

PHARMACOTHERAPY

Longitudinal Changes in Asthma Control with Omalizumab: 2-Year Interim Data from the EXCELS Study

MARK D. EISNER, M.D., M.P.H.,^{1,*} JAMES L. ZAZZALI, PH.D., M.P.H.,¹ MARY K. MILLER, M.S.,¹
MARY S. BRADLEY, M.S.,¹ AND MICHAEL SCHATZ, M.D., M.S.²

¹Product Development, Inflammation & Respiratory, Genentech, Inc., South San Francisco, CA, USA.

²Department of Allergy, Kaiser Permanente Medical Center, San Diego, CA, USA.

Background. Asthma guidelines emphasize the importance of achieving and maintaining asthma control; however, many patients with moderate to severe asthma fail to achieve adequate control. **Objective.** This 2-year interim analysis evaluated the longitudinal effects of omalizumab on asthma control in patients treated in real-world clinical practice settings. **Methods.** EXCELS is an ongoing observational cohort study of approximately 5000 omalizumab-treated and 2500 non-omalizumab-treated patients aged ≥ 12 years with moderate to severe asthma. Asthma control was measured using the Asthma Control Test (ACT) every 6 months. **Results.** Subgroups of the omalizumab cohort included those who initiated omalizumab at baseline (new starts, $n = 549$) and those treated with omalizumab >7 days before baseline (established users, $n = 4421$). For reference, data are also presented for patients who were not receiving omalizumab prior to or at the time of enrolment (non-omalizumab, $n = 2867$). Over half of the new starts (54%) achieved improvement in ACT consistent with the minimally important difference (MID, defined as ≥ 3 -point improvement) by Month 6 and this proportion increased throughout the follow-up period, reaching 62% at Month 24. Similar results were observed in patients stratified by moderate and severe asthma. Established users of omalizumab maintained asthma control throughout the observation period. **Conclusion.** Over a 2-year period, patients initiating omalizumab therapy experienced clinically relevant improvements in asthma control, which were maintained during 2 years of longitudinal follow-up. Established users of omalizumab maintained asthma control over the 2-year period with a small improvement similar to that seen in non-omalizumab users.

Keywords allergic asthma, asthma control, immunoglobulin E, impairment, longitudinal, minimally important difference, moderate-to-severe asthma, observational, omalizumab

INTRODUCTION

Asthma involves a complex interaction of variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation (1). The interaction of these features determines the severity of asthma, clinical features, and response to treatment (1). Asthma control is the downstream manifestation of these factors.

The most recent guidelines from the National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-3 and the Global Initiative for Asthma (GINA) emphasize that therapy should focus on achieving and maintaining asthma control (1, 2). The NAEPP guidelines define asthma control by the domains of impairment and risk (1). The impairment domain encompasses pulmonary function and patient-reported symptoms, physical activity, quality of life, and need for short-acting β_2 -agonists for quick relief of symptoms, whereas the risk domain includes asthma exacerbations, risk of progressive loss of lung function, and treatment-related adverse effects (1). The guidelines also recommend that ongoing monitoring of asthma control should ensure that the treatment is reducing both impairment and risk (1). Similarly, the GINA

guidelines emphasize the variable course of asthma and the importance of ongoing monitoring and adjusting treatment as needed to maintain control when symptoms worsen or the patient develops an acute exacerbation (2). Nevertheless, despite the availability of disease management guidelines and therapeutic advancements, a large proportion of patients with moderate to severe persistent asthma continue to have poorly controlled disease (3).

Omalizumab, a recombinant humanized monoclonal antibody, is approved by the US Food and Drug Administration for the treatment of adults and adolescents (aged ≥ 12 years) with moderate to severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids (4). By binding to free immunoglobulin E (IgE), omalizumab prevents the binding of IgE to receptors on mast cells and basophils and thereby interrupts the IgE-mediated inflammatory cascade. The therapeutic efficacy and safety of subcutaneously administered omalizumab as add-on therapy has been demonstrated in patients with moderate to severe allergic asthma in several randomized, double-blind clinical trials (4–7). These pivotal trials for omalizumab have primarily focused on reducing the risk of asthma exacerbations as the primary efficacy outcome (5–7). Omalizumab trials have also examined individual components of the impairment domain as secondary or exploratory endpoints showing improvement with omalizumab treatment in daily lung function (5, 6): total asthma symptom score (5–7), need for rescue

