



Does Omalizumab Make a Difference to the Real-life Treatment of Asthma Exacerbations?

Results From a Large Cohort of Patients With Severe Uncontrolled Asthma

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Background: Omalizumab has been shown to decrease the risk of hospitalization or ED visits in patients with uncontrolled severe allergic asthma compared with placebo. This longitudinal study observed the conditions under which omalizumab is prescribed in real-life settings and assessed whether its use as an add-on therapy alongside standard treatments decreases the risk of severe asthmatic exacerbations.

Methods: A cohort of adult patients with uncontrolled severe asthma despite optimal treatment with inhaled and oral corticosteroids and a long-acting β_2 -agonist but no treatment with omalizumab upon entry was assembled. Risk of hospitalization or ED visits for asthma exacerbation was assessed using the Andersen-Gill extension of the Cox model for repeated events, controlling for age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, allergic rhinitis, treatment, and hospitalization or ED visits for asthma in the 2 months prior to omalizumab treatment.

Results: Overall, 163 physicians recruited 767 patients, of whom 374 took omalizumab at least once (mean observation period, 20.4 months). Omalizumab use was associated with an adjusted relative risk of 0.57 (95% CI, 0.43-0.78) for hospitalization or ED visits for asthma. In users of omalizumab, the adjusted relative risk of hospitalization or ED visits for asthma during omalizumab treatment vs nontreatment periods was 0.40 (95% CI, 0.28-0.58).

Conclusions: Add-on omalizumab is associated with a significantly decreased risk of hospitalization or ED visits in patients with uncontrolled severe asthma in real-life practice.

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Abbreviations: AHR = adjusted hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist

Asthma affects 300 million people worldwide, accounting for one in 250 deaths and 15 million disability-adjusted life years lost annually.^{1,2} Up to 5% of adult patients have persistent symptoms and frequent exacerbations despite treatment with medium- to high-dose inhaled corticosteroids (ICSs) plus a long-acting β_2 -agonist (LABA).^{3,4} Potential consequences of uncontrolled disease in this patient subgroup, including fatal or near-fatal asthma exacerbations, represent an unmet clinical need with a disproportionate use

of health-care resources. An increase from medium to high doses of ICSs provides relatively little additional benefit.⁵ Moreover, adding oral glucocorticosteroids is associated with severe side effects. Alternative treatments, therefore, are necessary.

Evidence indicates that 50% to 80% of difficult-to-treat patients have an allergic component, with IgE playing a key role in triggering and maintaining allergic airway inflammation.⁶⁻⁹ Omalizumab, a recombinant monoclonal anti-IgE antibody, has demonstrated

efficacy in clinical trials conducted in patients with moderate to severe and severe persistent allergic (IgE-mediated) asthma, reducing the risk of exacerbations, hospitalization, and ED visits.^{6,10} The European Medicines Agency approved omalizumab for the treatment of inadequately controlled severe persistent allergic asthma despite the use of high-dose ICS plus LABA.⁴ Omalizumab was granted prescription coverage by the national health insurance in France in 2006 for this indication provided that the manufacturer conducted an independent postmarketing usage and real-life effects study. Herein, we report the observations of the conditions under which omalizumab was prescribed and assess whether the real-life use of omalizumab would result in a decreased risk of severe asthma exacerbations as estimated by the number of asthmatic episodes requiring hospitalization or ED visits.

A cohort of patients with severe uncontrolled asthma free of omalizumab treatment at entry was historically assembled and described before and after marketing omalizumab. Physicians were free to prescribe drugs that they considered appropriate for their patients. Therefore, the effect of omalizumab treatment was observed under natural conditions by comparing the experience of patients before and after initiation of omalizumab in addition to that of patients whose asthma was uncontrolled despite the use of ICS plus LABA and no treatment with omalizumab.

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MATERIALS AND METHODS

Centers and Participants

All French physicians recorded as pulmonologists were first invited by letter to participate in the study during June 2007; subsequent approaches were made by telephone. Participating pulmonologists identified all consenting patients aged ≥ 18 years with uncontrolled severe asthma and followed by the investigator for at least 1 year prior to identification. Asthma was considered uncontrolled if exacerbations had occurred in the previous year despite treatment with 1,000 μg beclomethasone equivalent, one LABA, and at least one of the following: (1) 5 mg prednisone equivalent per day for at least 6 months; (2) at least three courses of oral corticosteroids over 1 year; or (3) two courses of oral corticosteroids over 1 year, with at least one recent FEV₁ measurement $< 80\%$ predicted or personal best.

