Journal of Cystic Fibrosis 19 (2020) 119–124

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Omalizumab for asthma and allergic bronchopulmonary aspergillosis in adults with cystic fibrosis

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ARTICLE INFO

Article history:
Received 5 June 2019
Revised 15 July 2019
Accepted 31 July 2019
Available online 9 August 2019

Keywords:
Cystic fibrosis
Omalizumab
Allergic bronchopulmonary aspergillosis
Asthma

ABSTRACT

Background: In cystic fibrosis (CF), omalizumab has been used for difficult-to-treat asthma and allergic bronchopulmonary aspergillosis (ABPA) but safety and efficacy data are limited for this population.
Methods: We assessed patients receiving omalizumab for asthma or ABPA in the Toronto adult CF center between 2005 and 2017. We evaluated treatment safety and efficacy by analyzing changes in FEV_1% predicted (FEV_1pp) max value, slope and variability captured by the area under the curve (AUC), the cumulative dose of systemic corticosteroids (SCS), use of intravenous (IV) antibiotics and hospitalization days before omalizumab and up to 1 year after treatment initiation. Linear mixed effects model was used for FEV_1pp slope and the trapezoidal rule for FEV_1pp AUC.
Results: Twenty-seven CF patients received omalizumab, 16 (59.3%) for asthma and 11 (40.7%) for ABPA. No significant omalizumab-related adverse effects were observed. In the asthmatic group, the max value of FEV_1pp improved on omalizumab and the cumulative dose of SCS decreased. In the ABPA group, the rate of FEV_1pp decline (slope) and the variability of FEV_1pp (AUC) improved on omalizumab. In ABPA patients, the cumulative SCS dose was not significantly different but 4 (36%) patients decreased their SCS dose by >50% compared to baseline. Days on IV antibiotics and hospital days did not differ significantly before and while on omalizumab therapy.
Conclusions: In adult CF patients with difficult-to-treat asthma or ABPA, omalizumab should be considered. Larger studies are needed to identify patient characteristics that may predict response to omalizumab.

1. Introduction

Cystic fibrosis (CF) patients are prone to allergic bronchopulmonary aspergillosis (ABPA), a complex immunologic response to *Aspergillus* antigens [1,2]. Diagnosis of ABPA relies on a combination of clinical, radiological and immunological criteria, and it can be particularly difficult in this patient population due to the overlapping symptoms and clinical characteristics of CF. Systemic corticosteroids (SCS) are the mainstay of treatment and antifungals are often used as SCS-sparing agents for their potential to decrease the *Aspergillus* antigenic burden [2]. Considering that CF patients are susceptible to complications such as diabetes and osteoporosis [3], tapering of SCS is of particular importance, however, in some cases, this may be difficult due to poor ABPA control.

Although asthma is common in patients with CF [4], diagnosis is rarely straightforward in this population [5]. In the absence of a consensus definition and established criteria, it is considered a diagnosis of exclusion. Symptoms such as prolonged exhalation and wheezing, bronchial hyper-reactivity which may be seasonal, atopy or allergic rhinitis and a family history of asthma have been considered suggestive of this diagnosis. Patients with CF-asthma may present with eosinophilia and increased IgE without fulfilling the diagnostic criteria for ABPA [5–8].

Omalizumab is a glycosylated IgG1 monoclonal antibody that binds to circulating IgE and creates biologically inert IgG-anti-IgE complexes. It is prescribed for severe, difficult-to-control allergic

Abbreviations: AUC, area under the curve; CF, cystic fibrosis; FEV_1pp, forced expiratory volume in 1 s % predicted; IQR, interquartile range; SCS, systemic corticosteroids.

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https://doi.org/10.1016/j.jcf.2019.07.011
1569-1993/

asthma to reduce the frequency and severity of exacerbations [9]. Since elevated total IgE levels are a central finding in ABPA, omalizumab has been used off-label to improve symptom control and to allow SCS tapering [10]. So far, no study has assessed omalizumab in CF-asthma whereas, regarding ABPA, limited data in pediatric CF patients have suggested that it may be associated with improved lung function, reduced frequency of respiratory symptoms and decreased use of SCS [11]. Data for omalizumab in adult CF patients with ABPA are scarce and contradictory [12–14], with the only randomized controlled study terminated early due to inability to recruit patients [15,16]. Published evidence on omalizumab use in CF are summarized in Table S1 of the supplement.

