

# Omalizumab adherence in an observational study of patients with moderate to severe allergic asthma

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## ABSTRACT

**Background:** Adherence to omalizumab is not well characterized and its association with asthma control has not been well established.

**Objective:** To evaluate adherence in patients initiating omalizumab in the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma (EXCELS) observational study.

**Methods:** Adherence was assessed over 5 years using the proportion of patients who missed any dose, rates of doses missed, and proportions of patients with good (<10% doses missed) or poor (≥30% doses missed) adherence. Multivariable analyses identified independent predictors of good adherence. Associations between adherence and asthma control were assessed using the minimum important difference for the Asthma Control Test at various time points.

**Results:** A total of 289 patients newly initiated on omalizumab completed 5 years of EXCELS. Of these, 83.0% on the 2-week dosing regimen (n = 152) and 65.0% on the 4-week dosing regimen (n = 137) missed at least 1 dose. More frequent dosing was associated with a larger number of missed doses. Older age (odds ratio per year 1.02, 95% confidence interval 1.01–1.03) and lower prebronchodilator percentage of predicted forced expiratory volume in 1 second (<76; odds ratio 1.88, 95% confidence interval 1.09–3.24) were independent predictors of good adherence.

**Conclusion:** Adherence to omalizumab is characterized by distinct factors. Patients receiving the 4-week dosing regimen achieved better adherence than those treated every 2 weeks. Improved adherence could be associated with better asthma control. Age and lung function could interact with dosing frequency to affect patient adherence, thus warranting prospective planning at the time of prescribing to support long-term adherence.

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## Introduction

Poor adherence to long-term medical therapies often results in poor health outcomes and increased health care costs.<sup>1</sup> Failure to adhere to prescribed asthma therapy is associated with poor asthma control, including increased exacerbations and decreased health-related quality of life, and increases in asthma-related emergency department visits, hospitalizations, and the need for oral corticosteroid treatment.<sup>1,2</sup>

Omalizumab is a recombinant, humanized monoclonal antibody indicated for the treatment of adults and adolescents (≥12 years

old) with moderate to severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids.<sup>3</sup> Randomized clinical trials have shown that omalizumab decreases the rate of exacerbations and asthma-related emergency department and hospital visits and improves quality of life in patients with moderate to severe persistent allergic asthma.<sup>4–6</sup> Studies examining adherence to omalizumab and its impact on asthma-related health outcomes are limited.<sup>7,8</sup> A retrospective study over 1 year was the first to compare adherence to omalizumab in new users (n = 213) vs inhaled medications. The mean adherence rate for omalizumab was 64.6%, more than double that achieved with the once-daily fixed-dose combination of 500 µg of fluticasone and 50 µg of salmeterol (29.5%); however, no attempt was made to relate this finding to asthma-related health outcomes.<sup>7</sup> A more recent retrospective cohort (N = 1,179) analysis reported a 12-month adherence rate for omalizumab (defined as ≥80% of days covered) of 47.3%.<sup>8</sup> Approximately 1 in 4 patients had consistent omalizumab

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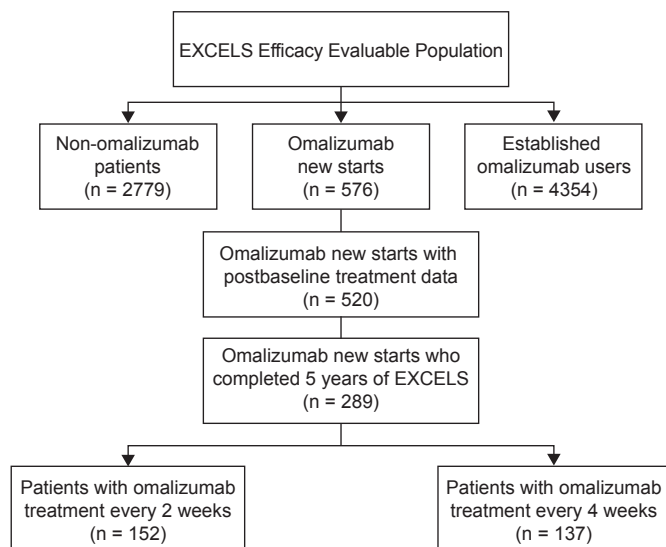


**Figure 1.** Patient cohort for inclusion in the 5-year adherence analysis of the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to severe Asthma (EXCELS).

treatment, defined as uninterrupted treatment without a gap of at least 28 days in omalizumab use, over 1 year, and this was associated with significant decreases in uncontrolled asthma events and asthma-related health care use; however, owing to the retrospective nature of the study, conclusions with regard to the causality of this association are limited.<sup>8</sup>

The primary objective of the present analysis was to evaluate adherence in patients newly treated with omalizumab and followed prospectively in the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma (EXCELS) multicenter, observational study.<sup>9</sup> Secondary objectives were: (1) to assess associations between demographic and clinical characteristics and adherence; and (2) to evaluate the relation between adherence and asthma control.

## Methods

### Study Design

The EXCELS is a multicenter, prospective, observational cohort study of approximately 5,000 omalizumab-treated and 2,500 non-omalizumab-treated patients recruited from different practice settings in the United States.<sup>9</sup> Patients were not assigned to protocol-mandated treatment regimens. Individualized treatment was at the discretion of physicians and patients according to the prescribing information and treatment guidelines.<sup>10,11</sup> Omalizumab was administered every 2 or 4 weeks according to the approved dosing tables. Dose and frequency were determined in each patient based on baseline serum total IgE and body weight.

