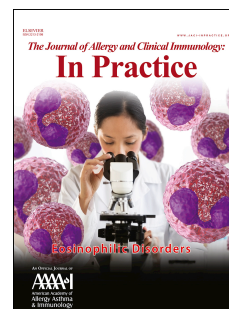


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Real world effectiveness of anti-IL5/5R therapy in severe atopic eosinophilic asthma with fungal sensitisation

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Conflicts of Interest:

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Background

Severe asthma with fungal sensitisation (SAFS) is a complex clinical phenotype associated with poorly-controlled type 2 (T2) inflammation and significant morbidity from both the disease itself and a high steroid burden.

Objective

To assess the effectiveness of biologic therapies targeting eosinophilic inflammation in SAFS

Methods

We assessed the effectiveness of treatment with mepolizumab or benralizumab in patients with SAFS, and compared outcomes with severe atopic asthmatics without fungal sensitisation (SAA) and severe non-atopic asthmatics (SNA). Baseline clinical characteristics and clinical outcomes at 48-weeks were evaluated. A sub-group analysis was performed of patients who met the criteria for allergic bronchopulmonary aspergillosis (ABPA) rather than SAFS.

Results

193 patients treated with mepolizumab (n=63) or benralizumab (n=130) were included. SAFS had higher baseline IgE compared to patients with SAA and SNA (733±837 IU/ml vs 338±494 and 142±171, respectively; both $p<0.001$). There were no other significant baseline differences in clinical characteristics between groups. At 48-weeks there were significant improvements in ACQ-6, exacerbation frequency and reduction in mOCS dose across all groups (all $p<0.05$). No significant between group differences in outcomes were observed at 48 weeks. Patients with ABPA (n=9) had a significant reduction in exacerbation frequency ($P=0.013$) with treatment.

Conclusion

Treatment with eosinophil targeting biologics lead to improvements in exacerbation frequency, OCS requirements and patient reported outcomes in SAFS patients, with a reduction in exacerbations in the subgroup of patients with ABPA. These data highlight the potential clinical utility of targeting eosinophilic inflammation in SAFS and ABPA.

Key Words

Severe atopic eosinophilic asthma, SAFS, ABPA, mepolizumab, benralizumab, real world

Abbreviations

ABPA: Allergic Bronchopulmonary Aspergillosis

ACQ6: asthma control questionnaire 6

AFAD: Allergic fungal airways disease

ANOVA: analysis of variance

AQLQ: mini asthma quality of life questionnaire score

ERS/ATS: European Respiratory Society and American Thoracic Society

FeNO: fractional exhaled nitric oxide

FEV1: forced expiratory volume in 1 second

ICS: inhaled corticosteroid

IgE: immunoglobulin E

IL-4R: interleukin-4 receptor

IL-5R: interleukin-5 receptor

IQR: interquartile range

ISHAM: International Society for Human and Animal Mycology

LABA: long acting β 2 agonist

mAB: monoclonal antibody

mOCS: maintenance oral corticosteroid

SAA: Severe atopic asthma without fungal sensitisation

SAFS: Severe asthma with fungal sensitisation

SEA: Severe eosinophilic asthma

SNA: Severe non atopic asthma

SPA: SAFS patients sensitised to *Penicillium chrysogenum* and/or *Aspergillus*

SD: standard deviation

SPT: skin prick test

T2: Type 2

Highlights Box**What is already known about this topic?**

Severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) are complex clinical phenotypes associated with poorly-controlled type 2 (T2) inflammation. The effectiveness of biologic agents targeting IL5/IL5 receptor alpha in patients with SAFS and ABPA remains unclear.

What does this article add to our knowledge?

We describe the first real-world experience of treatment with mepolizumab and benralizumab in a large cohort of patients with SAFS. Patients with SAFS and ABPA have significant improvements in clinical outcomes following treatment, which are of the same magnitude as those observed in other T2 high severe asthma phenotypes.

How does this study impact current management guidelines?

Targeting eosinophilic inflammation is an effective therapeutic intervention in patients with SAFS leading to improvements in asthma symptoms and reductions in exacerbation frequency and prednisolone use.

