Original Article

Real-World Effectiveness of Biologic Therapy in Allergic Bronchopulmonary Aspergillosis

Charlotte Carter, MBChB[a], Irene Berrar Torre, MSc[b], Sophia Blackburn, MSc[a], Lisa Nwankwo, MSc, BPharm Hons[c], Tom Semple, MDRes[d,e], Bhavin Rawal, MDRes[d], Darius Armstrong-James, PhD[a,b], Pujan H. Patel, MD[b], and Anand Shah, PhD[a,b] *London, United Kingdom*

What is already known about this topic? There is increasing evidence from case reports, case series, and small clinical trials of the effectiveness of biologics in patients with allergic bronchopulmonary aspergillosis (ABPA), but there is still a paucity of evidence.

What does this article add to our knowledge? We describe to date the largest real-world cohort experience of biologic therapy efficacy in patients with ABPA. There are improvements in exacerbation frequency and oral corticosteroids (OCS) similar in magnitude to patients with severe asthma.

How does this study impact current management guidelines? Targeting eosinophilic and atopic inflammation in ABPA may be a useful treatment strategy in patients whose disease is refractory to OCS or triazole antifungal therapy and in patients who need steroid sparing treatment options.

BACKGROUND: Allergic bronchopulmonary aspergillosis (ABPA) is characterized by a severe hypersensitivity reaction to *Aspergillus* species. Current treatment relies on oral corticosteroids (OCS) and triazole antifungal therapy, but there is increasing evidence of the benefits of biologic therapies targeting type 2 inflammatory pathways.

OBJECTIVE: To assess the real-world effectiveness of biologic therapies in patients with ABPA.

METHODS: We performed a large retrospective single-center analysis of patients with ABPA as defined by the modified International Society for Human and Animal Mycology (ISHAM) criteria between 2014 and 2022. Baseline characteristics were recorded. Clinical outcomes were assessed at 12 months after commencement of a biologic including symptom scores, exacerbation frequency, corticosteroid use, and multidisciplinary team consensus of effectiveness.

RESULTS: A total of 74 patients received a biologic, of whom 32% (n = 24) received anti-IgE therapy, 65% (n = 48) anti-IL5/5Rα therapy, and 3% (n = 2) anti-IL4-Rα therapy. Of the total, 65% (n = 48) patients were deemed to have a successful response at 12 months with a ≥50% reduction in OCS use and 35% (n = 26) stopped or changed biologic during the follow-up period because of failed clinical response (n = 21), side effects (n = 4), or medical comorbidities (n = 1). There was a significant reduction in the 6-item Asthma Control Questionnaire score ($P < .0001$), exacerbation rate over 12 months ($P < .0001$), and maintenance OCS use ($P = .0173$). Univariate analysis revealed that mucus plugging was associated with nonresponse to biologic therapy ($P = .0189$).

CONCLUSION: Biologic therapies are effective in a number of patients with ABPA. However, further prospective clinical trials are required to determine the effectiveness and which phenotypes likely to respond. These data nevertheless increase the evidence base for biologics in ABPA. **© 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article**

[a]Department of Infectious Disease, Faculty of Medicine, Imperial College London, London, United Kingdom
[b]Department of Respiratory Medicine, Royal Brompton Hospital, Guy's & St. Thomas' NHS Foundation Trust, London, United Kingdom
[c]Department of Pharmacy, Royal Brompton Hospital, Guy's & St. Thomas' NHS Foundation Trust, London, United Kingdom
[d]Department of Diagnostic Radiology, Royal Brompton Hospital, Guy's & St. Thomas' NHS Foundation Trust, London, United Kingdom
[e]National Heart and Lung Institute, Imperial College London, London, United Kingdom

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Corresponding author: Anand Shah, PhD, Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust, Sydney St, London SW3 6NP, United Kingdom. E-mail: s.anand@imperial.ac.uk.

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Abbreviations used
ABPA- Allergic bronchopulmonary aspergillosis
ACQ6- Asthma Control Questionnaire (6-item Asthma Control Test)
CI- Confidence interval
CT- Computed tomography
ERS- European Respiratory Society
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
HRCT- High-resolution computed tomography
ISHAM- International Society for Human and Animal Mycology
MDT- Multidisciplinary team
mOCS- Maintenance oral corticosteroid
NICE- National Institute for Health and Care Excellence
OCS- Oral corticosteroid
PPFE- Pleuroparenchymal fibroelastosis
RCT- Randomized controlled trial

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Allergic bronchopulmonary aspergillosis (ABPA) is a complex allergic pulmonary condition due to a hypersensitivity reaction to fungal *Aspergillus* species, most commonly *Aspergillus fumigatus*. Patients with ABPA typically present with poorly controlled respiratory symptoms, such as wheezing, mucus plugging, pulmonary infiltrates, and, occasionally, systemic symptoms. ABPA can complicate asthma (with a prevalence of 2.5%) and cystic fibrosis (with a prevalence of 7.8%).[1,2] ABPA can present with exacerbations (symptomatic flares often characterized by increased breathlessness, wheeze, and sputum production) as well as a drop in lung function.[2,3] The diagnosis is based on a constellation of criteria updated in 2024 by the International Society for Human and Animal Mycology (ISHAM). They established a diagnostic criterion based on the presence of 2 obligatory criteria (elevated *Aspergillus*-specific IgE positivity and raised total IgE levels) and the presence of 2 of 3 secondary criteria (raised *Aspergillus*-specific IgG levels, presence of blood eosinophilia, and compatible radiological findings).[4]

