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Early decreases in blood eosinophil levels with reslizumab

To the Editor:

Some patients with asthma have a persistent eosinophilic phenotype that is difficult to control, even with high doses of corticosteroids.[1] In addition, high blood eosinophil levels have been shown to be associated with future asthma exacerbation risk, rescue medication use, and worse symptoms and lung function.[2,3] Reslizumab is an IgG_4 kappa humanized mAb that targets IL-5, thereby disrupting the maturation, activation, and survival of eosinophils.[4] Intravenous (IV) reslizumab is approved in the United States and Europe as add-on therapy for adult patients (≥18 years) with severe asthma and elevated blood eosinophils. In phase 3 trials in patients with inadequately controlled, moderate-to-severe asthma and elevated blood eosinophil counts, IV reslizumab significantly reduced blood eosinophil levels.[5-7] Reslizumab was also associated with a 50% to 59% reduction in asthma exacerbations over 1 year, and improvements in lung function, asthma symptoms, and control that were apparent 4 weeks after the first reslizumab dose and sustained through 52 weeks.[5-7]

Detection of changes in blood eosinophil levels earlier than 4 weeks after the first dose of reslizumab has not previously been reported. Early assessment of blood eosinophil levels could potentially provide prescribers with reassurance of biologic activity of reslizumab shortly after commencing therapy. In 2 clinical trials of reslizumab, US study centers collected eosinophil count data at day 2 or 3 and/or week 2 or 3 after the first IV infusion of reslizumab. The aim of this *post hoc* subgroup analysis was to use data from the centers that collected early eosinophil data to determine how soon after initiation of treatment with reslizumab changes in blood eosinophil levels could be identified.

Data for this analysis were pooled from 2 phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group trials (study 1 [NCT01287039] and study 2 [NCT01285323]),[5] which were part of the BREATH clinical trial program. Detailed description of the study designs has been reported previously.[5] In brief, eligible patients were aged 12 to 75 years with inadequately controlled moderate-to-severe eosinophilic asthma, using at least medium-dose inhaled corticosteroid (fluticasone propionate ≥440 μg/d or equivalent) ± another controller, and had a screening blood eosinophil count of greater than or equal to 400 cells/μL. Patients were randomized 1:1 to treatment with IV reslizumab (3.0 mg/kg) or placebo every 4 weeks for 52 weeks (13 doses), in addition to their regular maintenance medication. Randomization was stratified for regular use of maintenance oral corticosteroids and region (United States or rest of the world).[5]

All patients had blood samples taken before each infusion at baseline and every 4 weeks through 52 weeks.[5] Patients at US study centers in study 1 also provided blood samples on day 2 or 3 and week 2 or 3 after the first infusion for determination of serum reslizumab concentrations and blood eosinophil counts. Blood eosinophil counts were measured using a standard complete blood cell count with differential blood test.

A total of 952 patients participated in the 2 studies, of whom 475 received placebo and 477 received IV reslizumab.[5] Early eosinophil data were available from 70 of 74 (95%) US patients (placebo, 34; reslizumab, 36) in study 1 (Table I). This subgroup did not differ from the overall study population, with the exception of a slightly higher proportion of men and slightly higher mean body mass index. In this subgroup, the mean baseline blood eosinophil level was 681 ± 53 cells/μL. There were no significant between-group differences in the overall study population[5] or in patients with early eosinophil counts measured at day 2 or 3 and/or week 2 or 3 (Table I).

After the first infusion of reslizumab, the eosinophil level decreased from a mean of 747 cells/μL at baseline to 220 cells/μL on day 2 or 3 (a decrease of ~71%), and 186 cells/μL by week 2 or 3 (~75% decrease) in the subgroup of patients with early eosinophil count data (Fig 1). No significant change in early blood eosinophil counts was observed in the group receiving placebo (baseline: mean, 611 cells/μL; day 2 or 3: mean, 606 cells/μL; and week 2 or 3: mean, 581 cells/μL). Reduction from baseline eosinophil levels was significantly greater with reslizumab versus placebo at day 2 or 3 (−526 cells/μL; 95% CI, −717 to −335; $P < .0001$) and at week 2 or 3 (−562 cells/μL; 95% CI, −740 to −384; $P < .0001$). Blood eosinophil levels remained low throughout the 52 weeks of treatment among all patients receiving reslizumab (Fig 1).

Our results show that substantial decreases in blood eosinophil levels were detected as early as 2 to 3 days after the first dose of IV reslizumab in patients with moderate-to-severe asthma and elevated blood eosinophil levels at baseline. The marked reduction in eosinophil counts occurred long before reslizumab levels had reached pharmacokinetic steady state (based on a reslizumab half-life of 24 days).[4] Across all patients receiving reslizumab 3.0 mg/kg in studies 1 and 2, the reduction in mean blood eosinophil levels to a low but detectable level was sustained over 52 weeks of treatment, consistent with previously demonstrated sustained improvements in lung function, asthma control, and quality of life over 52 weeks.[5]

TABLE I. Baseline demographic and clinical characteristics of subjects with early eosinophil data (study 1 only)*

