

Original Article

Omalizumab Is an Effective Intervention in Severe Asthma with Fungal Sensitization

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What is already known about this topic? Fungal sensitization and allergic bronchopulmonary aspergillosis are important complications of asthma, associated with more exacerbations and chronic airway changes such as bronchiectasis. Omalizumab is an effective intervention for severe allergic asthma, although its role in fungal-sensitized asthma is unclear.

What does this article add to our knowledge? Using registry data, we demonstrate that those with severe asthma and fungal sensitization are just as likely to respond to treatment as those without fungal sensitization. The response in those with allergic bronchopulmonary aspergillosis appeared just as effective, although there were few subjects.

How does this study impact current management guidelines? Omalizumab is an effective treatment in those with severe asthma and fungal sensitization, and it should be considered as an add-on therapy, improving asthma symptoms and reducing prednisone use and exacerbation frequency.

BACKGROUND: Severe asthma with fungal sensitization (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) are important complications of severe asthma. The evidence for treating them with omalizumab is limited.

OBJECTIVE: To determine the effectiveness of treatment with omalizumab in patients with severe allergic asthma comparing those with and without evidence of fungal sensitization using data recorded in the Australian Xolair Registry.

METHODS: Data from 205 patients who received omalizumab and recorded in the Australian Xolair Registry were analyzed to determine change in the Juniper 5-item Asthma Control Questionnaire (ACQ-5) score, exacerbation frequency, and oral corticosteroid dose over a 24-month period of omalizumab treatment. Patients were grouped into cohorts on the basis of fungal sensitization, and an analysis of improvement in outcomes between baseline and 24 months was conducted within each group. A further subgroup analysis of patients with ABPA was also conducted.

RESULTS: Patients with SAFS (n = 62), including those with ABPA (ASAFS), were as likely to demonstrate significant improvements in ACQ-5 score and exacerbations and reduced regular oral corticosteroid dose over 24 months as those with severe asthma without sensitization to fungi (n = 156). After adjusting for age, sex, body mass index, smoking history, and

baseline FEV₁%, the effects still remained. A subgroup analysis of 11 patients with ABPA similarly demonstrated a significant improvement on omalizumab.

CONCLUSIONS: Omalizumab is an effective therapy in ASAFS, leading to sustained improvements in symptoms and exacerbations for 24 months. The benefit for ABPA is less clear because of the small sample size. Crown Copyright © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Severe asthma with fungal sensitization; Allergic bronchopulmonary aspergillosis; Severe asthma; Omalizumab

INTRODUCTION

Fungal sensitization is an important trigger for asthma. Fungi that are thermo-intolerant can trigger acute asthma symptoms in much the same way as any inhaled allergen in those who become sensitized to them, depending on environmental exposure.¹ In contrast, thermo-tolerant fungi, such as *Aspergillus* or *Candida*, have the potential to cause more complicated disease in asthma, with evidence of a heightened type 2 immune response² and the

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Abbreviations used

ABPA- Allergic bronchopulmonary aspergillosis
 ACQ- Asthma Control Questionnaire
 ASAFS- All patients with severe asthma and fungal sensitization
 (includes patients with a diagnosis of ABPA)
 AXR- Australian Xolair Registry
 BMI- Body mass index
 ICS- Inhaled corticosteroid
 NFS- No fungal sensitization
 OCS- Oral corticosteroid
 SAFS- Severe asthma with fungal sensitization

possibility that they can persist within the airway.³ Allergic bronchopulmonary aspergillosis (ABPA) is an important complication of asthma, defined by IgE sensitization to *Aspergillus* (either by skin prick test or by radioallergosorbent test), an elevated total IgE level of more than 1000 IU/mL, and at least two-third of blood eosinophils (>500 cells/ μ L), pulmonary infiltrates, or *Aspergillus* IgG antibodies with or without bronchiectasis.⁴ However, relatively few patients even with severe asthma meet the strict diagnostic label of ABPA, although it has been noted that sensitization to *Aspergillus* alone is associated with poor asthma control, worsened lung function, heightened eosinophilic inflammation, and even airway damage in the form of bronchiectasis,^{5,6} leading to these individuals being classified as having severe asthma with fungal sensitization (SAFS), arbitrarily with a total serum IgE level of less than 1000 IU/mL.⁷

