Blood Cells, Molecules and Diseases 63 (2017) 62–65

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

# The targeted eosinophil-lowering effects of dexpramipexole in clinical studies

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ARTICLE INFO

*Article history:*
Submitted 22 December 2016
Accepted 14 January 2017
Available online 16 January 2017

*Keywords:*
Eosinophils
Basophils
Eosinophil-associated disorders
Eosinopoiesis
Eosinophilia

ABSTRACT

Dexpramipexole, an orally bioavailable small molecule previously under clinical development in amyotrophic lateral sclerosis, was observed during routine safety hematology monitoring to demonstrate pronounced, dose- and time-dependent eosinophil-lowering effects, with minor reductions on other leukocyte counts. Analysis of hematology lab values across two double-blind, randomized placebo-controlled clinical trials at total daily doses ranging from 50 mg to 300 mg demonstrated that dexpramipexole consistently and markedly lowered peripheral blood eosinophils. This effect developed after 1 month on treatment, required 3–4 months to reach its maximum, remained constant throughout treatment, and partially recovered to baseline levels upon drug withdrawal. All doses tested were well tolerated. The overall adverse event rate was similar for dexpramipexole and placebo, and notably with no increase in infection-related adverse events associated with eosinophil-lowering effects. Given the reliance on and insufficiency of off-label chronic corticosteroid therapy for hypereosinophilic syndromes and other eosinophilic-associated diseases (EADs), a need exists for less toxic, more effective, targeted therapeutic alternatives. Further clinical studies are underway to assess the eosinophil-lowering effect of dexpramipexole in the peripheral blood and target tissues of EAD patients and whether such reductions, if observed, produce clinically important benefits.



## 1. Introduction

Eosinophils are white blood cells of myeloid lineage for which data continue to emerge demonstrating their involvement in both health and disease [1,2]. Eosinophils have multiple beneficial roles, including in the innate response to parasitic infection, modulation of adaptive immune responses, and maintenance of tissue homeostasis [1,2]. However, under a variety of pathophysiological conditions, eosinophils accumulate to abnormally high levels in the blood and infiltrate target organs and tissues, secreting inflammatory proteins that may cause serious, potentially irreversible, tissue damage [3,4].

Eosinophil-associated diseases (EADs) are a heterogeneous group of disorders with poorly understood pathogenic mechanisms. The pathologic consequences of eosinophilia, both direct and indirect, span a wide clinical spectrum from gastrointestinal and respiratory disorders such as colitis and asthma to hematological disorders such as hypereosinophilic syndromes (HES) and chronic eosinophilic leukemia (CEL). Many EADs remain treated with chronic corticosteroid administration, which has a well-established, deleterious side-effect profile [5]. Monoclonal antibodies against IL-5, an eosinophil-promoting cytokine, have recently been approved for the treatment of severe eosinophilic asthma [6] and also show promise in other EADs. However, treatment options remain limited and thus a need remains for effective, easily administered, and cost-effective treatments for EADs.

Dexpramipexole is a small synthetic molecule with high oral bioavailability, linear pharmacokinetics, and a well-characterized safety profile [7]. Its eosinophil-lowering effect, observed initially in a dose-ranging phase 2 study, was confirmed in a large phase 3 trial ($n$=942) in amyotrophic lateral sclerosis (ALS) subjects, a generally non-atopic population with a normal hematologic status. An agent that safely, significantly, and durably lowers circulating eosinophils with a potential for a decrease in target tissues merits investigation for its potential to reduce the eosinophilia characteristic of many EADs and to improve clinical outcomes.

## 2. Methods

Hematology laboratory data sets were reviewed from two randomized, double-blind, placebo-controlled clinical trials in ALS [8,9]. Baseline hematology values were compared to the reference ranges

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http://dx.doi.org/10.1016/j.bcmd.2017.01.008
1079-9796/

prespecified for each study. Eosinophil levels were summarized over available time points and statistically analyzed using an analysis of variance model (ANOVA) to compare means change from baseline between an active treatment and the placebo group. In the phase 2 and 3 studies, changes from baseline for other peripheral blood cells were also assessed to evaluate the broader hematologic effects of the drug. Adverse events were reviewed by preferred term and system organ class and their incidences compared between the treatment and placebo groups to assess the risk of dexpramipexole-associated infection rates as a potential side effect.