Entry into the cohort was set at 10 months before patient identification. Any patient who received omalizumab on or 2 months prior to that date were excluded. Patients were also excluded if unable to communicate or had a history of aspergillosis or Churg-Strauss syndrome. Participants were followed until the end of the study or loss to follow-up.

The study protocol was submitted to the Ethical Review Committee of Paris-Ile de France III (Comité de Protection des Personnes Ile de France III) and approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). All participants signed an informed consent form.

Collected Information

Patients were described according to the following risk factors: sex, age, BMI, history of asthma, smoking (current, past, or never), allergic rhinitis, urticaria, angioedema, allergy to drugs, gastroesophageal reflux, presence of chronic comorbid conditions, and allergies. Allergies were ascertained further by results from skin and serologic tests reported in the medical charts and were recorded as certain when a perennial aeroallergen or a specific IgE was recorded as positive, absent (nonallergic) when both were recorded as negative, and uncertain in all other instances. Circulating serum IgE levels were also reported.

To minimize observation bias, all data on drug exposure and outcomes (hospitalization and ED visits) were obtained by clinical research associates within the research team and independent of the investigator. The clinical research associates extracted this information through a medical chart review conducted on site. Several visits were necessary for centers with large patient recruitment.

The prescribed medicines were listed with the corresponding dates of prescription or renewal, dosage, and eventual dates of discontinuation. For omalizumab, motives for discontinuation were classified into adverse event occurrence, clinical improvement, patient preference, and none. Adverse drug reactions were recorded, and serious or severe adverse drug reactions were expeditiously reported.¹¹ All visits to EDs or hospitalization episodes (with corresponding dates and duration) were recorded for the year before and during the prospective follow-up period.

Statistical Analysis

Population Exposure Times: Population exposure times were calculated by adding the individual contributions to the cohort and were expressed in person-years (overall observation period from entry to end of follow-up). Population exposure times were categorized according to patients' exposure status into active omalizumab time, definite nonomalizumab time, and indeterminate exposure time. Active omalizumab time was defined from 60 days after the start of the first prescription (with time lag allowed to

ensure induction of the drug), followed by a period covered by successive prescriptions until 60 days following eventual drug discontinuation (accounting for residual drug effects).¹² Prescriptions were considered successive if <1 month apart. If >1 month elapsed between a prescription and its renewal, the drug was considered discontinued. If omalizumab was prescribed again at a later date, it was considered a new start. The omalizumab induction time-lag period of 60 days after any new start was considered an indeterminate exposure time. The 60-day period following the 60 days of omalizumab's residual effect time was considered a wash-out period and classified as indeterminate exposure time. The definite nonomalizumab time accounted for all the time without active omalizumab or indeterminate exposure status. The 2 months preceding the period of observation characterized the cohort at entry. Similarly, the 2 months before each change in the drug exposure status (active omalizumab or definite nonomalizumab) were used to characterize the status of risk factors applying to the new exposure status. Severe exacerbation was defined as an exacerbation requiring ED visits or hospitalization; severe exacerbation rates were estimated according to omalizumab exposure by dividing the number of asthmatic episodes requiring ED visits or hospitalization episodes by the population time accumulated in the category considered. Rates were estimated for the whole observational period and preidentification and postidentification follow-up periods separately. ED visits or hospitalization episodes separated by <14 days were considered single events.

Sample Size Calculations: Patients with no subsequent visits after giving consent (ie, no follow-up) were described and compared with followed-up patients through risk factor analysis, using Student *t* test for continuous variables and Pearson χ^2 test for categorical variables. Such tests compared patients who eventually started treatment with omalizumab during the follow-up period with those who did not. The propensity to be prescribed omalizumab was assessed by logistic regression where omalizumab prescription (yes, no) was the predicted variable and the predictive variables were year of initiation and factors associated with omalizumab use and severe exacerbation episodes in univariate analysis, such as age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, use of oral corticosteroids or leukotriene receptor antagonists (LTRAs), and severe exacerbation episodes in the 2 months preceding the beginning of any new exposure status.