Patients enrolled in EXCELS were assessed at baseline and every 6 months thereafter for 5 years. This analysis was limited to patients newly initiated on omalizumab (“new starts”) at baseline (Fig 1). The EXCELS protocol was approved by a local or a central institutional review board at each study site, and informed written consent was obtained from study participants before enrollment.

### Patients

Patients were included in EXCELS if they were at least 12 years old with a physician diagnosis of moderate to severe persistent asthma and a positive response to allergy skin testing or in vitro reactivity to a perennial aeroallergen. New starts were defined as

patients who began omalizumab treatment with a start date ranging from no more than 7 days before the baseline visit date and up to 30 days after the baseline visit date.<sup>9</sup> Patient exclusion criteria included a known contraindication to omalizumab therapy, diagnosis of cystic fibrosis, acute asthma exacerbation within the 2 weeks before screening, or an acute flareup of significant disease or hospitalization within 2 months before screening.<sup>9</sup>

### Assessment of Adherence

Adherence in clinical trials has been shown to range anywhere from 43% to 78%, but there is no consensual standard for what constitutes adequate adherence.<sup>12</sup> Adherence to omalizumab treatment in this study was assessed by examining the rates of missed doses for those patients who missed at least 1 dose. In addition, the proportion of patients who missed fewer than 10% of all doses over 5 years (good adherence) and the proportion of patients who missed at least 30% of all doses over 5 years (poor adherence) were used as end points to evaluate adherence. Each occurrence of a missed dose was recorded on the EXCELS case report form, which asked how many doses a patient missed every 6 months over the 5-year observation period.

### Assessment of Asthma Control and Asthma Severity

Asthma control was assessed by the Asthma Control Test (ACT) at baseline and at each 6-month visit thereafter. The ACT is a validated 5-item instrument for assessing the impact of asthma on home and work activities, shortness of breath, night-time awakenings, rescue medication use, and overall perception of asthma control.<sup>13,14</sup> An ACT total score of at least 20 is indicative of well-controlled asthma and a score no higher than 19 is indicative of poorly controlled asthma.<sup>13</sup> Asthma severity was based on physician subjective evaluation.<sup>9</sup>

### Statistical Analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. Measurements of adherence were summarized by dosing frequency for patients who completed 5 years of EXCELS. Missed doses during 5 years of omalizumab treatment were examined for the overall new-start group by treatment regimen (2 and 4 weeks). Missed doses also were examined by demographic and clinical variables.

Logistic regression was used to assess the demographic and clinical variables predictive of good adherence (missing <10% of all doses over 5 years) by fitting variables to the outcome one at a time and then fitting a final joint model inclusive of all variables that were significant ( $P \leq .10$ ) in the individual models. The models included a wide range of covariates (age, sex, race or ethnicity, education, body mass index, smoking status, physician-assessed asthma severity, time since asthma diagnosis, prior asthma-related hospitalization, physician specialty, primary health care plan, dosing regimen, lung function [as a categorical variable, <76 vs  $\geq 76$ ], and asthma control).

Similar models were used to assess the association between adherence and its impact on asthma-related health outcomes. Separate models were used for the 10% and 30% adherence cut points, using 3 time points for adherence (12, 24, and 60 months) and all time points for the minimum important difference (MID; 12, 24, 36, and 60 months). Models were reproduced using asthma-related health care usage as the outcome, but data are not presented because of a lack of significant findings.

In addition, plots over time of the proportion of patients meeting the MID<sup>15</sup> in the ACT by patient adherence status were examined to better understand the potential link between adherence and asthma control.

**Table 1**

Baseline demographic and clinical characteristics for new omalizumab users in EXCELS

|                                             | New omalizumab users (n = 520) |
|---------------------------------------------|--------------------------------|
| Age (y), mean (SD)                          | 44.4 (16.2)                    |
| Sex, n (%)                                  |                                |
| Men                                         | 189 (36.4)                     |
| Women                                       | 331 (63.7)                     |
| Race, n (%)                                 |                                |
| White                                       | 409 (78.7)                     |
| Nonwhite                                    | 111 (21.4)                     |
| Education, n (%)                            |                                |
| High school graduate or less                | 142 (27.5)                     |
| Any college                                 | 294 (57.0)                     |
| Advanced degree                             | 80 (15.5)                      |
| Body mass index (kg/m <sup>2</sup> ), n (%) |                                |
| <30                                         | 263 (51.1)                     |
| ≥30                                         | 252 (48.9)                     |
| Unknown                                     | 5 (0.97)                       |
| Smoking, n (%)                              |                                |
| Current                                     | 32 (6.2)                       |
| Former                                      | 148 (28.5)                     |
| Never                                       | 340 (65.4)                     |
| Asthma severity, n (%)                      |                                |
| Moderate                                    | 263 (50.8)                     |
| Severe                                      | 255 (49.2)                     |
| Unknown                                     | 2 (0.38)                       |
| Time since asthma diagnosis (y), mean (SD)  | 21.8 (17.4)                    |
| Prior asthma-related hospitalization, n (%) |                                |
| Yes                                         | 246 (47.5)                     |
| No                                          | 268 (52.1)                     |
| Unknown                                     | 6 (1.15)                       |
| Physician specialty, n (%)                  |                                |
| Allergist                                   | 325 (62.5)                     |
| Pulmonologist                               | 95 (18.3)                      |
| Allergist or pulmonologist                  | 14 (2.7)                       |
| Unknown or other specialty                  | 86 (16.6)                      |
| Primary health care plan, n (%)             |                                |
| Commercial or PPO                           | 285 (54.9)                     |
| HMO                                         | 95 (18.3)                      |
| Medicaid or Medicare                        | 101 (19.5)                     |
| Military or veteran                         | 7 (1.35)                       |
| Other                                       | 31 (6.0)                       |
| Asthma Control Test score, mean (SD)        | 15.2 (5.2)                     |
| FEV <sub>1</sub> , % predicted, mean (SD)   |                                |
| Prebronchodilator <sup>a</sup>              | 76.5 (24.0)                    |
| Postbronchodilator <sup>b</sup>             | 80.5 (23.2)                    |