## 3. Results

The phase 2 clinical trial was a two-part, double-blind study that evaluated the safety, tolerability, and clinical effects of dexpramipexole in 102 ALS subjects [8]. In Part 1, subjects were randomized to placebo ($n$=27), 50 mg/day ($n$=23), 150 mg/day ($n$=26), or 300 mg/day ($n$=26) of dexpramipexole ($n$=26) for 3 months. From baseline to month 3, mean blood eosinophils increased by 29.2% in the placebo group and declined by 17.7% ($p = 0.038$), 69.9%, ($p < 0.0001$), and 43.5% ($p = 0.0008$) in the 50 mg, 150 mg, and 300 mg groups, respectively (Fig. 1A). In the 150 mg and 300 mg groups, statistically significant differences from baseline could first be observed at month 1 and month 2, respectively, with the magnitude of effect greatest at month 3 (Fig. 1A). During a one-month drug washout following month 3, mean eosinophils at month 4 recovered to 46.6% and 76.6% of baseline levels in the 150 and 300 mg/day groups, respectively (data not shown). Following the drug washout, subjects were re-randomized to 50 and 300 mg/day in part 2 of the study. Subjects on 300 mg/day had a greater decline in eosinophils from month 4 to month 10 than subjects re-randomized to 50 mg/day (78.9% vs. 17.6%), consistent with the dose-dependent effect on eosinophils observed in part 1. Also noted in part 1, a substantial reduction in peripheral blood basophils occurred at month 3 in the 150 mg and 300 mg groups (45.6%, $p = 0.0004$ and 32.6%, $p = 0.018$), respectively. In contrast, non-significant changes in peripheral blood neutrophils (−6.6%), lymphocytes (−15.8%), monocytes (−6.3%), platelets (+11.0%), or red blood cells (+1.9%) were observed at month 3 in the 300 mg group.

The phase 3 clinical trial was a double-blind study of dexpramipexole in 942 ALS subjects randomized 1:1 to placebo or dexpramipexole 300 mg daily treatment for up to 18 months [9]. As in the phase 2 study, the eosinophil-lowering effect developed slowly, and in this trial reached plateau at month 4 (Fig. 1B), and persisted through end-of-study. The eosinophil lowering onset was observed by month 2 with a 36.6% decrease in eosinophils for dexpramipexole, $p < 0.0001$ compared to placebo. At month 6, the change from baseline in blood eosinophil counts was +18.7% in the placebo group and −69.1% in the dexpramipexole-treated group ($p < 0.0001$). The effect of dexpramipexole in reducing eosinophil counts was observed in most subjects, with 76.8% of dexpramipexole-treated subjects experiencing a 50% or greater decline in eosinophil count after 6 months of treatment. Dexpramipexole also reduced basophil counts with a similar onset of action, reaching plateau by month 4 and persisting through end-of-study. As shown in Fig. 2A, at month 6, the change from baseline in blood basophil counts was +4.5% in the placebo group and −46.7% in the dexpramipexole-treated group ($p < 0.0001$). At month 6, minor, but statistically significant reductions were observed in neutrophils (−6.6%), lymphocytes (−13.6%), and monocytes (−13.7%) in subjects receiving dexpramipexole (Fig. 2B-D), with no significant drug effect on red blood cells (+1.3%) or platelet counts (+7.5%).