Introduction

The role of fungal allergens in asthma encompasses a spectrum of clinical disease including both severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA). The nomenclature for SAFs was first proposed in 2006, describing a cohort of patients with severe asthma and evidence of sensitisation to one or more fungal allergens in the absence of ABPA (1). It is estimated that 20-30% (2) of patients with asthma have evidence of fungal sensitisation, with the prevalence increasing to almost 80% in some reports of severe asthma (3). Patients with SAFS have been shown to experience worse clinical outcomes including reduction in lung function, alongside increased risk of hospitalisation and intensive care admission with asthma exacerbations (4-6). ABPA is an important clinical syndrome associated with asthma defined by sensitisation to *Aspergillus* (either on skin prick test or *Aspergillus* IgE), a total IgE >1000 IU/mL, and raised peripheral eosinophil count >500 cells/ μ L, positive specific *Aspergillus* IgG or radiographic abnormalities including bronchiectasis (7). A significant proportion of patients with severe asthma and evidence of *Aspergillus* sensitisation do not meet the full diagnostic criteria for ABPA, and are therefore classified as SAFS. Compared to ABPA, SAFS is less well characterised and there is a paucity of clinical data regarding effective treatment in this subgroup of patients.

Atopic asthma is classically associated with type 2 (T2) inflammatory responses. Pre-clinical studies have identified that exposure to fungal allergens is capable of generating robust T2 responses, with production of the cytokines interleukin 5(IL-5) and IL-13, resulting in airway eosinophilia (8). Oral corticosteroids (OCS) are recommended in the initial management of asthma exacerbations and ABPA (9). However, prolonged treatment with OCS is associated with significant long term morbidity (10, 11). The place of triazole antifungal agents in ABPA/SAFS/allergic fungal airways disease (AFAD) remains uncertain with controlled trials showing only a modest benefit at best, but several case series and uncontrolled trials suggesting they do ameliorate the condition (12, 13). In addition, these treatments are

associated with a number of significant side effects that can lead to early discontinuation of therapy, including hepatotoxicity and photosensitivity. Azoles can also potentiate the systemic effects of OCS, further exacerbating steroid toxicity. A case series assessing treatment with Omalizumab, a monoclonal antibody (mAb) directed against immunoglobulin E (IgE), has shown it to be effective in treating ABPA and SAFS, with similar improvements in asthma control, exacerbation frequency and reduction in OCS to those seen in severe asthmatics without fungal sensitisation (14). However, treatment is limited by the licensed dosing range of Omalizumab, thus excluding a significant number of patients with SAFS from treatment with this drug.

Although biologic agents targeting IL-5 or IL-5 receptor alpha (IL-5R) have been shown to be highly effective in improving clinical outcomes and reducing OCS exposure in patients with severe eosinophilic asthma (15, 16), little is known regarding the clinical effectiveness of these treatments in patients with SAFS and ABPA. However, a recent post-hoc analysis of the anti-IL5R mAb benralizumab highlighted clinical efficacy even in subjects with the highest baseline IgE levels(17). Herein, we report on real-world effectiveness of anti-IL5/IL5R antibodies in patients with SAFS and ABPA.

Methods

Study Design and Approval

We performed a retrospective analysis of all patients with severe eosinophilic asthma (SEA) who commenced treatment with mepolizumab and benralizumab between April 2017 and April 2019 at our regional, tertiary level asthma centre in the UK. All patients provided written informed consent (15/NI/0196).

Study Participants

All patients were reviewed by an asthma physician, fulfilled the ERS/ATS definition of severe asthma (18), and had confirmed adherence to background therapy (via ICS/LABA prescription record, FeNO suppression testing and/or paired blood prednisolone/cortisol levels(19)). Patients were subsequently commenced on either mepolizumab or benralizumab if they met eligibility criteria. Patients began benralizumab therapy if they had a blood eosinophil count of $\geq 0.4 \times 10^9/L$ in the preceding 12 months and a minimum of three exacerbations in the prior year, a blood eosinophil count of $\geq 0.3 \times 10^9/L$ in the preceding 12 months and a minimum of four exacerbations in the prior year, were receiving mOCS therapy, or a combination thereof. Patients began mepolizumab if they had a blood eosinophil count $\geq 0.3 \times 10^9/L$ in the preceding 12 months and a minimum of four exacerbations in the prior year, were receiving mOCS therapy, or a combination thereof.

