



Invited Review Article

Biologics for severe asthma: The real-world evidence, effectiveness of switching, and prediction factors for the efficacy

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ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AD, Atopic dermatitis; ADCC, Ab-dependent cell-mediated cytotoxicity; AE, Adverse event; CRSwNP, Chronic rhinosinusitis with nasal polyps; ECP, Eosinophil cationic protein; ED, Emergency department; EDN, Eosinophil-derived neurotoxin; ER, Emergency room; GETE, Global evaluation of treatment effectiveness; IL-5R, IL-5 receptor; OCS, Oral corticosteroid; PMS, Post-marketing surveillance; QoL, Quality of life; RA, Rheumatoid arthritis; RCT, Randomized controlled trial; SGRQ, St George's Respiratory Questionnaire; SNOT-22, Sino-Nasal Outcome Test-22

ABSTRACT

Biologics have been a key component of severe asthma treatment, and there are currently biologics available that target IgE, IL-5, IL-4/IL-13, and TSLP. Randomized controlled trials have established clinical evidence, but a significant portion of patients with severe asthma in real-life settings would have been excluded from those trials. Therefore, real-world research is necessary, and there is a growing body of information about the long-term efficacy and safety of biologics.

Multiple clinical phenotypes of severe asthma exist, and it is crucial to choose patients based on their phenotypes. Blood eosinophil count is an important biomarker for anti-IL-5 therapies, and FeNO and eosinophil counts serve as prediction markers for dupilumab. Reliable markers for predicting response, however, have not yet been fully established for omalizumab. Identification of clinical or biological prediction factors is crucial for the path toward clinical remission because the current treatment goal includes clinical remission, which is defined as a realistic goal for remission off treatment.

Additionally, since there are now multiple biologic options and overlaps in eligibility for biologics in clinical practice, the evidence regarding the effectiveness of switching the biologics is crucial. Investigations into the clinical trajectory following the cessation of biologics are another important issue.

Recent research on omalizumab, mepolizumab, benralizumab and dupilumab's real-world effectiveness, the prediction factor for the efficacy, and the impact of switching or discontinuation will be reviewed and discussed in this review.

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Introduction

In a recent database study, it was found that 7.8% of asthma-treated patients had severe asthma, which comes with physical, social, and economic burdens with an impaired quality of life (QoL).¹ Since omalizumab was approved in 2009, biologics have played a significant role in the management of severe asthma. Biologics that target IgE, IL-5, IL-4/IL-13, and TSLP are currently available in Japan.

Although randomized controlled trials (RCTs) have established clinical evidence, ~80% of patients with severe asthma in real-life settings would have been excluded from RCTs.^{2,3} In Japan, a study

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that included 355 users of biologics was recently carried out using a database of health insurance claims.⁴ By demonstrating the lower incidence ratio of asthma exacerbation and the corticosteroid-sparing effects, this real-world study supported the conclusions from RCTs. The study also found that users of biologics had heterogeneous baseline characteristics, highlighting the importance of further gathering data from cases in real-world.

Severe asthma is a heterogeneous syndrome composed of several clinical phenotypes. The significance of the phenotype-based selection of patients has been established during biologics development.⁵ Although blood eosinophil counts and FeNO have been proven to be crucial biomarkers for choosing biologics,⁶ additional prediction factors have been increasingly investigated.

Additionally, because we now have a variety of biologic options, it is clinically important to consider the effectiveness of switching biologics when deciding on the best treatment order. Thirty percent of patients with severe asthma had overlapping eligibility for all four biologics, and 75% of patients with severe asthma were qualified for two or more biologics.⁷ Additionally, it is crucial to establish discontinuation criteria and conduct research on the clinical trajectory following the cessation of biologic treatment as well as the patient traits necessary for successful cessation.

The current review aims to provide an overview of recent findings about the real-world effectiveness, the impact of switching or discontinuation of biologics, and the prediction factor for the effectiveness.

IgE-targeted therapy

Overview

Since IgE produced by B lymphocytes is the central player in the pathogenesis of allergic diseases, omalizumab, a humanized IgG1 monoclonal antibody that binds IgE with high affinity has been developed and has become the first biological drug approved for the treatment of moderate-to-severe allergic asthma. Allergen-specific IgE binds to high-affinity receptors on the surface of mast cells and basophils, and induces the release of mediators such as histamine, and enhances the synthesis of lipid mediators including cysteinyl-LTs and various cytokines critical in allergic inflammation. In the clinical settings, omalizumab limited allergen-induced early- and late-phase asthmatic responses in allergen-challenge models in mild allergic asthma.⁸ RCTs demonstrated omalizumab's effectiveness and safety in lowering asthma exacerbations, enhancing asthma control, reducing corticosteroid use, and decreasing rescue medication use.^{9–15} Omalizumab has also been authorized for the treatment of chronic spontaneous urticaria and severe Japanese cedar pollinosis in Japan, as shown by the results of clinical trials.^{16–19} Since omalizumab is the oldest biological drug for asthma, it has the longest history and a sufficient data for drug safety in which includes that the most frequent adverse events being local reactions at the site of injection and rarely, anaphylaxis occurs in 0.1 to 0.2% of patients.^{20,21}

However, not all patients respond to omalizumab and as a result, the clinical community was very interested in the predictive biomarker for responders of omalizumab. From INNOVATE, the post hoc analyses of five clinical studies, the authors were unsuccessful in identifying valid pre-treatment baseline characteristics for predicting response to omalizumab.²² In a similar vein, a real-world prospective study found no baseline biomarker was reliable for predicting response to omalizumab.²³ On the other hand, high baseline FeNO, blood eosinophils, and serum periostin may be

a biomarker to predict the treatment effect of omalizumab, according to a post hoc analysis of an RCT called EXTRA.²⁴ According to a retrospective real-world analysis, non-responder of omalizumab had significantly higher rates of psychological co-morbidity and more baseline exacerbations than the responder group.²⁵ There is still a need for the discovery of biomarkers that correctly forecast a therapeutic response to omalizumab.²³

