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Review Article

Treatment of allergic bronchopulmonary aspergillosis with biologics

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ABSTRACT

Patients with allergic bronchopulmonary aspergillosis (ABPA) respond well to standard treatments (oral corticosteroids and/or antifungals); however, approximately in half of the patients, the condition recurs during tapering or early after treatment discontinuation. To avoid the adverse effects of long-term treatment, biologics targeting immunoglobulin E (IgE), eosinophils, or type 2 immune responses have been used in refractory ABPA. Omalizumab, an anti-IgE antibody, as well as mepolizumab and benralizumab targeting eosinophils has been consistently shown to decrease co-morbid asthma exacerbation and dose of oral corticosteroids. Furthermore, mepolizumab and benralizumab effectively improved chest radiographic abnormalities, such as mucus plugs in the bronchi. Data on dupilumab and tezepelumab are limited; however, they may be effective in patients who are resistant to treatment with omalizumab/mepolizumab/benralizumab. Future studies examining the effects of these biologics in preventing the recurrences/exacerbations of ABPA are warranted.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disease caused by a hypersensitivity reaction to *Aspergillus fumigatus* (*A. fumigatus*) that colonizes the airways.[1-3] ABPA is characterized by the presence of fungus-specific immunoglobulin E (IgE) and markedly increased levels of total serum IgE. Serum IgE levels are used not only for the diagnosis of ABPA but also as the primary biomarker to monitor disease activity.[4,5] Therefore, IgE is considered essential in the pathogenesis of ABPA.

Another unique feature of ABPA is the presence of highly viscous mucus plugs enriched with eosinophils and Charcot–Leyden crystals, which impact the large bronchi.[6] Recent studies have shown that *A. fumigatus* can induce the extracellular release of nuclear DNA and citrullinated histones (extracellular trap) from eosinophils.[7] Extracellular trap cell death (ETosis) of eosinophils plays an important role in the formation of tenacious mucus plugs in various eosinophilic airway diseases such as eosinophilic rhinosinusitis and ABPA.[7-9] Galectin-10 in the cytoplasm of eosinophils polymerizes into Charcot–Leyden crystals during ETosis, further enhancing mucus plug formation.[10,11]

In addition to the pathogenetic roles, IgE and eosinophils are the key elements in the clinical presentation of ABPA; a factor analysis on a Japanese cohort has identified three essential components that define the clinical presentation of ABPA: allergic, eosinophilic, and fungal.[12] Although high levels of total IgE and presence of fungus-specific IgE in serum have been emphasized as the essential factors for the diagnosis of ABPA,[1,3] diagnostic criteria equally emphasizing the allergic, eosinophilic, and fungal components have demonstrated better sensitivity and specificity.[13] Therefore, it is reasonable to consider that both IgE and eosinophils are the targets for the treatment of ABPA.

Standard treatment for acute ABPA

Oral corticosteroids are the first-line of treatment for acute ABPA.[3] Corticosteroids act on both the innate and acquired immune systems to suppress type 2 inflammation and IgE production, and they strongly induce apoptosis of eosinophils. The recommended protocol of oral corticosteroids for the treatment of ABPA is to start with a medium dose (prednisolone: 0.5 mg · kg^{-1} · day^{-1}) for 2 weeks, followed by halving the dose for 8 weeks and further tapering thereafter; corticosteroids are supposed to be discontinued after 3–5 months of treatment.[14] Higher doses and longer periods of corticosteroid treatment have no benefit in reducing the recurrence rate after discontinuation and significantly increase the side effects.[14]

Azole antifungals for 4 months are recommended as second-line treatment[3]; either itraconazole or voriconazole is effective.[15,16] Because these antifungals do not suppress the immune responses to fungi directly, the appearance of treatment effects is delayed with this class of drugs compared to treatment with oral corticosteroids.[3] Antifungals are good alternatives when conditions such as poorly controlled diabetes or chronic infection are present.[17]

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Table 1
Clinical stages of ABPA and goals for the treatment with biologics.

Clinical stage of ABPA	Description	Goals for the treatment with biologics			
		Relief of symptoms	Prevent irreversible bronchiectasis	Reduce adverse effects	Prevent recurrences
Acute ABPA	Newly diagnosed ABPA or exacerbation of ABPA	√	√		
ABPA in remission	Clinico-radiological improvement for ≥6 months without oral corticosteroids				√
Treatment-dependent ABPA	Exacerbation of ABPA or worsening of symptoms after tapering oral corticosteroids	√		√	√
Advanced ABPA	Extensive bronchiectasis or respiratory failure	√		√	

ABPA: Allergic bronchopulmonary aspergillosis.

