

Biologics for oral corticosteroid-dependent asthma

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ABSTRACT

Background: Oral corticosteroid (OCS) dependent asthma is one of the severe asthma phenotypes that requires personalized treatment.

Objective: To review the role of biologic treatments in OCS-dependent asthma.

Methods: A nonsystematic review was performed of emerging multiple novel biologics for potential treatment of OCS-dependent asthma.

Results: The serious adverse effects of OCS can be seen as a result of their regular long-term administration. Anti-interleukin (IL) 5 (mepolizumab), anti-IL-5R (benralizumab), and anti-IL-4R α (dupilumab) are the therapies of choice for OCS-dependent severe asthma. Results of studies showed the efficacy of mepolizumab, benralizumab, and dupilumab, especially in patients with the OCS-dependent severe eosinophilic asthma phenotype and with nasal polyps. Dupilumab may be the therapy of choice of monoclonal antibodies in cases of moderate-severe atopic dermatitis accompanied by OCS-dependent severe asthma. For reslizumab and omalizumab, placebo controlled double-blind studies conducted with OCS-dependent patient populations are needed.

Conclusion: Biologics are effective in the "OCS-dependent asthma" phenotype as add-on therapy. It seems that chronic OCS use in OCS-dependent asthma will be replaced by biologic agents that specifically target type 2 inflammation, along with a much better safety profile. However, real-life studies that compare these biologics in OCS-dependent severe asthma are urgently needed.

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Severe asthma, especially in patients whose disease cannot be controlled sufficiently with the Global Initiative for Asthma (GINA) step 5 treatment, which consists of a high-dose inhaled corticosteroid (ICS) and long-acting β 2 agonists (LABA), requires personalized disease management. Although intermittent oral corticosteroid (OCS) usage is present in ~40% of the severe asthma population, Patients with OCS-dependent asthma and who require regular OCS administration represent ~3.5% of this population.^{1–5} However, the long-term administration of OCS is associated with serious adverse effects. In recent years, biologic treatments have been developed with a potential of decreasing the dosage or of discontinuing the OCS treatment. In this review, relevant definitions with regard to OCS-dependent asthma as well as when to use and which biologics to use in this condition will be discussed.

OCS-Dependent Asthma

The OCS-dependent asthma phenotype is a type 2 (T2) high asthma phenotype that requires regular use of add-on OCS treatment to control asthma and

prevent exacerbations in patients whose asthma remains uncontrolled and/or those who have recurrent exacerbations, despite adherence to treatment and the use of the appropriate technique with inhalers used in GINA step 5 treatment.^{6–8} However, to initiate OCS treatment in these patients, the diagnosis of severe asthma has to be confirmed, and all factors presented in Fig. 1 below, which can lead to uncontrolled asthma, need to be excluded.^{8,9}

T2-High Asthma

Asthma has been characterized as T2-high asthma and non-T2 (T2-low) asthma based on the type of underlying airway inflammation.¹⁰ Recently, terms such as T2 asthma, T2-high asthma, T2 asthma endotype, T2 asthma phenotype, T2-high inflammation, and T2 cytokine are commonly being used in published studies. In fact, these terms represent similar conditions. T2 asthma, T2-high asthma, T2 asthma endotype, and T2 asthma phenotype define the underlying type of inflammation in asthma. In the absence of this type of inflammation, the condition would be named as a non-T2 asthma phenotype or T2-low asthma. However, T2 inflammation (T2-high inflammation) is a broader concept. It is one of the underlying inflammatory phenotypes in conditions such as asthma, allergic rhinitis, chronic rhinosinusitis/nasal polyps, and atopic dermatitis. It describes all of the cytokines, effector cells, and mediators that cause the underlying inflammation in these conditions. The term T2 cytokine is used to describe the cytokines that take