Abbreviations: EXCELS, Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to severe Asthma; FEV<sub>1</sub>, forced expiratory volume in 1 second; HMO, health maintenance organization; PPO, preferred provider organization.

<sup>a</sup>n = 514.

<sup>b</sup>n = 504.

As a sensitivity analysis, results using 2-year interim data from EXCELS were examined using the same approach as for the 5-year analysis.

## Results

### Patient Demographic and Clinical Characteristics

Of 576 patients newly treated with omalizumab, 520 had post-baseline treatment data available and were included in the analysis. Patients newly treated with omalizumab had a mean age at baseline of 44.4 ± 16.2 years, with an average of 21.8 years since asthma diagnosis; 63.7% were women, 78.7% were white, 72.5% had received a college education, and 65.4% had never smoked (Table 1). Nearly two thirds of patients (62.5%) received asthma care from an allergist and 18.3% from a pulmonologist; asthma severity was classified by treating physicians as moderate in 50.8% of patients and severe in 49.2%. Mean ACT score was 15.2 ± 5.2, indicating poorly controlled asthma, and mean prebronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) was 76.5 ± 24.0% of predicted. Overall,

**Table 2**

Missed doses among new omalizumab users who completed 5 years in EXCELS

|                                   | Treatment every 2 wk (n = 152) | Treatment every 4 wk (n = 137) |
|-----------------------------------|--------------------------------|--------------------------------|
| Any missed dose, n (%)            |                                |                                |
| Yes                               | 126 (83.0)                     | 89 (65.0)                      |
| No                                | 26 (17.1)                      | 48 (35.0)                      |
| Rate of missed doses <sup>a</sup> | 10.7                           | 3.8                            |
| Annual rate of missed doses       | 2.1                            | 0.76                           |

Abbreviation: EXCELS, Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to severe Asthma.

<sup>a</sup>Number of missed doses per patient of those who completed 5 years of the study and had any missed dose.

289 patients (55.6%) newly started on omalizumab completed 5 years of EXCELS. Of these, 152 patients (52.6%) were treated every 2 weeks and 137 patients (47.4%) were treated every 4 weeks.

### Adherence

Of the patients who completed 5 years of EXCELS, 83.0% who received omalizumab every 2 weeks missed at least 1 dose, and 65.0% of patients treated every 4 weeks missed at least 1 dose (Table 2). The mean annual rate of missed doses was 2.14 doses per patient for biweekly treatment and 0.76 doses per patient for treatment every 4 weeks. Of patients newly treated with omalizumab every 2 weeks, 55.9% of patients missed fewer than 10% of doses and 19.2% of patients missed at least 30% of doses. Of patients treated every 4 weeks, 62.6% missed fewer than 10% of doses and 14.3% missed at least 30% of doses. No association between asthma severity and patient adherence was observed; however, study inclusion criteria were limited to patients with moderate and severe asthma.

### Factors Associated with Adherence

The rate of missed doses over the 5-year observation period was higher in younger (<45 years) than in older patients for the 2 dosing schedules; a larger proportion of older patients missed fewer than 10% of prescribed doses (61.3% of older vs 50.7% of younger patients treated every 2 weeks; 73.3% of older vs 48.5% of younger patients treated every 4 weeks; Table 3). The rate of missed omalizumab doses in patients of nonwhite race was greater than the rate for white patients (11.4 vs 7.4 doses per patient treated every 2 weeks and 5.4 vs 3.1 doses per patient treated every 4 weeks). The rate of missed omalizumab doses in patients with greater lung function (prebronchodilator FEV<sub>1</sub> ≥76% predicted) was higher for the 2 dosing schedules, with a larger proportion of patients with lesser lung function missing fewer than 10% of doses. A similar pattern was observed for postbronchodilator FEV<sub>1</sub> percentage of predicted.

Of those treated every 4 weeks, patients who had an advanced degree had a lower rate of missed doses and were least likely to miss at least 30% of doses compared with patients with any college education or were a high school graduate or less. No difference in missed dose was observed for either treatment regimen by asthma severity. For the 2-week dosing regimen, a larger proportion of patients treated by allergists missed at least 30% of prescribed doses than patients treated by pulmonologists (21.9% and 11.4%, respectively); for the 4-week dosing regimen, the frequency of missed doses was higher for patients treated by pulmonologists than by allergists (17.7% and 15.8%, respectively).

