

Original Article

Possible Protective Effect of Omalizumab on Lung Function Decline in Patients Experiencing Asthma Exacerbations

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What is already known about this topic? Loss of lung function with aging can be accelerated in patients with asthma and is greater in patients who experience exacerbations.

What does this article add to our knowledge? In treatment-refractory asthma, omalizumab may prevent the loss of lung function due to exacerbations in patients with allergic asthma.

How does this study impact current management guidelines? Omalizumab is recommended for severe uncontrolled allergic asthma despite inhaled corticosteroids, with efficacy reflected in fewer exacerbations. But, even in those with asthma exacerbations on therapy, omalizumab may have benefits protecting against lung function decline.

BACKGROUND: Frequent exacerbations are associated with greater FEV₁ decline in patients with asthma. The effect of omalizumab versus placebo on lung function in patients experiencing asthma exacerbations has not been previously examined.

OBJECTIVE: To evaluate the relationship between postbaseline (treatment phase) exacerbation status and lung function decline in children, adolescents, and adults treated with omalizumab versus placebo using data from 3 pediatric and adolescent/adult studies.

METHODS: Changes in percent predicted FEV₁ (ppFEV₁) and FEV₁ by treatment (omalizumab/placebo) and postbaseline exacerbation status (exacerbators/nonexacerbators) were assessed in patients aged 6 to 11 years (IA05, n = 576) and 12 to 75 years (EXTRA/INNOVATE pooled, n = 1202). Pediatric patients

were examined at treatment weeks 12, 24, 28, 40, and 52, and adolescent/adult data at weeks 4, 12, 20, and 28.

RESULTS: Omalizumab-treated patients experienced larger increases in ppFEV₁ and FEV₁ compared with placebo-treated patients in the pediatric and pooled adolescent/adult populations. The response was observed in pediatric exacerbators, with significantly larger increases in ppFEV₁ and FEV₁ at week 12 (mean difference [95% CI], 4.11% [0.93%-7.30%], *P* = .011 for ppFEV₁; 80 [10-140] mL, *P* = .017 for FEV₁) and week 28 (mean difference [95% CI], 3.65% [0.11%-7.19%], *P* = .043 for ppFEV₁; 100 [30-170] mL, *P* = .007 for FEV₁). In the adolescent/adult population, both exacerbators and nonexacerbators derived similar benefit with omalizumab compared with placebo. **CONCLUSIONS:** Findings from this post hoc analysis suggest that omalizumab may confer some protection against lung

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Conflicts of interest: W. W. Busse has consultant arrangements with AstraZeneca, Genentech, Inc., GlaxoSmithKline, Novartis, Sanofi, and Teva, and is on the data safety monitoring boards for Boston Scientific and Genentech, Inc. S. J. Szeffler is an advisory panel member for AstraZeneca, Boehringer Ingelheim, Genentech, Inc., GlaxoSmithKline, Merck, Novartis, Propeller Health, Regeneron, and Sanofi, and has received a research grant from Propeller Health. T. Haselkorn is a paid

consultant to Genentech, Inc. and Novartis Pharmaceuticals Corporation. A. Iqbal is an employee of Genentech, Inc., and holds stock in Genentech, Inc., GlaxoSmithKline, and Pfizer. B. Ortiz is a former employee of and stockholder in Novartis, and a current employee of Regeneron. B. Q. Lanier is a consultant for Novartis, and speaker bureau member for Genentech, Inc. B. E. Chipps has received consulting/advisory board and speaker bureau fees from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Inc., Novartis, and Teva.

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*Abbreviations used**COPD- Chronic obstructive pulmonary disease**ICS- Inhaled corticosteroids**LABA- Long-acting beta-agonist**LSM- Least squares mean**ppFEV₁- Percent predicted FEV₁**PROSE- Preventative Omalizumab or Step-up Therapy for Fall Exacerbations*

function decline among patients who experienced exacerbations during treatment. © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Lung function; Airway remodeling; Inflammation; Lung function decline; Obstructive airway disease

INTRODUCTION

Asthma is a chronic obstructive airway disease that is characterized by airway reversibility.¹ Normally, FEV₁ increases in late adolescence to a plateau, which then gradually declines in adulthood.² Some patients with asthma experience a decline in lung function that ultimately results in irreversible airflow obstruction.³ Reduced adolescent-related growth in FEV₁, resulting in a low maximal FEV₁, is associated with the subsequent development of chronic airflow obstruction.² In a large cohort of children (aged 5-12 years at enrollment) with mild to moderate asthma who were followed for 13 years, 36% of those with abnormal lung function growth (reduced growth and/or early decline) compared with 8% of those with normal lung function growth developed irreversible obstructive airway disease (chronic obstructive pulmonary disease [COPD]).² This illustrates the concordance of reduced lung function growth with the development of irreversible airway obstruction.

A greater frequency of acute severe exacerbations is associated with a more rapid decline in FEV₁ in patients with asthma and those with irreversible obstructive airway disease (COPD).⁴⁻⁷ The association between severe exacerbations and lung function decline has been highlighted in randomized double-blind studies, which have indicated that preventing exacerbations with early interventional inhaled corticosteroid (ICS) treatment reduces the rate of lung function decline.⁶ In addition, measures of lung function, including FEV₁, have been proposed as a component of strategies to predict future exacerbations in patients with asthma.^{8,9} This has been supported by a retrospective analysis of children from the Inner City Anti-IgE Therapy for Asthma study, which demonstrated a greater likelihood of suffering an exacerbation in children presenting with reduced pulmonary function.¹⁰

Airway and systemic inflammation are predictors of more frequent asthma exacerbations.¹¹ T_H2 lymphocytes are major regulators of the inflammatory response by stimulating IgE secretion from B lymphocytes, the recruitment of eosinophils to airway epithelium, and the activation of mast cells and eosinophils.¹² IgE plays an important role in airway inflammation and has been hypothesized as a risk factor for airway remodeling.¹³

In patients who do not respond to ICS and long-acting beta-agonists (LABAs; ICS ± LABA), omalizumab, a targeted

anti-IgE antibody,¹⁴ may be beneficial in preventing irreversibility of airway obstruction by reducing exacerbation frequency¹⁵⁻¹⁸ because anti-IgE effects may neutralize mechanisms of airway remodeling.¹⁹ Although some studies have illustrated efficacy of omalizumab at improving lung function in patients with moderate to severe asthma,^{16,20,21} there are limited data examining the effect of omalizumab on lung function decline in adults and children with asthma, particularly in those patients experiencing asthma exacerbations. This post hoc analysis examined the relationship between asthma exacerbation status and lung function decline in children, adolescents, and adults treated with omalizumab versus placebo using data from 3 published randomized studies.¹⁵⁻¹⁷

