Blood Eosinophil Depletion with Mepolizumab, Benralizumab and Prednisolone in Eosinophilic Asthma

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To the Editor:

Eosinophilic airway inflammation is present in approximately half of patients with asthma and it is associated particularly with asthma attacks. Interleukin (IL)-5 is a major cytokine involved in eosinophil differentiation, proliferation, activation and eosinophil-mediated inflammatory responses (1). Severe eosinophilic asthma can now be effectively treated using anti-IL-5 biologic therapies. The two anti-IL-5 monoclonal antibodies which are licensed for use in asthma and can be administered subcutaneously are mepolizumab, targeting IL-5, and benralizumab, targeting the alpha-chain of the IL-5 receptor. They both have proven efficacy in decreasing the frequency of asthma exacerbations and oral corticosteroid (OCS) requirement (2-5). In preclinical studies, benralizumab has additional antibody-dependent cell-mediated cytotoxicity effects and might therefore deplete blood eosinophils more quickly and completely than mepolizumab (6).

Pharmacodynamic studies of mepolizumab and benralizumab have only been undertaken over longer time periods and their findings are difficult to compare as baseline and change in blood eosinophils have been expressed differently (7-9). There are no data comparing the effect of mepolizumab and benralizumab on blood eosinophils in the first 24 hours after administration. This is an important gap in knowledge as rapid onset depletion of blood eosinophils is likely to be an important property if anti-IL-5 biologics are to be used as an alternative for prednisolone as a treatment of acute eosinophilic exacerbations (10). We hypothesised that benralizumab and prednisolone might work equally rapidly and faster than mepolizumab due to induction of apoptosis and antibody-dependent cell-mediated cytotoxicity. We have therefore undertaken a study to compare the rate of blood eosinophil
depletion after administration of the first dose of mepolizumab, benralizumab and prednisolone in patients with severe eosinophilic asthma.

**Methods**

This was a sub-study of the Oxford Airways Study (Integrated Research Application System Project number: 234581; Oxfordshire Research Ethics Committee B Reference: 18/SC/0361). The Oxford Airways Study is an observational study of patients with asthma and COPD, which allows blood, sputum and bronchoscopy sampling at stable state and during exacerbations, before and after clinical treatment. The main outcome of this sub-study was time to reach a 50% reduction in blood eosinophil count after administration of mepolizumab, benralizumab and prednisolone. Patients were recruited from the Oxford Special Airways Clinic. Inclusion criteria were having a known diagnosis of severe asthma and baseline blood eosinophil count above 300 cells/µL. Subjects who had taken prednisolone in the preceding 2 weeks or who were already on a biologic treatment were excluded. We recruited 18 patients who were either commencing prednisolone 30 mg daily for 5 days (n=6) for the treatment of poorly controlled eosinophilic asthma, or commencing maintenance treatment with mepolizumab 100 mg subcutaneously (sc) (n=6) or benralizumab 30 mg sc (n=6) for poorly controlled severe eosinophilic asthma (5.4 subjects in each group is needed for a statistical power of 90% (α=0.05) to detect a between-group difference larger than one standard deviation (SD)). We assessed blood eosinophil counts at baseline (generally 9 am) and, 2 and 4 h after the first dose for all patients, and at 6, 8, 24 and 96 h if the blood eosinophil count remained higher than 150 cells/µL. A 30-day blood eosinophil count was obtained for those who received the mepolizumab or benralizumab injection. There is no previous information on the onset of action of mepolizumab and benralizumab, however the effect of prednisolone starts in about
2 hours, so we included the time points 2 and 4 hours, and later time points to show the predicted slower onset of mepolizumab. Haematological analysis was done by laboratory staff using an Abbott Architect ci8200 analyser.

**Results**

Demographics, inhaled corticosteroid dose, lung function, baseline blood eosinophil count and exhaled nitric oxide levels were not significantly different between groups (Table 1). The mean (SD) time for blood eosinophil level to decrease 50% from baseline was 25.8 (14.3) h on mepolizumab, 1.7 (0.7) h on benralizumab and 2.5 (0.3) h on prednisolone (p<0.001 for both benralizumab and prednisolone compared to mepolizumab, p=0.874 between prednisolone and benralizumab by one way analysis of variance (ANOVA) with least significant difference (LSD) post-test) (Figure 1). A blood eosinophil count ≤ 100 cells/µl was achieved by one patient treated with mepolizumab at 96 hours and by three patients at 30 days; this threshold was achieved by 4 hours in five participants treated with benralizumab and five treated with prednisolone. Blood eosinophil count in the mepolizumab arm was significantly higher than in the benralizumab arm at 2 and 4 hours and 30 days (p=0.045, <0.001 and 0.002, respectively), and higher than in the prednisolone arm at 4 hours (p<0.001, Figure 1). There was no statistically significant difference between the prednisolone and benralizumab arms at any of the time points (p=0.601 at 0 h, p=0.296 at 2 h, p=0.767 at 4 h). The geometric mean (SD) blood eosinophil counts 30 days post benralizumab and mepolizumab were 8 (22) and 92 (48) cells/µl, respectively (p=0.002).