Long-term outcomes in ABPA are poorly understood. If left untreated, ABPA can lead to recurrent exacerbations, the development of central bronchiectasis, advanced fibrocavitatory disease, a poor quality of life, and death due to end-stage bronchiectasis. A total of 25% to 50% of patients experience exacerbation on cessation of initial therapy, and the likelihood of an exacerbation is highest in the first 3 years.[5] Also, 20% to 45% of patients become glucocorticoid dependent for the long-term management of their ABPA.[6,7] There is however significant heterogeneity in presentation and radiological manifestation with previous studies showing that individuals with serological ABPA may not go on to develop central bronchiectasis even if they continue to have recurrent exacerbations by respiratory symptoms and/or pulmonary infiltrates or become glucocorticoid dependent.[8] The extent of bronchiectasis, age, female sex, and peripheral eosinophilia have all been shown to be independent predictors of exacerbation.[5,9]

To date, the available evidence for ABPA treatment and management is based on either oral corticosteroids (OCS) or azole antifungal therapy with OCS primarily used in the initial management of a patient. Medium-dose OCS has been shown to be as effective a treatment as high-dose OCS, with no difference in exacerbation rate or prevalence of glucocorticoid-dependent ABPA and with less side effects.[10] Itraconazole and voriconazole can be used as monotherapy in acute ABPA but are often used as an adjunct or steroid-sparing therapy in patients with glucocorticoid-dependent ABPA.[11,12] Azole use has been shown to reduce corticosteroid dose, sputum inflammatory markers, serum IgE levels, and exacerbation frequency.[13,14]

Long-term daily OCS use is associated with significant side effects, including weight gain, osteoporosis, and hyperglycemia.[10] Likewise, long-term tolerability of triazole antifungals is often poor; hepatotoxicity and photosensitivity are common side effects, which can lead to discontinuation of therapy. This is evidenced in a randomized controlled trial (RCT) of itraconazole and prednisolone combination therapy versus prednisolone monotherapy in ABPA management, where although no treatment discontinuation was necessary, 73% of participants on combination therapy experienced treatment-related side effects.[15] As such, there is an increasing need to find alternative treatment options for refractory disease and to improve prognosis.

The introduction of monoclonal antibody therapies that target the type 2 inflammatory response has dramatically altered outcomes for patients with severe asthma, with a number of RCTs and real-world cohort studies demonstrating significant reductions in exacerbation frequency, hospitalizations, and maintenance oral corticosteroid (mOCS) use.[16-20] However, patients with ABPA have been excluded from asthma biologic RCTs. To date, a few case series and limited trials with small numbers of participants have reported the effectiveness of biologic therapies in treating ABPA with improvements in symptom control, reduction in mOCS use, and reduction in exacerbation frequency.

Omalizumab has been available on the NHS in England since 2007 and is a monoclonal antibody against IgE. A recent systematic review evaluating the evidence of omalizumab in ABPA identified 49 studies, mostly case studies or case series, and 2 small RCTs including 267 patients in total.[21] Omalizumab reduced exacerbations and OCS use, improved lung function and asthma control in patients with ABPA, and was well tolerated. It was compared with placebo in an RCT with a small number of patients and significantly reduced exacerbation rate and fractional exhaled nitric oxide (FeNO).[22] Mepolizumab (available since 2016) and reslizumab (available since 2017) are monoclonal antibodies to IL5, and benralizumab (available since 2018) is a monoclonal antibody against IL5 receptor α (IL5Rα); they have been shown in retrospective analysis of small numbers of patients to reduce exacerbations and mOCS dose with no adverse effects.[23] Dupilumab (available since 2021) is a monoclonal antibody against IL4Rα and has been shown in case reports to improve symptoms and to allow tapering of steroids in ABPA.[24] Tezepelumab was approved T2-targeted biologic therapy for asthma in March 2023, but there is limited data on its effectiveness in ABPA with only 2 case reports suggesting that potential benefit.[25,26]

In this study, we outline 12-month retrospective outcomes from the largest real-world cohort of individuals with ABPA receiving biologic therapies to date, analyzing exacerbation frequency, corticosteroid burden, and symptoms. We analyzed whether computed tomography (CT) morphology or baseline phenotype affects treatment outcomes in these patients.

METHODS

This was a retrospective analysis of all patients with ABPA who were commenced on an asthma biologic between January 2015 and November 2023 at a tertiary-level severe asthma center in the United Kingdom. Ethical approval was received from the project from the UK Health Research Authority (REC ref: 21/HRA/3400). Patient data were collected from electronic patient records.

