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Concomitant asthma medications in moderate-to-severe allergic asthma treated with omalizumab

Hubert Chen^{a,b,*}, Mark D. Eisner^a, Tmirah Haselkorn^a, Benjamin Trzaskoma^a

^a Genentech, Inc., South San Francisco, CA, USA

^b University of California San Francisco, School of Medicine, Pulmonary and Critical Care Division, San Francisco, CA, USA

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Summary

Background: Omalizumab is a recombinant humanized monoclonal anti-IgE antibody approved in adults and adolescents with moderate-to-severe persistent allergic asthma inadequately controlled with inhaled corticosteroids (ICS). EXCELS is an ongoing prospective observational cohort study of approximately 5000 omalizumab-treated and >2800 non-omalizumab-treated patients aged ≥ 12 years.

Objective: We evaluated concomitant medication use changes (total ICS dose [including monotherapy and combination therapy, fluticasone equivalent], short-acting beta-agonists [SABA], and leukotriene modifier [LTM]) over 2 years among subsets of patients enrolled in EXCELS.

Methods: Patient subsets included “new starts” (omalizumab initiated at baseline [$n = 549$], “established users” (omalizumab initiated >7 days before baseline [$n = 4421$]), and “non-omalizumab” patients (not treated with omalizumab [$n = 2867$]).

Results: At baseline, mean $\pm$ SD total daily ICS doses were 680 ± 414 $\mu\text{g/d}$ in new starts, 642 ± 431 $\mu\text{g/d}$ in established users, and 548 ± 382 $\mu\text{g/d}$ in non-omalizumab patients. From baseline through year 2, total ICS dose decreased in 65% of new starts (mean $\pm$ SD change, -393 ± 504 $\mu\text{g/d}$), 57% of established users (-287 ± 492 $\mu\text{g/d}$), and 54% of non-omalizumab patients (-232 ± 431 $\mu\text{g/d}$). At baseline, SABA use for new starts, established users, and non-omalizumab patients was 1.9, 1.3, and 1.4 puffs/d, respectively. At year 2, SABA use decreased in 65% of new starts, 55% of established users, and 54% of non-omalizumab patients. At year 2, LTM dose decreased in 52% of new starts, 44% of established users, and 40% of non-omalizumab patients.

* Corresponding author. 1 DNA Way, MS #453A, South San Francisco, CA, USA.
E-mail address: chen.hubert@gene.com (H. Chen).

Conclusion: Omalizumab therapy initiation was associated with decreased doses of ICS, SABA, and LTM over 2 years of follow-up for the majority of patients in a “real-world” cohort study of moderate-to-severe allergic asthma patients.

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Introduction

National guidelines recommend that asthma medications be titrated to the lowest doses needed to achieve and maintain asthma control.¹ Use of the lowest effective dose is intended to promote patient safety and reduce the occurrence of adverse events. Oral corticosteroids (OCS), for example, are associated with recognized adverse events, including cataracts and bone fractures.² Inhaled corticosteroids (ICS) are considered safer than oral corticosteroids; however, concerns with prolonged use of high-doses of ICS remain³ and the risk of adverse events increases with ICS dose.¹ Due to risks of asthma-related hospitalization and death, the US Food and Drug Administration (FDA) has recommended that long-term beta-agonists (LABAs) be discontinued once asthma control has been achieved.⁴

Despite treatment with high-dose ICS plus LABA combination therapy, many patients with asthma continue to have inadequately controlled symptoms.^{5,6} Omalizumab, a recombinant humanized monoclonal antibody that binds to immunoglobulin E (IgE), is approved by the FDA for the treatment of adolescents and adults (≥ 12 years) with moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids.⁷ In addition to demonstrating the efficacy of omalizumab for improving asthma control and reducing exacerbations, several randomized clinical trials (RCTs) have shown that omalizumab has an ICS-sparing effect.^{8–10} In a pooled analysis of RCTs, omalizumab has also demonstrated an ability to reduce the need for oral corticosteroid bursts.¹¹

The efficacy of new therapies as demonstrated in RCTs may not necessarily translate to effectiveness in actual clinical practice. Subjects in clinical trials are carefully selected, closely monitored, and often managed within the context of a strict study protocol. Moreover, most RCTs are not designed to evaluate longer-term outcomes. Large prospective, observational studies have the advantage of yielding more generalizable results that more closely reflect treatment outcomes as observed in “real-world” settings. In this study, we examined differences in concomitant medication use following initiation of omalizumab in the Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) study.¹²