Relative hazards for omalizumab exposure were estimated using the Andersen-Gill extension of the Cox model, allowing for repeated events.¹³ Nonadjusted hazard ratios were estimated as well as hazard ratios adjusted for the propensity score as described.

Rates of hospitalization or ED visits during periods with and without omalizumab were analyzed exclusively for patients treated with omalizumab at least once during follow-up. To further explore potential characteristics to be associated with a positive outcome, we stratified patients according to who would be considered a best candidate for omalizumab. Analyses were then conducted for those with and without confirmed allergic status; with and without use of oral corticosteroids at entry; and with and without allergic rhinitis, angioedema, urticaria, or allergy to drugs. Additional analyses explored the effects of factors associated with omalizumab use and exacerbation risk. One analysis matched sex and age (± 3 years), and other analyses were conducted separately in patients with and without allergic rhinitis, LTRA use, or gastroesophageal reflux. Finally, sensitivity analyses were performed with various methods to estimate adjusted relative hazards, including factors individually rather than through a propensity score, using the Prentice-Williams-T extension of the Cox model with gap time for repeated events instead of the Andersen-Gill extension. An intention-to-treat analysis based on initial omalizumab exposure considered patients who had discontinued omalizumab but were still exposed throughout the entire follow-up period. The

study sample size was set so that a difference in the yearly rates of exacerbations of 30% against 20% in the periods of omalizumab use and nonuse, respectively, could be detected with 95% confidence (ie, for two-sided 5% type 1 error) and 80% power. These exacerbation rates were based on data from previously published trials.¹⁴⁻¹⁶ A minimum of 300 person-years both in the active omalizumab and definite nonomalizumab categories of exposure was required to accomplish this objective. Statistical analysis was performed using the SAS, version 9.1 (SAS Institute Inc) statistical software.

RESULTS

Of the 2,692 pulmonologists invited to participate, 163 (6%) agreed by including at least one patient. Participating pulmonologists were spread throughout the territory; 54% were hospital practitioners, and 41% were professionals in private practice. Overall, 982 patients with uncontrolled severe asthma were identified, of whom 828 (84%) were eligible and willing to participate in the study. The remaining noneligible patients withdrew their consent ($n = 10$), were not free of omalizumab use in the 2 months preceding entry ($n = 129$), did not meet other eligibility criteria ($n = 5$), or emerged from centers unable to accommodate the onsite visits ($n = 10$). Table 1 summarizes the characteristics of the cohort participants. Excluded omalizumab users compared with participants for all the risk factors listed in Table 1 except female sex (77% excluded vs 64% included, $P < .01$). No reason was found to explain this difference.

Among the patients meeting the eligibility criteria, 767 (92.6%) were seen at least once after giving consent, and 61 (7.4%) were lost to follow-up. Overall, patients with follow-up did not appear to differ significantly from those without follow-up on any of the risk factors studied except for the distribution across age categories. Patients who were followed up were older, and a higher proportion was taking omalizumab. Patients without follow-up were not considered for the main analysis. The 767 studied patients accumulated 1,281.5 person-years of observation (mean, 1.67 years each) plus 127.8 person-years for the 2 months preceding entry into the cohort, 639.2 person-years for the period before identification (10 mo/patient) and 642.3 person-years thereafter (mean, 10.4 months). Regarding the exposure status, 298.9 person-years were classified as active omalizumab time, 909.7 person-years as definite nonomalizumab time, and 72.9 person-years as indeterminate exposure time.

A total of 445 severe exacerbations occurred during the entire follow-up period (360 hospitalizations and/or 106 ED visits), with a mean rate of severe exacerbations of 30.6 per 100 person-years. The strongest predictor of severe exacerbation (Table 2) was either previous hospitalization for asthma (adjusted hazard ratio [AHR], 2.73; 95% CI, 2.00-3.73) or previous ED visit for asthma (AHR, 1.92; 95% CI, 1.11-3.31).

