

REVIEW

The evolving algorithm of biological selection in severe asthma

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Abstract

New therapeutic options for severe asthma have recently emerged, mostly in the form of monoclonal antibodies ("biologics") targeting relevant inflammatory pathways. Currently available agents target different aspects of "Type 2" immunity, and their indications often include overlapping patient groups. We present a round-table discussion that took place during the Annual Meeting of the Respiratory Effectiveness Group (REG), on the reasoning behind the use of different add-on medications for severe asthma, and crucially, on selection strategies. The proposed rational is based on current evidence, including real-life studies, as well as on the appreciation of the relevant complexities. Direct head-to-head comparisons of biologics are lacking; therefore, algorithms for initial choice and potential switch between agents should be based on understanding the key characteristics of different options and the development of a clear plan with predefined targets and shared decision-making, in a structured way.

KEYWORDS

asthma, biologics, eosinophils, IgE, inflammation

1 | INTRODUCTION

Severe asthma is a subset of difficult-to-treat asthma¹ and affects up to 10% of the adult asthma population.^{1,2} In recent decades, the mainstay of treating severe asthma has been a combination of

high-dose inhaled corticosteroid and long-acting beta agonist (ICS/LABA), followed by a trial of tiotropium bromide. If thoroughly investigated subjects remain uncontrolled or continue to experience frequent exacerbations, oral corticosteroids (OCS) are usually required episodically. A minority of patients become prednisone-dependent

to maintain asthma control. However, partly by definition, severe asthma patients often do not respond to regular treatment in a satisfactory manner and require additional interventions. Because of the cost of the new biologicals and the serious short- and long-term side effects associated with OCS, before such interventions are considered, issues such as adherence, inhaler technique and treatment of comorbidities need to be considered.³ The rational choice of such interventions should reflect, if possible, the underlying endotype, which may have Type 2 (T2) or non-Type 2 (non-T2) immunity characteristics. Only recently have new therapeutic options become available, mostly in the form of monoclonal antibodies ("biologicals") targeting relevant inflammatory pathways. We present a round-table discussion that took place during the 2019 Annual Meeting of the Respiratory Effectiveness Group (REG), on the reasoning behind the use of different biological and nonbiological add-on medications for severe asthma, and crucially, on selection strategies. The proposed reasoning is based on current evidence, including real-life studies, as well as on the appreciation of the relevant complexities. The key characteristics of different options are presented, followed by a structured approach to disease evaluation, choice of medication and monitoring/switching between agents.

2 | NONBIOLOGICAL TREATMENTS

Currently, nonbiological add-on treatments for severe asthma are generally less effective than biologicals, detailed below. Oral nonbiological therapies that can be used on T2 severe asthma include the anti-leukotrienes (CysLT₂-R antagonists, such as montelukast), which have a weak anti-eosinophilic effect and a small add-on effect to ICS in severe asthma, are inexpensive and have a favourable side-effect profile. More effective than the anti-leukotrienes are the 5-lipoxygenase inhibitors (eg zileuton); however, zileuton can cause side effects such as hepatic dysfunction and diarrhoea and needs to be taken 4 times a day, which is inconvenient and is not available in most countries. Another inexpensive alternative is theophylline, which reduces the eosinophils when given orally in low doses and has been shown to have an add-on effect in severe asthma on top of maximum ICS therapy.⁴ In general, these drugs have not been studied extensively in patients with severe asthma.

Up to 50% of severe asthma patients are characterized as non-T2, although there is ongoing discussion about the true proportion in the view of possible effects of treatment on T2-biomarkers. Nevertheless, these biomarker low patients are not candidates for T2 biological therapies, while the precise mechanism of their persisting symptoms remains unclear,⁵ making this population much more difficult to target. Several known mechanisms can be targeted with drugs such as CXCR2 antagonists that are in development and block the receptor for interleukin-8 expressed on neutrophils and related neutrophilic chemokines, by biological therapies which target the allergen-driven neutrophilia and by anti-inflammatory treatments that are thought to work mainly on signalling mechanisms of airway epithelial cells and neutrophil products. But thus far results

for this class of therapy have been disappointing. Of the available treatments, the macrolide azithromycin has been shown to be effective in reducing exacerbations and improving the quality of life in neutrophilic asthma, and also interestingly in the AMAZES study was effective as well in eosinophilic severe asthma patients.^{6,7} The efficacy of azithromycin has been confirmed in a recent individual patient meta-analysis.⁸ In part, its efficacy may relate to the high prevalence of bronchiectasis in patients with severe asthma.

