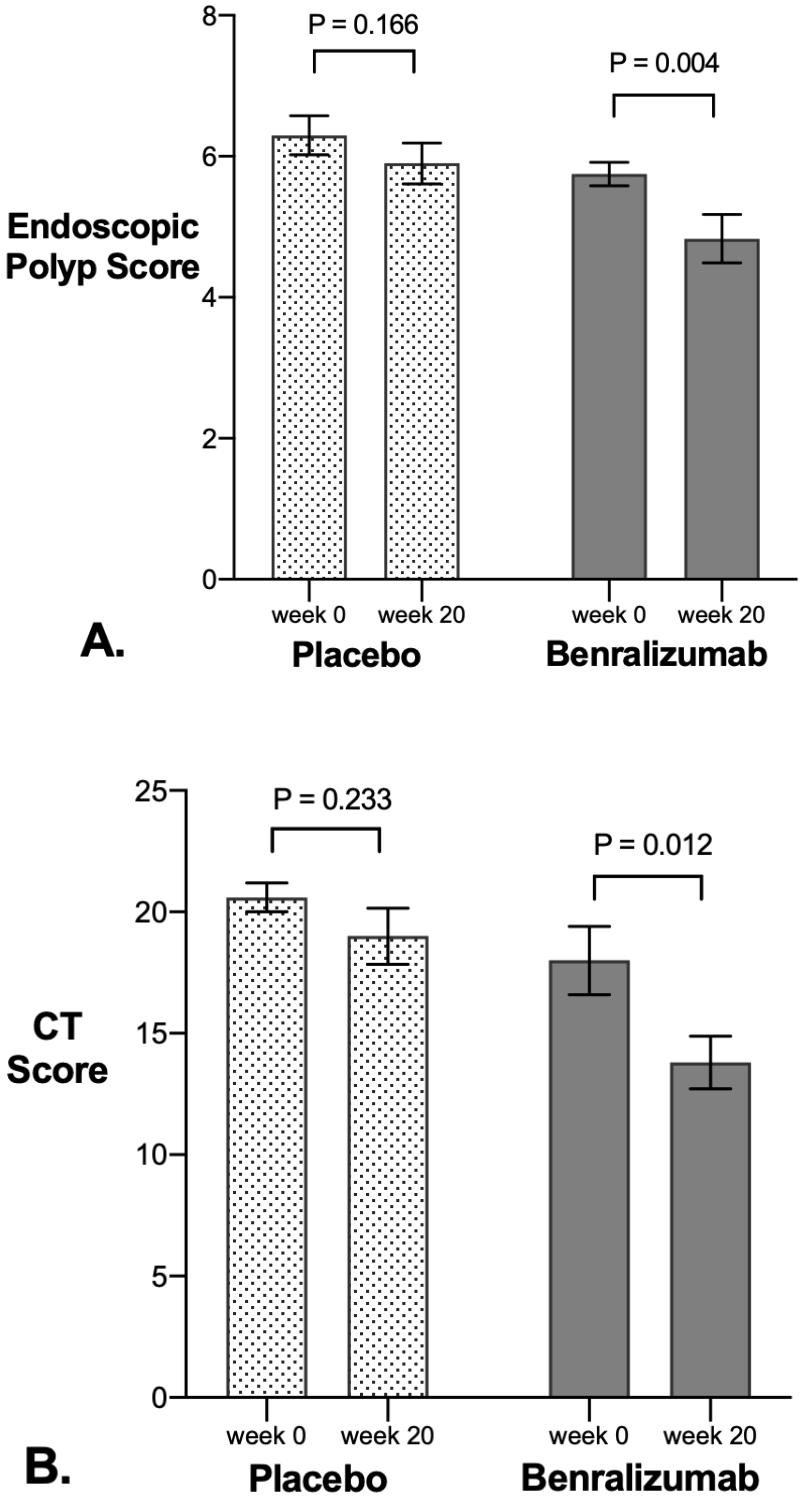


Figure 2. Primary outcome (A), the bilateral endoscopic nasal polyp score at 20 weeks treatment is significantly lower compared to baseline in benralizumab group (P=0.004) but not placebo (P=0.166). (B)

Similarly, CT polyp score is lower in the benralizumab group (P=0.012) but not placebo (P=0.233).