*Corresponding author: Mark D. Eisner, M.D., M.P.H., Product Development, Inflammation & Respiratory, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990, USA; Tel: +650-467-5524; Fax: +650-467-2232; E-mail: eisner.mark@gene.com

medication (5–7), and nocturnal symptoms score (6). However, the pivotal trials did not assess a comprehensive measure of asthma control. Considering the importance of the impairment domain in assessing asthma control, a more comprehensive analysis of the impact of omalizumab on asthma control would provide valuable information for clinicians and patients, especially in a real-world clinical setting.

The Asthma Control Test (ACT) is a validated tool for assessing the impairment domain of asthma control (8–10). In this study, we used the ACT to elucidate the longitudinal impact of omalizumab therapy on asthma control in an epidemiologic study of Xolair (omalizumab): evaluating clinical effectiveness and long-term safety in patients with moderate-to-severe asthma (EXCELS). EXCELS is an ongoing 5-year prospective, observational study of patients with allergic asthma treated with or without omalizumab (11). The present interim analysis of EXCELS includes data through the first 2 years of the study. The 2-year time point was chosen because it provides longitudinal data over a time span greater than twice as long as the pivotal trials for omalizumab (5–7). Furthermore, 2 years is currently the latest time point of the EXCELS study for which follow-up data are complete and confirmed. The 2-year time point provides insight into the longer-term effects of omalizumab on the most currently complete EXCELS dataset.

METHODS

Study Design

EXCELS is an ongoing multicenter, prospective, observational cohort study of the long-term safety and effectiveness of omalizumab in real-world clinical practice settings. The study design, baseline demographics, and clinical characteristics of EXCELS patients have been published previously (11). Briefly, two cohorts of patients with asthma, those treated with omalizumab and those not treated with *omalizumab*, were enrolled from a variety of US-based practice settings, including managed care organizations, community practices, and academic health centers in an approximate ratio of 2:1. Since EXCELS is an observational study, patients are not assigned to a particular protocol-mandated treatment. The treatment regimen, including omalizumab, is at the discretion of physicians and patients based on the indication statement for omalizumab and treatment guidelines (1, 2). Asthma severity was based on the physician's subjective assessment at the baseline visit. The primary objective of EXCELS was to evaluate the long-term safety of omalizumab (safety analyses will be published when the study is complete). Assessment of asthma control was a preplanned secondary objective. This interim analysis evaluated the impact of asthma control during the first 2 years of follow-up study for patients in the omalizumab ($n = 4970$) and non-omalizumab ($n = 2867$) cohorts. The EXCELS protocol was approved by a local Institutional Review Board (IRB) or Central IRB at each study site and informed written consent was obtained from study participants prior to enrolment.

Study Participants

EXCELS includes patients aged ≥ 12 years with a physician diagnosis of moderate to severe persistent asthma and a history of a positive response to allergy skin testing or *in vitro* reactivity to a perennial aeroallergen. Patients were excluded if they had a known contraindication to omalizumab therapy, acute asthma exacerbation within the 2 weeks prior to screening, diagnosis of cystic fibrosis, or prior malignant neoplasm (during the enrolment period from 2004 to September 2005, but not thereafter).

Study Groups

The current analysis assessed the two baseline patient cohorts defined at enrolment: omalizumab and non-omalizumab. This analysis further subdivided the omalizumab cohort into two mutually exclusive subcohorts: new starts and established users. The new starts subcohort was defined as patients in the omalizumab cohort who had an omalizumab start date ranging from ≤ 7 days prior to the baseline visit date up to 30 days after the baseline visit. The established users subcohort was defined as patients who had an omalizumab start date > 7 days prior to the baseline visit date. For the new starts and established users patients, data collected > 6 months after omalizumab treatment was stopped are excluded from the summaries. The non-omalizumab cohort included patients who had never been treated with omalizumab at the time of enrolment. If a patient in the non-omalizumab cohort initiated omalizumab during the 24-month follow-up period, the data collected after their omalizumab start date were excluded from this analysis.