The safety profile of dexpramipexole has been characterized in clinical studies of >1000 ALS subjects. Dexpramipexole was well-tolerated in both the phase 2 and phase 3 studies, with no dose-limiting toxicities and with adverse event rates similar across treatment groups. In particular, the number of treatment-emergent adverse events classified in the phase 3 trial as infections was similar in the placebo group (57%) compared with the dexpramipexole-treated group (56%). In phase 3, transient, laboratory-defined neutropenia (ANC < $1.5 \times 10^9$ cells/L) was observed in 6.1% of dexpramipexole-treated subjects ($n$=29) vs. 1.7% receiving placebo ($n$=8). Approximately 75% of ALS subjects in phase 3 received concomitant riluzole, which has a label warning for severe neutropenia. Of the phase 3 subjects with a laboratory event of neutropenia, 2/7 placebo subjects receiving riluzole (29%), 15/23 dexpramipexole subjects receiving riluzole (65%), and 0/6 subjects receiving only dexpramipexole had more than one episode.

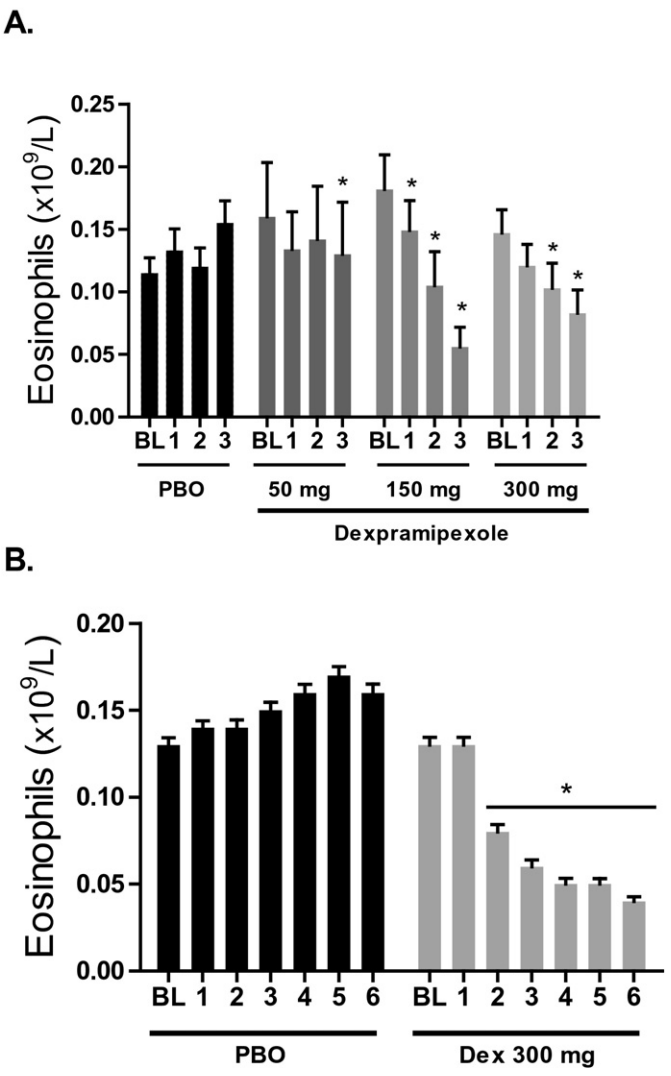


**Fig. 1.** Time- and dose-dependent eosinophil lowering effects of dexpramipexole in phase 2 and phase 3 ALS clinical trials. (A) In the phase 2 study, a 3-month dose ranging study in ALS subjects, mean blood eosinophils rose by 29.2% in the placebo group ($n$=27) and declined by 17.7% ($p = 0.0.038$), 69.9%, ($p < 0.0001$), and 43.5% ($p = 0.0008$) in the 50 mg ($n$=23), 150 mg ($n$=26), and 300 mg ($n$=26) dexpramipexole treatment groups from baseline to week 12, respectively. (B) In the phase 3 trial, a marked decrease in peripheral blood eosinophil count was observed after 2 months of treatment with dexpramipexole that persisted for the duration of the trial. At month 6, eosinophil counts were reduced from baseline levels by 69.1% in the dexpramipexole-treated group ($n$=474, $p < 0.0001$) while there was an 18.7% increase in eosinophil count in patients receiving placebo ($n$=468).

## 4. Discussion

During the course of any clinical trial, hematology laboratories are routinely monitored for potential adverse events and safety signals. In the development of dexpramipexole for the treatment of ALS, we