



Biologic drugs in treating allergic bronchopulmonary aspergillosis in patients with cystic fibrosis: a systematic review

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Biologic drugs may represent a therapeutic option in allergic bronchopulmonary aspergillosis. However, randomised clinical trials are required to assess their efficacy and safety.

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Abstract

Background *Aspergillus fumigatus* is a common saprophytic fungus causing allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis (CF). The recommended first-line treatment for ABPA is oral steroids, followed by antifungal therapy. However, both treatments are not free from adverse effects; thus, efforts are being made to identify new drugs showing the same effectiveness but with fewer or no side-effects. Therein, biologic drugs have been significantly implemented in clinical practice in treating ABPA in patients with CF.

Objective To systematically review the available literature, providing evidence for the administration of biologic drugs as a new potential treatment of ABPA in both the paediatric and adult populations with CF.

Methods A systematic review of the literature published between January 2007 and July 2021 was performed, using a protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42021270932).

Results A total of 21 studies focusing on the use of biologics in treating ABPA in CF patients was included. We highlighted a paucity of data providing evidence for biologic drug use in ABPA.

Conclusion Scientific evidence is insufficient to support firm conclusions and randomised clinical trials are urgently required to investigate the efficacy and safety of biologics for ABPA in CF patients.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (chromosome 7), and mainly characterised by chronic airway infections leading to progressive lung disease and, finally, respiratory failure [1, 2]. *Aspergillus fumigatus* is the most common saprophytic, spore-forming, filamentous fungus detected in patients with CF [1, 2]. By releasing tiny spores in the environment, *A. fumigatus* can reach the terminal alveoli of the respiratory tree, where it leads to a significant and persistent inflammatory status resulting in the following clinical phenotypes: 1) colonisation, when *A. fumigatus* persists in the airways without affecting respiratory functionality; 2) bronchitis, when *A. fumigatus* causes infection and or inflammation; 3) worsening of respiratory functionality without evidence of allergic responses; and 4) allergic bronchopulmonary aspergillosis (ABPA), resulting in airway inflammation, bronchiectasis, fibrosis and, clinically, pulmonary exacerbation [3–5].

The prevalence of ABPA in patients with CF ranges significantly according to age, from 2% to 25%, and across countries (from less than 1% in Serbia up to 18.6% in central Europe), as it is likely to be underdiagnosed [6]. The pathophysiology of ABPA has still not been elucidated, but it has been hypothesised that, following a chronic inhalation of *A. fumigatus* spores, a chronic airway inflammation



occurs, inducing T-helper (Th) cell type 2 immune response, release of pro-inflammatory cytokines and proteolytic enzymes, and, lastly, a polyclonal antibody response characterised by high serum immunoglobulin (Ig)E, IgG and IgA levels [7, 8]. All these events appear more marked in CF patients with human leukocyte antigen (HLA)-associated susceptibility since they are likely at higher risk for ABPA [7, 8]. The symptoms most commonly reported are productive cough, expectoration of golden-brownish mucus plugs, pulmonary exacerbations not responding to antibiotic treatment, and wheezing. Furthermore, fever, weight loss, chest pain with or without haemoptysis, night sweats and weight loss are also reported. Up to one-third of patients may be relatively asymptomatic [9]. As symptoms are not specific and a considerable overlap exists with other bacterial exacerbations [9], the diagnosis of ABPA can be difficult. Moreover, there is not a single laboratory test that can definitively diagnose ABPA; thus, the diagnosis is made through clinical characteristics, laboratory tests and radiological findings [10]. Hence, different diagnostic criteria of ABPA have been proposed through the years, without a unanimous definition. These include the Rosenberg–Patterson criteria and the ABPA Working Group of the International Society for Human and Animal Mycology (ISHAM) criteria [9, 11]. The former refers to patients with asthma; the latter refers to patients with asthma and CF. In 2003 the Cystic Fibrosis Foundation (CFF) consensus defined the following diagnostic criteria for classical ABPA in patients with CF: 1) acute or subacute clinical deterioration (*e.g.* cough) not attributable to another aetiology; 2) serum total IgE concentration $>1000 \text{ IU}\cdot\text{mL}^{-1}$ unless the patient is receiving systemic corticosteroids; 3) immediate cutaneous reactivity to *A. fumigatus* (prick skin test wheal of ≥ 3 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or *in vitro* presence of serum IgE antibody to *A. fumigatus*; 4) precipitating antibodies to *A. fumigatus* or serum IgG antibody to *A. fumigatus* by an *in vitro* test; 5) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest computed tomography (CT) (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy. Since the diagnosis of ABPA in CF is challenging and may be underestimated due to the recurrence of pulmonary exacerbations, the CFF consensus also defined minimal diagnostic criteria. For diagnosis of ABPA in patients with CF, in contrast to classical ABPA, the total serum IgE concentration was changed to $>500 \text{ IU}\cdot\text{mL}^{-1}$ and only one of points 4) and 5) is needed to make a diagnosis [7]. Moreover, despite the higher prevalence of ABPA recorded in the paediatric population, to date, a consensus on appropriate diagnostic criteria for ABPA in this cohort of patients is lacking; thus, the diagnostic criteria for ABPA adopted in the adult population are also used in children [10].

Patients who do not meet the diagnostic criteria of ABPA are classified as having severe asthma with fungal sensitisation (SAFS). SAFS represents a clinical entity characterised by severe asthma, sensitisation to *A. fumigatus* or other fungi, airway inflammation and damage, but, unlike ABPA, there is no evidence of radiological signs (mucoid impaction and bronchiectasis) and increased levels of serum total IgE [12].