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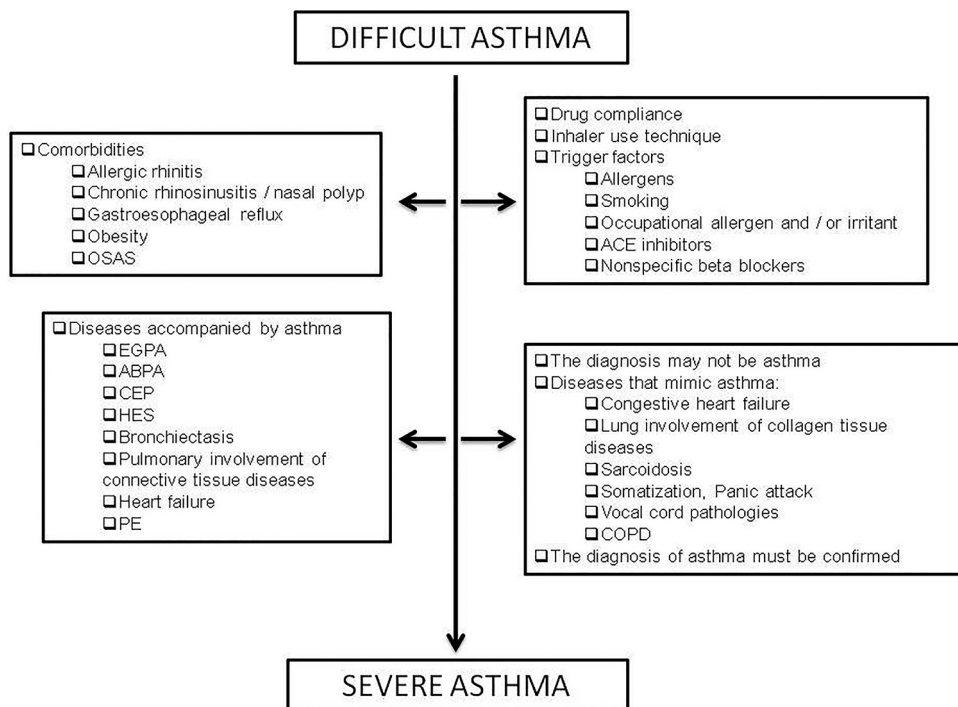


Figure 1. Differentiation between difficult asthma and severe asthma. OSAS = obstructive sleep apnea syndrome; EGPA = eosinophilic granulomatosis with polyangiitis; ABPA = allergic bronchopulmonary aspergillosis; CEP = chronic eosinophilic pneumonia; HES = hypereosinophilic syndrome; PE = pulmonary embolism; ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease.

part in T2 inflammation (mainly interleukin [IL] 4, IL-5, IL-13). Although these terms are deemed similar according to a number of different articles, a clear definition for T2 inflammation does not exist.^{11–16} T2-high inflammation, the underlying immunopathobiology of T2-high asthma, can be described as follows:

- It is the type of inflammation in which an adaptive immune response (T-helper 2 [Th2] cells) and/or an innate immune response activation innate lymphocyte cells (ILC) 2 and cytokines such as IL-4, IL-5, IL-9, IL-13, which are secreted from these cells as downstream mediators that generate and regulate airway inflammation.
- It is the type of inflammation in which specific immunoglobulin E (IgE) (secretion of IgE by B cells in response to aeroallergen) antibody, prostaglandin D₂–prostaglandin D₂ receptor pathway, effector cells such as eosinophils, and mast cells and mediators secreted from these cells takes place.
- Cytokines, such as Thymic stromal lymphopoietin (TSLP), IL-33, IL-25, which are danger signals released after epithelial damage by allergens, toxic agents, irritants, and viruses, and which are upstream mediators of T2, called alarmin, take part in this inflammation by stimulating both Th2 and ILC2.
- These cytokines, mediators, antibodies, and cells may produce different subphenotypes (endotype is an association of the dominant T2 inflammatory pathway with the T2 phenotype [e.g., IL-5 dominant,

IL-4/IL-13 dominant, specific IgE–mast cell dominant pathways]).

