Dexpramipexole Depletes Blood and Tissue Eosinophils in Nasal Polyps With No Change in Polyp Size

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Objective: Chronic rhinosinusitis with nasal polyps (CRSsNP) and eosinophilia is a disease of the upper respiratory tract for which few therapies are available. Because the oral investigational drug dexpramipexole serendipitously decreased blood eosinophils in amyotrophic lateral sclerosis studies, we assessed its safety, eosinophil-lowering activity, and preliminary clinical efficacy in patients with CRSsNP and eosinophilia.

Methods: Sixteen subjects with CRSsNP, absolute eosinophil count (AEC) ≥ 0.300 × 10^9/L, and polyp tissue eosinophils were evaluable for efficacy in a 6-month open-label, multi-center study of dexpramipexole 150 mg twice daily. The coprimary endpoints were change in AEC and change in total polyp score (TPS) from baseline to month 6, with additional clinical and histologic endpoints assessed.

Results: Thirteen of 16 subjects completed 6 months of dexpramipexole treatment. Geometric mean baseline AEC was 0.525 ± 0.465 eosinophils/μL and decreased to 0.031 ± 0.019 after 6 months of dexpramipexole treatment, a 94% reduction (P < 0.001). Ten of 16 subjects had eosinophil counts reduced to ≤ 0.020 × 10^9/L at month 6. In 12 subjects with nasal polyp biopsies at baseline and month 6, tissue eosinophils were reduced from a mean of 168 ± 134 to 9 ± 2 per high-power field (HPF) (P = 0.001), a 97% reduction from baseline. There was no significant reduction in TPS or improvement in other clinical endpoints. Dexpramipexole was well tolerated, with no drug-related serious adverse events.

Conclusion: Dexpramipexole treatment produced profound eosinophil-lowering in peripheral blood and nasal polyp tissue. Despite the near-elimination of polyp eosinophils, decreased TPS and nasal symptom improvement were not observed.

Key Words: Nasal polyps, chronic sinusitis, eosinophils, dexpramipexole.

Level of Evidence: 2

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INTRODUCTION

The term chronic rhinosinusitis (CRS) refers to a heterogeneous set of disorders united by nasal and paranasal sinus inflammation. Individuals with CRS can experience nasal congestion, rhinorrhea, facial pressure, and hyposmia or anosmia that often persist for years. CRS is divided into two general subtypes based on the presence of nasal polyps: CRS with nasal polyposis (CRSsNP) and CRS without nasal polyposis (CRSsNP), which are believed to have differing pathogenesis. In the United States and Europe, nasal polyps are primarily described as having type 2 inflammation, mediated by IL-4, IL-5, and IL-13, and are usually marked by extensive tissue infiltration of eosinophils. However, even within the subgroup of patients with CRSsNP and eosinophilia, the clinical presentation can be heterogeneous and the underlying mechanisms that contribute to disease pathology are not fully understood.

Histologically, nasal polyp tissue eosinophilia is found in 80% to 90% of CRSsNP cases in the Western world, and in many of these cases eosinophils constitute over 60% of the leukocytes in the polyp. Although the recruitment of eosinophils to the tissue is a typical feature of many inflammatory responses, this process can also promote tissue damage. In CRSsNP, both higher polyp tissue eosinophil density and higher blood eosinophil levels have been associated with greater postoperative polyp recurrence. However, neither the trigger(s)
for eosinophil recruitment into the tissues nor which of the pathologic consequences are directly eosinophil-driven have been fully elucidated. Available treatment options for patients with CRSwNP are currently limited to intranasal and systemic corticosteroids, antibiotics, and repeated surgeries.

Dexpmamipexole is a small molecule that has been in development as a treatment for amyotrophic lateral sclerosis (ALS). During the clinical development program in ALS, a significant reduction in peripheral blood eosinophils was observed. In the majority of ALS subjects exposed to dexpmamipexole, a persistent and marked reduction in peripheral blood eosinophil counts was seen beginning 1 to 2 months after drug initiation. Because dexpmamipexole was well tolerated in over 1 thousand ALS subjects following exposures up to 18 months, it may represent a novel therapeutic approach for the treatment of CRSwNP or other eosinophil-associated diseases.

Given the reduction of peripheral blood eosinophils observed in patients with ALS treated with dexpmamipexole, as well as the correlation observed in previous studies between the extent of eosinophilia and the degree of nasal polyp recurrence in CRSwNP, we hypothesized that dexpmamipexole treatment would lower peripheral blood eosinophils, reduce polyp size, and improve symptoms in patients with CRSwNP and eosinophilia. To test this hypothesis, we conducted an open-label, multi-center study of dexpmamipexole treatment in subjects with CRSwNP and eosinophilia.