Table 1—Characteristics of Cohort Participants

Variable	Lost to Follow-up (n = 61)	Followed Up (n = 767)	P Value
Female sex	40 (66)	485 (63)	.72
Age, y	51.0 ± 15.8	54.4 ± 15.6	.10
18-40	19 (31)	143 (19)	.04
41-60	28 (46)	366 (48)	...
> 60	14 (23)	258 (34)	...
Nonsmoker	41 (67)	509 (66)	.89
BMI ≥ 30 kg/m ²	16 (26)	181 (24)	.11
Specific allergy	44 (72)	486 (68)	.30
Total circulating IgE, IU/mL			.19
0-30	1 (2)	59 (8)	
30-700	28 (47)	403 (53)	
700-1,000	2 (3)	30 (4)	
≥ 1,000	5 (8)	62 (8)	
Not reported	23 (39)	203 (27)	
Comorbid conditions			
Allergic rhinitis	41 (67)	426 (56)	.09
Angioedema	6 (10)	71 (9)	.89
Urticaria	7 (11)	119 (16)	.40
Allergy to drugs	9 (9)	184 (24)	.09
Gastroesophageal reflux	22 (36)	287 (38)	.82
Severe exacerbations	3 (4.9)	74 (9.7)	.29
Duration of asthma, y	25.6 ± 16.0	27.3 ± 17.1	.44
Medication at start			
ICS	60 (98)	751 (98)	.81
LABA mimetic	59 (97)	746 (97)	.80
Oral corticosteroid	23 (37.7)	309 (40.3)	.69
Omalizumab	14 (23)	284 (37)	.03
LTRA	33 (54.1)	365 (47.6)	.33
Other	18 (30)	265 (35)	.42

Data are presented as No. (%) or mean ± SD. ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist.

Other significant factors were younger age and gastroesophageal reflux history.

Of the 767 participants, 393 (51.9%) were never prescribed omalizumab, whereas 374 (48.1%) were prescribed omalizumab. Among these 767 patients with severe uncontrolled asthma, 163 (21.3%) took 5 mg prednisone equivalent per day for at least 6 months, 342 (44.6%) took at least three courses of oral corticosteroids over 1 year, and 336 (43.8%) took two courses of oral corticosteroids over 1 year, with at least one recent FEV₁ measurement <80% predicted or personal best. Among participating pulmonologists, 34 (20.8%) never prescribed omalizumab. Active omalizumab time accumulated 298.9 person-years, that is, 24.7% of the active time in the cohort.

Skin and serologic tests used to diagnose allergy were reported in 81.6% and 63.1%, respectively, of the 767 participants. Allergies were ascertained as certain in 486 (63.5%), absent (nonallergic) in 101 (13.2%), and uncertain in 178 (23.3%). IgE values were missing in some instances, particularly for patients not treated with omalizumab, because monitoring of this parameter was not mandatory for such patients. For patients treated at least once with omalizumab, titration of IgE was missing in just 4% (Table 3). Patients

receiving omalizumab were more frequently confirmed as allergic compared with nonusers (Table 3), with 94% showing total circulating IgE levels at ≥30 IU/mL (against 39% of nonusers); equally, patients receiving omalizumab experienced allergic rhinitis more often (confirmed by LTRA treatment). Patients receiving omalizumab were also significantly younger (49.7 ± 14.6 years vs 58.8 ± 15.2 years) and more likely to be former smokers. Users and nonusers did not differ on other variables, and notably, assessment of asthma showed a similar severity and lifetime duration profile between the two groups.

Among the 374 patients taking omalizumab, 61 (16.3%) eventually stopped completely during follow-up because of lack of efficacy (18 [4.8%]), adverse event occurrence (14 [3.7%]), clinical improvement (8 [2.1%]), and patient preference or other reason (20 [5.3%]), and the motive was not reported for one patient (0.3%). Three deaths occurred during follow-up (none of which in patients exposed to omalizumab).