All patients with ABPA met the modified ISHAM criteria for ABPA with a total IgE of $\geq$1000 IU/L and a positive specific IgE to *A. fumigatus* of >0.35 kUA/L. Patients were also required to have at least 2 of the following additional criteria: raised peripheral blood eosinophil count $>0.5 \times 10^9$, historical high-resolution CT chest imaging consistent with ABPA, or an *Aspergillus*-specific IgG level higher than 27 mgA/L. A total IgE of >500 IU/L was allowed if all 3 additional criteria were met.

All patients were reviewed and started on an appropriate asthma biologic as add-on therapy after review in a multidisciplinary team (MDT) meeting and confirmation that they met the drug-specific National Institute for Health and Care Excellence (NICE) criteria. All patients were on high-dose inhaler corticosteroid and long-acting β_2-agonist inhaler therapy. As per the NICE criteria, anti-IL5s can be prescribed if the blood eosinophil count is raised at $\geq 0.3 \times 10^9$ or 0.4×10^9 and there is either a requirement for mOCS or 3 or 4 exacerbations during a 12-month period. Anti-IgE therapy can be prescribed if there is evidence of reactivity to a perennial aeroallergen, airflow obstruction, frequent asthma symptoms, and a need for mOCS or at least 4 exacerbations requiring OCS. Dupilumab can be prescribed if the patient is not eligible for mepolizumab, benralizumab, or rezlizumab and they have an FeNO $\geq$25 ppb, serum eosinophil count $\geq 0.15 \times 10^9$, and have had 4 or more exacerbations requiring courses of OCS in the preceding 12 months.

Clinical assessment was performed at baseline and 12 months after biologic commencement with data collected from these 2 time points. Baseline demographics collected included blood eosinophil count, *Aspergillus* serology, 6-item Asthma Control Questionnaire (ACQ6), mOCS dose, number of exacerbations, clinic spirometry, and FeNO. Clinical MDT decision at 12 months on success of the biologic in each patient was recorded.

Baseline CT chest imaging outside of exacerbation and before the initiation of biologic therapy was analyzed by an expert thoracic radiologist (B. Rawal) and scored for the presence of pleuroparenchymal fibroelastosis (PPFE), mycetoma, emphysema, bronchiectasis, varicose bronchiectasis, nodules, ground glass opacification, collapsed/destroyed lung segments, consolidation, mucous plugging, and high-attenuation mucus plugging. CT images were further scored by a second expert thoracic radiologist (T. Semple).

Statistical analysis

Data were analyzed by Prism[23] software (GraphPad version 10.4.1, GraphPad Software, Boston, Massachusetts). Data are given as mean $\pm$ standard deviation if normally distributed or median (interquartile range) if nonparametric. Shapiro-Wilk or Kolmogorov-Smirnov tests were used to gauge the normality of data distribution. Wilcoxon signed rank tests were used to compare paired nonparametric data with the paired Student *t* test for parametric data. The Fisher exact test was used to analyze whether categorical baseline demographics impacted minimal clinical improvement in ACQ with the Mann-Whitney *U* test used to analyze continuous variables. *P* values of less than .05 were considered statistically significant. All *P* values are 2-sided. The effectiveness of monoclonal antibodies as a group was analyzed as well as the effects of anti-IL5/5Rα and anti-IgE therapies alone. Anti-IL4-Rα therapies were not analyzed as a subgroup because of small numbers of patients. Interobserver agreement for CT analysis was assessed using Cohen's Kappa statistic.

RESULTS

A total of 74 patients met the ABPA inclusion criteria and were taken forward for further analysis of outcomes. Of these, 24 (32%) patients received anti-IgE therapy, 48 (65%) received anti-IL5/Rα therapy, and 2 (3%) received anti-IL4-Rα therapy. Of the patients receiving IL5/Rα therapy, 12 received benralizumab, 31 received mepoluzimab, and 5 received resiluzumab. Fifty percent of patients were female with an average age of 56.2 $\pm$ 17.3 years, with 53 (72%) White patients. Baseline demographics are shown in Table I.

Nine (12%) patients had evidence of *Aspergillus* airway colonization based on sputum microbiology, with 33 (44%) having an *Aspergillus* IgG level of $\geq$27 mgA/L. Eight (11%) patients were receiving a triazole antifungal at baseline. Baseline measures revealed poor ABPA control with a mean 12-month exacerbation frequency of 4 $\pm$ 4 and an ACQ-6 score of 3 $\pm$ 1.42. A total of 46 (61.2%) patients required mOCS with an average maintenance prednisolone dose of 5 $\pm$ 10 mg/d.

A total of 69 (93%) patients had baseline CT imaging before biologic commencement available for review. The radiological phenotypes are shown in Table I, with mucus plugging (48%) and bronchiectasis (45%) being the most common radiological features identified. Thirty-eight percent of individuals had no radiological features of ABPA at the time of CT before the initiation of biologic therapy, indicative of a serological ABPA phenotype. There was evidence of significant airways obstruction in the cohort with a mean forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of 0.60 $\pm$ 0.14. The kappa score was 0.710 (95% confidence interval [CI]: 0.636-0.783), indicating substantial agreement between observers.

