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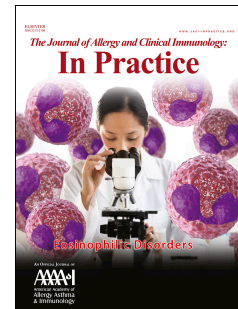
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Determinants of lung function improvement with omalizumab in adults with allergic asthma

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Conflict of interest: N.A. Hanania is a consultant for AstraZeneca, Boehringer Ingelheim, Genentech, Inc., GlaxoSmithKline, Novartis, and Sanofi/Regeneron. R. Djukanovic is a consultant for Novartis, Synairgen, and Teva; is on speaker's bureaus for Novartis and Teva; is an investigator for Novartis; and is a co-founder of Synairgen. L.G. Heaney has received research funding from Amgen, AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Inc./F. Hoffmann-La Roche, GlaxoSmithKline, MedImmune, Novartis UK, and Vitalograph; is a consultant for AstraZeneca, GlaxoSmithKline, F. Hoffmann-La Roche, Novartis, and Teva; and is on speaker's bureaus for AstraZeneca, Circassia, F. Hoffmann-La Roche, Novartis, and Teva. M. Yang and B. Yoo are employees of Genentech, Inc. A. Iqbal is an employee of Genentech, Inc., and is a shareholder in Genentech, Inc., Pfizer, and Roche. N.M. Griffin is a former employee of Genentech, Inc., and is a current employee of Global Blood Therapeutics. B.E. Chipps is an advisor and consultant and is on speaker's bureaus for AstraZeneca, Boehringer Ingelheim, Sanofi, Genzyme, Regeneron, Circassia, Genentech, Inc., Novartis, and Teva.

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31 *Clinical Implications*

32 Younger age and higher baseline reversibility were predictive of substantial lung function

33 improvement in patients with moderate-to-severe asthma who initiated omalizumab.

34

35 Clinical Trial Number: NCT01922037

TO THE EDITOR:

In patients with moderate-to-severe allergic asthma, omalizumab significantly reduces the rate of clinically significant asthma exacerbations.¹ Omalizumab also improves lung function in adolescents, but consistent improvements have not been demonstrated in adults.¹ Post hoc analyses from phase III clinical trials of omalizumab suggest that clinically relevant reductions in exacerbation frequency are preferentially observed in patients with asthma with higher baseline blood eosinophil (EOS) levels and previous hospitalizations.² However, no predictors of lung function improvements with omalizumab have been identified. Using data from the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) 48-week study, we sought retrospectively to ascertain the clinical phenotype of adult patients with asthma who experienced lung function improvements following omalizumab initiation.

PROSPERO (NCT01922037) was a US-based, single-arm, open-label, multicenter, prospective study of omalizumab.^{1,3} Patients with moderate-to-severe allergic asthma were enrolled if they: 1) were initiating omalizumab based on physician-assessed need, 2) had not received omalizumab in the previous year, and 3) had access to omalizumab through insurance or other funding.^{1,3} Patients aged ≥ 18 years with both baseline and post-baseline lung function data were included in this cross-sectional analysis. Lung function, blood EOS, and fractional exhaled nitric oxide (FeNO) were evaluated at baseline, 6, and 12 months. Lung function improvements were defined as ≥ 120 -mL, ≥ 150 -mL and ≥ 200 -mL improvements in forced expiratory volume in 1 second (FEV₁) from baseline to 6 or 12 months. This was based on the assumption that improvements of 100-200-mLs were likely to be clinically relevant.⁴ Exacerbations (defined as worsening of asthma symptoms requiring oral corticosteroid use, emergency department visit or hospitalization, and asthma-specific healthcare utilization) were recorded at baseline for the previous 12 months and monthly throughout the study.

Multiple logistic regression analyses evaluated the association between dichotomized lung function outcome (< 120 , 150 or 200-mL versus ≥ 120 , 150 or 200-mL FEV₁ improvement from baseline) in omalizumab-treated patients (mean [median] duration: 9.7 [11.2] months) and baseline

clinical and biomarker variables. Baseline variables included in the analysis were age, absolute FEV₁ (pre-bronchodilator), forced vital capacity (FVC), reversibility following 400 µg salbutamol, blood EOS (<300 versus ≥300 cells/µL), and FeNO (<25 versus ≥25 ppb). Area under the curve (AUC) of receiver operating characteristic curves from simple logistic model quantified the potential of baseline variables to predict clinically relevant lung function improvements. Cut-points of predictors of clinically relevant lung function improvements were determined using classification and regression tree (CART) analysis with selection of pruning variables based on cross-validation. Examination of clinical variables by baseline reversibility cut-points identified by CART analysis and an additional >20% cut-point identified from previous studies⁵ identified the relationship between baseline reversibility and other variables.

Baseline and post-baseline FEV₁ data were available for 573 (77.7%) of 737 adults enrolled in PROSPERO. From baseline to study end, 34.0% (195/573) of adults demonstrated ≥120-mL FEV₁ improvements. By multivariable logistic regression analysis, baseline bronchodilator reversibility (odds ratio [OR] [95% CI] 1.063 [1.040–1.087]; $P < .0001$) and age (OR [95% CI] 0.968 [0.952–0.983]; $P < .0001$) were significantly associated with 120-mL FEV₁ improvements. By CART analysis, 12% reversibility was identified as the cut-point for achieving lung function improvements. ROC analysis confirmed that baseline FEV₁ reversibility had the greatest potential among baseline clinical variables for predicting lung function improvement, with AUC values of 0.705 for FEV₁ reversibility, 0.603 for FEV₁, 0.574 for age, 0.571 for FVC, 0.563 for FeNO, and 0.545 for EOS. Age as a continuous variable was negatively associated with lung function improvement, but no specific cut-point could be determined. Baseline FeNO (OR [95% CI] 0.699 [0.458–1.067]; $P = .0970$), EOS levels (OR [95% CI] 0.961 [0.623–1.480]; $P = .8552$), FEV₁ (OR [95% CI] 0.762 [0.405–1.433]; $P = .3986$), and FVC (OR [95% CI] 0.809 [0.493–1.325]; $P = .3989$) were not associated with ≥120-mL FEV₁ improvements. Similar results were obtained with ≥150-mL and ≥200-mL FEV₁ cut-points (Table 1).