Findings from multivariable analyses identified older age (odds ratio per year 1.02, 95% confidence interval 1.01–1.03) and lower prebronchodilator FEV<sub>1</sub> (<76% predicted; odds ratio 1.88, 95% confidence interval 1.09–3.24) as independent predictors of good adherence (defined as missing <10% of doses). Multivariable analyses were repeated using poor adherence as the outcome (defined

**Table 3**  
Baseline patient demographics and clinical characteristics by omalizumab treatment regimen and adherence status (good, missed <10% doses; poor, missed ≥30% of doses) in new users who completed 5 years in EXCELS

|                                                    | Omalizumab every 2 wk |                             |                             | Omalizumab every 4 wk |                             |                             |
|----------------------------------------------------|-----------------------|-----------------------------|-----------------------------|-----------------------|-----------------------------|-----------------------------|
|                                                    | Rate of missed doses  | Missed <10% of doses, n (%) | Missed ≥30% of doses, n (%) | Rate of missed doses  | Missed <10% of doses, n (%) | Missed ≥30% of doses, n (%) |
| Age (y)                                            |                       |                             |                             |                       |                             |                             |
| <45                                                | 10.0                  | 73 (50.7)                   | 31 (21.5)                   | 4.9                   | 50 (48.5)                   | 20 (19.4)                   |
| ≥45                                                | 6.8                   | 84 (61.3)                   | 23 (16.8)                   | 2.3                   | 99 (73.3)                   | 14 (10.4)                   |
| Sex                                                |                       |                             |                             |                       |                             |                             |
| Men                                                | 8.3                   | 76 (58.9)                   | 24 (18.6)                   | 2.9                   | 40 (66.7)                   | 7 (11.7)                    |
| Women                                              | 8.6                   | 81 (53.3)                   | 30 (19.7)                   | 3.6                   | 109 (61.2)                  | 27 (15.2)                   |
| Race                                               |                       |                             |                             |                       |                             |                             |
| White                                              | 7.4                   | 119 (57.2)                  | 39 (18.8)                   | 3.1                   | 130 (65.0)                  | 24 (12.0)                   |
| Nonwhite                                           | 11.4                  | 38 (52.1)                   | 15 (20.6)                   | 5.4                   | 19 (50.0)                   | 10 (26.3)                   |
| Education                                          |                       |                             |                             |                       |                             |                             |
| High school graduate or less                       | 9.3                   | 41 (51.3)                   | 14 (17.5)                   | 3.2                   | 44 (71.0)                   | 8 (12.9)                    |
| Any college                                        | 7.9                   | 92 (56.4)                   | 32 (19.6)                   | 3.8                   | 71 (54.6)                   | 23 (17.7)                   |
| Advanced degree                                    | 9.7                   | 21 (60.0)                   | 8 (22.9)                    | 2.6                   | 34 (75.6)                   | 3 (6.7)                     |
| Asthma severity                                    |                       |                             |                             |                       |                             |                             |
| Moderate                                           | 8.5                   | 71 (53.0)                   | 29 (21.6)                   | 3.6                   | 78 (60.9)                   | 19 (14.8)                   |
| Severe                                             | 8.5                   | 84 (57.9)                   | 120 (82.8)                  | 3.3                   | 71 (64.6)                   | 15 (13.6)                   |
| Ever hospitalized for asthma                       |                       |                             |                             |                       |                             |                             |
| Yes                                                | 8.4                   | 71 (51.5)                   | 27 (19.6)                   | 4.1                   | 64 (59.8)                   | 19 (17.8)                   |
| No                                                 | 8.6                   | 82 (59.0)                   | 27 (19.4)                   | 2.9                   | 84 (65.1)                   | 15 (11.6)                   |
| Physician specialty                                |                       |                             |                             |                       |                             |                             |
| Allergist                                          | 9.5                   | 96 (53.9)                   | 39 (21.9)                   | 3.9                   | 81 (55.5)                   | 23 (15.8)                   |
| Pulmonologist                                      | 5.9                   | 27 (61.4)                   | 5 (11.4)                    | 5.9                   | 37 (72.6)                   | 9 (17.7)                    |
| Baseline ACT score                                 |                       |                             |                             |                       |                             |                             |
| ≤19 points                                         | 8.3                   | 118 (57.6)                  | 40 (19.5)                   | 3.4                   | 108 (62.1)                  | 25 (14.4)                   |
| >19 points                                         | 8.7                   | 33 (49.3)                   | 12 (17.9)                   | 3.6                   | 41 (65.1)                   | 9 (14.3)                    |
| FEV <sub>1</sub> , % predicted, prebronchodilator  |                       |                             |                             |                       |                             |                             |
| <76%                                               | 7.0                   | 98 (65.8)                   | 23 (15.4)                   | 3.2                   | 71 (66.4)                   | 20 (18.7)                   |
| ≥76%                                               | 10.2                  | 56 (44.1)                   | 31 (24.4)                   | 3.6                   | 77 (59.2)                   | 14 (10.8)                   |
| FEV <sub>1</sub> , % predicted, postbronchodilator |                       |                             |                             |                       |                             |                             |
| <80%                                               | 8.3                   | 89 (62.24)                  | 26 (18.2)                   | 2.9                   | 69 (64.5)                   | 16 (15.0)                   |
| ≥80%                                               | 8.9                   | 59 (46.5)                   | 27 (21.3)                   | 3.7                   | 76 (60.3)                   | 17 (13.5)                   |

Abbreviations: ACT, Asthma Control Test; EXCELS, Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to severe Asthma; FEV<sub>1</sub>, forced expiratory volume in 1 second.

as missing ≥30% of doses over 5 years). Younger age was significantly associated with poor adherence (odds ratio per year 0.98, 95% confidence interval 0.97–0.99).