Table 4 shows the rates of severe exacerbations according to exposure to omalizumab. These account for 909.7 per 100 person-years in the absence of omalizumab treatment and 298.9 per 100 person-years during its active use. Hospitalization rates among

Table 2—Rates and Risk Factors for Severe Exacerbations (Hospitalization and/or ED Visits) (n = 445)

Variable	Rate per 100 Person-y	Adjusted Rate Ratio (95% CI)
Sex		
Female	32.4	1.14 (0.90-1.44) ^a
Male	26.6	Reference
Age, y		
18-40	35.0	1.50 (1.03-2.20) ^a
41-60	31.0	1.22 (0.93-1.61) ^a
≥ 61	26.7	Reference
Smoking		
Current	42.6	1.25 (0.87-1.81) ^a
Past	29.6	1.08 (0.82-1.43) ^a
Never	28.7	Reference
BMI, kg/m ²		
≥ 30	37.8	1.09 (0.82-1.43) ^a
> 25-29	24.2	0.80 (0.61-1.06) ^a
≤ 25	30.5	Reference
Specific allergy		
Certain	28.0	0.99 (0.70-1.38) ^b
Uncertain	30.5	0.88 (0.61-1.25) ^b
No	40.8	Reference
Comorbid conditions of interest		
Allergic rhinitis, angioedema, urticaria, or allergy to drugs	28.0	0.75 (0.58-0.97) ^b
Gastroesophageal reflux	40.0	1.48 (1.18-1.85) ^b
Recent ^c severe exacerbation	83.1	2.68 (1.98-3.63)
Previous hospitalization	90.4	2.73 (2.00-3.73) ^b
Previous ED visit	73.9	1.92 (1.11-3.31) ^b
Recent ^d medication		
Oral corticosteroid	41.2	1.28 (0.99-1.64) ^b
LTRA	26.9	0.81 (0.64-1.02) ^b

See Table 1 legend for expansion of abbreviation.

^aAgainst reference.

^bCategorical variable yes vs no.

^cHospitalization or ED visits.

^dIn the 2 mo before entry.

participants were 33.4 and 20.8 per 100 person-years during nonuse and use of omalizumab, respectively. The AHR for all risk factors considered was 0.57 (95% CI, 0.43-0.78), which was very similar to the unadjusted hazard ratio (0.56).

When only patients who used omalizumab at least once were considered, the rate of severe exacerbations dropped from 32.3 per 100 person-years in the absence of use (definite nonomalizumab time) to 20.8 per 100 person-years during use (active omalizumab time) (AHR, 0.40; 95% CI, 0.28-0.58). When only allergic patients were retained, the rate of severe exacerbations was 28 per 100 person-years overall, with 31.9 and 20.2 per 100 person-years during the definite nonomalizumab and active omalizumab times, respectively (AHR, 0.53; 95% CI, 0.39-0.75). When only patients treated with oral corticosteroids at entry were retained, the rate of severe exacerbations was associated with an AHR of 0.76 (95% CI, 0.48-1.21) vs an AHR of 0.46 (95% CI, 0.31-0.68) for those

without oral corticosteroids at entry. Further, when only patients with allergic rhinitis, angioedema, urticaria, or allergy to drugs were retained, the rate of severe exacerbations was associated with an AHR of 0.60 (95% CI, 0.42-0.84) vs an AHR of 0.46 (95% CI, 0.25-0.91) for those without any of these allergies.

In the sensitivity analyses, AHRs were (1) 0.62 (model using individual risk factors), (2) 0.66 (Prentice-Williams-T model), (3) 0.45 (study matched on sex and age), (4) 0.65 (intention-to-treat analysis), (5) 0.42 (LTRA users), (6) 0.71 (LTRA nonusers); (7) 0.55 (patients with allergic rhinitis), and (8) 0.58 (patients with gastroesophageal reflux). CIs varied according to the size of the subgroups (data not shown).

The rate of oral corticosteroids courses was 73.8 and 49.2 per 100 patient-years in the absence of and during omalizumab use, respectively ($P = .0001$). The impact on the number of dose increases (> 20 mg over baseline) for continuous use of oral corticosteroids was not significant (nonusers, 9.1 per 100 person-years; during omalizumab, 7.3 per 100 person-years; $P = .36$).

