



Review article

Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: A synthesis review of published literature



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ABSTRACT

Omalizumab, a humanized mAb that binds to IgE, has been an effective therapy for patients with severe allergic asthma; however, there are few clinical trials examining the efficacy of Omalizumab in patients with allergic bronchopulmonary aspergillosis (ABPA) except some case reports. To assess the clinical and immunological effects of Omalizumab in ABPA patients, we made a synthesis review of 102 cases from 30 published literature, analyzed the effects of Omalizumab therapy in ABPA and conducted subgroup analyses to determine factors that influenced the therapy endpoints. We found that Omalizumab treatment not only provided a clinically important reduction in serum IgE, exacerbation rates and steroid requirement, but also showed attenuated asthma symptoms and improved pulmonary function parameters in patients with ABPA. Moreover, further discussion was made when interpreting the results. Double-blind, randomized, placebo-controlled trials are necessary to establish the efficacy and safety of this novel therapeutic intervention for ABPA patients.

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Abbreviations: ABPA, Allergy bronchopulmonary aspergillosis; IgE, Immunoglobulin E; mAb, monoclonal Ab; TB, Tuberculosis; CF, Cystic Fibrosis; FeNO, Fractional Concentration of Exhaled Nitric Oxide; FEF_{25–75}, Forced Expiratory flow from 25%–75% of FVC; FEV₁, Forced expiratory volume in one second; FVC, Forced vital capacity; ACT, Asthma control test; FcεR1, The high-affinity receptor for immunoglobulin E; PBMC, Peripheral Blood Mononuclear Cell; IFN-α, Interferon-α; AE, Adverse events.

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1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA), a severe allergic pulmonary complication caused by *Aspergillus* species [1,2], which occurs almost exclusively in patients with asthma [3–5] or cystic fibrosis [6,7]. The global prevalence of ABPA has been estimated to be as high as 2.5% [8], since its initial description by Hinson in 1952 [9]. Delays in diagnosis or under-treatment of ABPA may lead to pulmonary fibrosis, bronchiectasis with chronic sputum production, and increasingly severe persistent asthma with loss of lung function. Recommend pharmacotherapy for ABPA involves systemic corticosteroids and itraconazole [10], the aim is to prophylaxis against, and treatment of, acute exacerbations, as well as prevention of end-stage fibrotic disease [10]. Although corticosteroids can control the symptoms of most patients, some patients become steroid-dependent, or for others, long-term use may not be possible due to adverse effects [11]. Anti-fungal agents may be an alternative for, or added to, steroids [12]. In an effort to decrease patients' exposure to systematic steroids, many clinicians have tried anti-IgE therapy.

Omalizumab, a humanized mAb that binds to the CH3 domain, near the binding site for the high-affinity type-I IgE Fc receptors of human IgE, can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cells and basophils [13]. Omalizumab has been a useful treatment for severe allergic asthma [14,15], especially for patients with high serum IgE levels. Improvements in asthma symptoms and health-related quality-of-life, and a significant reduction in the frequency of asthma exacerbation as well as significant reductions of inhaled corticosteroids dosage were observed in allergic asthmatic patients after anti-IgE therapy [14,16,17]. Clinical trials and real life experiences that focus on adverse effects of Omalizumab tested its safety [18]. Omalizumab has been found effective for not only allergic asthma but also a number of other atopic conditions including allergic rhinitis and chronic idiopathic urticaria [19].

Since Van der Ent CK first reported the case of Omalizumab therapy in a 12-year-old girl with ABPA which resulted in the rapid and clear improvement of clinical signs and lung function [20], a series case reports of ABPA treatment with Omalizumab have been published [12,20–49]. In total, 116 individuals including 14 stopped during treatment. Although cases reports have been published, there are no randomized, placebo-controlled trials evaluating this treatment approach. Herein, we present a synthesis report of the published cases on the potential efficacy of Omalizumab as treatment for ABPA.

2. Methods

2.1. Search strategy

We searched Medline, Cochrane Database of Systematic Reviews (CDSR), EMBASE, Ovid, and Web of science databases for all

reports published from inception until November 2015, using the following search terms: “anti-immunoglobulin E” or “anti-IgE” or “Omalizumab ” or “ Xolair ” and “ Allergic Bronchopulmonary Aspergillosis ” or “ ABPA ”. Trials were not excluded on the basis of language. All eligible studies were retrieved, and their reference lists were checked for additional articles. To ensure a complete review of the available studies, the abstracts of relevant scientific meetings were also examined. We also contacted authors in cases where relevant data were unclear.

Furthermore, we also searched the ongoing trial registry clinicaltrials.gov for any ongoing trials using “anti-IgE and ABPA” and “Omalizumab and ABPA”.

2.2. Selection of studies

Studies were included only if they evaluated assessment criteria prior to and after Omalizumab use from original description.

2.3. Data management and extraction

For data extraction, we used a standardized data collection form, which included the following items: source (First author, Journal, Location); study methods; participants (No. of cases, sex, age, race, clinic history with TB/Asthma/CF, duration from ABPA diagnosed to use Omalizumab); baseline characteristics (total eosinophil count, serum IgE, specific IgE for *Aspergillus fumigatus*, FeNO, FEF_{25–75}, FEV1%, FVC%, FEV1/FVC%, exacerbation rate, prednisone dose, ACT score), interventions (Omalizumab dose, duration, follow-up time); outcomes (similar to baseline characteristics); results (the decline of total IgE, FeNO, exacerbation rate, prednisone dose; the improvement of ACT score, FEV1%, FVC%, FEV1/FVC%) and adverse outcomes. We resolved any disagreement which arose by consensus discussion. Data was extracted in cases of unpublished reports or multiple publications.