Azithromycin, however, is not without problems, mainly the potential for developing resistant bacteria. Whether this is an antibiotic and/or an anti-inflammatory effect of the macrolide is something not yet resolved. In non-T2-mediated severe asthma, although residual inflammatory cells are lacking while on baseline therapy, patients still experience asthma symptoms. Thus, the addition of a bronchodilator such as the long-acting muscarinic antagonist (LAMA) tiotropium to ICS/LABA therapy has been shown to improve lung function but not symptoms and reduce exacerbations by 21% when added to a ICS/LABA combination inhaler.^{9,10} Moreover, recent data among a broader population of patients with uncontrolled asthma, a triple combination inhaler (ICS + LABA + LAMA) also showed improved lung function and reduced severe exacerbations.¹¹ Interestingly, the recent report of a triple inhaler with all three components in a single device was not found to be more effective than a combination inhaler and a LAMA (tiotropium) in a separate inhaler device. Given there is no predictor of which patients will benefit from the addition of a LAMA, elderly patients with more fixed airway obstruction that have non-T2 severe asthma and, in particular, those who have asthma-COPD overlap (ACO) should undergo a trial of additional LAMA therapy, and if proven to be beneficial, then they can be switched to a triple inhaler which is more convenient. The exact duration of a therapy trial is not defined but given its main purpose is the prevention of future risk, that is exacerbations, an extended trial of 6 months is probably reasonable. Carefully selected patients with non-T2-mediated severe asthma may benefit from bronchial thermoplasty, which destroys airway smooth muscle cells.¹² Clinical benefits have been shown (but not yet approved) by destroying the innervations of the airways through a bronchoscope (targeted denervation).¹³

3 | TREATMENT WITH ANTI-IgE

Omalizumab is a monoclonal antibody directed against immunoglobulin E (IgE) and has been used in severe asthma for over 15 years. Up to 70% of asthma occurs in association with allergy. Omalizumab selectively binds allergen-specific IgE, preventing it from both initiating and maintaining the inflammatory response characteristic of asthma (Table 1). The INNOVATE study among 419 people with moderate-to-severe asthma showed a 50% reduction in severe exacerbations at week 28 follow-up,¹⁴ as well as improvements in patient reported outcomes measures. A post hoc analysis of INNOVATE showed a greater (54%) reduction in annualized exacerbations when both blood eosinophils were ≥ 300 cells/ μ L and IgE > 75 IU/mL, which is similar to the effect of the other biologicals for severe asthma.¹⁵

TABLE 1 Monoclonal antibody therapies for severe asthma

Name	Description	Indication (add-on treatment)	Dosage and route of administration
Omalizumab (<i>Xolair</i>)	Anti-IgE Humanized monoclonal antibody against IgE	Uncontrolled severe allergic asthma in adults, adolescents and children aged ≥ 6 y	Prefilled syringe for SC injection Dose calculated according to baseline IgE and body weight and total IgE levels Usual dose every 2-4 wk (larger doses divided into 2 and administered every 2 wk)
Benralizumab (<i>Fasenra</i>)	Anti-IL-5 receptor Humanized monoclonal antibody against IL-5 receptor α	Uncontrolled severe eosinophilic asthma in adults and adolescents aged ≥ 12 y	Solution for injection in a single-use prefilled syringe or prefilled pen 30 mg SC every 4 wk for three injections then every 8 wk
Mepolizumab (<i>Nucala</i>)	Anti-IL-5 Humanized monoclonal antibody against IL-5	Uncontrolled severe eosinophilic asthma in adults, adolescents and children aged ≥ 6 y	Solution for injection in a single-use prefilled syringe or prefilled pen 100 mg SC every 4 wk
Reslizumab (<i>Cinqaero</i>)	Anti-IL-5 Humanized monoclonal antibody against IL-5	Uncontrolled severe eosinophilic asthma in adults aged ≥ 18 y	Concentrate for solution for infusion, to be prepared aseptically IV infusion every 4 wk Weight-adjusted dose (3 mg/kg)
Dupilumab (<i>Dupixent</i>)	Anti-IL-4/IL-13 (IL-4R α) Human monoclonal antibody against IL-4 receptor α	Uncontrolled severe eosinophilic asthma in adults and adolescents aged ≥ 12 y	Prefilled syringe for SC injection 400 mg or 600 mg initially, then 200 mg or 300 mg every fortnight