The aim of this retrospective study was to evaluate treatment efficacy and safety of omalizumab as a rescue therapy in adult CF patients with difficult-to-treat ABPA or asthma. We hypothesized that response to omalizumab may differ in these groups of patients regarding lung function, use of SCS and outcomes reflecting disease control.

2. Methods

Adult CF patients who received omalizumab in the Toronto Adult CF center between 2005 and 2017 were included in this study. Omalizumab had been prescribed for a first or a recurrent episode of asthma or ABPA by an Immunology specialist with experience in CF. The dose was adjusted for body weight and total IgE levels according to the recommendations for allergic asthma. For patients with total pre-omalizumab IgE levels higher than 700 IU/ml, the administered dose did not exceed 375 mg every two weeks. Data were retrieved from the Toronto CF registry and clinical charts. All individuals included in the registry gave their written informed consent to have their data collected and used for research purposes. The study protocol was approved by the ethics committee of St Michael's Hospital.

Included patients were evaluated by two study investigators (ET, ALS) independently to confirm the diagnosis of ABPA or CF-asthma. No disagreements were observed. ABPA was diagnosed when at least the minimal diagnostic criteria, previously described by Stevens et al. [2], were fulfilled; namely, acute or subacute clinical deterioration with total serum IgE > 500 IU/ml in steroid naïve patients and serum IgE antibody or immediate skin test reactivity for *Aspergillus* species, in association with at least one of the following: a) precipitins or IgG antibody to *A. fumigatus* or b) radiologic abnormalities such as infiltrates or mucus plugs which did not improve by antibiotics and physiotherapy. CF-asthma was a diagnosis of exclusion, used for patients with asthma-like symptoms (e.g. wheezing, atopy) and clinical deterioration which could not be attributed to another diagnosis. These patients did not fulfil the minimal diagnostic criteria for ABPA [5,6]. Of note, the establishment of asthma diagnosis in this cohort did not rely on post-bronchodilator reversibility considering that all patients receiving omalizumab as rescue therapy were already on bronchodilators which could not have been safely discontinued.

Treatment safety and efficacy were assessed by comparing the periods before and up to one year on omalizumab treatment. For patients who received omalizumab for less than one year, the same periods of time before and while on omalizumab were compared. Regarding treatment safety, adverse effects (type, severity) and reasons for omalizumab discontinuation were recorded. Concerning treatment efficacy, we evaluated changes of the forced expiratory volume in 1 s (FEV_1) % predicted (FEV_1pp), calculated with the Global Lung function Initiative (GLI) reference Eqs. [17]. More specifically, we assessed the mean absolute difference (best FEV_1pp while on omalizumab treatment compared to best FEV1pp before omalizumab initiation), the slope and the variability of FEV_1pp. The latter was calculated with the area under the curve (AUC). To assess the steroid-sparing effect of omalizumab, we compared changes in the cumulative dose of SCS expressed as the equivalent of prednisone and we also calculated the proportion of patients who decreased the cumulative SCS dose by ≥50% of the dose administered before omalizumab was started. Additional outcomes were changes in the number of days on intravenous (IV) antibiotics, days of hospitalization and spirometry measurements (reflecting the number of visits) before and while on omalizumab. Patient death or lung transplantation were assessed within 1 year and within the longest available follow-up after omalizumab initiation.

2.1. Statistical analysis

Descriptive statistics are summarized by reporting the median (interquartile range - IQR) for continuous variables and the frequency (proportion) for categorical variables. Comparisons between patients with ABPA and asthma were done using chi-square test for categorical variables and Mann-Whitney test for continuous variables.

Pre- and post-omalizumab data were analyzed using the Wilcoxon signed-rank test. The rate of change in FEV_1pp pre- and post-omalizumab was calculated by fitting a linear mixed effect model. A random intercept and random slope term were used. Values of each patient were modeled as a cluster. An autoregressive-1 term was added to the residuals to account for the fact that measurements taken closer together in time would be more highly correlated than measurements taken farther apart. The AUC of FEV_1pp was calculated using the Trapezoidal rule. The relationship of the IgE levels and eosinophil count before omalizumab initiation with the FEV_1pp mean absolute difference, slope, AUC and cumulative SCS dose was assessed with Spearman's correlation. All analyses were done in R version 3.4.3. All p-values are two-sided and assessed at $p < .05$ unless otherwise stated.