METHODS

Study design

Post hoc exploratory analyses of data from 3 large randomized placebo-controlled studies of omalizumab were used, including the pediatric study population aged 6 to 11 years from IA05, and the adolescent/adult study populations aged 12 to 75 years from EXTRA and INNOVATE. All studies required institutional review board approval and written informed patient consent and were conducted in accordance with national and international guidance for study conduct. The methods for all studies have been published previously,¹⁵⁻¹⁷ and brief study methods are provided below. In all studies, dosing of omalizumab was based on body weight and total serum IgE as in the prescribing information.¹⁴

IA05

IA05 (ClinicalTrials.gov identifier: NCT00079937) was a 52-week trial in children aged at least 6 to 11 years (n = 627) with inadequately controlled moderate to severe allergic asthma. Reversibility was not a requirement for enrollment. Children were randomized to receive either placebo or omalizumab (75-375 mg) subcutaneously every 2 or 4 weeks for 52 weeks. ICS dosing was kept constant during the first 24 weeks of the study unless there was an exacerbation requiring intervention (steroid dose-stable period). Thereafter (weeks 25-52), the ICS dose could be modified on the basis of the patient's clinical status (steroid dose-adjustment period). Spirometry was performed at baseline and weeks 12 and 24 during the steroid dose-stable period, and at weeks 28, 40, and 52 during the steroid dose-adjustment period.¹⁷

EXTRA

EXTRA (ClinicalTrials.gov identifier: NCT00314574) was a 48-week multicenter study of adolescents and adults aged 12 to 75 years (n = 850) with inadequately controlled severe asthma despite high-dose ICS and LABA. Reversibility was not a requirement for enrollment. Patients entered a 2- to 4-week run-in period until 2 weeks of inadequate asthma control was demonstrated. No adjustment of any medication was permitted during the study. Systemic steroids were permitted for management of an asthma exacerbation. Spirometry was performed every 4 weeks from weeks 0 to 48.¹⁵

INNOVATE

INNOVATE (ClinicalTrials.gov identifier: NCT00046748) was a parallel-group multicenter study of adolescents and adults aged 12 to 75 years (n = 419) with severe persistent allergic asthma inadequately controlled despite high-dose ICS and LABA as described in step 4 of the Global Initiative for Asthma 2002 guidelines.¹⁶ Inclusion required reduced lung function (FEV₁ between 40% and

<80% of predicted) and FEV₁ reversibility at least 12% from baseline within 30 minutes of inhaled salbutamol. Randomization to omalizumab or placebo was stratified by country and other medications. The treatment phase, in which patients were randomized to omalizumab or placebo, was 28 weeks, and patients were followed for an additional 16 weeks. Concomitant controller medication doses remained constant throughout the study unless patients suffered an exacerbation. Spirometry testing was conducted at weeks 0, 2, 4, 12, 20, and 28 of the treatment phase and weeks 4 and 16 of the follow-up phase.¹⁶

Statistical analyses

Patients who experienced an asthma exacerbation during the treatment period in which they were enrolled were classified as “exacerbators” and those who did not were classified as “non-exacerbators.” For all analyses, asthma exacerbations were defined according to American Thoracic Society guidelines²² as worsening of symptoms requiring treatment with systemic corticosteroids for at least 3 days.¹⁵⁻¹⁷

Changes from baseline in prebronchodilator percent predicted FEV₁ (ppFEV₁) and FEV₁ were examined by treatment status (omalizumab vs placebo) at baseline and weeks 12, 24, 28, 40, and 52 for IA05. ppFEV₁ and FEV₁ by treatment status were examined at baseline (week 0) and weeks 4, 12, 20, and 28 in the pooled population from EXTRA and INNOVATE. Analyses were stratified by treatment and treatment phase exacerbation status (exacerbators vs nonexacerbators) for pediatric and pooled adolescent/adult data. Last observation carried forward was used to account for missing lung function parameter data. The impact of using last observation carried forward is low in this analysis due to dropout/missing data being low. Statistical significance was assessed using an analysis of covariance model adjusted for dosing schedule (every 2 or 4 weeks), country grouping, exacerbation history, and baseline ppFEV₁ value for continuous ppFEV₁ and FEV₁ outcomes. Results were summarized by least squares mean (LSM) difference in both absolute value and change from baseline value, with *P* values and 95% CIs calculated for each visit. No adjustments were applied to the *P* values and confidence coefficients because of the post hoc nature of the analyses.

RESULTS

Baseline patient characteristics

This pooled data set included all modified intention-to-treat patients with both baseline and at least 1 postbaseline lung function measurement. The pediatric data from study IA05 included 576 children (omalizumab exacerbators, *n* = 143; placebo exacerbators, *n* = 94; omalizumab nonexacerbators, *n* = 241; placebo nonexacerbators, *n* = 98). The mean age of the analysis subgroups was between 8.3 and 8.7 years, and all study groups were predominantly male (range, 66.3%-68.5%). Baseline mean $\pm$ SD ppFEV₁ was slightly lower in the omalizumab exacerbators (81.4% $\pm$ 18.6%) and placebo exacerbators (85.8% $\pm$ 19.9%) than in the omalizumab nonexacerbators (87.1% $\pm$ 16.8%) and placebo nonexacerbators (86.9% $\pm$ 17.3%; Table I).

A total of 1202 adolescents and adults from EXTRA and INNOVATE were included in the pooled data set (omalizumab exacerbators, *n* = 178; placebo exacerbators, *n* = 219; omalizumab nonexacerbators, *n* = 426; placebo nonexacerbators, *n* = 379). The pooled population had a mean age range of 43.7 to 44.9 years in the analysis subgroups, and was predominantly female (range, 61.5%-71.7%) and white (range, 75.3%-79.0%).