Currently, the recommended first-line treatment for ABPA in patients with CF is oral steroids as these may interfere with antifungal host responses, decreasing the inappropriate inflammatory response [13]. When steroids fail to induce a clinical improvement or patients experience recurrent pulmonary exacerbations or become glucocorticoid dependent, the patient can benefit from an antifungal therapy, such as itraconazole [14]. Globally, both steroids and antifungals can fail to induce a clinical improvement, and are not free from potential adverse effects [13]. Accordingly, efforts have been made to identify new drugs showing greater effectiveness but with fewer or no side-effects, which is the aim of precision medicine [15]. In this regard, biologic drugs, such as monoclonal antibodies (mAbs), represent targeted therapies. These drugs have shown effectiveness in treating severe Th2-high asthma, targeting specific molecules based on the underlying asthma endotype. Specifically, omalizumab is an anti-IgE mAb, mepolizumab is an anti-interleukin (IL)-5 mAb and dupilumab is an anti-IL-4 receptor alpha mAb [16]. Since ABPA shares a Th2 inflammatory pattern with asthma, the use of biologic drugs has been significantly implemented in clinical practice for the treatment of ABPA in patients with CF, especially for those who do not respond to the first- or second-line treatment; however, the evidence supporting their use is lacking [8].

Here, we systematically review the available literature findings, providing evidence for the administration of biologic drugs as a new potential treatment of ABPA in both the paediatric and adult populations with CF.

Methods

Literature review

We performed this systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [17] and including guidelines published between January 2007 and July 2021. We registered the protocol of our systematic review and published the protocol with the International Prospective Register of Systematic Reviews (PROSPERO register number CRD42021270932).

Two reviewers (S. Manti and A. Giallongo) independently conducted searches of electronic medical literature databases, including PubMed, Global Health and EMBASE. The search strategy of each reviewer is detailed in Search Strategy (supplementary appendix E1). Manual searches of the current literature were also performed by referring to Web of Science, Google Scholar, BMJ Best Practice, National Institute for Health and Care Excellence and the World Health Organization (WHO). The following variations and terms were used: “biologic drugs”, “biological”, “monoclonal antibody”, “omalizumab”, “mepolizumab”, “dupilumab”, “cystic fibrosis”, “allergic bronchopulmonary aspergillosis”, “child”, “children”, “adolescent”, and “adult”. Lastly, selected references of the included papers were searched to find any other relevant documents in accordance with the inclusion criteria.

Eligibility criteria

The inclusion criteria were: any language, publication in peer-reviewed journals, children and adults who have been diagnosed with CF and suffering from ABPA; meta-analysis, systematic review, review, original article, case series, case report and letter. Exclusion criteria were: guidelines; any publication (meta-analysis, systematic review, review, original article, case series, case report and letter) not focusing on ABPA treatment in the paediatric and adult populations suffering from CF.

Guideline review

Two independent reviewers (S. Manti and A. Giallongo) performed data extraction using standard templates to report recommendations in support of or against the use of biologic drugs in treating ABPA in patients with CF. Based on these templates, treatment was considered beneficial if one of the following conditions occurred: improvement in lung function (forced expiratory volume in 1 s (FEV₁)) and/or symptoms and/or quality of life, corticosteroid dose reduction or suspension, reduction in pulmonary exacerbations, reduction in school/workdays lost, and a lower healthcare resource utilisation [18]. Articles were excluded by title, abstract or full text if not relevant to the investigated issue.

Results

A total of 21 studies focusing on the use of biologic drugs in treating ABPA in patients with CF was included in this review (figure 1 and supplementary appendix E2) [19–40].

Characteristics of included manuscripts

Tables 1 and 2 detail the characteristics of the 21 studies included in this systematic analysis. The included manuscripts were published between 2007 and 2021. Overall, 117 and four individuals underwent treatment with omalizumab and mepolizumab, respectively. No patient received dupilumab. For omalizumab, 40 patients out of 85 (47%) were children aged under 18 years old [19–27, 29–31, 33–35, 37–40]. Two studies did not give details of individual patients’ ages [28, 32]. A review of 13 children included individuals mentioned in other case reports or studies [36]. All patients treated with mepolizumab were greater than 18 years of age [39, 40].

Omalizumab in treating ABPA in patients with CF

Omalizumab, an anti-IgE mAb, is currently indicated for severe persistent asthma and chronic idiopathic urticaria for people aged ≥ 6 and ≥ 12 years old, respectively [16] and it is prescribed off-label for ABPA. As regards ABPA in patients with CF, data on omalizumab are limited to case reports or case series, which makes it hard to obtain clear data about its effectiveness (table 1) [19–38].

Generally, omalizumab was started as rescue therapy in patients with ABPA with poor or no response to standard treatment or in whom corticosteroid dependence and/or side-effects occurred [19–22, 24, 26–29]. Overall, 82 patients out of 106 (77.3%) had been previously treated with an antifungal agent, mainly itraconazole, associated with corticosteroids at first or as second-line treatment [19–29, 31–38]. Even if antifungal treatment was associated with a good response, ABPA relapses occurred. Two patients were moved from itraconazole to voriconazole due to itraconazole side-effects [25, 27]. KOUTSOKERA *et al.* [30] did not report detailed data on antifungal treatment. NOVÉ-JOSSERAND *et al.* [19] reported that 18 out of 32 (56%) patients underwent concomitant treatment with antifungals and omalizumab. EMIRALIOGLU *et al.* [33] reported that all the enrolled patients received itraconazole during omalizumab treatment.

The largest case series included 32 patients (11 children (34%)) with ABPA, recruited in seven CF centres in France. Here, the authors showed that omalizumab had a corticosteroid-sparing effect (50% patients reduced corticosteroid dose and 27.5% patients stopped corticosteroids) [19]. This finding was consistent with other smaller case series and case reports, where treatment with omalizumab reduced systemic corticosteroid use or led to its suspension [20–28, 38].

