

The Effect of Desloratadine on Eosinophil/Basophil Progenitors and Other Inflammatory Markers in Seasonal Allergic Rhinitis: A Placebo-Controlled Randomized Study

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Key Words

Antihistamine · Eosinophil/basophil progenitors ·
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Abstract

Background: Eosinophil/basophil (Eo/B) progenitors fluctuate in the peripheral circulation during seasonal allergen exposure in atopic subjects. Several drugs have been shown to modulate Eo/B progenitor levels in the peripheral blood but, to date, the possible effect of antihistamines on Eo/B progenitors has not been explored. Our objective was to evaluate whether the antihistamine desloratadine (DL) can modulate peripheral blood Eo/B progenitors or other markers of allergic inflammation.

Methods: We performed a randomized double-blind placebo-controlled study on the effects of DL on peripheral blood Eo/B progenitors in subjects with symptomatic, seasonal allergic rhinitis during a ragweed pollen season. Forty-five subjects were randomized to treatment for 4 weeks with DL 20 mg daily or placebo. **Results:** The expected fall in the number of Eo/B progenitors from baseline to 2 weeks of treatment was seen in the placebo group [median drop of 1.0 colony-forming unit (CFU)/10⁶

cells], and was greater than in the DL group (median drop of 0.0 CFU/10⁶ cells) ($p = 0.013$). The change in histamine concentration per colony from baseline to 2 weeks of treatment was lower in the DL group (median decrease of 6.1 pg/colony) compared to placebo (median increase of 1.8 pg/colony) ($p = 0.01$). An increase in the nasal lavage eotaxin concentration from baseline to 4 weeks of treatment was statistically significant in the placebo group but not in the DL group. Eo/B CFU were not affected by varying in vitro concentrations of DL. **Conclusion:** These results suggest that DL can modulate aspects of allergic inflammation in vivo through mechanisms other than simple blockade of H₁ histamine receptors.

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Introduction

The eosinophil, long recognized as a central player in allergic inflammation, shares a common myeloid progenitor with the basophil, termed the eosinophil/basophil (Eo/B) progenitor. Single hemopoietic progenitors separated by density gradient from bone marrow (BM) or peripheral blood will form pure eosinophil, pure basophil and/or mixed eosinophil-basophil colonies [Eo/B colony-

forming units (CFU)] when incubated in semisolid media for 10–14 days with appropriate hemopoietic cytokines such as IL-3, IL-5 and granulocyte/macrophage colony-stimulating factor (GM-CSF).

The clinical relevance of Eo/B CFU progenitors in the blood and BM of patients with a variety of allergic airway disorders, especially those with allergic rhinitis, nasal polypsis and asthma has previously been demonstrated [1–9]. In these patients, fluctuations of Eo/B CFU in the peripheral blood are observed: higher out of season, and increased immediately after allergen exposure, the latter presumably related to systemic signaling of the BM by hemopoietic cytokines elaborated from involved tissues [1–4, 6, 7, 9]. During pollen season, the numbers of peripheral blood Eo/B CFU decline possibly due to their migration to sites of allergic inflammation. We have consistently shown selective and relevant fluctuations in circulating progenitors for Eo/B CFU in patients with a variety of allergic airway disorders [1, 3, 8, 10, 11], supporting our working hypothesis that these hemopoietic progenitor cells contribute to the unique inflammatory cell infiltrate associated with allergic inflammation and that the tissue eosinophilia seen in allergic tissue is, at least in part, a result of *in situ* differentiation of Eo/B progenitors.

The mechanisms by which Eo/B progenitors traffic from the BM through the blood and into allergic tissue have not yet been fully elucidated, but clearly involve multiple steps. These include release of progenitors from storage pools in the BM, chemotaxis, and cell adhesion. The chemokine eotaxin likely plays an important role releasing Eo/B progenitors from the BM [12] and CCR3, the eotaxin receptor, is expressed on progenitor cells and is upregulated after allergen challenge in asthmatics [13].

