

Real-world health care utilization and effectiveness of omalizumab for the treatment of severe asthma



Mina Tadrous, PharmD, PhD ^{*,†,‡}; Wayne Khuu, MPH [†]; Gerald Lebovic, PhD ^{*,§}; Matthew B. Stanbrook, MD, PhD ^{†,§}; Diana Martins, MSc [†]; J. Michael Paterson, MSc ^{†,§}; Muhammad M. Mamdani, PharmD, MA, MPH ^{†,‡,§,||}; David N. Juurlink, MD, PhD ^{†,§,¶}; Tara Gomes, MHSc, PhD ^{*,†,‡,§}

^{*} Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada

[†] Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada

[‡] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

[§] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

^{||} Li Ka Shing Centre for Health care Analytics Research and Training, St. Michael's Hospital, Toronto, Ontario, Canada

[¶] Sunnybrook Research Institute, Toronto, Ontario, Canada

ARTICLE INFO

Article history:

Received for publication April 28, 2017.

Received in revised form August 10, 2017.

Accepted for publication August 15, 2017.

ABSTRACT

Background: Omalizumab is indicated for the treatment of moderate to severe asthma. There is limited observational evidence on the costs and effectiveness of omalizumab.

Objective: To examine the costs and effectiveness of omalizumab for treatment of severe asthma relative to nonusers.

Methods: We conducted a within-person repeated-measures matched cohort study in Ontario, Canada from April 1, 2012 to March 31, 2014. Continuous users of omalizumab were matched with up to 4 nonusers according to age, sex, recent specialist visits, oral corticosteroid use, asthma severity, and Charlson comorbidity score. The primary outcome was direct health care costs. Secondary outcomes were asthma-related hospitalizations or emergency department visits and oral corticosteroid use. The association between omalizumab use and each outcome was assessed using mixed-effects models adjusting for confounders.

Results: Ninety-five omalizumab users and 352 nonusers were matched. Among users, there was a significant increase in health care costs of \$1,796 per person owing to the cost of the medication at treatment initiation ($P < .0001$). Costs did not change significantly among nonusers (\$85 increase in average monthly costs per person; $P = .59$). We found no significant changes in the rates of asthma-related hospitalizations or emergency department visits among omalizumab users ($P = .44$) or nonusers ($P = .99$) between pre- and postintervention periods.

Conclusion: The use of omalizumab was associated with increased costs but no evidence of lower rates of clinically important outcomes. These results suggest omalizumab had limited effectiveness in our study population. Future studies should further explore subsets of patients most likely to benefit from omalizumab therapy.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Reprints: Mina Tadrous, PharmD, PhD, Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada; E-mail: tadrousm@smh.ca.

Disclosures: Dr Mamdani has received honoraria from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Bayer. The other authors have nothing to disclose. Brogan Inc (Ottawa) allowed the authors to use its Drug Product and Therapeutic Class Database.

Disclaimers: The opinions, results, and conclusions reported in this article are those of the authors and are independent of the funding sources. No endorsement by the ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this

material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of the CIHI.

Funding Sources: This study was funded by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and supported by the Institute for Clinical Evaluative Sciences (ICES), a nonprofit research institute sponsored by the Ontario MOHLTC.

This work was presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management; Dublin, Ireland; August 2016.

Introduction

Asthma is a chronic respiratory condition caused by inflammation of the airways in the lungs. Chronic inflammation causes airway obstruction that is associated with wheezing, coughing, chest tightness, and shortness of breath.¹ Severity of asthma presents heterogeneously with varying levels of disease severity. Patients with uncontrolled asthma are at increased risk of exacerbations, which are associated with increased rates of hospitalization and lower quality of life.^{1,2} Inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy and have been shown to decrease exacerbations and improve quality of life.^{1,2} Furthermore, add-on therapy with other agents is sometimes necessary to lower doses of ICS, with regimen changes approached in a stepwise manner. However, even with combination therapy, symptoms remain uncontrolled in some patients, with severe refractory asthma estimated to occur in approximately 4% of patients with asthma.³

Omalizumab (Xolair; Novartis Pharmaceuticals Corp, East Hanover, New Jersey) is a humanized monoclonal antibody targeting immunoglobulin E (IgE). The binding of omalizumab with free IgE blocks activation of mast cells and basophils and decreases mediator release and allergic response.^{4,5} Omalizumab is currently indicated in adults and adolescents for the treatment of moderate to severe persistent asthma as last-line treatment indicated for use in patients whose symptoms are not controlled with conventional treatment including an ICS.^{5–7} Omalizumab has been shown in clinical trials to decrease corticosteroid doses and hospitalizations in patients with severe asthma^{4,8–11}; however, it is unclear how this translates to the wider population, because much of the currently available observational evidence is limited in methodology and does not involve comparator groups.^{12–18} This issue is important because payers grapple with the high cost of omalizumab treatment, which is in the range of \$1,400 to \$1,800 CAD per month depending on dosing regimen. Criteria for drug insurance coverage of omalizumab frequently differ from the eligibility criteria in omalizumab clinical trials. Understanding the real-world effectiveness of omalizumab is important to payers and clinicians who are facing difficult decisions regarding access to this costly treatment. Accordingly, we examined the real-world costs and effectiveness of omalizumab for treatment of severe asthma compared with treatment without omalizumab using health care administrative databases in Ontario, Canada.