Patients with >20% reversibility had more severe asthma compared with patients in the >12% to ≤20% and ≤12% reversibility subgroups as indicated by slightly lower mean (SD) baseline

FEV₁ (1.6 [0.6], 2.0 [0.6], and 2.4 [0.8] L, respectively) and more prior exacerbations (3.7 [3.2], 3.6 [3.2], and 2.9 [3.3]/person-year, respectively). Baseline FeNO levels were higher in the >20% reversibility subgroup when compared with the >12% to ≤20% and the ≤12% reversibility subgroups (46.3 [37.5], 42.7 [40.9], and 29.4 [25.3] ppb, respectively). Patients with the highest baseline reversibility also demonstrated larger improvements in FEV₁ (Figure 1, A) and predicted FEV₁ % (Figure 1, B) and were more likely to achieve ≥120-mL, ≥150-mL or ≥200-mL FEV₁ improvements. The percentage of patients achieving FEV₁ improvements decreased incrementally with increasing cut-points in all reversibility subgroups (Figure 1, C). Omalizumab was well tolerated, and adverse events were consistent with the established safety profile.¹

The lung function improvements reported here are similar to those from previous studies of omalizumab⁶ and to studies of other asthma biologics, which enrolled patients with higher mean baseline reversibility (>20% for all biologics versus 8% for omalizumab in PROSPERO).^{3,5} These data support previous findings showing increased likelihood of FEV₁ improvements in patients with higher baseline reversibility⁷ and extend the knowledge showing improvements by baseline reversibility subgroups. The cut-points chosen reflect those within the range of repeatability of a test (120-mL) to clinically relevant FEV₁ improvements (200-mL).⁴ Although the percentage of patients achieving FEV₁ improvements decreased with increasing cut-points, a significant proportion of patients still achieved FEV₁ improvements with all cut-points.

The finding that older patients were less likely to have an improvement in lung function is consistent with previous studies.⁸ Although it has been reported that FEV₁ changes required for perception of change decreased from 280-mL in patients with asthma under 33 years to 170-mL in patients aged over 33 years,⁹ if smaller FEV₁ improvements in aged populations leads to improved asthma control has not been studied.

Our study has some limitations. The open-label, single-arm nature of the study limits the interpretation of our findings because a direct causal relationship between omalizumab and treatment effects cannot be established. Background medications, medication alterations and

114 medication adherence were not recorded in PROSPERO.¹ Lung function improvements and baseline
115 FeNO levels could have been influenced by concomitant controller medications used throughout the
116 study. Finally, because this analysis was not prespecified or controlled, our findings should be
117 confirmed in larger prospective studies with prespecified endpoints.

118 In conclusion, this study identified clinical features predictive of greater lung function
119 improvements following omalizumab therapy, with younger age and higher baseline reversibility
120 being associated with clinically relevant lung function improvements in adults treated with
121 omalizumab. These results help to define a patient population that is highly responsive to
122 omalizumab.

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Previous presentation of data: These data were previously presented at the 2018 American Thoracic Society Conference, May 18–23, 2018, San Diego, CA, USA.

Data sharing statement: Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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TABLE 1 Odds ratio (95% CI) estimates from multivariable logistic analysis of FEV₁ change from baseline cut-points of ≥ 120 mL, ≥ 150 mL, and ≥ 200 mL

	FEV ₁ change from baseline cut-point		
	≥ 120 mL	≥ 150 mL	≥ 200 mL
Age (y)	0.968 (0.952-0.983)	0.969 (0.953-0.986)	0.961 (0.944-0.979)
FEV ₁ (L)	0.762 (0.405-1.433)	0.658 (0.341-1.267)	0.586 (0.294-1.170)
Reversibility (%)	1.063 (1.040-1.087)	1.061 (1.038-1.085)	1.064 (1.040-1.088)
FVC (L)	0.809 (0.493-1.325)	1.005 (0.607-1.663)	1.032 (0.608-1.752)
Eosinophils*	0.961 (0.623-1.480)	0.764 (0.489-1.192)	0.823 (0.513-1.319)
FeNO*	0.699 (0.458-1.067)	0.597 (0.384-0.928)	0.713 (0.446-1.141)

FeNO, Fractional exhaled nitric oxide; *FEV₁*, forced expiratory volume in 1 second; *FVC*, forced vital capacity.

*Categorized as low versus high (eosinophils, <300 cells/ μ L versus ≥ 300 cells/ μ L; FeNO, <25 ppb versus ≥ 25 ppb).

173 **FIGURE 1** Mean (95% CI) change in FEV₁ (mL) from baseline (A), mean (95% CI) change in predicted
174 FEV₁ % from baseline (B), and percentage (95% CI) of patients achieving improvements in FEV₁ from
175 baseline at end of study (C). FEV₁, forced expiratory volume in 1 second.

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