Methods

EXCELS study design

EXCELS is an ongoing, multicenter, prospective, observational cohort study of the long-term clinical safety and effectiveness of omalizumab. The study has approximately

5000 omalizumab and 2500 non-omalizumab-treated patients with moderate-to-severe asthma who were recruited from a variety of practice settings across the United States.¹² The study design and baseline patient characteristics have been published previously.¹² Because EXCELS is an observational study, patients are not assigned to any protocol-mandated treatment.¹² The EXCELS protocol was approved by a local or central institutional review board at each study site and informed written consent was obtained from study participants prior to enrolment.

Participants

Eligible patients were older than 12 years 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.¹² Asthma severity was assessed by managing physicians and classified as moderate or severe.¹² Key exclusion criteria were a known contraindication to omalizumab therapy, diagnosis of cystic fibrosis, acute asthma exacerbation within the 2 weeks prior to screening, or acute flare-up of significant disease or hospitalization within 2 months prior to screening.¹² More detailed inclusion and exclusion criteria are available elsewhere.¹²

Medication use

Medication management in EXCELS is determined entirely by the physician and there is no requirement for attempting medication tapering.¹² All medications (including omalizumab) are initiated, adjusted, and discontinued at the physician's discretion.¹² Medication type and dose information is collected by a study coordinator during patient interviews and verified by visual inspection of medication containers provided by patients.

Analytic cohort

This interim analysis of concomitant medication use was conducted using data from the first 2 years of follow-up in EXCELS,¹² and included patients with medication and dose information at baseline and at least 1 follow-up (month 12 or month 24) study visit. The study population is comprised of three pre-defined cohorts based on previous use of omalizumab: *New starts* had an omalizumab start date ranging from ≤ 7 days prior to the baseline visit date up to 30 days after the baseline visit. *Established users* had an omalizumab start date > 7 days prior to the baseline visit date. *Non-omalizumab* patients had never been treated with omalizumab at the time of enrolment.¹²

Analytic outcomes

Primary analytic outcomes were *percent change in dose of concomitant asthma medications and proportion of patients with any change in dose* from baseline to month 12 and baseline to month 24. Both outcome measures were evaluated for ICS and short-acting beta-agonists (SABA); percent change in leukotriene modifier (LTM) dose could not be reported, as there is no standard for dose equivalence across agents.

ICS was measured as total dose (monotherapy and combination therapy) and as monotherapy. The doses of all ICS medications (used as monotherapy or combination therapy) were converted to fluticasone equivalent prior to analysis. SABA was measured as number of puffs per day of regular use, excluding nebulized medications and doses taken "as needed." Rescue SABA use was not included due to inadequate data to allow accurate calculation of numerical changes. LTM medications included leukotriene receptor antagonists (montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). Because dose-equivalence conversion is not possible for LTM, patients who switched from one LTM to another were excluded from the analysis for the period when the switch occurred. Oral corticosteroid use was not systematically collected at follow-up in this study and was, therefore, not included in this analysis.

Statistical analysis

Changes in medication dose were assessed within each patient subgroup. Statistical tests for between-group comparisons were not performed due to the observational, non-randomized nature of EXCELS. For this analysis, omalizumab *new starts* patients were of primary interest, as this group was anticipated to best reflect changes in concomitant medication use following initiation of omalizumab therapy; *established users* and *non-omalizumab* patients served as reference groups.¹³ Sensitivity analyses examining patients who switched groups, i.e., non-omalizumab users who became omalizumab users, or omalizumab users who discontinued use, showed no substantial differences from the overall findings reported. In addition, sensitivity analyses adjusting for various baseline imbalances, including baseline medication use, showed no substantial differences from the overall findings reported.

Demographic and clinical characteristics at baseline were summarized by group (*new starts*, *established users*, *non-omalizumab*) and by medication subset (ICS, SABA, LTM) using descriptive statistics. Classification of medication increase or decrease was based on subtraction of baseline dose from month 12 and month 24 follow-up dose, and were reported as percent change in dose from baseline and the proportion of patients with an increase or decrease in dose over time. In addition to the primary analysis, which evaluated any change in dose for patients, a wide range of sensitivity analyses were conducted applying different thresholds for defining "change" in dose. The results from these analyses were not appreciably different from those reported in the primary analysis.