The reflection of this T2-high inflammation on clinical practice in asthma should be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS: blood eosinophils ≥ 150 cells/ μ L, and/or fractional exhaled nitric oxide level (FeNO) ≥ 20 ppb, and/or sputum eosinophil values $\geq 2\%$, and/or asthma clinically allergen driven, and/or patients who require maintenance OCS.⁷ The current consensus is that, in patients with asthma, a blood eosinophil count of > 150 cells/ μ L is a good indicator of T2 inflammation and a diagnosis of eosinophilic asthma.¹⁷ Through the use of T2 biomarkers, only a subset (40–70%) of patients with asthma show increases in airway T2-high inflammation, with the remaining subgroup demonstrating low-to-normal T2 inflammatory measures (T2-low). Adult-onset atopic asthma frequency also is 45%.^{18,19}

The approved biologics in OCS-dependent severe eosinophilic asthma show their effects via blocking T2 cytokines such as IL-4, IL-5, and IL-13, or their receptors. IL-4, IL-5, and IL-13 are significant contributors to T2 inflammation in asthma. IL-5 is a cytokine that affects the maturation, activation, migration, and survival of eosinophils in both blood and airway tissue.²⁰ IL-4 and IL-13 induce the chemokine eotaxin secretion, which increases the vascular cell adhesion protein 1 expression on vascular tissue and facilitates the eosinophil migration into the airway tissue. IL-4 and IL-13

also promote B cells to class switch from IgM to IgE, goblet cell development, and the secretion of mucus to the airway lumen; increase the fibroblast development and collagen accumulation in the submucosa; and increase the nitric oxide synthase activity and nitric oxide production by activating the epithelium.^{21–23}

Low-Dose OCS and Biologics for OCS-Dependent Asthma

OCS-dependent asthma belongs to the T2-high asthma phenotype.⁷ OCS plays an important role in severe asthma management. When considering the adverse effects of OCS, low-dose OCS are recommended as an add-on controller option in GINA step 5 treatment to prevent exacerbations and for better asthma control.^{7,8} However, the biologics approved for the treatment of severe asthma have drastically changed the treatment approach of OCS-dependent severe asthma. Indeed, one of the main targets of biologics is to decrease the OCS requirement in severe asthma.²⁴ The development of biologics for the treatment of T2-high severe asthma, the regular administration of OCS is no longer a preferred treatment choice.^{8,25}

As the first-line treatment in the uncontrolled severe asthma, the GINA guideline suggests using biologics as add-on treatment. ICS plus LABA, tiotropium, leukotriene modifiers should be given before biologics or OCS.⁸ However, OCS are known to be very potent and efficacious drugs on clinical parameters (symptoms, forced expiratory volume in the first second of expiration (FEV₁), exacerbation, provocative concentration causing a 20% decline in FEV₁ (PC₂₀), comorbid diseases [e.g., nasal polyposis, atopic dermatitis]) and biomarkers (blood eosinophil, FeNO, IgE) in T2-high asthma.²⁵ OCS are effective in all clinical and/or inflammatory phenotypes, such as atopic, eosinophilic, atopic-eosinophilic or comorbid eosinophilic nasal polyposis, and atopic dermatitis.

In other words, in severe asthma, in which T2 inflammation is the underlying cause, OCS are the effective and the cheapest treatment option. The possible adverse effects due to long-term use are the most important limiting factor for the use of these drugs. When patients were grouped according to low-, intermediate-, and high-dose prednisone equivalent systemic corticosteroids (SCS) exposure (<6, 6–12, and >12 mg/day, respectively), the patients with medium- and high-dose SCS exposure had significantly higher risks of SCS-related complications, including infections and cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications versus those with low SCS exposure.²⁶

Some patients may present with a cushingoid appearance after long-term administration of 5 mg/

day prednisolone.²⁷ Moreover, chronic administration of OCS (>7 mg/day prednisolone equivalent) has been found to be associated with an increased incidence of bone fractures.²⁸ Hence, due to their OCS sparing effects, in patients who are high-dose OCS dependent (≥ 5 mg prednisolone or equivalent) or patients who are low-dose OCS dependent but developed adverse effects, preferring biologics is of great importance to prevent adverse effects secondary to OCS.