#### Adherence and Asthma Control

Although generally not statistically significant, the impact of good adherence (based on <10% missed doses) on improvement in ACT scores (MID) was more evident for patients on the 4-week dosing regimen, particularly in the short term (Table 4, eFig 1A–C). Larger proportions of patients on the 4-week dosing regimen who demonstrated good adherence at 12 months achieved the MID for the ACT at 12 and 24 months compared with patients with poor adherence (12 months, 56.7% vs 35.1%,  $P = .018$ ; 24 months, 63.3% vs 40.6%,  $P = .020$ ). A similar pattern was seen in patients on the 2-week regimen who demonstrated good adherence compared with those with poor adherence at 24 months (12 months, 57.8% vs 38.5%,  $P = .017$ ; 24 months, 62.0% vs 50.0%,  $P = .182$ ). When adherence and the MID for the ACT were assessed using 60-month adherence status data, differences in the MID were observed at 12, 24, and 36 months but were not statistically significant, possibly owing to small numbers. A potential, sustained separation between patients with good adherence and patients with poor adherence on the 2-week dosing regimen was observed when adherence and the MID for the ACT were assessed using 60-month data; however, the differences were not statistically significant.

When examining the proportion of patients with good adherence achieving an MID response for the ACT based on fewer than 30% missed doses, the 2 dosing regimens were combined to conserve statistical power (Table 5). A larger proportion of patients who demonstrated good adherence at 12 months achieved an MID response for the ACT at 12 and 24 months compared with patients

with poor adherence (58.5% vs 38.1%,  $P = .012$ ; 61.4% vs 44.4%,  $P = .049$ , respectively). The impact of good adherence was generally more evident in the short term (eFig 2A–C).

To evaluate how these observed relations between adherence and the MID response for the ACT might change after adjustments by other potential predictors of outcome, multivariable analyses were conducted on the overall omalizumab new-start group, allowing the 2- and 4-weekly dosing regimens to be included as potential predictors to conserve statistical power. After adjusting for age, sex, and treating specialist, good adherence at 12 months (defined as missing <30% doses) predicted an MID response at 24 months ( $P = .028$ ).

Results from the sensitivity analyses examining adherence using 2-year interim data from EXCELS were consistent with those from the 5-year data.

#### Discussion

Data characterizing adherence patterns in omalizumab users are limited and, to the best of the authors' knowledge, no prior published study has prospectively evaluated the relation between adherence to omalizumab and asthma-related health outcomes. In this prospective, observational, real-world study of omalizumab users from different practice settings, good adherence (defined as missing <10% of doses) was observed in 55.9% of patients treated biweekly and in 62.6% of patients treated every 4 weeks. Nearly twice as many new users on the biweekly dosing regimen missed at least 1 dose in the first 5 years compared with those receiving treatment every 4 weeks. This finding is generally consistent with previous studies of adherence rates of 48% to 65%, despite methodologic differences in the definition of omalizumab adherence.<sup>7,8</sup>

**Table 4**  
Percent ACT MID based on adherence status (4-week dosing)

| Adherence at time point       | With MID response in ACT, % (n) |             |
|-------------------------------|---------------------------------|-------------|
|                               | 2-wk dosing                     | 4-wk dosing |
| <b>12-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <10% missed doses             | 63.7 (135)                      | 56.7 (157)  |
| ≥10% missed doses             | 53.2 (79)                       | 35.1 (37)   |
| P                             | .129                            | .018        |
| 24 mo                         |                                 |             |
| <10% missed doses             | 59.2 (125)                      | 63.3 (128)  |
| ≥10% missed doses             | 63.2 (57)                       | 40.6 (32)   |
| P                             | .613                            | .020        |
| 36 mo                         |                                 |             |
| <10% missed doses             | 60.4 (111)                      | 63.4 (112)  |
| ≥10% missed doses             | 62.5 (48)                       | 57.1 (21)   |
| P                             | .800                            | .587        |
| 60 mo                         |                                 |             |
| <10% missed doses             | 59.8 (97)                       | 58.6 (111)  |
| ≥10% missed doses             | 70.5 (44)                       | 57.1 (21)   |
| P                             | .224                            | .904        |
| <b>24-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <10% missed doses             | 62.3 (122)                      | 57.8 (142)  |
| ≥10% missed doses             | 56.5 (92)                       | 38.5 (52)   |
| P                             | .394                            | .017        |
| 24 mo                         |                                 |             |
| <10% missed doses             | 60.7 (112)                      | 62.0 (121)  |
| ≥10% missed doses             | 60.0 (70)                       | 50.0 (40)   |
| P                             | .304                            | .182        |
| 36 mo                         |                                 |             |
| <10% missed doses             | 60.2 (103)                      | 62.8 (102)  |
| ≥10% missed doses             | 62.5 (56)                       | 62.5 (32)   |
| P                             | .776                            | .980        |
| 60 mo                         |                                 |             |
| <10% missed doses             | 63.0 (92)                       | 56.9 (102)  |
| ≥10% missed doses             | 63.3 (49)                       | 64.5 (31)   |
| P                             | .979                            | .449        |
| <b>60-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <10% missed doses             | 62.3 (114)                      | 54.8 (124)  |
| ≥10% missed doses             | 57.0 (100)                      | 48.6 (70)   |
| P                             | .432                            | .401        |
| 24 mo                         |                                 |             |
| <10% missed doses             | 64.5 (107)                      | 61.9 (105)  |
| ≥10% missed doses             | 54.7 (75)                       | 53.6 (56)   |
| P                             | .182                            | .306        |
| 36 mo                         |                                 |             |
| <10% missed doses             | 62.5 (96)                       | 64.8 (91)   |
| ≥10% missed doses             | 57.8 (64)                       | 58.1 (43)   |
| P                             | .552                            | .454        |
| 60 mo                         |                                 |             |
| <10% missed doses             | 64.8 (88)                       | 54.4 (90)   |
| ≥10% missed doses             | 60.4 (53)                       | 67.4 (43)   |
| P                             | .601                            | .155        |

Abbreviations: ACT, Asthma Control Test; MID, minimum important difference.