Given differences in asthma severity at baseline between groups, additional analyses were conducted stratifying by asthma severity. Findings stratified by asthma

severity were not appreciably different from the cohort as a whole, and thus are presented in the text only.

Results

Demographic and baseline clinical characteristics

New starts, *established users*, and *non-omalizumab* patients were similar with respect to most demographic and baseline characteristics. Overall average age was approximately 45 years, 65% of patients were female and 80% were white (Table 1); however, the patient groups differed in asthma severity. Almost half (49.6%) of patients treated with omalizumab (*new starts*, 48.3%, *established users*, 49.6%) were classified (by their physician) with severe asthma at baseline, but only 23.1% of patients in the non-omalizumab cohort were similarly classified. The distribution of demographic and clinical characteristics for all patients was similar to those distributions for the ICS, SABA, and LTM medication subsets. At baseline, *established users* had received an average of 8.6 months of omalizumab treatment.

Changes in concomitant medication use

Longitudinal changes in medication dose for total ICS, ICS as monotherapy, and regular SABA use are shown in Table 2. Mean total daily dose of ICS ($\mu\text{g}/\text{d}$) decreased in all groups from baseline to month 12 and month 24. The percent reduction was greatest for *new starts* (57.7% at month 24) compared with *established users* (44.7%) and *non-omalizumab* users (42.4%). The proportion of patients with change in total ICS dose is shown in Fig. 1. Nearly two-thirds of omalizumab *new starts* exhibited a decrease in total daily ICS dose from baseline to month 24, compared with 57% of *established users* and 54% of *non-omalizumab*. When stratified by asthma severity, the proportion of patients with an observed decrease in total ICS dose at month 24 was similar in patients with moderate and severe asthma (*new starts*: 64% moderate, 65% severe; *established users*: 56% moderate, 58% severe; *non-omalizumab*: 54% moderate, 53% severe).

While the percent reductions in dose for ICS monotherapy were larger than those for ICS total dose for all groups (both at month 12 and at month 24), the data exhibited a similar trend overall, with the greatest percent reduction observed among omalizumab *new starts*.

For regular SABA use, number of SABA puffs/day decreased in all groups from baseline to month 12 and month 24, and the percent reduction was greatest in the *new starts* (73.7% at month 24), followed by *established users* (69.2%), and *non-omalizumab* users (64.3%). Fig. 2 shows the proportion of patients in each subgroup with changes in daily SABA use; decreased dose at month 24 was observed in a greater proportion of *new starts* (65%) than *established users* (55%) or *non-omalizumab* patients (54%). When stratified by asthma severity, a decrease in regular SABA dose at month 24 was observed in a somewhat larger proportion of patients with severe than moderate asthma (*new starts*: 62% moderate, 69% severe; *established users*: 49% moderate, 60% severe; *non-omalizumab*: 52% moderate, 58% severe).

Table 1 Demographic and baseline clinical characteristics.