Characteristic	Placebo (N = 34)	Reslizumab (N = 36)	Total (N = 70)
Age (y), mean ± SD	41.6 ± 17.5	45.7 ± 16.5	43.7 ± 17.0
Sex, n (%)			
Male	18 (53)	17 (47)	35 (50)
Female	16 (47)	19 (53)	35 (50)
BMI (kg/m^2), mean ± SD	31.5 ± 7.7	30.1 ± 6.9	30.8 ± 7.3
Baseline asthma medications, n (%)			
Oral corticosteroids†	4 (12)	5 (14)	9 (13)
LABA	32 (94)	35 (97)	67 (96)
High-dose ICS	13 (38)	16 (44)	29 (41)
LABA + high-dose ICS	13 (38)	16 (44)	29 (41)
FEV_1 (mL), mean ± SD	2100 ± 800	2000 ± 700	2000 ± 700
Baseline blood eosinophil count (cells/μL), mean ± SD	611 ± 343	747 ± 654	681 ± 528
No. of asthma exacerbations in preceding 12 mo, mean ± SD	1.7 ± 1.3	1.8 ± 1.0	1.7 ± 1.1
GINA asthma severity stage, n (%)			
3	1 (3)	1 (3)	2 (3)
4	29 (85)	28 (78)	57 (81)
5	3 (9)	5 (14)	8 (11)
Allergic history, n (%)			
Chronic sinusitis	11 (32)	10 (28)	21 (30)
Nasal polyps	12 (35)	11 (31)	23 (33)
Aspirin sensitivity	2 (6)	4 (11)	6 (9)

BMI, Body mass index; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist.
*The baseline characteristics for the overall population of studies 1 and 2 can be found in Castro et al.[5]
†Patients were allowed to be on a maximum of 10 mg/d prednisone or equivalent at baseline.

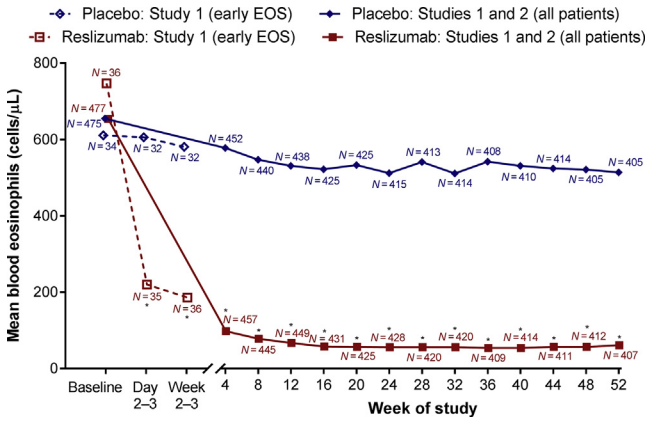

FIG 1. Mean eosinophil counts over 52 weeks of treatment with reslizumab or placebo in patients with early eosinophil data (study 1 only) and all patients in studies 1 and 2. *EOS,* Eosinophil count data. *P* values shown for treatment difference (reslizumab vs placebo) at specified time point. All *P* values derived from Student *t* test. Treatment differences at baseline were not significant in study 1 or studies 1 and 2. *$P < .001$.

Early reductions in blood eosinophils have also been seen with the anti–IL-5Rα mAb benralizumab in a phase 1 study of patients with moderate asthma, and in a phase 2a study of patients with mild-to-moderate asthma. Subcutaneous benralizumab administered every 4 weeks for a total of 3 doses was associated with blood eosinophil decreases from baseline observed on day 1 and persisting until day 84.[8] A rapid, marked reduction in blood eosinophils was also seen with infusion of the anti–IL-5 mepolizumab at doses of 250 and 750 mg in patients with moderate persistent asthma. This reduction was significant at week 1 and sustained for 12 weeks after treatment until the end of the study.[9]

The early observed pharmacodynamic changes in the current analysis may provide support for an early onset of a clinically relevant response to IV reslizumab. In addition, these changes may provide additional evidence for clinicians that reslizumab is acting at the IL-5 target in their patients. Elevated baseline blood levels of eosinophils are a well-recognized biomarker for predicting response to treatment with IL-5–directed therapies; patients with baseline eosinophil levels of greater than or equal to 400/μL experience greater improvement in lung function and asthma control with such therapies.[7] This preliminary study did not assess the relationship between blood eosinophil reduction and clinical efficacy in individual patients. Larger studies of the relationship between biomarker response and clinical response, including identification and characterization of patients without an eosinophil response to anti–IL-5 therapy and the implications for clinical outcomes, should be done.

In conclusion, IV reslizumab demonstrates a marked effect on eosinophils within 2 to 3 days of the first infusion, providing clinicians with early reassurance of biological effect. Reductions in eosinophil levels with IV reslizumab are sustained during long-term treatment. Further research is needed to determine whether an early effect on blood eosinophils can be used to help predict clinical response to anti–IL-5 therapy.

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MSD; has received lecture fees from Boston Scientific, BI, Centocor, GSK, AZ, Novartis, Teva, and Chiesi; and has received industry-sponsored grants from ALK, BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi, and Roche. M. McDonald was an employee of Teva Pharmaceuticals at the time the study was conducted. M. Garin is an employee of Teva Pharmaceuticals. K. Murphy has received consultancy and speaker fees and has participated in advisory boards for AZ, BI, Genentech, Greer, Meda, Merck, Mylan, Novartis, and Teva.

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