Real-world evidence of omalizumab for asthma

As omalizumab has been used for almost a decade in the world and more than thirteen years in Japan, there are plenty of real-world data on omalizumab for moderate-to-severe asthma. A study from France that was published in 2013, a cohort of 374 severe uncontrolled asthma patients who started omalizumab was described.²⁶ Omalizumab use was associated with an adjusted hazard ratio of 0.57 (95%CI, 0.43–0.78) for hospitalization or emergency department (ED) visit due to asthma.²⁶ After receiving omalizumab for 16 weeks, the eXpErience, an international, open-label, observational registry of 943 asthma patients with uncontrolled persistent allergic asthma revealed that 69.9% of the patients had improved in physician's global evaluation of treatment effectiveness (GETE) which was consistent with the clinical trials.²⁷ Then, in 2015, a systematic review of 24 real-life studies of omalizumab for severe asthma that included 4,117 unique patients from 32 countries clearly showed its effectiveness in clinical outcomes, i.e., lung function, decrease in severe exacerbations, improved symptom control, improved GETE, declined hospitalizations and ED visits, and decreased use of ICS and oral corticosteroid (OCS).²⁸ A 2017 meta-analysis of 25 observational studies revealed significant improvements in FEV1, QoL, and Asthma Control Test (ACT), reduction in oral and inhaled corticosteroid use, and reductions in exacerbations and hospitalizations and large proportions of patients who were good to excellent treatment responders as determined by the GETE.²⁹

A real-world multicenter analysis in 10 French hospitals with 207 patients also revealed that the pre-bronchodilator FEV1 improved in responders of omalizumab at 6 months and remained stable for 2 years.³⁰ It is interesting to note that real-world data from Spain, which included 345 patients treated with omalizumab demonstrated the effectiveness of omalizumab regardless of clinical phenotypes,³¹ and its' efficacy even among non-atopic severe asthma patients.³²

Omalizumab underwent post-marketing surveillance (PMS) in Japan between 2009 and 2017.³³ Adachi *et al.* evaluated 3,620 patients on omalizumab and followed them for 52 weeks, the majority of patients showed clinical improvements as determined by GETE (58.3% at 16 weeks and 62.4% at 52 weeks). Additionally, adverse events (AEs) were reported in 32.2%, serious AEs in 15.3%, and adverse drug reactions in 8.1%. According to the report's findings, PMS confirmed the clinically meaningful benefits and safety of omalizumab in Japan in a real-life clinical setting.³³ Notably, nearly half of the patients were over 65 years, demonstrating the clinical efficacy of omalizumab even among the elderly.

Eighty-six publications were examined in a recent meta-analysis of observational studies on omalizumab for severe allergic asthma.³⁴ The findings showed that 77% of patients at 16 weeks (risk difference: 0.77; 95% CI: 0.70–0.84) and 82% of patients at 12 months had GETE that was good or excellent (risk difference: 0.82; 95% CI: 0.73–0.91). At 16 weeks, 6 months, and 12 months, the mean improvement in FEV1 was 160, 220, and 250 mL, respectively. Additionally, omalizumab significantly decreased the

annualized rate of severe exacerbations (risk ratio RR:0.41, 95% CI:0.30–0.56), indicating the potential benefit of additional omalizumab in real-world settings to support the results from RCTs.

Long-term efficacy and discontinuation of omalizumab

A RCT on withdrawal of omalizumab among moderate-to-severe persistent asthma has shown that continuation of omalizumab after long-term treatment (approximately 5 years) resulted in continued benefit (Table 1), in terms of improved symptom control and reduced exacerbation risk.³⁵ In addition, discontinuing omalizumab after prolonged therapy reversed the effects on IgE and basophils which correlated with deterioration in asthma control.³⁵ Omalizumab has been in use for more than ten years, and there have been a few reports on the long-term use of omalizumab in real-world situations. Sposato *et al.* recruited 340 severe asthma patients with omalizumab and split them into 4 groups according to the treatment length: <12, between 12 and 24, between 24 and 60, and >60 months (n = 39, 94, 171, 36, respectively), and compared the treatment results.³⁶ They discovered that a higher significant positive increase in FEV1% in subjects treated for 12–24 ($\beta = 9.49$; $p = 0.034$) or 24–60 months ($\beta = 8.56$; $p = 0.043$) compared to the patients treated for shorter period. Treatment duration was positively linked with a step down of the other asthma therapies (OR: 1.013; $P = 0.019$) suggesting that long-term use of omalizumab, even after 60 months, did not lose its' efficacy. Similar results of long-term use of omalizumab in real-world settings are reported from other places in the world showing the effectiveness of omalizumab and its' safety and well tolerability even after long-term use (Table 1).^{37–40}

Omalizumab discontinuation has also been elucidated in real-world settings (Table 2). Molimard *et al.* described data from 61

responder patients who had discontinued omalizumab after a mean duration of 22.7 ± 13.1 months of treatment to find that 55.7% documented loss of asthma control with a median interval of 13.0 months (mean 20.4 ± 2.6).⁴¹ Even after stopping omalizumab for 12 months, a population-based database cohort study in Taiwan found there was a decrease in exacerbations and emergency room (ER) visits.⁴² A very recent study by Humbert *et al.* by using the French Healthcare Database System including data from 19,203 patients and covering more than 10-years found adult asthma patients with asthma being controlled who discontinued omalizumab for at least 16 weeks, 70, 39, and 24% remained controlled and did not resume omalizumab at 1, 2, and 3 years after discontinuation.⁴³ However, for discontinuation of omalizumab, further studies are necessary to clearly define the criteria for discontinuation of omalizumab.

Switching from omalizumab to other biologics

There are several real-world reports on switching biological drugs from omalizumab to another one because several biological drugs have been developed since the introduction. One hundred forty-five asthma patients receiving omalizumab but had asthma exacerbations more than 2 times/year were switched to be on mepolizumab for 32 weeks in one study.⁴⁴ The outcome demonstrated improvement in asthma control, health status, exacerbation rate, and lung function as well as a reduction in the number of blood eosinophils.⁴⁴ Similar to these studies, others have examined patients with uncontrolled severe eosinophilic asthma who were taking omalizumab and switched to mepolizumab or benralizumab. These patients showed improved clinical outcomes in terms of exacerbation rate, pulmonary functions, IgE, FeNO, and eosinophil counts.^{45–47} The most frequent first switch was from omalizumab to an anti-IL-5 therapy (49.6%), with insufficient efficacy

Table 1
Summary of real-world evidence on the long-term effectiveness of omalizumab.