Abbreviations: HCP, healthcare professional; IgE, immunoglobulin E; IL-13, interleukin-13; IL-4, interleukin-4; IL-4R α , interleukin-4 receptor-alpha; IL-5, interleukin-5; IV, intravenous; SC, subcutaneous.

Thus, patients appear to be responding well on all the different biologicals when eosinophils are above 300 cells/ μ L. Since omalizumab has been used for many years, a substantial volume of real-world evidence is available.¹⁶⁻²⁴ One real-life study, APEX II, showed a reduction in the mean number of days hospitalized for a severe exacerbation (15 days vs 4 days) in adults.²³ The STELLAIR study looked at “responders” vs “non responders,” where the definition for responder was having a decrease in exacerbations and a “pass” as assessed by the Global Evaluation of Treatment Effectiveness (GETE) criteria. This study showed that independent of blood eosinophil cut-off (either $<$ or ≥ 300 cells/mL), patients were just as likely to respond to omalizumab.²⁵ There is also evidence that omalizumab can significantly reduce OCS requirements.^{20,25} Omalizumab is a very safe drug with over a million patient-years of experience and has been proven safe to continue during pregnancy. In addition, there is considerable experience with its use in children aged ≥ 6 years, while a current study is looking into potentially preventive effects in preschool children to prevent the atopic march.²⁶ With omalizumab, there is a unique 16-week opportunity to stop the drug if there is no response. Therefore, if a patient is eligible for either, an anti-eosinophilic or anti-IgE biological, the anti-IgE agent might be prioritized, as it is safe, it does not affect eosinophil biology, and if the patient remains uncontrolled, it can be directly switched to another biological without a washout period.²⁷ However, relative efficacy in reduction of exacerbations, OCS sparing effect and prevalent phenotype

can alternatively be considered. Currently, in Europe omalizumab is licensed for home administration, with home administration coming soon for the other biologicals as well. This potentially presents a series of different issues around medication adherence and when a dose is missed. Overall, omalizumab is effective in severe allergic asthma and severe allergic eosinophilic asthma¹⁶ and has an early decision mechanism to allow for switching without a washout period. It is very safe, can be given during pregnancy and does not increase risk of malignancy, does not seem to increase parasitic risk and can be safely given to children aged ≥ 6 years.

4 | ANTI-IL5 AND ANTI-IL5 RECEPTOR THERAPIES

Anti-interleukin 5 (anti-IL5) treatments target a key component of the T2 cytokine axis. IL5 can be produced by more than one cellular source within two different nonmutually exclusive pathways that induce eosinophilic inflammation¹⁰ and is a key component in eosinophil biology, as it is the main factor for eosinophil activation, proliferation and survival. Three monoclonal antibodies targeting eosinophils are currently available: mepolizumab, reslizumab and benralizumab. Key differences exist across these three therapies—the first two therapies bind IL5 leading to a reduction in the production and survival of eosinophils, whereas benralizumab binds