Across all collected demographic and clinical variables, younger age, greater lung function, and more frequent dosing were associated with a larger number of missed doses per year (worse adherence). Although 2 of these factors are immutable, these findings have potential clinical application. It might be useful for clinicians to think prospectively about which patients might need more support to maintain adherence. The authors also observed that the rate of missed omalizumab doses in patients of nonwhite race was greater than the rate for white patients. Clinicians can take age, race, and lung function into consideration when prescribing treatment to their patients. Given that the frequency of dosing is fixed (based on the omalizumab label and determined using the approved dosing tables), patients who require biweekly dosing should be queried about potential barriers, such as work demands, childcare responsibilities, transportation problems, and parking difficulties.

The influence of age and lung function can affect adherence independently or in combination. Age is related to poor asthma

**Table 5**  
Percent ACT MID based on adherence status (combined regimens)

| Adherence at time point       | With MID response in ACT, % (n) |             |
|-------------------------------|---------------------------------|-------------|
|                               | 2-wk dosing                     | 4-wk dosing |
| <b>12-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <30% missed doses             | 58.5 (366)                      |             |
| ≥30% missed doses             | 38.1 (42)                       |             |
| P                             | .012                            |             |
| 24 mo                         |                                 |             |
| <30% missed doses             | 61.4 (306)                      |             |
| ≥30% missed doses             | 44.4 (36)                       |             |
| P                             | .049                            |             |
| 36 mo                         |                                 |             |
| <30% missed doses             | 61.7 (264)                      |             |
| ≥30% missed doses             | 60.7 (28)                       |             |
| P                             | .915                            |             |
| 60 mo                         |                                 |             |
| <30% missed doses             | 59.8 (244)                      |             |
| ≥30% missed doses             | 69.0 (29)                       |             |
| P                             | .341                            |             |
| <b>24-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <30% missed doses             | 57.3 (354)                      |             |
| ≥30% missed doses             | 50.0 (54)                       |             |
| P                             | .311                            |             |
| 24 mo                         |                                 |             |
| <30% missed doses             | 61.5 (301)                      |             |
| ≥30% missed doses             | 47.6 (42)                       |             |
| P                             | .087                            |             |
| 36 mo                         |                                 |             |
| <30% missed doses             | 61.8 (259)                      |             |
| ≥30% missed doses             | 61.8 (34)                       |             |
| P                             | .999                            |             |
| 60 mo                         |                                 |             |
| <30% missed doses             | 60.3 (244)                      |             |
| ≥30% missed doses             | 66.7 (30)                       |             |
| P                             | .496                            |             |
| <b>60-mo adherence status</b> |                                 |             |
| 12 mo                         |                                 |             |
| <30% missed doses             | 56.8 (345)                      |             |
| ≥30% missed doses             | 54.0 (63)                       |             |
| P                             | .676                            |             |
| 24 mo                         |                                 |             |
| <30% missed doses             | 62.1 (293)                      |             |
| ≥30% missed doses             | 46.0 (50)                       |             |
| P                             | .032                            |             |
| 36 mo                         |                                 |             |
| <30% missed doses             | 61.5 (252)                      |             |
| ≥30% missed doses             | 61.9 (42)                       |             |
| P                             | .961                            |             |
| 60 mo                         |                                 |             |
| <30% missed doses             | 60.8 (237)                      |             |
| ≥30% missed doses             | 62.2 (37)                       |             |
| P                             | .871                            |             |

Abbreviations: ACT, asthma control test; MID, minimum important difference.

control and has been widely studied for adherence,<sup>1,16–18</sup> with younger patients often having poorer adherence than older patients. Patients with good lung function might have worse adherence if they perceive that they are well and not in need of ongoing persistent therapy, failing to appreciate the long-term benefit of consistent treatment. In contrast, those with poor lung function are more likely to have chronic respiratory symptoms of dyspnea, cough, or wheeze that prompt regular attendance at treatment visits. Race is another frequently studied variable that is confounded by socioeconomic disparity between whites and nonwhites in studies of adherence in patients with asthma and other chronic diseases.<sup>18–20</sup> In this analysis, the rate of missed omalizumab doses in patients of nonwhite race was greater than the rate for white patients; however, in multivariable analysis, race was not a significant factor when considered alongside age and lung function. This suggests that race as an individual characteristic could adequately distinguish patients who adhere from those who do not adhere, particularly if age and lung function measurements are

unavailable. Therefore, clinicians should be encouraged to participate in collaborative, shared decision making with patients on omalizumab therapy about how to improve and maintain adherence to dosing schedules.<sup>21,22</sup> Although these strategies are important in all prescribed therapies, the cost of omalizumab therapy makes this prospective approach essential. Based on the present findings from the EXCELS data, one can project that a younger nonwhite patient with asthma and better lung function is likely to have more problems with consistent adherence than older white patients with worse lung function. This suggests that clinicians can start discussions with their patients about adherence early, at the time of the first prescription of therapy.