Omalizumab is a humanized mAb to IgE indicated for moderate to severe allergic asthma. In binding to IgE at the same site as the high-affinity Fc ϵ RI receptor, omalizumab selectively blockades the IgE-dependent allergic response.⁸ A meta-analysis of the data from 3 studies demonstrated that the addition of omalizumab to subjects with moderate to severe asthma reduced exacerbations and improved asthma symptoms.⁹

Omalizumab then would appear to be a rational choice in the treatment of either ABPA or SAFS, with the strong association between an IgE-mediated response to *Aspergillus*, associated with worsened asthma and progressive lung damage. A recent Australian randomized controlled trial examining the use of omalizumab in patients with ABPA did demonstrate a reduction in exacerbation frequency, but was limited to only 13 subjects.¹⁰ Other evidence surrounding the potential benefit of omalizumab in the treatment of both ABPA and SAFS is limited to case series.¹¹⁻¹⁴ A single observational study comparing the effectiveness of omalizumab in fungal sensitization and no fungal sensitization (NFS) asthma suggested that those with SAFS had less improvement in terms of asthma-related quality of life, but this study was limited by its small sample size and brief response period.¹⁵

Therefore, the aim of this study was to determine the effectiveness of treatment with omalizumab in patients with severe allergic asthma comparing those with and without evidence of fungal sensitization using data recorded in the Australian Xolair Registry (AXR).

METHODS

This was a cohort study that retrospectively analyzed data recorded in the AXR, an observational database of Australian patients with severe allergic asthma treated with omalizumab and

described in detail by Gibson et al.¹⁶ The data were obtained from 221 subjects, enrolled across 21 sites in Australia. All subjects had severe asthma, despite treatment with high-dose inhaled corticosteroids (ICSs) and long-acting β -agonists, with uncontrolled asthma symptoms (Juniper 5-item Asthma Control Questionnaire [ACQ-5] score >2) and at least 2 exacerbations requiring oral corticosteroids (OCSs) or the use of regular OCSs in the previous 12 months (see this article's Online Repository at www.jaci-inpractice.org). They were commenced on omalizumab between July 2011 and January 2016. Follow-up data on outcomes were collected at 6-month intervals, with this study examining outcome data for a maximum of 2 years (5 visits) from initial enrollment (a full description of the Australian prescribing requirements for omalizumab is outlined in the Online Repository). Data were then collated to examine the primary outcomes of interest, which were ACQ-5 scores, ongoing daily OCS dose, and exacerbations requiring the use of OCS within each 6-month interval. Fungal sensitization status was determined from the results of skin prick tests or radioallergosorbent tests. This included responses to *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus terreus*. All patients with ABPA or SAFS were defined as having severe asthma with fungal sensitization (ASAFS). They were compared with those with NFS. ABPA diagnosis, for the subgroup analysis, was determined by the treating specialist physician and recorded. The registry did not record all the criteria that would be required to confirm whether a diagnosis of ABPA was present at the time of commencing treatment with omalizumab, and nor it allowed us to confirm whether ABPA had been diagnosed in the past. Fourteen subjects had a total IgE level of more than 1000 IU/mL. Eleven had an existing diagnosis of ABPA, made by a specialist respiratory physician or immunologist, but we could not confirm or refute whether the other 3 may have had a diagnosis. These 3 have been included in those we defined as ASAFS but not ABPA.

Proportions of patients lost to follow-up were analyzed using χ^2 tests. Continuous variables measured at baseline (commencement of omalizumab) were compared between the 2 groups (ASAFS and NFS) using the Student *t* test or the Wilcoxon rank-sum test, with χ^2 or Fisher exact test conducted for comparison of categorical variables. Between-group differences in changes from baseline outcome values were assessed using mixed-effects regression models with random intercepts for subjects to account for repeated measures on subjects over the study period. Differences in change scores are presented together with 95% CIs and *P* values. Within-group changes from baseline obtained from the mixed model are also presented with 95% CIs and *P* values. Unadjusted models included the ASAFS/NFS exposure, visit, and a visit/exposure interaction, whereas the final model adjusted for age, sex, body mass index (BMI), visit, smoking status, and baseline FEV₁% predicted as well. A linear mixed model with a robust variance estimator was used for comparison of ACQ-5 scores. A Poisson mixed model was used for exacerbation frequency (results presented as incident rate ratios), and a mixed ordered logistic model was used for examination of change in OCS dose (results presented as odds ratios). Data were analyzed using STATA version 15 (StataCorp, College Station, Texas).