Methods

We conducted a retrospective cohort study using a within-person repeated-measures design leveraging administrative claims data in Ontario, Canada from April 1, 2012 through March 31, 2014.

Data Source

The Ontario Drug Benefit claims database was used to identify all drugs dispensed to individuals eligible for public drug coverage in Ontario. Drug coverage is available for all residents with financial need (owing to high drug costs relative to income), those living in long-term care facilities or needing home care, and all residents at least 65 years of age. We identified hospitalizations and emergency department (ED) visits using the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System, respectively. We used the Ontario Health Insurance Plan Claims History Database to identify physician visits. Demographics, place of residence, and vital status information were obtained from the Ontario Health Insurance Plan

Registered Persons Database. These databases, which are securely linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (www.ices.on.ca), are routinely used to examine drug safety and effectiveness.^{19–21} This project was approved by the research ethics board of the Sunnybrook Health Sciences Centre (Toronto).

Study Cohort

We created cohorts of patients who were new continuous users or nonusers of publicly funded omalizumab from April 1, 2012 through March 31, 2013. New use was defined as no previous claim for omalizumab in the year before study entry, and continuous use was defined as having a prescription claim for omalizumab within 60 days of the previous claim. All omalizumab users were followed for up to 365 days after drug initiation. All users younger than 66 years were required to have public drug coverage in the previous year, defined as any prescription claim in the 270 to 365 days before the index date. All omalizumab users were presumed to have severe asthma, because this is a reimbursement criterion under the Ontario Drug Benefit Plan (Table 1).²³ We created a matched cohort of patients with severe asthma not treated with omalizumab (nonusers) using the Ontario Asthma Database,²² with severe asthma defined by medication use equivalent to stage 4 or 5 in the Global Initiative for Asthma (GINA) guidelines.¹

The index date for omalizumab users was the date of the first omalizumab claim. Nonusers were randomly assigned an index date during the study period based on the same distribution of dates as omalizumab users. All users were required to be alive for a full year after the index date. Users were matched to up to 4 nonusers on index date (within 30 days), age (within 2 years), sex, specialist visit (respirology or clinical immunology) in the past 90 days, oral corticosteroid (OCS) dose in the past 90 days (within 100 mg), stage of asthma severity as defined by GINA guidelines,¹ any hospitalization or ED visits for asthma in the past 90 days, and Charlson comorbidity score. Dosing schedule was determined using the days' supply field on the initial index omalizumab prescription.

Outcomes

The primary outcome for our study was median monthly total health care resource usage cost from a payer perspective, which includes all actual government costs related to prescription drugs, hospitalizations, ED visits, physician visits, same-day surgeries, rehabilitation services, laboratory tests, and home care services. In a prespecified sensitivity analysis, drug costs were excluded given the high cost of omalizumab. Costs are reported in nominal Canadian dollars. Secondary outcomes included asthma-related

Table 1

Ontario Public Drug Program Criteria for Reimbursement of Omalizumab for Severe Uncontrolled Asthma^a

Patients who meet ALL the following criteria:	
1	Severe asthma as defined by one of the following:
a	Asthma hospitalization; OR
b	2 urgent or emergency visits for asthma; OR
c	2 courses of high-dose oral corticosteroids
2	≥12 y old
3	Positive skin test reaction to perennial aeroallergen
4	Baseline immunoglobulin E 30–700 IU/mL
5	Actual body weight 20–150 kg
6	Currently receiving high-dose inhaled corticosteroid in addition to long-acting inhaled β_2 -agonist
7	Adherent to therapy with proper technique

^aCurrent Exceptional Access Program reimbursement criteria from the Ontario Public Drug Programs.²² Request must be made by a specialist (respirology or allergy and immunology).

hospitalizations or ED visits, prescription for an OCS, high levels of short-acting β -agonist (SABA) use (defined as >400 doses dispensed per quarter), and number of physician visits. We report the proportion of users with the outcome per quarter. We also conducted 2 unmatched sensitivity analyses. The first was a within-person analysis conducted for the entire cohort of omalizumab users (matched and unmatched), and the second was a post hoc subgroup analysis of patients who were treated using triple therapy (ICS, long-acting β -agonist, and long-acting muscarinic antagonist) in the 120 days before the index date.