Study design	Patient	Patient numbers	Period	Main results Adverse effects	Ref
Retrospective, Italy, 2022	SAA	8	16 y	Exacerbation: 1.8 to 0.88/y Hospitalization: 0.3 to 0/y No adverse effects	136
Retrospective, Greece, 2021	Asthma	45	10.6 y	Exacerbation: 4.1 to 1.1/y (1 y) OCS: 7.8 to 1.6 mg/d (8 y) No severe adverse events	137
Retrospective, Poland, 2020	SAA	854	4 y	Mini AQLQ: 2.9 to 5.0 points OCS: 10.8 to 2.7 mg/d (4 y)	138
Prospective, Germany, 2020	SAA	153	3 y	ACQ-6: 2.2 to 1.7 points (NS) No unexpected safety signals	139
Retrospective, Turkey, 2018	Asthma	465	>5 y	Exacerbation reduced to 54.8% (5 y) No hospitalization (5 y)	140
Observational, Kuwait, 2018	Poor- control asthma	65	4 y	Adverse effects: 12.7% (mild-to-moderate) OCS user: 99 to 17%, ACT: 15 to 23 points %FEV1 55.6 to 76.6%, Adverse effects: Mild 15%, Serious 4.6%	141
Observational, Italy, 2018	SAA	15	>5 y	ACT: 14.6 to 21.7 points, Exacerbation: 3.7 to 0.6/y (5 y) OCS: 22.5 to 1.7 mg/d (5 y) FEV1: 1.64 to 1.93 L (5 y)	39
Retrospective, United Kingdom, 2017	SAA	45	60.7 m	OCS: 25.8 to 6.0 mg/d, ACQ: 4.1 to 2.3, %FEV1: 59.2 to 75.7% No anaphylaxis or deaths	38
Retrospective, Italy, 2017	Difficult asthma	91	3.8 y	Adverse events: 6.6% discontinued No anaphylaxis	37
Retrospective, Italy, 2017	SAA	340	4 m to 120 m	Treatment duration was positively associated with a step down, did not affect ACT, exacerbations	36
Retrospective, Greece, 2012	SAA	60	4 y	%FEV1: +24.5%, ACT: +24% Exacerbation: –70% (4 y)	142

ACT, Asthma Control Test; AQLQ, Asthma Quality of Life questionnaire; ER, emergency room; Exac, exacerbation; GETE, Global Evaluation of Treatment Effectiveness; NS, not significant; OCS, oral corticosteroid; SAA, severe allergic asthma.

Table 2
Summary of real-world evidence of discontinuation of omalizumab.

Study type	Patient numbers	Period	Main results	Ref
Healthcare Database System France 2022	16,750 adults 2,453 children	Median 51.2 m in adults	Among adults, 70%, 39% and 24% remained controlled at 1, 2 and 3 years after discontinuation. Over 2 years after discontinuation, healthcare resource use remained stable in adults. Rate of hospitalizations increased from none to 1.3% at 2 years after discontinuation. Use of OCS increased from 20.0 to 33.3% at 2 years after discontinuation. Twelve (24.5%) patients relapsed in the first year of follow up. 61% remained controlled over the 4-year follow-up.	43
Prospective open study Spain 2018	49	mean 5.8 y	During 12 months after discontinuation 68–77% reduction in ICS + LABA 65–72% reduction in OCS 69–87.5% reduction in exacerbations 29.4–36.5% reduction in ER visits	135
Retrospective data base cohort Taiwan 2016	282	243.8 day	34 patients (55.7%) lost asthma control with a median interval of 13.0 months	42
Retrospective France 2014	61	22.7 m	At 3 years after discontinuation, 12/18 patients improved or unchanged 16/18 had not increased nightly attacks 14/18 little or no increase in medication CD-sens to cat remained lower than untreated patients at 3 years after discontinuation	41
Open study Sweden 2010	18	6 y		143

CD-sens was defined as the inverted value for the allergen concentration giving a 50% of maximum CD63 upregulation multiplied by 100. ER, emergency room; OCS, oral corticosteroid.

and/or adverse effects as the most common reasons for switching, according to a recent real-world cohort study of 3,531 asthma patients.⁴⁸ However, the switching studies were mainly performed with eosinophilic asthma in which anit-IL-5 biological drugs should be more advantageous, so prospective studies with structured switching criteria would be required to identify patients who might benefit from switching.

IL-5-targeted therapy

Overview

Through tissue damage caused by the release of granule proteins and tissue remodeling, eosinophils are strongly associated with the pathogenesis of asthma.⁴⁹ Eosinophil activation and survival prolongation is mediated by IL-5, IL-3, and GM-CSF, which binds to cytokine-specific α chain.⁵⁰ However, IL-5 has been proposed as a selective therapeutic target for eosinophilic diseases due to specific expressions of the IL-5 receptor (IL-5R) in human eosinophils and basophils.⁵¹ Although, mepolizumab was established as the first humanized mAb targeting IL-5,⁵² the efficacy was not proven in the first small and second large clinical trials.^{53,54} The fact that patients with an eosinophilic phenotype were not specifically sought out for those studies was a significant flaw. In the following study recruiting eosinophilic asthma, a significant decrease in exacerbation was proven.^{55,56} When using an anti-IL-5 treatment, it is important to recognize eosinophilic asthma, according to the process for establishing the efficacy of mepolizumab.

When administering mepolizumab to patients in Japan, the entry criteria for MENSA study⁵⁶ were used to refer patients who had a peripheral blood eosinophil count $\geq$ of 150 cells/ μ L at screening.⁶ The improvement in QoL and the glucocorticoid-sparing effect were also demonstrated in later clinical trials, specifically the MUSCA⁵⁷ and SIRIUS study,⁵⁸ respectively. In the COSMOS,⁵⁹ COLUMBA⁶⁰ and COSMEX,⁶¹ studies, which followed

patients for up to 4.8 years after treatment began, long-term safety and tolerability were also demonstrated.

Benralizumab is a humanized afucosylated mAb, specific for the human IL-5R α .⁶² As afucosylation increases Ab-dependent cell-mediated cytotoxicity (ADCC),⁶³ its efficacy of eosinophil-depletion is rapid.⁶⁴ In two separate phase 3 trials, SIROCCO and CALIMA, benralizumab significantly decreased the exacerbation in patients with blood eosinophil counts of at least 300 cells/ μ L and improved FEV1.^{65,66} The glucocorticoid-sparing effect was shown in ZONDA study⁶⁷ and improvement in QoL was also demonstrated.⁶⁸ Benralizumab was confirmed to be long-term safe and tolerable for up to 5 years.^{69–71}

Another anti-IL-5 mAb, reslizumab, is approved for severe asthma in the United States and European countries but not in Japan.