However, in countries with low economic income, if no serious adverse effect secondary to OCS has been developed, due to its cost-effectiveness, then we believe that low-dose OCS (<5 mg prednisolone) should be continued in selected patient groups (patients who do not have osteoporosis, diabetes, glaucoma, any serious systemic comorbidity) without the need for initiating biologics treatment, provided that the precautions against adverse effects that may develop secondary to OCS have been taken (e.g., vitamin D replacement, regular ocular examination, influenza and pneumococcal prophylaxis, low sodium diet).

OCS-Dependent Asthma and Biologics

In patients with OCS-dependent severe asthma, airway ILC2 cells may be more dominant than CD4⁺ Th2 cells as the main source of IL-5 and IL-13.^{11,29} Treatment options for suppressing eosinophils in the airways are the following: IL-5 blocking monoclonal antibodies (mAb) such as reslizumab or mepolizumab; anti-IL5R (benralizumab), which decreases mature or immature eosinophils *via* antibody-dependent cellular cytotoxicity; anti-IL-4R α (dupilumab), which suppresses the inhibition of migration of progenitor cells to the airways; mAbs that block the upstream cytokines of T2-high inflammation, such as anti-thymic stromal lymphopoietin and anti-IL-33; anti-IgE (omalizumab was the first and, for a long time, the only available mAb for the add-on treatment of severe asthma), which has the potential to decrease the eosinophilic inflammation in blood and airways *via* decreasing the free IgE and the Fc epsilon receptor 1 (Fc ϵ R₁) on basophils and mast cells.^{11,30,31} The biologics that have been approved for T2-high asthma and have the potential to be used for OCS-dependent asthma are mentioned next. A summary of studies with anti-IL-5/anti-IL-5R and anti-IL-4R α treatments for OCS-dependent asthma is shown in Table 1.

OCS-Dependent Asthma and Anti-IL-5/Anti-IL-5R

Large placebo controlled trials showed mepolizumab (anti-IL-5) to be well tolerated, which resulted in a significant reduction of exacerbations and the use of OCS.^{32–34} One of these studies is called SIRIUS (Steroid Reduction with Mepolizumab study).³² In this study, mepolizumab treatment (150 mg/every 4 weeks,

Table 1 Summary of the studies with anti-IL-5/anti-IL-5R and anti-IL-4R treatments for OCS-dependent asthma

Study, yY	Target	Target Patient Population	Clinical Outcomes with Regard to the Use of OCS
SIRIUS, ³² 2014*	IL-5	OCS-dependent asthma	The reduction in OCS dosing at 24 wk was 50% in the group that received mepolizumab compared with 0% in the placebo group ($p = 0.007$)
ZONDA study, ³⁹ 2017*	IL-5R	OCS-dependent asthma	Benralizumab dosed every 4 wk or every 8 wk led to a median percentage reduction from baseline in the OCS requirement of 75% compared with a 25% with placebo at 28 wk ($p < 0.001$)
VENTURE trial, ⁴⁴ 2018*	IL-4R α	OCS-dependent asthma	The percentage change in the OCS dose was -70.1% in the dupilumab group compared with -41.9% in the placebo group at 24 wk ($p < 0.001$)
Nair <i>et al.</i> , ³⁵ 2009*	IL-5	OCS-dependent asthma	Patients who received mepolizumab were able to reduce their prednisone dose by a mean of 83.8% of their maximum possible dose compared with 47.7% in the placebo group at 20 wk ($p = 0.04$)
Mukherjee <i>et al.</i> , ³⁸ 2018 [#]	IL-5	OCS-dependent asthma	The decrease in sputum eosinophil was greater with reslizumab compared with mepolizumab; this was associated with a greater improvement in Asthma Control Questionnaire (five-question instrument [ACQ-5]) ($p = 0.01$)

IL = Interleukin; OCS = oral corticosteroid; SIRIUS = Steroid Reduction with Mepolizumab study; ZONDA = Efficacy and Safety of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy; VENTURE = Evaluation of Dupilumab in Patients with Severe Steroid Dependent Asthma.