Baseline mean $\pm$ SD ppFEV₁ was slightly lower in omalizumab exacerbators (59.9% $\pm$ 14.5%) and placebo exacerbators (61.7% $\pm$ 15.0%) than in omalizumab nonexacerbators (65.6% $\pm$ 15.0%) and placebo nonexacerbators (64.4% $\pm$ 13.4%; Table II).

ppFEV₁ and FEV₁ by treatment group

Pediatric population from IA05. At baseline, there was no difference between pediatric patients treated with omalizumab or placebo in ppFEV₁ or FEV₁. During the treatment phase, ppFEV₁ was slightly but significantly higher in omalizumab-treated patients compared with placebo-treated patients at week 12 (LSM difference [95% CI], 2.3% [0.2%-4.5%], *P* = .0329) and week 28 (LSM difference [95% CI], 2.8% [0.4%-5.1%], *P* = .0213; Figure 1, A). For FEV₁, small but significant differences were observed at week 12 (LSM difference [95% CI], 0.04 [0.0-0.1] L, *P* = .0424) and were maintained until week 40 (Figure 1, B).

Adolescent/adult population from EXTRA/INNOVATE

In the pooled adolescent/adult population, there was no difference between omalizumab- and placebo-treated patients in ppFEV₁ or FEV₁ at baseline (Figure 2, A and B). During the treatment phase, omalizumab- versus placebo-treated patients saw significantly higher values in ppFEV₁ at week 4 of treatment (LSM difference [95% CI], 1.6% [0.3%-2.8%], *P* = .0175; Figure 2, A) and FEV₁ (LSM difference [95% CI], 0.1 [0.0-0.1] L, *P* = .0129; Figure 2, B). Significant differences were maintained throughout treatment.

Change in ppFEV₁ and FEV₁ by treatment group and treatment phase exacerbation event

Pediatric population from IA05. Omalizumab exacerbators showed improvement in ppFEV₁ from baseline to week 12. ppFEV₁ decreased to baseline levels by week 52. Placebo exacerbators showed a decline in ppFEV₁ between baseline and week 12. In this group, ppFEV₁ remained below baseline levels for the whole study period (Figure 3, A). Compared with placebo exacerbators, ppFEV₁ was significantly higher for omalizumab exacerbators at week 12 (mean difference [95% CI], 4.11% [0.93%-7.30%], *P* = .011) and week 28 (mean difference [95% CI], 3.65% [0.11%-7.19%], *P* = .043). Omalizumab and placebo nonexacerbators showed similar mean change in ppFEV₁ throughout the 52-week study, with an initial improvement followed by a decline in ppFEV₁ (Figure 3, A).

Change from baseline absolute FEV₁ increased linearly from baseline to week 52 in all 4 subgroups. The overall increase was similar in omalizumab exacerbators versus omalizumab nonexacerbators at all time points, and the increase was higher in omalizumab-treated groups compared with placebo-treated groups. Compared with placebo exacerbators, the increase in FEV₁ was larger in omalizumab exacerbators at all time points and reached significance at week 12 (mean difference [95% CI], 0.08 [0.01-0.14] L, *P* = .017), week 28 (mean difference [95% CI], 0.10 [0.03-0.17] L, *P* = .007), and week 40 (mean difference [95% CI], 0.09 [0.01-0.16] L, *P* = .027). In nonexacerbators, the increase was larger in omalizumab nonexacerbators compared with placebo nonexacerbators from week 24 onward, and this difference reached significance at week 52 (mean difference [95% CI], 0.07 [0.00-0.13] L, *P* = .042; Figure 3, B).

TABLE I. Baseline characteristics of children aged 6 to 11 y from IA05

Characteristic	Exacerbators		Nonexacerbators	
	Placebo (n = 94)	Omalizumab (n = 143)	Placebo (n = 98)	Omalizumab (n = 241)
Age (y)				
Mean $\pm$ SD	8.6 $\pm$ 1.7	8.7 $\pm$ 1.8	8.3 $\pm$ 1.7	8.7 $\pm$ 1.7
Median	9.0	9.0	8.0	9.0
n	94	143	98	241
Sex, n (%)				
Male	64 (68.1)	98 (68.5)	65 (66.3)	161 (66.8)
Female	30 (31.9)	45 (31.5)	33 (33.7)	80 (33.2)
n	94	143	98	241
ppFEV ₁				
Mean $\pm$ SD	85.8 $\pm$ 19.9	81.4 $\pm$ 18.6	86.9 $\pm$ 17.3	87.1 $\pm$ 16.8
Median	86.4	81.8	89.2	87.5
n	94	142	98	241
Serum total IgE (IU/mL)				
Mean $\pm$ SD	479.1 $\pm$ 350.7	422.8 $\pm$ 318.8	458.8 $\pm$ 329.6	520.8 $\pm$ 350.3
Median (IQR)	406.5 (189.0-748.0)	337.0 (161.0-643.0)	398.5 (184.0-708.0)	448.0 (233.0-806.0)
n	94	143	98	241
Eosinophils (count/ μ L)				
Mean $\pm$ SD	559.6 $\pm$ 410.4	504.2 $\pm$ 358.0	508.2 $\pm$ 344.5	508.8 $\pm$ 316.6
Median (IQR)	500.0 (200.0-800.0)	400.0 (200.0-700.0)	450.0 (200.0-700.0)	450.0 (300.0-700.0)
n	94	143	98	240

IQR, Interquartile range.

Adolescent/adult population from EXTRA/INNOVA-

TE. At week 4, ppFEV₁ had increased in all subgroups by approximately 4% to 6%. ppFEV₁ then plateaued until week 28 in all subgroups except placebo exacerbators, who saw a decline in ppFEV₁ between weeks 4 and 12. Omalizumab exacerbators showed greater improvements in ppFEV₁ compared with placebo exacerbators, and these differences reached significance at week 12 (mean difference [95% CI], 3.53% [0.90%-6.16%], $P = .009$) and week 20 (mean difference [95% CI], 3.39% [0.71%-6.07%], $P = .013$). Significantly higher ppFEV₁ values observed in omalizumab nonexacerbators were evident by week 4 (mean difference [95% CI], 1.61% [0.03%-3.18%], $P = .045$) and were maintained to week 28 (mean difference [95% CI], 2.88% [0.79%-4.97%], $P = .007$; Figure 4, A).

Change from baseline FEV₁ showed an initial increase at week 4 followed by a plateau in all subgroups except placebo exacerbators, whose FEV₁ decreased from weeks 4 to 12. The improvements in FEV₁ were larger in omalizumab exacerbators versus placebo exacerbators at all time points, but these differences were significant at week 12 (mean difference [95% CI], 0.11 [0.03-0.20] L, $P = .009$) and week 20 (mean difference [95% CI], 0.10 [0.02-0.19] L, $P = .020$). Significantly larger improvements in FEV₁ in omalizumab nonexacerbators were evident by week 4 (mean difference [95% CI], 0.06 [0.00-0.11] L, $P = .031$) and were maintained to week 28 (mean difference [95% CI], 0.09 [0.03-0.16] L, $P = .006$; Figure 4, B).