Real-world evidence of IL-5-targeted therapies including Japan

Due to the requirements for airflow obstruction, bronchodilator reversibility, and smoking history, about 80% of real-life patients with severe eosinophilic asthma would have been excluded from RCTs for IL-5-targeted therapies.^{2,3} In comparison to trial populations, the real-world population was older, more frequently male, and showed better lung function at lower OCS maintenance doses.³ The mean age of patients recruited to RCTs was around 50 years in MENSA⁵⁶ and 49 years in SIROCCO and CALIMA.^{65,66} The age in the real-life study, in contrast, was 54.0 years in REALITI-A,⁷² 56.6 years in REDES,⁷³ and 62.2 years in Japanese database study.⁷⁴

Numerous studies have demonstrated the efficacy of IL-5-targeted therapies in clinically relevant settings. In studies using insurance databases, the reduction in exacerbation, hospitalization, and OCS use was demonstrated for mepolizumab (Table 3). Additionally, numerous retrospective analyses and large-scale observational studies, such as REDES⁷³ and REALITI-A,⁷² demonstrated improvements in symptom scores, pulmonary function, and QoL.

Table 3

Real-world effectiveness of mepolizumab.

Study	Exacerbation	Main results	Ref
Insurance database			
Japan	–43%	OCS dose: 8 to 3 mg/day, discontinue 38%	75
N = 61, 12 m		Hospitalization: –58%	
Japan	–40.6%	OCS dose: –44.6%, Hospitalization –55.8%	74
N = 377, 12 m		Exacerbation-related cost: 192,865 to 112,149 JPY/y	
United States	–38% ~ –55%	OCS: >50% dose reduction: 39%–47%	104
N = 639, >12 m		Hospitalization and ED visit: –57% ~ –83%	
United States	–53.1%	OCS use: 99.1% to 86.5%	144
N = 327, 12 m			
United States	–33.6%	Hospitalizations: –35.3%	145
N = 201, 12 m			
Prospective observational			
Australia	ND	OCS dose: 10 to 2 mg/day	146
N = 309, 6 m		OCS bursts: 96% to 50%	
REDES, Spain	–77.5%	ACT: 14.1 to 20.8 points, FEV1: +210 mL	73
N = 318, 12 m		OCS daily dose –59.9%, discontinue: 47.8%	
REALITI-A	–69%	OCS dose: 10 to 5 mg/day	72
N = 368, 1 y		Hospitalization and/or ED visit: –77%	
Retrospective			
France	–86%	OCS dose: 20.6 to 7.8 mg/day	147
N = 146, 24 m		OCS dependent patients: 92.8% to 34.7%	
Germany	↓	ACT: 13 to 19 points, %FEV1: 59% to 74%	148
N = 123, 12 m		OCS dose: 8 to 5 mg/day	
Italy	–81%	Hospitalizations: 0.6 to 0.1/y, ED visit: 0.5 to 0.1/y	149
N = 138, >12 m		ACT: 17 to 22 points, FEV1: +340 mL	
United Kingdom	–54%	OCS dose: 10.1 to 2.0 mg/day, dependent: 80% to 28%	
N = 99, >16 w		Hospitalizations: 0.4 to 0/y, ED visit: 0.5 to 0.1/y	94
United Kingdom	–3.60 ~ –4.58/y	OCS dose: 10 mg to 0 mg/day	
N = 193, 48 w		ACQ-6: –0.52 ~ –0.98 points	111
United States	–38.4%	OCS dose: –100%	150
N = 346, >12 m		Exacerbation-related cost: 5,178 to 2,383 USD/y	
Systematic review (N = 2040)	–54 ~ –97%	Hospitalizations: –72.7%	151
		ACT: +5.00–8.53 points, AQLQ: +1.24 to 1.5 points	
		FEV1: –30 ~ +400 mL, OCS discontinue: 27–84%	

Studies including more than 50 patients are mainly shown. ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ED, emergency department; JPY, Japanese Yen; ND, not determined; OCS, oral corticosteroid.

Table 4

Real-world effectiveness of benralizumab.

Study	Exacerbation	Main results	Ref
Prospective observational			
Spain	ND	ACT: 13.9 to 20.1 points, FEV1: +291 mL	152
N = 42, >6 m		OCS dose: 19.6 to 5 mg/day, dependent: –50%	
Italy	–100%	ED visits: 1 to 0/y	110
N = 111, 6 m		ACT: 13.3 to 21.9 points, FEV1: +530 mL	
		OCS dose: 5 to 0 mg/day, dependent: 72% to 20%	
		AQLQ: 3.0 to 6.0 points	
Retrospective, Insurance data base, Meta-analysis			
United Kingdom	–72.8%	ACQ-6: 2.90 to 2.15 points, FEV1: +140 mL	94
N = 130, 48 w		OCS dose: 10 mg to 0 mg/day, discontinue: 51.4%	
United States (Insurance data)	–55%	Mini AQLQ: 3.46 to 4.35 points	153
N = 204, >12 m		OCS dependent: 82% to 50%,	
Germany	↓	Hospitalizations –42%, ED visit –46%	148
N = 64, 12 m		Exacerbation-related cost: \$13,559 to \$7120	
Italy	–100%	ACT: 12 to 22 points, %FEV1: 63% to 72%	102
N = 137, 24 w		OCS dose: 7.5 mg to 5 mg/day	
ANANKE, Italy	–93.3%	ACT: 13 to 22 points, FEV1: +460 mL	154
N = 218, >3 m		OCS dose: 10 mg to 0 mg/day	
Meta-analysis	–3.79/y	ACT: 14 to 22 points, FEV1: +300 mL	155
5 studies		OCS dose: 10.0 to 4.4 mg/day, discontinue: 43.2%	
		ACQ-6: –0.78 points, ACT: +5.82 points	
		OCS dose: –8.35 mg/day	

Studies including more than 50 patients are mainly shown. ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ED, emergency department; ND, not determined; OCS, oral corticosteroid.

Table 5
Switching effect concerning anti-IL-5 therapies.

Study type	Patient numbers Period	Exacerbation	Symptom, FEV1, OCS sparing effect	Ref
Omalizumab to mepolizumab OSMO, Open label, Single-arm	145 32 w	–64%	ACQ-5: 3.20 to 1.75 points FEV1: +159 mL, SGRQ: –19.0 points	44
Retrospective	33 11.7 m	–94%	FEV1: +190 mL OCS dependent: 87.9% to 12.1% Annual costs: Omalizumab €12,239, Mepolizumab: €12,639	46
Omalizumab to benralizumab Retrospective, real-life	20 >1 y	–81.5%	ACT: 15 to 20 points, FEV1: +390 mL OCS dose 5.0 to 0.0 mg/day SNOT-22: 53.9 to 43.4 points	47
Mepolizumab to benralizumab Retrospective, real-life	60 5 m	–38.9%	ACT: 16 to 19 points, FEV1: +255 mL OCS dose: 5.0 to 0.0 mg/d OCS dependent: 53.3% to 31.7%	77
Retrospective	33 48 w	–57.8%	ACQ-6: 3.2 to 2.4 points, FEV1: +270 mL OCS dose: 10 to 5 mg/d, dependent: 78.8 to 42.4% Mini AQLQ: 3.61 to 4.20 points	78
Observational, retrospective	19 >3 m	–54.5%	ACT 14.8 to 18.1 points, FEV1: +155 mL OCS dose: 15.1 to 21.8 mg/day OCS dependent: 88.9% to 78.9% Mini AQLQ: 3.6 to 4.7 points	79

ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; OCS, oral corticosteroid; SGRQ, St George's Respiratory Questionnaire; SNOT-22, Sino-Nasal Outcome Test-22.