Statistical Analysis

We reported descriptive characteristics at the index date for matched omalizumab users and nonusers. We conducted an individual-level repeated-measures analysis using mixed-effects models. Outcomes were fit using the appropriate link function and distribution. In particular, cost outcomes were fitted to a gamma distribution using a log link, dichotomous outcomes (hospitalizations and ED visits, high SABA use, and OCS prescriptions) were fitted to a binomial distribution using log links, and physician visits were fitted to a normal distribution using an identity link. We examined health care usage costs and physician visits monthly, and all other outcomes were measured quarterly. All outcomes were analyzed using interaction terms in the model to examine differences in outcomes between exposed and unexposed groups before and after initiation of omalizumab. The model included fixed effects for exposure groups with time,

before and after drug initiation, and the 3-way interaction between exposure groups and initiation of omalizumab. A random effect was used to account for correlation arising from repeated measures within the same individual over time. We adjusted models for unbalanced covariates, which were defined as any covariate with a standardized difference greater than 0.1.²⁴ All statistical analyses were completed using SAS 9.4 (SAS Institute, Cary, North Carolina) at the Institute for Clinical Evaluative Sciences in Toronto.

Results

From April 1, 2012 through March 31, 2014, there were 109 new users of publicly funded omalizumab in Ontario, of whom 95 (87.2%) were matched with 352 omalizumab nonusers (Table 2). Omalizumab users were largely adherent to therapy at 6 (85.3%) and 12 (69.5%) months, and omalizumab was most commonly administered biweekly (41.1%), weekly (36.8%), or monthly (22.1%). The average age of subjects was 61 years (standard deviation [SD], 14 years), approximately one third were men, and two thirds visited a specialist in the 90 days before the index date. Few omalizumab users ($n \leq 5$) and nonusers (1.7%; $n = 6$) users had an asthma-related hospital or ED visit in the 90 days before the cohort entry date. Approximately two thirds of omalizumab users and nonusers (64.2% and 62.5%, respectively) were classified as having severe asthma before the cohort entry based on GINA guidelines. Most omalizumab users (76.0%; $n = 72$) and nonusers (65.6%; $n = 231$) were on at least dual therapy before the index date.

Table 2
Characteristics of Matched Users and Nonusers of Omalizumab in Ontario From April 2012 to March 2014

	Matched users (n = 95)	Matched nonusers (n = 352)	Standardized difference ^a
Duration of omalizumab use (d), mean (SD)	373 (150)	—	—
Men, n (%)	31 (32.6)	110 (31.3)	0
Age (y), mean (SD)	61.1 (14.0)	61.3 (14.1)	0.02
Specialist visit in past 90 d, n (%)	62 (65.3)	224 (63.6)	0
Hospital or ED visit for asthma in past 90 d, n (%)	$\leq 5^b$	6 (1.7)	0
Severe asthma based on GINA guidelines, n (%)	61 (64.2)	220 (62.5)	0
Rural residence, n (%)	9 (9.5)	30 (8.5)	0.03
Income quintile, n (%)			
1 (lowest)	24 (25.3)	112 (31.8)	0.16
2	23 (24.2)	75 (21.3)	0.07
3	15 (15.8)	63 (17.9)	0.04
4	13 (13.7)	56 (15.9)	0.07
5 (highest)	20 (21.1)	45 (12.8)	0.23
Charlson comorbidity score, n (%)			
No hospitalization	59 (62.1)	234 (66.5)	0
0	9 (9.5)	29 (8.2)	0
1	19 (20)	64 (18.2)	0
2+	8 (8.4)	25 (7.1)	0
Asthma medication dispensed in past 120 d, n (%)			
ICS	31 (32.6)	53 (15.1)	0.41
LABA	≤ 5	≤ 5	0.15
ICS + LABA combination	68 (71.6)	223 (63.4)	0.14
Short-acting muscarinic antagonists	≤ 5	21 (6.0)	0.06
Long-acting muscarinic antagonists	31 (32.6)	99 (28.1)	0.08
Theophylline	11 (11.6)	8 (2.3)	0.38
Total asthma medications in past 120 d, n (%)			
0	14 (14.7)	82 (23.3)	0.19
1	9 (9.5)	39 (11.1)	0.04
2	43 (45.3)	142 (40.3)	0.09
3	23 (24.2)	83 (23.6)	0.01
4	6 (6.3)	6 (1.7)	0.25
SABA puffs in past 90 d (n), mean (SD)	296.84 (428.78)	204.77 (285.24)	0.25
OCS prescriptions in past 90 d (n), mean (SD)	1.05 (1.32)	0.87 (1.17)	0.09
Physician office visits in past year (n), median (IQR)	18 (11–27)	13 (7–20)	0.32

Abbreviations: ED, emergency department; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β -agonist; OCS, oral corticosteroid; SABA, short-acting β -agonist.

^aA value higher than 0.1 generally indicates a meaningful difference.

^bIn accordance with Institute for Clinical Evaluative Sciences privacy policies, when the number of total users was no larger than 5, this number was suppressed to ensure confidentiality.