2.4. Data analysis

Total IgE, FeNO, exacerbation rate, prednisone dose, ACT score, FEV1%, FVC%, FEV1/FVC% were primary efficacy endpoints of the present data synthesis. The mean and standard deviation of baseline characters and outcomes were calculated. For single case, we used SPSS17.0 to analyze data and calculated Mean and SD. For cases with calculated median and range (minimum to maximum), we used the following formula [50] to calculate mean(x) and SD(S):

$$\bar{x} \approx \frac{a + 2m + b}{4}$$

Fig. 1. Flow diagram of included study, from inception to 2015 Nov.

Table 1

Summary of analyzed case reports on the administration of Anti-IgE (Omalizumab) for Allergic Bronchopulmonary Aspergillosis.

First author, year	Journal	Study Type	Location	Sex	Age(y)	Total IgE (IU/mL)	With CF
D.Hirsch (2012)	IFAC	Case report	USA	1F	14	not available	No description
I.Sastre (2011)	J Investig Allergol Clin Immunol	Case report	Spain	1F	53	3090	N
Keith (2015)	Allergy Rhino	Case report	USA	1F	42	5236	N
Cornelis K (2007)	Thorax	Case report	The Netherlands	1F	12	5200	Y
Brinkmann,F (2010)	Allergy	Case report	Germany	1F	15	234	Y
ZicarI.AM (2014)	European Review for Medical and Pharmacological Sciences	Case report	Italy	1F	13	695	Y
Richard B. (2012)	Ann. N.Y. Acad. Sci.	Case report	USA	1F	23	683	Y
Adaobi K et (2008)	Pediatric Pulmonology	Case report	USA	1F	13	947	Y
Alcorta,A (2009)	Allergy	Case report	Spain	1M	21	not available	N
Bhargave,G (2010)	Allergy	Case report	USA	1M	54	10,200	N
Laura M.(2009)	Arch Bronconeumol.	Case report	Germany	1M	71	327	N
Randhawal (2009)	Journal of Asthma	Case report	USA	1M	14	2487	Y
Thomas.MF (2009)	J R Soc Med	Case report	UK	1M	11	9178	Y
Martorell,C (2013)	EAACI	Case report	Spain	1M	31	3500	N
Tetsuya H (2013)	J Microbiology, Immunology and Infection	Case report	Japan	1M	51	1011	N
Lebecque, P (2009)	BMJ	Case report	Belgium	1F1M	14	2893	Y
Bulut, I (2014)	Allergy	Case report	Turkey	1F1M	50	not available	N
Hatziagorou.E	EAACI	Case report	Greece	1F2M	17.1	not available	Y
Collins J (2012)	J Asthma and Allergy	Case report	USA	2F2M	50.5 (44–58)	1730 (565–4362)	N
Bhargave GA (2010)	J Asthma.	Case report	USA	2M	39	6331	N
Dominic AF) (2013)	Pediatric Respiratory Reviews	Case report	Australia	2M	14–15	3636	Y
EIMallah MK(2012)	JPPT	Case report	USA	2M	14	1410	Y
Carlos EM (2008)	Pediatric Pulmonology	Case report	USA	3M	14.2	3509	Y
Sylvia L.et (2014)	Therapeutic Advances in Respiratory Disease	Case report	Germany	4F2M	19.47 (5.3–33.2)	1908	Y
Novartis (2008)	Cochrane Database Syst Re	the double-blind study	Multicentre	5F4M	21 (16.9–25.1)	not available	Y
Bavbek.S (2015)	Allergy Asthma Proc	Case report	Turkey	7F7M	44.21 (31.2–57.22)	1057 (502–1602)	Y
Leblond.IT	EAACI	Case report	France	8F8M	56 (29–76)	582 (131–3766)	N
Astrid L et (2015)	American Academy of Allergy, Asthma & Immunology	a placebo-controlled randomized trial	Australia	9F4M	59 (26–69)	2314 (346–7860)	N
Perezde.LA (2011)	Thorax	Case report	Spain	13F5M	49 (32–66)	698 (478–977)	2 are CF
Meyer.P	clinicaltrials. gov	Case report	Sweden	16	not available	not available	Y

Definition of abbreviations: M = male, F = female, CF = cystic fibrosis, Y = yes, N = no, I.V = intravenous injection, S.C&S.Q = subcutaneous injection.

3.2. Characteristics of the patients included

From the included cases reports, original articles, conference reports and clinic trials all over the world, a total of 170 ABPA patients were treated with Omalizumab. We included 102 patients in our systematic review since some clinical trials terminated prematurely, thus 54 individuals were excluded due to lack of original reports. Fig. 2 shows the detail process of patients' selection. Table 3 outlines the baseline characteristics and medication requirements at study entry. Age ranged from 7 to 76, including 22 (21.57%) teenagers, with 98 Caucasian, three were melanoderm and one xanthoderm. A total of 40 patients had comorbidity with CF, while 17 with asthma and two were diagnosed with TB. The average level of total IgE was 1901 IU/ml, the highest was 10,200 IU/ml while mean specific IgE for *Aspergillus fumigatus* was 31.72 IU/ml. Mean baseline FEV1 values ranged from 21 to 115% of predicted values. Almost all patients (99.03%) suffered from treatment failure with systemic steroids or anti-fungal treatment, such as side effects of prednisone, uncontrolled asthma symptoms, or frequent exacerbation.