Refractory cases of ABPA

Initial responses to standard treatments such as oral corticosteroids and antifungals are generally good in patients with ABPA.[14-16] However, approximately half of the patients who have improved clinically with standard treatment experience recurrence early after the reduction or discontinuation of treatment, requiring prolonged or repeated administration of corticosteroids/antifungals.[14,18,19] Corticosteroid dependence results in various side effects, including chronic airway infection with *Pseudomonas aeruginosa* and non-tuberculous *Mycobacterium* at the site of bronchiectasis.[20] Administration of antifungal agents for more than 6 months may induce fungal resistance to azole antifungals.[21] Combination therapy with corticosteroids and antifungal agents is recommended when the initial therapy fails. However, a randomized controlled trial (RCT) comparing corticosteroid monotherapy and corticosteroid/antifungal combination therapy in patients with ABPA showed no significant difference in response rate or recurrence frequency within 1 year.[22] Therefore, improved salvage treatments are warranted.

Biologics targeting type 2 immune responses, IgE, or eosinophils have been used in patients with severe asthma complicated by ABPA, who have failed to achieve long-term remission with standard therapy.[23] Omalizumab, an anti-IgE antibody, is the first biologic for the treatment of severe asthma and has been the subject of research as a possible ABPA treatment; not only case reports, but also one meta-analysis and one small-scale RCT have been published.[24,25] Several case series studies are available on mepolizumab, a neutralizing antibody against the eosinophil growth factor interleukin (IL)-5, and benralizumab, an anti-IL-5 receptor alpha chain antibody.[26-29] By contrast, the efficacy of the anti-IL-4 receptor alpha-chain antibody dupilumab and the antithymic stromal lymphoprotein (TSLP) antibody tezepelumab, both of which more broadly suppress type 2 inflammation, remains limited to case reports. This review discusses the indications and selection of biologics for refractory ABPA.

Clinical goals for the treatment of ABPA with biologics

The clinical goals for the treatment of ABPA are to (1) alleviate the symptoms of ABPA and concomitant asthma, (2) prevent (or stem) the progression of irreversible bronchiectasis with mucus plugs and lung destruction, (3) reduce the adverse effects of treatment, and (4) prevent recurrence after ABPA remission.[30] Several issues must be considered when evaluating the clinical efficacy of biologics for the treatment of ABPA.

First, the priority of treatment differed according to the ABPA stage (acute, remission, treatment-dependent, or advanced) (Table 1).[3] In acute ABPA, relief of symptoms and removal of mucus plugs are important, whereas the prevention of adverse effects from therapeutic agents is important in treatment-dependent diseases. In the remission stage, prevention of recurrence is the major goal (Table 1). Therefore, the outcomes of biologics should differ depending on the stage of ABPA.[31]

Second, we must carefully distinguish between the exacerbation/recurrence of ABPA and the exacerbation of asthma or bronchiectasis.[3] ABPA exacerbation requires 3-month to 5-month long therapy with corticosteroids/antifungals as the primary therapy, whereas asthma and bronchiectasis exacerbations only require short-term treatment with systemic corticosteroids and/or antibiotics. The ABPA Working Group of the International Society for Human and Animal Mycology (ISHAM) has defined ABPA exacerbation as a condition with worsening clinical symptoms or chest imaging findings (pulmonary opacities, intrabronchial mucus plugs, etc.) accompanied by an increase in serum IgE levels from the baseline level.[3] Case reports of ABPA treated with biologics often do not clearly distinguish ABPA from asthma exacerbation.

