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Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: study of efficacy and safety.

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Short running title:

Long-term effectiveness and safety of omalizumab

Abstract:

Omalizumab has been shown to be an effective add-on therapy for patients with uncontrolled severe persistent allergic asthma. There has been a steady accumulation of evidence on the long-term effectiveness of omalizumab; however, data on real-life outcomes beyond one year of treatment is limited. In this study, we report on long-term outcomes of omalizumab treatment. We collected data from our severe asthma registry on hospitalisations, exacerbations, corticosteroid sparing, asthma control, lung function, biomarkers and side effects, to determine if the benefit was sustained and treatment was safe on the long term. Forty-five patients [mean age 44.9 years (range 19–69), females 37/45 (82%), mean duration of omalizumab treatment = 60.7 ± 30.9 months (range 23–121)] were included in the analysis. We observed a reduction in the annual acute asthma related hospital admissions for the total population from 207 at baseline to 40 on treatment (80.7% reduction), whilst the per patient annual hospitalisations were reduced from a mean of 4.8 to 0.89 post-omalizumab treatment ($p < 0.00001$). There was a 76.7 % reduction in daily mean maintenance OCS dose (prednisolone equivalent) from 25.8mg ($n=43$) to 6.0mg ($p < 0.0001$), associated with clinically significant improvement in asthma control questionnaire (ACQ) from mean score of 4.1 (range 3.7–4.7) to 2.27 (range 0.5–4.1) ($p < 0.0001$). The mean % predicted FEV₁ has improved from 59.2% at baseline to 75.7% on treatment ($p=0.001$). There was a statistically non-significant reduction in median peripheral blood eosinophils (PBE) from 300 cells/ μ l (range 40-1050) at baseline to 175 cells/ μ l (range 0-1500) post-treatment ($p=0.068$), and statistically significant reduction of median fraction exhaled nitric oxide (FeNO) level from 37 parts per billion (range 12-178) to 24ppb (range 7-50) ($p=0.0067$). The work/school missed days were reduced in 17/19 patients who were at employment or school. The overall safety profile of the treatment seemed acceptable and was consistent with published experience. In conclusion, results from this real-life study demonstrate that improved outcomes in patients with severe allergic asthma are sustained with longer-term omalizumab therapy.

Introduction

Asthma is characterised by bronchial inflammation, airway hyper-responsiveness and reversible bronchial obstruction [1]. Inadequately controlled severe asthma is associated with increased risk of exacerbations, leading to increased emergency room (ER) visits and hospital admissions [2].

Over 70% of severe asthma patients have allergic immunoglobulin E (IgE)-mediated disease. Many require maintenance oral corticosteroids (OCS) therapy which is associated with significant adverse effects [3-5], which prompted the need for the development of more effective and safe treatment through specific targeting of IgE.

Omalizumab is a recombinant humanised IgG1 monoclonal anti-IgE antibody that binds IgE at the same epitope that binds to the IgE receptor [6]. Clinical trials have demonstrated efficacy of omalizumab as an adjunctive treatment in severe allergic asthma (SAA) (reducing the rate of exacerbations and asthma-related ER visits/hospitalisations, as well as improving asthma-related quality-of-life and enabling a significant reduction in the dose of inhaled or oral corticosteroids) [7-12]. It is approved in the European Union (EU) as adjunctive therapy in patients with persistent SAA that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) and a long-acting β 2-agonist [13]. In the UK, it has been approved for use by the National Institute of Care Excellence (NICE) for patients fulfilling certain criteria [14], which include a total serum IgE range between 30-1500 international units/mL (IU/mL). Using omalizumab outside this range may also be effective [15,16]. Omalizumab is the only available anti-IgE therapy in clinical use, with potential predictors of a good response to it include pretreatment high fractional exhaled nitric oxide (FeNO), peripheral blood eosinophil (PBE) counts, serum periostin, and impaired baseline lung function [17,18].

