# Monitoring and Evaluation of Therapeutic Response in Patients with Severe Asthma on Biologics

3.2

**Sanda Škrinjarić Cincar**[1,2]

1 School of Medicine Osijek University J.J. Strossmayer

2 Health Center Osijek

*Abstract*

Five biologics with different mechanisms of action have been available for uncontrolled severe T2 high asthma in clinical practice worldwide for years, and the first drug in a class of new biologics targeting the top of the inflammatory cascades, thymic stromal lymphopoietin (TSLP) is available from the beginning 2022. The results of randomized and real-life studies as well as experience in daily clinical practice confirm that the safety profile of biological drugs is very good. Biologics have a good potential to achieve remission during treatment, but not all patients respond equally well. The effectiveness of all biologics in severe asthma is approximately 60% in the real life conditions. An important task of the clinician is the correct assessment of the therapeutic response to biologics and the evaluation of patients who have a satisfactory response to treatment and those who do not. Therapeutic response to biologics should be assessed individually according to pre-defined goals every 3 to 6 months. In patients with a good response to biological drugs, continuation of treatment and continuous monitoring of efficacy and safety is recommended. If there is no satisfactory response to the initially introduced biologic, switching to another biologic is a rational option. During therapy with biologics, it is necessary to closely monitor the effect on exacerbations and symptoms. Research has shown that improving the overall quality of life is the most important outcome for most patients with severe asthma. Also, one of the most important effects of biological therapy is the possibility of excluding or reducing the dose of corticosteroids in patients who need them for disease control. The effect of biologics on improving lung function is important, but not critical for evaluating the effectiveness of treatment. However, previous reports have not yet provided precise instructions for long-term treatment with biologics in daily clinical practice, and there are questions still need to be answered.

*Keywords*: severe asthma, biologics, therapeutic response, evaluation

## Introduction: a new treatment options for uncontrolled severe asthma

Severe asthma is a disabling disease that accounts for not more than 5% of all asthmatics[1]. Although patients with severe asthma represent a minority of the total asthma population, they carry a majority of the morbidity and healthcare costs. Accurate treatment with biologics in the form of monoclonal antibodies has made it possible to attack certain pathogenic pathways or mechanisms and modifies them in order to control disease. In recent years the treatment of severe asthma with biological drugs in selected patients with T2-high inflammation has become very successful. The development of biological drugs for T2-low asthma was not so successful[3].

https://doi.org/10.26493/978-961-293-297-8.63-75

Patients with "problematic" asthma should be carefully examined and distinguished from those whose asthma is uncontrolled due to poor adherence and/or poor inhalation technique as well as difficult to treat for other reasons such as uncontrolled asthma triggers and comorbidities. Comorbidities in patients with asthma need to be treated appropriately. Some comorbidities, such as nasal polyps, allergic rhinitis, or atopic dermatitis, are favorably affected by biologics, while others, such as gastroesophageal reflux disease, obesity, and bronchiectasis, do not diminish the therapeutic response to biologics. Before assessing the severity of asthma itself, it is necessary to address all factors that have a potential effect on health status, and also to have them under control during treatment with biologics[1,4].

It is well known that asthma is a heterogeneous disease. Clinical diversity and inflammatory phenotype are reflected as a consequence of the pathogenetic mechanism and histopathological characteristics of asthma. Clinical features such as frequent exacerbations, emergency room visits, hospital admissions, lost days from work, school, or leisure time, poor asthma symptom control, poor lung function and poor quality of life, as well as oral corticosteroid use are characteristics of severe asthma[5]. The clinical features and inflammatory phenotype of severe asthma are currently fundamental determinants for assessing the indication for introduction as well as assessing the effect of treatment with biologic drugs. The phenotyping of severe asthma is today embedded in clinical practice and is used to assess the feasibility of available biologics[6]. The use of monoclonal antibodies against immunoglobulin E (IgE) and interleukin (IL) -5 and recently IL-13/IL-4 has been shown to be efficient and safe in clinical trials as well as in everyday clinical practice[7].

Efficacy and effectiveness are not identical concepts and it is not possible to investigate both in the same type of research. Efficacy can be tested in randomized controlled trials (RCTs) under controlled study conditions. Effectiveness can be tested in real-life trials under real living conditions. Efficacy results show what we can expect in a population that has the characteristics of the examined sample, and effectiveness results show what we have really observed[8]. Both types of research have shown that biologics are very successful in treating patients with severe asthma[1]. Biologics have good potential for achieving remission during treatment, but not all patients are good responders and usually not all criteria for complete remission or good asthma control are met[9]. An important task for clinicians is to properly assess the therapeutic response to biologics and to identify which patients have a satisfactory response to treatment and which do not.