*Randomized, double-blind, placebo controlled trial.

[#]Single-blind, placebo-controlled sequential trial.

subcutaneous [SC]) decreased the OCS dose by 50% and made it possible to discontinue the OCS treatment in 14% of patients with OCS-dependent asthma.³² The presence of eosinophilic inflammation was determined by a blood eosinophil level of either ≥ 300 cells/ μ L during the 12-month period before screening or ≥ 150 cells/ μ L during the optimization phase.³² This corticosteroid-sparing effect occurred while maintaining the effects of reduced exacerbations (32%) and improved asthma control.³²

A glucocorticoid-sparing effect of mepolizumab was seen by Nair *et al.*³⁵ in a small pilot study in which 20 patients were selected based on elevated sputum eosinophil levels. These patients were given 750 mg of mepolizumab or placebo intravenously (IV) every 4 weeks for 20 weeks, which resulted in a reduction of 84% in the prednisone dose in the mepolizumab

group.³⁵ Mepolizumab 750 mg IV administered to patients with persistent sputum eosinophilia significantly reduced both blood and sputum eosinophils and allowed a significant reduction in OCS, along with improved asthma control.³⁵ In comparison, in patients with a severe enough condition to require daily prednisone, the clinical benefits seem to be better with the higher doses of mepolizumab administered IV than with the lower dose administered SC.^{32,35}

In another small study, of 10 patients with severe uncontrolled asthma and on 100 mg SC mepolizumab, showed a significant decline in blood eosinophils; however, an increased sputum eosinophil count correlated with asthma exacerbations.³⁶ For some patients, lower-dose mepolizumab does not seem to suppress the local eosinophilopoietic activity.^{36,37} We speculate that, for patients with OCS-dependent asthma and

who do not respond sufficiently to mepolizumab 100 mg SC, high-dose mepolizumab treatment could be administered.

Further, although the steroid-sparing effect of reslizumab in OCS-dependent asthma has not been studied, unlike mepolizumab, because its dose is selected according to body weight, reslizumab might be the right choice for administering high-dose anti-IL-5. In accordance with this, results of one study suggests that fixed-dose mepolizumab administered SC may not be effective in reducing airway eosinophilia in some patients with severe OCS-dependent asthma. In these patients, higher doses of anti-IL-5 mAb administered in the form of reslizumab IV controls airway eosinophilia and leads to better improvement of asthma control and lung function.³⁸

It remains to be studied if targeting the IL-5 receptor,¹⁹ which is an effective therapy for these patients with severe conditions, is a better strategy than targeting the IL-5 ligand.³⁸ In the ZONDA (Efficacy and Safety of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy) trial specifically evaluated the OCS-sparing effect of benralizumab (anti-IL-5R) in patients with severe persistent asthma with an eosinophil level of ≥ 150 cells/ μL , despite chronic OCS use.³⁹ This study showed that patients who were receiving benralizumab were able to reduce their OCS dose by 75%, and 52% of the patients who received benralizumab were able to completely discontinue OCS.³⁹ In this study, despite the reduction in OCS use, there was a 70% reduction in asthma exacerbations in those who received benralizumab.³⁹ Every 8 weeks benralizumab treatment effect was enhanced with each baseline factor (OCS use, nasal polyposis, low lung function, a history of frequent exacerbations, and adult onset of disease) for all the patients and those with eosinophils $\geq 300/\mu\text{L}$ relative to the overall population.⁴⁰⁻⁴² Hence, the above factors with regard to treatment response can be taken into consideration when administering benralizumab in OCS-dependent asthma.

Based on the mechanism of action and dosage differences of different biologics, mepolizumab works best in patients on high doses of ICS with or without low doses of OCS, whereas reslizumab and benralizumab may be preferred in patients with persistent eosinophilia despite high doses of OCS.^{37,39,43} However, to compare the steroid-sparing effects of these three biologics, head-to-head comparative studies are urgently needed.