The optimal duration of treatment with omalizumab is uncertain with current practice advocates lifelong treatment [19,20]. Majority of post license real life studies have described efficacy up to 52 weeks [21-27], with few further studies reported on omalizumab efficacy and safety beyond 52 weeks in both adults and children [31]. . The “eXpeRience” international registry open label study from 14 countries reported on 943 patients with up to 2 years of follow up, demonstrating sustained benefit in asthma outcomes including exacerbations reduction [28]. Similar sustained benefit of up to 2 years was also observed in a paediatric French population [29]. Up to 3 years benefit was reported in 26 patients demonstrating significant improvement in symptoms and lung function [30], and up to 7 years benefit was reported in 7 patients from Italy showing incremental year on year improvement in asthma outcomes [32]. In the UK to date, there were no reports on omalizumab efficacy/safety beyond the 52 weeks. Apex I study was of 136 patients from 10 centres in UK with 52 weeks follow up data, reported 64% reduction in OCS use and 53% reduction in exacerbations [26]. Apex II enrolled 252 patients from 22 centres in the UK with 52 weeks follow up data showing an improvement in symptoms, lung function, and a reduction in exacerbations [33]. The Birmingham regional severe asthma service (BRSAS) has considerable experience in the clinical use of omalizumab that extends over 10 years. In this study, we report on the effectiveness and safety of omalizumab in a responder population with mean treatment duration of 5 years (range 2-11 years).

Methods

This was a retrospective severe asthma registry and case note review conducted at a single tertiary referral centre (The Birmingham Regional Severe Asthma Centre “BRSAS”) in the UK. Patients with SAA who were treated with omalizumab 150–600 mg every 2 or 4 weeks for longer than 23 months, in accordance with the European Union label and NICE guidelines for the use of omalizumab [13,14] were included. These patients were classified as omalizumab responders, following a physician’s Global Evaluation of Treatment Effectiveness (GETE) assessment after 16 weeks treatment trial. The selection criteria for this study meant that only patients who responded to

omalizumab 16 weeks treatment trial and remained on long-term treatment up to March 2013 were included in the analysis. All data were entered onto a Microsoft Excel[®] spreadsheet. Statistical evaluation was conducted through paired pre and post treatment comparisons using a Wilcoxon signed ranks test and student t-test using MedCalc[®] version 12.7.0.0 statistical software (Ostend, Belgium). The cut-off level for statistical significance used in this study was $p < 0.05$ unless specified otherwise.

All included patients provided written consent. Patients were evaluated for the frequency of acute asthma related general practitioner (GP) visits, emergency department (ED) visits and hospitalisations. We also collected data on the use of oral corticosteroids (OCS), Asthma Control Questionnaire (7 questions [ACQ7]) scores lung function (forced expiratory volume in 1 second [FEV₁]), inflammatory biomarkers (FeNO and PBE), and work/school days missed (patient self-reported data, obtained by telephone interview). Data were compared between baseline (the 12 months preceding omalizumab therapy) and on-omalizumab treatment (the most recent “latest” 12 months on treatment..

Results

Demographics

In March 2013, there were 625 patients on the BRSAS dendrite registry (figure1) with severe/difficult to treat asthma, 169 (27%) met the NICE criteria for omalizumab use in severe asthma, 122 had 16 week omalizumab treatment trials, and 100/122 (82%) had good to excellent response and continued longterm on the treatment. Twenty-two patients discontinued due to lack of response (12 patients), pregnancy during the treatment (5 patients), or due to side effects (5 patients). Fifty-five patients were repatriated to their local hospital and not included in this analysis. The included 45 patients had a mean age of 44.9 years (range 19–69), predominantly females

(81%), with a mean bodyweight of 85.9 kg (range 51.2–116) (table 1). All of these patients had omalizumab therapy for ≥ 23 months (mean duration 60.7 ± 30.9 months, range 23–121).

Healthcare resource utilisation

Long-term treatment with omalizumab was associated with reductions in unscheduled hospitalisations, intensive care unit (ICU) admissions, and emergency attendances, when compared with baseline or pre-omalizumab treatment values (figure 2, table 2). For the total group, there were 207 hospitalisations and 80 emergency attendances at baseline versus 40 and 42 respectively on long term treatment. This corresponds to 80.7% and 48.5% reduction in hospital admissions and emergency attendances, respectively. The mean annual per patient hospitalisations was reduced from 4.8 to 0.89 ($p < 0.00001$) (figure 2). The mean annual per patient emergency attendances were reduced from 4.4 to 3.0 (p -value 0.17). There was also statistically non-significant reduction in mean ICU admissions per patient per annum from 0.48 to 0.19 ($p = 0.13$) (Table 2).