Many drugs are known to have effects on Eo/B progenitors including corticosteroids [14, 15], leukotriene antagonists [16], and retinoic acid [17]. While antihistamines are a mainstay for treatment of allergic diseases such as allergic rhinitis [18], their effect on Eo/B progenitors has not yet been explored. In this study, the effects of the antihistamine desloratadine (DL) on the numbers and characteristics of Eo/B CFU in the blood of subjects with seasonal allergic rhinitis (SAR), as well as the concurrent levels of allergic inflammatory mediators and cytokines in the nose, have been examined in order to investigate the therapeutic potential of DL on one of the key components of systemic manifestations of allergy.

Materials and Methods

Study Patients and Design

Prior to the ragweed pollen season of 2000, adult subjects with SAR due to ragweed pollen were recruited at McMaster University in Hamilton, Ontario, Canada. Subjects had a positive history of allergic rhinitis symptoms during the 2 previous ragweed pollen seasons (mid-August to late-September) and a positive skin prick test to ragweed pollen extract. Subjects were excluded if they had any significant medical conditions (other than SAR) or if they had significant allergic symptoms in the 2 months prior to the ragweed pollen season. Forty-five subjects gave informed consent, and were enrolled. At the onset of allergic symptoms, subjects were randomized in a double-blind manner to treatment for 4 weeks with placebo or DL 20 mg daily, a dose previously shown to be both safe and effective. They were not allowed any concurrent treatment with steroids or other antihistamines but were supplied with rescue medications if severe symptoms of allergic rhinoconjunctivitis occurred. Rescue medications included intranasal oxymetazoline (Dristan®), oral pseudoephedrine, and sodium cromoglycate eye-drops (Opticrom®). Subjects were studied 2 weeks into the treatment period (peak ragweed season), and then again at 4 weeks after the onset of treatment (end of season). At each visit, blood samples were taken and nasal lavage was performed. Symptoms and rescue medication use were recorded throughout the study in a diary. No subjects were lost to follow-up. The study was approved by the Ethics Committee of the Hamilton Health Sciences Center.

Eo/B Colonies

Methylcellulose assays for peripheral blood Eo/B CFU were performed as previously described [2]. Mononuclear cells were separated from whole peripheral blood via density gradient separation and incubated in plastic flasks for 2 h at 37°C and 5% CO₂ to remove adherent cells. Nonadherent mononuclear cells (NAMC) were cultured in duplicate at 1×10^6 cells per 35×10 -mm tissue culture dish in the presence of 10 ng/ml recombinant human GM-CSF and incubated for 14 days at 37°C and 5% CO₂. For a separate *in vitro* DL experiment, varying concentrations of DL (10^{-8} – 10^{-6} M) were added to the NAMC in addition to recombinant human GM-CSF. At day 15, Eo/B type granulocyte colonies (>40 cells) were enumerated in two replicate methylcellulose plates under inverted light microscopy and expressed as Eo/B CFU per 1×10^6 NAMC plated. As previously described [1, 19], the Eo/B colonies were identified by morphology as tight, granulated, round refractile cell aggregations.

Nasal Lavage and Cytokines

Briefly, 5 ml of PBS (Gibco) were instilled into each nostril while the neck was held extended approximately 30 degrees from horizontal and the head held back. The saline was held in the nasal cavity for 10 s and then drained into a plastic specimen cup. This was done twice each sampling day 15 min apart and the 2 samples were pooled. An equal volume of 10% dithiothreitol (Calbiochem) was added. The sample was then vortexed, rocked for 15 min, then centrifuged. Supernatants were stored at –20°C and assayed together at a later date. The cell pellet was resuspended with D-PBS (Gibco) and cytopins were prepared. Slides were stained with Diff Quick (Dade Behring) then covered with permamount. Eosinophils were enumerated as a percentage of the total nucleated cell count.