All patients in the cohort were experiencing persistent recurrent exacerbations, which was a necessary indication for the initiation of biologic therapy. According to recent European Respiratory Society (ERS) consensus criteria, 46 of 72 patients (63.9%) met the criteria for treatment-dependent ABPA. An additional 26 patients (36.1%) were corticosteroid-dependent, but retrospective data were not available to confirm treatment-dependent ABPA.[4]

At the 12-month post-biologic clinical assessment point, 48 patients (65%) were deemed at MDT review to have had a positive clinical outcome. Of the 48 patients who were deemed to have responded, 18 (37.5%) met the criteria for primary remission as defined in a recent analysis by the UK Severe Asthma Registry.[27] Patients were considered in remission if they had no significant symptoms (ACQ-5 was $\leq$ 1.5), no further OCS use as maintenance therapy or during exacerbations (OCS $\leq$ 5 mg/d was accepted for hypothalamic-pituitary-adrenal axis

TABLE I. Baseline characteristics of the patients before receiving a biologic agent (N = 74)

Characteristic	Value
Age (y), mean ± SD	56.2 ± 17.3
Female, n (%)	37 (50)
Ethnicity, n (%)	
White	53 (71.6)
Non-White	21 (28.4)
BMI, mean ± SD	28.8 ± 7.1
Lung function, mean ± SD	
FEV_1 (% predicted)	63.4 ± 20.8
FVC (% predicted)	85.2 ± 17.5
Radiology (descriptive baseline phenotype) (n = 69), n (%)	
No radiological features	26 (37.7)
Bronchiectasis	31 (44.9)
Varicose Bronchiectasis (n (%)	11 (35.5)
Mucous plugging	33 (47.8)
High-attenuation mucous plugging	2 (2.9)
Pleuroparenchymal fibroelastosis	8 (11.6)
Nodules	11 (15.9)
Consolidation	4 (5.8)
Mycetoma	1 (1.4)
Serology	
Baseline IgE (IU/L), mean ± SD	2817.4 ± 2479.6
Baseline IgE >1000, n (%)	51 (69)
Baseline IgE >500, n (%)	23 (31)
Baseline *Aspergillus*-specific IgE (kUA/L), mean ± SD	18.4 ± 29.1
Baseline *Aspergillus*-specific IgG (mgA/L), mean ± SD	44.6 ± 51.6
Baseline blood eosinophils ($\times 10^9$/L), mean ± SD	0.66 ± 0.41
No. of patients on mOCS, n (%)	46 (62)
Baseline mOCS dose (mg/d prednisolone), median (IQR)	5 (10)
Positive microbiology for *Aspergillus sp.*, n (%)	9 (12)
Receiving azole therapy, n (%)	8 (11)
Itraconazole	3 (37.5)
Voriconazole	3 (37.5)
Isavuconazole	2 (25)

BMI, Body mass index; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *IQR*, interquartile range; *mOCS*, maintenance oral corticosteroid; *SD*, standard deviation.

support) during the follow-up period and where available, a FEV_1 above the lower limit of normal or no more than 100ml less than their pre-biologic baseline.

After biologic initiation, patients were reviewed after 6 months of therapy to determine their initial response and then reviewed again a further 6 months later (ie, 12 months after biologic initiation). A total of 26 patients stopped their biologic at or before the 12-month review point. Of these patients, 21 (28%) were deemed to have had an inadequate clinical response and 4 (5%) stopped therapy because of side effects that included recurrent infections, rash, fatigue, muscle cramps, and headaches. One (1.3%) patient stopped their biologic because of the development of severe mental health issues. Table E1 in this article's Online Repository at www.jaci-inpractice.org shows all patients in the study who switched or changed biologic therapy with individual drug response. At the time of writing, 91% (62 of 68) patients continued on biologic therapy with MDT consensus of ongoing efficacy or continued assessment. Of the 6 patients who discontinued, 5 ceased therapy due to a lack of efficacy and 1 due to significant side effects. In addition, 2 patients were lost to follow-up and 4 patients had died from nonrespiratory etiologies.

As shown in Figure 1, there was a significant improvement in ACQ-6 scores in patients after 12-month biologic therapy (baseline: 3.0 [1.49]; post-biologic: 1.69 [1.91]; *P* value <.0001 [95% CI: −0.81, −1.40]), which was maintained when analyzing patients receiving anti-IgE and anti-IL5/Rα therapy separately. There was a significant improvement in 12-month exacerbation frequency within the cohort (baseline: 4.0 [4.0]; post-biologic: 1.0 [1.0]; *P* value <.0001 [95% CI: −1.74, −3.09]). When analyzing subgroups, a significant improvement was only seen in patients receiving anti-IL5/Rα therapy (baseline: 4.0 [3.0]; post-biologic: 1.0 [2.75]; *P* value <.0001 [95% CI: −2.03, −3.71]). Across all groups, there was a reduction in mOCS use after 12-month biologic therapy (baseline: 5 mg/d [1 mg]; post-biologic: 3 mg/d [5 mg]; *P* value = .0173 [95% CI: −0.26, −3.6]).

