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Effect Of Rademikibart On Blood Eosinophil Counts In Patients With Asthma: Is There An IL-4Rα Class Effect?

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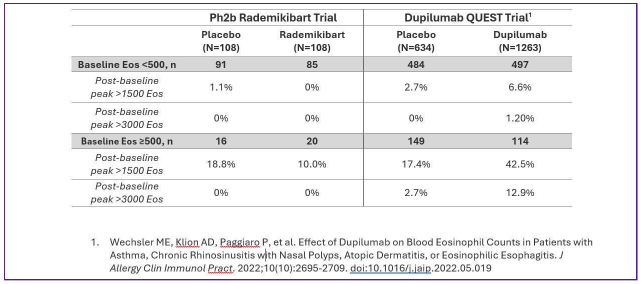
Abstract:
RATIONALE: Type 2 inflammatory airway disease can be considered as a subset of respiratory conditions characterized by chronic inflammation driven by T2 cytokines (IL-4, IL-5, IL-13), high serum IgE, increased fractional exhaled nitric oxide, and elevated eosinophil (Eos) counts. Hypereosinophilia has been reported following treatment with dupilumab, an IL-4Rα-blocker, particularly in patients with baseline eosinophils levels >500 cells/μL.[1] Rademikibart, a next generation IL-4Rα-blocker, has demonstrated significant improvements in lung function by Week 1 that were sustained through 24-weeks of treatment in a Phase 2 trial. To determine if hypereosinophilia is a class (IL-4) effect, we assessed the safety data from the Phase 2 trial to examine rademikibart's effect on eosinophils in patients with uncontrolled moderate-to-severe asthma.
METHODS: This Phase 2b trial (NCT04773678) was a global, placebo-controlled study conducted in 79 sites with 322 patients randomized 1:1:1 to rademikibart 150 mg every two weeks (Q2W; n=106), 300 mg Q2W (n=108) each with a loading dose of 600 mg or placebo (n=108). Rates of eosinophilia (eosinophils >1500) and hypereosinophilia (eosinophils >3000) were examined in the overall population and in patients with high eosinophils counts at baseline (eosinophils >500). Data from the higher 300 mg Q2W dose are discussed.
RESULTS: Following 24 weeks of treatment with rademikibart, overall percent change from baseline eosinophil counts were reduced with treatment vs placebo early in treatment (Week 1: -4.6% vs -0.3%, respectively; Week 4: -11.9% vs -1.7%) with further reductions observed by Week 24 (-38.5% vs -10.7%). For those with baseline eosinophils >500 cells/μL, 10% of patients had a peak eosinophil level above 1500 cells/μL at any point during treatment compared to 18.8% on placebo and no person (0%) exhibited hypereosinophilia with a peak eosinophils level of >3000. Consistent with previous experience, treatment with rademikibart was generally well tolerated.
CONCLUSIONS: Previous reports with dupilumab have shown eosinophilia in 42% and hypereosinophilia in 13% of patients (see table) leading one to suppose that increases in eosinophils may be a class effect with IL-4R blockers. Although from distinct trials, eosinophil changes are similar in the placebo groups in the table below indicating that differences in the treatment groups must be due to drug effect. Therefore, the current analysis suggests that the effect on eosinophil levels seen with dupilumab may not be a class effect and support the notion that rademikibart and dupilumab are distinct possibly due to molecular structural differences in their interactions with the IL-4R.



	Ph2b Rademikibart Trial		Dupilumab QUEST Trial[1]	
	Placebo (N=108)	Rademikibart (N=108)	Placebo (N=634)	Dupilumab (N=1263)
Baseline Eos <500, n	**91**	**85**	**484**	**497**
Post-baseline peak >1500 Eos	1.1%	0%	2.7%	6.6%
Post-baseline peak >3000 Eos	0%	0%	0%	1.20%
Baseline Eos ≥500, n	**16**	**20**	**149**	**114**
Post-baseline peak >1500 Eos	18.8%	10.0%	17.4%	42.5%
Post-baseline peak >3000 Eos	0%	0%	2.7%	12.9%

1. Wechsler ME, Klion AD, Paggiaro P, et al. Effect of Dupilumab on Blood Eosinophil Counts in Patients with Asthma, Chronic Rhinosinusitis with Nasal Polyps, Atopic Dermatitis, or Eosinophilic Esophagitis. *J Allergy Clin Immunol Pract*. 2022;10(10):2695-2709. doi:10.1016/j.jaip.2022.05.019

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