For cytokine measurements, nasal lavage supernatants were thawed then analyzed with specific cytokine kits for GM-CSF (Quantikine® HS, R&D Systems; detection limit 1 pg/ml), IL-5 (Quantikine, R&D Systems; detection limit 7.8 pg/ml), and eotaxin (Opt-EIA™, Pharmingen; detection limit 6.3 pg/ml).

Colony Histamine Assay

The composition of Eo/B colonies is influenced by the duration of the incubation period, with basophil-rich colonies appearing earlier than those containing primarily eosinophils [20]. To identify basophil-containing colonies, the histamine content of single colonies was measured, thus providing an indirect measure of colony maturity. Histamine content of individual colonies was measured by modified radioenzymatic histamine assay as previously described [21]. Samples were stored at -70°C until time of the histamine assay. Cultured cell suspensions were boiled to inactivate histaminase.

Statistics

Medians were used for data that were not normally distributed. The Wilcoxon rank sum test was used to compare between treatment groups, while the *p* value for comparison within a treatment group at different time intervals was based on the sign test. Results were deemed statistically significant for $p < 0.05$. The correlation of nasal lavage cytokine levels and peripheral blood Eo/B CFU was performed with Spearman's rho correlation.

Results

Subjects

Forty-five subjects with SAR and ragweed allergy were entered into the study; 22 were randomized to DL and 23 to placebo. Baseline demographic characteristics were similar in the two groups (table 1). The placebo group was slightly older than the DL group (mean age 36.5 and 30.7 years, respectively) and had a longer history of SAR (20.9 and 14.8 years, respectively). None of these differences was statistically significant.

Pollen Counts

Ragweed pollen counts began to rise on August 17, peaked on August 27, and then quickly dropped by the first week of September (fig. 1).

Symptom Scores

At the end of treatment, both total nasal and non-nasal symptom severity scores were lower in the DL group, but comparison with the placebo group did not reach statistical significance. For individual symptom scores, there was a significant improvement for nasal itching and ocular itching and burning in the DL group compared to the placebo group, with mean reductions in symptom scores from day 1 to day 28 of 0.5 ($p = 0.005$) and 0.8 ($p = 0.003$),

Table 1. Baseline characteristics of the placebo and DL treatment groups prior to randomization

Characteristic	Placebo (n = 23)	DL (n = 22)	p value
Sex			
Male	10 (43.5)	9 (40.9)	
Female	13 (56.5)	13 (59.1)	NS
Age			
18 to <30	9 (39.1)	14 (63.6)	
30 to <60	14 (60.9)	8 (36.4)	NS
≥ 60	0	0	
Mean	36.5	30.7	
Height, cm			
Mean ± SD	167.1 ± 11.4	171.2 ± 10.4	NS
Weight, kg			
Mean ± SD	72.7 ± 16.8	75.7 ± 16.0	NS
Duration of SAR, years			
Mean ± SD	20.9 ± 10.6	14.8 ± 12.1	NS
Perennial rhinitis history			
Yes	4 (17.4)	2 (9.1)	NS
Symptoms at study onset, mean ± SD			
TSSS	9.0 ± 2.6	8.1 ± 3.1	NS
TNSSS	5.0 ± 1.8	4.8 ± 2.0	NS
TNNSSS	4.0 ± 1.6	3.3 ± 2.1	NS

NS = Not significant ($p > 0.05$); TSSS = total symptom severity score; TNSSS = total nasal severity symptom score; TNNSSS = total non-nasal symptom severity score. Figures in parentheses indicate percentages.

respectively. Rescue medication use was higher in the placebo group for both oral pseudoephedrine and sodium cromoglycate eyedrops.

Eo/B Colonies

Changes in Eo/B CFU counts from day 1 to day 15 and day 28 were compared between the placebo and DL groups (fig. 2). The Eo/B CFU counts decreased significantly in the placebo group (median decrease of $1.0 \text{ CFU}/10^6$ cells) when compared to the DL group at day 15 (median decrease of $0.0 \text{ CFU}/10^6$ cells) ($p = 0.013$). No significant changes were seen at day 28 in either the placebo or DL group when compared to day 1. At the time of randomization, an unexpected difference was seen in baseline Eo/B CFU between the placebo group (median 4.3) and the DL group (median 0.9).