the IL5 receptor Ra expressed on eosinophils (and basophils), leading to direct cell-mediated destruction and depletion of eosinophils and basophils in the airways. There are also differences in route of administration (sc or iv) and dosing frequency across the three therapies, which have important consequences for patients in terms of scheduling of dose (Table 1). A number of clinical trials for each of the three drugs (ie pivotal phase III studies; MENSA, Reslizumab Studies I and II, SIROCCO and CALIMA) have been conducted with exacerbations as the primary outcome.²⁸⁻³¹ These pivotal studies were not only enriched for exacerbations by recruiting patients who had exacerbations in the previous year, but also enriched for biology of interest; that is, they had certain thresholds for or stratification by blood eosinophil count. Further, there were also differences in terms of the population (severe vs moderate-to-severe asthma), background treatment and lung function. These differences, particularly different populations, are important to remember when comparing treatments. Nevertheless, all studies showed that the molecules worked well over and above placebo, with significant reduction in the annual rate of severe exacerbations defined as requiring OCS use. Interestingly, a difference was noted between the replicate studies SIROCCO and CALIMA for benralizumab, with a larger than anticipated reduction in exacerbation rates in the placebo arm—whether this was due to baseline medication adherence, good asthma care, the Hawthorne effect or a true placebo effect remains unclear. Further, a pooled analysis of the SIROCCO and CALIMA showed greater improvements in annual exacerbation rate with benralizumab compared to placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations.³² A Cochrane systematic review of 13 randomized clinical trials evaluating the anti-IL5 therapies concluded that all three reduced exacerbations rates (rescue OCS ≥ 3 days) by approximately 50%; however, improvements in ACQ and asthma quality of life (AQOL) or lung function were modest.³³ Importantly, a greater effect size was observed in patients with higher blood eosinophil counts (often those not on maintenance OCS). Finally, there were no serious adverse effects reported compared to placebo.³³ While there have been no head-to-head studies comparing the anti-IL5 therapies, a number of indirect comparisons have attempted to show superiority or equivalence of these particular molecules and have reached slightly different conclusions.³³⁻³⁷ These differences characteristically have occurred with the sponsoring company for the publications generally showing benefits for its compound. Another important effect of anti-IL5 therapies is their steroid-sparing effect, evaluated in patients on maintenance OCS therapy. In the SIRIUS study (mepolizumab 100 mg s/c Q4W), there was a 50% reduction in daily maintenance OCS dose, compared with no reduction in the placebo arm.³⁸ In the ZONDA study (benralizumab 30 mg s/c Q8W), there was a 75% reduction in OCS use, compared with 25% reduction in the placebo arm.³⁹ These studies were relatively short, that is 24 or 28 weeks, respectively. A recent 2-year integrated analysis showed persisting efficacy and safety with the long-term use of benralizumab for patients with severe, uncontrolled eosinophilic asthma.⁴⁰ Other postlicensing clinical trials are now being conducted

to clarify this.⁴¹ Importantly, these studies show a reduction of systemic steroid exposure on two levels—reduction in maintenance dose and a concomitant reduction in exacerbations requiring OCS. With regard to benralizumab, while there is complete depletion of eosinophils, there is a residual background rate of exacerbations and it remains unclear what is driving these events. In the UK, two studies (MEX and BENREX) are now being conducted aimed at phenotyping exacerbations for people who are established on these biologicals and gaining a better insight into the characteristic profile of these events. Another important aspect regarding these therapies is the clinical response to treatment: patients appearing “biologically” similar may have considerably divergent responses. A traffic light approach, consistent with the NICE guidelines,⁴² has been developed to assess responses, classifying patients as “non-responders,” “intermediate responders” and “super responders” based on residual systemic steroid exposure.⁴³ Nevertheless, defining what a reasonable response is for the “intermediate” group remains the biggest challenge. Although all anti-IL5 therapies so far appear to be safe, longer term follow-up is needed to ensure that there is no increase in worm or parasite infection, particularly in tropical countries.