The reduction in polyp size and CT score were not uniform among all subjects treated with benralizumab. The benralizumab treated group ranged from no improvement to a three-point reduction in total bilateral endoscopic polyp score. CT score reduction was likewise variable among the benralizumab treated group. Figure 3, shows the endoscopic image and sinus CT scan of two representative patients that improved with benralizumab treatment.

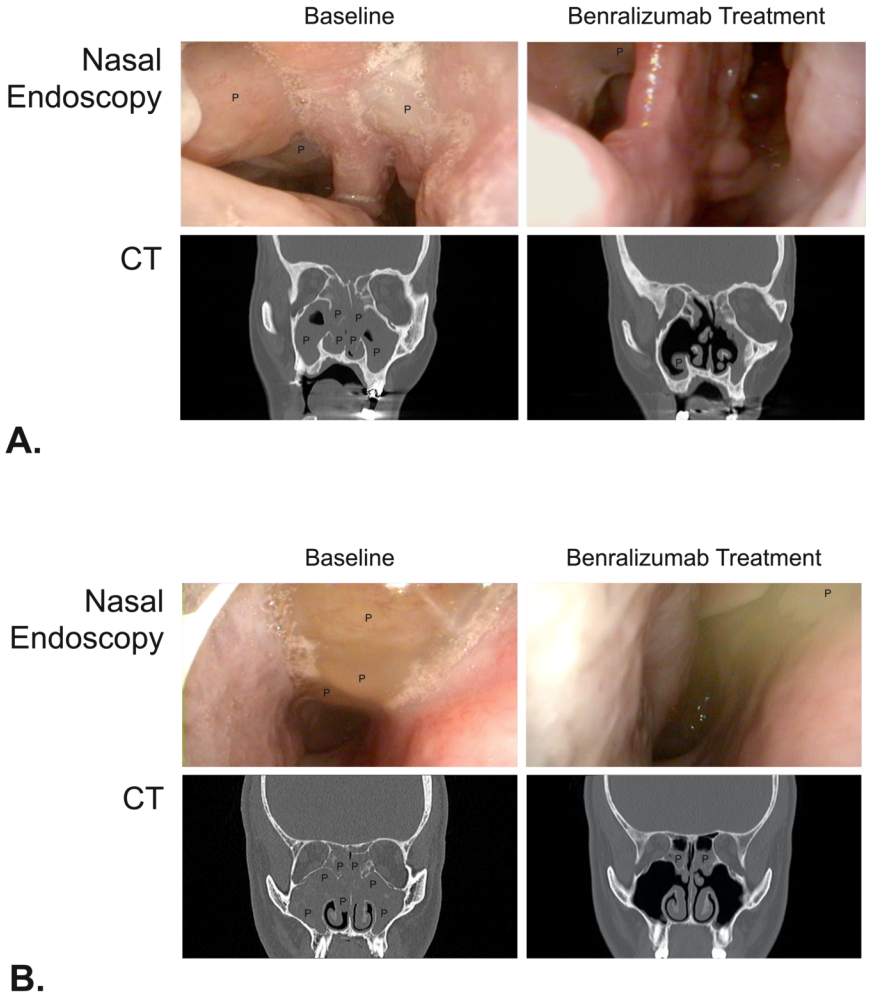
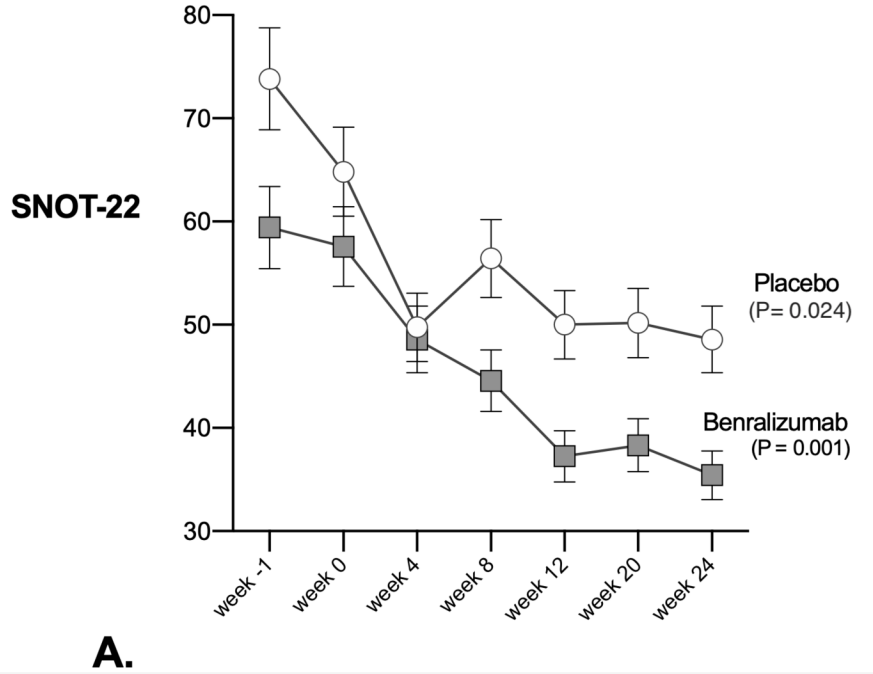