DISCUSSION

This post hoc analysis in children, adolescents, and adults provides the opportunity to examine lung function in relation to treatment and treatment phase exacerbation status in patients with moderate to severe persistent allergic asthma. Across all age groups, omalizumab-treated patients showed improvement in

ppFEV₁ and FEV₁ compared with placebo-treated patients. When analyzed by exacerbation status, the data suggest that patients who experience exacerbations while on omalizumab preserve their lung function. Indeed, improvements in lung function observed in omalizumab exacerbators were similar to those in omalizumab nonexacerbators in both the pediatric and adolescent/adult populations. Furthermore, lung function improvements in omalizumab exacerbators reached statistical significance compared with lung function changes in placebo exacerbators at several time points over the study period in both the pediatric and adolescent/adult populations. In the pooled adolescent/adult population, statistically significant improvements in lung function over placebo were also seen in omalizumab nonexacerbators. In this population, improvements in FEV₁ and ppFEV₁ were slightly larger in nonexacerbators compared with exacerbators.

In the current analysis, findings differed slightly in the pediatric and adolescent/adult study populations. In particular, benefits with omalizumab were seen only in exacerbators in pediatric patients, but in both exacerbators and nonexacerbators in adolescent/adult patients. The findings in pediatric patients were consistent with previous findings. For example, in the Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study, inner-city children aged 6 to 17 years with asthma and a history of exacerbations in the run-in period received greater benefit from omalizumab therapy than did children without recent exacerbations.¹⁸ It should be noted, however, that PROSE concentrated on pretreatment exacerbation status, whereas this study concentrated on postbaseline exacerbation status. This makes the present study prone to more bias and confounding issues. It is possible that differences in baseline demographic characteristics in the pediatric and adolescent/adult study populations in this analysis contributed to the differences in patterns of improvement and decline between

TABLE II. Baseline characteristics of adolescents and adults (pooled data from EXTRA and INNOVATE)

Characteristic	Exacerbators		Nonexacerbators	
	Placebo (n = 219)	Omalizumab (n = 178)	Placebo (n = 379)	Omalizumab (n = 426)
Age (y)				
Mean $\pm$ SD	44.1 $\pm$ 14.3	44.6 $\pm$ 14.2	44.9 $\pm$ 13.3	43.7 $\pm$ 13.9
Median	44.0	44.5	46.0	45.0
n	219	178	379	426
Sex, n (%)				
Male	62 (28.3)	57 (32.0)	131 (34.6)	164 (38.5)
Female	157 (71.7)	121 (68.0)	248 (65.4)	262 (61.5)
n	219	178	379	426
Race, n (%)				
White	173 (79.0)	134 (75.3)	290 (76.5)	323 (75.8)
Black	30 (13.7)	36 (20.2)	60 (15.8)	61 (14.3)
Asian	5 (2.3)	3 (1.7)	7 (1.8)	8 (1.9)
Other	11 (5.0)	5 (2.8)	22 (5.8)	34 (8.0)
n	219	178	379	426
ppFEV ₁				
Mean $\pm$ SD	61.7 $\pm$ 15.0	59.9 $\pm$ 14.5	64.4 $\pm$ 13.4	65.6 $\pm$ 15.0
Median	63.6	60.7	65.1	66.3
n	219	178	376	423
Total IgE (IU/mL)				
Mean $\pm$ SD	176.1 $\pm$ 138.6	163.0 $\pm$ 124.0	180.7 $\pm$ 141.9	192.2 $\pm$ 142.9
Median (IQR)	137.0 (68.0-259.0)	122.5 (70.0-223.0)	136.5 (67.0-259.0)	144.0 (82.0-271.0)
n	219	178	378	426
Eosinophils (count/ μ L)				
Mean $\pm$ SD	401.4 $\pm$ 317.1	343.5 $\pm$ 287.5	330.7 $\pm$ 297.3	342.7 $\pm$ 272.4
Median (IQR)	300.0 (180.0-500.0)	280.0 (150.0-450.0)	250.0 (140.0-430.0)	300.0 (170.0-420.0)
n	215	175	361	402

IQR, Interquartile range.

the 2 groups. In the pediatric study populations, baseline FEV₁ was lowest in the exacerbators subgroup, possibly explaining why omalizumab exacerbators saw a larger increase over the placebo group. However, it is unlikely that these differences played a major role, because the study populations were generally matched with respect to baseline demographic and clinical characteristics.

Another difference observed between the pediatric and adolescent/adult study populations was that the pediatric group within this study saw continued increases in FEV₁ over the whole study period. In contrast, in the pooled adolescent/adult study population, FEV₁ increased from baseline to week 4 and then either remained the same or decreased slightly. Because the increases in FEV₁ in the pediatric study population occurred irrespective of treatment or exacerbation status, it is likely that they reflect lung function growth associated with physical growth in children.²

Contrary to omalizumab exacerbators, who experienced lung function improvements, placebo exacerbators experienced minimal increases in the pooled adolescent/adult study population or small reductions in lung function in pediatric patients at study end. These findings, together with the observed improvements in lung function in omalizumab exacerbators, suggest that omalizumab treatment may have a protective effect on lung function in children, adolescents, and adults who experience asthma exacerbations. These findings corroborate those from a

post hoc analysis of the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab, in which omalizumab was associated with ppFEV₁ improvement and preservation over the 48-week study in patients with asthma-COPD overlap,²³ a population that usually experiences frequent exacerbations and substantial yearly decline in lung function.²⁴

The association between exacerbation frequency and lung function has been identified in patients with asthma and COPD.⁴⁻⁷ Indeed, even a single COPD exacerbation was shown to result in a significant increase in the rate of decline in lung function in 1 retrospective analysis.²⁵ The importance of the exacerbation frequency and lung function relationship has been illustrated by clinical studies with other asthma medications such as tiotropium bromide + ICS, which have noted that improvements in lung function parallel reductions in asthma exacerbations.²⁶ An observational study of 40 weeks of add-on omalizumab therapy in 16 patients found that mean $\pm$ SD decreases in monthly exacerbations (from 1.1 $\pm$ 0.6 to 0.2 $\pm$ 0.4; $P < .01$) were associated with stable improvements in FEV₁ (from 53.6% $\pm$ 14.6% to 77.0% $\pm$ 14.9% of predicted values; $P < .01$).²⁷