Study Outcomes

Multidimensional factors associated with asthma control from the patient's perspective were assessed using the ACT at baseline, 6 months, 12 months, 18 months, and 24 months. The ACT is a validated five-item patient-reported outcome questionnaire that measures the impact of asthma on home and work activities, shortness of breath, nocturnal asthma symptoms, rescue medication usage, and overall self-assessment of asthma control over the previous 4 weeks. Each item includes five response options with values ranging from 1 to 5, thereby yielding a final score ranging from 5 to 25, with higher values indicating better control (8). Based on the ACT score, patients were categorized as well controlled (≥ 20), not well controlled (16–19), and poorly controlled (≤ 15). The minimally important difference (MID) for the ACT score has been established as a change of ≥ 3 points and represents the minimal change in score over time that suggests clinically meaningful change in asthma control (12).

Statistical Analysis

The objective of this analysis is to examine the longitudinal impact of omalizumab on asthma control. Consequently, the primary focus of this analysis is to assess within-group changes in ACT scores over time in the omalizumab new starts subcohort, which best reflects the effect of the drug on asthma control. The other

groups—established users and non-omalizumab—are presented for reference purposes. Due to the observational nature of EXCELS and because the cohorts differ at baseline with respect to asthma severity, comorbid conditions, and other baseline disease characteristics, the asthma control measures are summarized with emphasis on longitudinal follow-up of these measures within each cohort rather than between-cohort comparisons.

Asthma control scores collected using the ACT questionnaire were summarized by cohort and baseline physician-assessed asthma severity using descriptive statistics (mean, median, and SD) for the total ACT score at each study visit. The number and percentage of patients with well-controlled, not well-controlled, and poorly-controlled asthma were summarized at each study visit by cohort. In addition, the number and percentage of patients with change from baseline of ≥ 3 points, the ACT MID, were summarized at each study visit by cohort. All summaries are based on observed data and there was no imputation for missing data. Thus, a patient need not have complete data at each 6-month follow-up visit from baseline to Month 24 to be included in the analysis. Derived scores are missing if responses to one or more of the component questions were missing. The EXCELS study is currently ongoing and these analyses were conducted using interim data.

RESULTS

Patient Demographics and Baseline Characteristics

A total of 7858 patients were enrolled in the EXCELS study: 4972 in the omalizumab cohort and 2867 in the *non-omalizumab* cohort and an additional 19 patients for whom cohort membership was undefined. The baseline demographics of the patient groups included in these interim analyses, that is, new starts ($n = 549$), established users ($n = 4421$), and non-omalizumab ($n = 2867$), are presented in Table 1. The average age of the patients was 45 years, and 66% were female and 80% were White. Almost 50% of patients in the omalizumab cohort were classified (by their physician) with severe asthma at baseline, whereas only 23% of patients in the non-omalizumab cohort were similarly classified. Other baseline

TABLE 1.—Demographic and baseline clinical characteristics.

	Omalizumab		Non-omalizumab ^c ($n = 2867$)
	New starts ^a ($n = 549$)	Established users ^b ($n = 4421$)	
Age (year)			
<i>n</i>	549	4420	2865
Mean (SD)	44.3 (16.0)	44.5 (16.6)	46.2 (17.1)
Sex, <i>n</i> (%)			
<i>n</i>	549	4421	2865
Male	195 (35.5)	1596 (36.1)	962 (33.6)
Female	354 (64.5)	2825 (63.9)	1903 (66.4)
Race, <i>n</i> (%)			
<i>n</i>	549	4420	2864
White	430 (78.3)	3493 (79.0)	2348 (82.0)
Black or African-American	77 (14.0)	632 (14.3)	366 (12.8)
Asian or Pacific Islander	17 (3.1)	102 (2.3)	61 (2.1)
Other	25 (4.6)	193 (4.4)	89 (3.1)
Body mass index (kg/m ²)			
<i>n</i>	547	4414	2859
Mean (SD)	32.2 (18.4)	31.0 (11.8)	31.3 (14.5)
Asthma severity as defined by investigator, <i>n</i> (%)			
<i>n</i>	546	4418	
Moderate	282 (51.6)	2222 (50.3)	
Severe	264 (48.4)	2196 (49.7)	
Smoking, <i>n</i> (%)			
<i>n</i>	549	4419	
Current	37 (6.7)	205 (4.6)	
Former	161 (29.3)	1310 (29.6)	
Never	351 (63.9)	2904 (65.7)	

Notes: ^aPatients in the omalizumab cohort who initiated omalizumab in the range of ≤ 7 days prior to the baseline visit date and up to 30 days after the baseline visit date.