Effect on OCS use

At baseline, 37/43 (82%) patients were receiving maintenance OCS, compared to 19/43 (44.2%) following long-term treatment with omalizumab [18/43 (41.9%) weaned off OCS treatment completely]. The mean daily maintenance OCS dose (prednisolone equivalent) was reduced from 25.8mg to 6.0mg ($p < 0.0001$) (76.7 % reduction) (figure 3a) . There was 49% reduction in the mean number of steroid courses per patient per annum (6.1 to 3.1 ($p < 0.001$)) (figure 3b). .

Changes in asthma control

Omalizumab treatment improved asthma control in all patients. The mean (SD) ACQ7 scores improved from 4.0 (± 0.9) at baseline to 2.3 (± 1.2) on treatment ($p < 0.0001$) (42.5% improvement) (figure 4). There was a clinically meaningful (≥ 0.5) reduction in ACQ score in 19 out of 20 patients. However, the post-treatment mean (SD) ACQ7 score, 2.2 (± 1.2), remained higher than the

recommended good control level of ≤ 1.5 [34]. At baseline all included patients with available ACQ data (20/20) had an ACQ >1.5 compared to 9/20 (45%) on treatment with 11/20 (55%) achieving the good control level of ACQ <1.5 .

Lung function and biomarkers outcomes

The mean % predicted FEV₁ increased from 59.2% at baseline to 75.7% on treatment (number 23, $p=0.0013$) (table 2).

At baseline 20/31 (65%) of patients had PBE of ≥ 150 cells/ μ l, and 14/31 (45%) had PBE ≥ 300 cells/ μ l. In 24 patients with paired data, the median PBE was reduced from 300 cells/ μ l (range 40-1050) to 175 cells/ μ l (range 0-1500) on treatment ($p=0.068$).

The majority of included patients had high FeNO level at baseline; 14/18 (78%) had FeNO ≥ 25 ppb, and 11/18 (61%) had FeNO ≥ 35 ppb. In the 17 patients with available paired data, we observed statistically significant reduction in FeNO level from a median baseline of 37ppb (range 12-178) to of 24ppb (range 7-50) on treatment ($p=0.0067$).

At baseline, 82% (20/24) had elevated PBE ≥ 300 cells/ μ l or FeNO ≥ 25 ppb, and 39% (7/18) had simultaneous increase in both. The FeNO and/or PBE high group had relative increase in baseline annual OCS requiring exacerbations (6.7 versus 6.0), mean daily prednisolone dose (25mg versus 17.5mg) and mean annual hospitalisations (4.85 versus 2.25) as compared to the PBE/FeNO low group. However, we observed no significant difference in response to omalizumab between the PBE and/or FeNO high versus PBE/ FeNO low groups, {mean OCS requiring exacerbations [6.7 to 2.67 (60%) versus 6.0 to 2.5 (58%)], mean annual hospitalisation [4.85 to 0.9 (81.4%) versus 2.25 to 0.5(78%)], and mean daily prednisolone [25mg to 5.4mg (78%) versus 17.5mg to 7.5 mg (57%)] respectively ($p=0.3$)}.}

Changes in work/school days missed due to asthma

Data on work/school attendance were available for 32 patients. Of those, 17 patients were in employment or full-time education. A total of 1,218 days were lost pretreatment, per annum, compared to 699 days lost on -treatment. This is equivalent to a mean of 30 days increase per patient, per annum, in attendance at work or school (Table 2). All of the 18 unemployed patients pre-treatment remained unemployed on treatment.

Safety data

These severe asthma patients with multiple co-morbidities generally tolerated omalizumab well.. Up to the time of this study, there were no reported episodes of anaphylaxis or deaths. One patient was diagnosed with breast cancer at 3 years of omalizumab treatment. The patient opted to continue on omalizumab treatment with the breast cancer treated by surgery and radiotherapy and the patient has since been in remission. Another patient developed multiple basal cell carcinomas after 2 years of treatment which were treated with local resection and again the patient continued on long-term treatment.

Other adverse effects

Two patients experienced generalized arthralgia and myalgia, one had these symptoms immediately after the first injection lasting 7-10 days during the first 2 years of treatment and the other experienced symptoms 2 days after the first 4 injections with each episode lasting 3 days. Both patients did not perceive their symptoms to be severe enough to discontinue the treatment. A further two patients developed headache, one 4 hours after the first injection lasting 2 hours and the other 4 days after the first injection lasting 5 days. One patient experienced symptoms of fatigue and sleepiness the following day after omalizumab injections, which was a regular feature but again did not lead to treatment discontinuation. Isolated episodes of skin rashes were observed in 2 patients on a background history of chronic idiopathic urticaria. The causality link between these episodes and

omalizumab was not certain and the skin rashes subsequently resolved. One patient noticed mouth ulcers and boils 1 and 3 days after injections respectively. One patient developed shingles in the third month of treatment, one developed gout associated with severe weight loss after one year of treatment which resolved over the ensuing year. However, none of these symptoms led to treatment withdrawal.