3.3. Omalizumab dosage

Different studies used various dosages of Omalizumab ranging from 225 mg to 750 mg according to weight and serum IgE level, and dosing frequency ranged from once per week to once monthly while the most commonly used dose was 375 mg every two weeks

(Table 2). One case from New York also used Omalizumab though the subject's IgE level ranged from 9541 to 10,200 IU/ml with systemic corticosteroid treatment [29]. A total of 70 cases (83.33%) received intravenous injections and 14 (16.67%) received subcutaneous injections, and no information was provided regarding the administration route of the other 18 subjects. The mean period of Xolair use was 13.4 months ranging from 3 months to 60 months depending on the effect of Omalizumab.

4. Evaluation of treatment effects

4.1. Symptom control

Control of ABPA symptoms clearly improved over the follow-up period (Table 4). The ACT score rose from 11.37 ± 6.2 to 18.53 ± 9.5 ($p = 0.0099$) in 19 cases. Additionally, a statistically significant (43.75%) decrease in FeNO was observed between 31.4 ± 24.36 and 17.66 ± 11.24 ($p = 0.0089$) in 14 cases, which included 13 subjects from Australia [49] and one from Japan [40].

4.2. Total IgE change

The total serum IgE level after Omalizumab use declined 59% compared with pre-Omalizumab use (Table 4), the mean IgE level after Omalizumab use was 804.5 ± 514.7 IU/ml while prior was 1901 ± 1971.67 IU/ml, $p < 0.001$.

Table 2
Summary of effects of Anti-IgE (omalizumab) for ABPA.

First author, year	treatment failure prior to anti-IgE	Dose/period of Omalizumab	decrease of serum IgE level	Improved persistent symptoms or fewer exacerbations	Prednisone discontinued or decrease	side effect
D.Hirsch (2012)	No description	450 mg every 6 weeks, I.V, 6y	Y	Y	Y	N
I.Sastre (2011)	Y	375 mg every 2 weeks, I.V, 3m	Y	Y	Y	N
Keith (2015)	Y	450 mg every 3 weeks, SC, 2y	Y	Y	Y	N
Cornelis K (2007)	Y	300 mg every 2 weeks, SC, 6w	N	Y	Y	N
Brinkmann,F (2010)	Y	300 mg 4-weekly,I.V, 1y	Y	Y	Y	N
Zicari,AM (2014)	Y	300 mg every 2weeks, I.V, 1y	Y	Y	Y	N
Richard B (2012)	Y	600 mg weekly, I.V, 5y	Y	Y	Y	N
Adaobi K et (2008)	Y	300 mg every 2 weeks, SC, 11w	Y	Y	Y	N
Alcorta,A (2009)	Y	not available, 8m	Y	Y	Y	N
Bhargava,G (2010)	Y	not available, 1y	Y	not available	not available	not available
Laura M.(2009)	Y	225 mg every 2 weeks, I.V, 20m	Y	Y	Y	N
Randhawal (2009)	Y	375 mg every 2weeks, SC, 11m	Y	Y	Y	N
Thomas.MF (2009)	Y	375 mg fortnightly, SC, 12m	Y	Y	Y	N
Martorell,C (2013)	Y	450 mg every 4 weeks, I.V, 6m	Y	Y	Y	N
Tetsuya H (2013)	Y	375 mg every 2 weeks,I.V, 2.5y	Y	Y	Y	N
Lebecque, P (2009)	Y	375 mg every 2 weeks, I.V, 22w	Y	Y	Y	N
Bulut,I (2014)	Y	225&600 mg every 2 weeks, i.v, 4m	Y	Y	Y	N
Hatziaorou,E	Y	Not described, 1–1.5y	Y	Y	Y	N
Collins J (2012)	Y	375 mg every 2 weeks, I.V, 1y	Y	Y	Y	N
Bhargava GA (2010)	Y	375 mg every 2 weeks, SC, 4m	Y	Y	Y	N
Dominic AF (2013)	Y	300 mg 4-weekly, SC, 4m	Y	Y	Y	N
ElMallah MK(2012)	Y	450 mg weekly, SC, 1–1.5y	Y	Y	Y	N
Carlos EM (2008)	Y	300–375 mg every 2 weeks,SQ, 1.5y	Y	Y	Y	N
Sylvia Let (2014)	Y	600 mg fortnightly, I.V, 32w	Y	Y	except one	N
Novartis (2008)	No description	600 mg every 2–4 weeks, S.C, 6m	terminated prematurely	terminated prematurely	terminated prematurely	Y
Bavbek.S (2015)	Y	375 mg every 2 weeks, I.V, 31.5 (27.51–34.49)m	Y	Y	Y	N
Leblond.IT	Y	Not described	Y	Y	Y	N
Astrid L et (2015)	Y	375 mg every 2 weeks,I.V, 4m	Y	Y	Y	N
Perezde.LA (2011)	Y	608 (500, 716) mg weekly, I.V, 4m	Y	Y	Y	N
Meyer.P	Y	not available, 3–6m	Y	Y	Y	N

Definition of abbreviations: M = male, F = female, CF = cystic fibrosis, w = weeks, m = months, y = years, Y = yes, N = no, I.V = intravenous injection, S.C&S.Q = subcutaneous injection.