^bPatients who initiated omalizumab > 7 days before the baseline visit date.

^cPatients who were not treated with omalizumab during the 24-month follow-up period (≥ 30 days after the baseline visit).

characteristics were generally similar among the groups. The cumulative omalizumab exposure in each of the study groups is presented in Table 2.

ACT Score from Baseline to Month 24

The ACT score from baseline to Month 24 is presented in Figure 1A and Table 3. Among new starts, the mean ACT score (SD) increased from 15.2 (5.2) at baseline to 18.4

TABLE 2.—Omalizumab exposure.

		New starts ^a ($n = 549$)		Established users ^b ($n = 4421$)	
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
Prior to study enrolment	Months of treatment	549	0.0 (0.1)	4421	8.7 (7.9)
	Number of doses	548	0.0 (0.1)	4420	14.0 (13.9)
	Cumulative dose (g)	548	0.0 (0.0)	4420	4.0 (4.5)
On study	Months of treatment	549	16.8 (9.2)	4421	18.6 (8.2)
	Number of doses	548	27.8 (18.3)	4420	30.5 (17.3)
	Cumulative dose (g)	548	8.2 (6.6)	4420	8.9 (6.3)
Total	Months of treatment	549	16.8 (9.2)	4421	27.3 (11.9)
	Number of doses	548	27.8 (18.3)	4420	44.5 (24.7)
	Cumulative dose (g)	548	8.2 (6.6)	4420	12.9 (9.0)

Notes: ^aPatients in the omalizumab cohort who initiated omalizumab in the range of ≤ 7 days prior to the baseline visit date and up to 30 days after the baseline visit date.

^bPatients who initiated omalizumab > 7 days before the baseline visit date.

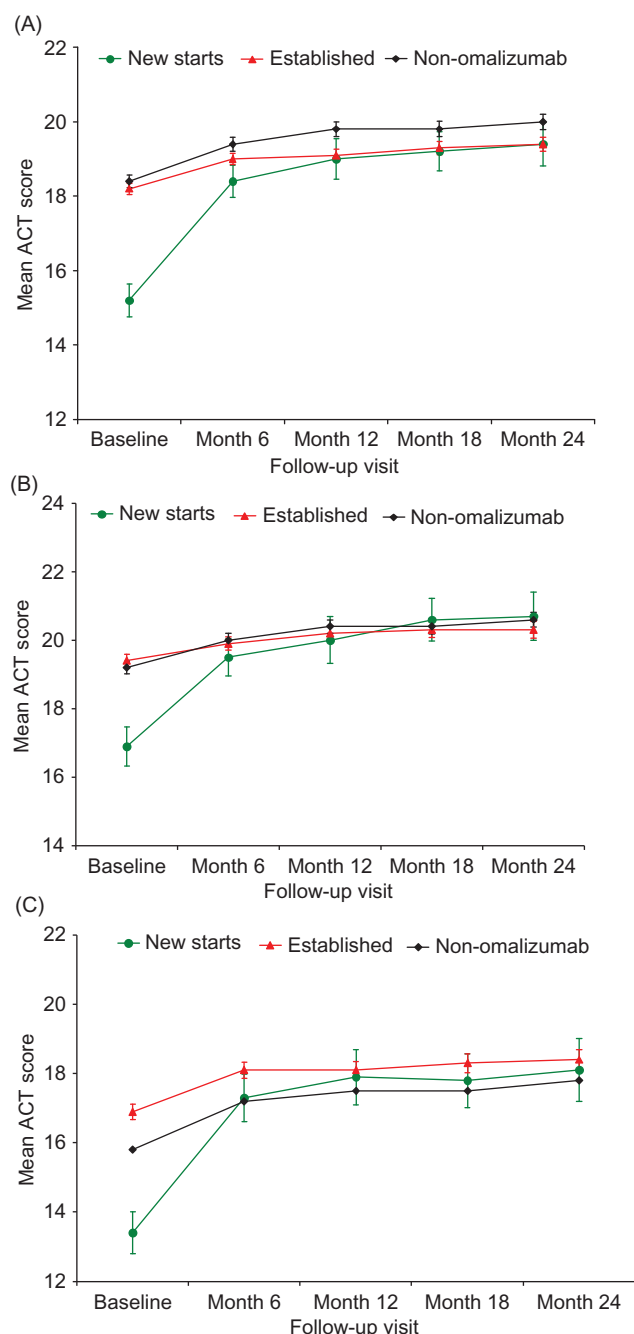


FIGURE 1.—Mean ACT score from baseline to Month 24 for (A) all patients, (B) patients with moderate asthma, and (C) patients with severe asthma in the new starts, established users, and non-omalizumab groups.