Figure 3. Nasal endoscopy and sinus CT scan are shown for two representative patients responsive to benralizumab treatment. Both patient (A) and patient (B) are shown at baseline and 20 weeks therapy. Polyp tissue, indicated with an upper case P, is significantly reduced in both patients shown.

SNOT-22 and Nasal Blockage Score (NBS)

Benralizumab treated subjects showed significant improvement in both the SNOT-22 clinical survey and nasal blockage score by week 20 (SD=20.8; P=0.001, and SD=1.2, P=0.038 respectively) compared to baseline screening (week 0). All patients treated with benralizumab had an improved SNOT-22 score with a mean decrease of -19.2 points (-33% decrease from baseline). More than half the benralizumab treated patients had an improved nasal blockage score (NBS) 7/12 (P=0.038).

There was also an improvement in the SNOT-22 score among placebo treated patients (SD=20.1; P=0.024) although the mean decrease of -14.6 points (-22%) was less than that seen in the benralizumab treated group. Placebo treated patients had no significant improvement in the nasal blockage score (P=0.399). Within the first month of treatment, the SNOT-22 scores in the placebo and benralizumab treatment groups overlapped. From that point on (week 4 to follow-up week 24), the benralizumab group continued to improve (mean change -13.1 points; P=0.077) but the placebo group had minimal change (mean decrease -1.2 points; P=0.851) as shown in Figure 4.



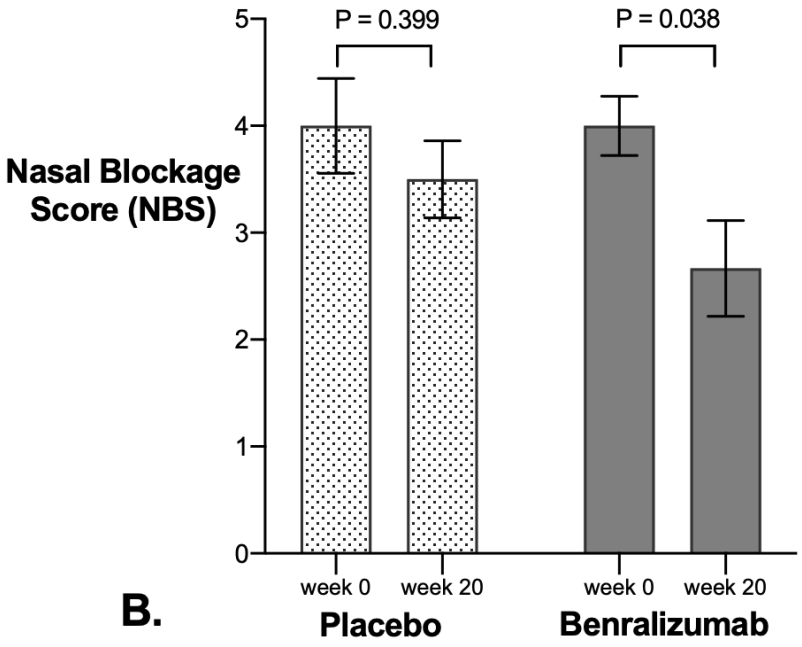


Figure 4. (A) Sino nasal outcome test (SNOT-22) symptoms survey is significantly reduced after 20 weeks treatment with benralizumab (P=0.001) and in the placebo group (P=0.024). (B) Nasal blockage score (NBS) component of the SNOT-22 questionnaire is significantly lower in the benralizumab treatment group (P=0.038) but not placebo (P=0.399).