3. Results

Twenty-seven adult CF patients received omalizumab during the study period [age median (IQR) 33.0 (26.9–42.7), male 12 (44.4%)], 16 (59.3%) for asthma and 11 (40.7%) for ABPA. Table 1 summarizes patients' characteristics. At omalizumab initiation, the median FEV_1pp of the asthmatic and ABPA groups were 44.1% and 39.5% respectively ($p = .65$). In the asthmatic group, the median IgE was 215.5 IU/ml. All asthmatic patients were assessed for *Aspergillus* sensitization either with a skin prick test [14 (87.5%) tested, 3 cases positive] and/or with *Aspergillus* specific IgE [7 (43.8%) tested, 6 cases positive]. Considering that one patient was positive for both, *Aspergillus* sensitization was found in 8 (50%) of patients. Thirteen (81.3%) were tested for precipitins; *Aspergillus* precipitins were positive in two patients whereas all asthmatic patients were negative for Micropolyspora faeni, Thermoactinomyces vulgaris, pigeon serum and Aureobasidium pullulans. Pulmonary colonization with *A. fumigatus* was found in 11 (68.8%) asthmatic patients. In the ABPA group, the median IgE was 889 IU/ml, 6 (55%) had immediate cutaneous reactivity to *Aspergillus*, all patients had *Aspergillus*-specific IgE and 3 (27%) had positive *Aspergillus* precipitins. Although not a necessary component for the diagnosis of ABPA, 9 (81.8%) of ABPA patients had a pulmonary colonization with *A. fumigatus*. Seven (63.6%) patients with ABPA presented with new radiological evidence compatible with ABPA (infiltrates n = 4, worsening mucous plugging n = 2, tree-in-bud n = 1).

Omalizumab was initiated due to one or a combination of the following: poor control despite first line treatment (n = 17) and/or contraindication or important secondary effects to SCS or antifungal agents (n = 16). For 24 (88.8%) patients, omalizumab was initiated for a relapse of asthma or ABPA. The time between

Table 1
Characteristics of ABPA and asthmatic CF patients receiving omalizumab.

Patient characteristics	Total (n = 27)	Asthma (n = 16)	ABPA (n = 11)	p value
Age at omalizumab initiation, years	33.0 (26.9–42.7)	36.9 (29.0–44.2)	27.8 (21.8–37.7)	0.08
Gender, Male	12 (44.4)	7 (43.8)	5 (45.5)	1.00
CF genotype				0.36
Homozygote F508del	13 (48.1)	6 (37.5)	7 (63.6)	
Heterozygote F508del	9 (33.3)	6 (37.5)	3 (27.3)	
Other	5 (18.5)	4 (25.0)	1 (9.1)	
Airway colonization				
Pseudomonas aeruginosa	22 (81.5)	13 (81.2)	9 (81.8)	1.00
Aspergillus spp.	20 (74.1)	11 (68.8)	9 (81.8)	0.66
Other fungi	2 (7.4)	2 (12.5)	0	0.50
FEV_1pp at omalizumab initiation	43.3 (34.9–57.2)	44.1 (37.2–50.0)	39.5 (33.0–59.0)	0.65
BMI	21.4 (19.5–23.4)	21.4 (20.2–23.5)	20.6 (19.5–23.0)	0.35
Nasal polyps	13 (48.1)	8 (50.0)	5 (45.5)	1.00
Pancreatic insufficiency	22 (81.5)	12 (75.0)	10 (90.9)	0.62
CF-related diabetes	19 (70.4)	10 (62.5)	9 (81.8)	0.40
Total IgE,[a] IU/ml	408.0 (192–875)	215.5 (115.5–379)	889 (715.5–2991.5)	**≤0.001**
Positive skin test for *Aspergillus* (n = 19)	9 (47.4)	3 (25.0)	6 (85.7)	**0.02**
Aspergillus-specific IgE (n = 18)	17 (94.4)	6 (85.7)	11 (100.0)	0.39
Aspergillus-specific precipitins (n = 21)	5 (23.8)	2 (15.4)	3 (37.5)	0.33
Eosinophils[a]	0.38 (0.23–0.56)	0.33 (0.25–0.56)	0.43 (0.18–0.56)	0.84

