

Switching between biologics in severe asthma patients. When the first choice is not proven to be the best

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Abstract

During the last decades, new treatments targeting disease mechanisms referred as biologics have been introduced in the therapy of asthma and currently, five monoclonal antibodies have been approved. Although these therapeutic agents have been formulated to target specific asthma endotypes, it is often difficult for the treating physician to identify which patient is the best candidate for each one of these specific treatments especially in the clinical scenario of a patient in whom clinical characteristics overlap between different endotypes, allowing the selection of more than one biologic agent. As no head-to-head comparisons between these biologics have been attempted, there is no evidence on the superiority of one biologic agent over the other. Furthermore, a physician's first therapeutic decision, no matter how carefully has been made, may often result in suboptimal clinical response and drug discontinuation, indicating the need for switching to a different biologic. In this short review, we discuss the available evidence regarding the switching between biologics in patients with severe asthma and we propose a simple algorithm on switching possibilities in case that the physicians' initial choice is proven not to be the best.

KEYWORDS

atopy, biologics, eosinophils, oral corticosteroids, severe asthma

1 | INTRODUCTION

During the last decades, new treatments targeting disease mechanisms referred as biologics have been introduced in the therapy of asthma, resulting in a revolution in disease control and medical history. These treatments include monoclonal antibodies, recombinant cytokines and fusion proteins, with the former to be, at the moment, the only approved biological therapy for severe refractory asthma, also included in the disease recommendations.¹

To date, five monoclonal antibodies have been approved for the treatment of asthma. Omalizumab, the first biologic drug approved for the treatment of severe allergic asthma, is a recombinant humanized monoclonal antibody that selectively targets circulating IgE and blocks it from binding to its receptor found on

mast cells and basophils. Omalizumab interrupts the IgE mediated asthma inflammatory cascade at an early stage² and thus, interrupts both early and late asthmatic responses.^{3,4} Mepolizumab and reslizumab both target IL-5, which is a key component in eosinophil proliferation, activation and recruitment, preventing consequently its binding to the α -chain of the IL-5 receptor (IL-5 α) on eosinophils.^{5,6} Benralizumab targets directly IL-5R α in all cells that express the receptor, such as eosinophils, basophils and mast cells, resulting not only in the blockade of IL-5 mediated survival of these cells but also in a direct eosinophil apoptosis augmentation, via antibody-dependant cell-mediated cytotoxicity (ADCC) induced by the enhanced activation of the Fc γ R11a part of the IL-5R α receptor of mature natural-killer (NK) cells and macrophages, leading in a near depletion of peripheral eosinophils.^{7,8} All three

antibodies reduce peripheral blood eosinophils and improve disease control in patients with severe eosinophilic asthma. Similarly, dupilumab blocks the α chain of the IL-4 receptor alpha (IL-4R α), which is common to both IL-4 and IL-13, two cytokines central in IgE production and recruitment of inflammatory cells.⁹ Dupilumab possesses more pleotropic properties as, in addition to the attenuation in airway inflammation, also inhibits goblet cell hyperplasia and attenuates airway hyperresponsiveness and remodelling, and has been shown to result in symptom improvement and exacerbation reduction in moderate to severe and in steroid-dependent asthma patients with increased blood eosinophils.¹⁰⁻¹³

2 | THE DIFFICULTY OF CHOOSING THE BEST BIOLOGIC TREATMENT FOR A PATIENT WITH SEVERE ASTHMA

Although the aforementioned therapeutic agents have been formulated to target specific asthma endotypes, it is often difficult for the treating physician to identify which patient is the best candidate for each one of these specific treatments. As no head-to-head comparisons between these biologics have been attempted, assertions of superiority of one biologic agent over the other made by indirect treatment comparisons using meta-regression and matching-adjusted analysis may be invalid or deceptive.¹⁴⁻¹⁶ The identification of molecular targets and a more precise understanding of patient characteristics that would benefit the most from a specific biologic would be helpful.¹⁷

The choice of the most appropriate biologic therapy is even more difficult in the clinical scenario of a patient in whom clinical characteristics overlap between different endotypes, allowing the selection of more than one biologic agent. Thus, a physician's first therapeutic decision, no matter how carefully has been made, may often result in suboptimal clinical response and drug discontinuation. Use of discriminatory predictive biomarkers could aid in deciding which biologic agent would lead to the most beneficial response in each patient.