We analyzed the effects of biologic therapy on lung function and serological markers of *Aspergillus* allergy. As shown in Table II, we identified a small but significant improvement in FEV_1 12 months after biologic therapy compared with baseline, with a trend toward improvement with anti-IL5/Rα therapy. No significant change was seen in serology when looking at all biologics or anti-IL5/Rα therapy when analyzing total and *Aspergillus*-specific IgE levels.

To further analyze whether baseline phenotype correlated with outcomes after biologic therapy in ABPA, we used the minimal important clinical difference in ACQ to identify clinical response or failure. Patients were excluded from the analysis if they had stopped their monoclonal antibody therapy due to side effects or the development of another medical condition. Four patients were also excluded from this analysis because of incomplete ACQ data. As shown in Table III, the only underlying phenotype that predicted a lack of a response to biologic therapy was mucus plugging. Univariate analysis of microbiological colonization (*Aspergillus* culture and/or *Aspergillus* IgG levels >27 mgA/L) or the radiological presence of bronchiectasis and PPFE did not associate with response to biologic therapy.

DISCUSSION

In this study, we present, to date, the largest cohort of real-world outcomes of biologic therapy in ABPA, demonstrating the effectiveness of anti-IgE- and anti-IL5-based therapy in reducing corticosteroid dependence and exacerbation frequency along with significant improvements in quality of life and lung function. Real-world studies of biologic use in severe asthma have demonstrated clinical response rates ranging from 80% to 85%, with potential cessation and switch rates of around 10%.[28,29] In our single-center retrospective real-world study, we show biologic therapy response rates in ABPA to be slightly reduced in comparison at 65% with similar cessation and switch rates. Although a T2-targeted biologic is recommended