Table 6
Prediction factors for the effectiveness of anti-IL-5 therapies.

Drug	Endpoint (N)	Factors	Ref
Factors related to the effectiveness			
Mepolizumab	Responder (62) Super-responder (99)	Low ACQ-6 Nasal polyp, Low BMI Low-dose OCS, Low ACQ	25 98
Benralizumab	Exacerbation (762)	OCS use, %FVC<65%, Nasal polyp, Exacerbation≥ 3/y Low ACQ, Nasal polyp, adult onset	101
	Super-responder (130) ACT, FEV1 (137) ACT, Exacerbation (111)	CRSwNP Skin prick test positive Onset within 10 years, %FEV1 >80%	94 102 110
Mepolizumab, Benralizumab, Reslizumab	Super-responder (114)	High serum EDN	99
Mepolizumab	Exacerbation (576, Post hoc) FEV1 (20)	High ECP, High Blood Eosinophils	112 96
Benralizumab	Super-responder (130) Responder (24) FEV1 (64)	High Blood Eosinophils High Blood Eosinophils, FeNO High Blood Eosinophils, FeNO, IgE	94 95 97
	Super-responder Cluster Analysis (41) Responder (17)	High expressions of Siglec 8, ALOX15, CCL23	156
Factors not related to the difference in the effectiveness		Low serum IL-4, 5, 6, 7, 12, 17, IFN γ , TNF α , TSLP, MMP-12, CCL-3, 4, 11	113
Mepolizumab	ACQ, Exacerbation (547, Post hoc) ACQ, Exacerbation (936, Post hoc) Exacerbation (1435, Meta-analysis)	Atopic asthma Age of onset, FEV1, Reversibility, Control Number of drugs, OCS use	106 100 103
Benralizumab	Exacerbation (639, Insurance Database)	Comorbidities (nasal polyp, sinusitis, obesity, depression)	104
Mepolizumab	Exacerbation (857, Post hoc)	Serum IgE	157
Mepolizumab + Benralizumab	ACQ, Exacerbation, OCS (193)	SAFS	111

ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; OCS, oral corticosteroid; SAFS, Severe asthma with fungal sensitization.

Numerous types of real-world studies on benralizumab produced the same conclusions (Table 4).

There are two insurance claim database studies in Japan, examining the real-life effectiveness of mepolizumab in 61 patients⁷⁵ and 377 patients.⁷⁴ The frequency of exacerbation, hospitalization, and daily OCS dose decreased in both studies. Additionally, from the baseline to follow-up periods, the exacerbation-related inpatient cost decreased by 65,996 Japanese Yen per patient year.⁷⁴

These real-world data show that real-life effectiveness is consistent with RCT results and suggests that effectiveness is

consistent across racial and social backgrounds in different countries.

Switching to or between IL-5-targeted therapies

From omalizumab to anti-IL-5 therapies (Table 5)

Several studies have investigated the omalizumab to mepolizumab switching effect. OSMO trial evaluated the change in asthma control of patients with blood eosinophil counts ≥ 150 cells/ μ L, not optimally controlled with omalizumab.⁴⁴ The exacerbations reduced from 3.26 to 1.18 events/year, after 32 weeks. The mean

Table 7

Summary of real-world evidence of dupilumab with patients with severe asthma.

Patients	Patient numbers	Treatment periods	Main results	Ref
Severe asthma	64	12 months	Exacerbations: 4 to 1/y ACT: 14 to 22 points, %FEV1: 58% to 68% OCS dose: 20 to 5 mg/day	117
Severe asthma	85	12 months	Reduction in exacerbations OCS dose: PSL 75.0 mg to 0.0 mg per person-year	4
Severe asthma	26	12.6 months	Exacerbations: 3.4 to 1.6/y, ACT: 18.2 to 21.5 points OCS dose: 11.3 to 5.3 mg/day	118
Severe asthma	18	12 months	Pulmonary function: No remarkable change Exacerbations: 2 to 1/y ACT: 15.7 to 22.4 points, %FEV1: 73.5 to 87.1% OCS dose: 10 to 0 mg/day	119
Severe asthma with CRSwNP	20	4 weeks	ACT: 11.9 to 21.3 points, FEV1: 2.04 L to 2.30 L OCS dose: 12.5 to 0 mg/day FeNO: 27.5 ppb to 2.5 ppb SNOT-22: 58.3 to 18.9 points	120
Asthma with ECRS	31	4 months	Improving depression symptoms	121

ACT, Asthma Control Test; CRSwNP, Chronic rhinosinusitis with nasal polyps; ECRS, Eosinophilic chronic rhinosinusitis; OCS, oral corticosteroid; PSL, prednisolone; SNOT-22, Sino-Nasal Outcome Test-22.