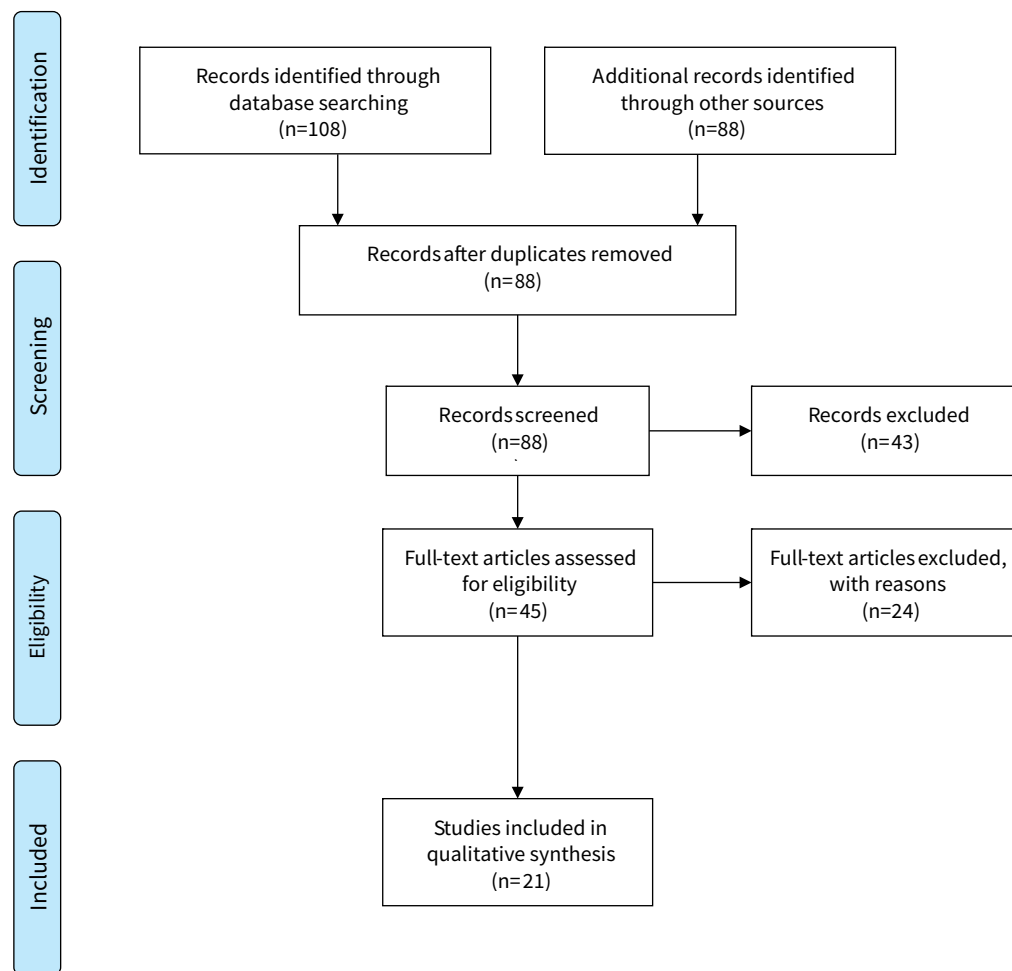


FIGURE 1 PRISMA flow diagram of the literature research.

Further evidence has come from a retrospective study performed on 18 patients with CF who were followed-up at specific time points (−3, 0, 3, 6, 12 months after starting omalizumab). The reduction in daily corticosteroid doses was significant after 3 months ($p < 0.01$) of treatment, leading to its suspension at month 12 of treatment in 15 patients (83%). Nevertheless, no significant changes in FEV₁ values were detected ($+4.2 \pm 8\%$) [28].

In contrast, in a international multicentre study recruiting nine patients, omalizumab effectiveness was limited to a partial reduction in corticosteroid use in four patients (44.4%) [30]. No significant changes were reported concerning FEV₁ and body mass index values. The authors hypothesised that these findings could be due to multiple factors, including lack of standardised dosages for omalizumab in ABPA, high IgE levels and/or the presence of different inflammatory features in patients with CF. Notably, patients with higher post-treatment IgE levels had better outcomes than those with reduced post-treatment IgE levels, calling into question the role of IgE levels as monitoring markers [29]. KOUTSOKERA *et al.* [30] reported similar outcomes in 11 patients. The FEV₁ decline was reduced ($p = 0.019$), and only one-third of patients could reduce corticosteroid use at least by half [30]. BRINKMANN *et al.* [31] also described a case of corticosteroid dependence associated with a relapse of ABPA despite treatment with omalizumab. Other studies found a reduction in the exacerbation rate or no ABPA relapses during treatment [21, 23–25, 27, 28, 33].

Overall, data on the effects of omalizumab on FEV₁ showed variability across studies, ranging from reduced decline [30] to stabilisation [24, 28, 31, 33] or improvement [21, 22, 26, 27, 34, 35, 37, 38]. ASHKENAZI *et al.* [29] reported four patients with a reduction in FEV₁.

TABLE 1 Studies investigating omalizumab in allergic bronchopulmonary aspergillosis (ABPA) treatment in patients with cystic fibrosis (CF)