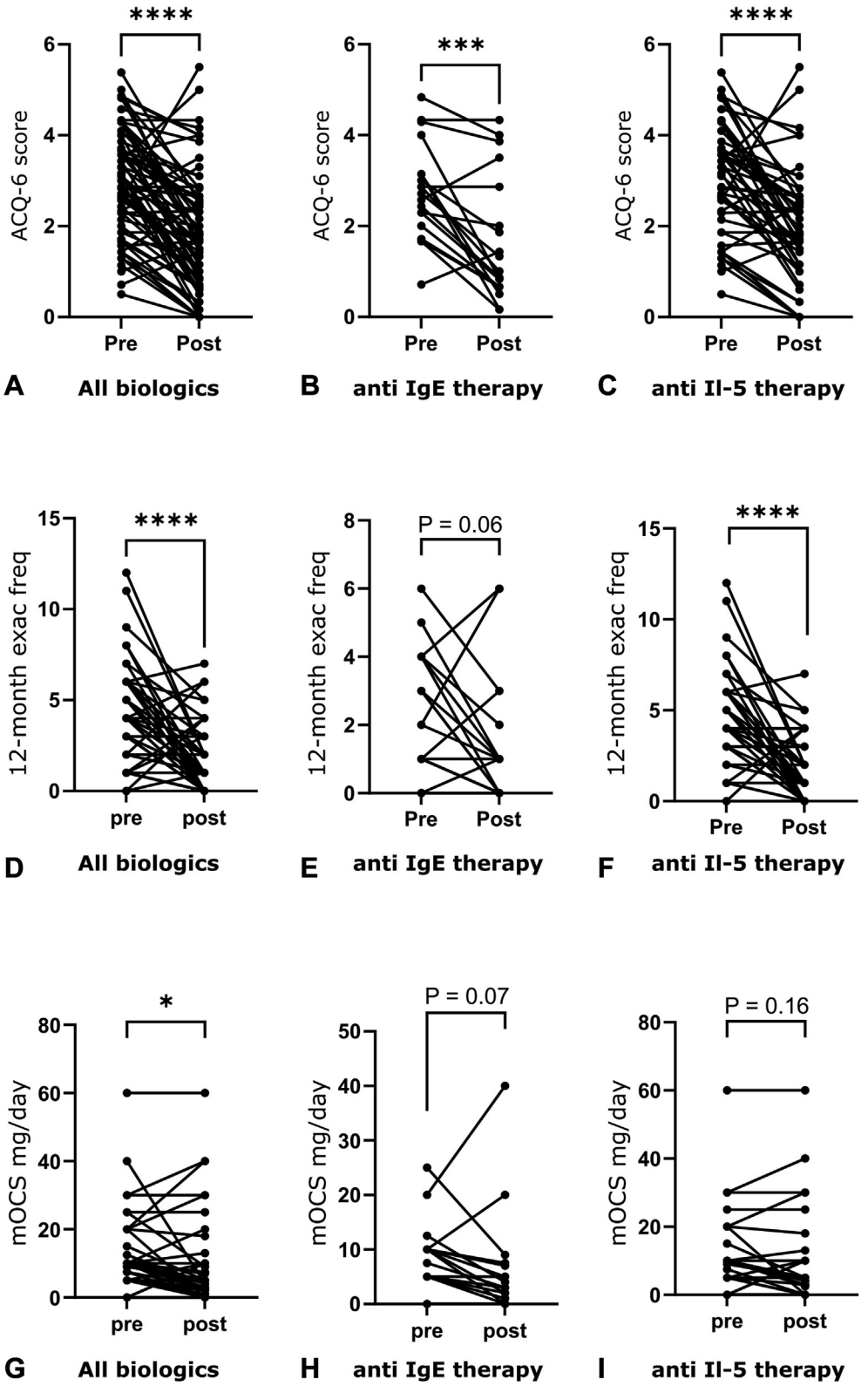

FIGURE 1. Twelve-month outcomes after biologic therapy on symptoms using the 6-item Asthma Control Questionnaire (ACQ-6) in all patients (**A**), anti-IgE therapy (**B**), and anti-IL5 therapy (**C**). Effect on exacerbation frequency in all patients (**D**), anti-IgE therapy (**E**), and anti-IL5 therapy (**F**). Effect on maintenance oral corticosteroid (mOCS) use in all patients (**G**), anti-IgE therapy (**H**), and anti-IL5 therapy (**I**).

TABLE II. Effects of biologic therapy on lung function and serological markers of *Aspergillus* allergy

Outcomes	Pre (n = 74)	Post	*P* value	95% CI
FEV_1 (L), mean ± SD		n = 42		
All biologic therapy	1.90 ± 0.81	2.00 ± 0.84	.03*	0.017 to 0.29
Anti-IgE therapy	1.81 ± 0.87	1.88 ± 0.81	.32	−0.076 to 0.22
Anti-IL5 therapy	1.94 ± 0.78	2.15 ± 0.86	.05	−0.004 to 0.43
Total IgE (IU/L), mean ± SD		n = 39		
All biologic therapy	2624 ± 2075	2749 ± 3556	.79	−828.5 to 1080
Anti-IL5 therapy	3395 ± 4019	3703 ± 4144	.83	−2584 to 3201
Aspergillus-specific IgE (kUA/L), mean ± SD		n = 30		
All biologic therapy	32.7 ± 23.3	32.1 ± 23.0	.46	−9.7 to 4.5
Anti-IL5 therapy	26.7 ± 23.6	27.9 ± 21.5	.68	−4.9 to 7.3
		n = 30		
Aspergillus-specific IgG (mgA/L) (all biologic therapy), mean ± SD	60.1 ± 49.9	53.6 ± 43.8	.12	−14.9 to 1.9

FEV_1, Forced expiratory volume in 1 second; *SD*, standard deviation.
*Significance.

TABLE III. Phenotype of responders vs nonresponders as identified by MCID in ACQ

Phenotype	Change in MCID in ACQ (n = 48)	No change in MCID in ACQ (n = 17)	*P* value	95% CI
Age (y), mean ± SD	56.71 ± 17.94	58.5 ± 16.44	.57	−7.09 to 12.73
Female, n (%)	28 (58)	5 (19)	.051	–
BMI, mean ± SD	28.85 ± 6.74	29.35 ± 6.33	.71	−2.81 to 4.13
Baseline FEV_1 % predicted, mean ± SD	66.65 ± 19.35	61.11 ± 26.53	.36	−17.60 to 6.54
Blood eosinophils ($\times 10^9$/L)*, mean ± SD)	0.67 ± 0.44	0.73 ± 0.42	.29	−38.65 to 11.89
Aspergillus IgG (mgA/L)*, mean ± SD	49.28 ± 48.37	35.90 ± 31.31	.60	−0.18 to 0.31
Aspergillus culture positive, n (%)	5 (10.4)	3 (17.6)	.42	–
Aspergillus colonized†, n (%)	24 (50)	10 (59)	.58	–
Radiological phenotype‡, n (%)				
Bronchiectasis	18 (41)	10 (62.5)	.16	–
No bronchiectasis	26 (59)	6 (37.5)		
Mucus plugging	20 (45.5)	13 (81)	.0189	–
No mucus plugging	24 (54.5)	3 (19)		
PPFE	6 (14)	2 (12.5)	1.0	–
No PPFE	38 (86)	14 (87.5)		

ACQ, Asthma Control Questionnaire; *BMI*, body mass index; *CI*, confidence interval; *MCID*, minimal important clinical difference; *PPFE*, pleuroparenchymal fibroelastosis; *SD*, standard deviation.
*Peak in 12 months before starting treatment with a biologic.
†Defined as *Aspergillus* culture positive of a peak *Aspergillus* IgG in the 12 months before starting treatment with a biologic >27 mgA/L.
‡Change in MCID (n = 44); no change in MCID (n = 16).

for treatment-dependent ABPA following recently published international consensus clinical guidelines, there are no licensed biologic therapies in ABPA, and recommendations are based on a paucity of clinical evidence. Our study confirms case reports and case series highlighting T2-targeted biologic therapy as a viable treatment option in refractory ABPA. There were no significant safety concerns during therapy with no relapse or dissemination of fungal disease.