Efficacy of individual biologics

Omalizumab

Omalizumab, an anti-IgE antibody, has been studied in detail as a therapeutic option for ABPA. Nine studies analyzing ≥10 patients treated with omalizumab for ABPA complicated by severe asthma, including eight retrospective case series and one RCT, have been published (Table 2).[24,32-39] All these studies demonstrated a reduction in the exacerbation rate of asthma, and nine of them showed a reduction in the dose of oral corticosteroids. However, as mentioned previously, it is unclear whether omalizumab reduces the rate of ABPA recurrence. Omalizumab has also been demonstrated to suppress the exacerbation of ABPA associated with cystic fibrosis that is defined as the worsening of symptoms accompanied by an increase in serum IgE levels,[40] suggesting that omalizumab can suppress exacerbations of ABPA. The effects of omalizumab on respiratory function have been inconsistent, and only one study has demonstrated radiological improvement, in which omalizumab decreased the endobronchial mucus plugs in three cases.[35]

A systematic review of 49 reports, including 267 patients treated with omalizumab for asthma- or cystic fibrosis-associated ABPA, was recently published.[25] Quantitative evaluation was possible in 14 reports including 186 cases. The study showed that exacerbations decreased from 1.75–4.25/year to 0.20–1.00/year, and that oral corticosteroids could be reduced in 65% of patients and discontinued in 53% of patients. However, improvements in the imaging findings have rarely been reported. Based on these results, omalizumab has the potential to improve the control of severe asthma associated with ABPA, and reduce or wean off systemic corticosteroids in patients who have become dependent on oral corticosteroids. However, there are insufficient data on mucus plug removal, which is an important outcome of acute ABPA.

One unresolved issue is the dosage of omalizumab administered to patients with ABPA. Although the dose of omalizumab must be adjusted according to serum IgE levels and body weight to neutralize free IgE, a substantial proportion of patients, especially those in the acute phase of ABPA, require omalizumab at doses that exceed the upper limit of dosing. The rationale for administering omalizumab to patients with high IgE levels outside the current dosing tables has been discussed.[41] Using a basophil activation test, Voskamp *et al*[24] demonstrated that a subopti-

Table 2
Clinical effects of omalizumab in case series studies of ABPA with asthma.

References	Published year	Nationality	Type of study	Number of patients	Number of patients on OCS	Duration of biologic treatment	Clinical effects of biologics						
							Improve symptoms	Reduce exacerbation of asthma	Reduce recurrences of ABPA	Reduce dose of OCS	Discontinue antifungals	Improve pulmonary functions	Improve radiographic abnormality
Perez-de-Llano et al	2011	Spain	Retrospective	18	17	16 weeks	+	+	ND	+	+	+	ND
Tillie-Leblond et al	2011	France	Retrospective	16	9	12 months	ND	+	ND	+	ND	-	ND
Aydin et al	2015	Turkey	Retrospective	14	ND	31.5 months (mean)	+	+	ND	+	ND	+	ND
Voskamp et al	2015	Australia	RCT	13	6	4 months	-	+	ND	ND	ND	-	ND
Tomomatsu etal	2020	Japan	Retrospective	25	19	4 months	ND	+	ND	+	ND	-	5/10 cases
Wark et al	2020	Australia	Retrospective	11	ND	24 months	+	+	ND	+	ND	ND	ND
Cai et al	2023	China	Retrospective	14	14	16 months (median)	+	+	ND	+	ND	+	ND
Chen et al	2024	China	Retrospective	26	ND	12 months	ND	+	ND	+	+	ND	ND
Korkmaz et al	2024	Turkey	Retrospective	13	13	33 months (mean)	ND	+	ND	+	ND	ND	ND

ABPA: Allergic bronchopulmonary aspergillosis; ND: Not demonstrated; OCS: Oral corticosteroids; RCT: Randomized controlled trial. +: Positive effects with omalizumab; -: Negative effects with omalizumab.

mal dose of omalizumab could reduce the amount of IgE and the number of IgE receptors expressed on the cell surface in patients with ABPA and high serum total IgE levels exceeding the upper limit of 1500 IU/mL, suggesting that the antibody may be clinically effective even at suboptimal levels. Therefore, the ISHAM-ABPA working group clinical practice guidelines revised in 2024 recommend using omalizumab at the dose "based on body weight and serum total IgE values not exceeding 375 mg subcutaneous injection twice a month".[3]

Another issue that remains undetermined is whether the omalizumab dose can be reduced after the disease has been stabilized.[39] The IgE–omalizumab complex has a longer half-life in the blood than free IgE, resulting in a transient increase in serum total IgE levels. However, these levels decrease as IgE production decreases, especially in patients without concomitant allergic diseases.[37] However, there is insufficient evidence to support a strategy to reduce the dose of omalizumab or extend its dosing interval.

