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Variability of Blood Eosinophil Count as an Asthma Biomarker

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LETTER TO EDITOR

In several recent clinical trials, the efficacy of novel targeted therapeutics, such as the monoclonal antibodies for IL-5 (e.g. mepolizumab), IL-13 (e.g. lebrikizumab) and IL-4 receptor (e.g. dupilumab), was demonstrated mainly in a subgroup of eosinophilic or “Th2 endotype” asthma patients [1–4]. In these studies, sputum eosinophil counts, serum periostin level, and blood eosinophil counts identified the patients who were likely to respond. Furthermore, a post-hoc analysis of COPD patients demonstrated that increased blood eosinophilia predicted response to the addition of inhaled corticosteroid [5]. The blood eosinophil count is an attractive biomarker due to the ease of availability and its ability to identify appropriate asthma patients for novel therapeutics. However, is the blood eosinophil count a stable and reliable biomarker?

Since 2008, we have recruited 82 subjects who have donated blood on at least 4 separate occasions (at least 8 weeks apart) for the purification of eosinophils and other blood cells for a total of 749 blood donations. Subjects were characterized initially with an extensive medical history, spirometry, exhaled nitric oxide (FeNO), aeroallergen skin prick testing, and manual blood eosinophil count. At each donation visit, typically between 7–8am, an update to the medical history (including medication changes), symptom questionnaire, FeNO, and eosinophil count was obtained. If subjects had an acute infection, were taking oral

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corticosteroids or increased doses of inhaled steroids, they were not allowed to donate. Subjects were classified as having asthma only (13%), allergic rhinitis only (23%) or both allergic rhinitis and asthma (63%) based on self-report with confirmation based on medical history, prescribed medications, skin prick testing and/or spirometry. Of these subjects, 55% were male and the average age at first donation was 34 years (range 18–53). Based on the availability of repeated blood eosinophil counts, we sought to determine its variability and consider the suitability of eosinophil count as a biomarker using a linear mixed effect model.

Eosinophil counts were greater in subjects with asthma alone (geometric mean 254 cells/mm³; 95% CI 189–342) and asthma with allergic rhinitis (244 cells/mm³; 95% CI 213–280) compared to those with allergic rhinitis alone (174 cells/mm³; 95% CI 139–219) ($p=0.05$ and $p=0.01$, respectively). The within-subject geometric coefficient of variation was 39.7%; in other words, a typical eosinophil count in any given subject is about 40% higher or lower than that subject's average. This variability was similar in each of the clinical diagnoses categories: 42.1% for allergic rhinitis only, 35.4% for asthma only, and 39.7% for allergic rhinitis and asthma. As shown in Figure 1, there was a wide range of blood eosinophil counts for each subject. When considering blood eosinophil cutoffs of 150 cell/mm³, the majority of subjects (57%) exhibited eosinophil counts both above and below the respective cutoff. In order to determine whether some of the variability in eosinophil counts could be attributed to seasonal allergies, the blood eosinophil counts for subjects with at least one documented allergen sensitivity were examined in relation to the month of sample collection (data not shown). Eosinophil counts varied slightly with the collection month with several pairwise comparisons of samples drawn in each month demonstrating differences, particularly when compared to October (data not shown). However, there remained considerable variability within each month indicating the contribution of season on the eosinophil count variability is minimal; only 2% of the within-subject variability in eosinophil counts could be attributed to the month of collection. We performed a similar analysis to consider effects of inhaled corticosteroid use and found <1% of the within-subject variability in eosinophil counts could be attributed to inhaled corticosteroid use.

In recent clinical trials of mepolizumab, different eosinophil counts have been used as a cutoff as part of the inclusion criteria, specifically 150 cells/mm³ or 300 cells/mm³ [1, 4]. The sensitivity and specificity were calculated for the initial blood draw correctly categorizing the geometric mean eosinophil count of the individual's subsequent blood draws above or below the respective cutoffs of 150 cells/mm³ (SENS 83%, SPEC 75%) and 300 cells/mm³ (SENS 78%, SPEC 92%). Therefore, due to the variability in eosinophil counts, 78% (18/23) of patients with an average eosinophil count greater than 300 cells/mm³ on a single blood draw had an initial count greater than 300 cells/mm³, and 83% (58/70) of patients with an average count greater than 150 cells/mm³, had an initial count greater than 150 cells/mm³. In other words, roughly 1 in 6 patients whose average count was above the 150 cells/mm³ cutoff value had initial counts below that cutoff value. These data suggest the use of a single eosinophil count as a criterion for eligibility for specific therapeutics is insufficient to identify all patients with potential to benefit.

The subjects examined in this study were predominantly mild asthmatics. So, it remains a possibility that more severe asthma patients, who are the expected population to receive

targeted biologic therapies, will exhibit more consistent blood eosinophil counts. Furthermore, our cohort enriches for subjects with higher eosinophil counts in order to provide greater numbers of cells for eosinophil purifications. As a result, we speculate our analyses overestimate likelihood of identifying an eosinophil count above a certain cutoff. The prospect of using the blood eosinophil count as a biomarker for eosinophilic asthma was also examined by Katz et al. [6]. They observed that 88% (98/111) of patients with a post-screening average eosinophil count above 150 cells/mm³ had an initial screening count above 150 cells/mm³. Similarly, in our cohort, the sensitivity of 83% for the 150 cells/mm³ cutoff suggests that 1 out of 6 blood draws in subjects with a mean eosinophil count above 150 cells/mm³ may report an initial count below the cutoff. Spector and Tan also examined the blood eosinophil count as a biomarker and observed a great deal of variability that could not be attributed to diurnal variation or seasonality [7]. Therefore, repeated measurements of the peripheral blood eosinophil count may be necessary to definitively identify patients that could benefit from the novel Th2 endotype targeted therapeutics currently available and in development.

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Figure 1.

Blood Eosinophil Counts. Each individual subject is represented along the x-axis with blood eosinophil counts from each of their donations represented as individual dots on the y-axis as eosinophils/mm³. Dashed line denotes a cutoff of 150 eosinophils/mm³. Subjects with donations of eosinophil counts both above and below cutoff are depicted in green.