From logistic analysis we determined that the declined level of total IgE was related to the baseline of IgE level and route of administration (Table 5). The patients whose serum IgE >1000 IU/ml were more sensitive to Xolair treatment than those with <1,000IU/ml. The comparative data was 3650.76 ± 2694.49 vs 713.11 ± 141.573 IU/ml, $p < 0.001$. The subcutaneous injection group demonstrated a reduction with 3867.79 ± 3148.27 IU/ml in total IgE versus the intravenous injection group with 1812.79 ± 1274.18 IU/ml ($p = 0.016$). The results suggested a greater benefit of Omalizumab for patients with higher levels of IgE at baseline and subcutaneous administration route.

4.3. Exacerbation

A significant decrease of exacerbation rate was observed with treatment, when compared with pre-treatment (Table 4). The mean rate of severe exacerbation decreased from 2.74 ± 2.31 (1–12) per patient during the previous year to 0.38 ± 0.70 (0–3) during the period of treatment ($p < 0.001$). This represented a reduction of 86% over the year. More obvious rate of exacerbation was observed in patients who had more than 4 times exacerbations at baseline, 5.6 ± 2.5 vs. 1.65 ± 1.11 , $p = 0.001$ (Table 5). Subcutaneous injection groups had better effect over intravenous injection groups, 4.22 ± 3.07 vs 2.21 ± 2.23 , $p = 0.049$. In addition, longer usage (≥ 1 year) group declined 3.08 ± 1.95 while short usage group (< 1 year) declined 1.5 ± 1.53 , $p = 0.004$. These data suggested that the effect of Omalizumab on exacerbation was influenced by baseline exacerbation, administration route and length of Omalizumab use.

4.4. The change of systemic steroid use

Table 4 shows the comparison of the data preceding and post the onset of treatment with Omalizumab. A total of 29 out of 96 patients with long term systemic steroids were able to discontinue prednisone, while the others reduced the dose to $\leq 90\%$ of the initial dose (16.39 ± 13.47 vs. 1.63 ± 2.25 , $p < 0.001$), and some subjects were prednisone-dependent with history of discontinuation failure due to relapse.

From subgroup analysis, we found that the male group reduced 22.18 ± 20.34 while the female group reduced 11.05 ± 4.14 mg/d per person, $p = 0.025$ (Table 5). This suggested that male subjects were more sensitive to prednisone reduction dose after Omalizumab therapy.

4.5. Lung function test

FEV1% was available in 96 and FVC% in 24 subjects over the follow-up time. The mean improvement of FEV1% predicted was 21.9% from 59.63 ± 19.34 to 72.21 ± 19 ($p < 0.001$), while the mean FVC% predicted improvement of 11.4% from 83.4 ± 21.6 to 94.83 ± 22.11 , but unpaired *t*-test with Welch's correction showed no statistical significant difference pre- and post- Omalizumab treatment (Table 4). In addition, FEV1/FVC% was 56.93 ± 14.14 in 31 cases before Xolair use (Table 3), but after Omalizumab treatment there were only three cases with reported data, and all had improvement in FEV1/FVC%. There was no significant association between the improvement of lung function and the demographic and clinical features of the patients, such as sex, age, baseline IgE

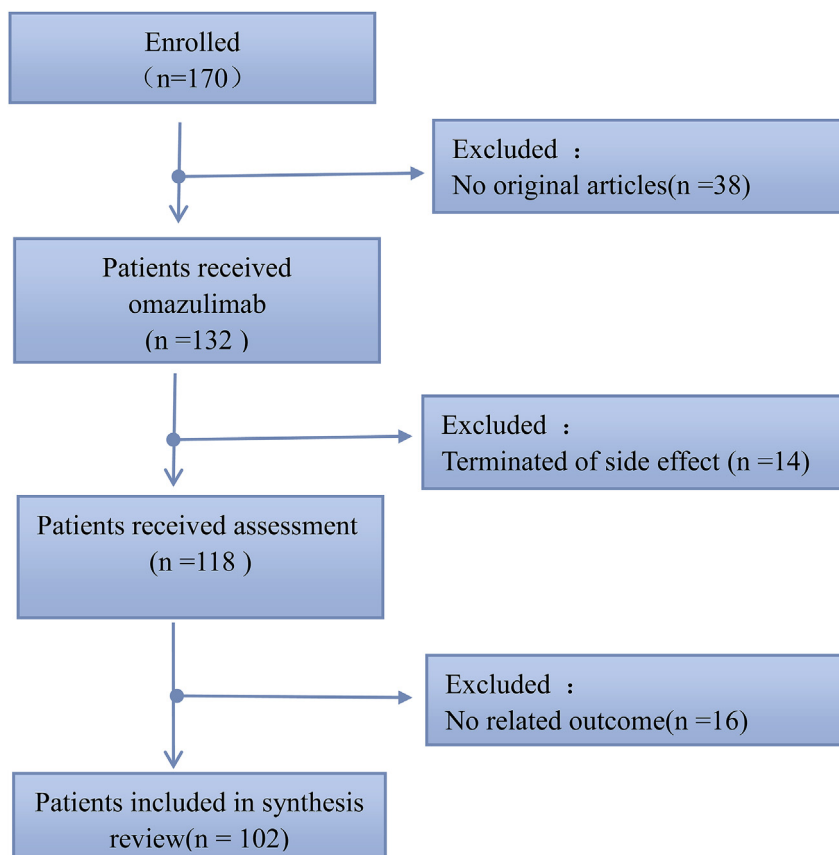


Fig. 2. Flow chart of study patients.

level and lung function, duration from ABPA diagnosis to Omalizumab use, dose/duration of Omalizumab treatment, anti-fungal therapy, the presence of comorbidity and diagnostic criteria of ABPA (Table 5).