In the separate in vitro laboratory study, Eo/B CFU were taken from subjects prior to the ragweed pollen season and were cultured with GM-CSF or IL-5 with various concentrations of in vitro DL from 10^{-8} to 10^{-6} M (plasma concentrations which would be expected by a typical

Fig. 1. Ragweed pollen counts for the year 2000 ragweed pollen season in the Hamilton area. Ragweed pollen was measured by rotation impaction sampling equipment and reported by the regional sampling station.

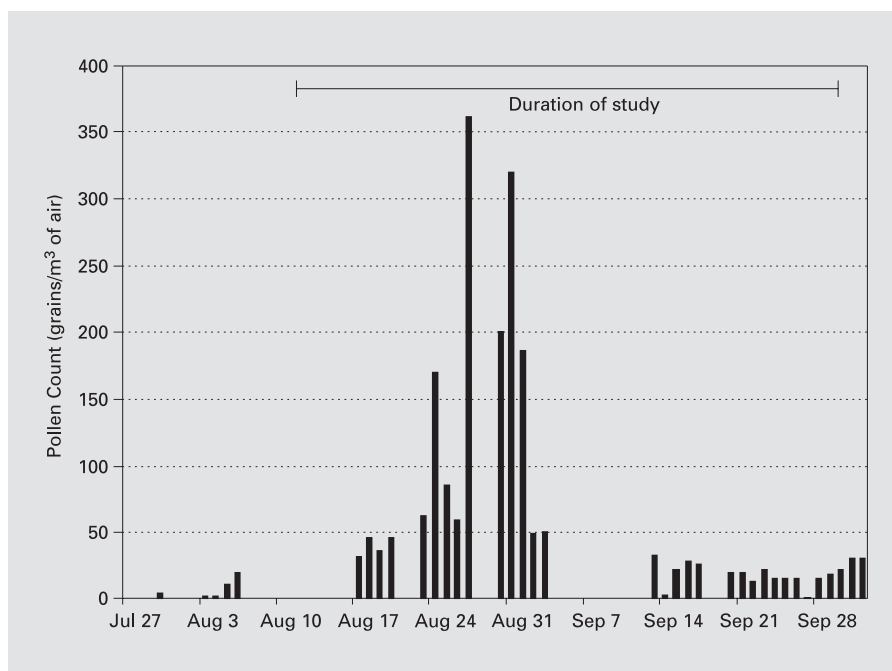
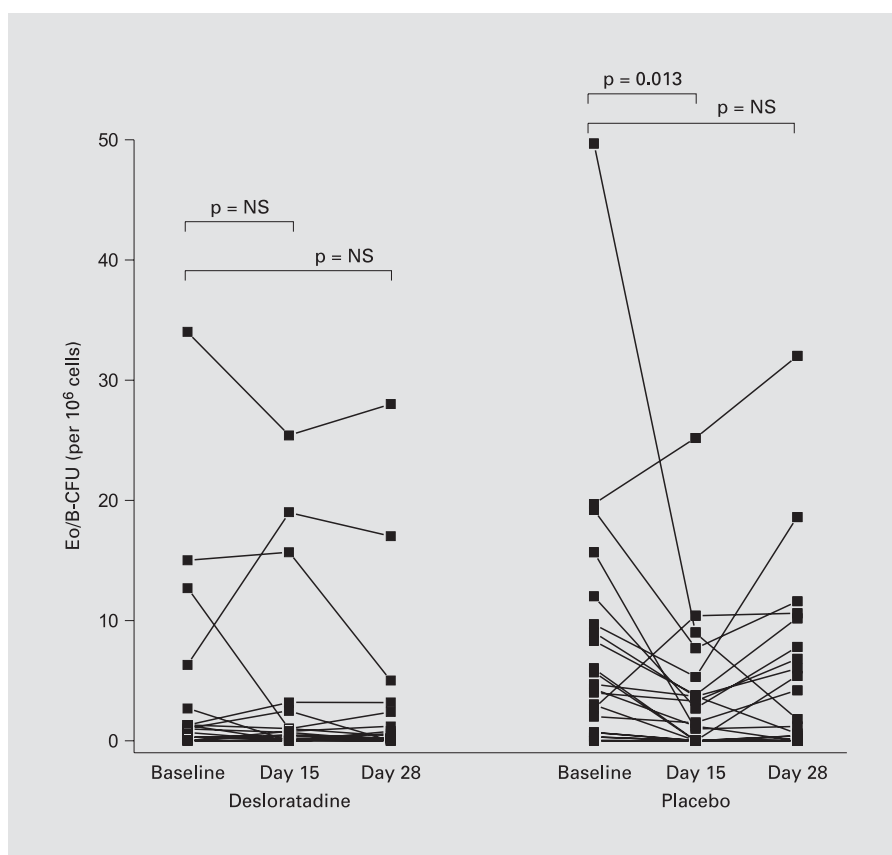