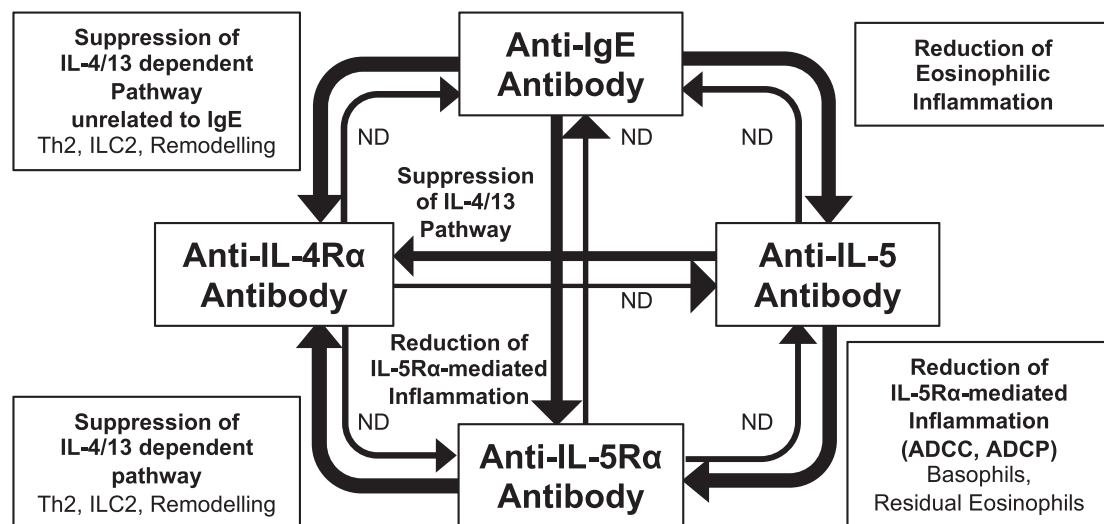


Fig. 1. Potential underlying mechanism of efficacy after switching biologics. The clinical effectiveness of switching biologics in patients not optimally controlled with baseline biologics has been investigated (bold arrows). The potential mechanism of efficacy after switching the biologics is shown in each box. ADCC, Ab-dependent cell-mediated cytotoxicity; ADCP, Ab-dependent cell phagocytosis; ND, Not determined by clinical studies.

Asthma Control Questionnaire (ACQ)-5 and St George's Respiratory Questionnaire (SGRQ) total scores significantly improved, and 77% and 79% of patients achieved scores above the minimum clinically important differences, respectively. The improvements were observed irrespective of baseline blood eosinophil count, comorbidities, prior exacerbation history, and maintenance OCS use.⁷⁶ A retrospective study,⁴⁶ found that switching to mepolizumab reduced the exacerbation rate, the proportion of OCS-dependent patients, and the number of lost working days. Additionally, in case of benralizumab, the switching effect from omalizumab was investigated in real-life study.⁴⁷ After receiving benralizumab for a year, significant improvements in exacerbation rate, ACT score, FEV1, and the score of Sino-Nasal Outcome Test-22 (SNOT-22) were observed. According to those studies, patients with severe eosinophilic asthma who were unresponsive to omalizumab benefited from switching to anti-IL-5-targeted therapies. The central endotype of such patients is speculated to be eosinophilic inflammation, but not IgE-mediated pathway (Fig. 1).

From mepolizumab to benralizumab (Table 5)

In patients who had an insufficient response, the effect of switching from anti-IL-5 mAb to anti-IL-5Rα mAb was also examined.⁷⁷ Of 665 patients treated with anti-IL-5 mAbs, 60 patients switched to benralizumab were included in the examination. FEV1 and ACT scores improved from 61% to 68%, 16 to 19 points, respectively after switching to benralizumab. Additionally, two retrospective studies also demonstrated improvements in exacerbation rate, ACT score, FEV1, QoL, and the dose of OCS following the switch to benralizumab from mepolizumab.^{78,79}

Although benralizumab appears to be more effective than mepolizumab at reducing the number of eosinophils in blood and lung tissue,^{80,81} a consistent difference in clinical efficacy has not been established.^{82,83} If the effectiveness of mepolizumab was insufficient, however, improvement was seen after switching from mepolizumab to benralizumab.^{77–79} Several differences in the mechanism of action of these drugs have been proposed. Firstly, as basophils express IL-5Rα, the elimination of basophils might be

induced by the ADCC activity of benralizumab, suggested by both in vitro experiment⁶³ and observation of the decrease in blood basophil numbers.^{84,85} Secondly, benralizumab can also induce eosinophil phagocytosis by macrophages, a process is known as antibody-dependent cell phagocytosis.⁸⁶ Thirdly, although the reduction of FeNO was not induced by mepolizumab,⁸⁷ benralizumab reduced the levels of FeNO from 100 ppb to 58 ppb at 1 year in patients with a high FeNO subgroup.⁸⁸ In addition to Th2 and ILC2 as major sources of IL-13,⁸⁹ IL-5R α expressing eosinophils⁹⁰ and basophils^{89,91} also produce functional IL-13. Benralizumab may therefore deplete IL-5R-expressing cells, such as eosinophils and basophils, which are a significant source of IL-13 in patients with the FeNO-high phenotype (Fig. 1).

Factors for the prediction of efficacy of anti-IL-5 therapies (Table 6)

The most reliable biomarker for predicting the effectiveness of mepolizumab⁹² and benralizumab is blood eosinophil count.^{93–97} Additionally, a number of patient traits or biomarkers are being looked into as prediction markers for effectiveness.

Clinical characteristics

A lower baseline ACQ-6 score was consistently linked with better responses to mepolizumab,^{25,98} and benralizumab.⁹⁴ %FEV1 >80% was also related to better response in one study,⁹⁹ but not in another study.¹⁰⁰ Lower prednisolone dose was linked to the super-response in patients receiving OCS.⁹⁸ These findings suggested that better response was associated with less severe disease.

Regarding comorbidities, a better outcome was associated with nasal polyps,^{94,98,101} or chronic rhinosinusitis with nasal polyps (CRSwNP).¹⁰² Other clinical factors related to better response were shorter asthma duration⁹⁹ and low BMI⁹⁸ for mepolizumab and, OCS use, forced vital capacity <65% and more than 3 exacerbation in the previous year was related to higher efficacy of benralizumab.¹⁰¹ The effectiveness of mepolizumab was established in a large-scale post-hoc analysis or meta-analysis, regardless of the age of onset, airway reversibility, asthma control,¹⁰⁰ number of background controller therapies, maintenance OCS use,¹⁰³ and various comorbidities.¹⁰⁴

The patients with a smoking history of ≥ 10 pack-years were excluded from RCTs. Nonetheless, the reduction in exacerbation was seen in patients with asthma-COPD overlap at 76.4 years with a smoking history of 50.6 pack-years¹⁰⁵ and the effectiveness was also displayed in patients with the diagnosis of asthma and COPD in the database study.^{74,104} These findings suggested mepolizumab's efficacy in patients with a smoking history, who would not be eligible for RCTs.