It has been proposed that exacerbations in patients with COPD and asthma may lead to structural alterations in the lung that permanently worsen airflow.^{28,29} However, it is not entirely clear whether exacerbations cause irrecoverable loss in

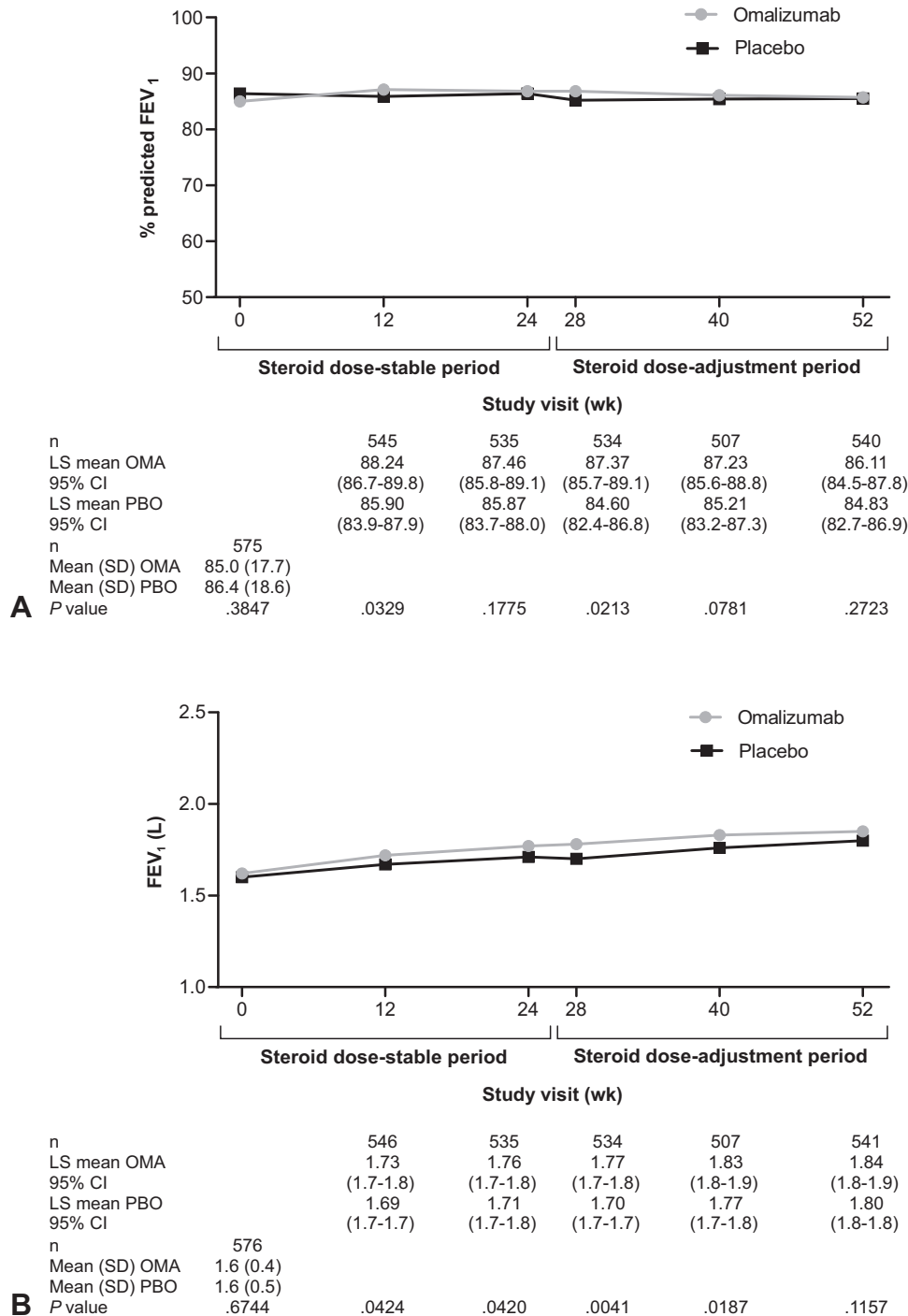


FIGURE 1. Prebronchodilator (A) ppFEV₁ and (B) FEV₁ by treatment in children aged 6 to 11 years from IA05. Treatment-specific LS means and their difference and associated 95% CIs were calculated using an analysis of covariance model adjusted for dosing schedule (every 2 or 4 weeks), asthma medication strata, country grouping, and baseline FEV₁. LS, Least squares; OMA, omalizumab; PBO, placebo.

lung function or whether those with low lung function represent a phenotype that is associated with exacerbations. A cluster analysis of 259 adult patients with asthma in Korea identified 4 subphenotypes, including 2 (late-onset nonatopic asthma with impaired lung function, early-onset atopic asthma with severely impaired lung function) who were exacerbation

prone and were also characterized by impaired lung function but with opposite atopic status.³⁰ Notwithstanding this, patients with a recent history of exacerbations may have higher levels of inflammation that is susceptible to the effects of omalizumab, translating into a greater likelihood of benefit with omalizumab therapy.¹⁸