Fig. 2. Effect of DL on GM-CSF-stimulated peripheral blood Eo/B progenitor counts throughout a ragweed pollen season. Eo/B CFU were cultured from the peripheral blood of subjects taking placebo or DL.



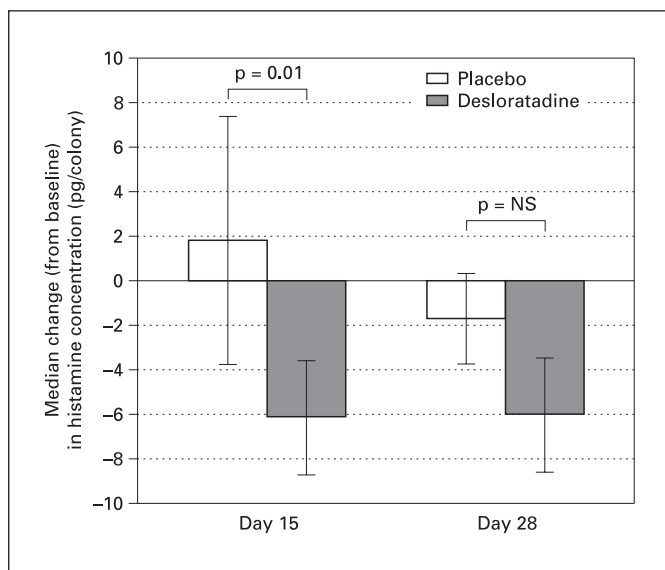


Fig. 3. Effect of DL on GM-CSF-stimulated peripheral blood Eo/B colony histamine content throughout a ragweed pollen season (expressed as median change from day 1 CFU $\pm$ SEM).

oral dose of DL). No statistically significant differences in Eo/B CFU between the groups were found (data not shown).

Eo/B Histamine Content

The median histamine concentration per colony for the DL group was 7.9 pg, 2.8 pg, and 2.2 pg at baseline, day 15 and day 28, respectively, and 3.6 pg, 9.2 pg, 0.7 pg at baseline, day 15 and day 28, respectively, for the placebo group. The median change in histamine concentration per colony from day 1 to day 15 of treatment was significantly less in the DL group (median decrease of 6.1 pg/colony) compared to placebo (median increase of 1.8 pg/colony) ($p = 0.01$; fig. 3). No difference was seen in the median change between the two groups at day 28.

Nasal Lavage Cytokines and Eosinophils

Nasal lavage cytokine concentrations were assessed. IL-5 and GM-CSF were below levels of detection. On examination of eotaxin, the mean eotaxin concentration for the placebo group was 21.1 mg, 21.8 mg, and 24.8 mg at baseline, day 15 and day 28, respectively, and 23.3 mg, 21.9 mg, and 25.0 mg at baseline, day 15 and day 28, respectively, for the DL group. The mean change in eotaxin levels at week 2 was +0.7 in the placebo group compared to -1.4 in the DL group ($p = 0.133$). At week 4, more subjects in the placebo-treated group had an eo-

taxin increase compared to the DL-treated group ($p = 0.011$ on placebo, $p = 0.167$ on DL). In addition, a negative correlation was found between Eo/B CFU and nasal lavage eotaxin levels for the placebo group ($r_s = -0.378$, $p = 0.001$), but no significant correlation was found for the DL group. Nasal lavage eosinophil counts were not significantly different between the placebo and the DL groups (data not shown).

