

### Omalizumab treatment reduces asthma exacerbations regardless of airway bronchodilator reversibility

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#### Clinical Implications

Omalizumab may provide clinical benefit in terms of reduced exacerbations for patients with moderate to severe asthma, regardless of airway bronchodilator reversibility.

In asthma, the type 2 inflammatory response mediated by IgE leads to airway remodeling and subsequent symptom presentation.<sup>1</sup> Blocking the action of IgE can decrease airway remodeling, including reducing wall thickness and inflammation.<sup>2,3</sup> Airway smooth muscle thickness and vascularity are inversely correlated with post-bronchodilator FEV<sub>1</sub>.<sup>4</sup> In patients with allergic asthma, bronchodilator reversibility can indicate pulmonary function and is associated with lung function improvement during omalizumab therapy.<sup>5</sup>

Omalizumab treatment can also reduce asthma exacerbations.<sup>6</sup> However, it is unclear whether response to omalizumab is affected by a factor such as bronchodilator reversibility. The aim of this post hoc analysis of Prospective Observational Study to evaluate Predictors of clinical Effectiveness in Response to Omalizumab was to investigate exacerbation rates in three baseline reversibility subgroups of adult patients with asthma after omalizumab therapy.

PROSPERO (ClinicalTrials.gov identifier NCT01922037) was a 48-week, multicenter, prospective, single-arm study in which patients were treated with omalizumab based on physician-assessed need.<sup>7</sup> Adult patients with moderate to severe allergic asthma and access to omalizumab through insurance or other funding were eligible to participate.<sup>7</sup> Exclusion criteria were omalizumab therapy in the previous year, previous allergic reaction to omalizumab, or an experimental drug treatment within 3 months of study enrollment.<sup>7</sup> All participants signed an informed consent form approved by the local institutional review board. The study was conducted according to the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, US Food and Drug Administration regulations, and any applicable local, state, and national laws.

Exacerbations were assessed monthly and were defined as worsening of asthma symptoms requiring the use of oral corticosteroids, an emergency department visit, or hospitalization.<sup>6</sup> Airway bronchodilator reversibility at baseline was determined as the percent change from prebronchodilator to post-bronchodilator FEV<sub>1</sub>.<sup>7</sup> The cutoff for baseline airway reversibility after bronchodilators was greater than 12% change in FEV<sub>1</sub>, and for a full response to bronchodilators it was greater than 20% change in FEV<sub>1</sub>. Accordingly, patients were divided into three subgroups: 12% or less, greater than 12% to 20% or less, and greater than 20%. Baseline demographic and clinical

characteristics were summarized by reversibility subgroups. Protocol-defined exacerbations were estimated by a Poisson regression model normalized by omalizumab treatment duration after adjusting for the previous-year exacerbation number, with corresponding 95% confidence intervals (CIs).

Of 801 omalizumab-treated adult patients enrolled in PROSPERO, 710 had both prebronchodilator and post-bronchodilator FEV<sub>1</sub> values at baseline and were included in this analysis. Compared with patients in the 12% or less and greater than 12% to 20% or less reversibility subgroups, patients in the greater than 20% reversibility subgroup had a lower mean age (50.4 vs 53.2 vs 47.9 years), higher mean blood eosinophil levels (284.5 vs 317.3 vs 326.6 cells/ $\mu$ L), higher mean FeNO (30.9 vs 40.2 vs 48.8 ppb), and worse lung function at enrollment (percent predicted FEV<sub>1</sub>, 78.7% vs 65.8% vs 54.6%; FEV<sub>1</sub>, 2.4 vs 1.9 vs 1.7 L) (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

In the year before enrollment, mean (SD) exacerbation rates were similar between subgroups, with 2.8 (3.3), 3.6 (3.3), and 3.6 (3.2) events/y in the 12% or less, greater than 12% to 20% or less, and greater than 20% reversibility subgroups, respectively (Figure 1). After omalizumab initiation, adjusted mean (95% CI) exacerbation rates decreased to 0.71 (0.60-0.83), 0.93 (0.65-1.33), and 1.13 (0.82-1.54) events/treatment duration in the 12% or less, greater than 12% to 20% or less, and greater than 20% reversibility subgroups, respectively (Figure 1). Overlapping 95% CIs suggest there were no differences between groups. However, a formal hypothesis test found that the 12% or less reversibility group had a lower exacerbation rate than the greater than 20% group reversibility group (exacerbation rate difference of -0.47 [95% CI, -0.82 to -0.12]; multiplicity unadjusted  $P = .008$ ).