Discussion

Considering NICE eligibility criteria [14], only 27% of our total severe asthma registry population was suitable for omalizumab treatment. Good clinical response to omalizumab treatment was observed in 82% of patients following 16-week treatment trial, which is consistent with previous reports [26,33]. This responder group continued on the treatment long-term (mean 5 years), and experienced sustained benefit with an acceptable safety profile. There were significant reductions in exacerbations, hospital admissions, and OCS use, and improvement in lung function, asthma control and quality of life. These data reflect the unique experience of a tertiary severe asthma centre and providing one of the longest follow-up to date. Studies of more than one year duration are limited with the longest duration of up to 7 years was of only 7 patients [32], whilst the largest in size had follow up duration of 2 years [28].

The overall reduction in asthma related admissions and emergency attendances we observed in this study over a mean treatment duration of 5 years of 80.7% and 48.5% respectively is comparable to that of 61% and 70% reductions observed in the Apex 1 study after one year of treatment [26]. Several other studies also reported a range of 29-96% reduction in hospitalisations and 65-87% reduction in emergency attendances at one year of year of treatment [35,36].

Our study population has probably more severe asthma as reflected in the higher proportion of patients treated with maintenance OCS (82%) than similar studies. Our mean baseline maintenance daily OCS dose was 25.8 mg which is higher than that measured in Apex I of 21.4mg [26]. Forty-one percent of our OCS dependent patients managed to wean off OCS completely with an overall reduction in the mean daily prednisolone dose of 76.7%. The mean reduction in the daily prednisolone dose of 19.8mg with a mean of 5 years of treatment is considerably higher than that of the Apex I study of one year duration (19.8mg versus 5.5mg, respectively). This may suggest that the more severe patients derive larger benefit from omalizumab or there is an incremental benefit from longterm omalizumab treatment. Data from the “eXpeRience” registry [28] and a real life study [29] also reported time-related incremental reduction in the mean maintenance daily OCS dose with omalizumab treatment over 2 years. However, the loss to follow up of a significant number of patients in the second year in our study is a potential confounding factor because of bias towards responders, and therefore these results should be interpreted with caution. Long-term systemic usage of OCS is associated with significant morbidity and risk of pre-mature mortality [37]. Therefore, discontinuing or keeping the OCS dose to the minimum possible level observed in this study may carry important implications to patients in terms of reduction in the OCS related morbidity in the short and longterm.

Long-term omalizumab treatment led to significant improvement in asthma control manifesting in a 42.5% reduction in the mean ACQ7 score from baseline with all but one patient reaching a clinically significant ≥ 0.5 reduction in the ACQ score. However, the mean post ACQ7 score of 2.2 (SD=1.2) remained higher than the recommended level of ≤ 1.5 for good control. The raised ACQ scores were a reflection of the severity of this asthma population where all patients had an ACQ score >1.5 at baseline. With treatment 9/20 (45%) achieved good control (ACQ7 <1.5). Therefore, despite the observed significant improvement in the ACQ score with long-term omalizumab treat-

ment, significant proportion of patients continued to have symptoms in keeping with inadequate asthma control.

A sizeable proportion of this patient group (47%) were not in employment or full time education at the start of treatment and continued to do so even following long-term treatment. Detailed data on the specific causes of unemployment in this group were unavailable, but were mostly driven by ill health due to the underlying asthma severity and associated co-morbidities. However, for those patients in employment or full-time education (53%), there was a clear reduction (57%) in days lost (in work/school) due to asthma. These data were based on telephone interviews and consequently there may be reporting bias. However, this remains as an important effect of omalizumab treatment on the patient's quality of life. The "eXpeRience registry" study also reported a significant increase in school and work attendance records with the proportion who did not miss any work days increased from the pre-treatment level of 16.4% to 57.6% in year one and 71.1% in year 2 of treatment [38]. Further research is warranted to confirm the impact of omalizumab on absentism from work/school which have an important effect on patients' quality of life and functionality.