Results are expressed as median (interquartile range) or as n (%). Statistically significant results are highlighted in bold.
Abbreviations: ABPA: allergic bronchopulmonary aspergillosis, BMI: body mass index, FEV_1pp: forced expiratory volume in 1 s % of predicted.
[a] Highest value during the year preceding omalizumab introduction.

diagnosis and omalizumab initiation did not differ significantly between the two groups [median 137.5 (range 30–1352) days for ABPA, 430 (104–1610) days for asthma, p = .21]. At omalizumab initiation, 17 (62.9%) patients received SCS, 8 (29.6%) a systemic antifungal, 6 (22.2%) montelukast, 2 (7.4%) were on oxygen therapy and 1 (3.7%) on non-invasive ventilation. The range of administered omalizumab dose was 150–750 mg per month. No omalizumab-related adverse effects were observed but one patient with CF-asthma described moderate chest tightness during administration of the first dose which was followed by a significant improvement of symptoms (compared to those reported before omalizumab) within 48 h. One patient discontinued omalizumab after 420 days due to lack of insurance coverage.

Within 1 year of follow-up, 3 (11.1%) patients died pre-transplant (1 of the asthmatic and 2 of the ABPA group, median time to death 318 days, IQR 251–328.5). The median (IQR) of FEV_1pp at omalizumab initiation was 34.4 (31.4–38.8) for patients who died within 1 year of follow-up and 45.1 (36.4–58.8) for those censored at last follow-up. Three (11.1%) patients were transplanted (1 of the asthmatic group) within 1 year of follow-up. Of note, within the maximal available follow-up (median 2.4, range 0.1–9.9 years), 6 (22.2%) of patients died pre-transplant (**Table 2**). Table 3 presents results relevant to treatment efficacy and compares outcomes before and after one year of omalizumab. In the *asthmatic group*, the FEV_1pp max value improved (median change 6.8%, p = .005) but no significant change was observed in the FEV_1pp slope or the FEV_1pp AUC before and while on omalizumab treatment. The cumulative dose of SCS decreased on omalizumab (median change 836.5 mg, p = .044) and 6 (37.5%) patients decreased the SCS dose by >50%. No significant changes were observed in the days of hospitalization or the days on IV antibiotics. In the *ABPA group*, the max FEV_1pp was not significantly different for the period before and while on omalizumab treatment but the rate of FEV_1pp decline (median change of slope − 0.021, p = .019) and the variability of FEV_1pp (median change of AUC 1099.5, p = .027) decreased on omalizumab. Although the cumulative dose of SCS was not significantly different, 4 (36%) patients decreased the SCS dose by >50%. Days on IV antibiotics and hospital days did not differ significantly before and while on omalizumab therapy. Compared to the period before omalizumab, patients with asthma had less spirometry measurements while on omalizumab suggesting less frequent visits [pre-omalizumab mean 14.5 (range

Table 2
Parameters reflecting disease control in ABPA and asthmatic CF patients before and while on omalizumab treatment.

Parameter	Total (n = 27)	Asthma (n = 16)	ABPA (n = 11)	p value
Cumulative dose of SCS[a] before omalizumab, mg	2955.0 (1106–3858)	2957.5 (1213.5–4372.5)	2955.0 (973.5–3802)	0.87
Cumulative dose of SCS[a] after omalizumab, mg	1863.0 (245–5060.5)	1142.5 (125–4630.3)	2028.0 (594–4994)	0.32
Decrease of cumulative SCS dose[a,b] by ≥50%, mg	10 (37.0)	6 (37.5)	4 (36.4)	1.00
Days of hospitalization before omalizumab	16.0 (6.5–58)	13.0 (3.8–46.8)	19.0 (12–58)	0.50
Days of hospitalization after omalizumab	28.0 (0–63.5)	5.0 (0–55.0)	35.0 (14.0–67.5)	0.34
Days on IV antibiotics before omalizumab	39.0 (17.5–88.0)	43.5 (10.5–105.0)	24.0 (19.5–71.0)	0.64
Days on IV antibiotics after omalizumab	39.0 (0–82.5)	45.5 (0–74.8)	37.0 (17.5–94.5)	0.88
LTx within 1-year of follow-up	3 (11.1)	1 (6.2)	2 (18.2)	1.00
Vital status, Deceased pre-transplant within 1-year of follow-up	3 (11.1)	1 (6.2)	2 (18.2)	1.00
LTx during longest available follow-up[c]	4 (14.8)	2 (12.5)	2 (18.2)	1.00
Vital status, Deceased pre-transplant during longest available follow-up[c]	6 (22.2)	4 (25)	2 (18.2)	1.00