Note: ACT, Asthma Control Test.

(4.7) at Month 6 and reached 19.4 (4.8) by Month 24. For established users, the mean ACT score increased from 18.2 (4.9) at baseline to 19.4 (4.8) by Month 24. Among non-omalizumab patients, the mean ACT score increased from 18.4 (4.7) at baseline to 20.0 (4.5) by Month 24.

Patients within each group assessed by their physician at baseline as having severe asthma exhibited lower mean ACT scores at each visit (baseline, Month 6, Month 12, Month 18, and Month 24) compared with those with moderate asthma. The change in mean ACT score over time followed a similar pattern for patients with moderate and severe asthma (Figure 1B and 1C).

TABLE 3.—Mean Asthma Control Test (ACT) score by visit.

	Omalizumab		
	New starts ^a (n = 549)	Established users ^b (n = 4421)	Non-omalizumab ^c (n = 2867)
Baseline			
n	540	4410	2850
Mean (SD)	15.2 (5.2)	18.2 (4.9)	18.4 (4.7)
Month 6			
n	460	3881	2418
Mean (SD)	18.4 (4.7)	19.0 (4.8)	19.4 (4.5)
Month 12			
n	358	3364	2170
Mean (SD)	19.0 (5.1)	19.1 (4.8)	19.8 (4.4)
Month 18			
n	307	2920	1973
Mean (SD)	19.2 (4.6)	19.3 (4.8)	19.8 (4.6)
Month 24			
n	269	2584	1818
Mean (SD)	19.4 (4.8)	19.4 (4.8)	20.0 (4.5)

Notes: ^aPatients in the omalizumab cohort who initiated omalizumab in the range of ≤ 7 days prior to the baseline visit date and up to 30 days after the baseline visit date.

^bPatients who initiated omalizumab > 7 days before the baseline visit date.

^cPatients who were not treated with omalizumab during the 24-month follow-up period ≥ 30 days after the baseline visit).

Baseline values for new starts, established users, and non-omalizumab patients are based on the date of enrolment into the study. The cohorts summarized in this table differ at baseline with respect to asthma severity, comorbid conditions, and other baseline disease characteristics; therefore, the asthma control measures are summarized with emphasis on longitudinal follow-up of these measures within each cohort rather than between-cohort comparisons.

Percentage of Patients Achieving MID Improvement in ACT Score from Baseline

Over half (54%) of the patients newly initiated with omalizumab (new starts) achieved MID improvement in ACT (defined as ≥ 3 -point change from baseline) by Month 6 and this proportion increased throughout the follow-up period reaching 62% at Month 24. The percentage of patients achieving MID improvement in the established users subcohort increased from 29% at Month 6 to 31% at Month 24. Among non-omalizumab users, the proportion of patients achieving an MID improvement in ACT score also increased over time from 26% at Month 6 to 31% at Month 24 (Figure 2A).

The proportion of patients achieving an MID improvement in the ACT score from baseline to each visit (Month 6, Month 12, Month 18, and Month 24) was numerically higher for those categorized as having severe asthma than in patients with moderate asthma across all groups. However, as shown in Figure 2B and 2C, the change over time followed a similar pattern in moderate and severe asthma.