Regardless of atopic status,^{106,107} allergic sensitivities,¹⁰⁰ the levels of IgE,^{107–110} and fungal sensitization, effectiveness was seen.¹¹¹ The therapeutic effects of anti-IL-5 therapies were generally independent of IgE levels and atopic traits in subjects with severe eosinophilic asthma, despite a study showing marginally better outcomes with benralizumab in patients with positive skin prick tests.¹¹⁰

Biomarkers

Some studies reported the potential use of eosinophil-derived proteins in addition to blood eosinophil counts. Reduced exacerbations with mepolizumab was shown in the high versus low baseline eosinophil-derived neurotoxin (EDN) but independent of eosinophil cationic protein (ECP) levels.¹¹² However, baseline blood eosinophil count has greater precision as a predictive biomarker than EDN. We demonstrated that higher eosinophil counts and ECP levels were associated with better FEV1 responses and that measurable ECP at 4 weeks after the start of mepolizumab was

associated with the further improvement in FEV1 toward week 32.⁹⁶

As the levels of FeNO are primarily controlled by IL-13, FeNO was not a reliable prediction marker for the efficacy of mepolizumab¹⁰⁸ and benralizumab.⁸⁸ However, a small study on benralizumab found that the responder could be predicted by FeNO at 40 ppb in Type 2 asthma.⁹⁵ A cluster analysis revealed that the phenotype of severe eosinophilic asthma with modest increases in total IgE and FeNO had the best response to benralizumab in terms of FEV1 improvement.⁹⁷

Various Type 2 and non-Type 2 cytokines, chemokines, IFN- γ , and TNF- α were found in significantly higher levels as investigational biomarkers in FEV1 non-responders,¹¹³ indicating that low baseline serum inflammatory cytokine levels may be helpful in predicting a positive benralizumab response.

IL-4/IL-13-targeted therapy

Overview

Since IL-4 and IL-13 play crucial roles in the pathogenesis of Type 2 asthma, several biologics targeting IL-4 and/or IL-13 signal pathways have been developed.¹¹⁴ Dupilumab (Dupixent®) is a fully humanized mAb belonging to IgG4, recognizing IL-4R α and blocking both the IL-4 and IL-13 signals.¹¹⁵ Dupilumab has a significant efficacy and a favorable safety profile in patients with moderate-to-severe asthma, according to RCTs. As of September 2019, dupilumab was approved for the treatment of uncontrolled asthma in Europe, the United States, and Japan. This approval was based on a large clinical trial involving about 2,800 adults and adolescents who participated in three pivotal trials from the global LIBERTY ASTHMA program, including a phase 2b trial and the phase 3 QUEST and VENTURE trials. Additionally, it has been approved for the treatment of uncontrolled asthma as well as moderate-to-severe atopic dermatitis (AD) and CRSwNP. Dupilumab has recently been shown to be safe and effective in patients with asthma over the long term in the open-label extension TRAVERSE study.¹¹⁶ Several Real-World Evidence of dupilumab for asthma have also been recently reported. The Real-World Evidence, switching therapy from other biologics, and the efficacy prediction factor is all covered in this section.

Real-world evidence including Japan (Table 7)

Several real-world data with dupilumab in severe asthma have been reported recently (Table 7). The effectiveness of dupilumab on various asthma indices was confirmed in a real-world retrospective multicenter study conducted in France involving 64 uncontrolled severe asthmatics.¹¹⁷ They measured the symptoms, pulmonary function, exacerbation rate, and OCS use. After dupilumab treatment for 12 months, patients had substantial improvement in ACT score and FEV1 and a reduction in exacerbation rate and OCS dose intake. Similarly, real-world data from Japan showed that dupilumab is effective. In a retrospective cohort study involving 85 patients with severe asthma, Kimura *et al.* assessed the exacerbation rate and use of OCS after 12 months.⁴ They demonstrated a significant reduction in asthma exacerbations and total dose of OCS. Numata *et al.* also verified the effectiveness of 26 Japanese patients with severe asthma who received dupilumab in a retrospective real-world setting.¹¹⁸ Dupilumab treatment demonstrated effectiveness in terms of improving ACT score and decreasing annual exacerbation rate and OCS maintenance doses. Due to the study's better baseline pulmonary function, there was no discernible improvement in pulmonary function after treatment with dupilumab. Eighteen patients with severe asthma who had lower baseline

pulmonary function showed a significant improvement in pulmonary function, along with improved asthma symptoms and decreased exacerbation rates, in another Italian real-world multicenter retrospective study.¹¹⁹

Since asthma and CRSwNP share a common pathogenesis of Type 2 airway inflammation, they are essential comorbidities of each other and are associated with refractory conditions. There are two real-world studies evaluating the effectiveness of dupilumab for severe asthma patients with CRSwNP. An Italian real-world study confirmed the short-term efficacy of dupilumab in severe asthma patients with CRSwNP.¹²⁰ Dupilumab had a number of therapeutic effects after 4 weeks of administration, including appreciable gains in symptom control and lung function and a significant reduction in FeNO. In a Japanese real-world setting, Koya *et al.* analyzed the effectiveness of depressive symptoms in asthmatics with eosinophilic chronic rhinosinusitis treated with dupilumab.¹²¹ Despite the fact that the majority of patients had a depressive state that was correlated with the nasal symptom score, after 4 months of dupilumab treatment, there was a significant reduction in the depressive state, and the reduction was more pronounced in patients whose nasal symptom score had been significantly reduced.

The real-world evidence reported above has also been evaluated with safety of dupilumab treatment. Adverse events associated with dupilumab treatment were similar to those reported in clinical trials, including injection-site reaction and blood eosinophilia. In a French study, 25% and 6.3% of patients showed blood eosinophil count $\geq 1,500/\mu\text{L}$ and $3,000/\mu\text{L}$, respectively, at least once during 12 months of dupilumab treatment.¹¹⁷ After administration, careful monitoring of blood eosinophils should be considered.

Switching to dupilumab

There may be many cases of switching from other biologics regarding the initiation of dupilumab because it is the most recently approved biologic for the treatment of asthma. The above-mentioned real-world evidence included some instances of switching therapy to dupilumab. For instance, most patients (97%) in a French study switched from mepolizumab or omalizumab to dupilumab.¹¹⁷ 60% of the patients in a Japanese study who were receiving switching therapy also displayed a significant decline in exacerbations and maintenance OCS doses.¹¹⁸ There have been a few studies reporting solely switch therapy to dupilumab. In 38 patients with severe asthma who had previously been treated with anti-IL-5/IL-5R or anti-IgE biologics without producing a satisfactory clinical outcome, a real-world study in Germany evaluated the response to dupilumab.¹²² These patients had better asthma control, improved lung function, and a decrease in FeNO, total IgE, OCS dosage, and exacerbation rate after switching to dupilumab for 3 to 6 months. Finally, 76% of patients showed signs of improvement, and patients with elevated FeNO (≥ 25 ppb) under previous biologics were more likely become responders than those with non-elevated FeNO (< 25 ppb). Another retrospective, a real-life study evaluated the response to switching therapy in Japanese severe asthmatics.¹²³ The effectiveness of this study was evaluated by the GETE score. In 13 patients with switching therapy from other biologics to dupilumab, 4 patients had improved GETE scores and 9 had no change. In these studies of switching therapy to dupilumab, a trivial elevation of blood eosinophils was reported, but no serious adverse events were.