Mepolizumab/benralizumab

Mepolizumab and benralizumab strongly suppress eosinophils by neutralizing the IL-5–IL-5 receptor pathway. There were two case series that examined more than 10 cases treated with these biologics, and another two case series that examined 9 cases (Table 3).[26-29] In cases treated with mepolizumab/benralizumab, a decrease in the exacerbation rate and oral corticosteroid dose was reproducibly observed, as with omalizumab, although there was no significant effect on respiratory function.

Notably, this class of biologics effectively reduced or eliminated mucus plugs in the bronchi, and a report from Japan demonstrated that 18 (82%) out of 22 patients who had mucus plugs before treatment demonstrated radiological improvement.[29] The effects on mucus plugs were greater with benralizumab, which was more potent than mepolizumab in suppressing the peripheral blood eosinophil counts. In some patients, switching from mepolizumab to benralizumab eliminated the residual mucus plugs after a treatment with mepolizumab.[29,42] Even in patients treated with mepolizumab, a greater reduction in peripheral blood eosinophil counts was associated with improved effects on mucus plugs.[29] Furthermore, mepolizumab may decrease the proportion of the $CD62L^{low}$ inflammatory eosinophils in the peripheral blood.[43] These findings suggest that the continuous migration of eosinophils into the airway lumen is necessary for the maintenance of mucus plugs in the bronchi.

Serum IgE levels are considered the most essential biomarkers for monitoring the disease activity of ABPA.[4,5] Although there are some reports demonstrating a decrease in serum IgE levels after mepolizumab/benralizumab administration, we did not find any significant decrease in serum total IgE levels, even in clinically effective cases.[29] Therefore, eosinophils and mucus plugs are among the pathophysiologies of ABPA independent of IgE.

In some cases, mepolizumab/benralizumab did not improve the control of concomitant severe asthma. In these cases, a combination of mepolizumab and omalizumab may be beneficial.[44]

Dupilumab

Dupilumab is a neutralizing antibody against the IL-4 receptor alpha chain, a common unit of the IL-4 and IL-13 receptors, that inhibits the bioactivities of both IL-4 and IL-13. The number of reported cases was limited.[45-56] Several cases refractory to omalizumab or mepolizumab/benralizumab were successfully treated with dupilumab.[44,46,50-52,54] Radiological improvement, including the elimination of mucus plugs, has also been reported.[47-49,51,52,54-56]

By contrast, a transient increase in peripheral blood eosinophil counts has been reported after the administration of dupilumab. In some patients treated for ABPA, peripheral blood eosinophilia exceeding 2000/mm^3 was observed, and the drug was discontinued in one

Table 3
Clinical effects of mepolizumab/benralizumab in case series studies of ABPA with asthma.

References	Published year	Nationality	Type of study	Number of patients	Number of patients on OCS	Duration of biologic treatment	Clinical effects of biologics						
							Improve symptoms	Reduce exacerbation of asthma	Reduce recurrences of ABPA	Reduce dose of OCS	Discontinue antifungals	Improve pulmonary functions	Improve radiographic abnormality
Schleich et al	2020	Belgium	Retrospective	20	7	6 months	+	+	ND	+	ND	±	ND
Dhariwal et al	2021	UK	Retrospective	9	3	48 weeks	±	+	ND	-	ND	-	ND
Caminati et al	2022	Italy	Retrospective	9	9	12 months	+	+	ND	+	ND	-	ND
Tomomatsu et al	2023	Japan	Retrospective	29	15	32 weeks	ND	+	ND	+	ND	-	18/22 cases

ABPA: Allergic bronchopulmonary aspergillosis; ND: Not demonstrated; OCS: Oral corticosteroids. +: Positive effects with mepolizumab/benralizumab; -: Negative effects with mepolizumab/benralizumab.

patient.[45,57] Particular caution should be exercised when oral corticosteroids and anti-IL-5 therapy are not administered concomitantly.

A company-initiated clinical trial (LIBERTY ABPA AIRED study) of dupilumab in ABPA-complicated severe asthma was conducted, and case enrollment was completed. The trial is scheduled to end in February 2024, and the results are awaited.