	All patients (n = 7837)			ICS subset ^a (n = 7133)			SABA subset ^a (n = 826)			LTM subset ^a (n = 4997)		
	New starts (n = 549)	Established users (n = 4421)	Non-Omalizumab (n = 2865)	New starts (n = 515)	Established users (n = 4009)	Non-Omalizumab (n = 2609)	New starts (n = 77)	Established users (n = 464)	Non-Omalizumab (n = 285)	New starts (n = 381)	Established users (n = 3029)	Non-Omalizumab (n = 1587)
Age, years, mean (SD)	44.3 (16.0)	44.5 (16.6)	46.2 (17.1)	44.5 (16.1)	44.5 (16.4)	46.2 (17.1)	49.4 (15.3)	46.7 (15.7)	47.5 (17.3)	44.0 (16.3)	44.0 (16.5)	46.2 (17.3)
Sex, n (%)												
Men	195 (35.5)	1596 (36.1)	962 (33.6)	191 (37.1)	1441 (35.9)	893 (34.2)	32 (41.6)	176 (37.9)	95 (33.3)	128 (33.6)	1042 (34.4)	496 (31.3)
Women	354 (64.5)	2825 (63.9)	1903 (66.4)	324 (62.9)	2568 (64.1)	1716 (65.8)	45 (58.4)	288 (62.1)	190 (66.7)	253 (66.4)	1987 (65.6)	1091 (68.7)
Race, n (%)												
White	430 (78.3)	3493 (79.0)	2348 (82.0)	400 (77.7)	3154 (78.7)	2152 (82.5)	61 (79.2)	371 (80.0)	229 (80.4)	292 (76.6)	2352 (77.7)	1295 (81.7)
Black or African American	77 (14.0)	632 (14.3)	366 (12.8)	74 (14.4)	585 (14.6)	330 (12.7)	11 (14.3)	59 (12.7)	40 (14.0)	60 (15.7)	477 (15.8)	218 (13.7)
Asian or Pacific Islander	17 (3.1)	102 (2.3)	61 (2.1)	17 (3.3)	94 (2.3)	53 (2.0)	1 (1.3)	10 (2.2)	7 (2.5)	13 (3.4)	71 (2.3)	29 (1.8)
Other	25 (4.6)	193 (4.4)	89 (3.1)	24 (4.7)	175 (4.4)	73 (2.8)	4 (5.2)	24 (5.2)	9 (3.2)	16 (4.2)	128 (4.2)	44 (2.8)
BMI, kg/m ² , mean (SD)	32.2 (18.4)	31.0 (11.8)	31.3 (14.5)	32.0 (15.9)	31.2 (11.7)	31.1 (12.5)	32.1 (6.7)	30.9 (8.5)	33.7 (25.7)	31.4 (11.1)	31.1 (9.9)	31.3 (11.3)
Asthma severity, ^b n, %												
Moderate	282 (51.6)	2222 (50.3)	2200 (76.9)	259 (50.4)	1960 (48.9)	1982 (76.1)	40 (51.9)	221 (47.6)	205 (71.9)	184 (48.4)	1418 (46.8)	1144 (72.2)
Severe	264 (48.4)	2196 (49.7)	660 (23.1)	255 (49.6)	2047 (51.1)	624 (23.9)	37 (48.1)	243 (52.4)	80 (28.1)	196 (51.6)	1610 (53.2)	440 (27.8)
Smoking, n, %												
Current	37 (6.7)	205 (4.6)	162 (5.7)	34 (6.6)	184 (4.6)	132 (5.1)	8 (10.4)	21 (4.5)	16 (5.6)	23 (6.0)	140 (4.6)	77 (4.9)
Former	161 (29.3)	1310 (29.6)	833 (29.1)	152 (29.5)	1192 (29.7)	773 (29.6)	29 (37.7)	172 (37.1)	89 (31.2)	115 (30.2)	870 (28.7)	475 (29.9)
Never	351 (63.9)	2904 (65.7)	1870 (65.3)	329 (63.9)	2631 (65.7)	1704 (65.3)	40 (51.9)	271 (58.4)	180 (63.2)	243 (63.8)	2018 (66.6)	1035 (65.2)

SD, standard deviation; BMI, body mass index.

^a Among patients with both a baseline and month 12 study visit with valid treatment assignment.^b As defined by investigator.

Table 2 Changes in concomitant medication dose at month 12 and month 24.^a

	ICS total dose, µg/day			ICS monotherapy, µg/day			SABA regular use, puffs/day		
	New starts (n = 515)	Established users (n = 4009)	Non-Omalizumab (n = 2609)	New starts (n = 150)	Established users (n = 1441)	Non-Omalizumab (n = 854)	New starts (n = 77)	Established users (n = 464)	Non-Omalizumab (n = 285)
Dose at baseline, mean (SD)	680.2 (414.1)	642.4 (430.6)	547.9 (382.4)	256.7 (278.0)	237.9 (263.7)	210.0 (224.6)	1.9 (1.7)	1.3 (1.6)	1.4 (1.7)
Change at month 12, mean (SD)	−297.0 (474.4)	−203.0 (457.2)	−158.0 (392.7)	−158.1 (325.6)	−115.8 (297.2)	−108.2 (261.5)	−1.5 (1.9)	−0.7 (2.0)	−0.9 (2.0)
Change at month 24, mean (SD)	−392.8 (503.5)	−287.1 (492.2)	−232.1 (430.6)	−174.0 (309.4)	−161.6 (289.1)	−126.1 (260.2)	−1.4 (1.9)	−0.9 (1.8)	−0.9 (1.8)
Percent reduction in dose									
Baseline to month 12, %	43.7	31.6	28.8	61.6	48.7	51.5	78.9	53.8	64.3
Baseline to month 24, ^b %	57.7	44.7	42.4	67.8	67.9	60.1	73.7	69.2	64.3

^a Study cohorts for baseline to month 12 analysis and baseline to month 24 analysis based on patients with study visits at those respective timepoints with valid treatment assignments; patient counts in table reflect patients with baseline and month 12 study visit with valid treatment assignment.