Prediction factor for the efficacy

Type 2 biomarkers, led by FeNO, were predictors of response to dupilumab treatment in the RCTs.¹¹⁴ However, the association

between Type 2 biomarkers and the therapeutic response was inconsistent in studies conducted in the real world, possibly as a result of the small sample size. A Japanese real-world study showed that the annual exacerbations significantly decreased in the subgroups with blood eosinophils $> 150/\mu\text{L}$ or $300/\mu\text{L}$, FeNO > 25 ppb and serum IgE > 167 IU/mL.¹¹⁸ Furthermore, blood eosinophils $\geq 300/\mu\text{L}$ before the administration of any biologic and blood eosinophils $> 150/\mu\text{L}$ in patients switching from other biologics to dupilumab were predictive factors of super-responders, defined by improvement in multiple clinical outcomes. By contrast, an Italian real-world study showed that baseline blood eosinophils ($<$ or $\geq 300/\mu\text{L}$) or FeNO ($<$ or ≥ 25 ppb) did not influence the improvement of symptoms, pulmonary function, and OCS dosage.¹¹⁹ According to baseline blood eosinophil and total IgE levels, a French real-world cohort study also found no differences in clinical efficacy.¹¹⁷ It is important to keep in mind that these studies had a small sample size and that there is still work to be done in this field.

In a post hoc analysis of the QUEST study, it was investigated whether baseline demographic and disease characteristics, such as FEV1 and the number of exacerbations in the year prior, influence the therapeutic effect of dupilumab on severe exacerbations and lung function in patients with a Type 2-high phenotype.¹²⁴ This study concluded that demographic and disease characteristics at baseline had no bearing on treatment effectiveness. Few real-world studies have reported treatment effects focused on patient background. Although patient background such as age, gender, and comorbidities were examined as predictors of super-responder in the Japanese study, there were no significant predictors among patient backgrounds.¹¹⁸

Conclusion

Dupilumab has been shown to be an effective and safe therapy for uncontrolled asthma, particularly in patients with Type 2 high subtype, according to a large body of real-world data and significant RCTs. It will take more research to accurately predict efficacy and to determine how effective it is to switch from other biologics to dupilumab therapy.

Discontinuation of biologics and the Way to remission

The current treatment goal includes clinical remission, which is defined as a realistic goal for remission off treatment. To best achieve the clinical remissions, identification of clinical or biological factors is important in addition to currently established biomarkers.

Compared to asthma, chronic inflammatory diseases such as rheumatoid arthritis (RA) have a longer history of biological therapy. The treatment goal in RA patients is remission or sustained reduction in disease activity. In RA patients, discontinuation of biologics is usually considered in patients who achieved deep remission.¹²⁵ Deep remission in RA patients is defined by several disease activity measures for RA, including arthritis symptoms, impaired joint count, and inflammation. It will be necessary to establish disease activity measures for asthma composed of various aspects when discussing the potential for disease modification in the condition. Recent consensus definitions for clinical/complete remission and super-response for severe asthma have been put forth by various expert groups.^{126,127} These definitions consist of various aspects of asthma, such as symptoms, exacerbations, lung function, and airway inflammation. Furthermore, several studies showed that biologics have achieved multiple remission criteria.¹²⁸ Therefore, it's time to focus on the discontinuation of biologics, so-called bio-free remission. There have been six studies on the discontinuation of biologics in severe asthma published so far.¹²⁹

The majority of reports indicated that after discontinuation, asthma symptoms worsened and/or exacerbations occurred more frequently. Contrarily, an observational analysis on biologic cessation using the United States insurance claim data showed that the exacerbation rate did not differ between the discontinuation and continuation groups.¹³⁰ In suitable severe asthmatics, discontinuing biologics is a feasible strategy because some patients could do so successfully.

Importantly, it is noteworthy to consider the characteristics of patients who successfully discontinued biologics. Firstly, discontinuation studies of biologics that included many patients with inadequate symptom control at the time of discontinuation had more cases of failure.¹³¹ It is impractical to stop taking biologics in poorly controlled conditions such as poor symptom control, presence of exacerbations, or airflow limitation. In the XPORT study, patients who successfully discontinued omalizumab had lower blood eosinophil counts during omalizumab treatment than those who failed to discontinue.³⁵ According to several reports, suppressing Type 2 inflammation may be necessary to achieve clinical remission.^{35,132–134} In a Spanish real-life prospective study, patients who successfully discontinued omalizumab tended to have fewer comorbidities such as sinusitis and nasal polyp, than those who failed to discontinue.¹³⁵ In two cases of severe eosinophilic asthma that had been receiving benralizumab treatment and had very well-controlled conditions, we described unique clinical courses of benralizumab discontinuation.¹²⁹ After discontinuation of benralizumab, one patient with comorbidities of CRSwNP and AD experienced worsening control of asthma, while one patient without comorbidity maintained a well-controlled status. These findings suggest that control of comorbidities in addition to clinical and immunological control of asthma may be of importance for the discontinuation of biologics. In the future, higher management goals and new treatment strategies in severe asthma will be needed. To date, there are no criteria for bio-free remission. Considering the findings of discontinuation studies and the expert consensus definitions for clinical/complete remission and super-response for severe asthma, we have proposed an algorithm for discontinuation of biologics.¹²⁹ Our proposed criteria comprises an absence of asthma symptoms (ACQ score <1.5 or ACT score >19), no asthma exacerbations, no use of oral corticosteroids, normalized spirometry (FEV1 ≥80%), suppressed Type 2 inflammation (blood eosinophil counts <300 μ L and FeNO <50 ppb), and control of comorbidities. To validate and improve our suggested discontinuation criteria, more research is required.

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Conflict of interest

HN has received speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharmaceutical, Novartis Pharma, and Sanofi. MS received grants from Astellas, AstraZeneca, Daiichi Sankyo, GlaxoSmithKline, Kyorin, Kyowa Kirin, MSD, Sanofi, and Shionogi, and speaker fees from AstraZeneca, GlaxoSmithKline, Novartis Pharma, and Sanofi. KM has received speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharmaceutical, Novartis Pharma, and Sanofi. KO has no conflict of interest.

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