OCS-Dependent Asthma and Anti-IL-4R α

In the VENTURE (Evaluation of Dupilumab in Patients with Severe Steroid Dependent Asthma) trial,

dupilumab (anti-IL-4R α) was also found to reduce OCS use by 70% in patients with a blood eosinophil count ≥ 300 cells/ μL at baseline, and nearly half of the patients were able to discontinue OCS.⁴⁴ Furthermore, in this study, the use of dupilumab decreased a patient's risk of having an exacerbation by 59% compared with placebo. Interestingly, the reduction in exacerbations and improvement in lung function seen in this study occurred despite a prespecified eosinophil count not being required for study enrollment.⁴⁴ However, in patients with moderate-to-severe asthma with eosinophils ≥ 150 cells/mL and a FeNO level ≥ 25 ppb, dupilumab's efficacy was greatest in relationship to preventing asthma exacerbations and improving FEV1.⁴⁵

FeNO is a biomarker that can be used to decide on dupilumab treatment and to evaluate the treatment response different from other biologics (anti-IL-5/anti-IL-5R).⁴⁵⁻⁴⁸ FeNO is unaffected by anti-IL-5 treatment but is markedly reduced by anti-IL-4R α .^{45,46} Clinical studies have also found that dupilumab decreases periostin as well as FeNO.^{45,47,48} Periostin is an extracellular matrix protein induced by IL-4 and IL-13, which is mainly secreted by bronchial epithelial cells and can be detected in peripheral blood.⁴⁹ Therefore, for patients with the OCS-dependent eosinophilic asthma phenotype, if FeNO and periostin are too high, then dupilumab would be a more appropriate option.⁵⁰ These studies show that using biomarkers such as FeNO and periostin might be beneficial for choosing effective mAb in this patient population.

Although a high blood eosinophil level is still a predictor of response, other predictors, including high FeNO levels, oral steroid dependence, and the presence of T2 comorbidities such as atopic dermatitis and nasal polyposis may also influence the choice of this biologic.^{25,51} Therefore, dupilumab treatment can be the therapy of choice in patients with OCS-dependent asthma who present with the above-mentioned predictive factors. Dupilumab is administered SC at a dose of 400 or 600 mg, followed by 200 or 300 mg every 2 weeks. The higher dose of dupilumab is indicated for those with OCS-dependence or comorbid moderate-to-severe atopic dermatitis.¹³

OCS-Dependent Asthma and Anti-IgE

The main target in patients who are OCS dependent should be to reduce the dose of OCS. Mepolizumab, benralizumab, and dupilumab have demonstrated an ability to reduce the need for OCS in this high-risk, high-morbidity population of patients with asthma. There are prospective and retrospective observational but not randomized, placebo controlled studies that show the OCS-sparing effect of omalizumab.⁵²⁻⁵⁶ However, to show the OCS-sparing or OCS-

discontinuation effects of omalizumab, a randomized double-blind, placebo controlled study conducted with patients with OCS-dependent severe asthma is needed. Interestingly, no such study has been reported with omalizumab.

CONCLUSION

When all of the above-mentioned studies are taken into consideration, anti-IL-5 (mepolizumab), anti-IL-5R (benralizumab), and anti-IL-4R α (dupilumab) are the therapy of choice for OCS-dependent severe asthma. There are studies that show the efficacy of mepolizumab, benralizumab, and dupilumab, especially in patients with the OCS-dependent severe eosinophilic asthma phenotype and nasal polyps. Dupilumab may also be more preferable over other biologics in case of moderate-severe atopic dermatitis accompanied by OCS-dependent severe asthma. For reslizumab and omalizumab, placebo controlled, double-blind studies conducted with OCS-dependent patient populations are needed. Also, real-life studies that compare these biologics in OCS-dependent eosinophilic severe asthma are urgently needed. Factors that determine the response to treatment, accessibility to biologics, and local payer eligibility criteria for biologics as well as factors such as cost, frequency of administration, route of administration, and inclusion of the patient in the treatment choice by informing them should also be taken into consideration.

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