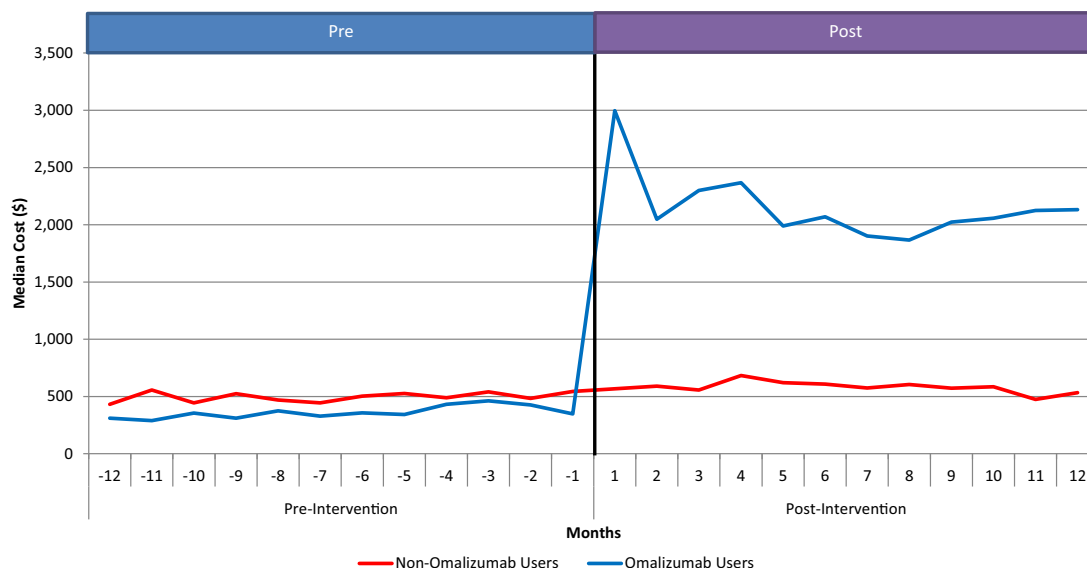


Figure 1. Total health care usage costs for matched omalizumab users and nonusers by month during the pre- and postintervention study periods.

Similarly, omalizumab users used more SABA puffs (296.8; SD, 428.78) in the 90 days before the index date relative to nonusers (204.77; SD, 285.24). The 2 groups had a similar number of OCS prescriptions in the 90 days before the index date. The 2 groups were high users of the health care system, with a large median number of physician office visits in the year before the index date for omalizumab users ($n = 18$; interquartile range, 11–27) and nonusers ($n = 14$; interquartile range, 11–19).

Primary Outcome

Trends in average median health care usage costs were stable for omalizumab users (\$361 per month) and nonusers (\$496 per month) in the year before the intervention date (Fig 1). After intervention, the average median monthly costs per person increased nearly 6-fold for omalizumab users (from \$361 to \$2,157; $P < .0001$), whereas these costs did not change significantly for nonusers (\$85 increase in average monthly costs per person; $P = .59$; Table 3). The average median monthly costs for omalizumab users remained high at \$2,157 during the postintervention period, whereas average median costs for nonusers remained similar to pre-intervention levels in the postintervention period (\$581 per month). There was no significant change in the slope of total health care usage cost among omalizumab users after drug initiation compared with nonusers ($P = .43$).

Secondary Outcomes

Omalizumab users had a higher average rate of asthma-related hospitalizations or ED visits before the intervention (6.6%) compared with nonusers (2.9%). There was no significant change in

the rate of asthma-related hospitalizations or ED visits for omalizumab users ($P = .44$) or nonusers ($P = .99$) between the pre-intervention and postintervention periods. Similarly, the average proportion of subjects with any OCS prescription per quarter was consistently larger among omalizumab users (49.0% per quarter) compared with nonusers (16.8 % per quarter) in the year before the intervention date. After the intervention date, the average proportion of subjects with any OCS prescription remained larger among omalizumab users (42.9% per quarter) compared with nonusers (19.1% per quarter). Although omalizumab users had a higher rate of OCS use (Table 4), we observed no change in the rate of OCS prescriptions associated with the use of omalizumab ($P = .61$). Our findings were similar in our analyses of SABA use and physicians visits (Supplemental Material, available online). In our within-person sensitivity analysis among all omalizumab users ($n = 109$), the results were consistent, with no significant impact of omalizumab initiation on any outcomes studied (Table 5). In our second within-person sensitivity analysis of a subgroup of triple-therapy users ($n = 25$), the results were similar with 1 exception. In the triple-therapy subgroup, there was a statistically significant decrease in the proportion of subjects receiving OCS prescriptions quarterly after omalizumab initiation, from an average of 70.5% users per quarter before the intervention to 50.9% users per quarter after the intervention ($P = .03$; Table 5).

Discussion

Our findings suggest a significant increase in median health care usage costs after the initiation of omalizumab and no significant impact on rates of hospitalizations, physician visits, or OCS use

Table 3
Change in Total Cost of Health Care Usage Before and After Intervention for Omalizumab Users and Matched Controls

Group	Cost/mo (\$), median (range)		Pre-post comparison	
	Before intervention	After intervention	Change in average cost (\$)	P value ^{a,b}
Omalizumab users	361 (289–463)	2,157 (1,867–2,996)	1,796	<.0001
Nonusers	496 (432–557)	581 (476–684)	85	.59

^aP values are derived from transformed and adjusted models.