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for omalizumab administration | Objectives | Omalizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|---------------------|---------------|------------|-----------|-------------|-------------|---------------|---|---|---|-------------------------|-----------|---|------------------|
| VAN DER ENT [20] | Case report | 1 | 0:1 | 12 | Yes | Yes | CSS dependence CSS side-effects ABPA exacerbations | NA | 300 mg every 2 weeks | 6 weeks | No | Symptoms resolution CSS suspension ↑ FEV ₁ (transient) = total IgE | Yes |
| NOVÉ-JOSSERAND [19] | Case series | 32 | 1:2 | 11–59 | Yes | Yes | CSS dependence or CSS side-effects | BMI, FEV ₁ , FVC, total IgE levels, concomitant treatment for ABPA | 450 mg (150–1200) every 2, 3 or 4 weeks | Median 18 months (3–50) | No | ↓ (50%) or stop (27.5%) in CSS use No change in FEV ₁ , but wide dispersion of values 9% stopped omalizumab after 20–24 months without exacerbations 22% stopped omalizumab because not effective 12.5% mild AEs | Yes |
| ZIRBES [21] | Case series | 3 | 3:0 | 12.8–17 | Yes | Yes | CSS dependence ABPA exacerbations CSS side-effects No response to itraconazole | NA | 300–375 mg s.c. every 2 weeks | 8–18 months | No | ↓ exacerbation rate ↓ hospitalisation Oral CSS suspension =/↑ FEV ₁ (–4–+19%) | Yes |
| RANDHAWA [22] | Case report | 1 | 1:0 | 14 | Yes | Yes | CSS dependence CSS side-effects (hyperglycaemia) ABPA exacerbations | NA | 375 mg s.c. every 2 weeks | 6 months | 11 months | CSS suspension Radiological resolution of pulmonary infiltrates ↑ FEV ₁ | Yes |

Continued

TABLE 1 Continued

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for omalizumab administration | Objectives | Omalizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|-----------------------|---------------|------------|-----------|-------------------------|-------------|---------------|--|------------|--|---|-------------|--|------------------|
| ELMALLAH [23] | Case report | 2 | 2:0 | 12–16 | Yes | Yes | CSS dependence ABPA exacerbations | NA | 450 mg s.c. every 2 or 4 weeks | 12–18 months | No | ↓ symptoms ↓ exacerbation rate ↓ oral CSS use ↑ FEV ₁ (+22%) ↓ free IgE (–88––96%) | Yes |
| WONG [24] | Case report | 2 | 2:0 | 14–15 | Yes | Yes | CSS dependence CSS side-effects ABPA exacerbations | NA | 300 mg s.c. every 4 weeks | 24–32 months | No | ↓ and stop oral CSS use ABPA exacerbation when omalizumab administered every 6 weeks in patient 1 = FEV ₁ ↓ free IgE | Yes |
| LEHMANN [25] | Case series | 6 | 1:2 | 5–33, 15.6 (±7.1) | Yes | Yes | CSS side-effects or standard treatment failure | NA | Dosage individually adapted to body weight and IgE level at the beginning up to 600 mg every 2 weeks | 19.6 months (±19.1); 2 patients had a 2nd treatment course 10 and 25 months after discontinuation | 7–56 months | No ABPA relapses during treatment ABPA relapses after treatment (2 patients) (33%) ↓ or stop CSS use ↑ FEV ₁ (+2.3%) | Yes |
| ZICARI [26] | Case report | 1 | 0:1 | 13 | Yes | Yes | CSS side-effects (IGT) | NA | 300 mg every 2 weeks, calculated on the weight and total IgE level | 12 months | No | ↓ and stop oral CSS use ↓ antibiotic use ↑ FEV ₁ (+21%) | Yes |
| DELGADO PECELLÍN [27] | Case series | 3 | 1:2 | 14–29 | Yes | Yes | CSS dependence | NA | 300 mg every 4 weeks to 600 mg every 2 weeks | 5–18 months | No | ↓ and stop oral CSS use No exacerbation ↑/≠ FEV ₁ | Yes |

Continued

TABLE 1 Continued

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for omalizumab administration | Objectives | Omalizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|-----------------|-----------------------------------|---|-----------|-------------|-------------|--------------------------|--|--|----------------------------------|--------------------|---------------|--|------------------|
| PERISSON [28] | Case series | 18 | 7:11 | 17.1±5.2 | Yes | Yes | Treatment-refractory ABPA, CSS dependence and CSS side-effects Nontuberculous mycobacteria infection | Evaluation at T-3, T0, T3, T6, T12 of: FEV ₁ , BMI, AEC, total IgE levels and <i>A. fumigatus</i> -specific antibody levels, side-effects | 489.7 mg (300–600) every 2 weeks | 12 months | No | ↓ exacerbation rate ↓ or stop CSS use (83%) = FEV ₁ (p=0.6) = total IgE and AEC ↑ BMI (p=0.01) | Yes |
| ASHKENAZI [29] | Case series retrospective study | 9 | 2:1 | 23±9 | Yes | Yes | CSS side-effects Contraindication for CSS Failure of antifungal treatment | FEV ₁ Number of pulmonary exacerbations BMI CSS dosage | 375 mg every 4 weeks | 13.9±8.6 months | No | No significant improvement of any outcome ↓ CSS use (4 patients) (44%) 3 (33%) patients with ↑ levels of IgE at the end of the treatment had better outcomes than the 6 (67%) patients with ↓ IgE post-treatment | No |
| KOUTSOKERA [30] | Retrospective observational study | 27 (11/27 with ABPA, 16/27 with asthma) | 4:5 | 26.9–42.7 | Yes | Yes (11 ABPA, 16 asthma) | Poor control despite 1st line treatment and/or contraindication or important secondary effects to CSS or antifungal treatment Relapse of asthma or ABPA | Δ FEV ₁ CSS use Days of hospitalisation Intravenous antibiotics Spirometry measures | 150–750 mg every 4 weeks | 12 months | 0.1–9.9 years | ABPA group: = FEV ₁ ↓ FEV ₁ decline and variability No significant change CSS dose (p>0.05) but 1/3 of patients ↓ CSS by 50% | Yes |
| BRINKMANN [31] | Case report | 1 | 0:1 | 15 | Yes | Yes | CSS dependence CSS side-effects (growth retardation) | NA | 300 mg every 4 weeks | 12 months | No | Initial ↓ oral CSS use CSS dependence 1 ABPA relapse = FEV ₁ | Doubtful |