RESULTS

There were 221 patients who enrolled in the registry as candidates for omalizumab treatment as determined by clinicians, although only 205 met the Australian Pharmaceutical Benefits Scheme criteria¹⁶ for omalizumab prescription. At each follow-up visit, participants discontinued enrollment in the

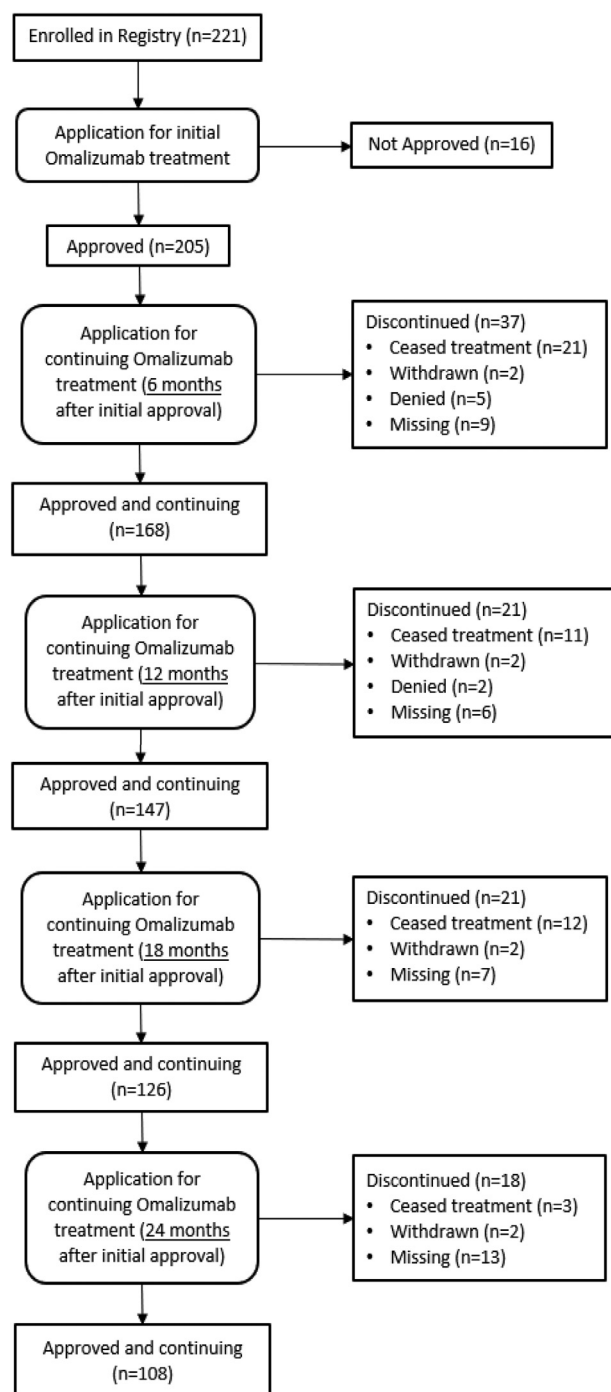


FIGURE 1. Disposition of patients enrolled in the AXR. Consort diagram regarding the outcomes of patients assessed for inclusion.

registry because of various reasons (Figure 1). Patients described as having “ceased treatment” did so at their personal determination or that of their treating clinician, whereas those “withdrawn” from the registry were discontinued because of concerns surrounding possible adverse events. Patients described as “denied” continuation were unsuccessful in their application for continuation of omalizumab (Figure 1). “Missing” patients were unavailable for follow-up data collection. At the conclusion of

the 24-month study period, 108 patients remained in the registry. There were 34 of 208 (31%) patients who ceased treatment because of loss of efficacy and 26 who were lost to follow-up. Analysis of the overall proportion of patients lost to follow-up over the course of the study was conducted between ASAFS and NFS severe asthma and did not determine a statistically significant difference between the 2 cohorts ($P = .18$).

