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Eosinophilic Asthma: insights into the effects of IL-5 Receptor Targeting

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The phase I study by Laviolette et al in this issue of the Journal is the sequel to the prior phase I study published also in the Journal by Busse et al. in 2010. (1,2) Benralizumab, then published under the name Medi-563, is a humanized, afucosylated monoclonal antibody, designed to target IL-5R α expressing cells (e.g. eosinophils and basophils). It was initially tested in the first phase I open trial in 44 subjects with mild asthma by a single iv infusion in an interesting sequential cohort study design to determine a safe and possibly effective dosing. The doses tested were: 0.0003, 0.003, 0.03, 0.1, 0.3, 1 and 3 mg/kg. (2) With the primary outcome being depletion of circulating peripheral blood eosinophil levels, MEDI-563 achieved the outcome within 24 hours at all doses administered. Blood eosinophils levels were reduced to nearly undetectable levels (~ 10 cells/ μ L) This effect persisted for at least 2 to 3 months in subjects dosed in the 0.03 to 3 mg/kg range. The study found that the drug was associated with a transient reduction of white blood cell counts in all cohorts with a marked decrease to <4000 cells/mL in over half the subjects. The decrease affected lymphocytes, monocytes and neutrophils. Four subjects had infusion related reactions, which was remedied by infusing the subsequent cohorts over a 30 minute duration instead of the previous 3-30 minute duration. (2)

In the current study, a 2 cohort randomized double blind placebo controlled design, the higher dose of 1 mg/kg was chosen for one intravenous dosing that was administered to 8 subjects (5 received placebo) and three subcutaneous doses of 100 mg and 200 mg were administered to 4 and 5 subjects respectively (4 received placebo). For an average 60 kg subject, these subcutaneous doses would be approximately equivalent to 1.6 and 3 mg/kg respectively. (1)

Included in the study were subjects who had a diagnosis of asthma based on any one of several parameters that identify reversible airway obstruction or hyperresponsiveness. But more pertinent is the requirement for having a sputum eosinophil count $\geq 2.5\%$ even though they were taking inhaled and/or oral corticosteroids at baseline. Thus, these subjects whose baseline sputum eosinophils ranged from 2.5% to 73.9%, fall into the category of eosinophilic asthmatics with resistance (at least in part) to corticosteroids. (1) It is interesting to note that this population of patients appears to be particularly sensitive to biological therapy for asthma including anti-IL-5, anti-IL-13 and anti-IgE (refs).

The primary outcome in this study moved us closer to the lung tissue, by examining the effect of benralizumab on eosinophil counts in airway mucosal/submucosal biopsies after 28 days of completing dosing. The investigators also examined eosinophils in bone marrow biopsies and the sputum in a subset of patients. While the study provides valuable information, it did not fulfill its primary outcome of a statistically significant reduction in eosinophils counts in airway/submucosal biopsies for any of the drug doses independently. It was not until the change in eosinophil counts in airway/submucosal biopsies were calculated in a post hoc analysis for all subjects dosed, whether by intravenous or subcutaneous dosing, did the study find a significant difference. Similarly the reduction in percent eosinophils in sputum was only significant when the two administration routes were combined. The study reports that a decrease in eosinophils in the biopsies occurred in 82% of the dosed subjects, implying that the majority of subjects had a beneficial response (the corresponding numbers for placebo dosing are not given in the manuscript). Importantly, the study reports that both eosinophil precursors and mature eosinophils were absent from the bone marrow after both administration routes. This finding suggests that while the medication may have completely blocked eosinophils from production in the marrow and hence removed them from the circulation, it did not have the same dramatic effect on the eosinophils that reside in the target organ, the lung tissue, or on the eosinophils in the sputum. This outcome is similar to the outcome of the effect of anti-IL-5, mepolizumab, when used in patients with eosinophilic esophagitis where the tissue eosinophils were reduced but not dramatically enough. (3, 4) Taken together, the results of this and other studies that aim to block eosinophils in asthma and in other eosinophilic disorders suggest the tissue eosinophil is at a different stage of maturation and becomes less responsive to certain anti-eosinophil agents, including corticosteroids, which renders the disease itself difficult to treat.

Whether the observed response on the eosinophils had any functional effect, on improvement of pulmonary function for example, is not reported in the current study. Previous studies have recently reported that lowering eosinophils by neutralizing IL-5, can have a marked effect on reducing the severity of asthma exacerbations. (5, 6). The results beg the question of whether the higher intravenous dose of 3 mg/kg may have been a more effective dose to test, although the counter argument is that the higher subcutaneous dose used (200 mg) approaches this higher 3 mg/kg dose.

As regards the adverse effect noted on other cell lineages, the authors offer no deep explanation. A speculative explanation may be that activation of the effector cells required for the antibody dependent cytotoxicity depleted neutrophils and platelets as innocent bystanders, at least initially. Alternatively, eosinophil released constituents during the cytotoxic response may promote pro-inflammatory changes that deplete other lineages.

In summary, the article by Lavioletta et al, deepens our understanding of the new and emerging therapies for difficult to treat eosinophilic asthma. It is hopeful that the reported decreases in airway eosinophils, elicited by benralizumab will translate into clinical benefit.

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