MATERIALS AND METHODS

Participant Selection and Eligibility

Eligible patients were aged 18 to 69 years, had CRSwNP and rhinocytostic-confined bilateral polyps or computed tomography (CT)-confirmed bilateral mucosal sinus disease, and were recruited from six academic sites in the United States. Subjects were required to have a bilateral rhinoscopic total polyp score (TPS) of ≥ 4 (out of maximum score of 8), with a score of at least 2 for each nostril, and to report at least two of the following symptoms at the screening visit: anterior and/or posterior mucopurulent drainage, sinonasal obstruction, or decreased sense of smell. Subjects were also required to have a blood absolute eosinophil count (AEC) of ≥ 0.300 × 10^9/L and the presence of eosinophils confirmed histologically in the polyp biopsy at screening. Additional inclusion criteria at screening included a Sino-Nasal Outcome Test (SNOT-22) score of ≥ 7, stable use of an intranasal corticosteroid spray (< 1,000 μg/day beclomethasone or equivalent) for at least 4 weeks prior to starting study drug, and a reported history of sinusitis symptom responsiveness to oral corticosteroid use. Subjects were excluded if they had acute sinusitis, a recent upper respiratory tract infection, CT findings suggestive of allergic fungal rhinosinusitis, nasal septal deviation occluding one or both nostrils, sinonasal surgery ≤ 6 months prior to baseline, a history of ≥ 5 prior sinonasal surgeries, a known genetic basis for their CRS, or concomitant conditions making them not evaluable for the primary end point. All patients had symptoms consistent with CRS for at least 3 months prior to enrollment. Current or recent treatment with systemic or intrapolyptide corticosteroids (within 8 weeks prior to baseline) or investigational or biological drugs for CRS or respiratory disease were not allowed.

Study Design

We conducted a prospective open-label study of dexpmamipexole in subjects with CRSwNP and eosinophilia. After a 2- to 3-week run-in period, eligible subjects received dexpmamipexole 150 mg twice daily. Subjects returned for clinic visits at months 1, 3, and 6 to assess clinical response and monitor for safety, and also had laboratory measurements taken at months 2, 4, and 5. Thirty days after the month 6 end-of-study visit, subjects returned for a safety follow-up visit. All patients were required to continue their daily use of intranasal corticosteroid spray, which was stabilized for at least 4 weeks prior to the first dose of study medication and remained constant throughout the study.

Procedures

At screening; baseline; and months 1, 3, and 6, subjects had nasal endoscopy with structured video recording. A deidentified copy of the video recording was evaluated in a blinded manner by a central endoscopy rater using the TPS. This score is based on poly size, recorded as the sum of the right and left nostril scores, yielding a range of 0 to 8, with higher scores indicating worse status. At each clinic visit, subject-reported symptoms were recorded with SNOT-22, University of Pittsburgh Medical Center (UPMC) Sinonasal questionnaire (UPMC-SNQ), Asthma Control Questionnaire (ACQ-6), and the Short Form-12 quality-of-life questionnaire. Lung function was tested with spirometry, and smell assessment was measured with the Sniffin’ Sticks 12-smell identification olfaction test (12 common odors are presented in felt marker-like dispensing devices, and the subject is asked to choose one of four answers that describe the odor from a multiple-choice list). At baseline and month 6, subjects had a sinus CT scan, which was scored by a blinded central rater using the Zinreich-modified Lund-Mackay scoring method.

Nasal polyp biopsies were obtained at the screening or baseline visits and the month 6 visit after completion of other protocol-dictated procedures. Topical 4% lidocaine or 0.45% tetracaine was used as a local anesthetic, and during nasal endoscopy a single 0.5-cm biop was removed using forceps. The biopsy tissue was placed in 10% formalin and processed for routine histopathology with hematoxylin and eosin (H&E) staining and toluidine blue staining (Quest Diagnostics, Teterboro, NJ). The number of eosinophils were quantified, and the number of mast cells were catorized assessed (“none,” “scattered/rare,” moderate,” or extensive”) per 450 × high-powered field by a pathologist blinded to the study design. A total of four fields in the area of maximal eosinophil infiltration were assessed, and the average of those values used.