Although a previous study has shown that omalizumab therapy seemed to be more effective in severe asthma patients with elevated blood eosinophil levels and FeNO levels,¹⁸ more recent studies concluded that the drug was effective irrespective of the patients baseline characteristics and biomarker levels.^{19,20} Thus, so far, no specific biomarker has been proven to be useful for predicting or monitoring response to omalizumab. For the three monoclonal antibodies that target the IL-5 axis, higher baseline absolute blood eosinophil counts and a history of exacerbations the previous year have been found to predict enhanced response to the biologics.⁹ Additionally, baseline oral corticosteroid use, history of nasal polyps and prebronchodilator FVC <65% predicted were associated with greater response to benralizumab, regardless of baseline blood eosinophil levels.²¹ Finally, the beneficial effect of dupilumab has been found to be greater in subjects with higher baseline blood eosinophil counts and FeNO levels.¹² However, as previously stated, all these results came

mainly from post hoc analyses and observational registries and to date no definite rule or algorithm exists to help the treating physician to select the 'most appropriate' biologic for each patient.

The frequent overlap of different asthma endotypes in the same patient,^{22,23} together with the availability of several therapeutic choices for the eosinophilic endotype, provides clinicians with the opportunity to an alternative biological therapy if their first choice is not proven to result in the optimal therapeutic effect. However, to our knowledge, to date no specific guidelines exist to provide a safe and effective way of switching between different biologics.

3 | WHEN SHOULD SWITCHING BEEN CONSIDERED?

Although the current GINA consensus for the management of severe asthma²⁴ suggests that a 4-month trial should be conducted in order to assess a patient's response to therapy, still the exact time to re-evaluation and judgment of a patient to be either a responder or non-responder to therapy has not yet been adequately defined. In some cases, this is imposed by the local health authorities to avoid waste of healthcare resources, but usually, this decision has to be made by the physician itself. The use of biomarkers and clinical indicators of response to biologic therapy earlier in the treatment course are reasonable indices of an earlier adjustment to therapeutic regimens. However, response biomarkers measured early in the course of therapy, as reductions in blood eosinophil counts after administration of an anti-IL-5/IL-5R α agent, have not been proven to predict reliably long-term response.²⁵ At the moment, the net effect on oral corticosteroid treatment with regard to steroid discontinuation may be considered as the only reliable marker for the assessment of clinical success of these therapies in patients with steroid-dependent asthma, as failure to reach this outcome may impose the requirement for switching from one biologic therapy to another.^{26,27}

Besides inadequate response to therapy, the treating physician may also be forced to switch from one biologic therapy to another in several other circumstances, such as the occurrence of adverse events, the necessity or desire for a more convenient dosing scheme, the patient's preferences, possible changes in the commercial availability of a particular agent, as well as special safety considerations in cases of comorbidities, pregnancy, lactation and incidental opportunistic infections. However, to our knowledge, all reported studies on switching have included patients with no response or suboptimal response to the first biologic and although in many RCTs some patients always discontinue therapy due to adverse events, no studies or cases of patients switched for adverse events are available.

To date, omalizumab is the only biologic agent which has available data showing no evidence of an increased risk of major congenital abnormalities among pregnant women exposed, compared with a disease-matched unexposed cohort.²⁸ Thus, omalizumab may be considered as the only appropriate switching option for eligible women of reproductive age who are planning to get pregnant. Furthermore, omalizumab is also considered acceptable for use

during breastfeeding^{29,30} while up to date, there is no information available regarding the safety of other biologics during lactation.

It is worth mentioning, that although there is no evidence of increased risk of opportunistic infections in asthmatic patients receiving biologics, cases of herpes zoster have been reported in patients treated with mepolizumab,^{31,32} and benralizumab^{33,34} indicating that anti-IL-5/anti-IL-5R treatment might increase the risk of shingles and revealing a possible need of switching to a different class (when possible) when this kind of infection occurs. Furthermore, although considerations were reported regarding the long-term eosinophil depletion and the incidence of opportunistic infections, neither benralizumab nor reslizumab has been proven to increase this risk.^{35,36} Finally, omalizumab therapy appeared to be associated with a modest (although not statistically significant) increase in the incidence of geohelminth infection in high-risk patients although there was no increased morbidity attributable to intestinal helminths or any decrease in the time to first infection compared to placebo.³⁷ Additionally, there is no evidence of increased helminthic parasitic infections in patients treated with anti-IL-5/Anti-IL5R agents.^{36,38,39} However, a switch to a different class of biologics (other than anti-IgE and anti-IL-5/anti-IL5R) should be considered in cases of a patient experiencing such an infection especially in the lack of response to the anti-helminthic treatment.