^bThere was no statistically significant ($P = .43$) difference in differences for the rate of change between groups.

Table 4

Change in Rates of Secondary Outcomes Before and After Intervention in Omalizumab Users and Matched Controls

Outcome	Group	Proportion (%), average (quarterly range)		Pre-post comparison	
		Before intervention	After intervention	Change in proportion (%)	P value ^{a,b}
Asthma-related hospitalization or ED visit	omalizumab user	6.6 (3.2–9.5)	— ^c	— ^c	.44
	nonuser	2.9 (1.9–4.0)	2.8 (2.1–3.7)	–0.1	.99
Oral corticosteroid use	omalizumab user	49.0 (45.3–54.7)	42.9 (38.9–45.3)	–6.1	.99
	nonuser	16.8 (13.9–19.3)	19.1 (17.4–21.6)	2.3	.22

Abbreviation: ED, emergency department.

^aP values are derived from transformed and adjusted models.^bThere was no statistically significant ($P = .53$ and $.61$, respectively) difference in differences for the rate of change between groups for the 2 outcomes.^cIn accordance with Institute for Clinical Evaluative Sciences privacy policies, when the number of total users was no larger than 5, this number was suppressed to ensure confidentiality. When a proportion was used to recalculate the number of users, the proportion was suppressed to avoid residual disclosure issues.

among patients who meet the public drug programs criteria for reimbursement. Our sensitivity analysis shows that in a specific subgroup of patients treated with triple therapy before omalizumab initiation, there could be a benefit in decreased use of OCS prescriptions. Further studies of this subgroup are needed.

The large increase in costs with no indication of a sizable and broad clinical benefit is important to payers who aim to maximize clinical benefit of medications they reimburse. Evidence regarding the effectiveness of omalizumab is derived primarily from clinical trials, which might not translate into real-world practice, where users might be older or have more severe asthma. Current omalizumab coverage might be discordant with demographics of the clinical burden of disease and thus might not be benefiting persons for whom omalizumab is most effective. The results of our study will be important as payers explore options to expand or refine funding eligibility criteria. The results of our sensitivity analysis do not exclude the possibility of some benefit from omalizumab, because there was evidence of lower OCS use in a subset of the population. As a result, policy makers might want to review funding criteria for omalizumab to restrict its use to the population most likely to benefit.

The vast majority of observational studies have been conducted among omalizumab users starting at baseline with no control group of unexposed individuals.^{12–17} The absence of comparator groups in most studies prevents a robust pre-post analysis, which is critical when studying a chronic disease such as asthma in which patients might improve or worsen over time and often regress toward a mean disease state. In contrast, our use of a repeated-measures design and a matched comparator group provides stronger evidence than is currently available. Our study leveraged many matching criteria to generate a comparator group of patients with asthma who were similar in age, sex, and recent health care usage. In the one other observational study that included a comparator group,¹⁷ omalizumab users ($n = 53$) were compared

with a matched usual-care group ($n = 53$), and the investigators reported no significant improvement in the rate of asthma exacerbations, which is consistent with our findings. This study did not conduct a repeated-measures analysis and did not control for disease progression before receiving omalizumab. The within-person repeated-measures analysis used in this study allowed us to account for the trajectory of the disease by comparing users with a matched group of nonusers with similar asthma severity, allowing each subject to also act as the control in a pre-post comparison. More importantly, the repeated-measures analysis decreased the risk of selection bias relative to other study designs by controlling for within-person variation.

Our findings of no association between omalizumab initiation and any outcomes studied might partly reflect differences between the publicly funded population in this study and those included in randomized controlled trials. First, there was a clinically important difference between patients treated with omalizumab in Ontario (and thus included in our study) and those in whom drug benefits have been observed in clinical trials (Table 6). In general, our study population was older (average age, 61) than those included in clinical trials (average age, 43 to 48).²⁵ Therefore, Ontario's criteria for eligibility to receive public coverage for omalizumab might not be targeting omalizumab to the demographic of patients with asthma who might benefit most from this treatment—those who are younger and whose asthma is more typical with less airway remodeling and more reversibility of obstruction.^{26–28} Furthermore, our sensitivity analysis suggests that among patients taking triple therapy, the benefits of omalizumab, in decreased OCS prescriptions, might be more pronounced. The small sample ($n = 25$) of this subgroup is a limitation and should be further explored in future studies. We estimate that a sample size of 34 to 80 individuals, depending on the level of correlation, would be required to detect a statistically significant effect estimate for our subgroup analysis. This estimate assumes a power of 80% and a

Table 5

Results of Sensitivity Analyses in a Cohort of All Omalizumab Users and a Subgroup of Triple-therapy Omalizumab Users

