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Dexpramipexole Responsiveness is Increased in Eosinophilic Subjects

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Introduction

Dexpramipexole is an oral investigational drug serendipitously noted to lower blood eosinophils during prior clinical trials in amyotrophic lateral sclerosis (ALS). In a subsequent trial in subjects with eosinophilic chronic rhinosinusitis and nasal polyps (CRSwNP) dexpramipexole lower peripheral blood eosinophils by 94%. In contrast, dexpramipexole lowered eosinophils by 44.70% in ALS subjects. We hypothesized that eosinophil lowering responsiveness to dexpramipexole was greater in subjects with eosinophilia.

Study Design/Methods

Patient level data from the randomized, double-blind, placebo-controlled study of dexpramipexole in ALS (EMPOWER, 223AS302) were retrospectively analyzed to assess eosinophil lowering as a function of baseline absolute eosinophil count (AEC). Baseline eosinophil count was defined as the mean of the AEC from all study visits prior to randomization. Subjects included in the initial analysis (left column bar graphs) had to have at least 2 AEC determinations during the 3 visits from month 4 to month 6.

The EMPOWER trial enrolled subjects 18–80 years with ALS at 81 medical centers in 11 countries. Duration of ALS symptoms was ≥ 24 months before randomization. Eligible subjects were randomized 1:1 dexpramipexole 150 mg twice daily or placebo for 12–18 months.

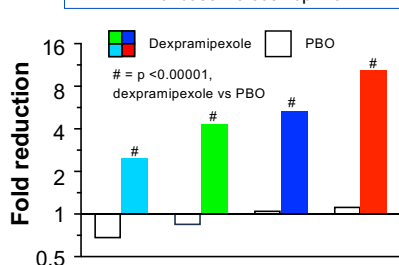
$$\text{Fold reduction} = \frac{\text{AEC Baseline}}{\text{Mean AEC Months 4-6}}$$

Baseline Eosinophil Strata

Baseline Eosinophil Strata ($\times 10^9/L$)	Dexpramipexole		Placebo	
	Subjects per stratum (n)	BL AEC ($\times 10^9/L$)	Subjects per stratum (n)	BL AEC ($\times 10^9/L$)
<0.100	188	0.062	175	0.061
0.100-0.199	159	0.138	177	0.131
0.200-0.299	50	0.232	57	0.235
≥ 0.300	22	0.387	20	0.371
Entire study population	419	0.108	429	0.109

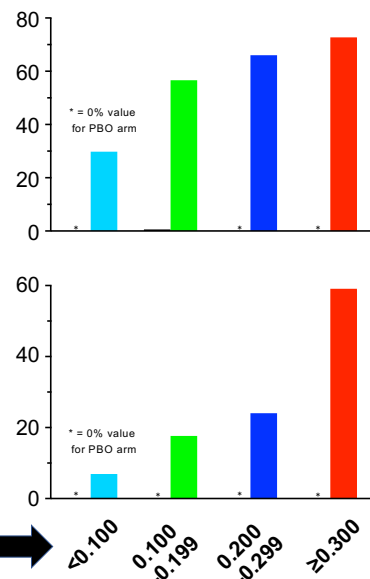
Baseline AEC strata ($\times 10^9/L$)

Magnitude of eosinophil lowering as a function of baseline eosinophilia



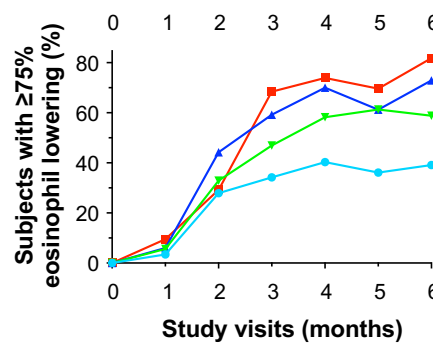
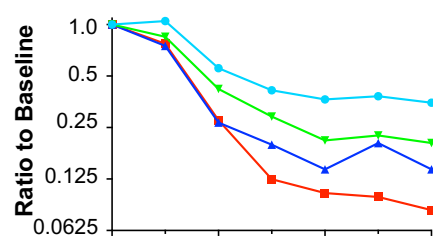
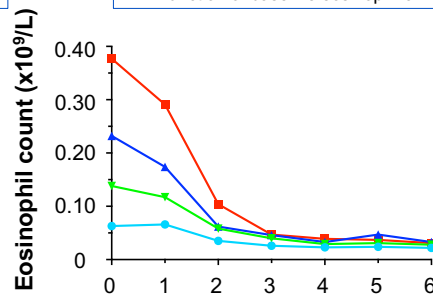
Subjects with $\geq 75\%$ eosinophil lowering

Subjects with $\geq 90\%$ eosinophil lowering

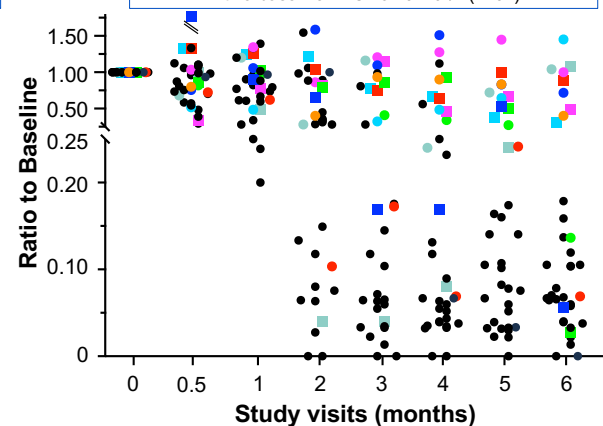


Results

Kinetics of eosinophil lowering as a function of baseline eosinophilia



Dexpramipexole eosinophil lowering in individual subjects with a baseline AEC $\geq 0.25 \times 10^9/L$ (n=37)



Conclusions

1. Dexpramipexole eosinophil lowering was seen in all strata of baseline eosinophil counts.
2. The magnitude of dexpramipexole eosinophil lowering increased in a stepwise manner in subjects with greater baseline eosinophilia.
3. The kinetics of dexpramipexole eosinophil lowering was not affected by baseline eosinophilia.
4. Dexpramipexole demonstrated heterogeneity of eosinophil lowering among subjects with baseline AEC $\geq 0.25 \times 10^9/L$.

Discussion

1. These findings demonstrate that dexpramipexole eosinophil lowering is greatest in subjects with eosinophilia, suggesting that dexpramipexole is most effective in a milieu with greater pro-eosinophilia signals. This suggests that dexpramipexole acts on a pathway driven by IL-5, other β_c , or other type 2 cytokines.
2. Despite widely differing baseline AEC, in all strata AEC was lowered to the 0.02-0.03 $\times 10^9/L$ range, suggesting that dexpramipexole may have modest effects on non-IL-5-driven homeostatic eosinophil populations.