Results are expressed as median (interquartile range) or as n (%). Statistically significant results are highlighted in bold.
Abbreviations: ABPA: allergic bronchopulmonary aspergillosis, IV: intravenous, LTx: lung transplantation, SCS: systemic corticosteroids.
[a] The cumulative dose of SCS was assessed as a prednisone equivalent.
[b] Among the 27 patients studied, 6 (22%) had an increase in the cumulative SCS dose while on omalizumab and 4 (15%) had a non-significant change (i.e. a modification of the cumulative SCS dose by 10% or less).
[c] The longest available follow-up was median 2.4 (range 0.1–9.9) years.

Table 3
Primary outcomes of CF patients receiving omalizumab for ABPA (n = 11) or asthma (n = 16) and comparisons before and after one year of omalizumab treatment.

Variables (change before and after one year[c] of omalizumab)	Asthma	[a]p value	ABPA	[a]p value	[b]p value
FEV_1pp maximum value[d]	6.809 (0.85–11.9)	**0.005**	3.939 (−0.41–7.13)	0.12	0.45
FEV_1pp slope	−0.006 (−0.03–0.007)	0.21	−0.021 (−0.04–0.002)	**0.019**	0.42
FEV_1pp AUC	1480.5 (−834.5–4283.0)	0.11	1099.5 (312.2–3124.5)	**0.027**	0.94
Cumulative dose of prednisone, mg	836.5 (197.5–2151.2)	**0.044**	150 (−160–964.5)	0.37	0.18
Days of hospitalization	4.5 (−3.3–13.3)	0.65	−10 (−31–0)	0.097	0.075
Days on IV antibiotics	8.5 (−16.3–42.0)	0.59	−7 (−16.5–14.9)	0.51	0.30

The values within the brackets are the IQR. Statistically significant results are highlighted in bold.
Abbreviations: AUC: area under the curve, FEV_1pp: forced expiratory volume in 1 s % of predicted, IV: intravenous.
[a] p value was assessed using the Wilcoxon signed-rank test.
[b] p value was assessed using the Mann-Whitney test.
[c] FEV_1 outcomes, days of hospitalization and days on IV antibiotics were also assessed at 3 months of omalizumab treatment. For the 3-month time-point, the only parameters reaching statistical significance were the FEV_1pp slope and the FEV_1pp AUC of the ABPA group. More specifically, the rate of FEV_1 decline (median change of FEV1pp slope − 0.008, p = .009) and the variability of FEV_1pp (median change of AUC 392, p = .012) decreased on omalizumab. These changes were towards the same direction with those observed for the ABPA group at one year of omalizumab treatment.
[d] Mean absolute difference: best FEV_1pp while on omalizumab treatment vs FEV_1pp at omalizumab initiation.

4–31), while on omalizumab 11 (2–26), p = .0009] whereas, for the ABPA group, the difference was not statistically significant (p = .11). Comparisons between the asthmatic and ABPA groups in regard to these outcomes (days on IV antibiotics, hospital days, number of spirometry measurements) did not reach statistical significance. The levels of IgE before and while on omalizumab were not possible to compare due to the very few available IgE measurements while on omalizumab.

No significant correlations were observed between the levels of IgE before omalizumab initiation and the change in FEV_1pp max value (r = 0.295), the slope (0.032) or the AUC (0.216) while on omalizumab. Eosinophils count assessed within 90 days before omalizumab initiation correlated weakly with the FEV_1pp slope (r = 0.13) and the AUC (r = −0.36) suggesting that a higher eosinophil count before omalizumab initiation was associated with less variability of FEV_1pp while on omalizumab treatment. However, interpretation of this latter analysis is hampered by the large number of missing values [for 10 (37%) patients, eosinophil count was not available within 90 days before omalizumab initiation].