Outcome Measures

The coprimary endpoints were 1) change from baseline in peripheral blood eosinophil counts after 6 months of dexpmamipexole treatment, and 2) change from baseline in TPS after 6 months of treatment. Secondary endpoints included the change from baseline in peripheral blood eosinophil counts after 3 months of treatment, change from baseline in TPS after 3 months of treatment, and incidence and severity of adverse events. Additional prespecified outcomes included the effect of 6 months of dexpmamipexole on sense of smell, CT scan evidence of sinonasal disease, asthma control, and quality-of-life measures.
**Statistical Analysis**

For the change in peripheral blood AEC, we compared the difference in AEC between the baseline eosinophil count (calculated as mean of the screening and baseline visit levels) and the on-treatment time points using a two-sided paired t test. Because the data were not normally distributed, the analysis was performed on a log scale and the geometric mean was presented. Reduction ratios were calculated for blood and tissue as the eosinophil count at month 6 on dexpramipexole divided by the baseline eosinophil count. Geometric means were calculated on the log scale and transformed back to the original scale. The change in TPS from baseline to month 3 and month 6 was also compared using a two-sided paired t test, as were the additional prespecified outcomes. For the month 6 coprimary endpoints, the last observation carried forward was used to replace missing data due to dropout after month 3. Correlation of blood and eosinophil lowering was determined using the Spearman rank test. If not otherwise noted, means were used as a measure of central tendency. The categorical histologic mast cell assessments in nasal polyp tissue were analyzed with a Wilcoxon matched-pairs signed rank test. Data are presented ± standard error, unless otherwise specified. Adverse event summaries were reported on the safety population. Clinical laboratory tests, electrocardiogram (ECG) measures, and vital signs were summarized using descriptive statistics.

**RESULTS**

**Study Population and Baseline Demographics**

Twenty subjects gave written consent, received study drug, and were included in the safety population. Of these, 16 subjects completed both a peripheral blood eosinophil count and a total polyp score at the month 3 visit and were included in the efficacy population, and 13 subjects completed the full 6-month primary assessment phase. Baseline characteristics for the efficacy population are shown in Table I. Notably, 13 of 16 subjects had a history of asthma. The subjects’ asthma was generally mild and well controlled, with a mean baseline ACQ-6 and forced expiratory volume in 1 second (FEV1) of 1.2 and 84% predicted, respectively.

**Absolute Eosinophil Count and Tissue Eosinophils and Mast Cells**

Peripheral blood AEC was significantly decreased by the month 1 visit, continued to drop through month 3, and was sustained through month 6 (Fig. 1A). The AEC at month 6 was significantly decreased by 94% (1 < 0.001) (Fig. 1B). Ten of 16 subjects (62.5%) had eosinophil counts reduced to < 0.020 × 10^9/L at month 6.

Eosinophil recovery after cessation of dexpramipexole was evaluated in the seven subjects who had an AEC from the safety follow-up visit and an AEC on dexpramipexole of ≤ 0.05 × 10^9/L at their end-of-study visit. In the five of seven subjects who discontinued dexpromipexole for a mean of 27 days (range 15–35 days), AEC recovered to only 1.4% (range 0%–7%) of baseline. In the other two subjects who were off dexpramipexole for 36 and 46 days, AEC recovered to 26% and 35% of baseline values, respectively. The other nine subjects either had insufficient eosinophil lowering to allow meaningful evaluation of recovery or did not have a complete blood count from the safety follow-up visit.

Nasal polyp biopsies were performed at screening/baseline and at the month 6 visit. In the 12 subjects with evaluable biopsies, eosinophil numbers decreased from a geometric mean of 168 ± 134 to 5 ± 2 per HPF, P = 0.001, demonstrating a 97% reduction in tissue eosinophilia (Fig. 2 and Fig. 3A). Mast cells increased significantly over the same period (Fig. 3B). There was no significant change in nasal polyp tissue neutrophils (data not shown). Additionally, blood and tissue eosinophil lowering were highly correlated, R = 0.80, P = 0.0018 (Fig. 3C).