Continued

TABLE 1 Continued

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for omalizumab administration | Objectives | Omalizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|------------------|---|------------|-----------|-------------|-------------|---------------|---|---|--|--------------------|-----------|---|----------------------------------|
| NCT00787917 [32] | Randomised, double-blind, placebo controlled study, phase 4 | 14 | | | Yes | Yes | Inclusion criteria: CF complicated by ABPA Oral CSS use for ABPA flare Age ≥ 12 years (except for Italy; ≥ 18 years) Total serum IgE levels ≥ 500 IU·mL ⁻¹ | Δ need of rescue CSS Δ ABPA exacerbation rate Δ FEV ₁ Time to CSS suspension Δ % oral CSS dosage Participants responding to omalizumab, as defined by a reduction in oral CSS dose use of $\geq 50\%$ as compared with baseline | Up to 600 mg daily + Itraconazole | 6 months | 12 months | Aborted due to difficulties in enrolling patients No published data Early termination of the study Participants dropped out of the intervention group: 1 due to AEs; 1 due to lack of efficacy; and 3 due to administrative problems 6 patients had serious AEs versus 1 in the placebo | |
| EMIRALIOGLU [33] | Case series | 6 | 1:2 | 11–32 | Yes | Yes | No response or adverse effects of CSS treatment | Monthly evaluation for: symptoms, exacerbation, IgE, spirometry, CSS dosage | 300 mg s.c. every 4 weeks; dosage adapted to body weight and IgE level at the beginning of treatment | 6–18 months | No | No pulmonary exacerbations in 4/6 (66.6%) No ABPA exacerbations in 6/6 (100%) \downarrow or stop CSS use \downarrow total IgE (p=0.028) = FEV ₁ (+3%, p=0.91) | Yes, especially if early started |
| LEBECQUE [34] | Case series | 2 | 1:1 | 14 | Yes | Yes | ABPA exacerbation Alternative to CSS treatment | NA | 375 mg every 2 weeks for 4 months then every 4 weeks for 3 months | 11 injections | No | \downarrow symptoms \uparrow FEV ₁ Stable up to 20 weeks following treatment withdrawal (FEV ₁ of 98% and 99% predicted) | Yes |

Continued

TABLE 1 Continued

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for omalizumab administration | Objectives | Omalizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|---------------|---------------|------------|-----------|-------------|-------------|---------------|--|------------|-------------------------------|--------------------|-----------|---|------------------|
| PARISI [35] | Case series | 3 | 3:0 | 11–28 | Yes | Yes | No or poor improvement with CSS and antifungal treatment | NA | 375–600 mg every 2 weeks s.c. | 8 weeks | No | ↓ symptoms ↓ total IgE (↓ 60–70%) ↑ FEV ₁ (+28–50%) | Yes |
| KANU [37] | Case report | 1 | 0:1 | 13 | Yes | Yes | CSS side-effects (IGT) | NA | 300 mg s.c. every 2 weeks | 11 weeks | No | ↓ symptoms ↑ FEV ₁ (+36%) | Yes |
| THOMAS [38] | Case report | 1 | 1:0 | 11 | Yes | Yes | CSS dependence CSS side-effects (IGT) | NA | 375 mg every 2 weeks s.c. | 16 weeks | No | ↓ symptoms ↓ systemic CSS use ↑ FEV ₁ BMI improvement 12 months after, patient needed omalizumab again | Yes |

M: male; F: female; CSS: corticosteroids; NA: not applicable; FEV₁: forced expiratory volume in 1 s; BMI: body mass index; FVC: forced vital capacity; s.c.: subcutaneous; IGT: impaired glucose tolerance; AEC: absolute eosinophil count; AE: adverse event.

TABLE 2 Studies investigating mepolizumab in allergic bronchopulmonary aspergillosis (ABPA) treatment in patients with cystic fibrosis (CF)

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | CF (yes/no) | ABPA (yes/no) | Reason for mepolizumab administration | Objectives | Mepolizumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|---------------|---------------|------------|-----------|-------------|-------------|---------------|--|---|----------------------|--------------------|-----------|---|------------------|
| ZHANG [39] | Case series | 3 | 0:3 | 24–63 | Yes | 2 out of 3 | ABPA/ABPM with high AEC and systemic CSS dependence | Effect on: FEV ₁ , total IgE, AEC, systemic CSS use, CF exacerbation rates | 100 mg every 28 days | 9–12 months | No | ↓ oral CSS use = exacerbation rate ↓ total IgE ↓ AEC (2 out of 3) ↑ FEV ₁ (1 out of 3) | Yes |
| BOYLE [40] | Case report | 1 | 0:1 | 43 | Yes | Yes | CSS dependence Side-effects with CSS, antifungal and omalizumab treatment | | 100 mg monthly | 20 months | No | Systemic CSS stop No ABPA exacerbations = FEV ₁ ↓ AEC = total IgE Improved chest radiograph | Yes |

M: male; F: female; ABPM: allergic bronchopulmonary mycosis; AEC: absolute eosinophil count; CSS: corticosteroids; FEV₁: forced expiratory volume in 1 s.

It has been hypothesised that the introduction of omalizumab at the first clinical presentation of ABPA may increase its effectiveness, and may be helpful to treat both acute ABPA exacerbations and chronic ABPA [26, 33, 34].

Omalizumab was generally well tolerated, and no severe adverse reactions were reported. NOVÉ-JOSSERAND *et al.* [19] reported mild side-effects in 12.5% of patients, such as pain at the injection site, skin rash and lip swelling.

In 2008, a randomised controlled trial (RCT) (NCT00787917), including 14 patients with CF and ABPA, was started to investigate the effectiveness and safety of the omalizumab. A higher number of adverse events were recorded in the treatment group (omalizumab plus itraconazole) than in the placebo group (itraconazole). These events were probably caused by the high dosage of omalizumab (up to 600 mg daily). However, the trial was stopped early because of difficulties enrolling patients (six patients (43%) dropped out for different reasons) [32].