5 | TREATMENT WITH ANTI-IL4/IL13 IN SEVERE ASTHMA

Among several potential molecules targeting either interleukin 4 (IL4), interleukin 13 (IL13) or both, only dupilumab is available in many countries. Dupilumab targets the α subunit of the IL4 receptor (IL-4R α), expressed on various cell types, inhibiting signalling of both IL-4 and IL-13, which are key drivers of allergic/T2 diseases such as atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) (Table 1).^{44,45} In a phase II clinical trial, dupilumab added to ICS/LABA improved lung function and reduced severe exacerbations, irrespective of the baseline eosinophil count.⁴⁶ In the recent phase III clinical trial of patients with moderate-to-severe asthma, both dupilumab 200 mg and 300 mg every 2 weeks, reduced annualized exacerbations, improved lung function and asthma control, with greater benefits in patients who had higher baseline levels of eosinophils.⁴⁷ Dupilumab has also been shown to reduce systemic steroid use, while reducing the rate of severe exacerbations and improving lung function.⁴⁸ Further, dupilumab can be effective in CRS and comorbid asthma,⁴⁹ severe CRSwNP,^{50,51} or moderate-to-severe atopic dermatitis.⁵² This is important, as a large proportion of patients with severe asthma will also suffer from such comorbidities. In 437 patients included in the Severe Asthma Network in Italy (SANI), 64% were taking chronic OCSs, 42.6% had CRSwNP, and 9.6% had atopic eczema.⁵³ A sub-analysis of data from SANI showed that among patients with early-onset asthma, 41% had CRSwNP, while among those with late-onset asthma, 61% had CRSwNP, had taken three courses of OCS in the previous year for sinus symptoms, and reported two sinus surgeries in their lifetime.⁵⁴ Reducing OCS use is clearly an important outcome for patients and the payer. An easy to measure biomarker for dupilumab response is fractional exhaled

nitric oxide (FeNO) as IL-4R α regulates inducible nitric oxide synthase expression in airway epithelial cells.

6 | DISCUSSION

With an increasing number of “biological” therapies available for severe asthma, with considerable phenotype target overlap and lack of head-to-head comparisons, it is clear that decision support for potential treatment strategies is needed. Proposals for severe asthma treatment algorithms have been already published^{55,56} and will most probably continue to appear in the literature. Taking into account that to a large extent this is an area of specialist interest, the discussion that follows intends to put forward principles for selection that should facilitate the process as shown in Figure 1, rather than any complex arbitrary algorithm. Key characteristics of each agent described above, should be taken into account.

6.1 | Step 1: clinical evaluation

The need for accurately diagnosing, differentially diagnosing, stratifying and phenotyping (severe) asthma has been frequently highlighted.^{3,55,56} A number of clinician-, patient- and guideline-related challenges associated with the evaluation process that were identified are avoidable or solvable to a certain extent. Clinician-related factors include the variability in intensity of assessment in both primary and secondary care and the variability in the assessment timeframe: both of these depend to a large extent on the particular health system; the challenge of distinguishing between severe asthma and difficult-to-treat asthma; the fact that severe asthma patients rarely have one disease and the need to investigate and evaluate comorbidities⁴⁵; the requirement of different health systems for provisional or concrete diagnoses; and of course the management of patient expectations. Major patient-related issues include nonadherence to therapy (intentional or not), poor inhaler technique and patient expectations with the new treatments. Guideline-related issues include a difficulty in phenotype/endotype classification/stratification, lack of better treatment options for non-T2 severe asthma and difficulty in proposing and implementing standardized criteria for referral to specialists by general practitioners. In some cases, suggested follow-up timeframes may not be realistic in busy clinical settings. Another guideline-related factor is that a paradox occurs in the definition of severe asthma, which is defined as “asthma that requires GINA Step 4-5 medications in the previous year, or OCS use for <50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy”,¹ despite the fact that poor adherence to treatment and poor inhaler technique are a reality in asthma.^{57,58} Approximately 30% of patients referred to specialists do not have asthma,⁵⁹ adherence rates to regular preventative therapy are low and often range from 30% to 40% in practice,⁵⁷ and anywhere up to 90% of people with asthma (depending on the device and patient population) demonstrate incorrect inhaler technique.⁵⁸ Extensive work on smart inhalers and other

e-Health approaches are currently focusing on this.^{60,61} In the meantime, the important point of how we objectively assess adherence and what is achievable remains. Patients cannot be precisely phenotyped if real exposure to background treatment is unknown. Nevertheless, most patients do not have large fluctuations in severity over the course of the disease, especially in regard to deterioration; among a cohort of over 70 000 patients with incident mild asthma, 8% of patients transitioned to moderate or severe asthma over a 10-year period⁶²; conversely in a cohort of over 13 000 patients with incident severe asthma, 83% of patients reverted to a less severe level (43% mild; 40% moderate) over 10 years.⁶³ A multidisciplinary, intensive approach is needed to better define the eligibility of the patient for the different add-on treatments in severe asthma.⁶⁴ Depending on the level of service and health system structure, referral is a key consideration.