**Discussion**
To the best of our knowledge this is the first study comparing the rate of depletion of blood eosinophils in the first 24 hours after treatment with mepolizumab and benralizumab. We found that, in contrast to mepolizumab, benralizumab caused rapid and near complete depletion of eosinophils with a speed of onset of effect very similar to that seen with oral prednisolone. The blood eosinophil count 30 days after the first injection was also significantly lower after benralizumab compared to mepolizumab. These findings are consistent with greater efficacy and a different mechanism of eosinophil depletion.

Mepolizumab and benralizumab have proven and similar efficacy and safety in the longer term treatment of severe eosinophilic asthma (2, 3) suggesting that the difference in the speed of onset and efficacy is not relevant to the chronic use of these agents. However, the faster onset of action of benralizumab suggests it has potential as an alternative non-corticosteroid treatment for acute exacerbations of eosinophilic asthma with the potential benefit of inhibiting eosinophilic airway inflammation for at least 30 days after one injection. A recent case-report supports the use of benralizumab in this way (10). Larger studies are needed to determine whether this strategy is clinically effective and cost effective.

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Table 1. Clinical characteristics of participants.

|                      | Mepolizumab | Benralizumab | Prednisolone | p   |
|----------------------|-------------|--------------|--------------|-----|
| N                    | 6           | 6            | 6            |     |
| Age†                 | 57 (53-64)  | 68 (54-69)   | 53 (46-67)   | 0.5 |
| Females              | 3 (50%)     | 2 (33%)      | 1 (17%)      | 0.8 |
| Ethnicity            |             |              |              |     |
| Caucasian            | 6 (100%)    | 5 (83%)      | 6(100%)      | 0.3 |
| African              | 1 (17%)     |              |              |     |
| Sensitisation to any | 3 (50%)     | 4 (67%)      | 2 (33%)      | 0.5 |
| respiratory allergens|             |              |              |     |
| ICS BDP equivalent   | 2000 (1900-3100) | 2000 (1750-2000) | 2000 (1900-2000) | 0.1 |
| dose (mcg/day)†      |             |              |              |     |
| No. OCS courses      | 8 (5-11)    | 4 (3-6)      | 3 (2-5)      | 0.2 |
| past 12 months†      |             |              |              |     |
| FEV₁ % predicted†    | 68 (37-78)  | 71 (57-98)   | 73 (57-87)   | 0.4 |
| FVC % predicted†     | 75 (69-89)  | 87 (70-128)  | 88 (73-96)   | 0.4 |
| FEV₁/FVC ratio†      | 0.66 (0.41-0.84) | 0.71 (0.39-0.74) | 0.75 (0.57-0.81) | 0.4 |
| Blood eosinophil     | 580 (132)   | 724 (255)    | 629 (347)    | 0.5 |
| count (cells/µL)††   |             |              |              |     |
| FeNO†                | 41 (16-97)  | 61 (33-130)  | 50 (20-81)   | 0.4 |

p-values are for chi-test, Kruskall-Wallis test, or analysis of variance. †Median, interquartile range. †† geometric mean (SD).

All other results are expressed as number and percentage of the group. BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 second; FVC, forced ventilatory capacity; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide.
Figure 1. Blood eosinophil count (thin transparent lines for individual data, thick lines with markers for geometric group mean, error bars represent 95 % confidence intervals for geometric mean) on logarithmic scale before and after treatment with mepolizumab (100 mg sc), benralizumab (30 mg sc) or oral prednisolone (30 mg). There was a statistically significant change (p<0.05 using repeated measures ANOVA and LSD post-test) from baseline at 2 and 4 hours in benralizumab arm, at 4 hours in prednisolone arm, and from 24 hours onwards in mepolizumab arm. There was no significant difference between the treatment arms at baseline, but mepolizumab arm differed significantly from benralizumab arm at 2 and 4 hours and 30 days, and from prednisolone arm at 4 hours (ANOVA with LSD post-test).