Patients were assessed for sensitisation to a panel of standard respiratory aeroallergens (cat, dog, house dust mite, tree and grass pollen) and fungal aeroallergens (*Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Candida albicans*, *Cladosporium herbarum* and *Alternaria*). SAFS was defined as presence of positive specific IgE to any fungal allergen in the absence of ABPA. A sub-group of SAFS patients sensitised

to *Aspergillus* and/or *Penicillium chrysogenum* (SPA) were also identified given the association with airways colonization and lung damage in severe asthma (20, 21). Patients with evidence of sensitisation to other fungal allergens but not to *Aspergillus* and/or *Penicillium* were not included in this group. SAA was defined as the presence of positive specific IgE to ≥ 1 aeroallergen excluding fungi. SNA patients were classified on the basis of absence of demonstrable positive specific IgE to any of the aeroallergens described above. Peripheral blood samples were analysed using the Phadia ImmunoCAP assay (ThermoFisher Scientific, MA) with values considered positive if >0.35 kUA/L.

ABPA patients were defined as having an existing diagnosis of ABPA made by a respiratory physician and according to the International Society for Human and Animal Mycology (ISHAM) criteria (7). All patients had a positive specific IgE to *Aspergillus fumigatus* >0.35 kUA/L and total IgE of ≥ 1000 IU/L. Patients were also required to have any 2 out of the following 3 additional criteria: raised historical peripheral blood eosinophil count $\geq 0.5 \times 10^9$, HRCT chest imaging consistent with ABPA or *Aspergillus* IgG >27 mgA/L. The baseline clinical data for this sub-group is available in the online repository (Table E1).

Clinical Outcomes and Analysis

Clinical assessment was performed at each biologic dosing visit. Data collected at these time-points included: clinic spirometry, fractional exhaled nitric oxide (FeNO), blood eosinophil count, asthma control questionnaire (ACQ6), mini asthma quality of life questionnaire (AQLQ) score, maintenance OCS (mOCS) dose and number of exacerbations since last clinic visit. Patient demographic data was collected from the electronic patient record. Exacerbations were defined as a worsening in asthma control requiring ≥ 3 days of oral prednisolone treatment (or a doubling of prednisolone dose if on mOCS). Patient response to the biologic was defined as previously described (15, 16).

231 *Statistics*

232 Data was analysed and figures were generated using Graphpad Prism (version 8)
233 (GraphPad Software, La Jolla, CA). Data are given as mean (standard deviation [SD]) if
234 normally distributed or median (interquartile range [IQR]) if nonparametric. Parametric
235 variables were compared using T tests (paired or independent) and non-parametric variables
236 using Mann-Whitney U test (unrelated) or Wilcoxon Signed Rank (related). Parametric and
237 non-parametric analysis of variance (ANOVA) was performed for analysis of three or more
238 groups. Categorical variables were analysed by Chi-Square test or Fisher's exact test.
239 Comparison of survival curves was performed using Log-rank (Mantel-Cox) test. Differences
240 were considered significant at $P < 0.05$. All P values are two-sided.

Results

A total of 193 patients completed 48 weeks treatment with either mepolizumab (n=63) or benralizumab (n=130). 36 patients received treatment with mepolizumab prior to being switched to benralizumab. Patients were switched from mepolizumab to benralizumab after a sub-optimal response as previously described by our group (22). Baseline clinical data and clinical outcomes for switch patients were only included in the benralizumab arm. 9 patients were defined as having ABPA and were analysed separately as outlined below. Of the remaining 184 patients 59% were female, with an average age of 52.9 ± 14 years. All patients were prescribed high dose ICS/LABA, with 64% requiring mOCS. Despite this, patients had evidence of poor asthma control with recurrent exacerbations, elevated T2 inflammation (defined as eosinophil count $\geq 0.3 \times 10^9/L$ and/or FeNO ≥ 50 parts per billion) and impaired patient reported outcome measures in the 12 months prior to initiation to biologic. At baseline, 31 patients were defined as SAFS (of which 23 patients were defined as SPA and 8 patients were sensitised to *Candida* alone), 100 as SAA and 53 as SNA. Patients with SAFS had a higher baseline IgE compared to patients with SAA and SNA (mean $\pm$ standard deviation: 733 ± 837 IU/ml vs 338 ± 494 ($p=0.0003$) and 142 ± 171 ($p<0.0001$), respectively. There were no other significant differences between groups in other baseline characteristics (Table 1).