Outcome	Group	Proportion or costs, average (quarterly or monthly range)		Pre-post comparison	
		Before intervention	After intervention	Change	P value
Total cost of health care usage	all omalizumab users	\$381 (294–493)	\$2,374 (1,895–3,105)	\$1,993	<.0001
	triple-therapy subgroup ^a	\$593 (406–760)	\$2,378 (1,843–3,250)	\$1,785	<.0001
Asthma-related hospitalization or ED visit	all omalizumab users	10.3% ^b	6.0% ^b	–4.3% ^b	.19
	triple-therapy subgroup ^a	10–15% ^b	5–10% ^b	–7.2% ^b	.95
Oral corticosteroid use	all omalizumab users	51.6% (45.9–56.9)	46.6% (41.3–50.5)	–5.0%	.67
	triple-therapy subgroup ^a	70.5% (57.1–82.1)	50.9% (46.4–53.6)	–19.6%	.03

Abbreviation: ED, emergency department.

^aTriple therapy is defined as the concurrent use of inhaled corticosteroids, long-acting β -agonists, and long-acting muscarinic antagonists.^bIn accordance with Institute for Clinical Evaluative Sciences privacy policies, when the number of total users was no more than 5, this number was suppressed to ensure confidentiality. We have supplied a summary average of all events from all quarters. When a proportion was used to recalculate the number of users, the proportion was suppressed to avoid residual disclosure issues.

Table 6
Comparison of Ontario Omalizumab Users and Clinical Trial Population

	Ontario population	Clinical trial population ^a
Age (y), mean (SD)	61.1 (14.0)	41.6 (14.8)
Men, %	32.6	40.5
Serum IgE (IU/mL), range	30–700 ^b	20–1,118
Prior LABA use, %	75 ^c	61.2

Abbreviations: IgE, immunoglobulin E; LABA, long-acting β -agonist.

^aBased on information from a systematic review by Korn et al.¹²

^bBased on reimbursement criteria.²²

^cApproximated because of censoring.

2-sided significance level of .05. A test for correlated proportions with a design effect (to account for repeated measures) that varied the intraclass correlation from 0.05 to 0.2 was used. The subgroup analysis is an important area of future research to help select the patient population most likely to benefit from omalizumab therapy. Second, effect sizes in clinical trials for decrease in exacerbations, although significant, were small and therefore might require larger observational studies than current usage in Ontario allows.^{8,29} For example, compared with placebo, omalizumab users with severe asthma were more likely to withdraw from corticosteroids (relative risk, 1.80; 95% confidence interval, 1.42–2.28) and have fewer asthma exacerbations (relative risk, 0.57; 95% confidence interval, 0.48–0.66).²⁹ However, the numbers needed to treat to avoid an asthma-related hospitalization among patients with moderate to severe disease were 33 (Rodrigo et al.²⁹) and 40 (Normansell et al.⁸) in these trials. A larger study by Normansell et al.⁸ found a lack of supportive evidence of efficacy in patients with severe asthma treated with OCSs or ICSs. Discordance in detecting exacerbations also could be due to our conservative definition of exacerbations limited to only hospitalizations and ED visits, which in a trial setting is often more liberal and includes absence from work or school, physician visits, and increases in medication use. Third, adherence to therapy has been cited as a possible explanation for decreased effectiveness of omalizumab outside clinical trials. In our study we found that a large majority of users were adherent to therapy at 6 (85.3%) and 12 (69.5%) months, only slightly lower than adherence rates found in randomized controlled trials, which ranged from 80.6% to 92.9%.³⁰

Some limitations of our study warrant emphasis. First, we did not have access to certain clinical variables such as IgE levels, and omalizumab users might have differed from nonusers on unmeasured clinical factors. Also, residual differences in the type and number of asthma medications used persisted despite our attempts at matching. Therefore, our failure to observe differences in comparisons between users and nonusers might have been affected by residual confounding by severity. However, our within-person sensitivity analysis of the entire cohort of omalizumab users demonstrated consistent findings, adding robustness to our findings that omalizumab was not associated with changes in clinical outcomes of interest in a real-world setting. Second, we did not have access to patient-reported outcomes, which would have allowed for more robust and sensitive analysis. Third, we did not explore the impact of adherence and dose scheduling on outcomes. We found variation in the scheduled administration of omalizumab; the most common was biweekly (41.1%) followed by weekly (36.8%) and monthly (22.1%).

Real-world evidence of the effectiveness of omalizumab for the treatment of asthma is limited. Our results found that omalizumab could have limited effectiveness and increased costs in currently reimbursed populations, specifically older patients. Further exploration of specific subpopulations that might benefit from omalizumab is essential to payers as they design strategies to reimburse more cost-effective treatment options.