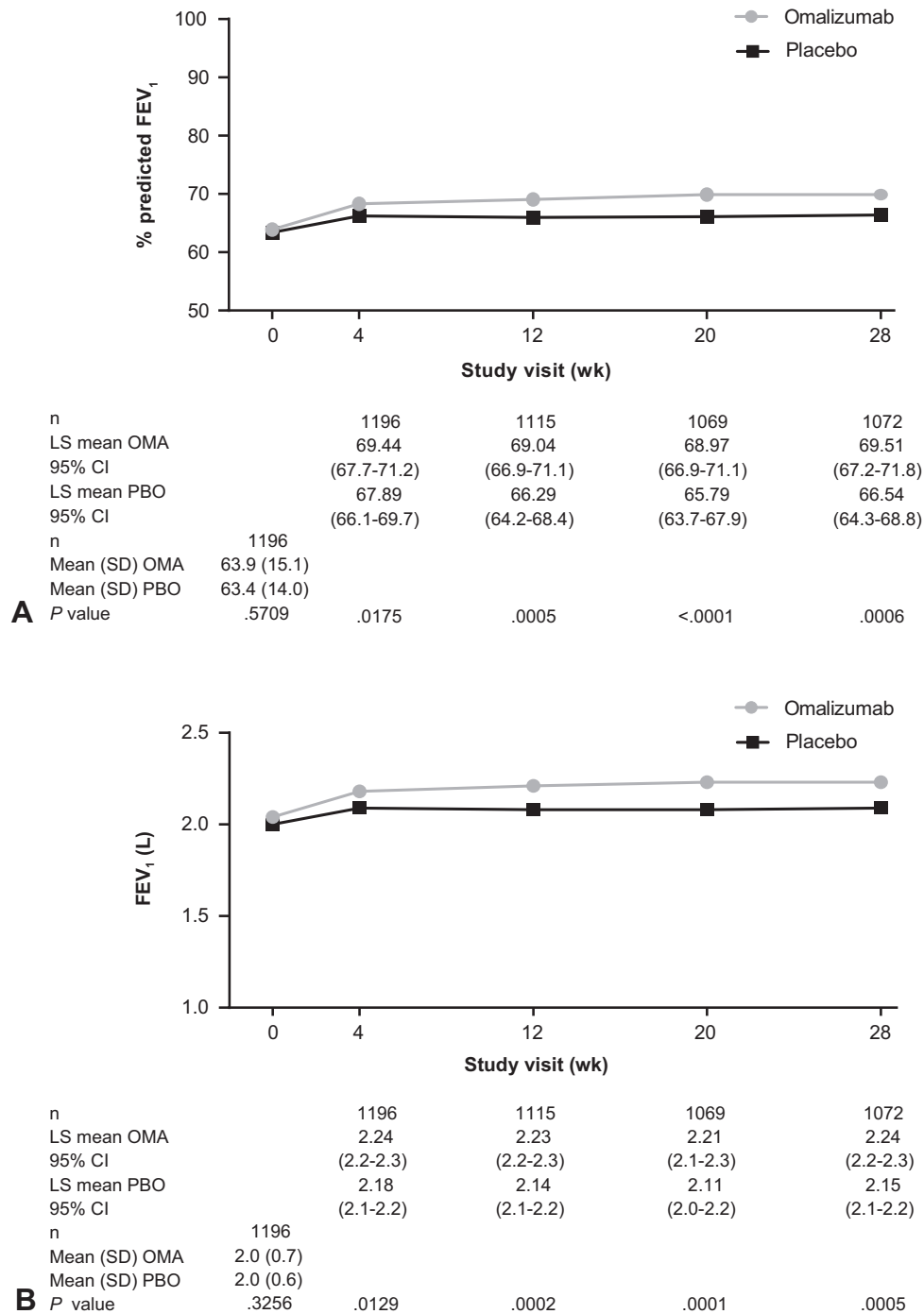


FIGURE 2. Prebronchodilator (A) ppFEV₁ and (B) FEV₁ by treatment in adolescents and adults aged 12 to 75 years pooled from EXTRA and INNOVATE. Treatment-specific LS means and their difference and associated 95% CIs were calculated using an analysis of covariance model adjusted for dosing schedule (every 2 or 4 weeks), asthma medication strata, country grouping, and baseline FEV₁. LS, Least squares; OMA, omalizumab; PBO, placebo.

Although substantial evidence exists of an association between exacerbations and lung function decline, this was demonstrated only in the pediatric population studied in this analysis. The pattern of improvement in both exacerbators and nonexacerbators in the pooled adolescent/adult population is suggestive of other mechanisms of improving lung function. This may be due to a primary

anti-inflammatory effect, because reducing inflammation using corticosteroids results in improved lung function.⁶ Omalizumab targets IgE, which stimulates an inflammatory cascade that causes airway remodeling and mucus production. IgE also directly affects airway remodeling,¹³ and both high IgE³¹ and mucus scores³² are associated with reduced lung function in patients with asthma.