Compared to baseline, the FEV₁% predicted improved by 16.5% with long-term omalizumab treatment. This finding is in keeping with reports from other studies albeit being of shorter follow up duration demonstrating improvement in lung function, e.g. 9.8% improvement in FEV₁% at 16 weeks [26], 9.8% at 12 months and 8.7% at 24 months [28]. Whether this represents reduction in airway remodeling with long-term treatment is uncertain and requires further research [39].

The majority of this omalizumab responder population (82%) had an elevated baseline FENO or PBE with FeNO more likely to be high (78%) compared to PBE (65%) (at cut-off level of 150 cells/ μ l). The T2 biomarker high group (FeNO or PBE) had greater number of baseline hospital

admissions and exacerbations. The clinical improvement was associated with statistically significant reduction in FeNO and a statistically non-significant reduction in PBE following long-term omalizumab therapy. The fact that majority of the responder patients were T2 biomarker high may suggest an omalizumab response prediction role for T2 biomarkers. However, in our study the T2 low group can still respond to treatment and obtain similar benefit. An omalizumab response predictor role for T2 high signature was previously reported [17]. FeNO, PBE and periostin all demonstrated a positive response prediction role (compared to the low group, high FeNO = 53% reduction of exacerbations, PBE=32%, periostin 30%). Notably the latter results were from a post-hoc study analysis which has not yet been confirmed prospectively. This area therefore requires further research to establish the potential use of a composite or individual T2 high score of the three markers in predicting omalizumab response [40].

Over the treatment period omalizumab was generally well tolerated with a good safety profile. We observed no episodes of anaphylaxis, which was previously reported as a rare event afflicting approximately 2 in 1000 patients [41]. There were no deaths during the study duration. Two of our patients had cancer whilst on omalizumab treatment (one was breast cancer and the second was multiple basal cell carcinomas). Both were treated and were in remission and continued on omalizumab treatment. A lack of causal link between omalizumab and malignancy has been previously investigated in a prospective large cohort followed up to 5 years and reported no association between omalizumab and increased malignancy risk [42]. Other observed adverse events were mostly non-serious of single nature and did not necessitate treatment discontinuation in this long-term responder population.

This study represents the unique real life experience of omalizumab in a tertiary severe asthma centre that extends over 10 years, thus providing the longest follow data so far in UK. The size of the study population is also relatively large considering the study duration. The limitations to this study

are its single arm retrospective design with its inherent liability to incomplete data as it relies on the accuracy, completeness and availability of information from the registry and clinical records. This was particularly the case for GP visits and admissions to other hospitals where complete medical records could not be accessed. A significant number of patients referred to our tertiary centre were repatriated to their local hospital once established on treatment and were not included in this long-term study due to lack of accessible clinical records. There was also no standardization of lung function done pre or post bronchodilator hence the lung function data should be interpreted with caution. Due to the lack of a control group, spontaneous improvement in asthma symptoms may also be a possible confounder although unlikely given the underlying asthma severity in the study population. Patients included in this study were a selected group of adults with severe allergic asthma and therefore the observed safety profile reported here would not necessarily apply to the general population. Furthermore, this group of patients suffered from multiple co-morbidities in addition to the underlying severe asthma. Some of the co-morbidities were iatrogenic secondary to excessive longterm corticosteroids exposure. Clinical outcomes would therefore be influenced with such complexity. Nonetheless, the magnitude of improvement observed here would still argue further in favour of omalizumab efficacy. Finally, this study included patients who met the NICE inclusion criteria that confirmed an-underlying IgE-mediated disease as demonstrated by elevated total IgE and positive specific IgE to perennial antigens such as house dust mite. The concept of omalizumab being only effective in IgE-mediated disease has been challenged since the observation of omalizumab efficacy in non-IgE mediated disease such idiopathic urticarial (reference). Therefore more research is now needed to elucidate omalizumab mechanisms of action further and explore its utility in non-IgE mediated diseases including non-allergic asthma.

In conclusion, over a mean 5 years follow up of severe asthma patients on omalizumab therapy, we observed reductions in healthcare resource use, OCS use and asthma-related absences from

work/school, and improvements in asthma control and lung function with an acceptable treatment safety profile. These data support previous studies results of largely shorter duration confirming omalizumab effectiveness and safety. The sustained long-term benefit from omalizumab would support its cost effectiveness through reducing the burden on health care systems, improving patient quality of life, and decreased use of medications with damaging side effects. Omalizumab is licensed for long-term use with the optimum duration of treatment is still unknown. Further research is therefore required to determine the predictors of response to omalizumab, its long-term cost-effectiveness and safety, and the optimum duration of the treatment.