4 | HOW SHOULD SWITCHING BEEN PERFORMED

However, even when switching from a biologic agent to another has been decided, several considerations regarding the time and way of administration of the new drug arise. For example, there are no data supporting the necessity of a wash-out period before administering the new biologic, and if so, its optimal duration and the appropriate actions that should be done if in the meantime the patient deteriorates. Furthermore, it is not known whether there are any considerations if both agents are present simultaneously on the same patient. How should the switching be performed? Is it possible to move from one agent to any other and what about switching between agents that target the same biologic pathway, that is between antibodies targeting the IL-5 signalling pathway?

Recently, a small number of case reports describing successful switching between biologics in severe asthma patients have been published.⁴⁰⁻⁴³ These reports mainly included patients eligible for both anti-IgE and anti-IL-5 treatments and, due to the different time points these biologics became available to the market, they mainly describe alterations from omalizumab to mepolizumab^{40,41} from omalizumab to benralizumab,⁴² and from mepolizumab to benralizumab.⁴³ The results of a recent post hoc meta-analysis of pooled data from 'Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma', (MENSA)⁴⁴ and 'Mepolizumab adjunctive therapy in subjects with Severe eosinophilic Asthma' (MUSCA)⁴⁵ studies indicate that mepolizumab reduced exacerbation frequency and

improved HRQoL and asthma control in patients with severe eosinophilic asthma, irrespective of prior omalizumab use.⁴⁶ However, these findings do not allow for definite conclusions on the most appropriate methodology of switching, regarding both effectiveness and safety issues.

Elimination half-life ($t_{1/2el}$) for the five biologics approved for the treatment of severe asthma varies from 15 to 25 days (24 to 26 days for Omalizumab, 25 to 30 days for Reslizumab, 16 to 22 days for Mepolizumab, and approximately 15 and 26 days for Benralizumab and Dupilumab, respectively).⁴⁷ Usually, the proposed wash-out period of a drug is estimated at 5 to 10 times of its elimination half-life, a fact which means that for a longer $t_{1/2el}$ of a biologic a prolonged wash-out period might be required.⁴⁸ However, a more rapid initiation of the new agent may be essential for more symptomatic patients and patients experiencing frequent exacerbations and this might lead to assumptions regarding the safety of such an early administration. This concern has been partially resolved by the 'Omalizumab Switch to Mepolizumab' (OSMO) study, which aimed to assess whether patients with asthma eligible for both omalizumab and mepolizumab therapy, but not optimally controlled with omalizumab, would experience improvements in asthma control when switched directly to mepolizumab.⁴⁹ Since the study was designed to mimic the everyday clinical practice, a pragmatic approach of switching from one (omalizumab) to another (mepolizumab) biologic without a standard wash-out period was attempted. The most important finding of this study was not only the substantial improvement of asthma control, lung function, health status and the reduction of asthma exacerbations, but also the fact that switching between these two biologics without a wash-out period did not result in any adverse events and/or tolerability issues, providing evidence that such an approach is feasible without significant safety concerns.^{49,50} Similarly, one retrospective observational and one prospective real-life study performed in patients poorly controlled with omalizumab who were seamlessly switched to mepolizumab provided similar results.^{51,52}

5 | SWITCHING BETWEEN AGENTS TARGETING THE SAME PATHWAY

To date, only scarce information exists regarding the effectiveness of switching between anti-IL5 agents. It is worth to mention that the approved dose of mepolizumab (100 mg SC) has little effect on airway eosinophilia as assessed by induced sputum.⁵³ On the contrary, in bronchial biopsies of asthmatic patients obtained during and after treatment with benralizumab showed that airway mucosal eosinophils decreased approximately 96% after three consecutive SC administrations of the antibody.⁵⁴ Similarly weight-adjusted dose of reslizumab, significantly reduces sputum eosinophilia by approximately 91%.⁵⁵ One publication described a case report of one patient with inadequate response to mepolizumab, who experienced clinical and functional improvement after switching to benralizumab,⁴³ while in a small case series of