Smell test

Sense of smell (UPSIT) improved significantly in all but one (92%) of the patients treated with benralizumab (SD=6.2; P=0.013). The change in mean UPSIT score at week 20 compared to baseline was 6.6 points, increasing from 12.2 to 18.8 answers correct out of a maximum of 40. Eight of twelve placebo patients also showed modest improvement in UPSIT scores but this did not reach statistical significance (SD=6.8; P=0.139).

Allergy Skin Testing and Eosinophils

Skin prick testing (SPT) was positive to at least one of the thirty aeroallergens tested at baseline in about half the patients in both the benralizumab and placebo groups. Benralizumab treated patients with six or more positive skin tests had minimal improvement in endoscopic nasal polyps score, whereas all five subjects with two or less positive SPT improved. As seen in Figure 5A, there was an inverse correlation between the number of skin tests positives and endoscopic NP score improvement (P=0.023). Total serum serum IgE and polyp score reduction were not correlated (P=0.071).

Benralizumab reduced blood eosinophil counts in all treated patients (100%). The absolute eosinophil count for the benralizumab treated group decreased from 698/µl (SD=412.7) to 20/µl (SD=49.7) at week twenty (P<0.001). Mean eosinophil count for the placebo group decreased slightly from 846/µl (SD=592.6) to 650/µl (SD=552.8) but was not significant (P=0.106). Blood eosinophils were undetectable in ten of the twelve patients treated with benralizumab but remained elevated in all subjects in the placebo group. In contrast to what was seen for allergen SPT, higher blood eosinophil counts correlated with better reduction in polyp scores, although this trend did not reach statistical significance (P=0.301). Nonetheless, as seen in Figure 5B, all benralizumab treated patients with blood eosinophil counts greater than 700/µl improved.