^b Patient counts for baseline to month 24 as follows (new starts, established users, non-omalizumab): ICS total dose: $n = 467$, $n = 3797$, $n = 2510$, respectively; ICS monotherapy: $n = 136$, $n = 1390$, $n = 829$, respectively; SABA regular use: $n = 78$, $n = 504$, $n = 297$, respectively SD, standard deviation.

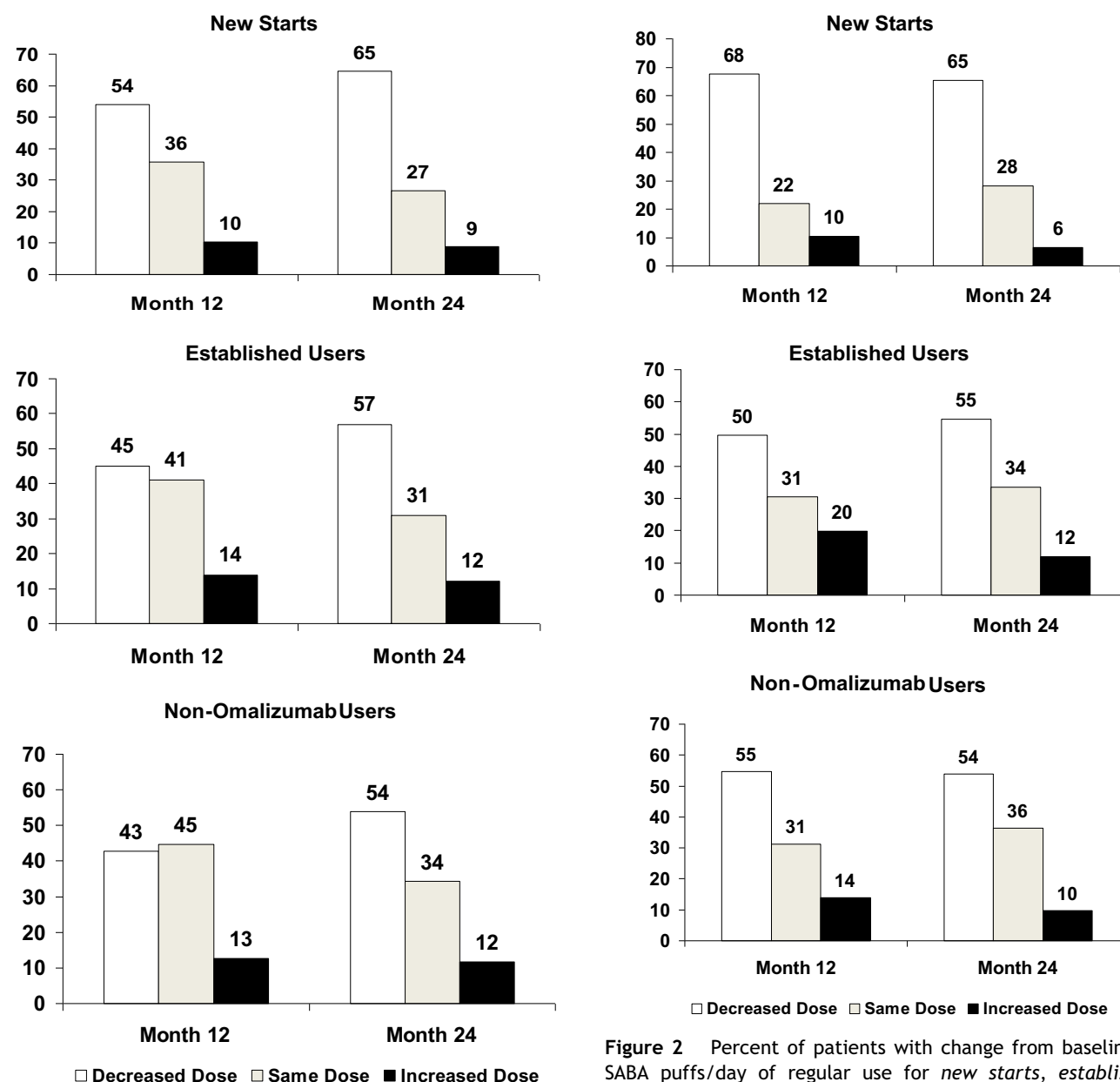


Figure 1 Percent of patients with change from baseline in total daily ICS dose ($\mu\text{g}/\text{d}$) for *new starts*, *established users*, and *non-omalizumab* patients.

Percent change in LTM dose cannot be reported, as there is no standard for dose equivalence across agents. Fig. 3 shows the proportion of patients in each subgroup with changes in LTM use. At month 24, more than 50% of omalizumab *new starts* exhibited reductions in LTM dose, compared to 44% of *established users* and 40% of *non-omalizumab* patients. For the vast majority of patients, a reduction in LTM dose resulted in complete discontinuation of the medication: 95.7% for montelukast, 89.6% for zafirlukast, and 91.7% for zileuton. When stratified by asthma severity, a decrease in LTM dose at month 24 was observed in a greater proportion of patients with moderate (57%) than severe (48%) asthma among omalizumab *new starts*, but was similar within the other groups (*established users*: 43% moderate, 45% severe; *non-omalizumab*: moderate 40%, severe 41%).