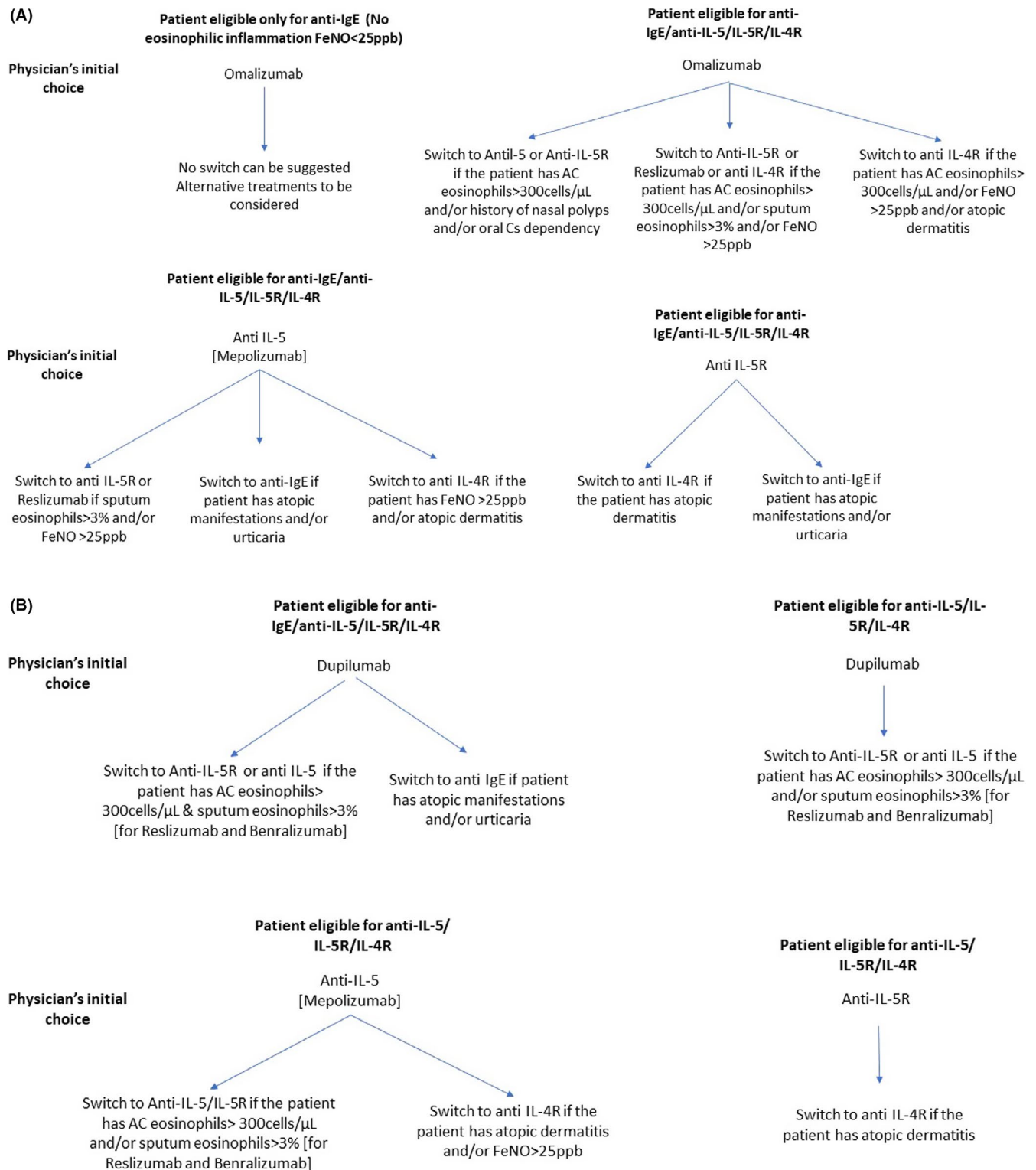


FIGURE 1 A proposed algorithm for switching between biologics based on biomarkers and some patients' characteristics.