4.6. Thoracic imaging

Only 30 patients were imaged before Omalizumab therapy, of whom only six patients' second thoracic CT scans revealed persistent bilateral bronchiectasis at multiple levels with less bronchial wall thickening (indicative of remission of inflammation), as well as a lower degree of bronchiectasis and a reduced number of micro-nodular peribronchial opacities (indicative of reduced impaction and inflammation of the distal airways).

4.7. Blood eosinophilia

Blood eosinophilia were measured in 40 patients during the diagnosis stage, but only one study evaluated eosinophil levels after Omalizumab use. Collins Jennifer reported that mean eosinophil counts decreased after 12 months of treatment by 38% [51].

4.8. Safety

There were no significant adverse effects reported during the study period related to Omalizumab use; most importantly, there were no reported episodes of anaphylaxis. Some patients had exacerbation during the wash-out period after Omalizumab use (Table 6).

5. Discussion

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease caused by extreme sensitivity to *Aspergillus Fumigatus* and may occur in 2%–15% of patients with cystic fibrosis [52]. Corticosteroids and anti-fungal therapy are the mainstay treatment strategies for ABPA, but long time use of systemic steroids often results in severe side effects such as growth retardation, diabetes, hypertension, cataracts and osteoporosis, and there is a concern of long term therapy in steroid-dependent disease [53]. The total IgE level in ABPA is also usually high, therefore, Omalizumab which can act against serum free IgE may be useful for ABPA patients.

Since Dr CK van der Ent reported the first case that Omalizumab was beneficial to a 12-year-old patient with ABPA [20], 28 cases report which include 89 subjects have been published. Perezde LA reported 18 cases in 2011, the largest number ever published [32]. A self placebo-controlled randomized trial involved 13 volunteers was recently finished in Australia and the authors found that clinical improvement was accompanied by decreased basophil reactivity to *A. fumigatus* and FcεR1 and surface-bound IgE level [49]. Novartis conducted a double-blind study evaluating the safety and efficacy of Omalizumab for the treatment of ABPA in patients with CF aged 12 years and older from November, 2008 (NCT00787917), but this study was terminated on July 11, 2011 due to adverse events [54]. More over 38 cases of ABPA treated with Omalizumab were mentioned in previous citations without any data available, so those cases were excluded from our analyses. Though Tanou K reported a synthesis review of Omalizumab therapy for ABPA in children with CF [55], there was no exact evaluation of Omalizumab use in ABPA, therefore we summarized all reported

Table 3
Baseline characteristics of 102 individuals.

Baseline characteristics	No of data gained	
Age (years)	N = 102 (100)	
Mean (SD)	41 (19)	
Median (range)	41 (7, 76)	
Gender n (%)		
Male	48 (47.1)	
Female	54 (52.9)	
Race n (%)		
Caucasian	98 (96.07)	
Melanoderm	3 (2.94)	
Xanthoderm	1 (0.98)	
Weight (kg)	N = 51 (50)	
Mean (SD)	74.27 (14.14)	
Median (range)	73 (45,102)	
Clinical history n (%)		
with TB	2 (1.96)	
with Asthma	17 (16.67)	
with CF	40 (39.21)	
ABPA duration prior to Anti-IgE(yrs)	N = 59 (57.8)	
Mean (SD)	5.4 (4.26)	
Anti-fungal treatment	47 (46.08)	
Treatment failure with systemic steroids or itraconazole prior to treatment n (%)	101 (99.03)	
Total eosinophil count	N = 22 (21.57)	
Mean (SD)	676.36 (190.16)	
Median (range)	676 (317, 1100)	
Total IgE (IU/ml)	N = 97 (95.1)	
Mean (SD)	1901 (1971.67)	
Median (range)	1901 (131, 10,200)	
Specific IgE for A.f (IU/ml)	N = 48 (47.05)	
Mean (SD)	31.72 (24.16)	
FEV1 of predicted (%)	N = 93 (91.17)	
Mean (SD)	59.63 (19.34)	
Median (range)	60 (21, 115)	
FVC of predicted (%)	N = 24 (23.5)	
Mean (SD)	83.4 (21.6)	
Median (range)	83 (45, 95)	
FEV1/FVC	N = 31 (30.39)	
Mean (SD)	56.93 (14.16)	
Median (range)	57 (41, 85)	
Exacerbations prior	N = 98 (96.07)	
Mean (SD)	2.74 (2.31)	
Median (range)	3 (0, 10)	
FeNO	N = 13 (12.74)	
Mean (SD)	30.5 (25.12)	
ACT score	N = 19 (18.62)	
Mean (SD)	11.36 (6.2)	

FeNO = fractional exhaled nitric oxide, ACT = asthma control test. FEV1 = Forced expiratory volume in one second, FVC = forced vital capacity, N = the number of.

cases and performed analysis to evaluate the effect of Omalizumab in ABPA patients.