It is also important to note that the inflammatory pathways driving severe asthma and ABPA are not identical, which may contribute to the difference seen in response rates. ABPA is driven by type 1, type 3, and type 4 hypersensitivity reaction. Germination of inhaled fungal conidia in the lumen of the lower airways leads to immunological responses including recruitment of eosinophils into the airway lumen, which recognize β-glucan in the fungal cell wall and induce cell death (ETosis) accompanied by the release of filamentous chromatin (extracellular traps) as well as the synthesis of IgE.[30] *A. fumigatus* is resistant to eosinophil-mediated cytotoxicity, which further promotes type 2 inflammation with histone citrullination and Charcot-Leyden crystal formation from cytosolic galectin-10, resulting in mucus plugs with abundant eosinophils, extracellular DNA, citrullinated histone H3, and Charcot-Leyden crystals.[31]

Although the total response rate was lower than that seen in severe asthma, in our ABPA cohort, over 35% of patients achieved primary remission with biologic therapy during the follow-up period, which is notably higher than seen in UKSAR data.[26] Further larger prospective studies are required for confirmation, and the reasons for significant response in a proportion of cases are as yet unclear. Given the retrospective nature of this study, there are also some missing lung function data that may contribute to the higher rate of remission seen in this study.

In ABPA, there is a poor understanding of factors predicting response that is critical given the radiological and microbiological

heterogeneity of ABPA with a spectrum ranging from serological ABPA with no evidence of bronchiectasis or significant fungal colonization, significant varicose bronchiectasis with high-attenuation mucus plugging, to features of chronic pleuropulmonary fibrosis, presence of fibrocavitatory lesions and mycetoma with crossover features with chronic pulmonary aspergillosis. Although this heterogeneity has been phenotypically well described, there remains a limited understanding of the immunological pathways driving phenotype and likely response to specific targeting of immune pathways. There has been a recent drive to better understand predictors of response to biologic therapy in severe asthma with a focus on a number of biomarkers including baseline FeNO, blood eosinophils, presence of comorbidities, and specific gene markers.[32-35] Unfortunately, given the retrospective and real-world nature of this study, there is a lack of standardized recording of FeNO at baseline and follow-up. FeNO is an established marker of type II airway inflammation and in particular IL13 activity and is an easy to measure parameter. Future prospective biomarker testing including FeNO would help establish individual baseline phenotype and the relationship to therapeutic response.

In our study, although limited by statistical power, we identified that the presence of mucus plugging was predictive of a lack of response to biologic therapy. This is in contrast to prior studies in severe asthma showing a reduction in the number of mucus plugs after the initiation of biologic therapies.[36-38] Whether baseline mucus plugging suggests a reduced response of airway eosinophilia to biologic therapy in ABPA requires further research with prospective analysis of airway eosinophilia, cytokines, and eosinophil granule proteins as markers of eosinophil ETosis. Previous studies have suggested a greater efficacy of benralizumab and tezepelumab in attenuating airway eosinophilia, and this could have implications on biologic choice in individuals with a more precision medicine approach guided by baseline phenotype.[39] Our cohort, however, does not include any patients receiving the newest approved T2-targeted biologic therapy tezepelumab, so further studies will be required to ascertain the effect in ABPA. A limitation of this paper is the reduced use of dupilumab in this cohort, which is primarily due to current restricted licensing in the United Kingdom for severe asthma. Although results from a recently completed phase 2B study of dupilumab are still pending, targeting the IL4/IL13 pathway presents an exciting therapeutic avenue. This approach has the potential to address eosinophilic-driven airway inflammation and IL13-driven epithelial MUC5AC production, which could enhance treatment effectiveness, particularly in patients with baseline mucus plugging, which is particularly relevant given the association of baseline mucus plugging with therapeutic failure in our study.[40] Although within our study, the initial success of biologic therapy was 65%, the high percentage of patients who remain on biologic therapy for the longer term suggest that the choice of biologic based on individual phenotype may be particularly important in ABPA to achieve therapeutic response.

Although nonsignificant, a lower response rate (41%) was noted in ABPA patients with bronchiectasis with further larger prospective cohort studies required to identify whether the presence of bronchiectasis impacts biologic therapy response. Nevertheless, our data suggest that a significant proportion of individuals with ABPA with the presence of underlying bronchiectasis or *Aspergillus* colonization may respond to a biologic therapy with improvements in exacerbation frequency, corticosteroid requirement, and quality of life. This is particularly important given recent data from within the European bronchiectasis registry (EMBARC) highlighting that individuals with ABPA experience more frequent exacerbations and hospitalizations compared with bronchiectasis due to other etiologies, strengthening the argument for identifying tolerable, effective novel therapeutic options.[41]

A limitation of this study is its retrospective nature, which impacted our ability to fully categorize all patients according to the most recent ERS consensus criteria for treatment-dependent ABPA. This underscores the need of larger-scale, real-world, prospective cohort studies that would help elucidate the overall rates of response and remission, as well as the impact on structural lung disease and lung function. In addition, given the complex immunological interplay in ABPA, further prospective research is required to understand the immune drivers involved in refractory disease and during exacerbation to allow for a more personalized treatment approach. In some cases, combination therapy with either antifungal therapy or multiple biologic therapies may be needed to achieve remission, with combination biologic therapy shown to be effective in a number of case reports in patients with severe asthma and eosinophilic granulomatosis with polyangiitis.[42,43] In our cohort, coexistent antifungal therapy was continued in 8 (11%) patients during biologic therapy administration at the discretion of the treating physician. Of these, 7 were deemed to have a clinical response by MDT decision at 12 months, with 3 meeting the criteria for primary remission.