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Legends to tables

Table 1

Baseline demographics and clinical characteristics of the study population.

Abbreviations: PBE= peripheral blood eosinophil, IgE= immunoglobulin E, FeNO= fraction exhaled nitric oxide, ppb= parts per billion, ICS=inhaled corticosteroid (*beclomethasone equivalent), OCS=oral corticosteroid, FEV₁=forced expiratory volume in 1 second, L=litre.

Table 2

Comparison of key clinical outcomes pre and post-omalizumab treatment

The table compares the baseline (pre-treatment) and post-omalizumab treatment data for the study subjects. Abbreviations: ICU=intensive care unit, FEV₁=forced expiratory volume in 1 second, ACQ=asthma control questionnaire, PBE=peripheral blood eosinophils, FeNO=fraction exhaled nitric oxide, ppb=parts per billion, SD= standard deviation, CI= confidence interval.

Legends to figures

Figure 1

Flow diagram of the Birmingham Regional Severe Asthma Service (BRSAS) registry demonstrating breakdown of the omalizumab eligibility, treated patients and the selection of this study population.

tion. *The number of severe asthma patients on the BRSAS registry up to March 2013. [‡] 73% of the patients on the registry did not meet the European license criteria or the NICE criteria for omalizumab prescribing in UK (2013) [14]. The IgE/weight criteria were based on the omalizumab dosing table. Patients were put through systematic assessment and in addition to the listed criteria, patients were deemed unsuitable for omalizumab treatment because of other factors such as significant smoking history or treatment non-adherence.

Figure 2

Demonstration of the annual number of hospitalisations during the pre and post-omalizumab treatment. Abbreviations; *One year pre-omalizumab treatment and during the most recent year of treatment.

Figure 3

The effect of omalizumab on OCS maintenance dose and OCS requiring annual exacerbations.

(a) mean OCS dose at baseline and on-omalizumab treatment, (b) mean number of steroid courses at baseline and on long-term omalizumab treatment.

Figure 4

The long-term effect of omalizumab on asthma control as measured by ACQ7. Mean ACQ7 at baseline compared with most recent measured for patients on long-term treatment.

Table 1

Parameter (no.)	Mean (SD)
Age (years) (45)	44.9 (12.7)
Sex (female, %)	37/45 (81%)
Body weight (kg)	85.9 (21.5)
Actual FEV ₁ L (28)	1.89 (0.86)
FEV ₁ % predicted (28)	61.1% (19.9)
FEV ₁ /FVC ratio (26)	69.5 (12)
PBE cells/ μ l (31)	314.8 (235.7)
FeNO ppb (18)	48.8 (38.8)
Total serum IgE iu/ml (36)	261.1 (170)
*Mean ICS mg/day (43)	2.9 (1.6)
Mean oral prednisolone mg/day (43)	26.2 (17.6)

Table 2

	Pre-omalizumab	Post omalizumab	p value
Mean GP attendance (SD)	4.4 (3.2)	3.0 (2.4)	p=0.17
Mean Hospitalizations (SD)	4.8 (5.2)	0.9 (1.3)	P<0.00001
Mean ICU admissions per patient (SD)	0.48 (0.71)	0.19 (0.62)	p=0.13
Mean FEV1%predicted (SD)	59.2 (21.3)	75.7 (19.4)	p=0.00132
Mean ACQ7 score (SD)	4.0 (0.9)	2.3 (1.2)	p<0.0001
Median PBE (cells/ μ l) (95% CI)	300 (217.3-450)	175 (104.9-330)	P=0.0675
Median FeNO (ppb) (95% CI)	37 (24.1-64.9)	24 (12.1-38.9)	P = 0.0067