ASAFS compared with NFS severe asthma

Demographic data were described for the 221 patients initially enrolled in the AXR, all of whom were considered eligible candidates for omalizumab treatment by clinician determination. Because fungal sensitization status could not be determined for 3 (1.4%) participants, a total of 218 patients were included in the analysis (Table I).

The ASAFS group was slightly older and had a slightly lower BMI. Both groups were well matched in terms of severity of airflow obstruction, total serum IgE, asthma control as measured by the ACQ-5, exacerbation frequency, and the dose of regular OCSs used.

Examining changes in outcomes from baseline to after 24 months of treatment demonstrated statistically significant improvements across all outcomes within each group, and the differences in changes were not statistically significantly different for any outcome (Table II). The ACQ-5 scores reduced by approximately 2 points in both groups ($P < .001$ for both groups). The mean exacerbation frequency reduced significantly in the ASAFS group from 1.1 to 0.35 and in the NFS group from 1.08 to 0.74 exacerbations per person per 6 months ($P = .005$ and $.03$, respectively). This reflected a total absence of recalled exacerbations over the previous 6-month period for many of the registry participants (76 of 108) by the 24-month visit. By 24 months, median OCS dose had reduced to 0 mg/d for both groups, indicating that most participants (87 of 104) had completely ceased regular OCSs. The overall reduction in OCS dose was also significant in both groups ($P < .001$). After adjusting for age, sex, smoking status, BMI, and FEV₁% predicted, fungal sensitization status was not found to have a statistically significant impact on change in ACQ-5 score (coefficient, -0.26 ; 95% CI, -0.65 to 0.14 ; $P = .2$).

Differences within and between groups were also adjusted for potentially confounding variables (age, smoking status, and sex). The adjusted within-group comparisons are presented in Table II, and it is clear that the significant changes in both groups are still present after adjustments in all outcomes except the number of exacerbations in the NFS group. However, inspection of the estimated incident rate ratios and 95% CIs reveals that there are very little practical differences, and so the observed nonsignificant finding could be due to loss of statistical precision when adjusting for covariates in multiplicative models.

ABPA compared with SAFS

There were 11 subjects with specialist-diagnosed ABPA, and we then compared them to the non-ABPA SAFS cohort. Most demographic variables were not significantly different between the ABPA subgroup and the non-ABPA SAFS subgroup (now referred to as SAFS), including BMI, smoking status, and sex (all $P > .05$). The ABPA subgroup was significantly older than the SAFS subgroup (mean age, 63.9 ± 6.6 and 54.2 ± 6.3 years, respectively; $P = .013$). The mean FEV₁% predicted at baseline was not significantly different between the ABPA and SAFS

TABLE I. Baseline characteristics of subjects

Characteristic	ASAFS	NFS	P value
No. of subjects	62	156	
Age (y), mean $\pm$ SD	55.95 $\pm$ 12.02	49.50 $\pm$ 16.11	<.001
BMI (kg/m ²), mean $\pm$ SD	28.10 $\pm$ 6.01	31.85 $\pm$ 7.98	<.001
Sex: male, n (%)	24 (38.7)	58 (37.4)	.86
Smoking status, n (%)			
Nonsmoker	30 (62.5)	85 (70.25)	.33
Ex-smoker	18 (37.5)	36 (29.75)	.86
FEV ₁ % predicted, mean $\pm$ SD	54.46 $\pm$ 3.51	57.35 $\pm$ 2.24	.49
Serum total IgE (IU/mL), mean $\pm$ SD	821.47 $\pm$ 160.37	630.02 $\pm$ 102.45	.32
IgE (IU/mL), n (%)			
≥ 1000	14 (22.6)	17 (10.9)	.45
<1000	48 (77.4)	139 (89.1)	.34
ACQ-5 score, mean $\pm$ SD	3.39 $\pm$ 0.85	3.51 $\pm$ 1.03	.37
Exacerbations, median (IQR)	1 (1-1)	1 (1-1)	.63
OCS dose (mg/d), median (IQR)	10 (10-20)	12.5 (10-25)	.32

IQR, Interquartile range.

