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Biomarkers Associated with Lung Function Decline and Dupilumab Response in Patients with Asthma

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To the Editor:

Patients with asthma are at risk for structural airway changes that lead to accelerated loss of lung function (1, 2). The identification of modifiable independent risk factors for lung function decline (LFD) is an important goal (3). The Type 2 biomarkers peripheral blood eosinophils and fractional exhaled nitric oxide (Fe_{NO}) have been shown to identify different aspects of Type 2 airway inflammation and, collectively, predict asthma exacerbations (4). Evidence exists that they both identify patients who are at risk of future LFD (5–10). However, the role of either biomarker or their combination as prognostic or predictive biomarkers and the effect of treatment have yet to be established definitively. This *post hoc* analysis of the QUEST (ClinicalTrials.gov ID: NCT02414854) study data was conducted to determine whether Fe_{NO} and blood eosinophils are independent prognostic biomarkers for LFD and predictors of dupilumab's treatment effect on this outcome.

Some of the results of QUEST have been previously reported in the form of abstracts (11–15).

QUEST was a phase-3, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of dupilumab in patients aged 12 years and older who had uncontrolled, moderate-to-severe asthma despite consistent treatment with inhaled corticosteroids (ICSs) plus one or two additional controllers. Full details of the inclusion and exclusion criteria and the study protocol have been published previously (16). The primary endpoints were the annualized rate of severe asthma exacerbations and the change from baseline to Week 12 in pre-bronchodilator (BD) FEV_1. This *post hoc* analysis took into consideration the adult (≥18-yr-old) population, and selection was determined according to baseline Fe_{NO} or eosinophil levels.

LFD (milliliters per year) and the treatment difference in LFD between dupilumab and placebo were defined as the annual loss of post-BD FEV_1, measured by the post-BD FEV_1 slope derived from five available measures from Week 8 through Week 52 in patients receiving either placebo or dupilumab across biomarker subgroups. Multivariate regression analyses were conducted to identify factors associated with LFD. Covariates were treatment, age, sex, height, baseline log Fe_{NO}, baseline log blood eosinophils, Asthma Control Questionnaire (ACQ-5) score, number of exacerbations during the previous year, age of asthma onset, ICS dose level, baseline post-BD FEV_1, time since randomization, time since randomization by treatment, and region. ACQ-5 score, exacerbations in the previous year, and age of asthma onset were not significant and were excluded from the final model. To identify predictive biomarkers associated with LFD and response to dupilumab, the treatment difference between dupilumab and placebo in LFD was assessed across baseline blood eosinophil and Fe_{NO} levels.

Baseline post-BD FEV_1, log blood eosinophils, and log Fe_{NO} were significantly associated with post-baseline post-BD FEV_1 ($P < 0.0001$). Lung function declined progressively with increasing baseline Fe_{NO} level in patients who received placebo, and the rate of decline was generally attenuated by treatment with dupilumab; the difference of the slope of the two lines was −11.8 (95% confidence interval [CI]: −71.5, 47.8) (Figure 1). In contrast, decline in lung function was similar in patients who received placebo, regardless of baseline blood eosinophils, and patients with higher baseline blood eosinophils had lower LFD attenuation with dupilumab. The treatment difference between dupilumab and placebo increased in populations defined by higher baseline Fe_{NO}, with a difference of 39 ml (95% CI: −5, 83) for the population with Fe_{NO} ≥25 parts per billion (ppb), 75 ml (95% CI: 19, 131) for the population with Fe_{NO} ≥35 ppb, and 86 ml (95% CI: 7, 166) for the population with Fe_{NO} ≥50 ppb. The middle cutoff point was established on the basis of an observed "turning point," whereby treatment differences were more prominent, whereas the lower cutoffs were nonsubstantial, and the higher cutoffs were not clinically meaningfully different.

In an analysis of the two biomarkers together, patients who received placebo with elevated baseline Fe_{NO} (≥25 and ≥50 ppb) showed higher LFD, with a range from 102 ml to 149 ml loss per year, regardless of baseline blood eosinophils (Figure 2). In addition, for patients who were treated with dupilumab, LFD was attenuated across biomarker threshold groups, with a range of 43 ml ($n = 27$) to 4 ml ($n = 99$) in the high-Fe_{NO}–low-eosinophil groups and −17 ml ($n = 363$) to −35 ml ($n = 172$) in the low-Fe_{NO}–high-eosinophil groups.

This *post hoc* analysis supports the use of Fe_{NO} as a risk biomarker identifying patients who are at increased risk of LFD, as well as identifying those with greater attenuation in LFD on dupilumab. This is key in identifying patients who might benefit from early specific intervention. The distinct added value of Fe_{NO}, compared with blood eosinophils, as a biomarker for prediction of LFD is in contrast to what has been seen for prediction of asthma exacerbations, with previous research indicating that Fe_{NO}'s prognostic value was additive in parallel with blood eosinophil counts

*The QUEST Lung Function Decline Study Group consists of the authors and Nami Pandit-Abid, Amr Radwan, Yamo Deniz, and Paul J. Rowe.