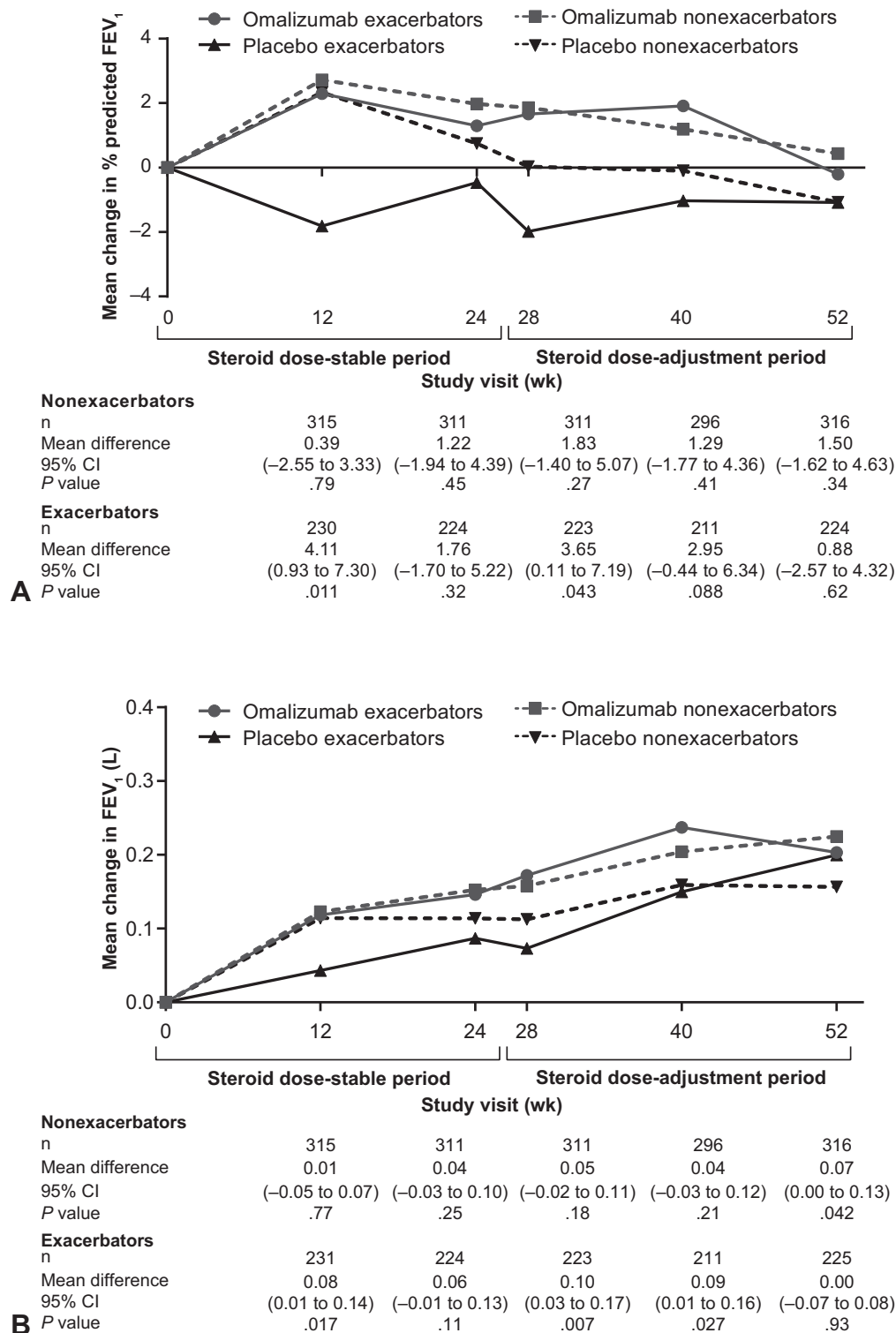


FIGURE 3. Mean change from baseline in prebronchodilator (A) ppFEV₁ and (B) FEV₁ by exacerbation status and treatment in children aged 6 to 11 years from IA05. Treatment-specific LSMs and their difference and associated 95% CIs were calculated using an analysis of covariance model adjusted for dosing schedule (every 2 or 4 weeks), asthma medication strata, country grouping, and baseline FEV₁.

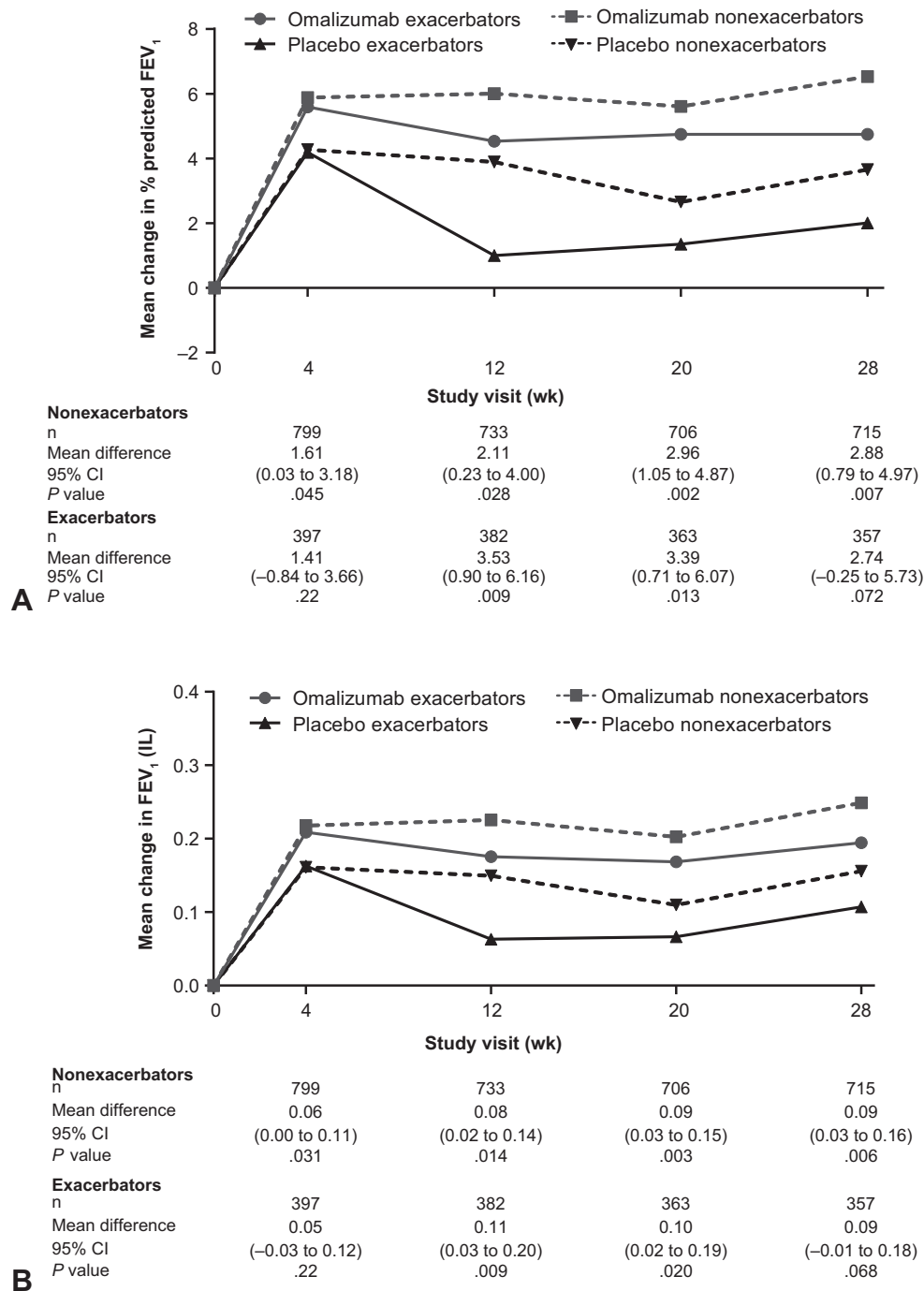


FIGURE 4. Mean change from baseline in prebronchodilator (A) ppFEV₁ and (B) FEV₁ by exacerbation status and treatment in adolescents and adults aged 12 to 75 years pooled from EXTRA and INNOVATE. Treatment-specific LSMs and their difference and associated 95% CIs were calculated using an analysis of covariance model adjusted for dosing schedule (every 2 or 4 weeks), asthma medication strata, country grouping, and baseline FEV₁ value. Deviations of n values from cohort size reflect missing values.