Although not all the results from this analysis of the EXCELS 5-year data were statistically significant, they generally suggest that good adherence to omalizumab, particularly in patients treated with the 4-weekly dosing regimen, might be associated with improved asthma control. In addition, these results indicate an association between early adherence to omalizumab and improved asthma control. These findings support a recent analysis that showed that patients with consistent omalizumab treatment at 12 months were less likely to have an uncontrolled asthma event between months 13 to 24 than the nonconsistent group (49% vs 54%, respectively,  $P = .02$ ).<sup>8</sup> Further study is required to confirm these observations. Although 4-weekly dosing of omalizumab might be associated with improved asthma control, missing a dose ultimately might be more problematic, because this would result in a patient on this dosing regimen invariably having less overall exposure to treatment than a patient who misses a dose on the 2-week dosing regimen. The findings also emphasize that the relation between adherence and asthma control is dynamic and involves perception of improvement from the patient's perspective and quantitative improvement in ACT scores.

The main strengths of the EXCELS study were the large numbers of patients enrolled and its prospective, observational design, allowing the study of a real-world asthma population drawn from a diverse range of clinical practices. A limitation of the study owing to the nature of the design is inherently difficult in adequately controlling for bias when comparing different groups. Patients were participating in a study and could have been more adherent than they would ordinarily be in clinical practice. In addition, the study was not designed to examine the relation between adherence and outcomes, and this precludes making any definitive conclusions about the observed associations between adherence and outcomes.

In this prospective, observational, real-world study of omalizumab, patients receiving the 4-week dosing regimen achieved better adherence compared with those treated biweekly. These findings suggest that improved adherence might be associated with better asthma control, as measured by the ACT score, although the observed differences were not large. Age, lung function, and possibly race are 3 variables that might interact with dosing frequency to affect patient adherence to therapy. These factors warrant consideration and prospective planning at the time of prescribing to support long-term adherence. Further research is warranted to provide a better understanding of the relation between adherence to omalizumab therapy and asthma outcomes. Respiratory clinic clinicians and staff should incorporate measures to promote and ensure regular attendance for omalizumab therapy visits to optimize outcomes.

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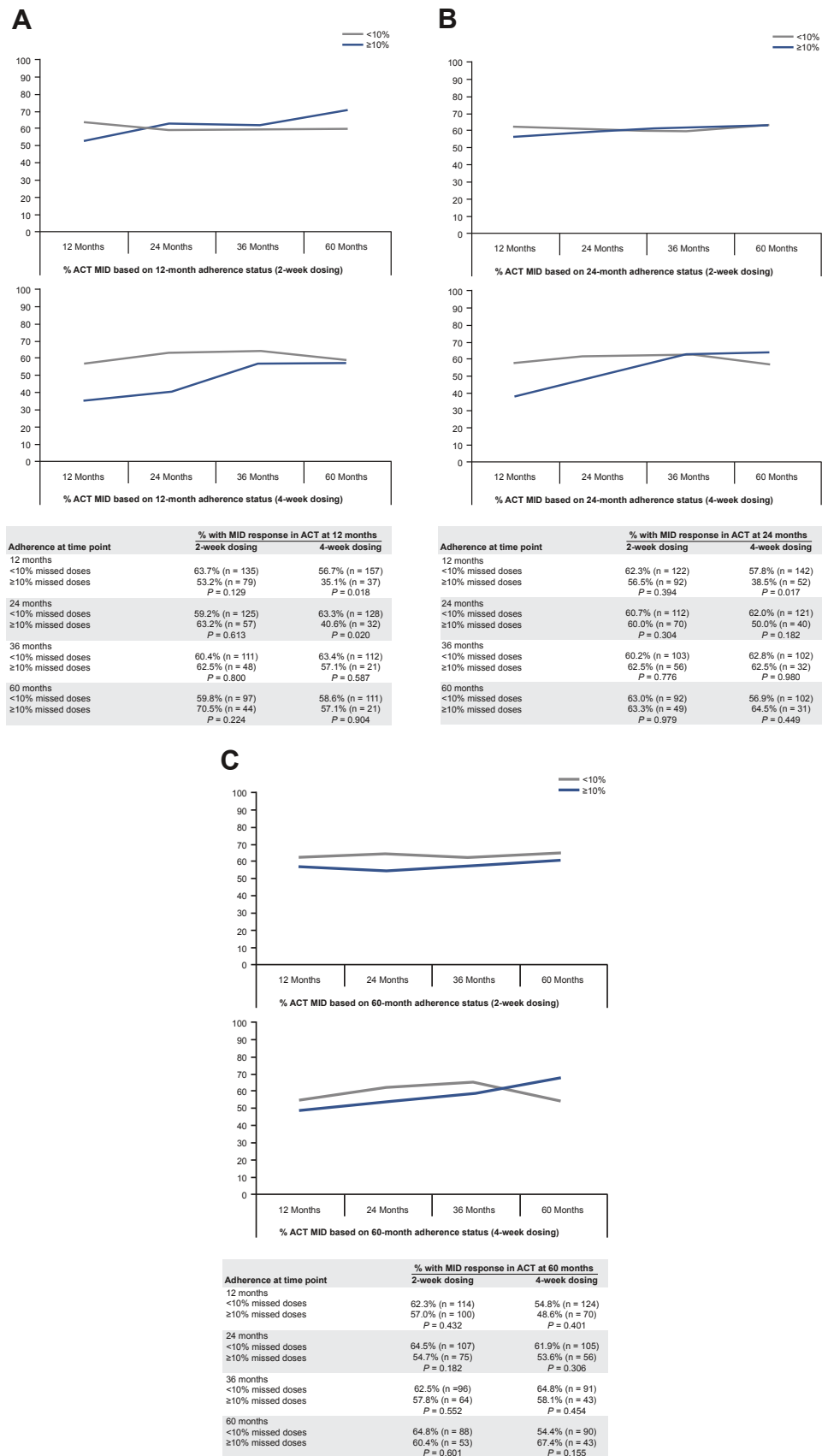
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## Supplementary Data