Tezepelumab

Tezepelumab is an antibody that neutralizes the cytokine TSLP, which is upstream of type 2 inflammation, and may suppress type 2 immune responses, IgE, and eosinophils, all of which are expected to have therapeutic effects against ABPA. However, only two case reports are currently available demonstrating the effects on symptoms, dose of oral corticosteroids, and mucus plugs.[58,59]

Selection of biologics for the treatment of refractory ABPA

According to reported studies, all biologics used for the treatment of severe asthma, such as omalizumab, mepolizumab, benralizumab, dupilumab, and possibly tezepelumab, improve the control of symptoms, reduce asthma exacerbation, and decrease the dose of oral corticosteroids; therefore, they would be useful for treatment-dependent ABPA [Table 1]. However, improvement in radiographic abnormalities, including mucus plugs, is more likely to be expected with anti-IL-5 treatments, especially benralizumab, and dupilumab, suggesting that these biologics should be selected in cases of acute ABPA with mucoid impaction. However, there is no evidence that these biologics prevent the exacerbation or recurrence of ABPA during remission, and future studies are warranted.

We have previously demonstrated that three components define the clinical presentation of ABPA: allergic, eosinophilic, and fungal components.[12] The eosinophilic component defined by peripheral blood eosinophil counts, the presence of mucus plugs, and high-attenuation mucus in the bronchi were consistent regardless of the type of ABPA, suggesting that eosinophils and eosinophilic mucus plugs are cardinal features of ABPA. In contrast, the allergic components defined by house dust mite- and *A. fumigatus*-specific IgE titers and total serum IgE levels were associated with treatment failure of standard treatment and early post-treatment exacerbation.[12]

Owing to the essential role of the eosinophilic component in the pathophysiology of ABPA, anti-IL-5 treatments are more effective in most ABPA cases than anti-IgE antibodies, which act only on allergic components. In contrast, anti-IL-5 therapy alone is not sufficient for patients with potent allergic and eosinophilic components; dupilumab or tezepelumab, which acts on both components, may be more effective. Evaluation of these clinical components would be useful in the selection of biologics for ABPA.

The recently revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying, and treating ABPA/allergic bronchopulmonary mycosis (ABPM) recommend biological agents as an option for managing treatment-dependent ABPA; however, the level of consensus was not unanimous (71%).[3] As the guidelines mentioned in the section of future directions, randomized trials to define the role of biologics as maintenance therapy for glucocorticoid-dependent ABPA and acute ABPA are required. In addition, the identification of appropriate clinical indicators or biomarkers useful for the selection, switching, and discontinuation of biologics is an important topic for the future research.

CRediT authorship contribution statement

Koichiro Asano: Writing–original draft, Funding acquisition, Conceptualization. **Katsuyoshi Tomomatsu**: Writing–review & editing, Investigation. **Naoki Okada**: Writing–review & editing, Investigation. **Jun Tanaka**: Writing–review & editing, Investigation. **Tsuyoshi Oguma**: Writing–review & editing, Investigation.

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Declaration of competing interest