ACT Category for All Enrolled Patients from Baseline to Month 24

The proportion of patients whose asthma was considered well controlled (ACT ≥ 20) and poorly controlled (ACT ≤ 15) from baseline to Month 24 is shown in Figure 3A and 3B. The new starts subcohort had a substantial increase in patients with well-controlled asthma from baseline (26%) to Month 6 (50%) and this proportion

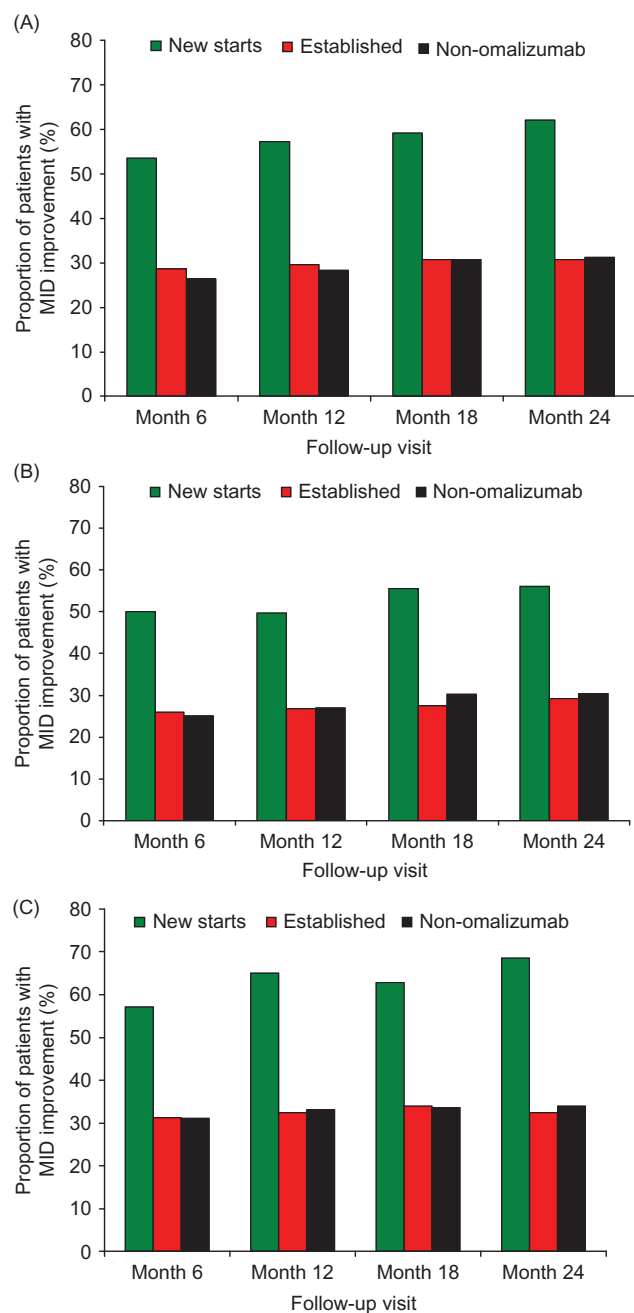


FIGURE 2.—Proportion of (A) all patients, (B) patients with moderate asthma, and (C) patients with severe asthma achieving MID improvement (≥ 3 points) in ACT from baseline at Month 6, Month 12, Month 18, and Month 24 in the new starts, established users, and non-omalizumab groups. Note: ACT, Asthma Control Test; MID, minimally important difference.

remained considerable through Month 24 (59%). The proportion of patients in the new starts subcohort with poorly controlled asthma decreased from 51% at baseline to 24% at Month 6, and this reduction also persisted until Month 24 (20%). In the established users subcohort, the proportion of patients with well-controlled asthma increased modestly from 48% at baseline to 58% at Month 24, and poorly controlled asthma decreased from 29% to 21%. In the non-omalizumab cohort, the percentage of patients with well-controlled asthma increased from 48% at baseline to 65% at Month 24, whereas the percentage of