subgroups (mean, 54 $\pm$ 19.9 and 55.4 $\pm$ 14.8, respectively; $P = .86$). However, total IgE titers were significantly higher in the ABPA group than in the SAFS group (mean, 2000.8 $\pm$ 2147.2 IU/mL vs 620.16 $\pm$ 771.0 IU/mL; $P < .001$), congruent with being an element of the diagnostic criteria for ABPA. Mean ACQ-5 scores at baseline were not significantly different between the ABPA and SAFS groups (3.31 $\pm$ 0.5 and 3.40 $\pm$ 0.8, respectively; $P = .74$). Median baseline exacerbation frequency for the ABPA subgroup was identical to that for the SAFS subgroup at 1 exacerbation per person per 6 months (interquartile range [IQR], 1-1). Baseline OCS dose was also similar at 10 mg/d for the ABPA subgroup (IQR, 10-12.5) and 12.5 mg/d for the SAFS subgroup (IQR, 10-25).

Given the small sample sizes, multivariable comparison of improvement between the subgroups was not valid; however, simple univariate analysis was conducted by means of the Wilcoxon rank-sum test. Both groups experienced a statistically significant reduction in median ACQ-5 score, with the ABPA subgroup improving from a median score of 3.6 to 1.5 ($P = .012$) and the SAFS subgroup improving from 3.2 to 1.0 ($P = .001$). Both groups reduced OCSs to a median dose of 0 mg/d at 24 months (both $P < .01$). Although median exacerbation frequency significantly improved in the ABPA subgroup (baseline, 1; at 24 months, 0; $P = .01$), a significant difference was not determined in the SAFS subgroup (baseline, 1; at 24 months, 0; $P = .08$). The between-group comparison of improvement was not determined to be statistically significant for any of the reported outcome measures (all $P > .05$). These results are shown in Figure 2.

DISCUSSION

We have shown that omalizumab is an effective add-on therapy in ASAFS, with treatment over 24 months. It results in improved asthma control, reduced exacerbations, and reduced use of OCSs, with outcomes not inferior to those seen in severe asthma with NFS. In those with a diagnosis of ABPA, disease severity and outcomes appear to have been equally good, although the low patient numbers with ABPA caution against firm conclusions.

Severe asthma is defined by treatment with high-dose ICSs plus a second controller (and/or systemic corticosteroids) to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite therapy.¹⁷ Only a small number of people with asthma have severe disease. However, they have a highly disproportionate burden of illness, high economic costs,¹⁸ and poor quality of life,¹⁹ making it an important chronic disease management problem. Severe asthma is also a disease of considerable heterogeneity, with distinct disease phenotypes,²⁰ multiple comorbidities,²¹ and important psychosocial and behavioral dimensions that lead to a complex disease burden.²² SAFS and ABPA represent important phenotypes of those with severe asthma. The intense airway immune response to persistent *Aspergillus* in the airways that is seen in both conditions is thought to play a crucial role in the distinct clinical features of both ABPA and SAFS, especially in worsening mucus hypersecretion and promoting the development of bronchiectasis.²³

This has led to the treatment of patients with SAFS and ABPA with antifungal agents. In the case of ABPA, antifungal agents such as itraconazole have been used with prednisone to prevent exacerbations and control disease activity with some success.^{24,25} Itraconazole has also been used in SAFS, although the improvements that were seen were at best modest.⁷ However, SAFS appears to be associated with more treatment-refractory asthma. Recently, Woolnough et al² performed a cross-sectional analysis of 431 patients with asthma and found that 76.3% were sensitized to *Aspergillus*. When compared with those not sensitized to *Aspergillus*, those sensitized had lower lung function and were more likely to have changes on a computed tomography scan, such as bronchiectasis, pulmonary infiltrates, collapse, consolidation, and fibrosis.² This association of lung damage was seen to be independently associated with IgE sensitization to *Aspergillus* but not dependent on total serum IgE or the need to meet the strict criteria of ABPA. The advent of mAb therapies for the treatment of severe asthma is an opportunity to see whether they can also modify the disease course in SAFS and ABPA.