DISCUSSION

Omalizumab has proven effective in double-blind placebo-controlled trials.¹⁷ We believe that this is the first study to assess the real-life impact of omalizumab in severe asthmatic exacerbations requiring hospitalization or ED visits in patients with severe uncontrolled asthma. The use of add-on omalizumab in such patients is statistically and clinically significant, decreasing the relative rate of severe episodes between 40% and 65% compared with nonuse of the drug. Of particular note, the rate of asthma exacerbations diminishes dramatically (60%) in patients prescribed omalizumab at least once compared with before and after treatment periods. Such improvement is very unlikely to be explained by confounding factors because the same patients were involved, and any status change before prescription was controlled for. The fact that similar rates of hospitalization (circa 30 per 100 person-years) were observed in patients not taking omalizumab and in those who had never taken omalizumab is also reassuring.

The magnitude of risk reduction found in this real-life study was similar to results from clinical trials,^{15,16} where the addition of omalizumab to standard asthma therapy showed a decreased risk of asthma exacerbations at the end of both stable and adjustable steroid phases. It has also been reported that hospitalizations for asthma exacerbations favored omalizumab (3.0% vs 7.4%) over periods where omalizumab was not used.¹⁵ Both clinical trials reported a significant corticosteroid-sparing effect of omalizumab,^{15,16} a finding that is similar to the rates found in the present real-life

Table 3—Comparison Between Patients Who Eventually Received Omalizumab and Those Who Did Not With the Corresponding Propensity

Variable	Omalizumab Not Used (n = 393)	Omalizumab Used at Least Once (n = 374)	Propensity to Use Omalizumab ^{a,b}
Sex			
Female	63	63	1.18 (0.87-1.61) ^c
Male	37	37	Reference
Age, y	58.8 ± 15.2	49.7 ± 14.6	< .001
18-40	11	26	2.93 (1.88-4.54) ^c
41-60	45	51	1.93 (1.41-2.64) ^c
≥ 61	44	23	Reference
Smoking			
Current	9	12	1.14 (0.70-1.86) ^c
Past	21	27	1.60 (1.12-2.28) ^c
Never	71	61	Reference
BMI, kg/m ²	26.3 ± 6.3	26.7 ± 6.1	.31
≥ 30	24	24	1.12 (0.78-1.60) ^c
> 25-29	28	29	1.20 (0.86-1.68) ^c
≤ 25	48	47	Reference
Specific allergy			
Certain	45	84	5.30 (3.40-8.25) ^c
Uncertain	35	10	1.07 (0.66-1.74) ^c
No	20	6	Reference
Total IgE, IU/mL	326 ± 587	531 ± 974	< .001
Not done	48	4	
0-30	13	2	
30-700	33	75	
700-1000	1	7	
≥ 1,000	5	12	
Comorbid conditions of interest			
Allergic rhinitis, angioedema, urticaria, or drug allergy	57	81	2.0 (1.46-2.74) ^d
Gastroesophageal reflux	38	37	0.88 (0.65-1.18) ^d
Medications ^e			
ICS	97	99	NCV
LABA mimetic	96	98	NCV
Oral corticosteroid	24	27	1.20 (0.78-1.87) ^d
LTRA	36	56	1.67 (1.18-2.36) ^d
Recent severe exacerbation ^f	6.6	7.5	0.88 (0.48-1.64) ^d
Asthma duration, y	28.2 ± 18.1	26.5 ± 15.9	.50

Data are presented as % or mean ± SD, unless otherwise indicated. NCV = not converged. See Table 1 legend for expansion of other abbreviations.

^aData are presented as adjusted OR (95% CI) or *P* value.

^bORs adjusted for all the risk factors listed in the table.

^cAgainst reference.

^dCategorical variable yes vs no.

^eMedication taken in the initial 2-mo observation period or return to nonomalizumab use; medication in the 2 mo preceding omalizumab use.

^fHospitalization or ED visits in the 2 mo preceding exposure status.

study in the absence of or during omalizumab use (73.8 vs 49.2 per 100 persons-years, respectively; *P* < .001).