These conflicting results raise the need for RCTs to evaluate the effectiveness of omalizumab [32, 41]. The relative rarity of this condition, affecting 8.9% of patients with CF, probably represents a limitation to recruiting an appropriate number of patients with CF affected by ABPA [42].

Mepolizumab in treating ABPA in patients with CF

Mepolizumab is an anti-IL-5 biologic drug approved to treat severe refractory eosinophilic asthma (≥ 6 years old) or Churg–Strauss syndrome [16]. Mepolizumab has been introduced as an off-label treatment with the same indications as omalizumab (corticosteroid dependence and/or side-effects), or after the failure of a trial with omalizumab, in patients with marked eosinophilia, since IL-5 acts as on eosinophils and B-cell proliferation, maturation and survival [43].

In a case series including two patients with corticosteroid-dependent ABPA and impaired glucose control, mepolizumab reduced corticosteroid use and eosinophil count. One of these patients had also been previously treated with antifungal therapy. No significant changes were observed regarding FEV₁, which remained stable, and exacerbation rate [39]. Of note, one patient started mepolizumab contemporarily with tezacaftor/ivacaftor, which may have contributed to the patient's clinical improvement [39].

BOYLE *et al.* [40] reported the use of mepolizumab in an adult with recurrent ABPA exacerbations, corticosteroid dependence and adverse drug effects related to corticosteroids, antifungal therapy (itraconazole *plus* voriconazole) and omalizumab. Following the mepolizumab treatment, the patient was gradually weaned from systemic corticosteroids; the patient's symptoms and chest radiological imaging improved; FEV₁ was stable; eosinophil count was reduced; and no ABPA exacerbations were recorded during the 20-month follow-up. The subsequent start of CFTR modulators, tezacaftor/ivacaftor, did not result in a further improvement of symptoms or FEV₁ [40].

The clinical applications for mepolizumab in treating ABPA in patients with CF are summarised in table 2.

Dupilumab in treating ABPA in patients with CF

Dupilumab acts as an anti-IL-4 receptor alpha mAb by inhibiting both IL-4 and IL-13 cytokine signalling involved in Th2 inflammation [44]. Currently, no data are available for dupilumab in patients with CF complicated by ABPA. However, dupilumab has been used to treat patients affected by asthma and ABPA [45–49]. MÜMLER *et al.* [45] switched to dupilumab a 49-year-old female experiencing corticosteroid side-effects and treatment failure to benralizumab, omalizumab and itraconazole. 8 months after starting the new treatment, the patient reported a significant increase in FEV₁, corticosteroid weaning and reduction of serum IgE levels [45]. Hence, the authors suggested that IL-4/IL-13 may be crucial in the ABPA inflammatory cascade [45]. Overall, seven adults in different case reports have been treated because of corticosteroid dependence and/or side-effects, or poor responses to other biologics (omalizumab, mepolizumab, benralizumab). Dupilumab induced clinical improvement and effectively reduced corticosteroid use [45–49]. One of these patients experienced asthma exacerbation, requiring hospitalisation. This flare was probably due to dupilumab-induced hypereosinophilia [46]. Indeed, some patients reported transient hypereosinophilia as a possible consequence of reduced lung eosinophil recruitment by blocking the IL-4 pathway [45, 46]. Interestingly, another patient had a positive sweat chloride test, but CFTR analysis was negative for mutations [47].

The clinical applications for dupilumab in treating ABPA are summarised in table 3.

TABLE 3 Studies investigating dupilumab in treating allergic bronchopulmonary aspergillosis (ABPA)

| Author [ref.] | Type of study | Patients n | Sex (M:F) | Age (years) | Cystic fibrosis (yes/no) | ABPA (yes/no) | Reason for dupilumab administration | Objectives | Dupilumab dosage | Treatment duration | Follow-up | Results | Benefit (yes/no) |
|----------------|---------------|------------|-----------|-------------|--------------------------|---------------|--|------------|---|--------------------|-----------|---|------------------|
| ERASO [50] | Review | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| RAMONELL [46] | Case series | 3 | 1:2 | 33–60 | No | Yes | Poor response to CSS CSS dependence Incomplete response to omalizumab and/or mepolizumab | NS | NS | 6 months | NS | Symptoms resolution No exacerbations CSS use reduction/suspension ↑ FEV ₁ ↓ total IgE ↑ AEC (2/3) A patient hospitalised for asthma exacerbation probably due to dupilumab-induced hypereosinophilia | Yes |
| MÜMLER [45] | Case report | 1 | 0:1 | 49 | No | Yes | CSS side-effects CSS dependence Incomplete or no response to benralizumab and omalizumab | NS | 600 mg loading dose, then 300 mg s.c. every 2 weeks | 8 months | NS | Symptom improvement Oral CSS suspension ↑ FEV ₁ ↓ F _{ENO} ↓ total IgE ↑ AEC (transient) | Yes |
| ALI [47] | Case report | 1 | 0:1 | 60 | No | Yes | CSS side-effects CSS dependence Omalizumab hypersensitivity reaction | NS | 300 mg s.c. every 2 weeks | 4 months | NS | Symptoms improvement ↓ oral CSS ↓ total IgE | Yes |
| MIKURA [48] | Case report | 1 | 1:0 | 45 | No | Yes | CSS dependence No improvement with mepolizumab | NS | 600 mg loading dose, then 300 mg s.c. every 2 weeks | 12 months | NA | Oral CSS suspension Radiological resolution ↓ total IgE | Yes |
| NISHIMURA [49] | Case report | 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

M: male; F: female; NA: not applicable; CSS: corticosteroids; s.c.: subcutaneous; NS: not specified; AEC: absolute eosinophil count; F_{ENO}: fractional exhaled nitric oxide.