Supplementary Data

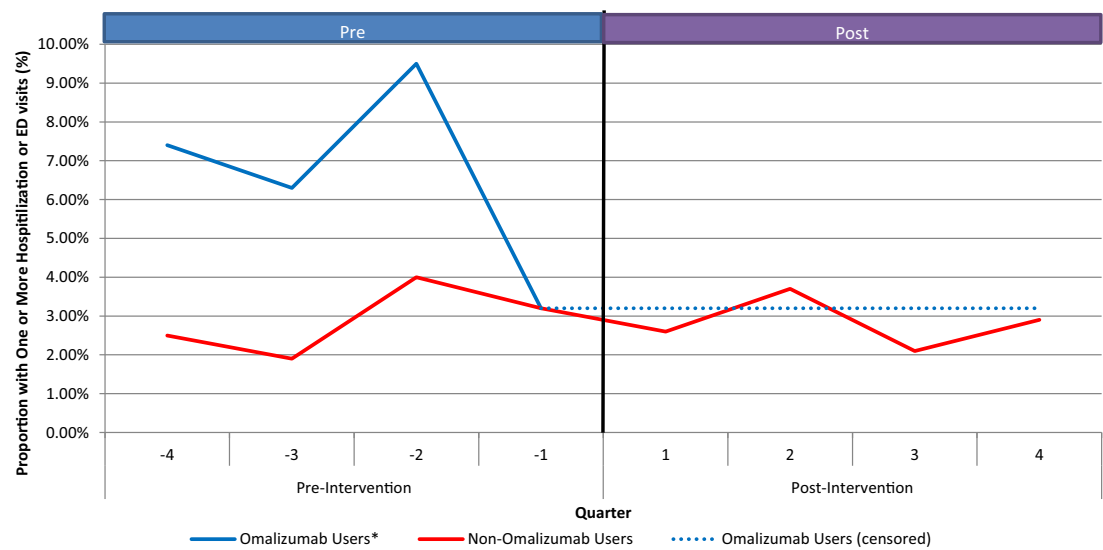
Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.08.016>.

References

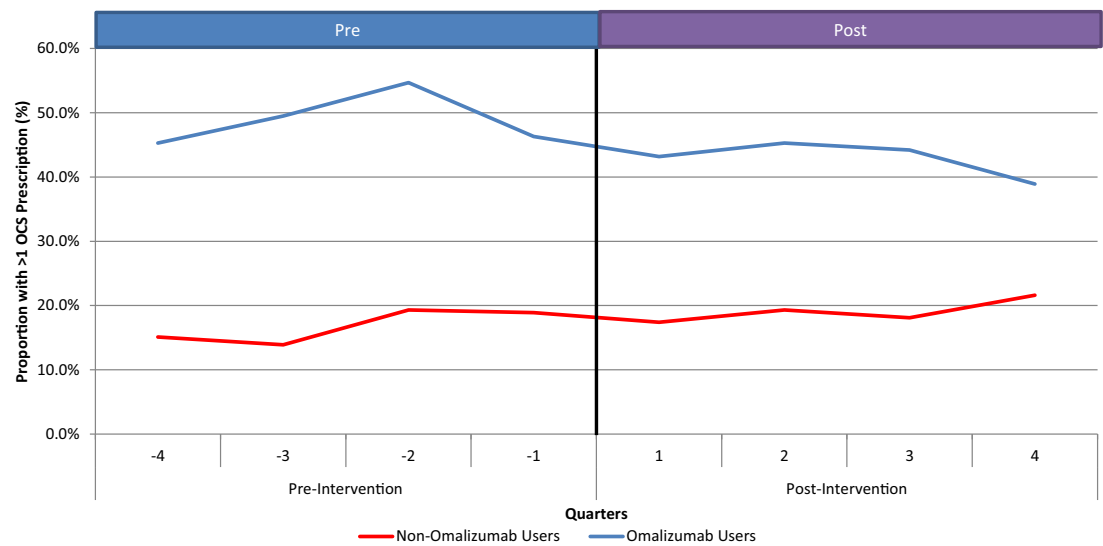
- [1] FitzGerald J, Bateman E, Boulet L. *Global strategy for asthma management and prevention. Global Initiative for Asthma*. <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>. Published 2012.
- [2] Loughheed MD, Lemiere C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J*. 2012;19:127–164.
- [3] Hekking PP, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135:896–902.
- [4] Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184–190.
- [5] Buhl R. Anti-IgE antibodies for the treatment of asthma. *Curr Opin Pulm Med*. 2005;11:27–34.
- [6] Sandstrom T. Targeting immunoglobulin E as a novel treatment for asthma. *Curr Allergy Asthma Rep*. 2005;5:109–115.
- [7] Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol*. 2008;122:569–573.
- [8] Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1:CD003559.
- [9] Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18:254–261.
- [10] Holgate S, Chuchalin A, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34:632–638.
- [11] Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy*. 2005;60:302–308.
- [12] Korn S, Thielen A, Seyfried S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med*. 2009;103:1725–1731.
- [13] Molimard M, de Blay F, Didier A, et al. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med*. 2008;102:71–76.
- [14] Tzortzaki EG, Georgiou A, Kampas D, et al. Long-term omalizumab treatment in severe allergic asthma: the South-Eastern Mediterranean “real-life” experience. *Pulm Pharmacol Ther*. 2012;25:77–82.
- [15] Vennema Mdel C, Perez De Llano L, Bardagi S, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry—some new approaches. *J Asthma*. 2012;49:416–422.
- [16] Verma P, Randhawa I, Klaustermeyer WB. Clinical efficacy of omalizumab in an elderly veteran population with severe asthma. *Allergy Asthma Proc*. 2011;32:346–350.
- [17] Wittchen HU, Muhlig S, Klotsche J, et al. Omalizumab versus ‘usual care’: results from a naturalistic longitudinal study in routine care. *Int Arch Allergy Immunol*. 2012;159:83–93.
- [18] Abraham I, Alhossan A, Lee CS, et al. ‘Real-life’ effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy*. 2016;71:593–610.
- [19] Mamdani M, Juurlink DN, Kopp A, et al. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. *BMJ*. 2004;328:1415–1416.
- [20] Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009;180:713–718.
- [21] Khan S, Moore JE, Gomes T, et al. The Ontario Drug Policy Research Network: bridging the gap between research and drug policy. *Health Policy*. 2014;117:392–398.
- [22] Gershon AS, Guan J, Wang C, et al. Trends in asthma prevalence and incidence in Ontario, Canada, 1996–2005: a population study. *Am J Epidemiol*. 2010;172:728–736.
- [23] Ontario Ministry of Health and Long-Term Care. *Ontario Public Drug Programs. Exceptional Access Program (EAP) reimbursement criteria for frequently requested drugs*. http://health.gov.on.ca/en/pro/programs/drugs/eap_criteria.aspx. Published 2015. Accessed September 26, 2017.
- [24] Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ*. 2005;330:960–962.
- [25] Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Technol Assess*. 2013;17:1–342.
- [26] Rasmussen F, Taylor DR, Flannery EM, et al. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV1/vital capacity ratio: a