After 48 weeks of treatment a significant improvement was seen in disease control across all 3 groups compared to baseline: there was a significant reduction in asthma exacerbation rates in patients with SAFS (-3.60 ± 2.71 ; $P<0.0001$), SAA (-4.58 ± 3.40 ; $P<0.0001$) and SNA (-3.68 ± 3.37 ; $P<0.0001$) after 48 weeks. There was no difference in the time to first exacerbation between groups with 34% of SAFS, 44% of SAA and 46% of SNA patients remaining exacerbation free at 1 year ($P=0.2903$) (Figure 1A). There was an improvement in asthma control as measured by reduction in ACQ6 score at 48 weeks in patients with SAFS (-0.82 ± 1.26 ; $P=0.0010$), SAA (-0.98 ± 1.38 ; $P<0.0001$) and SNA (-0.52 ± 1.51 ; $P=0.0155$)

(Figure 1B). Similar improvements were observed in mini-AQLQ score across all 3 groups, with SAFS ($+0.82 \pm 1.33$; $P=0.0038$), SAA ($+1.17 \pm 1.95$; $P<0.0001$) and SNA ($+0.74 \pm 1.59$; $P=0.0083$) (Figure 1C). The changes observed for both ACQ and AQLQ exceeded the minimal clinically important difference (MCID) of 0.5. For those patients on mOCS, daily OCS dose was significantly reduced at 48 weeks for SAFS (median percentage OCS reduction 100 [60-100]; $P<0.0001$), SAA (100 [68-100]; $P<0.0001$) and SNA (100 [37-100]; $P<0.0001$) (Figure 1D). 67% of patients with SAFS were able to discontinue all OCS, compared to 67% with SAA and 68% with SNA ($P=0.9959$). There was a significant increase in FEV1 compared to baseline in the SAA group only ($+186 \pm 0.63$ mL; $P=0.0046$) (Figure 1E). There was no significant change at 48 weeks in FeNO compared to baseline in any group (Figure 1F). No significant differences were observed in the magnitude of change in any outcome measure at 48 weeks between all 3 groups (Figure 1). The subgroup of SAFS patients with SPA had a similar improvement in clinical outcomes to the SAFS group overall.

Nine patients included in the analysis met criteria for ABPA (Table 2). Three patients (33%) had received prior treatment with Omalizumab. Two patients (22%) had to stop prior treatment with azoles due to systemic side effects. ABPA patients had similar clinical outcomes to the cohort overall. There was a statistically significant reduction in AER at 48 weeks (3.67 ± 3.2 at baseline vs 0.22 ± 0.44 at 48 weeks; $P=0.013$). Patients with ABPA also had significant suppression of their peripheral blood eosinophil count at 48 weeks (0.30 [0.05-0.60] at baseline vs 0.00 [0-0.10] at 48 weeks; $P=0.023$). Patient reported outcome measures including ACQ6 (2.06 ± 0.87 at baseline vs 1.39 ± 1.06 at 48 weeks; $P=0.086$) and mini-AQLQ (4.07 ± 1.57 at baseline vs 5.00 ± 1.33 at 48 weeks; $P=0.095$) improved, but not to a statistically significant degree, with the observed changes in both exceeding the MCID of 0.5. There was no significant change in FeNO or FEV1 after treatment. Three out of 9 (33%) ABPA patients were on mOCS at baseline for asthma and all 3 were successfully weaned off OCS at 48 weeks.

Discussion

Fungal airways disease is associated with more severe asthma, and current treatment options in this patient population have focussed on OCS, reduction of fungal burden in the airways through the use of the triazole anti-fungal agents, or attenuating the IgE-mediated response to the fungal allergen with Omalizumab (14, 23-26). Treatment with steroids or azoles are either associated with significant systemic side effects or have displayed limited clinical efficacy (13). We report real-world experience of using the anti-IL5/IL5R mAbs, mepolizumab and benralizumab, in a large cohort of patients with severe eosinophilic asthma with fungal sensitisation. Patients with SAFS had a significant reduction in exacerbations and mOCS dose after 48 weeks of therapy, in addition to improvements in the patient reported outcome measures ACQ6 and mAQLQ. Moreover, approximately 70% of SAFS patients who were mOCS dependent were able to fully discontinue OCS at 1 year. The magnitude of these changes was similar to those seen in patients with either SAA in the absence of fungal sensitisation or SNA.