4. Discussion

In this retrospective observational study, we evaluated the safety and efficacy of omalizumab up to one year of treatment in adult CF patients with asthma or ABPA. This is the first study evaluating omalizumab in CF asthma and the biggest study to-date assessing anti-IgE treatment in adult CF patients. In all cases, omalizumab was initiated due to poor disease control and/or contraindication for or significant secondary effects related to SCS or antifungal agents. Omalizumab was well tolerated and no significant drug-related adverse effects were observed. The main findings were an improvement of FEV_1pp max value and a decrease of the cumulative SCS in asthmatic patients and an improvement of the FEV_1pp slope and FEV_1pp variability in ABPA patients between the period before and while on omalizumab treatment. In the latter group, there was no significant change in the cumulative SCS dose but one third of patients decreased SCS by >50%.

Previous studies in non-CF populations reported a good safety profile of omalizumab for persistent uncontrolled asthma. In a recent meta-analysis, common adverse events included lower respiratory tract infection, nasopharyngitis, headache, arthralgia and injection site pain or local reaction, observed with a similar frequency in controls [18]. In the CF population, most studies also reported good treatment tolerance (Table S1 of the supplement) with one case of allergic reaction motivating treatment interruption after 2 months [12]. In our study, one CF patient with asthma experienced moderate chest tightness during the administration of the first omalizumab dose. This patient described an improvement of dyspnea compared to pre-treatment symptoms within 48 h. Although a rapid improvement of symptoms is very rare, it has been previously described in one pediatric CF patient with ABPA who improved symptoms and FEV_1 within a few hours after a single dose of omalizumab [19].

Regarding asthma, diagnostic criteria used for non-CF patients may be difficult to apply in CF due to the coexistence of CF-related symptoms and recurrent infectious exacerbations. In the non-CF literature, an increasing number of studies considers asthma an umbrella diagnosis for different phenotypes and endotypes [20] but information regarding asthma characteristics and pathogenesis in CF is extremely limited [5–8]. Although ABPA is more prevalent in asthmatic patients, no studies have evaluated the natural history of asthma as a predisposing factor for ABPA in CF. Interestingly, allergic fungal airway disease has been described as a continuum having asthma and ABPA at its extremes [21,22]. One of the asthma phenotypes called “severe asthma with fungal sensitization” (SAFS) [21] has been described as part of this continuum but has not been studied yet in CF. In this study, 50% of CF-asthma patients were sensitized for *Aspergillus*. Due to the small sample size, these patients were not possible to study as a separate group. Future studies focusing on CF-asthma are needed to characterize different asthma phenotypes and to evaluate whether they may have a different response to treatment.

Evidence regarding the efficacy of omalizumab in CF patients with ABPA is limited and contradictory (Table S1 of the supplement). As mentioned above, a randomized controlled trial was prematurely terminated [15,16]. The rarity of the studied population but also the disproportionally high dose of omalizumab used for this study (600 mg daily) [15] may have contributed to its low patient recruitment and to its early termination. Most observational studies have assessed pediatric patients and a meta-analysis including 13 children reported an improved FEV_1, fewer respiratory symptoms and decreased use of SCS [11]. Regarding omalizumab in adult CF patients with ABPA, five studies [12–14,23,24] included 40 patients in total but only one provided results for adults separately [13]. The larger study including 32 patients (21 adults) reported no significant difference in FEV_1 but a steroid sparing effect with 50% of patients being able to reduce their daily dose of SCS [13]. Interestingly, in another study, a subset of 3 patients with higher post-treatment IgE experienced improved outcomes (e.g. no exacerbation, stable or improved BMI and FEV_1) [12]. Although we also did not find a significant difference in outcomes relevant to exacerbation rate (days of hospitalization, days on IV antibiotics) nor in the FEV_1pp max, we observed an improvement in the rate of FEV_1pp decline (slope) and FEV_1pp variability (AUC) during omalizumab treatment suggesting that these variables may reflect disease control more accurately in this setting.