- longitudinal population study from childhood to adulthood. *Am J Respir Crit Care Med*. 2002;165:1480–1488.
- [27] Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376:803–813.
- [28] Lehmann S, Vollset SE, Nygaard HA, et al. Factors determining performance of bronchodilator reversibility tests in middle-aged and elderly. *Respir Med*. 2004;98:1071–1079.
- [29] Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139:28–35.
- [30] Caminati M, Senna G, Stefanizzi G, et al. Drop-out rate among patients treated with omalizumab for severe asthma: literature review and real-life experience. *BMC Pulm Med*. 2016;16:128.

Supplemental Material



eFigure 1. Proportion of subjects with at least 1 asthma-related hospitalization or emergency department (ED) visit for matched omalizumab users and nonusers by quarter during the pre- and postintervention study periods. In accordance with Institute for Clinical Evaluative Sciences privacy policies, when the number of total users was no larger than 5, this number was suppressed to ensure confidentiality. When a proportion was used to recalculate the number of users, the proportion was suppressed to avoid residual disclosure issues.



eFigure 2. Proportion of subjects with at least 1 oral corticosteroid (OCS) prescription for matched omalizumab users and nonusers by quarter during the pre- and post-intervention study periods.

eTable 1

Change in Proportion of SABA Inhaler Use and Physicians Visits Between Pre- and Postintervention Periods

Outcome	Group	Proportion, average (quarterly range)		Pre-post comparison	
		Before intervention	After intervention	Change in units	P value ^{a,b}
>400 puffs of SABA use per quarter	omalizumab user	36.4% (29.5–41.1)	42.4% (40.0–46.3)	6.0%	.35
	nonuser	30.0% (27.0–31.4)	31.0% (27.5–33.1)	1.0%	.72
Physician visits per quarter	omalizumab user	4.8 (4.5–5.1)	5.2 (5.0–5.2)	0.4%	.06
	nonuser	4.0 (3.8–4.4)	4.0 (3.9–4.2)	0 visit	.07

Abbreviation: SABA, short-acting β -agonist.^aP values are derived from transformed and adjusted models.^bThere was no statistically significant ($P = .52$ and $.46$, respectively) difference in differences for the rate of change between groups for the 2 outcomes.**eTable 2**

Components of Monthly Total Health Care Costs for Matched Omalizumab Users and Nonusers During the Pre- and Postintervention Study Periods by Major Contributing Cost Categories

Cost component	Group	Cost (\$), monthly mean (range) ^a	
		Before intervention	After intervention
Total	omalizumab user	654 (412–904)	2,787 (2,383–3,309)
	nonuser	1,028 (782–1,339)	1,148 (847–1,660)
Drug costs	omalizumab user	207 (173–248)	2,204 (1,921–3,021)
	nonuser	280 (260–295)	326 (287–503)
Emergency department visits	omalizumab user	33 (15–76)	33 (18–47)
	nonuser	39 (23–54)	44 (26–64)
Inpatient hospitalizations	omalizumab user	83 (0–228)	195 (0–558)
	nonuser	196 (45–56)	245 (78–528)
Physician services	omalizumab user	204 (151–248)	222 (173–281)
	nonuser	204 (152–247)	208 (156–271)

^aValues are weighted monthly means that are based on weighted matched controls. These costs include all individuals, even those with 0 cost, in any category.