Omalizumab has been shown to reduce the duration and frequency of rhinovirus infections.³³ Given the association of respiratory tract infections with pulmonary complications such as exacerbations and lung function decline, the prevention of infection is another possible mechanism through which omalizumab could work to prevent lung function decline in patients with asthma.^{34,35}

The findings of these post hoc analyses are based on large randomized trials and showed statistically significant improvement in lung function across age groups. The studies included in this analysis differed markedly in inclusion criteria, study design, and population, and this may have had an impact on the consistency of findings between the pediatric and pooled adolescent/adult study populations. In particular,

reversibility was an inclusion criterion in the INNOVATE study, but not in the other 2 studies, which may have impacted results given that treatment effect on lung function decline is likely to be superior in patients with greater reversibility than in those with little or no reversibility. The current analysis was not stratified by reversibility, and this is an area for further research in future studies. It should also be noted that the adolescent and adult populations were pooled, preventing the identification of the age group in which the patterns of improvement may alter. There was no formal analysis looking at frequency or severity of exacerbations and changes in lung function. Because higher frequency and severity of exacerbations are associated with larger reductions in lung function, an exploration of the differences between subgroups may help to explain the differences in improvements in pediatric and adolescent/adult exacerbators. Because this was a post hoc subgroup analysis by exacerbation status during the treatment phase, interpretation of the findings should be cautionary and should not be used to assess the efficacy of omalizumab. Furthermore, they may not extend to all patients treated with omalizumab. In addition, lung function decline occurs over an extended period of years or decades,³⁶ and the studies included within this analysis were less than 1 year in length. This analysis focused on prebronchodilator rather than post-bronchodilator FEV₁ and thus may reflect bronchial tone (spasm) rather than airway remodeling. Despite these limitations, the findings suggest that long-term investigation of omalizumab in lung function decline is warranted to ascertain whether omalizumab prevents the development of irreversible airway obstruction.

CONCLUSIONS

Findings from this post hoc analysis suggest that omalizumab may confer some protection against lung function decline among children, adolescents, and adults who experience asthma exacerbations while on therapy. Additional long-term studies are needed to confirm these findings and to elucidate the mechanisms underlying the relationship between lung function and exacerbation frequency.

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Data sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). 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).

REFERENCES

1. Global Initiative for Asthma. Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap. Available from: <https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf>. Accessed January 8, 2019.
2. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842-52.
3. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;69:805-10.
4. Calhoun WJ, Haselkorn T, Miller DP, Omachi TA. Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2015;136:1125-7.e4.
5. Halpin DMG, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis* 2012;7:653-61.
6. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, START Investigators Group. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19-24.
7. Ortega H, Yancey SW, Keene ON, Gunsoy NB, Albers FC, Howarth PH. Asthma exacerbations associated with lung function decline in patients with severe eosinophilic asthma. *J Allergy Clin Immunol Pract* 2018;6:980-6.e1.
8. Sato R, Tomita K, Sano H, Ichihashi H, Yamagata S, Sano A, et al. The strategy for predicting future exacerbation of asthma using a combination of the Asthma Control Test and lung function test. *J Asthma* 2009;46:677-82.
9. Wu AC, Gregory M, Kymes S, Lambert D, Edler J, Stwalley D, et al. Modeling asthma exacerbations through lung function in children. *J Allergy Clin Immunol* 2012;130:1065-70.
10. Teach SJ, Gergen PJ, Szeffler SJ, Mitchell HE, Calatroni A, Wildfire J, et al. Seasonal risk factors for asthma exacerbations among inner-city children. *J Allergy Clin Immunol* 2015;135:1465-73.e5.
11. Fu J-j, McDonald VM, Baines KJ, Gibson PG. Airway IL-1 β and systemic inflammation as predictors of future exacerbation risk in asthma and COPD. *Chest* 2015;148:618-29.
12. Caminati M, Pham DL, Bagnasco D, Canonica GW. Type 2 immunity in asthma. *World Allergy Org J* 2018;11:13.
13. Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev* 2015;24:594-601.
14. Xolair [prescribing information]. South San Francisco, CA: Genentech Inc.; 2019.
15. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573-82.
16. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
17. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Fernandez Vidaurre C. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;124:1210-6.
18. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476-85.
19. Roth M, Zhao F, Zhong J, Lardinois D, Tamm M. Serum IgE induced airway smooth muscle cell remodeling is independent of allergens and is prevented by omalizumab. *PLoS One* 2015;10:e0136549.
20. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
21. Busse WW, Humbert M, Haselkorn T, Ortiz B, Trzaskoma BL, Stephenson P, et al. Effect of omalizumab on lung function and eosinophil levels in adolescents with moderate-to-severe allergic asthma. *Ann Allergy Asthma Immunol* 2020;124:190-6.
22. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.

23. Hanania NA, Chipps BE, Griffin NM, Trzaskoma BL, Iqbal A, Casale TB. Decreased exacerbations and improvement in asthma symptom control in asthma COPD overlap (ACO) treated with omalizumab: data from the PROSPERO cohort study. Poster presented at: CHEST 2017 Annual Meeting; October 28–November 1, 2017; Toronto, ON, Canada. Available from: [https://journal.chestnet.org/article/S0012-3692\(17\)32325-5/fulltext](https://journal.chestnet.org/article/S0012-3692(17)32325-5/fulltext). Accessed January 8, 2019.
24. Tantucci C, Modina D. Lung function decline in COPD. *Int J Chron Obstruct Pulmon Dis* 2012;7:95-9.
25. Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med* 2017;128:85-91.
26. Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. *Respir Med* 2016;117:198-206.
27. Pelaia G, Gallelli L, Romeo P, Renda T, Busceti MT, Proietto A, et al. Omalizumab decreases exacerbation frequency, oral intake of corticosteroids and peripheral blood eosinophils in atopic patients with uncontrolled asthma. *Int J Clin Pharmacol Ther* 2011;49:713-21.
28. Hur GY, Broide DH. Genes and pathways regulating decline in lung function and airway remodeling in asthma. *Allergy Asthma Immunol Res* 2019;11:604-21.
29. Matsunaga K, Hirano T, Oka A, Tanaka A, Kanai K, Kikuchi T, et al. Progression of irreversible airflow limitation in asthma: correlation with severe exacerbations. *J Allergy Clin Immunol Pract* 2015;3:759–64.e1.
30. Kim MA, Shin SW, Park JS, Uh ST, Chang HS, Bae DJ, et al. Clinical characteristics of exacerbation-prone adult asthmatics identified by cluster analysis. *Allergy Asthma Immunol Res* 2017;9:483-90.
31. Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, et al, TENOR Study Group. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;130:332-342.e10.
32. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al, National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program (SARP). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;128:997-1009.
33. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;196:985-92.
34. Kennedy JL, Pham S, Borish L. Rhinovirus and asthma exacerbations. *Immunol Allergy Clin North Am* 2019;39:335-44.
35. Chan JYC, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. *Pediatrics* 2015;135:607-16.
36. Speizer FE, Tager IB. Epidemiology of chronic mucus hypersecretion and obstructive airways disease. *Epidemiol Rev* 1979;1:124-42.