The global prevalence of ABPA has been estimated to be as high as 2.5% [8]. The morbidity of ABPA ranges from 0.1‰ to 5.075‰ of the population in India [56]. Majority of ABPA incidences have been

reported in Western countries, with few cases in Asian countries such as China, where Omalizumab is little used. Thus, the effect of ABPA on Asian populations remains unclear. ABPA is a severe type of allergic asthma that occurs in approximately 10% of patients with severe asthma, while ABPA complicates only 2% of patients with mild asthma [57]. Approximately 16.67% of ABPA patients published treated with Omalizumab had asthma comorbidity (Table 3). Thus the use of Omalizumab in asthma requires further investigation. Additionally, ABPA afflicts 2%–15% of patients with cystic fibrosis (CF) [52], and about 39.21% ABPA cases in our study complicated with CF, although CF has no effect on the evaluation of therapeutic efficiency. Robert Y.L reported two cases of ABPA with TB history that benefited from Omalizumab [30]. Approximately one-third of the ABPA cases were initially misdiagnosed as pulmonary TB in India indicating a need for better recognition of this entity [58]. Almost all subjects failed to respond to systemic prednisone or had serious adverse effects; therefore, it remains unclear whether all ABPA patients can benefit from Xolair. Hirsch reported one case diagnosed with severe asthma and treated with Xolair for 4 years before a diagnosis of ABPA was confirmed [35].

All the studies used various doses of Omalizumab (Table 2). Dosing recommendations were based on a patient's baseline total IgE and weight (0.016 mg/kg/IgE) up to a maximum of 750 mg monthly [59]. Dose calculation were based on requirement to bind 90% free IgE *in vitro*. As ABPA patients by definition have baseline IgE levels exceeding the dosing table upper limit (>1000 IU/ml), and many ABPA patients may yet have IgE levels above the dosing table range, therefore patients with ABPA generally exceed the current dosing parameters of Omalizumab due to their often very high serum IgE levels. Several cases with serum IgE higher than 7000 IU/ml used 375 mg every two weeks [27,29,30,49], and L. A. Perezde (2011) reported one case that used Omalizumab as high as 716 mg per week [32]. From published literature, apparent clinical efficacy has been administration of doses at or only modestly greater than the dosing table, thus suggesting that dosing for ABPA was greater than that currently recommended for patients with lower baseline IgE levels and may observed in asthma patients receiving 0.016 mg of Omalizumab per kg per IU/ml of IgE for a minimum duration of 12 weeks [60]. However, the ideal treatment duration of Omalizumab for ABPA is still ambiguous; Richard B. Moss (2012) reported a case of Omalizumab use as long as 5 years wherein an attempt to discontinue Omalizumab in late 2010 resulted in an exacerbation, decline in lung function, and rise in IgE levels, which were resolved with reinstitution of Omalizumab [39]. Sylvia L et al. (2014) also reported two subjects that experienced exacerbation after Omalizumab withdrawal [46].

Omalizumab, a member of the biological class of medications, is a humanized monoclonal IgG1 antibody to IgE that binds to free serum IgE, it can block IgE combining with IgE receptors on the surface of inflammatory cells, preventing the immune response of effector cells and the signaling strength. Previous studies have

Table 4
Effect of omalizumab on ABPA patients.

	prior			poster			P value
	Mean	SD	N	Mean	SD	N	
Total IgE (IU/ml)	1901	1971.67		804.5	514.7		<0.001
Exacerbation rate (per year per patient)	2.7404	2.3117		0.38	0.698		<0.001
FEV1 of predicted (%)	59.63	19.34		72.21	19		<0.001
FVC%	83.4	21.6		94.83	22.11		0.0767
FENO(ppm)	31.4	24.36		17.66	11.24		0.0713
ACT score	11.367	6.2		18.53	9.5		0.0099
Prednisone dosage (mg/d)	16.39	13.47		1.63	2.25		<0.001
No. of PSL use			96			67	<0.001

Table 5
Efficacy endpoints of the change of total IgE, acute onset, PSL usage, the change of FEV1% evaluated by sex, age, with CF or not, ABPA duration prior to omalizumab treatment, serum IgE and specific IgE for *Aspergillus fumigatus*, no of acute onset, FEV1%, medication ways and duration.