Discussion

A systematic review of the available evidence on the efficacy and safety of biologic drugs in treating ABPA in paediatric and adult patients affected by CF has been performed.

Although several decades have passed since its discovery, ABPA is still one of the primary causes of morbidity in patients with CF. Treatment of CF remains uncertain and is a field that still requires further investigation. Systemic corticosteroids are considered the first line and the mainstay of ABPA treatment [51]. However, their effectiveness might be sometimes unsatisfactory due to poor responses or the need for long-term treatment, which exposes patients to corticosteroid-related side-effects. This is particularly concerning in children who may experience growth retardation, diabetes and osteoporosis [52]. Antifungals also represent the mainstay of ABPA treatment. The rationale for using antifungal agents relies on the reduction of *A. fumigatus* colonisation and the subsequent induced immune response [53]. However, this assumption is in contrast with the absence of *A. fumigatus* colonisation detected by sputum cultures that can be negative in up to 63% of patients with ABPA, with a higher detection rate (74%) by PCR [54]. To date, the evidence to support antifungal treatment in ABPA is limited to two RCTs on patients without CF, which showed a reduction in steroid usage after itraconazole [14]. Furthermore, itraconazole use is burdened with poor bioavailability, side-effects (e.g. hepatotoxicity, peripheral neuropathy), an increasing rate of *A. fumigatus*-resistant strains, and potential interactions with other drugs that are metabolised by hepatic cytochrome P450 [10, 55]. Notably, by acting as a cytochrome P450 inhibitor, itraconazole, as with the other triazoles, may determine an increase in the serum concentrations of CFTR modulators; thus, drug monitoring and dose adaptation is required to avoid toxicity [56].

Voriconazole is another triazole which has better bioavailability than itraconazole. It induced a statistically significant improvement in FEV₁ in 13 children with CF and ABPA (p=0.01). Two of them reported clinical improvement with voriconazole without corticosteroids. Photosensitivity was the most common adverse effect [57]. Posaconazole is a newer triazole and has a greater lung tissue affinity than itraconazole. In nine children with CF and ABPA, oral posaconazole, in association with or after unsuccessful steroid treatment, induced improvement in cough and showed a good safety profile [58]. Therefore, posaconazole and voriconazole may represent therapeutic alternatives to itraconazole, although more expensive. This review cannot draw conclusions about the effectiveness of antifungals because 76% of the included patients had received one or multiple courses of antifungal treatment with poor or no response, which was often one of the reasons to start treatment with biologics. Antifungals may have a role as a complementary treatment with biologics since they have a different mechanism of action. Nevertheless, when antifungals were associated with biologics their benefit was not assessed. Therefore, RCTs focused on antifungals are needed to their effectiveness and safety in ABPA, especially in patients with CF.

Recently, new therapeutic targets have been investigated for their potential in treating ABPA in patients with CF. The pathogenic mechanism of ABPA is based on a type 1 hypersensitivity reaction to *Aspergillus* antigens, with subsequent release of the Th2 cytokines pattern (IL-4, IL-5 and IL-13) and IgE activation [59]. This inflammatory pathway is significantly enhanced in CFTR knockout mice, probably due to impaired channel calcium function in CD3⁺ T-cells induced by defective CFTR [60, 61]. In patients with CF, impaired mucociliary clearance and thick mucus make these individuals more susceptible than patients with asthma to fungal colonisations/infections and then inflammatory/allergic responses [62]. The lung microbiome also plays a role in fungal colonisation through bacterial and fungal interactions. *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* infections, common colonisations in CF patients, have been associated with increased risks of *A. fumigatus* infection [63].

Since the Th2-driven inflammatory response is generally characterised by high blood levels of IgE and eosinophils, biologic drugs, specifically anti-IgE and anti-IL-5, have been suggested and attempted in patients with asthma or CF complicated by ABPA [50]. Most of the included studies reported variable improvement of symptoms, pulmonary tests (FEV₁), and, above all, a reduction in systemic corticosteroids dosage until their suspension in a significant percentage of individuals [19–28, 30, 33–38]. Interestingly, VAN DER ENT *et al.* [20] described a patient reporting clinical and spirometry improvement 4 h after omalizumab administration, highlighting a possible role of omalizumab as a diagnostic test for ABPA.

As regards mepolizumab, data are encouraging but limited to only three patients, and, to date, no definitive conclusions can be drawn about its effectiveness [39, 40].

Dupilumab has only been tested in patients suffering from asthma and ABPA, showing promising results [45–49].

The data mentioned above refer exclusively to the adult population as no findings have been reported in the paediatric population, except for some studies focusing on omalizumab. This result appears in contrast with the evidence supporting the long-term efficacy and safety of biologics in children affected by other chronic, pulmonary and/or allergic diseases, such as asthma [64–66]. Since few of the included studies focused on children, RCTs in children and adolescents are urgently required because the results obtained from RCTs on the adult population cannot be directly transferable to the paediatric population.

This systematic review noted a wide variability in reported evidence supporting the use of biologic drugs in treating ABPA in patients with CF. Notably, the analysis was limited by heterogeneity of several factors, such as varying ABPA definitions, the severity of CF disease and ABPA, the previous number of ABPA exacerbations, various concomitant treatments, different times to start treatment, different lengths of treatment duration and follow-up, lack of standardised dosages, and use of control groups.

Firstly, there is no unanimous definition of ABPA; thus, it is not possible to have a unique definition of ABPA severity. Accordingly, we hypothesised that this wide variability could be due to the difficulty in staging the disease, hampered by a lack of validated diagnostic tools with minimum acceptable cut-offs. Variable recommendations between guidelines may reflect differences in healthcare systems, broad economic and social issues, and changes in the evidence base for ABPA management. Comprehensive and updated guidelines, compliant with international standards for guidelines, could promote evidence-based recommendations, improve the clinical practice quality, and provide uniformity and appropriateness of treatment.