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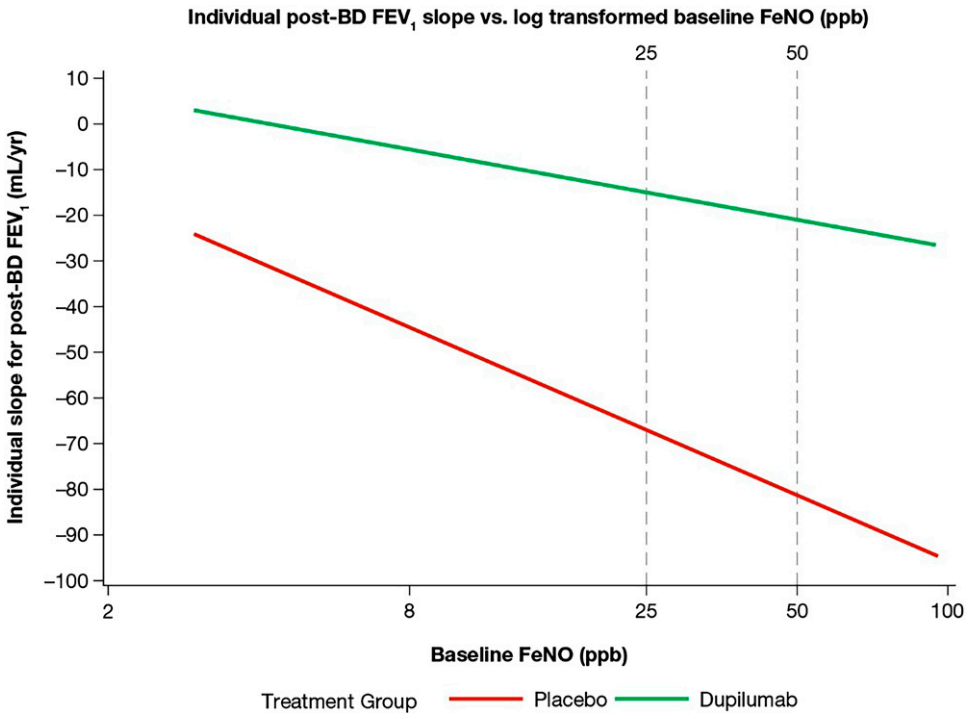

Figure 1. Rate of lung function decline across baseline F_{ENO} levels. The slope difference between the two lines is −11.8, with a 95% confidence interval of −71.5, 47.8. BD = bronchodilator; F_{ENO} = fractional exhaled nitric oxide; ppb = parts per billion.

Treatment	Subgroup	Post-BD FEV_1 change (mL/year)* Blood eosinophils (cells/μL) <150	≥150	≥300
Placebo	FeNO <25	**−49** (SE=26) (N=104)	**−56** (SE=19) (N=187)	**−71** (SE=27) (N=90)
Dupilumab	FeNO <25	**−12** (SE=17) (N=253)	**−17** (SE=14) (N=363)	**−35** (SE=20) (N=173)
Placebo	FeNO ≥25	**−116** (SE=37) (N=53)	**−47** (SE=20) (N=253)	**−59** (SE=24) (N=181)
Dupilumab	FeNO ≥25	**4** (SE=29) (N=99)	**−23** (SE=15) (N=475)	**−30** (SE=18) (N=334)
Placebo	FeNO ≥50	**−102** (SE=70) (N=20)	**−122** (SE=36) (N=109)	**−149** (SE=41) (N=85)
Dupilumab	FeNO ≥50	**43** (SE=61) (N=27)	**−41** (SE=27) (N=199)	**−50** (SE=32) (N=152)

Figure 2. Lung function decline difference in populations selected by combined baseline F_{ENO} and eosinophil levels. *Estimated from a mixed-effects model with repeated post-BD FEV_1 as outcome, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization, and Treatment × Time interaction and baseline post-BD FEV_1 as covariates. Intercept and time since randomization are random effects. BD = bronchodilator; F_{ENO} = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in one second; SE = standard error.

(17). This finding, coupled with the relationship between baseline F_{ENO} and LFD that was independent of exacerbations, suggests that the mechanisms leading to LFD and exacerbations are somewhat distinct.

The nature of this analysis prompts limitations such as a small sample size in some subgroups, which allows for only mean analysis of limited data. A decline in ICS adherence during QUEST might be expected to have a bigger impact on patients with higher baseline biomarkers and may, therefore, account for some of the observed LFD; however, adherence to background therapy was more than 80% in QUEST, and additional findings have shown that pre-BD FEV_1 was consistent across baseline F_{ENO} levels in the placebo group (18); therefore, it is an unlikely confounder. Finally, alternative causes for LFD were not captured. The present data should, therefore, be seen as hypothesis generating while providing a strong basis for further studies of appropriate power and duration to definitively evaluate F_{ENO} as a predictive and prognostic biomarker for LFD.

In conclusion, this analysis provides robust data supporting F_{ENO} as a clinically viable prognostic biomarker for accelerated LFD and predictive of the treatment response to dupilumab. Additional research is needed to establish patterns of LFD in patients with moderate-to-severe asthma, as well as the prognostic and predictive role of F_{ENO}. ■

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Identification of Alpha-1 Antitrypsin–Deficient Subjects with Normal Spirometry Who May Benefit from Alpha-1 Antitrypsin Replacement

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To the Editor:

Fraughen and colleagues (1) showed that alpha-1 antitrypsin (AAT) augmentation conferred a survival advantage by comparing the survival probability of AAT-deficient subjects from Ireland (where

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