Chance is an unlikely factor because the 95% CI upper bound around the main result is 0.74. We also explored whether a regression to the mean could explain the findings, and experiencing a recent severe asthmatic exacerbation was not associated with prescribing omalizumab. Instead, a placebo effect is likely to have occurred because patients treated with omalizumab are closely monitored while under treatment. This is partly desirable, with compliance and fine-tuning of treatments being relevant goals to managing this debilitating disease. Despite a low rate

of discontinuation because of inefficacy, patients maintained on treatment were likely to be responders. The two phenomena may explain why the observed effect seems stronger than that observed against placebo in pivotal studies (30% annual risk vs circa 20% in the present study).¹⁵⁻¹⁷ None of the risk factors associated with omalizumab use decreased the risk for hospitalization or ED visits.

As expected, omalizumab users were more likely to be allergic. Similar results were found when allergy was controlled for in the analysis.

Today, there are neither clinical nor biologic markers to predict the success or failure of add-on

Table 4—Rates and AHRs of Severe Exacerbations Following Exposure or Not to Omalizumab

Variable	Rate per 100 Person-y			UHR ^a	AHR ^b (95% CI)
	Total	Absence of Omalizumab	During Omalizumab Use		
Hospitalization and ED visit					
Entire cohort (n = 767, 1,208 person-y)	30.6	33.4	20.8	0.56	0.57 (0.43-0.78)
In users of omalizumab at least once (n = 374, 564.9 person-y) during omalizumab use (298.9 person-y) and in the absence of omalizumab use (265.9 person-y)	26.2	32.3	20.8	0.53	0.40 (0.28-0.58)
Allergic patients only (n = 486, 750 person-y)	28.0	31.9	20.2	0.50	0.53 (0.39-0.75)
Use of oral corticosteroids (entire cohort)	...	73.8	49.2	<i>P</i> < .001	...

AHR = adjusted hazard ratio; UHR = unadjusted hazard ratio. See Table 1 legend for expansion of other abbreviation.

^aCox proportional hazard model.

^bAndersen-Gill extension of the Cox proportional hazard model for correlated data, adjusted with a propensity score for age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, allergic rhinitis, use of oral corticosteroids or LTRAs, and recent severe exacerbations.

omalizumab in patients for whom the drug is indicated (ie, patients whose asthma is severe and treated at most by conventional drugs). It appears that allergic asthma or condition comorbidities, such as allergic rhinitis, urticaria, angioedema, or drug allergy, do not seem to modify the association between omalizumab and the outcome compared with the general result (AHR, 0.53 and 0.60, respectively, vs 0.57). However, it seems that patients treated with oral corticosteroids at entry are unlikely to respond as well to omalizumab compared with the general result (AHR, 0.76 vs 0.57).

Observation bias was minimized by the independent collection of data. Physicians were blinded to the drug being studied throughout the period of identification. Therefore, there should be no particular reason why physicians record less-severe exacerbations in omalizumab users. The opposite usually occurs after starting a new treatment. The historical collection of data, with results close to that of the prospective follow-up period, excludes a desirability bias toward omalizumab.

A reduction in the rate of asthma exacerbations was observed for the pivotal study with omalizumab in severe uncontrolled asthma. However, an imbalance in severity found between the treatment and the placebo arms occurred by chance at randomization, requiring a multivariate modeling or subgroup analysis to generate a conclusion. Regulatory authorities were concerned that in day-to-day practice, omalizumab would ultimately replace conventional treatments, with accordingly higher costs and undetermined benefit as a result. The present study alleviates these concerns given that it demonstrates that omalizumab is indicated as an add-on therapy and not as a substitute for the treatment of chronic asthma. In conclusion, real-life use of omalizumab is associated with a significantly decreased risk of severe exacerbation requiring

hospitalization or ED visits in patients with uncontrolled severe asthma.

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Dr Grimaldi-Bensouda: contributed to the conception of the research theme, conception and design of the study, statistical analysis, writing of the manuscript, and approval of the final manuscript.

Dr Zureik: contributed to the conception of the research theme, conception and design of the study, statistical analysis, and approval of the final manuscript.

Prof Aubier: contributed to the conception of the research theme, conception and design of the study, statistical analysis, and approval of the final manuscript.

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Additional information: The e-Appendix can be found in the "Supplemental Materials" section of the online article.

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Does Omalizumab Make a Difference to the Real-life Treatment of Asthma Exacerbations?

Results From a Large Cohort of Patients With Severe Uncontrolled Asthma

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e-Appendix 1.

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