Figure 2 Percent of patients with change from baseline in SABA puffs/day of regular use for *new starts*, *established users*, and *non-omalizumab* patients.

Discussion

The EXCELS study, with its prospective, observational design and large number of enrolled patients, provides a unique opportunity to examine concomitant medication use in “real-world” settings of omalizumab users in clinical practice. For each of the common asthma medication classes examined – ICS, SABA, and LTM – the majority of patients newly treated with omalizumab were able to decrease medication doses. Although decreases in concomitant medication use were observed across all three medication groups, new omalizumab users demonstrated the greatest percent reduction based on both percent change in dose of concomitant asthma medications and proportion of patients with change in dose.

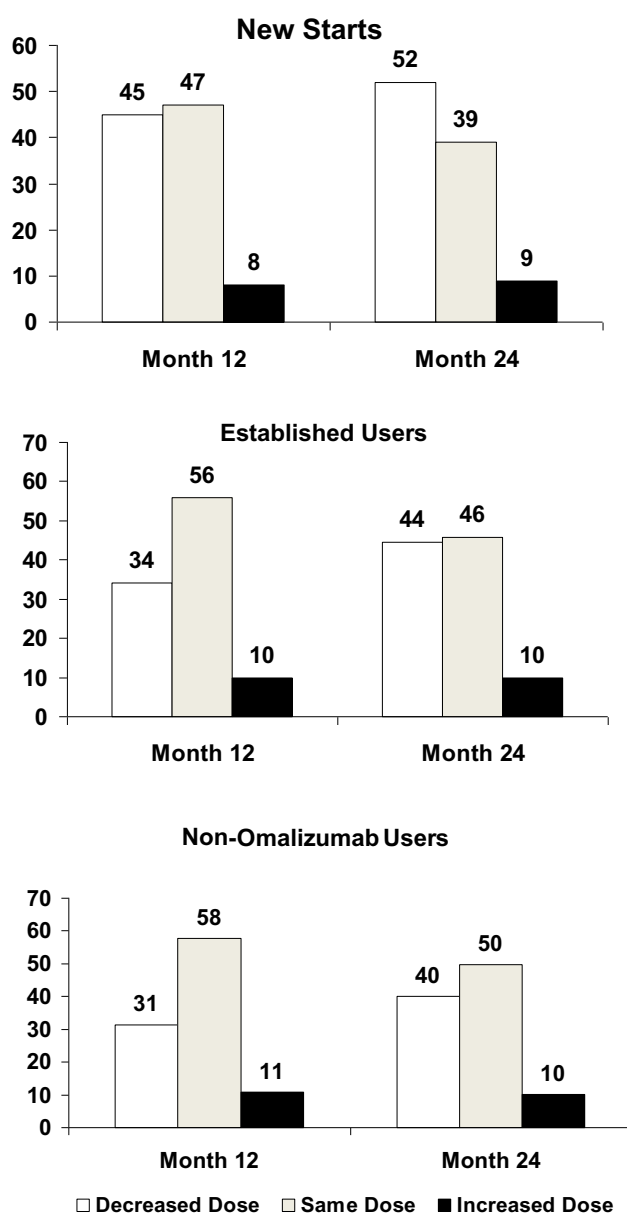


Figure 3 Percent of patients with change from baseline in daily LTM dose for *new starts*, *established users*, and *non-omalizumab* patients.