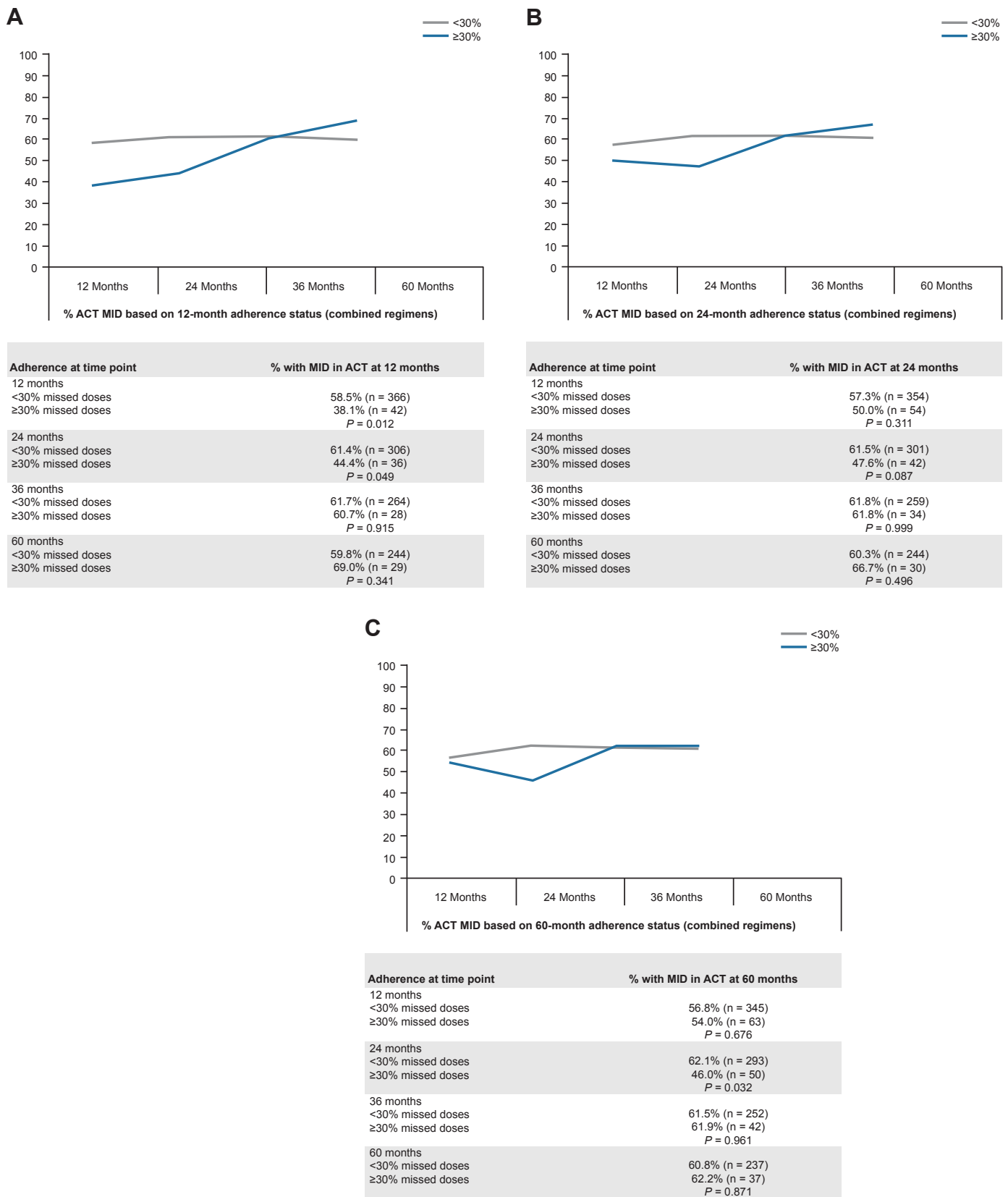
Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.04.010>.

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**eFigure 1.** Proportion of patients achieving the minimum important difference (MID) for the Asthma Control Test (ACT) in patients classified as good (<10% of missed doses) and poor (≥10% of missed doses) adherers at (A) 12 months, (B) 24 months, and (C) 60 months for omalizumab treatment regimens (2 or 4 weeks). The MID for the ACT is a 3-point change from baseline.



**eFigure 2.** Proportion of patients achieving the minimum important difference (MID) for the Asthma Control Test (ACT) in patients classified as good (<30% of missed doses) and poor (≥30% of missed doses) adherers at (A) 12 months, (B) 24 months, and (C) 60 months for omalizumab treatment (combined regimens). The MID for the ACT is a 3-point change from baseline.