Figure 1

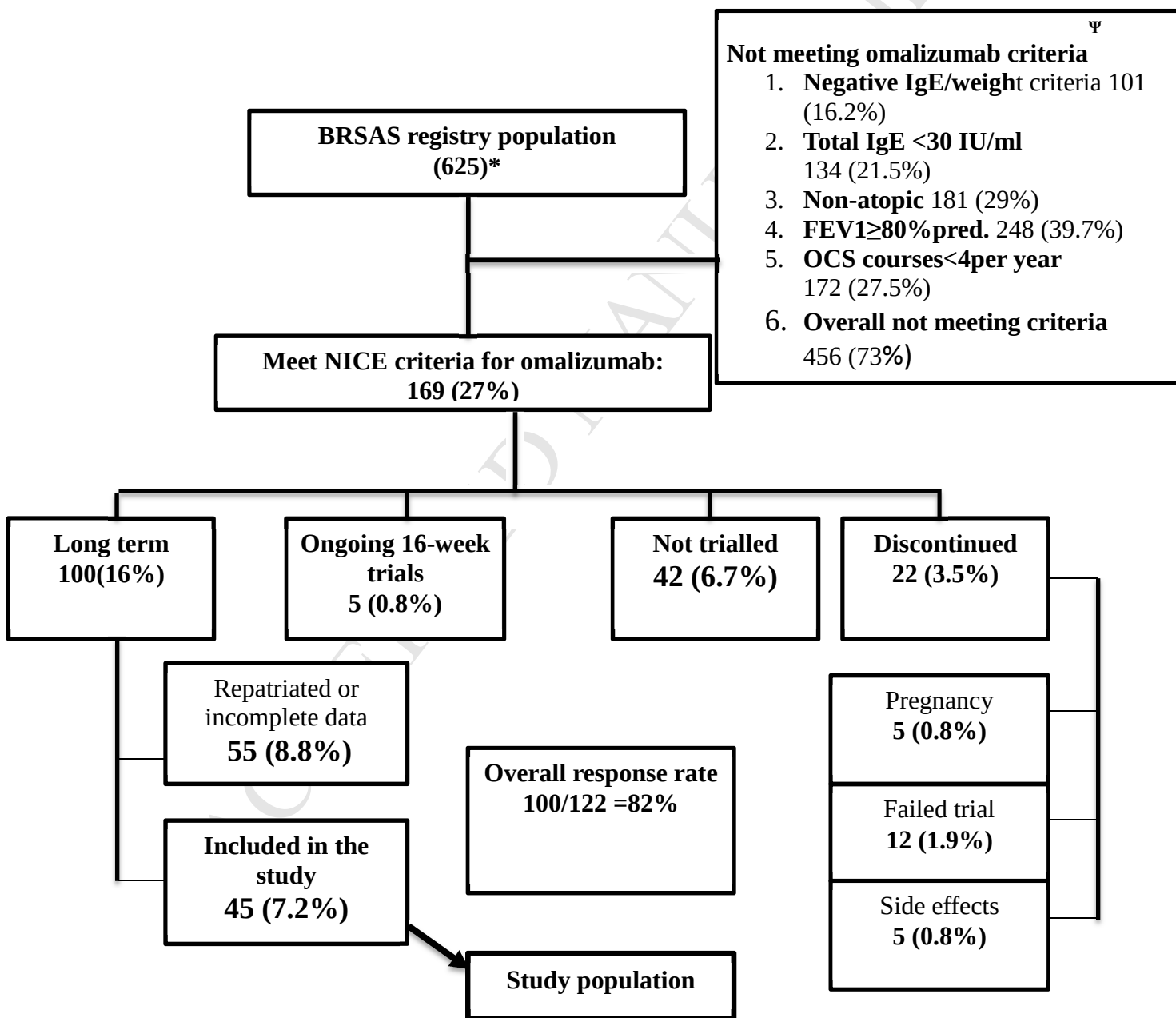


Figure3a

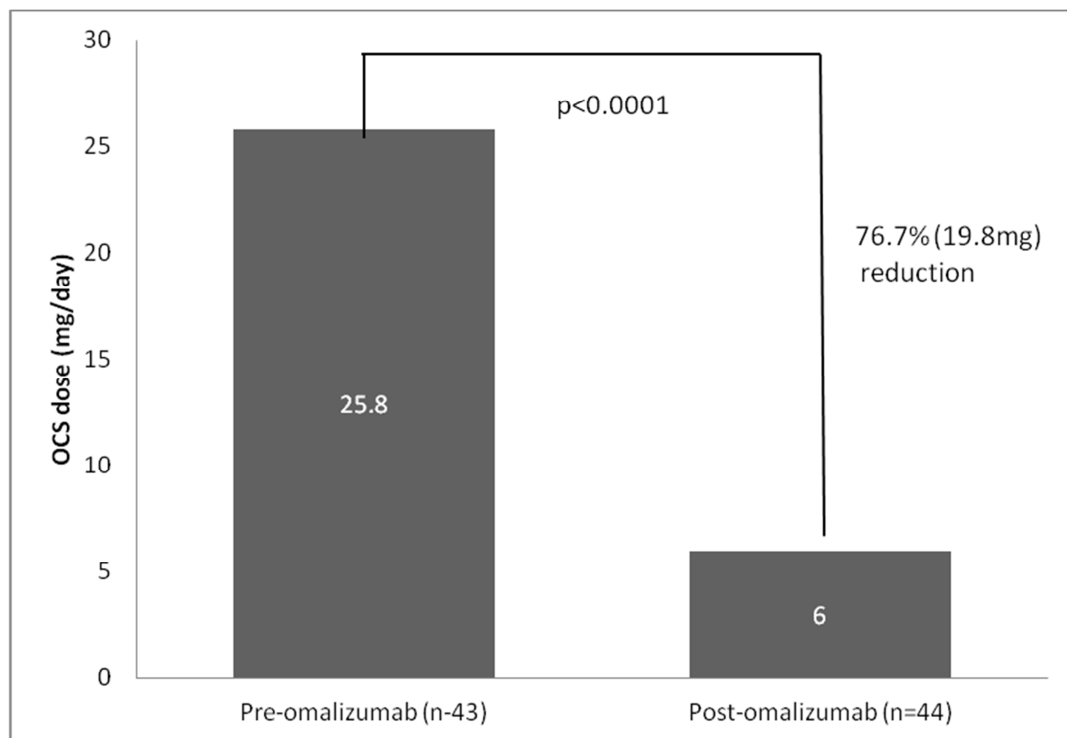