In non-CF patients with asthma, some characteristics have been shown to predict response to omalizumab. A recent, prospective observational study evaluated 801 patients with allergic asthma aged 12 years or older and assessed response to omalizumab treatment using multiple criteria. Considering the results of this study collectively, responders were more likely to be females, to have at least one positive allergen-specific IgE, high baseline eosinophil levels and a worse control of asthma before omalizumab as described by their reported symptoms. The use of asthma medications in addition to inhaled corticosteroids/long-acting β2 agonist alone and the number of exacerbations during the previous 12 months were also predictive of response to treatment [25]. Regarding total IgE, the predictive role in this context has not been established and, although decreased levels after omalizumab treatment have been described, IgE levels are difficult to interpret in this setting unless omalizumab-free IgE assays are used [26,27]. In CF patients, previous studies have shown inconsistent results regarding predictors of response. Notably, in one case series [23], patients with severe initial disease did not improve FEV1pp on omalizumab whereas in another article omalizumab was less effective in patients with severe lung disease and long-term ABPA [24]. In our study, no significant correlations were observed between the levels of IgE before omalizumab initiation and the change in FEV_1pp max value, the slope or the AUC while on omalizumab. The eosinophil count before omalizumab correlated weakly with the FEV_1pp slope and the AUC while on omalizumab but the results are difficult to interpret due to the important number of missing values. An important finding was that patients with ABPA or asthma severe enough to be prescribed omalizumab rescue therapy were at a high mortality risk, indicating that early referral for lung transplantation should be considered for these patients. Indeed, the 1-year mortality rate of this population (14.8%) is high given the median FEV_1pp of 43.3% (Table 1).

This study has several limitations mainly due to its retrospective design, small sample size and lack of control groups. Asthma diagnosis not being confirmed by spirometry criteria is an additional limitation, however, as mentioned above, diagnosis of asthma in CF is challenging and relies on the exclusion of other diagnoses. Another limitation is the heterogeneity of treatment used in our patient population regarding SCS and antifungal agents at omalizumab initiation. The assessment of CF patients with difficult-to-control asthma or ABPA leads to an inherent indication bias which may limit the generalizability of our results. Moreover, the small sample size did not allow for subgroup analyses (e.g. those with a first episode of asthma/ABPA compared to those with a relapse) nor the identification of specific patient characteristics that could help identify responders to treatment. Although the parameters we assessed may also reflect changes in symptoms, it was not possible to evaluate patients' subjective perception of symptoms and, in those presenting at least a partial response to treatment, we were not able to evaluate the long-term effects of omalizumab after the first year of administration. Considering these points, our findings should be interpreted with caution and will need to be confirmed by larger studies and ideally by a randomized controlled trial. However, performing such a study is difficult due to the rarity of the studied condition, as also denoted by the early termination of a previous randomized controlled trial focusing on CF and ABPA [15].

In summary, this retrospective study suggests that, in adult CF patients with difficult-to-control asthma or ABPA, omalizumab should be considered as it may allow improvement of FEV_1 – increase of FEV_1pp max in asthmatic patients, and improvement of FEV_1pp slope and FEV_1pp variability in ABPA patients – and help decrease SCS in a subset of patients. Patients with ABPA or asthma severe enough to be prescribed omalizumab as a rescue therapy are a population of high risk for mortality and transplant assessment should be considered early. Larger studies with control groups are needed to confirm these findings, to identify patient characteristics that may predict response to treatment and to investigate the effect of omalizumab on long-term outcomes.

Contributors

AK contributed to the study design, data collection, manuscript drafting and revision. SC contributed to data collection, manuscript drafting and revision. JS and AC contributed to data analysis and revision of the manuscript. DC contributed in data collection and revision of the manuscript. PV, CC and KM contributed to study design and revised the manuscript for important intellectual content. ET and ALS contributed to study design and supervision, and revised the manuscript for important intellectual content. All authors reviewed the study findings, read and approved the final version before submission.

Support statement

During this study, AK was supported by the Swiss National Science Foundation (grant P300PB_164733) and the University Hospital of Lausanne (Fond de perfectionnement). AC was supported by a post-doctoral fellowship from the Canadian Lung Association. The funding sources had no role in study design, data collection, data analysis or writing of the report.

Data availability statement

The deidentified data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.07.011.