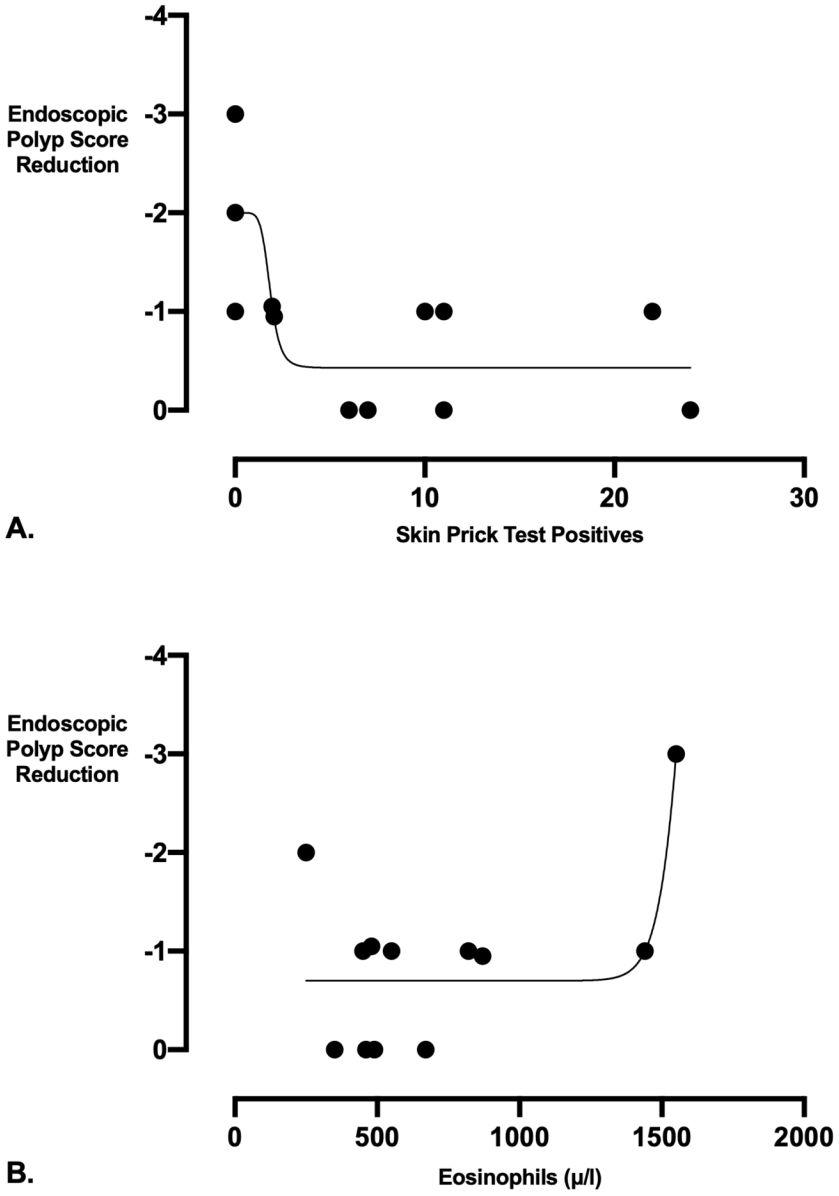


Figure 5. (A) Endoscopic polyp score reduction is inversely correlated with the number of allergen skin prick tests positives (P=0.023) such that in 100% (5/5) patients with 2 or less positive SPT benralizumab treatment reduced polyp size. (B) In contrast, 100% (4/4) of patients with blood eosinophil counts greater than 700/µl improved, although correlation was not significant (P=0.301). Four-parameter logistic curves interpolate the correlation inflection points of each graph.

If we divide the absolute blood eosinophil count by the number of positive allergen skin prick tests (Eos/SPT), the ratio appears to be a good predictor of benralizumab induced endoscopic nasal polyp score reduction (P=0.005). In other words, we found that high baseline eosinophil count and low number of positive allergen skin prick tests correlates with better benralizumab induced nasal polyp score reduction as seen in Figure 6A. Similarly, the ratio of blood eosinophil count to SPT correlates with benralizumab induced CT scan polyp score reduction, and this too was statistically significant (P=0.048) as shown in Figure 6B. These

preliminary findings in a small group of highly selected patients may suggest that there is a relationship between allergy skin testing, blood eosinophil count and benralizumab induced nasal polyp reduction.