**Total Polyp Score and Other Endpoints**

In contrast to the substantial change in blood AEC and the histologic finding of dramatically decreased tissue eosinophilia, TPS was unaffected at either the month 3 or 6 time points (Fig. 3D) (Table II). A subgroup analysis of the 10 subjects whose AEC was reduced ≥ 95% at month 6 did not show TPS lowering (data not shown). Other indices of CRS disease activity, including SNOT-22, sinus CT score, and Sniffing Sticks olfactory test, were also not affected (data not shown). In subjects with a history of

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**TABLE I.** Baseline Characteristics of Efficacy Population

<table>
<thead>
<tr>
<th>Dexpromipexole Efficacy Population (n = 16)</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex, n (%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
</tr>
<tr>
<td>Previous sinonasal surgery, n (%)</td>
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<tr>
<td>Number of systemic corticosteroid</td>
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<tr>
<td>interventions within the past year n</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<tr>
<td>Snot22</td>
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<tr>
<td>Number of sinus infections in the past year Mean (SD) 1.9 (1.8)</td>
</tr>
<tr>
<td>Yes 15 (93.8) No 1 (6.2)</td>
</tr>
<tr>
<td>Asthma history</td>
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<tr>
<td>Aspirin-exacerbated respiratory disease</td>
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SD = standard deviation.
asthma, the ACQ-6 and FEV1 values were unchanged by treatment with dexpramipexole (Table II).

Safety and Adverse Events
Eighteen of the 20 subjects in the safety population reported at least one treatment-emergent adverse event. Of these, five subjects reported adverse events that were assessed by the site investigator as possibly related to study drug, including dyspepsia, worsened nasal congestion and headache, decreased appetite, insomnia (2 subjects), urticaria, intranasal paresthesia, and vertigo. All of these resolved, either despite continuation of study drug or—for three subjects with adverse events of vertigo, nasal congestion and headache, and dyspepsia, respectively—following study drug discontinuation. One subject had a serious adverse event of abdominal pain, which ultimately was diagnosed as cholecystitis and resolved after cholecystectomy.

At month 6, mean neutrophil, monocyte, and lymphocyte counts were decreased 11% to 16% from their baseline values (Supporting Table SI). Basophil counts were reduced 27%. There were no events of neutropenia (defined as neutrophil count < 1.50 x 10^9/L). Platelet counts and red cell counts were not substantively changed. There were no significant changes in clinical laboratory tests, ECG measures, or vital signs.

DISCUSSION
This open-label study aimed to determine whether treatment with dexpramipexole could reduce the magnitude of blood and nasal polyp tissue eosinophilia and decrease nasal polyp size in patients with severe CRSwNP and eosinophilia. The study demonstrated a highly statistically significant change from baseline in peripheral eosinophilia after 6 months of treatment, with a reduction of 94% (Fig. 1). Significant lowering of blood eosinophil was seen by the month 1 visit, with near maximal reduction measured by month 2 (Fig. 1), which was sustained throughout the 6-month primary assessment phase. Notably, the onset of eosinophil lowering was more rapid, and the magnitude greater than that seen in either of the prior clinical trials in ALS,9,10 suggesting that the targeted eosinophil-lowering effect of dexpramipexole may be more robust in patients with eosinophil-associated disease.
A responder analysis demonstrated that eosinophil lowering by dexpramipexole was bimodal. The majority of subjects (62.5%) were hematologic responders with high-magnitude eosinophil lowering (> 95%), whereas a minority were partial responders with only a 30% to 50% reduction. This heterogeneity of response may represent genetic, pathophysiologic, or adherence differences among subjects.

Given that sinus and polyp tissue eosinophilia are thought to play an important role in CRSwNP and eosinophilia pathogenesis, change from baseline in polyp tissue eosinophil count after 6 months of treatment was evaluated in the 12 subjects who had histologically evaluable nasal polyp biopsies. Indeed, a 97% reduction in polyp eosinophil counts was noted (Fig. 2 and 3), which is an even greater tissue reduction than is seen after treatment with prednisone.14 Given that most patients with CRSwNP and eosinophilia report therapeutic benefit from prednisone treatment, including reduction in nasal congestion and improvement in sense of smell,15,16 it could be expected that the eosinophil-lowering properties of dexpramipexole would lead to similar symptomatic improvements. However, there was no change in the size of nasal polyps, measured as TPS during rhinoscopy, or in any of the measured nasal symptoms. This suggests that other cells play a significant role in both the size/bulk of nasal polyps and the consequent symptoms. In fact, other data from anti-IL-5 agents may suggest the same conclusion. Mepolizumab, a humanized anti-IL-5 monoclonal antibody, decreases the eosinophil numbers in bronchial mucosa biopsies by half17 in patients with eosinophilic asthma (to date, no nasal polyp biopsy results have been published with mepolizumab). However, the mepolizumab-induced changes in nasal polyp size are quite small, with modest reductions observed in slightly more than half of the nasal polyp patients treated with mepolizumab.18 Therefore, initial data suggest that solely targeting eosinophils for cellular depletion from existing nasal polyps may be an insufficient therapeutic approach for these patients. Whether eosinophils play a driving role in the development of the polyps, either at the initial start of the disease process or during the regrowth of polyps following surgical polypectomy, remains an unanswered question. Accordingly, the efficacy of dexpramipexole in controlling polyp regrowth in conjunction with surgical polypectomy or corticosteroid-induced remission should be evaluated.