Despite the above challenges, a diagnostic decision needs to be taken, following a structured investigation, including phenotyping, taking into account that close monitoring and re-evaluation are essential parts of the process.

6.2 | Step 2: choice of biological and target-setting

Biologicals are the current treatment of choice in T2 uncontrolled severe asthma, taking into account all the considerations described above. While indications are not identical for all the agents, there is considerable overlap and probably most patients fall under this category.^{1,65,66} Evidence on biomarkers is mostly about response prediction for each agent, rather than differential response between agents. Since no head-to-head studies have been published to date, and indirect comparisons are few,³³⁻³⁷ the challenge will only increase with new agents coming in the market. It is also possible that response may be personalized. Therefore, the choice of the initial treatment agent should take into account patient preference and practical issues such as dosing schedules, ease of administration or availability for home administration. Comorbidities, such as eczema, and current treatment, particularly systemic steroids, should be considered. Shared decision-making, predefining a target and prioritizing steroid-sparing effect, should take place following detailed characterization/phenotyping of the patient that usually requires prospective evaluation and a robust monitoring plan. Particular conditions, such as pregnancy, exposure to parasites or cognitive status should be taken into account.

6.3 | Step 3: monitoring and switching

To discuss about switching, one needs to keep in mind that to a large extent it refers to patients who fulfil the indication for more than one biological agent. There can be exceptions to this; however, atypical choices should only take place in highly specialized settings in an individualized manner and, therefore, should not be generalized. Having said that, indications often reflect the registration study designs, more than the broader potential efficacy of each agent that may need to be further explored.