In the year before the initiation of omalizumab therapy, 43.7% to 58.5% of patients experienced three or more exacerbations, with higher rates in the greater than 12% to 20% or less and greater than 20% subgroups compared with the 12% or less subgroup, and between 16.3% (greater than 20% subgroup) and 26.6% (12% or less subgroup) of patients experienced no exacerbations (Figure 2). Conversely, in the year after the initiation of omalizumab therapy, more than half of patients experienced no exacerbations in all reversibility subgroups (range, 51.2 to 64.7%) (Figure 2). Interestingly, the percentage of patients experiencing no exacerbations decreased with increasing baseline reversibility.

This is one of the first studies to examine asthma exacerbations by bronchodilator reversibility subgroup in adult patients receiving omalizumab in a real-world setting in which exacerbations before treatment and a reduction in exacerbations after omalizumab initiation were independent of reversibility. This is despite patients with higher reversibility at baseline having higher blood eosinophil levels, higher FeNO, and worse lung function at baseline.

High reversibility at baseline has been correlated with type 2 inflammation.<sup>8,9</sup> Studies hypothesized that patients with high airway reversibility have an asthma endotype characterized by type 2 inflammation and eosinophil infiltration, whereas those with low airway reversibility may have an endotype characterized by subepithelial fibrosis,<sup>9</sup> which may explain the improvements we observed in lung function, although this is inconsistent across studies.<sup>8,9</sup>

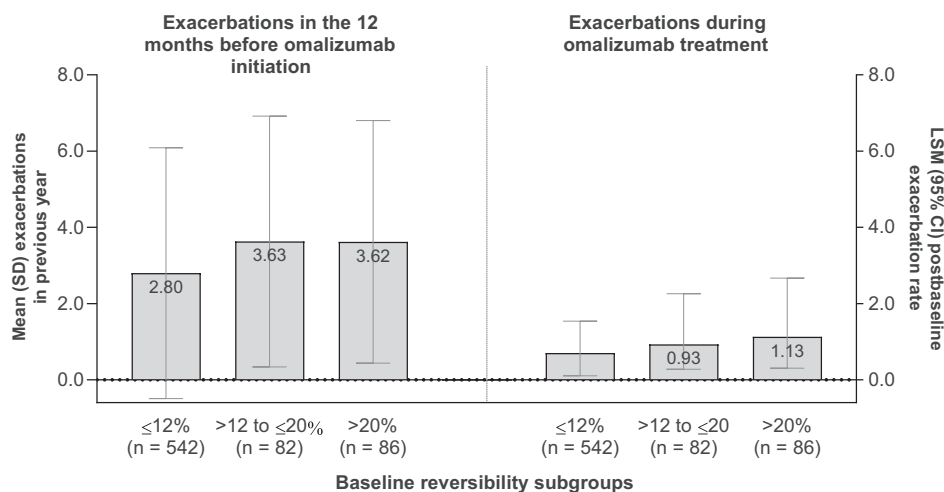


**FIGURE 1.** Exacerbation rate by baseline bronchodilator reversibility subgroup during 12 months before omalizumab initiation and during omalizumab treatment. The average (range) postbaseline follow-up was 9.7 (0-16) months. *CI*, confidence interval; *LSM*, least-squares mean.