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References

1. Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43:850–873. doi:10.1111/cea.12141.
2. Asano K, Kamei K, Hebisawa A. Allergic bronchopulmonary mycosis – pathophysiology, histology, diagnosis, and treatment. *Asia Pac Allergy*. 2018;8:e24. doi:10.5415/apallergy.2018.8.e24.
3. Agarwal R, Sehgal IS, Muthu V, et al. Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses. *Eur Respir J*. 2024;63:2400061. doi:10.1183/13993003.00061-2024.
4. Agarwal R, Aggarwal AN, Sehgal IS, Dhooria S, Behera D, Chakrabarti A. Utility of IgE (total and *Aspergillus fumigatus* specific) in monitoring for response and exacerbations in allergic bronchopulmonary aspergillosis. *Mycoses*. 2016;59:1–6. doi:10.1111/myc.12423.
5. Agarwal R, Sehgal IS, Muthu V, et al. Long-term follow-up of allergic bronchopulmonary aspergillosis treated with glucocorticoids: a study of 182 subjects. *Mycoses*. 2023;66:953–959. doi:10.1111/myc.13640.
6. Bosken CH, Myers JL, Greenberger PA, Katzenstein AL. Pathologic features of allergic bronchopulmonary aspergillosis. *Am J Surg Pathol*. 1988;12:216–222. doi:10.1097/00000478-198803000-00007.
7. Muniz VS, Silva JC, Braga YAV, et al. Eosinophils release extracellular DNA traps in response to *Aspergillus fumigatus*. *J Allergy Clin Immunol*. 2018;141:571–585.e7. doi:10.1016/j.jaci.2017.07.048.
8. Arima M, Ito K, Abe T, et al. Eosinophilic mucus diseases. *Allergol Int*. 2024;73:362–374. doi:10.1016/j.alit.2024.03.002.
9. Miyabe Y, Fukuchi M, Tomizawa H, et al. Aggregated eosinophils and neutrophils characterize the properties of mucus in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2024;153:1306–1318. doi:10.1016/j.jaci.2023.11.925.
10. Ueki S, Tokunaga T, Melo RCN, et al. Charcot-Leyden crystal formation is closely associated with eosinophil extracellular trap cell death. *Blood*. 2018;132:2183–2187. doi:10.1182/blood-2018-04-842260.
11. Persson EK, Verstraete K, Heyndrickx I, et al. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. *Science*. 2019;364:eaaw4295. doi:10.1126/science.aaw4295.
12. Okada N, Yamamoto Y, Oguma T, et al. Allergic bronchopulmonary aspergillosis with atopic, nonatopic, and sans asthma-factor analysis. *Allergy*. 2023;78:2933–2943. doi:10.1111/all.15820.
13. Asano K, Hebisawa A, Ishiguro T, et al. New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. *J Allergy Clin Immunol*. 2021;147:1261–1268.e5. doi:10.1016/j.jaci.2020.08.029.
14. Agarwal R, Aggarwal AN, Dhooria S, et al. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J*. 2016;47:490–498. doi:10.1183/13993003.01475-2015.
15. Agarwal R, Dhooria S, Singh Sehgal I, et al. A randomized trial of itraconazole vs prednisolone in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Chest*. 2018;153:656–664. doi:10.1016/j.chest.2018.01.005.
16. Agarwal R, Dhooria S, Sehgal IS, et al. A randomised trial of voriconazole and prednisolone monotherapy in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J*. 2018;52:1801159. doi:10.1183/13993003.01159-2018.
17. Agarwal R, Muthu V. Benralizumab as a first-line treatment for ABPA: is it really indicated? *Intern Med*. 2021;60:2519. doi:10.2169/internalmedicine.6807-20.
18. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest*. 2006;130:442–448. doi:10.1378/chest.130.2.442.
19. Oguma T, Taniguchi M, Shimoda T, et al. Allergic bronchopulmonary aspergillosis in Japan: a nationwide survey. *Allergol Int*. 2018;67:79–84. doi:10.1016/j.alit.2017.04.011.
20. Ishiguro T, Takayanagi N, Takaku Y, et al. Allergic bronchopulmonary aspergillosis with repeated isolation of nontuberculous mycobacteria. *Intern Med*. 2013;52:1721–1726. doi:10.2169/internalmedicine.52.9537.
21. Tashiro M, Izumikawa K, Hirano K, et al. Correlation between triazole treatment history and susceptibility in clinically isolated *Aspergillus fumigatus*. *Antimicrob Agents Chemother*. 2012;56:4870–4875. doi:10.1128/AAC.00514-12.
22. Agarwal R, Muthu V, Sehgal IS, et al. A randomised trial of prednisolone *versus* prednisolone and itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J*. 2021;59:2101787. doi:10.1183/13993003.01787-2021.
23. Asano K, Suzuki Y, Tanaka J, Kobayashi K, Kamide Y. Treatments of refractory eosinophilic lung diseases with biologics. *Allergol Int*. 2023;72:31–40. doi:10.1016/j.alit.2022.10.004.
24. 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;3:192–199. doi:10.1016/j.jaip.2014.12.008.
25. Jin M, Douglass JA, Elborn JS, et al. Omalizumab in allergic bronchopulmonary aspergillosis: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract*. 2023;11:896–905. doi:10.1016/j.jaip.2022.12.012.