The emergence of mAbs as treatments targeting specific aspects of asthmatic inflammation has been the most important advance seen in the management of severe asthma since the emergence of ICSs. However, their efficacy relies on careful

TABLE II. Response to treatment with omalizumab

	ASAFS baseline	ASAFS 24 mo	Mean change/adjusted mean change (95% CI), P value	NFS baseline	NFS 24 mo	Mean change/adjusted mean change (95% CI), P value	Difference (SAFS – NFS) in change over time (95% CI), P value
No. of subjects	62	42		156	66		
ACQ-5, mean $\pm$ SD	3.39 $\pm$ 0.74	1.31 $\pm$ 0.88	–2.1 (–2.54 to –1.67), <.001	3.51 $\pm$ 0.92	1.75 $\pm$ 1.17	–1.81 (–2.10 to –1.52), <i>P</i> < .0001	–0.30 (–0.82 to 0.22) <i>P</i> = .25
			–1.60 (–1.85 to –1.35), <.001			–1.84 (–2.22 to –1.45), <i>P</i> < .001	
Exacerbations, mean $\pm$ SD	1.11 $\pm$ 0.51	0.35 $\pm$ 0.65	IRR = 0.35 (0.16 to 0.73), .005	1.08 $\pm$ 0.68	0.74 $\pm$ 1.23	IRR = 0.67 (0.50 to 0.96), <i>P</i> = .03	IRR = 0.51 (0.22 to 1.12), <i>P</i> = .11
			IRR = 0.40 (0.17 to 0.91), .029			IRR = 0.73 (0.44 to 1.22), <i>P</i> = .23	
OCS dose (mg/d), median (IQR)	10 (10 to 20)	0 (0 to 0)	OR = 0.06 (0.16 to 0.22), <.001	12.5 (10 to 25)	0 (0 to 0)	OR = 0.04 (0.02 to 0.10), <.001	OR = 1.32 (0.30 to 0.59), .71
			OR = 0.09 (0.02 to 0.38), .001			OR = 0.08 (0.03 to 0.22), <.001	

IQR, Interquartile range; IRR, incident rate ratio; OR, odds ratio.

targeting of severe asthmatic phenotypes. Omalizumab is an mAb directed against IgE that plays a critical role in allergic inflammation. A systematic review has shown that treatment of those with severe allergic asthma with omalizumab reduces the risk of acute exacerbations (odds ratio, 0.55; 95% CI, 0.46–0.65) (*n* = 3261 in 10 studies).²⁶ Those with allergy, persistent symptoms, and evidence of type 2 inflammation (exhaled nitric oxide or blood eosinophilia), despite ICSs, derive the most benefits.^{27,28} This is the first study to assess the effectiveness of omalizumab in a registry population defined by fungal sensitization. The demographic characteristics of our population with severe asthma were similar to those found in the literature, except that the participants were slightly older (mean age, 51.3 years).^{29,30} Mean baseline IgE levels within our study population were also considerably elevated in comparison with similar studies (mean, 684.5 IU/mL), whereas mean baseline FEV₁% predicted values were slightly lower than values reported in other publications (mean, 56.6%). However, both measures have been demonstrated to be highly variable within severe asthma populations. In addition, many studies examining severe asthma populations excluded patients above a pre-determined IgE threshold because of ineligibility for omalizumab management.²⁹ We have previously demonstrated in the data from the AXR that omalizumab appeared to perform equally well, even when this total IgE threshold was exceeded, with baseline IgE not found to be a predictor of treatment response in multivariate analysis.¹⁶ Much less though is known about the efficacy of omalizumab in ABPA and SAFS. Recently, an Australian study prospectively randomized 13 patients with ABPA to receive omalizumab and the study was able to demonstrate a reduction in exacerbation frequency.¹⁰ We now describe the largest group with SAFS (including ABPA) treated with omalizumab and for a 24-month period of follow-up, demonstrating that it appears to maintain its effectiveness. In regard to SAFS, we have been preceded by only 1 publication evident in the literature that similarly examined the relative effectiveness of omalizumab between fungal- and nonfungal-sensitized cohorts.¹⁵ The study demonstrated a poorer response in SAFS in terms of the Asthma Quality of Life Questionnaire. However, this study included a relatively brief follow-up period of only 16 weeks, limited reporting of sample characteristics, and an inferential analysis that did not account for likely confounders and variables known to affect omalizumab response.¹⁶

Our study had several strengths. Data were collected from a well-designed registry of patients with confirmed severe allergic asthma initiating omalizumab, which has previously been described in depth.¹⁶ Registry participants were recruited at multiple centers throughout Australia, and data collection pertaining to participant characteristics, disease severity, and outcomes of interest was remarkably complete. The mixed-modeling techniques used allowed for multivariate analysis considering intersubject variability while also being capable of handling a substantially imbalanced data set with highly variable numbers of repeated measures. Our greatest limitation though was in our ability to assess effectiveness in subjects with ABPA. We had limited numbers with only 11 subjects, and we were unable to confirm that these individuals met the diagnostic criteria for ABPA, having to rely upon the diagnosis being identified by their treating clinicians.