Whilst we have observed improvements in objective and patient-reported outcomes with eosinophil-targeting biologics, the evidence for the efficacy of anti-fungal agents in SAFS is primarily limited to clinical studies. The Fungal Asthma Sensitisation Study assessed response to itraconazole in a small group of patients with SAFS demonstrating improvement in AQLQ at 32 weeks (12). However, the patient population studied in FAST was not as severe as those in our cohort, with only 7% requiring continuous OCS. (12). In contrast the EVITA3 study, which assessed response to voriconazole, did not show any significant reduction in exacerbation frequency or improvement in patient outcome measures (13).

Exposure to fungal allergens has been shown to generate robust T2 immune responses in the airways, resulting in airway eosinophilia (27-29). Therefore, strategies targeted at

depleting circulating eosinophils are an attractive therapeutic option in this patient group. A recent post-hoc analysis of the MENSA Phase III clinical trial identified a reduction in exacerbations following treatment with mepolizumab in patients with severe eosinophilic asthma sensitised to *Aspergillus* and/or *Penicillium* (30). However, the findings of our current study are the first to describe the clinical response to mepolizumab and benralizumab in a real world population of severe eosinophilic asthmatic patients. To our knowledge there have been no published data on the efficacy of benralizumab in patients with SAFS, although recent case reports have highlighted the potential clinical utility of benralizumab in patients with ABPA (31).

We have also characterised a subgroup of patients with ABPA, >50% of whom had previously had to discontinue treatment with either an azole or Omalizumab due to lack of clinical response or side effects. Following treatment with anti-IL5/IL5R mAbs, there was a significant reduction in exacerbation frequency compared to baseline, with numerical improvements seen in OCS requirements and patient reported outcome measures. However, outcomes in this group were limited by the small numbers involved, highlighting the need for further prospective studies investigating this subgroup of severe asthma patients. There has been a single case report of disseminated aspergillosis requiring treatment with voriconazole in a patient treated with reslizumab (32). However, treatment with reslizumab was continued in this patient given the significant clinical improvement in the patient's asthma and no further adverse events were noted. We did not observe any evidence of worsening fungal lung disease in our cohort suggesting that the eosinophil does not appear to play an important role in host defence against fungal infection. There has been an increasing number of case series identifying the clinical effectiveness of anti-IL5 mAbs in patients with ABPA (31). We would argue that the significant benefits observed through improved clinical outcomes and the reduction in OCS exposure identify these treatments as an effective add-on therapy in both in SAFS and ABPA.

The observation that sensitisation to thermotolerant fungi is the major risk factor for the development of lung damage in asthma has led to the concept of AFAD encompassing both patients with ABPA and the majority of patients with SAFS. We have therefore included analysis of a subgroup of SAFS patients sensitised to *Aspergillus* and *Penicillium*. This group did not have significantly different clinical outcomes compared to the SAFS group overall following treatment with anti-IL-5/5R mAbs. Future studies should consider the role of AFAD to provide further mechanistic insights into the spectrum of fungal disease complicating severe asthma. It has also previously been demonstrated that there is an approximately 20% discordance between specific IgE to fungal allergens and skin prick tests (SPT) (3). The patients in our study were identified on the basis of specific IgE alone which may have not have identified some patient's with SAFS in our cohort. We did not observe a significant improvement in lung function in this study overall, consistent with the modest improvements seen in the context of large scale clinical trials of mepolizumab and benralizumab in severe asthma. Eosinophil counts were suppressed in all groups following treatment supporting the mechanism of targeting eosinophilic inflammation to improve clinical outcomes in this group of patients.

In summary, we describe the first real-world experience of treatment with mepolizumab and benralizumab in a large cohort of patients with SAFS. We have identified significant improvements in multiple clinical outcome measures, comparable to other T2-high severe asthma phenotypes, highlighting the clinical effectiveness of targeting eosinophilic inflammation in this group. Mechanistically, it is likely that anti-IL4R may also be effective in this phenotype and a recent post-hoc analysis of the Liberty Asthma Quest study has identified improvement in clinical outcomes in patients with serological ABPA treated with Dupilumab (33). Prospective head to head studies of anti-IL-5/5R and anti-IL-4R mAbs are now needed in this patient group.