3 patients with eosinophilic asthma and suboptimal response to mepolizumab, significant clinical improvement was also achieved after switching to benralizumab.⁵⁶ In another small study from a cohort of patients with eosinophilic asthma, a subgroup was directly switched from mepolizumab to benralizumab without

a wash-out period and experienced significant improvement in all study outcomes.⁵⁷ Finally, in a small study, ten prednisone-dependent patients with blood (>300 cells/μL) and sputum (>3%) eosinophilia and poor response to mepolizumab (100 mg SC, every 4 weeks), improved lung function and asthma control

when they were switched to weight-adjusted intravenous reslizumab.⁵⁵ These observations support the hypothesis that in patients with eosinophilic asthma failure to respond to mepolizumab does not preclude subsequent response to reslizumab and benralizumab.

There are currently no published data regarding switching from any biological agent to dupilumab, probably due to the relatively recent approval of this agent for use in patients with severe asthma, by the regulatory authorities, namely the FDA and EMA.

6 | COMBINING DIFFERENT BIOLOGICS: THE 'MIX AND MATCH' APPROACH

In patients with severe asthma that remain uncontrolled despite receiving add-on treatment with monoclonal antibodies, the use of combination therapy could be considered. Although the OSMO study Subgroup analysis confirmed no additional benefit during the first half of the study, when both biologics were present in the patient, nor a clinical deterioration as omalizumab was naturally washed-out in the second half of the study,⁴⁹ there are still some speculations on whether there could be any adding beneficial effect of the combination of two or more monoclonal antibodies targeting different biological pathways in patients with overlap of different asthmatic endotypes. Apart from the concerns of this 'mix and match' approach regarding the increased cost of therapy, it is also unclear whether safety issues could occur. Recently, Ortega et al⁵⁸ have reported 3 different cases of patients with refractory disease in whom clinical improvement was achieved using multiple combinations of different biologic agents. These patients received a combination of omalizumab with either mepolizumab, benralizumab or dupilumab, in different schemes and for different period of times. Interestingly, clinical improvement together with improved control of comorbid conditions (i.e. urticaria) was achieved with the combination of different biologics.⁵⁸ Although these reported cases did not reveal any adverse events on patients receiving two different classes of biologics, it cannot be ensured that the co-administration of two monoclonal antibodies would not result in increased risk of adverse events. However, since such an approach has not yet been studied thoroughly, careful recognition of patients who may benefit from targeting multiple inflammatory pathways is important, in order to achieve best disease control.

7 | CONCLUSION

Recognition of eosinophilic airway inflammation as a treatable trait has resulted in the emergence of biologic agents in patients with severe asthma, with identification of specific biomarkers constituting the basis of biologic-related personalized medicine. The current GINA consensus for asthma suggests the addition of a biologic as the first line add-on treatment on step 5, however,

as severe asthma endotypes often overlap, some patients may be candidates for treatment with more than one monoclonal antibodies. Therefore, treating physicians should make their best effort to recognize those patients who will benefit the most from each of the available and approved therapies. A future network meta-analysis could be extremely helpful in this direction. A proposed algorithm for switching between biologics based on biomarkers and some patients' characteristics is shown on Figure 1. Although there is increasing evidence suggesting that in cases of inadequate asthma control, another agent should be tried in order to achieve better disease outcomes, identification and validation of precise biomarkers that will present a better ability to predict response to the different biologic treatments is still an unmet need and a lot of research is still an unmet need and further research is needed in this direction. The observed inconsistency between known Th2 biomarkers and clinical response to biologic treatment suggests that the underlying inflammatory pathways may be much more complex than expected and targeting one mechanism may not be enough, highlighting the potential for multiple treatments in selected cases. Early during the course of the therapeutic process, several clinical indicators may allow a shared decision-making with the patient, of whether one biologic should be continued or a switch to an alternate treatment is indicated. Finally, the available data, although limited, show that switching can be probably performed without a wash-out period. However, since high quality of data able to provide a guidance for switching is lacking, the development of international databases of patients (including children) on biologics would be extremely helpful.

CONFLICT OF INTERESTS

AIP, EF and SP has received advisory board and speakers' fees from Novartis, AstraZeneca and GSK. DP has received grants from GSK and AstraZeneca and honoraria from Novartis and AstraZeneca. SL has received advisory board and speakers' fees from Novartis, AstraZeneca, GSK and Sanofi.

AUTHOR CONTRIBUTIONS

AIP, SL, SP and DP organized the manuscript and the references. AIP, EF and SL wrote the manuscript. SL, AIP and EF provided the switching algorithm. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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