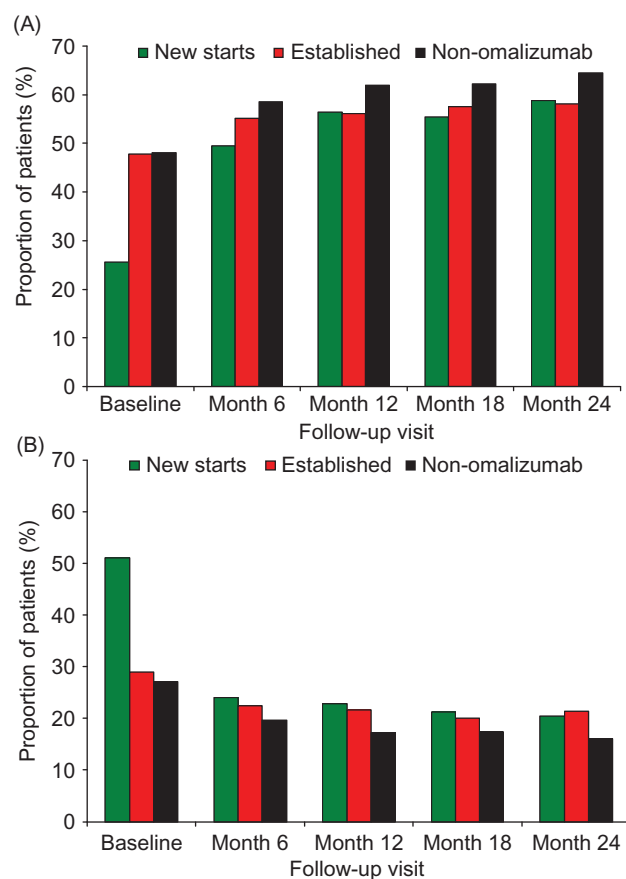


FIGURE 3.—Percentage of patients in the new starts, established users, and non-omalizumab groups with (A) well-controlled asthma and (B) poorly controlled asthma at baseline, Month 6, Month 12, Month 18, and Month 24.

patients with poorly controlled asthma decreased from 27% at baseline to 16% at Month 24.

DISCUSSION

This interim analysis was conducted to determine the longitudinal changes in asthma control in patients treated and not treated with omalizumab using data from the EXCELS observational cohort study. EXCELS is an ongoing study focusing on the evaluation of the long-term clinical safety and effectiveness of omalizumab in patients with moderate to severe persistent asthma in real-world clinical practice settings. EXCELS data were selected for the present analysis because this study captures information on the ACT, a validated questionnaire developed to assess asthma control. To date, none of the existing omalizumab clinical trials have assessed the benefit of omalizumab treatment as determined by the ACT over such a long period of time.

The group of new starts patients on omalizumab had a clinically significant improvement in ACT score (+4.2 points) and over 60% of these patients achieved the MID (ACT ≥ 3 points) within 24 months of starting omalizumab. Results from the analysis of change from baseline to Month 24 showed consistent results for patients with data at baseline and Month 24. Improvements in asthma control among new starts patients were observed by the 6-month

follow-up visit and persisted until the end of the follow-up period. A similar pattern of ACT improvement was observed in patients with both moderate and severe asthma. These results suggest that starting omalizumab may be associated with improved asthma control that persists over time. Moreover, established users of omalizumab maintained asthma control throughout the observation period; this group showed a small change in ACT score of +1.2 points at Month 24. A similar degree of improvement was in fact seen in the non-omalizumab cohort (change in ACT score of +1.6). These findings suggest that the small incremental improvements in ACT score and slight increases in proportions of patients with MID improvement over the course of the study seen in established users of omalizumab and the non-omalizumab cohort may reflect the improved general medical care and treatment adherence typically associated with enrolment in a clinical study.

This study has several strengths. Patients were enrolled from hundreds of sites throughout the United States that broadly reflect the population of patients with moderate to severe asthma eligible for treatment with omalizumab. The sample size was large and included a diverse group of patients based on various sociodemographic and clinical factors. The longitudinal design also allowed examination of trends over time. In addition, use of ACT, which is a validated measure, enabled a rigorous assessment of asthma control. Consequently, the real-world observational cohort design provides information complementary to the pivotal randomized controlled trials that were conducted in highly controlled settings. In addition, this study's focus on the impairment domain of asthma control complements the focus of the pivotal trials on the risk domain.

The observational design of EXCELS and the fact that treatment regimen, including use of omalizumab, was at the discretion of physicians and patients, increase the generalizability of these findings. Physicians were instructed to base their assessment of asthma severity on the global GINA asthma guidelines using the totality of clinical information about the patient's asthma status. In addition, previous work demonstrates that physician's overall assessment of asthma severity is comparable to and, in some cases, better than the GINA and NAEPP classification schemes for identifying severe asthma defined by emergency health care utilization, systemic corticosteroid treatment, and other intensive controller therapy (13). However, these features of the study design of EXCELS do not allow for rigorous control of confounding or bias like the randomized trials of omalizumab. To address this limitation, it was determined *a priori* that the new starts subcohort and the other groups would not be statistically compared, but data would be provided for the established users and non-omalizumab groups for reference. Because the study is so large, many results are likely to achieve conventional statistical significance, which could be confused with clinical significance. Moreover, it would be difficult to adequately control for confounding factors due to confounding-by-indication (i.e., patients in the omalizumab cohort have more severe asthma than those in the