Discussion

The association of eosinophils with allergic inflammation has been known for nearly a century. An important contribution to this eosinophilic inflammation is made by Eo/B progenitors supplied by the BM that traffic through the peripheral circulation and migrate to local tissues. The results obtained from the placebo group in our study confirm previous observations that peripheral blood Eo/B CFU decline at the peak of a pollen season in sensitized symptomatic atopic individuals [2, 8]. Since this drop in Eo/B CFU did not occur in the DL group, we propose that this reflects the efficacy of DL in blocking mechanisms involved in the mobilization of Eo/B CFU from the peripheral circulation to tissue sites of inflammation. Accompanying the expected drop in peripheral blood Eo/B CFU at day 15 from baseline was an increase in colony histamine content and in nasal lavage eotaxin. Conversely, in the DL group, the expected drop in peripheral blood Eo/B CFU was not seen at day 15, and accompanied by a decrease in colony histamine content and in nasal lavage eotaxin. The change in histamine content was statistically significantly different between the 2 groups ($p = 0.01$), and trended toward significance ($p = 0.133$) for nasal lavage eotaxin. These data, taken together, are compatible with an inhibitory effect of DL on basophilic differentiation within the colonies, and therefore on the process of basophil/eosinophil differentiation in general.

To investigate the possibility that our results could be explained by a direct effect of DL on Eo/B differentiation, we cultured Eo/B CFU in the presence of concentrations of DL in vitro that would be achieved therapeutically in plasma in the presence of IL-5 and GM-CSF; no such direct effect of DL was noted. Since in vitro DL showed no significant direct effect on Eo/B production, we propose that the significant differences found between the DL and placebo groups are the result of systemic in vivo direct or indirect effects on progenitor migration and/or maturation.

One possible mechanism to explain the lack of decline of the Eo/B progenitors in the DL group is suggested by the nasal lavage cytokine data. There was a statistically significant increase in the nasal lavage concentration of eotaxin at the end of the treatment period in the placebo group but not in the DL group. Since eotaxin is an important chemokine for eosinophils [22], and has effects on Eo/B CFU, allowing mobilization from the BM into the peripheral blood [12], DL may therefore be exerting an effect on Eo/B progenitor migration and tissue recruitment, directly or indirectly, by inhibiting local eotaxin production from the nasal mucosa and preventing systemic trafficking of Eo/B progenitors from the blood to the local nasal tissue. Our finding of a negative correlation between Eo/B CFU and nasal lavage eotaxin levels for the placebo, but not DL group, is consistent with the notion that eotaxin plays a role in directing progenitors into the nasal tissue, and that this process is partially blocked by DL treatment. Recently, Sergejeva et al. [23] have demonstrated that intranasal corticosteroid therapy during a pollen season inhibited chemokine-mediated recruitment of hematopoietic progenitors into nasal tissue; i.e., subjects with allergic rhinitis had significant seasonal increases in CD34+ cells and CD34+ progenitors expressing the chemokine receptor CXCR4 in the nasal mucosa, a process which was blocked by pretreatment with intranasal fluticasone.

Two other potentially relevant cytokines, GM-CSF and IL-5, were undetectable in the nasal lavage samples (data not shown). Linden et al. [8], in a similar SAR study, were also unable to detect IL-5 and were only able to assay GM-CSF at levels near the lower limits of detection. One possible explanation for our difficulty in assaying these cytokines may be a dilutional effect of PBS used for preparation of the nasal lavage. A more recent study [24] was able to demonstrate high concentrations of GM-CSF and IL-5 in nasal mucosal fluid by using undiluted fluid sampled by direct application of filter paper to the inferior nasal turbinates. This study also differed from ours by utilizing an intranasal allergen challenge rather than seasonal allergen exposure, a method which may have induced a more vigorous cytokine response.