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486 **Table 1.** Baseline characteristics

	All n = 184	SAFS n = 31	SPA n=23	SAA n=100	SNA n = 53	P value
Age, years	52.9 (14.1)	52.9 (13.4)	54 (14.4)	50.7 (14.5)	56.8 (13)	0.0835
Female subjects, n (%)	108 (59%)	19 (61%)	12 (52%)	56 (56%)	33 (62%)	0.7969
Peak blood eosinophil count in the year preceding anti-IL5/IL5RA (cells x 10 ⁹)	0.6 (0.4-0.9)	0.6 (0.4-0.7)	0.6 (0.5-0.9)	0.6 (0.4-0.8)	0.6 (0.5-1.0)	0.7023
Baseline blood eosinophil count (x 10 ⁹ /L)	0.2 (0.1-0.4)	0.3 (0.1-0.5)	0.3 (0.1-0.4)	0.2 (0.1-0.4)	0.1 (0-0.4)	0.3438
Total IgE (IU/L)	348 (555)	733 (837)	568 (421)	338 (494)	142 (171)	<0.0001
FeNO (ppb)	43 (26-76)	30 (19-54)	30 (19-54)	48 (26-72)	41 (27-82)	0.1591
Exacerbation rate in year prior to anti-IL5/IL5R	4.8 (3.3)	4.0 (2.6)	4.4 (2.7)	5.3 (3.5)	4.3 (3.1)	0.1378
Number on mOCS	115 (63%)	18 (58%)	13 (57%)	57 (57%)	40 (75%)	0.1311
Median mOCS dose (prednisolone, mg/day)	10 (5-15)	10 (5-11)	10 (5-13)	10 (5-15)	10 (6-14)	0.7325
FEV1 (L)	1.78 (0.69)	1.74 (0.76)	1.76 (0.81)	1.80 (0.72)	1.77 (0.61)	0.9708

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ACQ-6	2.80 (1.33)	2.72 (1.18)	2.82 (1.28)	2.86 (1.34)	2.74 (1.42)	0.9346
Mini-AQLQ	3.70 (1.47)	3.85 (1.31)	3.81 (1.39)	3.50 (1.53)	3.97 (1.43)	0.2811

Data presented as n (%), mean (SD) or median (interquartile range). Abbreviations: SAFS = severe asthma with fungal sensitization; SPA = sensitised to *Penicillium* and/or *Aspergillus*; SAA= severe atopic asthma without fungal sensitization; SNA= severe non atopic asthma; FeNO =Fraction of exhaled nitric oxide; mOCS = maintenance Oral Corticosteroid; FEV1= Forced expiratory volume in 1 second; ACQ6 = Asthma Control Questionnaire 6; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire

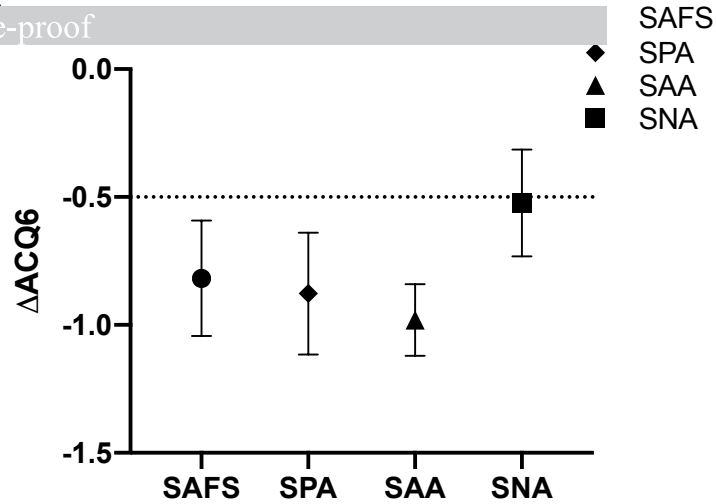
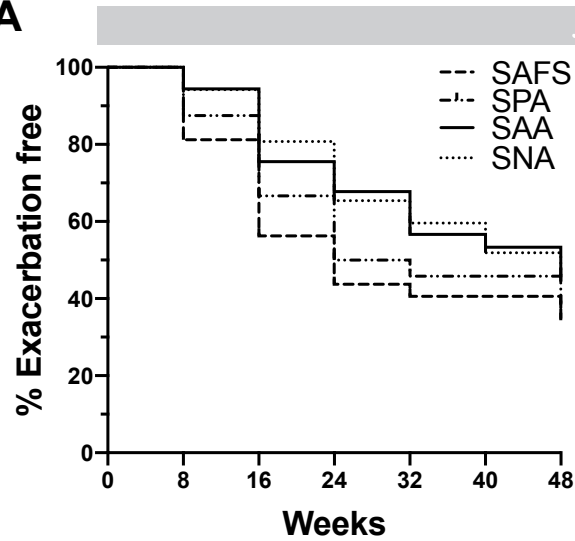
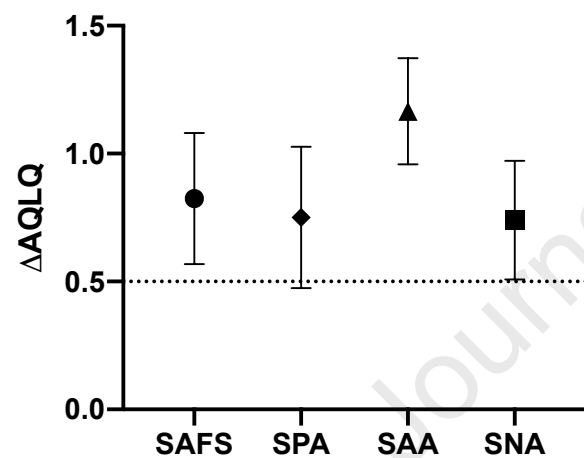
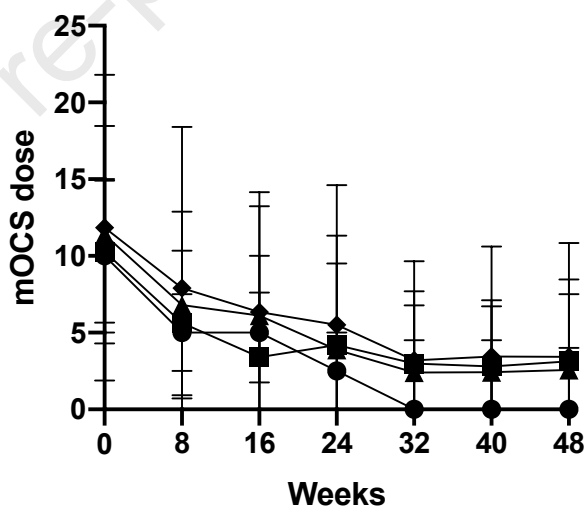
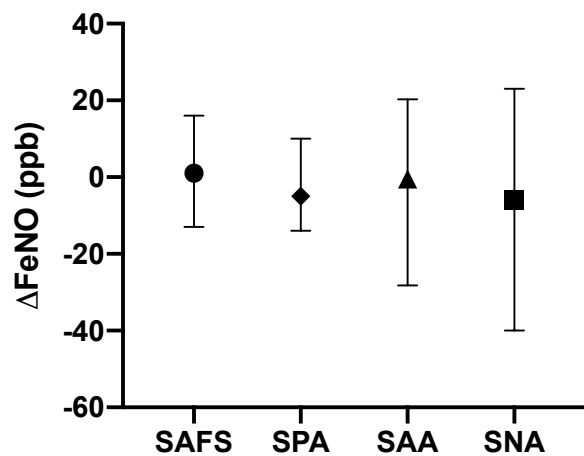
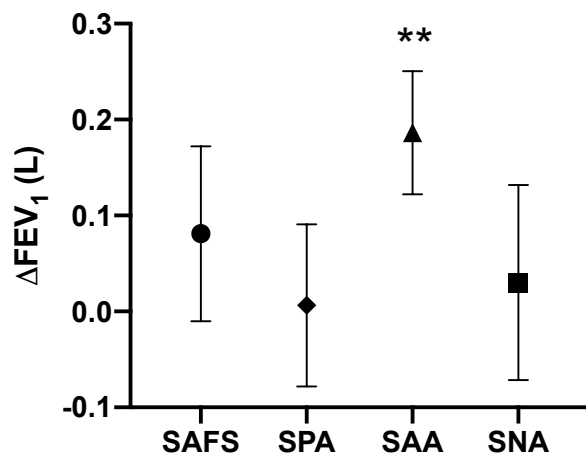
Table 2. One-year outcomes in ABPA