	Change of total IgE(IU/ml)				Change of acute onset				Change of PSL use (mg/d)				Change of FEV1%			
	Mean	SD	N	p-value	Mean	SD	N	p-value	Mean	SD	N	p-value	Mean	SD	N	p-value
Sex																
male	3247	3179.718	18	0.416	3.5238	1.9652	21	0.204	22.1776	20.34,152	21	0.025	19.5929	22.02332	28	0.86
female	2412.29	1772.007	12		2.5385	2.4364	13		11.0489	4.14,342	9		18.6105	12.0395	19	
Age (y)																
≥18	3163.07	3068.937	15	0.621	2.74	1.71	23	0.115	18.8259	18.0373	22	0.729	17.2	22.78,708	26	0.416
<18	2662.17	2355.925	15		4	2.828	11		21.5714	18.0449	7		21.6667	11.1863	21	
With CF or not																
With	2416.18	2160.176	19	0.19	2.8571	1.976	28	0.231	15.6895	10.60,619	22	0.209	18.1842	13.1804	38	0.656
No	3771.45	3385.946	11		2.0556	2.4846	18		31.4286	29.29,225	7		23.4667	33.7	9	
ABPA duration prior to anti-IgE(yrs)																
≥4.21	2205.67	1478.451	12	0.558	3.2308	2.3507	13	0.42	23.8711	26.9085	9	0.246	19.6133	26.6939	15	0.569
<4.21	2730.19	2700.131	13		2.67	1.5	18		12.6222	2.9111	15		16.1154	12.304	26	
Serum IgE (IU/ml)																
≥1000	3650.76	2694.49	23	<0.001	3.0526	1.5802	19	0.598	17.2381	12.1157	16	0.571	15.9111	12.9144	27	0.483
<1000	713.11	141.573	9		2.6923	2.2504	13		21.1967	23.8698	12		19.0941	16.7824	17	
Specific IgE(IU/ml)																
≥30	2397	1339	7	0.536	3.8	1.48,324	5	0.658	14.1667	5.21,416	3	0.352	15.8	12.657	7	0.574
<30	3275.27	374.922	11		4.5	3	4		32.9167	31.32,158	6		12.418	11.916	11	
NO.of acute onset																
≥4	2325	1610.604	7	0.663	5.6	2.5	10	0.001	16.667	8.756	6	0.96	27.78	32.43	9	0.312
<4	2043.56	899.291	9		1.65	1.11	37		17.092	19.591	18		15.8	14.27	24	
FEV1 of predicted (%)																
≥60	3259.38	2672.159	8	0.272	2.93	2.3	14	0.656	18.495	13	13	0.339	17.1667	15.663	18	0.88
<60	2296.16	1540.213	16		3.31	2.36	16		14.3	6.24	11		17.8522	13.2573	23	
Medication ways																
SC&SQ	3867.79	3148.266	12	0.016	4.222	3.073	9	0.049	20.111	15.893	9	0.28	18.1429	13.575	14	0.442
I.V	1812.79	1274.178	19		2.2174	2.2352	23		35	34.141	5		23.31	22.03	20	
Anti-IgE duration (months)																
≥12	3011.1	3184.306	20	0.548	3.08	1.95	22	0.004	17.83	18.08	23	0.335	16.715	14.928	33	0.199
<12	2513.63	1388.194	12		1.5	1.53	24		25.83	16.33	6		23.85	23.2	16	

CF = cystic fibrosis, ABPA = allergic bronchopulmonary aspergillosis, I.V = intravenous injection, SC&SQ = subcutaneous injection, FEV1 = forced expiratory volume in 1 s, PSL= Prednisone.

shown that anti-IgE therapy results in reductions in cell surface IgE of 90–99% [61], the reduction in free IgE levels leads to reductions in high-affinity IgE receptor (FcεRI) expression on mast cells, basophils, and dendritic cells [61–63]. The allergic response of effector cells to allergen stimulation decreased after a period of

Table 6
Adverse effects has been reported.

Different kinds of AEs	No.	Percent (%)
Participants with AE(s)	9	7.76
Non-serious AEs		
Infective pulmonary exacerbation of CF	7	6.03
Cough	4	3.45
Headache	4	3.45
Pyrexia	3	2.59
Hemoptysis (blood in sputum)	4	3.45
Injection site swelling	4	3.45
Injection site warmth	4	3.45
Injection site erythema (redness)	3	2.59
Hypokalemia	2	1.72
Nasopharyngitis	2	1.72
Sputum increased	1	0.86
Bronchopulmonary aspergillosis allergic	2	1.72
Rhonchi (noisy expiratory breathing sound)	1	0.86
Non-cardiac chest pain	1	0.86
SAEs		
Patients with any SAE	6	5.17
Infective pulmonary exacerbation of CF	5	4.31
Allergic Bronchopulmonary Aspergillosis	2	1.72
Distal intestinal obstruction syndrome	1	0.86
Hemoptysis	1	0.86
Rhonchi	1	0.86

AE = adverse effect. SAE = serious adverse effect.

Omaliuzumab use. Treatment with Omaliuzumab can also reduce inflammatory cells recruiting (especially eosinophils), tissue remodeling and the change of pulmonary function [64]. Omaliuzumab obviously reduces the free IgE level of ABPA patients, especially for these with >1000 IU/ml baseline IgE levels. Voskamp A.L (2015) used SPT and allergen provocation *in vitro* with PBMCs from ABPA patients to monitor the efficacy of Omaliuzumab therapy, and found that basophile sensitivity to *A. fumigatus* and surface-bound IgE and FcεR1 levels decreased significantly after Omaliuzumab treatment, with no effect observed with placebo treatment [49]. Van der Ent (2007) observed no changes in total or specific immunoglobulins (IgE, IgG, and IgA) during the treatment period in a 12-year old girl with 5200 IU/ml of total serum IgE levels [20].