Secondly, though some studies reported CFTR mutations and colonisations for each patient, none of the research assessed if these factors might affect the efficacy of the biologics. Patients with CF are complex, and several infectious agents often coexist, causing the same clinical signs/symptoms, thus, masking and delaying ABPA diagnoses. Moreover, patients with CF are subjected to different treatments (in drugs, dosage, timing and duration); thus, figuring out if it is a single drug rather than a combination of treatments that are improving clinical status, laboratory and instrumental findings is complicated. Furthermore, significant heterogeneity is also apparent in the appeared in time to start treatment. We argue that administration of biologic drugs as second- or third-line treatment faces the advanced stages of an inflammatory response, which may reduce treatment response. Indeed, the early introduction of biologics has been associated with better outcomes [26, 33], which should be investigated in future studies. The included studies reported significant variability in the dosage and duration of treatment with biologic drugs. In some of these, omalizumab dosage was calculated based on weight and IgE levels. Further, in accordance with the guidelines for severe asthma [67], omalizumab can be administered in patients with total IgE levels lower than $1500 \text{ IU}\cdot\text{mL}^{-1}$; in contrast with this recommendation, omalizumab was used in patients with total IgE levels higher than $1500 \text{ IU}\cdot\text{mL}^{-1}$; thus, the dosage may have been underestimated, reducing its effectiveness [29]. Also, high doses of omalizumab with daily administration have been associated with an increased rate of adverse events [32]. However, no concern has been raised about biologics' safety in the other included studies, in which "standard" dosage and frequency of administration were applied. Indeed, biologics were well tolerated and any severe adverse reaction was reported. Only one patient was moved from omalizumab to mepolizumab because of severe arthralgia and myalgia [40]. NOVÉ-JOSSERAND *et al.* [19] reported mild side-effects in 12.5% of patients treated with omalizumab, such as pain at the injection site, skin rash and lip swelling. These data highlight biologics' good safety profile compared with corticosteroids, which are burdened by significant side-effects (*e.g.* impaired glucose tolerance, growth retardation, immunosuppression). This evidence is consistent with data on a large population of patients with moderate-to-severe asthma who underwent long-term treatment with omalizumab [68–70]. Notably, no significant difference was seen for the risk for infections between the omalizumab and placebo groups [70], which may be a limitation in prescribing biologics in patients with CF because of their susceptibility to infections.

Limitations

The main limitation of this systematic review is the lack of RCTs. The absence of control groups represents a critical bias as researchers are unable to determine whether the investigated treatment significantly affects the experimental group, increasing the risks of erroneous conclusions. As previously mentioned, the included studies showed heterogeneity and were conducted on small sample sizes. In addition, the definition of ABPA is variable among the studies. For example, NOVÉ-JOSSERAND *et al.* [19] applied the CFF consensus definition, including both patients who met the criteria for classical ABPA and patients who met the minimal diagnostic criteria for ABPA. Treatment with biologics was started in different stages of CF disease, with different dosages and duration and mainly as second/third-line treatment.

Reporting bias could also be another limitation as cases with unsuccessful treatments may not have been reported in the literature, as suggested by ASHKENAZI *et al.* [29].

Conclusions

The evidence is insufficient to support firm conclusions, and RCTs are urgently required to investigate the efficacy and safety of biologic drugs in ABPA in patients with CF. It is urgent to go deep into the mechanism of action of biologic drugs to better understand their potential utility in treating ABPA. Identifying the pathways shared by biologic drugs and ABPA could provide the rationale for implementing biologic drugs in clinical practice to resolve inappropriate inflammatory responses featuring ABPA. Knowledge of these pathways may be needed to move from phenotype to endotype since the inflammatory response, occurring in ABPA, changes among patients, as confirmed by the different responses to the same therapeutic regimes. Accordingly, the identification of the underlying pathogenic/inflammatory patterns of ABPA based on biomarkers would allow patients to be selected correctly and have targeted therapies set up to improve outcomes and reduce drug-related side-effects, which are the aims of precision medicine [15]. Lastly, the need to standardise the treatment regimen in terms of dosage and duration is urgently required; the option to administer biologic drugs alternatively or in combination with other drugs should also be evaluated.

In the context of targeted therapies, the advent of CFTR modulators and their significant impact on CF disease course has not yet been investigated *in vivo* regarding ABPA; however, a reduction in *A. fumigatus* colonisation was reported in patients with CF with treated with ivacaftor, which may suggest a consequent reduction in ABPA incidence [71, 72]. CFTR modulators *in vitro* have been shown to reduce radical oxygen species production by phagocytes induced by *A. fumigatus*, in both CF and control cells [73]. A case report signalled the occurrence of ABPA in a 13-year-old boy, despite treatment with ivacaftor [74].

In conclusion, the included studies are affected by qualitative weaknesses that make it difficult to come to firm conclusions on the efficacy and safety of biologic drugs. Nevertheless, mAbs could represent a valid therapeutic option in treating ABPA in patients with CF in whom conventional immunomodulatory treatment is not practical. Thus, if the risk of complications may occur, the use of biologics can be justified after a critical calculation of the risks and benefits. Large and prospective studies are required, especially in a population with a few therapeutic alternatives. However, no trial is currently ongoing. It would also be of value to include a cost-effectiveness analysis. Indeed, though expensive, omalizumab or mepolizumab, if effective, may positively impact patients' quality of life and hospitalisation rates for ABPA/respiratory exacerbations, thus reducing healthcare expenditure.

Points for clinical practice

The current mainstay of treatment for ABPA, corticosteroids and/or antifungals, can fail to induce clinical improvement and are burdened with possible side-effects. mAbs, by acting as targeted therapies, may represent a therapeutic option in ABPA. However, RCTs are required to assess their efficacy and safety.

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