References

[1] Patterson K, Strek ME. Allergic bronchopulmonary aspergillosis. Proc Am Thorac Soc 2010;7(3):237–44.
[2] Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis - state of the art: cystic fibrosis foundation consensus conference. Clin Infect Dis 2003;37(3):S225–64.
[3] Plant BJ, Goss CH, Plant WD, Bell SC. Management of comorbidities in older patients with cystic fibrosis. Lancet Respir Med 2013;1(2):164–74.
[4] CF Foundation Registry. 2016 annual data report accessed August 2018 https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf.
[5] Balfour-Lynn IM, Elborn JS. "CF asthma": what is it and what do we do about it? Thorax. 2002;57(8):742–8.
[6] Kent BD, Lane SJ, van Beek EJ, Dodd JD, Costello RW, Tiddens HA. Asthma and cystic fibrosis: a tangled web. Pediatr Pulmonol 2014;49(3):205–13.
[7] Morgan WJ, Butler SM, Johnson CA, et al. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the U.S. and Canada. Pediatr Pulmonol 1999;28(4):231–41.
[8] Koch C, McKenzie SG, Kaplowitz H, et al. International practice patterns by age and severity of lung disease in cystic fibrosis: data from the epidemiologic registry of cystic fibrosis (ERCF). Pediatr Pulmonol 1997;24(2):147–54 [discussion 159-161].
[9] Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014(1):CD003559.
[10] Voskamp AL, Gillman A, Symons K, et al. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract 2015;3(2):192–9.
[11] Tanou K, Zintzaras E, Kaditis AG. Omalizumab therapy for allergic bronchopulmonary aspergillosis in children with cystic fibrosis: a synthesis of published evidence. Pediatr Pulmonol 2014;49:503–7.

[12] Ashkenazi M, Sity S, Sarouk I, et al. Omalizumab in allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. J Asthma Allergy 2018;11:101–7.
[13] Nove-Josserand R, Grard S, Auzou L, et al. Case series of omalizumab for allergic bronchopulmonary aspergillosis in cystic fibrosis patients. Pediatr Pulmonol 2017;52(2):190–7.
[14] Perisson C, Destruys L, Grenet D, et al. Omalizumab treatment for allergic bronchopulmonary aspergillosis in young patients with cystic fibrosis. Respir Med 2017;133:12–15.
[15] Novartis. An exploratory study to assess multiple doses of Omalizumab in patients with cystic fibrosis complicated by acute bronchopulmonary aspergillosis (ABPA). Clinicaltrials.gov (www.clinicaltrials.gov) (accessed 21/01/2013) 2008:ClinicalTrials.gov Identifier: NCT00787917. [CRS: 5500100000010742].
[16] Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev 2018(3):CD010288.
[17] Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177(3):253–60.
[18] Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep 2015;5:8191.
[19] van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. Thorax 2007;62(3):276–7.
[20] Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2018;56(2):219–33.
[21] Agarwal R. Severe asthma with fungal sensitization. Curr Allergy Asthma Rep 2011;11(5):403–13.
[22] Woolnough K, Fairs A, Pashley CH, Wardlaw AJ. Allergic fungal airway disease: pathophysiologic and diagnostic considerations. Curr Opin Pulm Med 2015;21(1):39–47.
[23] Emiralioglu N, Dogru D, Tugcu GD, Yalcin E, Kiper N, Ozcelik U. Omalizumab treatment for allergic bronchopulmonary aspergillosis in cystic fibrosis. Ann Pharmacother 2016(3):188–93.
[24] Lehmann S, Pfannenstiel C, Friedrichs F, Kroger K, Wagner N, Tenbrock K. Omalizumab: a new treatment option for allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Ther Adv Respir Dis 2014;8(5):141–9.
[25] Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real–world study. J Allergy Clin Immunol Pract 2018;7(1):156–64.
[26] Gon Y, Ito R, Maruoka S, et al. Long-term course of serum total and free IgE levels in severe asthma patients treated with omalizumab. Allergol Int 2018;67(2):283–5.
[27] ElMallah MK, Hendeles L, Hamilton RG, Capen C, Schuler PM. Management of patients with cystic fibrosis and allergic bronchopulmonary Aspergillosis using anti-immunoglobulin E therapy (omalizumab). J Pediatr Pharmacol Ther 2012;17(1):88–92.