Figure3b

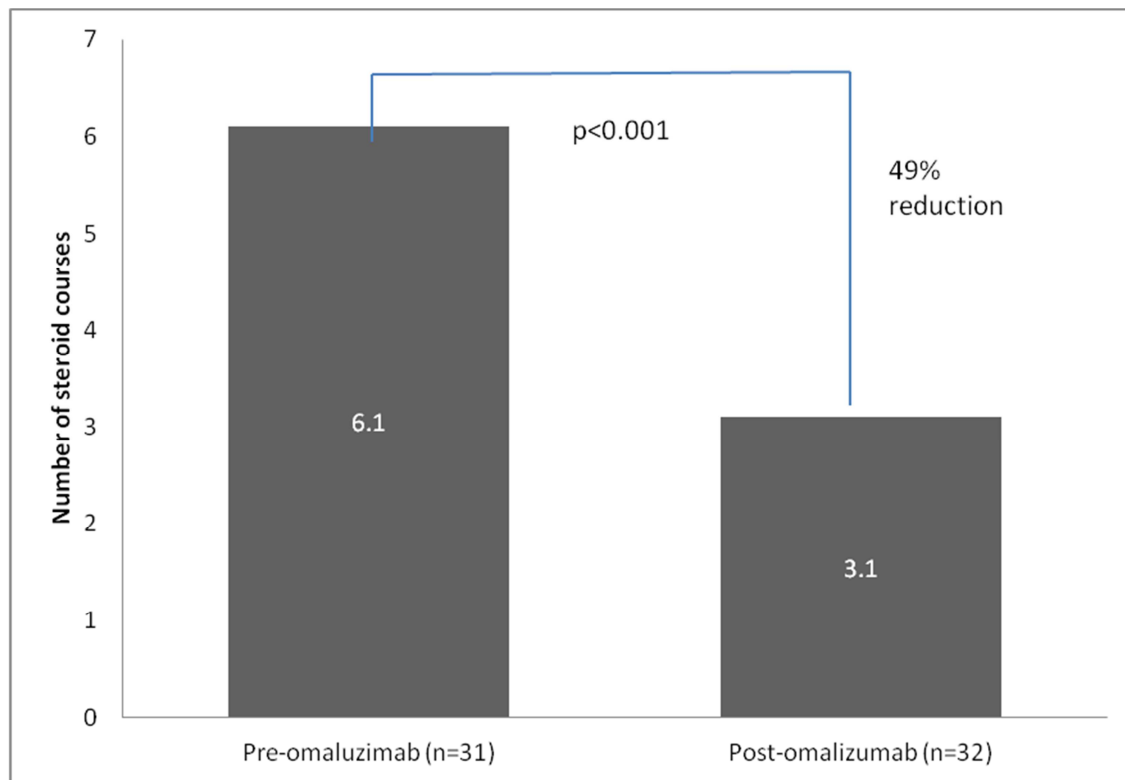


Figure4