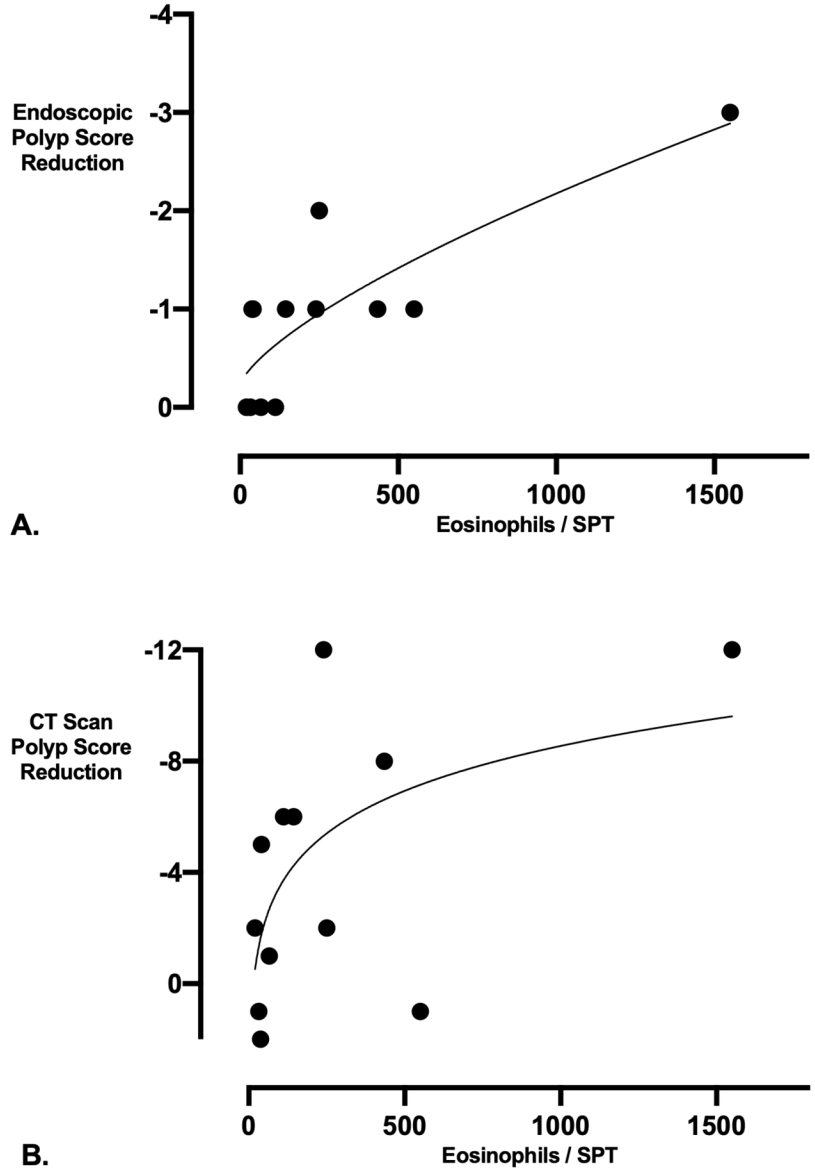


Figure 6. (A) Endoscopic polyp score reduction is well correlated with the Eos/SPT ratio (P=0.005). Higher baseline eosinophil count along with low number of allergen SPT positives predicts better response to benralizumab. (B) Similarly, the Eos/SPT ratio correlated with CT scan polyp score and also reached statistical significance (P=0.048). Four-parameter logistic curves interpolate the correlation inflection points.

Safety and Tolerability

Rescue medication use of triamcinolone nasal spray was 63% higher in the placebo group over the course of treatment (P=0.063). Prednisone use was discouraged with utilization being the same in both groups (P=0.972). There were no abnormalities seen on blood chemistry or liver function tests in either group.

Minor adverse events such as headache, URI or injection site discomfort was similar in both cohorts. One patient receiving placebo inadvertently became pregnant during the study but had already completed therapy and reported no adverse outcomes. Two patients receiving placebo developed an asthma exacerbation. There were no other significant adverse events and no drop-outs.

Discussion

This study represents the first randomized clinical trial designed to evaluate the use of benralizumab for nasal polyps. We showed that 30mg of benralizumab administered in four subcutaneous doses over a 20 week period significantly reduced nasal polyp size and nasal blockage score and reversed the impaired sensation of smell for the majority of patients. The reduction in nasal polyp size was evaluated by CT scan and endoscopy with independent confirmation by three blinded investigators. Benralizumab was well tolerated with no significant adverse events reported. Taken together, these observations suggest that benralizumab may have a role in the treatment of patients with severe CRSwNP.

Both benralizumab and placebo resulted in improved SNOT-22 scores, although by week 4 of treatment and upon regression towards the mean, only the benralizumab group continued to improve. One explanation for the initial SNOT-22 improvement in the placebo arm is that these patients received almost twice the amount of triamcinolone nasal spray rescue medicine compared to the benralizumab group. Furthermore, the nasal blockage score, arguably the most important SNOT-22 survey metric in this cohort, improved significantly only with benralizumab. Benralizumab resulted in improved sense of smell in all but one patient. For many patients sense of smell is the single most relevant clinical outcome.(13, 25) Future studies will need to address whether or not polyp size reduction follows the same course as SNOT-22 scores in that an initial reduction is followed by a plateau phase or if there is gradual continued reduction in polyp size over time. A large international phase 3 study on the effect of benralizumab on nasal polyps is currently underway designed to address this and other questions.

The absolute reduction in nasal polyp size was similar to that seen with other anti-IL-5 and anti-IL-4R biologic mAbs.(11, 15, 26) Benralizumab reduced mean nasal polyp size by approximately one point (range 0-4 each side). As with others studies of biologics or intranasal steroids, even a seemingly small decrease in polyp size for example from a score of 3 to a score of 2 can be associated with very significant clinical improvement.(11, 15, 26, 27)

We chose to enrol only NP patients refractory to standard therapies who had at least one previous polypectomy because this represents a group of patients with severe debilitating disease and high healthcare utilization. We do not know what the effects of benralizumab would be on patients with milder disease or those who may have recently underwent polypectomy. All patients required a blood eosinophil count of 300/µl or more for entry into our study but some improvement in nasal polyp scores were seen across a range of values.

Notably, all participants with a blood eosinophil count greater than 700/µl improved with benralizumab. Conversely, while a few aeroallergen sensitive subjects noted some reduction in polyp size, 5/5 patients with negative skin prick testing improved with benralizumab, although this represented only a small subset of the overall patient population studied. The ratio of blood eosinophils to SPT was highly correlated with a reduction in polyp size as demonstrated by endoscopy and CT scan. In other words, all patients with a high eosinophil count and low number of positive allergen skin prick tests improved with benralizumab. This correlation appears to be driven largely by one patient with a blood eosinophil count greater than 1500/µl, however even with removal of this outlier, the one-tailed Spearman rank correlation between eos/SPT and polyp size remains significant (P=0.024). Nonetheless, our data will need to be replicated in larger studies in order to consider incorporating these findings into clinical practice.