Our study also demonstrated the radiological heterogeneity in ABPA, with mucus plugging emerging as a predictor of reduced biologic efficacy, independent of microbiological culture results or *Aspergillus* IgG levels. This observation suggests that the mechanisms underlying treatment response involve a complex interplay of factors influencing therapeutic outcomes. Within ABPA, the presence of mucus plugging may relate to bacterial superinfection in the context of bronchiectasis, persistent airway fungal colonization, eosinophil-derived Charcot-Leyden crystals, or T2-dependent mucus plugging. Hence, to understand how baseline mucus plugging is affecting biologic therapeutic effectiveness requires a better understanding of the underlying pathophysiology evident within the spectrum of ABPA. Future prospective studies are required to quantify radiological features of ABPA including mucus plugging, the immunological and microbiological etiology of mucus plugs in ABPA, and whether IL13-targeted therapy, given its effects on MUC5AC-dependent mucus production, or combination antifungal therapy may improve outcomes.

Given the retrospective single-center nature of this study, there are several additional limitations that warrant consideration. Although our ABPA cohort had significant radiological heterogeneity, there were very few patients with high attenuating mucus on baseline imaging. As such, findings cannot be extrapolated to acute exacerbation management. A total of 26 (38%) patients had serological ABPA based on CT imaging, likely reflecting a bias in phenotypic selection of individuals for biologic therapy consideration. Only 1 patient in the cohort had CT evidence of mycetoma, indicating the inclusion of few chronic pulmonary aspergillosis/ABPA crossover patients and hence little inference into the effects of T2-targetted biologic therapy in this phenotype. Given current licensing in the United

Kingdom, only patients with underlying demonstrable evidence of reversible airways obstruction can be considered for biologic therapy. As such, findings are not necessarily translatable to ABPA sans asthma phenotypes that have been widely reported.[44,45] Further research is required to understand the specific immune drivers in ABPA sans asthma and the role of T2-targetted biologic therapy, along with the role of *Aspergillus* sensitization and T2-skewed immune responses in driving chronic pulmonary aspergillosis progression.

In summary, this study describes the largest real-world experience to date of the treatment of ABPA with biologic therapy, showing significant improvements in exacerbation frequency and OCS use comparable to those seen in patients with severe asthma. Prospective research and clinical trials are required to better understand clinical response rates in ABPA as well as predictors of response across the full heterogeneous phenotype in ABPA.

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TABLE E1. Patient biologic therapy switches for ABPA before, during, and after the time period defined in the study

Patient ID	First biologic	Reason for switch	Second biologic	Reason for switch	Third biologic	Reason for switch	Fourth biologic	Reason for switch
AB 3	Omalizumab	No response	Mepolizumab	No response	Dupilumab	Responded		
AB 6	Benralizumab	Increased infections	Mepolizumab	Responded				
AB 8	Dupilumab	No response	Tezepelumab	Responded				
AB 9	Benralizumab	No response	Dupilumab	Responded				
AB 12	Mepolizumab	Hair loss	Benralizumab	Responded				
AB 13	Mepolizumab	No response	Reslizumab	No response	Dupilumab	Responded		
AB 14	Mepolizumab	Responded but stopped due to infections	Benralizumab	No response	Dupilumab	Responded		
AB 16	Reslizumab	No response	Mepolizumab	Side effects	Dupilumab	Rash	Benralizumab	Responded
AB 20	Mepolizumab	No response	Benralizumab	No response	Tezepelumab	Responded		
AB 22	Mepolizumab	No response	Benralizumab	No response	Omalizumab	No response	Resiluzumab	Responded
AB 24	Mepolizumab	No response	Benralizumab	Responded but stopped due to malignancy				
AB 25	Mepolizumab	No response	Benralizumab	Unable to assess response				
AB 28	Omalizumab	No response	Mepolizumab	Responded				
AB 33	Mepolizumab	Mental health issues	Benralizumab	No response	Omalizumab	No response		
AB 35	Mepolizumab	Side effects	Reslizumab	No response	Benralizumab	No response		
AB 39	Omalizumab	Rash	Mepolizumab	No response	Dupilumab	Responded		
AB 40	Mepolizumab	No response	Benralizumab	No response				
AB 42	Omalizumab	No response and joint pains	Mepolizumab	Responded				
AB 46	Mepolizumab	Variable response	Benralizumab	Responded				
AB 49	Omalizumab	No response	Benralizumab	No response	Dupilumab	Responded		
AB 50	Omalizumab	No response	Mepolizumab	No response	Benralizumab	Responded		
AB 54	Omalizumab	No response	Benralizumab	Responded				
AB 55	Omalizumab	Responded but stopped due to polymyositis	Mepolizumab	Responded				
AB 56	Omalizumab	No response	Tezepelumab	Variable response				
AB 57	Omalizumab	No response						
AB 60	Omalizumab	No response	Mepolizumab	No response				
AB 62	Omalizumab	No response	Tezepelumab	Responded				
AB 69	Omalizumab	No response	Mepolizumab	No response				

ABPA, Allergic bronchopulmonary aspergillosis.