26. Schleich F, Vaia ES, Pilette C, et al. Mepolizumab for allergic bronchopulmonary aspergillosis: report of 20 cases from the Belgian Severe Asthma Registry and review of the literature. *J Allergy Clin Immunol Pract*. 2020;8:2412–2413.e2. doi:10.1016/j.jaip.2020.03.023.
27. Dhariwal J, Hearn AP, Kavanagh JE, et al. Real-world effectiveness of anti-IL-5/5R therapy in severe atopic eosinophilic asthma with fungal sensitization. *J Allergy Clin Immunol Pract*. 2021;9:2315–2320.e1. doi:10.1016/j.jaip.2021.02.048.
28. Caminati M, Batani V, Guidolin L, Festi G, Senna G. One-year mepolizumab for allergic bronchopulmonary aspergillosis: Focus on steroid sparing effect and markers of response. *Eur J Intern Med*. 2022;99:112–115. doi:10.1016/j.ejim.2021.12.026.
29. Tomomatsu K, Yasuba H, Ishiguro T, et al. Real-world efficacy of anti-IL-5 treatment in patients with allergic bronchopulmonary aspergillosis. *Sci Rep*. 2023;13:5468. doi:10.1038/s41598-023-32246-8.
30. Greenberger PA, Bush RK, Demain JG, Luong A, Slavin RG, Knutsen AP. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2014;2:703–708. doi:10.1016/j.jaip.2014.08.007.
31. Greenberger PA. Defining the outcome markers and therapeutic role for omalizumab in treatment of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2023;11:906–907. doi:10.1016/j.jaip.2023.01.013.
32. Pérez-de-Llano LA, Vennera MC, Parra A, et al. Effects of omalizumab in *Aspergillus*-associated airway disease. *Thorax*. 2011;66:539–540. doi:10.1136/thx.2010.153312.
33. Tillie-Leblond I, Germaud P, Leroyer C, et al. Allergic bronchopulmonary aspergillosis and omalizumab. *Allergy*. 2011;66:1254–1256. doi:10.1111/j.1398-9995.2011.02599.x.
34. Aydın Ö, Sözener ZÇ, Soyyiğit Ş, et al. Omalizumab in the treatment of allergic bronchopulmonary aspergillosis: one center's experience with 14 cases. *Allergy Asthma Proc*. 2015;36:493–500. doi:10.2500/aap.2015.36.3909.
35. Tomomatsu K, Oguma T, Baba T, et al. Effectiveness and safety of omalizumab in patients with allergic bronchopulmonary aspergillosis complicated by chronic bacterial infection in the airways. *Int Arch Allergy Immunol*. 2020;181:499–506. doi:10.1159/000507216.
36. Wark P, Hussaini S, Holder C, Powell H, Gibson P, Oldmeadow C. Omalizumab is an effective intervention in severe asthma with fungal sensitization. *J Allergy Clin Immunol Pract*. 2020;8:3428–3433.e1. doi:10.1016/j.jaip.2020.05.055.
37. Cai C, Qu J, Zhou J. Effectiveness and safety of omalizumab in patients with allergic bronchopulmonary aspergillosis with or without allergic rhinitis: a retrospective chart review. *BMC Pulm Med*. 2023;23:389. doi:10.1186/s12890-023-02696-x.
38. Chen P, Yu Y, He L, et al. Efficacy of omalizumab in adult patients with allergic bronchopulmonary aspergillosis: a multicentre study in China. *Clin Exp Med*. 2024;24:6. doi:10.1007/s10238-023-01267-y.
39. Korkmaz ET, Aydin O, Mungan D, Sin BA, Demirel YS, Bavbek S. Can dose reduction be made in patients with allergic bronchopulmonary aspergillosis receiving high-dose omalizumab treatment? *Eur Ann Allergy Clin Immunol*. 2024;56:26–33. doi:10.23822/EurAnnACI.1764-1489.261.
40. 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;49:503–507. doi:10.1002/ppul.22937.
41. Menzella F, Just J, Sauerbeck IS, et al. Omalizumab for the treatment of patients with severe allergic asthma with immunoglobulin E levels above >1500 IU/mL. *World Allergy Organ J*. 2023;16:100787. doi:10.1016/j.waojou.2023.100787.
42. Tomomatsu K, Sugino Y, Okada N, Tanaka J, Oguma T, Asano K. Rapid clearance of mepolizumab-resistant bronchial mucus plugs in allergic bronchopulmonary aspergillosis with benralizumab treatment. *Allergol Int*. 2020;69:636–638. doi:10.1016/j.alit.2020.03.003.
43. Vultaggio A, Accinno M, Vivarelli E, et al. Blood CD62L^{low} inflammatory eosinophils are related to the severity of asthma and reduced by mepolizumab. *Allergy*. 2023;78:3154–3165. doi:10.1111/all.15909.
44. Altman MC, Lenington J, Bronson S, Ayars AG. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2017;5:1137–1139. doi:10.1016/j.jaip.2017.01.013.
45. Ramonell RP, Lee FE, Swenson C, Kuruvilla M. Dupilumab treatment for allergic bronchopulmonary aspergillosis: a case series. *J Allergy Clin Immunol Pract*. 2020;8:742–743. doi:10.1016/j.jaip.2019.11.031.
46. Ali M, Green O. Dupilumab: a new contestant to corticosteroid in allergic bronchopulmonary aspergillosis. *Oxf Med Case Reports*. 2021;2021:omaa029. doi:10.1093/omcr/omaa029.