Exacerbation rate declined following Omaliuzumab treatment (Table 4). Our findings suggested that baseline exacerbation rate, route of administration and treatment duration influenced the efficacy of Omaliuzumab (Table 5). As most of the cases reported were not adequately controlled by prednisone, Omaliuzumab showed potential benefits of severe ABPA. Omaliuzumab also reduced asthma exacerbation, particularly among those with a recent or frequent exacerbation [65]. Nonetheless, the mechanisms underlying ABPA exacerbation are complex. Omaliuzumab removes free circulating IgE, reducing IgE binding to mast cells and basophils, thus the allergic response of effector cells to *Aspergillus* stimulation decreased after a period of Omaliuzumab use, as well as suppression of allergic reactions and Type 2 inflammation. Voskamp AL (2015) found basophile sensitivity to *A. fumigatus* and surface-bound IgE and FcεR1 levels decreased significantly and decline in exacerbation [49].

One of the additional benefits observed in these cases of ABPA was the prednisone-sparing effect. Overall, 96 (94.11%) patients

stopped or reduced prednisone at the time of data collection; 29 (28.43%) stopped while 67 (65.68%) reduced prednisone dose. The drop of systemic steroid use may be a consequence of the dramatic reduction in exacerbation from Omalizumab treatment. The prednisone reduction in ABPA patients was in agreement with the observation from various clinical trials of Omalizumab for asthma [66,67]. Adverse effects of steroid therapy include growth retardation, diabetes, hypertension, cataracts, and osteoporosis, which resolve after Omalizumab use. Zirbes JM reported the improvement in height percentile from the 7th to the 16th CDC percentile of a teenage patient following Omalizumab therapy [24]. Additionally, Thomas MF observed facial appearance improvement and normalization of blood glucose profile after Omalizumab in an 11-year-old male subject [28]. By subgroup analysis we determined that males showed more sensitivity to dose reduction of prednisone after Omalizumab use (Table 5). Further analysis of the data showed the baseline of prednisone male group was 21.41 ± 13.609 mg/d versus 11.55 ± 4.398 mg/d in the female group, resulting in a significant variance of decline prednisone dosage.

In contrast to the significant effects of Omalizumab on inflammation in large and small airways, its effects on pulmonary function were limited to improvements in mean FEV1% of pred values. Omalizumab resulted in a positive outcome, while a decline in lung function was described in severe asthmatic children followed up for many years [17]. Tillie-Leblond (2011) reported no changes in pulmonary function while subject's conditions were well controlled [33]. Martorell, C (2013) [42] and Carlos EM (2008) [21] also reported no changes in lung function because the baseline was maintained within normal limits. However, other measurements of lung function should be evaluated in future clinical trials.

We also determined that the ACT score and FeNO also improved with Omalizumab treatment. Although the increase was small and may be not clinically relevant, there was a trend of the symptoms being controlled by omalizumab, just as the improvement in ACT score endpoint in other asthma studies [68]. Thoracic CT scan also revealed reduced impaction and inflammation of the distal airways.

Overall, none of the 102 subjects experienced any side effects due to Omalizumab during the treatment period, while one double-blind randomized parallel assignment placebo-controlled study terminated prematurely (clinic trial No.NCT00787917) due to adverse events. From clinicaltrials.gov, we listed the side effects in this study in Table 6. However, while the cases reported suggested a general well tolerance of omalizumab, we speculated that non-serious AEs may have been unreported. To further examine this, we searched reported AEs in asthma patients following Omalizumab treatment and found that the common adverse events included lower respiratory tract infection, nasopharyngitis, headache, injection site pain, injection site reaction and arthralgia. Serious adverse events, such as death, asthma exacerbation, pruritus, acute appendicitis, sphenoid sinusitis, intestinal obstruction, and mild chest pain were also reported [16,69]. However, none of these AEs were considered drug-related. No clinically relevant abnormalities in laboratory tests (including platelet count) were observed; therefore, we consider that add-on Omalizumab is an effective and well tolerated treatment in patients with severe ABPA.

There are several limitations to this study. First, we used systematic review of case-reports in outcome investigations of a treatment, putative selection bias is inevitable. Second, there may be some cases with negative outcome have not been reported, and our study did not involve those data. Third, clinical examination index data were not available in all enrolled patients; several data such as, total eosinophil count, specific IgE for *A.fumigatus*, FeNO, FEF_{25–75} of predicted (%) and ACT score were available for less than half of the patients in the overall study; and the other measurements were not integral prior to and after Omalizumab. In addition,

most of studies are cases reports, and the sample size of this systematic review is relatively small, which limits the significance of this study. Furthermore, most of the analyses presented were post hoc and from case reports, and no statistical type I error control plan was implemented.

6. Conclusion

This systematic review shows that Omalizumab has an acceptable safety profile and was well tolerated by ABPA patients. FeNO, symptoms, exacerbation rate, steroid use and serum IgE were reduced while lung function was not significantly improved after Omalizumab treatment. Omalizumab may be an alternative therapy for ABPA patients. However, double-blind, randomized, placebo-controlled trials are necessary to establish the efficacy and safety of this novel therapeutic intervention for ABPA.

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Author contributions

Prof. Xu JF, Prof. Cao WJ and Dr Li JX contributed to conceive and design of the study, acquisition, analysis and interpretation of data, and drafting of the manuscript. Dr Fan LC contributed to study conception, literature search, data acquisition, interpretation of results. Dr Li MH contributed to study design, data interpretation and critical suggestion and revision of the manuscript. All authors have read and approved the final version of the manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

The authors have no conflict of interest to declare.

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