non-omalizumab cohort) and selection bias (the established users subcohort is potentially enriched with patients who have superior efficacy and tolerability of omalizumab; others could have stopped treatment and never been enrolled in the study). In addition, for patients who changed their omalizumab treatment status within their first 2 years in the EXCELS study (i.e., new starts or *established users* who stopped omalizumab and non-omalizumab patients who started omalizumab), it is likely they did not have 24 full months of follow-up data available after the treatment change. This resulted in fewer patients with assessments available at the later time points. Another potential limitation of the analyses is missing data due to premature discontinuation, loss to follow-up, or incomplete ascertainment of ACT data, which may be compounded by the observational design and length of follow-up in the EXCELS study. These results are based on interim results of the first 2 years of the planned 5 years of follow-up study; the final analyses and results based on the completed study could differ. The study design did not include assessment of certain factors that may have contributed to changes in asthma control over time, such as the impact of seasonal allergy which limits interpretation of the meaning of modest improvements in asthma control seen in the established users and non-omalizumab patients.

CONCLUSION

In conclusion, improvements in asthma control were seen in all groups of patients with moderate to severe allergic asthma followed up during this 2-year observational study. Over 60% of patients who initiated omalizumab had clinically important improvements in asthma control within 2 years. Established users of omalizumab maintained asthma control over the 2-year period with a small improvement similar to that seen in nonusers of omalizumab. Further, longitudinal data from EXCELS will provide additional long-term effectiveness and safety information regarding omalizumab.

DECLARATION OF INTEREST

Dr. Eisner, Dr. Zazzali, Ms Miller, and Ms Bradley are employees of Genentech, Inc. Dr. Schatz receives research support for investigator-initiated grants from Aerocrine, Genentech, GlaxoSmithKline, and Merck, and is a research consultant for Amgen, GlaxoSmithKline, and Merck.

The study and the third-party writing assistance for this article were supported by Genentech, Inc., South San Francisco, CA, and Novartis Pharmaceuticals Corporation, East Hanover, NJ.

AUTHOR CONTRIBUTIONS

Dr. Eisner provided input into the design of the study, analysis of data, and writing of the article.

Dr. Schatz reviewed the data and edited the article.

Dr. Zazzali provided input into the design of the study, analysis of data, and writing of the article.

Mary K. Miller provided input into the design of the study, analysis of data, and writing of the article.

Mary S. Bradley provided input into the design of the study, analysis of data, and writing of the article.

REFERENCES

1. National Heart Lung and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Full Report. Bethesda, MD: NHLBI, 2007:1–440.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2011. Available at: <http://www.ginasthma.org/guidelines-global-strategy-for-the-diagnosis.html>. Accessed March 1, 2012.
3. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004; 170:836–844.
4. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab versus placebo as add on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest* 2011; 139:28–35.
5. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108:184–190.
6. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18:254–261.
7. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, Cioppa GD; Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34:632–638.
8. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113:59–65.
9. Schatz M, Mosen DM, Kosinski M, Vollmer WM, Magid DJ, O'Connor E, Zeiger RS. Validity of the Asthma Control Test completed at home. *Am J Manage Care* 2007; 13:661–667.
10. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, Kosinski M, Pendergraft TB, Jhingran P. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549–556.
11. Long AA, Fish JE, Rahmaoui A, Miller MK, Bradley MS, Taki HN, Demeo AN, Tilles SA, Szeffler SJ. Baseline characteristics of patients enrolled in EXCELS: a cohort study. *Ann Allergy Asthma Immunol* 2009; 103:212–219.
12. Schatz M, Kosinski M, Yarlus AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009; 124:719–723.
13. Miller MK, Johnson C, Miller DP, Deniz Y, Bleecker ER, Wenzel SE; TENOR Study Group. Severity assessment in asthma: an evolving concept. *J Allergy Clin Immunol* 2005; 116: 990–995.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.