

Reductions in Eosinophil Biomarkers by Benralizumab in Patients With Asthma

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We have read with great interest the study by Pham *et al.*, (1), in which they have retrospectively investigated the effects of subcutaneous doses of benralizumab, an anti-IL-5R α monoclonal antibody (mAb), on blood eosinophil counts and serum levels of eosinophil toxic granule proteins and several other inflammatory mediators in two groups of patients with mild to moderate asthma. Blood eosinophils were decreased almost completely (by 99% and 96% in the two groups), as early as 1 day after the first dosing in all dose groups (i.e. 25, 100 and 200 mg). This potency and rapidity of eosinophil depletion are superior to mAbs which unlike benralizumab, target IL-5 ligand instead of the receptor (2), and may stem from the unique antibody-dependent cell-mediated cytotoxicity (ADCC) activity of benralizumab. A logical concern is that this massive apoptosis of eosinophils after benralizumab treatment would result into their toxic degranulation, which could have deleterious effects on airway function via the cytotoxic granule proteins such as eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) (3). However, in this study, the serum levels of EDN and ECP were reduced by 73% and 74% by benralizumab treatment, respectively. Although the results are interesting, we think given that the effect of benralizumab on blood eosinophil counts and ECP/EDN levels had been convincingly and consistently clarified in previous studies (4-6), maybe it would have been more interesting to address more controversial issues, such as the compound's effect on airway and tissue eosinophilia, airway function, and clinical disease severity.

In our opinion, the most important result of the study was the increase in IL-5 and eotaxin serum levels after treatment with benralizumab (1). IL-5 and eotaxin are retrospectively known as the most crucial cytokine and chemokine responsible for eosinophil survival, activation and infiltration (7). Considering that their upregulation in this study was shown to occur

simultaneously with successful depletion of eosinophils and their effector proteins, this finding proves for the first time that benralizumab's efficacy is not affected by increased serum levels of IL-5 after anti-IL-5 treatment, probably because it targets the inflammatory cascade initiated by IL-5 at the receptor (not the ligand) level, and moreover, because it works not only by depriving the eosinophils of the essential cytokines and chemokines but also by directly killing them via ADCC. Keeping these reasons in mind, it would be reasonable to assume that the similar increase in IL-5 serum levels previously reported after treatment with anti-IL-5-ligand mAbs (8) and also during acute asthma (9) can result in the inferior effectiveness of anti-IL-5-ligand mAbs compared with benralizumab.

Another notable point of the study was that the 25 mg SC dose of benralizumab showed inferior effectiveness compared with 100 and 200 mg doses (1). Previous studies of benralizumab have used various SC doses, ranging from 2 to 200 mg. Their results indicated inefficacy of the 2 mg dose, but the similar effectiveness of 20, 100 and 200 mg doses (6). In the current study, although the 25 mg dose successfully reduced blood eosinophilia and ECP/EDN levels, but eosinophil counts and serum EDN levels increased after Day 84; in contrast, the effects of 100 and 200 mg doses were persistent at least until the last study checkpoint (Day 161) (1). These results call for more caution in choosing 20 or 25 mg SC doses in future studies.

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