Although the present analysis did not examine clinical outcomes, a previous interim analysis of the EXCELS study demonstrated that initiation of omalizumab was also associated with significant improvements in asthma control from baseline to year 2. On the Asthma Control Test (ACT), 62% of patients newly started on omalizumab achieved the minimal clinically important difference (≥ 3 point increase) at year 2,^{13,14} and 59% were well-controlled (≥ 20 points on the ACT) compared with 26% at baseline.¹⁵ Thus, the observed reductions in concomitant medication in this analysis occurred within the context of an overall clinical improvement in asthma control in EXCELS.

Notably, results of this analysis parallel similar findings of ICS dose reduction observed in key clinical trials of omalizumab. One pivotal trial¹⁰ was designed to evaluate the ability of omalizumab to decrease ICS use and demonstrated

a 57% reduction from baseline in the fluticasone-equivalent ICS dose after 32 weeks of treatment. Two other trials^{8,9} included a 4-month steroid-stable phase followed by a 3-month steroid-reduction phase, in which ICS dose was reduced according to protocol until discontinuation or worsening of asthma symptoms. More than 70% of omalizumab-treated patients were able to reduce ICS dose by at least 50%, and 40% of patients were able to discontinue ICS use.^{8,9} In the current study, mean ICS dose was reduced by more than 50% among patients treated with omalizumab, even though the EXCELS study design did not require steroid reduction and all medication changes were based on the clinical judgment of the managing physician.¹²

When treatment with omalizumab is initiated,¹ patients are frequently using multiple other asthma controller medications. In a recent study of insurance claims from more than 6000 patients, Lafeuille et al.¹⁶ found that almost 90% of patients were using agents from three or more asthma medication classes during the 12 months prior to initiation of omalizumab. A similar proportion were using ICS as part of their treatment regimen,¹⁶ which is consistent with the findings from EXCELS. Long-term exposure to multiple medications raises concerns about adverse effects. Unlike OCS, which are associated with a number of well-known adverse effects, use of ICS is considered relatively safe.^{1,2} The adverse effects of ICS increase with dose, however, and current guidelines recommend using the lowest dose of ICS that maintains asthma control.¹ To the extent that treatment with omalizumab may facilitate the decrease or discontinuation of ICS, adverse effects of steroids may be avoided while maintaining adequate asthma control.

The observational design of EXCELS has both strengths and limitations. Patients were not assigned to treatment groups and health care providers made treatment decisions according to their clinical judgment, thus the results may have more generalizability to patients as treated in actual practice.^{12,13} Nonetheless, sizable reductions in concomitant medication use were observed across all groups likely as a result of participating in a prospective observational study with routine follow-up visits. As with most observational studies, this analysis also has potential for confounding (i.e., differences between groups with respect to asthma severity at baseline) and selection bias (e.g., the *established users* group is potentially enriched for patients who have superior response and tolerability of omalizumab). This analysis should therefore be considered in conjunction with results from randomized clinical trials. Other limitations include the fact that dose changes in LTM could not be evaluated and information about rescue SABA use was not systematically collected. Finally, it should also be noted that these results are based on interim data.¹³

Conclusions

In this real-world observational study of omalizumab use in patients with moderate-to-severe asthma, the greatest percent reduction in concomitant medication use (ICS, SABA and LTM) over a 2-year period, based on both percent change in dose and the proportion of patients with change in dose, was observed in new omalizumab users when compared with established users and non-omalizumab users. These findings

were identified within the context of improved asthma control in the EXCELS study from baseline to year 2 and support similar findings of ICS dose reduction in pivotal trials of omalizumab.

Conflict of interest statement

Drs. Chen and Eisner and Mr. Trzaskoma are employees of Genentech, Inc.

Dr. Haselkorn is a paid consultant to Genentech, Inc.

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