	Baseline n=9	48 weeks n=9	P value
Total IgE (IU/L)	2699 (2461)	- ^a	- ^a
Annual exacerbation rate	3.67 (3.20)	0.22 (0.44)	0.01298
OCS dose (prednisolone, mg/day, n=3)	10 (10-15)	0.0 (0-0)	0.2500
ACQ-6	2.06 (0.87)	1.39 (1.06)	0.0863
Mini-AQLQ	4.07 (1.57)	5.00 (1.33)	0.09501
Peak Blood eosinophil count in the year preceding anti- IL5/IL5RA (x10 ⁹ /L)	0.8 (0.45-1.45)	- ^a	- ^a
Baseline blood eosinophil count (x10 ⁹ /L)	0.3 (0.05-0.6)	0.0 (0-0.1)	0.0234
FeNO (ppb)	51 (28-73)	28 (18-68)	0.6523
Post-bronchodilator FEV1 (L)	1.99 (0.80)	1.88 (0.73)	0.5823

Data presented as mean (SD) or median (interquartile range). Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; FeNO =Fraction of exhaled nitric oxide; OCS = Oral Corticosteroid; FEV1= Forced expiratory volume in 1 second; ACQ6 = Asthma Control Questionnaire 6; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire; -^a= not available

Figure Legend

Figure 1: Between group comparison of clinical outcomes at 48 weeks post initiation of anti IL-5/5R mAB. A: Kaplan-Meier curve of exacerbation free survival, B: absolute change in asthma control questionnaire-6, C: absolute change in mini-asthma quality of life questionnaire, D: mOCS dose across 48 weeks of treatment, E: absolute change in Fraction of exhaled nitric oxide (FeNO), F: absolute change in forced expiratory volume in 1 second (FEV1). Dotted line represents minimal clinically important difference of 0.5. All differences between groups are non-significant. *P* values: ** < 0.01 within group change from baseline.

A**C****D****E****F**

Online Data Supplement

Real world effectiveness of anti-IL5/5R therapy in severe atopic eosinophilic asthma with fungal sensitisation

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Table E1. Baseline Characteristics of ABPA patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age, years	54	48	40	79	55	45	48	71	66
Sex	F	M	M	M	M	F	F	F	M
Aspergillus IgE kUA/L	2.11	5.34	2.53	65.6	0.68	0.85	8.43	75.8	77.7
Total IgE (IU/L)	1409	1848	2041	2400	1007	1014	2023	3643	8903
Aspergillus IgG mgA/L	30.4	n/a	36.4	n/a	n/a	34.2	n/a	n/a	n/a
Peak historical blood eosinophil count	1.3	1.4	0.8	0.5	1.5	0.6	0.5	0.7	2.4
On mOCS for asthma	Y	N	N	N	N	Y	Y	N	N
mOCS dose (prednisolone, mg/day)	15	0	0	0	0	10	10	0	0
Exacerbation rate in year prior to anti-IL5/IL5R	4	4	3	2	10	0	3	0	7
ACQ-6	1	3.57	2.14	1.3	2.17	1.67	3	1.17	2.5
Mini-AQLQ	5.33	2.13	2.27	6.13	2.80	6.33	3.80	3.93	3.87
FEV1 (L)	1.98	2.02	3.8	1.52	2.6	1.73	1.17	1.76	1.34
HRCT Chest findings	Mucous Plugging	Left lower lobe bronchiectasis	Bronchial wall thickening.	Bronchial wall thickening. Scattered consolidation	Bilateral stable lung nodules	No abnormality detected	Lower lobe bronchiectasis	Left lower lobe bronchiectasis	Bronchial wall thickening and mucous plugging

Abbreviations: ABPA = Allergic Bronchopulmonary Aspergillosis; mOCS = maintenance Oral Corticosteroid; FEV1= Forced expiratory volume in 1 second; ACQ6 = Asthma Control Questionnaire 6; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire; HRCT=high resolution computed tomography