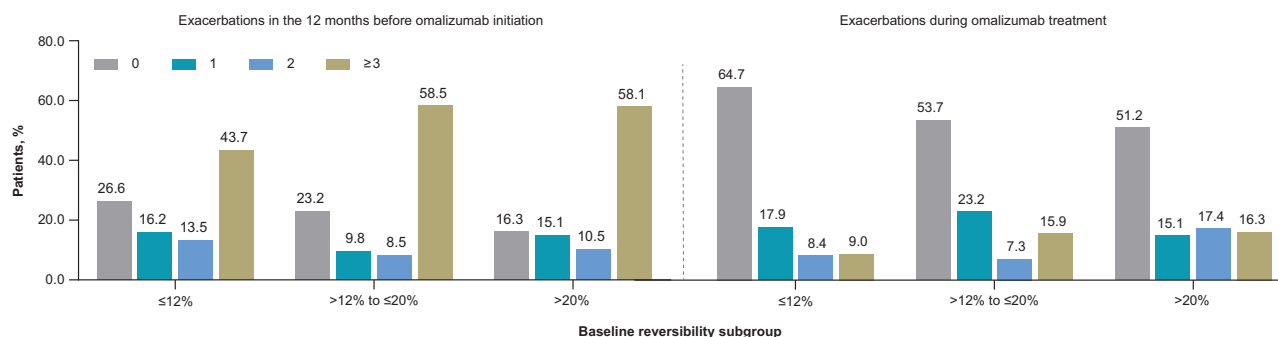


**FIGURE 2.** Exacerbation distribution during omalizumab treatment by baseline bronchodilator reversibility subgroup in 12 months before omalizumab initiation and during omalizumab treatment.

As a real-world study, PROSPERO has some limitations, including the lack of a control group. Moreover, exacerbations in the year before omalizumab initiation were based on patients' health records, which may have increased the possibility of inaccurate reporting. The nature of this post hoc analysis and small sample sizes for some subgroups did not allow for extensive statistical comparisons.

Omalizumab provided clinical benefit in terms of reduced exacerbation rates versus exacerbation rates before treatment for all airway bronchodilator reversibility groups. The exacerbation rate was statistically lower in patients with 12% or less versus greater than 20% bronchodilator reversibility. Our findings correlate with a previous study of PROSPERO, which found that the response to omalizumab was independent of classical type 2 biomarkers, including baseline blood eosinophil or FeNO levels.<sup>6</sup> Together, this supports the concept that omalizumab is efficacious independent of airway reversibility and associated type 2 inflammation biology, and may be a valuable option for managing a broad patient population with moderate to severe allergic asthma. Furthermore, our study proposes that selecting patients for clinical trials based on airway reversibility may not reflect the

real-world population seen in clinical practice and may exclude patients who may benefit from biologic therapies.

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Conflicts of interest: C.T.J. Holweg, B. Yoo, and B. Creasy are employees of Genentech, Inc. M.E. Wechsler has received personal fees from AstraZeneca, Boehringer Ingelheim, Genentech, Inc., GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Regeneron, Sanofi, Sentien, and Teva. The rest of the authors declare that they have no relevant conflicts of interest.

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## ONLINE REPOSITORY

**TABLE E1.** Baseline demographics and clinical characteristics by baseline reversibility subgroups

| Characteristic*                        | Baseline reversibility subgroup |                       |               |
|----------------------------------------|---------------------------------|-----------------------|---------------|
|                                        | ≤12% (n = 542)                  | >12% to ≤20% (n = 82) | >20% (n = 86) |
| Age, y                                 | 50.4 (14.8)                     | 53.2 (14.5)           | 47.9 (13.3)   |
| Female, n (%)                          | 356 (65.7)                      | 55 (67.1)             | 58 (67.4)     |
| Race,† n (%)                           |                                 |                       |               |
| White                                  | 390 (72.0)                      | 59 (72.0)             | 61 (70.9)     |
| Black                                  | 82 (15.1)                       | 9 (11.0)              | 12 (14.0)     |
| Asian                                  | 26 (4.8)                        | 4 (4.9)               | 2 (2.3)       |
| Other/multiple                         | 44 (8.1)                        | 10 (12.2)             | 11 (12.8)     |
| Body mass index, kg/m <sup>2</sup>     | 31.8 (8.0)                      | 30.7 (8.6)            | 30.8 (7.4)    |
| Blood eosinophils, cells/μL            | 284.5 (244.3)                   | 317.3 (216.1)         | 326.6 (314.8) |
| FeNO, ppb                              | 30.9 (30.2)                     | 40.2 (39.4)           | 48.8 (39.3)   |
| IgE, IU/mL                             | 454.4 (1,047.5)                 | 420.2 (568.9)         | 471.5 (721.0) |
| Percent predicted FEV <sub>1</sub> (%) | 78.7 (19.8)                     | 65.8 (14.7)           | 54.6 (15.0)   |
| FEV <sub>1</sub> , L                   | 2.4 (0.8)                       | 1.9 (0.6)             | 1.7 (0.6)     |
| FEV <sub>1</sub> reversibility (%)     | 2.6 (6.3)                       | 15.7 (2.3)            | 34.2 (21.0)   |

\*Mean (SD), unless otherwise stated.

†Race was self-reported. Other/multiple includes American Indian, Alaska native, native Hawaiian, other Pacific Islander, and other.