An important mechanism for the selective recruitment of eosinophils to sites of allergic inflammation is by regulation of adhesion pathways such as β_2 integrin/ICAM-1, VLA-4/VCAM-1 and integrin β_7 [25–27]. DL has been shown to downregulate the adhesion molecule ICAM-1 [28, 29], which binds to its natural ligand LFA-1 present on eosinophils [30] and CD34+ progenitors [25, 26]. Histamine has been shown to increase VCAM-1 expression

on endothelial cells and this effect can be blocked with the addition of antihistamine [31]. It is possible that by altering expression or function of these or other adhesion molecules, DL can inhibit trafficking of Eo/B progenitors out of the peripheral blood and into tissue. Other speculative mechanisms which may be operative include: histamine receptor-mediated differentiation effects on hematopoietic progenitors [32–34], and histamine-mediated eosinophil and/or eosinophil progenitor chemotaxis [35].

Since basophils are prominent early in Eo/B colony formation relative to eosinophils while the reverse is true in more mature colonies [20], the histamine content, a reflection of basophils, of a colony provides an indirect measure of the colony maturity [19]. We found a significantly lower concentration of histamine/colony at day 15 in the DL group compared to the placebo group, and interpret this as an inhibition of colony maturation; similar findings have been reported by us in colonies derived from the marrow of cysteinyl leukotriene receptor antagonist-treated mice with experimental allergic rhinitis [36]. This decrease in colony histamine could also be interpreted as a relative maturing effect of DL on eosinophils in colonies. Precisely how DL may alter colony histamine content was not directly examined, although we can speculate that it may inhibit Eo/B CFU maturation potentially indirectly by modulating the release of colony-supporting cytokines from mast cells [37] or T cells [38], since it has been shown that DL can inhibit both IgE- and/or non-IgE-mediated mast cell [39] and basophil degranulation [40]. DL may interfere with Eo/B maturation by inhibiting the release of mast cell-derived hemopoietic cytokines, such as IL-3, IL-5, and GM-CSF. Future in vitro and ex vivo studies could examine this further.

Overall, symptom scores were lower in the DL group compared to the placebo group, a difference that reached statistical significance for both nasal itching and eye itching/burning. The symptom improvement, however, was less pronounced than in other studies [41]. Possible reasons for this difference are (1) the study was designed to measure potential differences in peripheral blood Eo/B progenitors between the DL and placebo group rather than to measure symptom efficacy, and, therefore, subjects may have had less severe symptoms than typical SAR study subjects, minimizing the potential for a treatment effect; (2) the study was not powered to detect differences in symptom scores, and (3) rescue medication use was higher in the placebo group than in the DL group which may have blunted significant differences in the overall effect.

The dose of DL used in this study, 20 mg daily, is higher than the usual prescription dose of 5 mg daily. The dose of 20 mg daily had previously been shown to be safe and effective. In this study, the higher dose was well tolerated and was chosen in an attempt to maximize potential pharmacologic effects on Eo/B CFU. Whether our results are generalizable to a lower dose of DL is open to interpretation.

Understanding the signaling leading to systemic responses between the tissue (especially the airways) and the BM may open up new avenues of therapy for allergic inflammation. Several other studies have demonstrated that other drugs such as steroids, cysteinyl leukotriene receptor antagonists [16, 36], and retinoic acid [17] may, in part, exert their therapeutic effects in allergic diseases

by their effects on Eo/B progenitors. This study demonstrates that DL may also have effects on Eo/B progenitors. DL may modulate aspects of allergic inflammation *in vivo* through mechanisms other than simple blockade of H₁ histamine receptors. Direct or indirect effects of DL may influence critical systemic processes that control Eo/B differentiation and/or mobilization.

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