47. Mikura S, Saraya T, Yoshida Y, et al. Successful treatment of mepolizumab- and prednisolone-resistant allergic bronchopulmonary aspergillosis with dupilumab. *Intern Med*. 2021;60:2839–2842. doi:10.2169/internalmedicine.6679-20.
48. Nishimura T, Okano T, Naito M, et al. Complete withdrawal of glucocorticoids after dupilumab therapy in allergic bronchopulmonary aspergillosis: a case report. *World J Clin Cases*. 2021;9:6922–6928. doi:10.12998/wjcc.v9.i23.6922.
49. Tashiro H, Takahashi K, Kurihara Y, Sadamatsu H, Kimura S, Sueoka-Aragane N. Efficacy of dupilumab and biomarkers for systemic corticosteroid naive allergic bronchopulmonary mycosis. *Allergol Int*. 2021;70:145–147. doi:10.1016/j.alit.2020.08.006.
50. van der Veer T, Dallinga MA, van der Valk JPM, et al. Reduced exacerbation frequency and prednisone dose in patients with ABPA and asthma treated with dupilumab. *Clin Transl Allergy*. 2021;11:e12081. doi:10.1002/clt2.12081.
51. Kai Y, Yoshikawa M, Matsuda M, et al. Successful management of recurrent allergic bronchopulmonary aspergillosis after changing from mepolizumab to dupilumab: a case report. *Respir Med Case Rep*. 2022;39:101723. doi:10.1016/j.rmcr.2022.101723.
52. Kotetsu Y, Ogata H, Sha K, Moriwaki A, Yoshida M. A case of allergic bronchopulmonary aspergillosis with failure of benralizumab and response to dupilumab. *Cureus*. 2023;15:e42464. doi:10.7759/cureus.42464.
53. Lamothe PA, Runnstrom M, Smirnova N, et al. Allergic bronchopulmonary aspergillosis in identical twins: effectiveness of dupilumab. *J Allergy Clin Immunol Pract*. 2023;11:1556–1558.e2. doi:10.1016/j.jaip.2022.12.049.
54. Hamakawa M, Ishida T. Efficacy of dupilumab as an alternative to corticosteroids in the treatment of exacerbations of allergic bronchopulmonary aspergillosis. *Respirol Case Rep*. 2024;12:e01354. doi:10.1002/rcr2.1354.
55. Kawasaki Y, Nishiki K, Ishizaki T. Successful treatment with dupilumab in mepolizumab-resistant allergic bronchopulmonary aspergillosis. *Respir Med Case Rep*. 2023;47:101964. doi:10.1016/j.rmcr.2023.101964.
56. Sumi T, Suzuki K, Koshino Y, Ikeda T, Yamada Y, Chiba H. Successful treatment of mucus plug due to allergic bronchopulmonary aspergillosis using dupilumab. *Cureus*. 2024;16:e55884. doi:10.7759/cureus.55884.
57. Eldaabossi SAM, Awad A, Anshasi N. Mepolizumab and dupilumab as a replacement to systemic glucocorticoids for the treatment of chronic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis – case series, Almoosa specialist hospital. *Respir Med Case Rep*. 2021;34:101520. doi:10.1016/j.rmcr.2021.101520.
58. Matsuno O. Allergic bronchopulmonary aspergillosis successfully treated with tezepelumab. *J Allergy Clin Immunol Pract*. 2023;11:2589–2591. doi:10.1016/j.jaip.2023.05.026.
59. Ogata H, Sha K, Kotetsu Y, et al. Tezepelumab treatment for allergic bronchopulmonary aspergillosis. *Respirol Case Rep*. 2023;11:e01147. doi:10.1002/rcr2.1147.