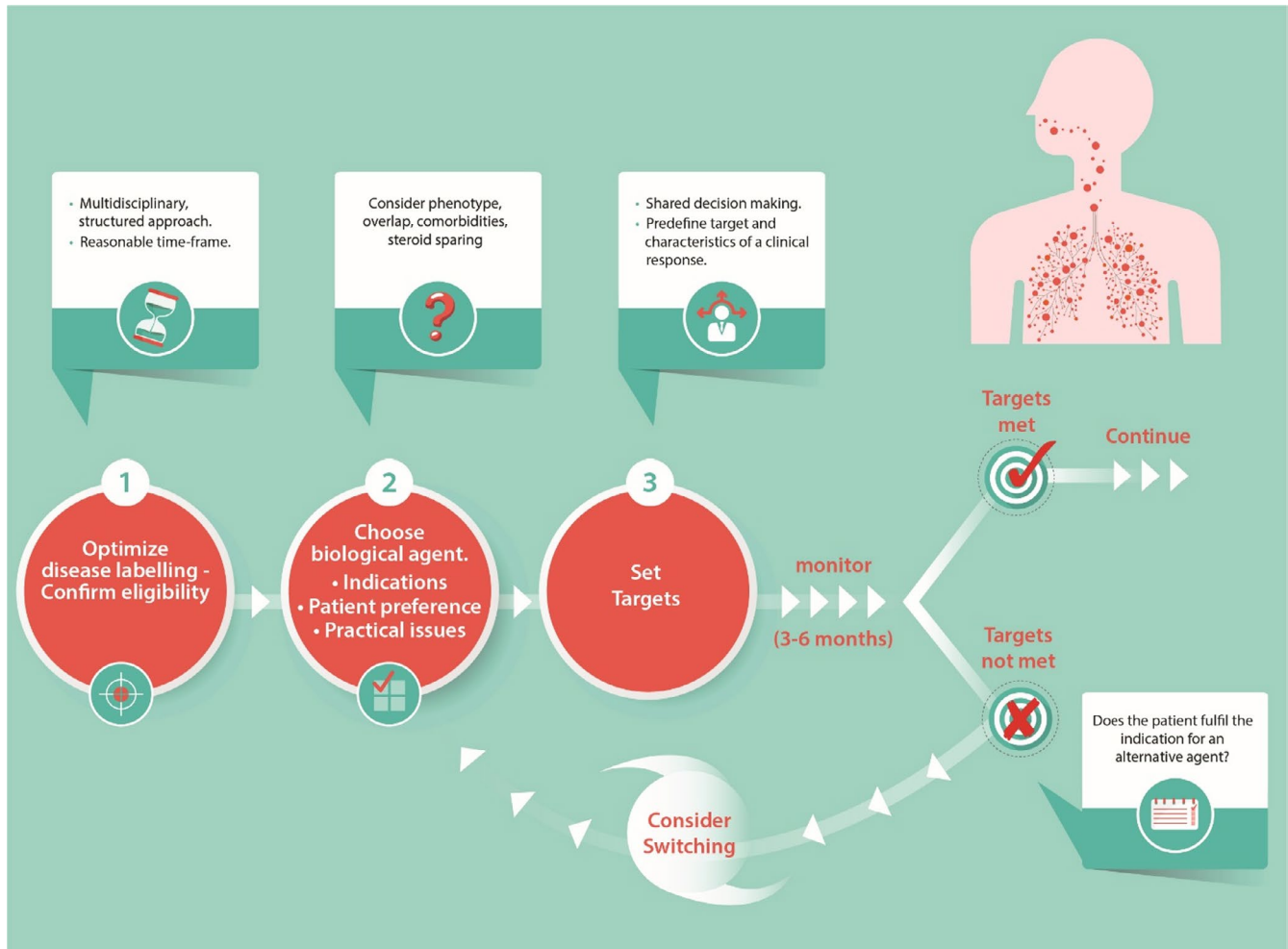


FIGURE 1 Principles of selection and possible switch between biological agents in severe asthma. 1-Diagnosis, differential diagnosis, phenotyping, and evaluation of comorbidities, adherence and inhaler technique are mandatory before considering a biological treatment. 2-All necessary phenotypic information (eg eosinophil levels, total IgE, specific IgE sensitizations, FeNO) should be available to assess that indications are met. Beyond these, little objective criteria for choosing are available; comorbidities, current therapy, patient preference and practical issues may inform decision. 3-Discuss targets and set a robust monitoring plan

Clearly, switching between biologicals should be considered when response is suboptimal or, more rarely, in case of severe adverse events. Switching due to changing circumstances or preferences in a responder is more challenging as evidence is lacking. Nevertheless, with increasing options, expectations are increasing as well. The major challenge therefore is to (pre)define the characteristics of a clinical response at the personal level. In this regard, access is an important consideration. A reasonable approach, also suggested by NICE,⁴² is to target overall systemic steroid exposure. With increasing experience and data from real-life studies, we may be able to better define specific cut-offs, but at the moment, a 50% reduction in chronic OCS dose seems a reasonable choice. Exacerbations are also a major target; however, as these are relatively rare events, they require a considerable period of time to be evaluated. While having no exacerbations is the ideal target, most agents have been shown to reduce exacerbations by approximately half. Symptoms, lung function, quality of life and fulfilment of patient expectations may add to the clinical decision. Such choices require medical judgement. The

Global Evaluation of Treatment Effectiveness score has been used to evaluate clinical response and continuation with omalizumab after 16 weeks.²⁵ Taking into account the extensive safety experience with this molecule, the short duration of time when the evaluation takes place, there is some sense in taking this as a first step, although this cannot be generalized. Nevertheless, a 4-6-month period appears to be the current consensus for evaluating the other molecules as well. Finally, comorbidities are important not only in relation to the choice of medication, but also in considering a switch, particularly in cases of intermediate responses with regard to asthma.

7 | CONCLUSIONS

For the right patient, treatment with a biological can be life-transforming. While specific entry criteria designed to maximize response are clear for each agent, patients who are apparently identical do not always respond; novel biomarkers are needed to increase the

response prediction. The list of unmet needs is still long, including non-T2 severe asthma. On an optimistic note, several new drugs and biologicals are being investigated. Nevertheless, biologicals have a potential far beyond their current formal indications.⁶⁷ There is therefore also an urgent need for real-life studies and registries, in which well-characterized populations are followed prospectively. Novel trial designs or adaptive designs may be able to address some of the gaps in our knowledge, and better define an improved patient journey for those with severe or difficult-to-treat asthma. For the time being, a multidisciplinary approach spanning from primary to tertiary care and among specialisms is needed and cannot be ignored. The proposed “algorithm,” resulting from this exercise, describes the current common sense, focusing on simple principles resulting from available evidence and prioritizing patient preferences in real life.

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CONFLICT OF INTEREST

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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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