It is unknown if these outcomes associated with allergen skin prick testing would hold true for specific IgE measured in serum since both the physiological capacity to degranulate mast cells and basophils and the diagnostic sensitivity is superior with SPT. Benralizumab is known to have affinity for the IL-5 receptor on both eosinophils and basophils so inherent differences associated with detection of specific IgE in the skin versus the blood may have relevance when evaluating nasal mucosal biology.

Whether or not the Eos/SPT ratio helps identify a true categorical CRS endotype, defined for example as a high IL-5 and low IL-4 subgroup, still needs to be determined. Our study was not powered to delineate these CRS subgroups in detail. However, several groups have discussed the importance of subdividing CRS patients into various endotypes based on a number of biological markers such as type 1 cytokines (IL-12 and interferons), type 2 cytokines (IL-5, IL-4, IL-13), type 3 cytokines (IL-17), eosinophilic cationic proteins, IgE synthesis, fibrin products, TLR expression, microbial populations, and many others.(28-32) A recent National Institute of Allergy and Infectious Disease workshop and position paper highlighted the need for novel research into treatment and diagnosis strategies for CRSwNP in the era of new biologics.(25) Others have argued further that differentiating CRS based on the presence of polyps alone falls short of fully characterizing the complex and multifaceted inflammatory cascade in general.(33) Indeed, clinically robust and practical biomarkers are scarce. With trends towards increased precision medicine and an expanding array of highly targeted biologics, it has become increasingly important to identify simple tools to help clinicians determine which treatment is best for their patients.

The fact that our study showed a correlation between improved efficacy of benralizumab in patients with a higher eosinophil counts and low allergen sensitivity as determined by SPT does not exclude the possibility of this treatment being effective for other patient subsets. In addition, blood eosinophil counts are likely to fail as a direct surrogate for nasal mucosal inflammation. Laidlaw et. al. showed that a reduction of blood eosinophils alone with dexpramipexole inherently had no effect on nasal polyp size.(34) Nonetheless, the effect of benralizumab may go beyond that of mere blood eosinophil depletion in part based on the presence of IL-5 receptor on the surface of basophils and an associated downregulation of other inflammatory cells.

Indeed, our demonstration that patients with high eosinophils responded well to benralizumab is not unexpected. Asthma studies have also shown that while benralizumab is effective across a broad range of blood eosinophil counts, there was a trend towards greater efficacy with higher baseline eosinophil levels.(19) Clearly, more work needs to be done to determine which biomarkers are both predictive and practical for clinicians. Nonetheless, our study suggests that currently available tools such as blood eosinophil count and allergen skin prick testing may help provide some initial guidance until more sophisticated biomarkers are developed. This information, along with knowledge about concomitant comorbidities such as asthma, aspirin sensitivity, or atopic dermatitis may help physicians select an appropriate therapy for their patients.

The primary limitation in this study is the modest sample size. Randomization resulted in balanced distribution of most but not all baseline characteristics. As such, the percentage of aspirin sensitive subjects at baseline were higher in the placebo group. It is possible that this could have affected the outcome.

We also noted a transient improvement in SNOT-22 among the placebo group. Nonetheless, benralizumab treated patients significantly improved across all major and minor indices including endoscopic polyp score, CT scan, SNOT-22, nasal blockage score and smell test. Future studies will need to determine if polyp size and symptoms continue to improve past twenty weeks therapy and if benralizumab ultimately reduces the frequency of polypectomies and the need for corticosteroids.

In summary, our study is the first randomized clinical trial of benralizumab for the treatment of nasal polyps. Benralizumab administered 30mg SC over a 20 week period significantly reduced nasal polyp size, nasal blockage score and improved the sensation of smell for the majority of patients we treated with severe CRSwNP. Larger studies will need to be performed to confirm that benralizumab can be added to our treatment armament for this debilitating disease.

CONCLUSIONS

Benralizumab (anti-IL-5 receptor antibody) significantly reduces the size of nasal polyps, nasal blockage score, and rates of anosmia after 20 weeks therapy compared to baseline. The ratio of blood eosinophil to positive allergen skin prick tests may help predict which patients benefit the most from this biologic therapy.

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