![Graphs and images](https://example.com/graphs.png)

**Fig. 3.** Changes from baseline in the efficacy population are shown for (A) eosinophil numbers (quantified) in nasal polyp biopsies, (B) mast cell numbers (categorical), and (D) total polyp score. Data are shown as geometric mean +SE (A) or mean + SD (D). Correlation between the eosinophil RRs, calculated as month 6 over baseline, in the blood and the nasal polyp tissue is shown in (C). Data points that overlapped were moved slightly to enhance visibility. RR = reduction ratio; SD = standard deviation; SE = standard error.

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**TABLE II.**

<table>
<thead>
<tr>
<th>Change From Baseline in Total Polyp Score in the Efficacy Population After 3 and 6 Months of Treatment With Dexpramipexole</th>
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<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Number of subjects</td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td><strong>Month 3</strong></td>
</tr>
<tr>
<td>Number of subjects</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<tr>
<td><strong>Secondary analysis</strong></td>
</tr>
<tr>
<td>Paired t test 95% CI</td>
</tr>
<tr>
<td>Paired t test P value</td>
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<tr>
<td><strong>Month 6/LOCF</strong></td>
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<tr>
<td>Number of subjects</td>
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<tr>
<td>Mean</td>
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<tr>
<td><strong>Primary analysis</strong></td>
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<tr>
<td>Paired t-test 95% CI</td>
</tr>
<tr>
<td>Paired t-test P value</td>
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</tbody>
</table>

CI = confidence interval; LOCF = last observation carried forward; SD = standard deviation.
The overrepresentation of mast cells and mast cell mediators within nasal polyps is well described, although the exact clinical consequences driven by the presence of mast cell are not fully understood.19–22 In our study, the unexpected qualitative finding of increased numbers of mast cells within the nasal polyp biopsies following treatment with dexpramipexole warrants further mechanistic investigation. It is not clear whether this finding represents a direct mast cell-enhancing drug effect of dexpramipexole or simply a histological consequence in which the absence of eosinophils allowed for a proportional increase in the numbers of mast cells that can be visualized in each HPF.

As seen in the phase 2 and 3 ALS trials, dexpramipexole produced minor mean reductions in neutrophil, monocyte, and lymphocyte counts, with a more substantial reduction in basophil counts.8 Notably, in this current study no subject had neutrophenic lab values at any time. Platelet count and hemoglobin changes were unsubstantial, recapitulating the previous findings in ALS. The eosinophil and basophil lowering observed in both the current and previous studies may reflect activity of dexpramipexole on signaling pathways affecting both eosinophil and basophil development, potentially targeting the common human eosinophil–basophil progenitor cell.23 Although the molecular target for the eosinophil-lowering activity of dexpramipexole remains under investigation, the slow onset of action suggests an effect on eosinophil hematopoiesis. In 3-week in vitro CD34 + human cell culture experiments, dexpramipexole was shown to significantly reduce the number of mature eosinophils and increase immature eosinophils (unpublished results), supporting a hypothesis of maturational arrest. This mechanism is further reinforced by results observed in bone marrow aspirates from subjects in a dexpramipexole hypers eosinophilic syndromes clinical trial.24 In subjects with hematologic responses to dexpramipexole, the biopsies showed a relative increase in eosinophil precursors with a lack of mature eosinophils, and no effect on other myeloid or erythroid cell lineages.

A limitation of this pilot study is the open-label design and lack of control group. That said, the high-magnitude eosinophil depletion observed in both blood and tissue in this study is not a feature of the natural history of this disease, is consistent with the highly significant eosinophil-lowering effect previously seen in placebo-controlled ALS trials, and therefore in our view is attributable to dexpramipexole.

CONCLUSION
Dexpramipexole was found to be a well-tolerated medication with high-magnitude eosinophil-lowering activity, both in the peripheral blood and inflammatory tissues of the nasal polyp. Specifically targeting eosinophils as a treatment modality for patients with chronic eosinophilic nasal polyps did not result in clinically meaningful improvements in this trial design; however, dexpramipexole is now positioned for potential use in other inflammatory diseases that may be more directly eosinophil-driven.

Acknowledgment

BIBLIOGRAPHY