ACQ-5 response at 24 months

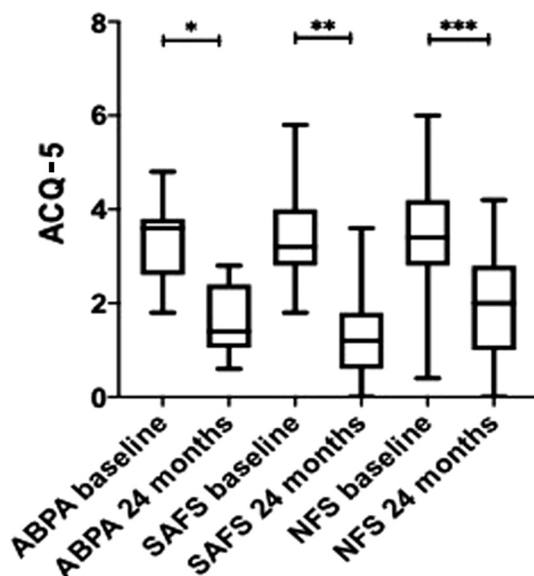


FIGURE 2. Data for ACQ-5 are demonstrated at baseline and after 24 months of treatment. Data are expressed in box and whisker plots, with the central line being the median, the box edges the 25th to 75th percentiles, and the whiskers the 5th to 95th percentiles. All cohorts demonstrated significant differences between baseline and 24 months in the ACQ-5 scores for those with *ABPA, **SAFS, and ***NFS.

CONCLUSIONS

Using data from the AXR, we have been able to demonstrate that treatment with omalizumab effectively improved asthma control, reduced exacerbations, and reduced OCS use in ASAFS, with efficacy equivalent to that with NFS. The value of omalizumab in ABPA though remains unclear, as does the efficacy for other mAb therapies in this setting. Given the relative rarity of ABPA and the difficulties of future prospective studies in ABPA, future interrogation of data registries for anti-IL-5 mAb agents may provide further insight into interventions for ABPA.

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METHODS

Australian Pharmaceutical Benefits Scheme requirements for omalizumab

Diagnostic criteria for severe asthma requiring treatment with omalizumab under the Australian Pharmaceutical Benefits Scheme were defined as follows: patients should be 12 years or older, should be treated by a respiratory physician or immunologist, should have a duration of asthma of at least 12 months, and should have a diagnosis of severe asthma. This is defined by (1) FEV₁ reversibility of 12% or more and 200 mL or more after administration of salbutamol, (2) airway hyperresponsiveness during a direct or indirect bronchial provocation test, or (3) peak expiratory flow variability of more than 15% between the 2 highest and the 2 lowest peak expiratory flow rates during 14 days. Using optimal ICSs and long-acting β -agonists (>1000 μ g

beclomethasone equivalent per day) and evidence of poor asthma control in the past 12 months is defined as either (1) an FEV₁ of less than 80% of predicted on at least 1 occasion, (2) treatment with OCSs either daily for at least 6 weeks or have a cumulative dose of OCSs of at least 500 mg prednisolone in the last 12 months, or (3) ACQ-5³⁰ score of 2 or higher, as assessed in the month before the initial visit. They also have to have an elevated total serum IgE of more than 30 IU/mL and past or current evidence of atopy documented by skin prick testing or radioallergen sorbent assay.

After 6 months of treatment, subjects were clinically assessed to determine whether the treatment had succeeded. The following criteria were used and regarded as the failure of the treatment: (1) improvement in ACQ-5 score of less than 0.5 (minimum clinically important difference) from baseline, (2) no reduction in regular prednisone dose or intermittent prednisone usage by at least 15%, or (3) an intolerance to the agent or the emergence of clinically significant side effects.