## Licensed biologics for uncontrolled severe asthma

A years ago, five biological drugs with different mechanisms of action are available in clinical settings worldwide for uncontrolled severe asthma with high T2. These are: omalizumab (Xolair, Genentech/Novartis), mepolizumab (Nucala, GlaxoSmithKline), reslizumab (Cinqair, Teva), benralizumab (Fasenra, AstraZeneca) and dupilumab (Dupixent, Sanofi/Regeneron). Tezepelumab (Tezspire, Amgen/Astra Zeneca) is available in clinical practice from the beginning of 2022 in the United States of America.

The Institute for Clinical and Economic Review (ICER) analyzes the value of first five biological drugs treating moderate to severe asthma associated with T2 inflammation. The ICER Report suggests that all five approved biologics are effective and safe. Each of the five analyzed drugs significantly reduced the exacerbation of asthma compared with placebo and improved patient quality of life. Treatment with omalizumab and mepolizumab is carried out for the greatest length of time. Thanks to long-term effi-

cacy and safety data from extended studies of key trials as well as experience from everyday clinical practice, the uncertainties associated with these treatments are very small[10].

The EAACI 2021 use the GRADE approach in making recommendations for each biologic both in terms of its use and therapeutic effect assessment[11].

According to the 2021 EAACI Guidelines, a reduction in exacerbations, an improvement in quality of life, a reduction in the use of ICS as well as the use of rescue drugs, and global efficacy can be expected with high certainty in patients treated with omalizumab. Improvement in asthma control is expected with moderate certainty[11]. Real-life studies have shown the efficacy of omalizumab regardless of blood eosinophil status[12,13]. Long-term treatment with omalizumab did not increase the risk of side effects, especially anaphylaxis[14].

The EAACI recommendations for treatment with mepolizumab to reduce asthma exacerbations and to resolve or reduce OCS are strong. The effect of mepolizumab on asthma control, quality of life and lung function in studies was good, but less clear[15,16]. The greatest positive change in symptoms and lung function observed during the first months of treatment with mepolizumab[17]. No serious side effects associated with mepolizumab were reported in real-life studies[18].

According to the EAACI 2021 recommendations, there is high certainty that benralizumab reduces asthma exacerbations and OCS in a subgroup of adult asthmatics with severe asthma with > 150 eosinophils/μL. There is also great certainty for patients treated with benralizumab that asthma control and quality of life will improve[11]. Follow-up of 1,600 asthma patients treated with benralizumab for 2 years did not indicate an increased risk of infections or malignancies, but further long-term follow-up is needed to assess possible risks of eosinophil depletion during benralizumab treatment[19]. Dosage of benralizumab every 8 weeks may also be important for some patients.

A weight-based dosing regimen of reslizumab may provide a good response in cases that have failed to respond to other anti-IL5 biologics. Only reslizumab has to be given intravenously, which may be important for some patients. Very rare cases of anaphylaxis have been reported in clinical studies within the first 20 minutes after reslizumab infusion[20].

Long-term efficacy of dupilumab has been demonstrated in both allergic and eosinophilic phenotypes. The good safety profile of dupilumab is known from previous studies for atopic dermatitis. Dupilumab is well tolerated, but ocular side effects are common[21].

In endemic areas, patients treated with anti IL-5 biologics, should be screened for parasitic infections[11].

Tezepelumab is the first drug in a class of new biologics that targets and blocks thymic stromal lymphopoietin (TSLP), which sits at the top of the inflammatory cascades. The mechanism and site of action of tezepelumab stops the release of inflammatory cytokines at the very source and therefore this drug has the potential to treat a wide population of patients with severe asthma regardless of phenotype. Randomized trials of tezepelumab showed fewer exacerbations, better lung function, better asthma control, and better health-related quality of life in patients with severe asthma who received it[22]. Considering that it has only recently been available in daily clinical practice, the experiences of clinicians are still expected.

## Comparison between biologics

The assessment of the therapeutic effect of biologic drugs in severe asthma depends on a number of factors that differed significantly between studies and that can modulate the therapeutic response. In differed studies, there are different inclusion or exclusion criteria related to asthma severity, lung function,

definition of atopic status, eosinophil count, frequency and severity of exacerbations, and duration of asthma[1,11]. Due to this, the expert opinion is that the indirect treatment comparison between these five biologics may be erroneous or biased and should not be done[11]. Studies that directly compare the therapeutic response of approved biologics have not yet been performed.

## Key elements for evaluating responses to biological treatment in clinical practice. How and when to evaluate? Estimation of response sizes to biological treatment of severe asthma

The effectiveness of all the biologics in severe asthma is approximately 60% in a real-world setting[23,24,25]. Most of the afore mentioned clinical features of severe asthma represent the elements for assessing the outcomes and clinical benefits from treatment with biologics (Figure 1.). Asthma control includes objective clinical outcomes (lung function parameters, number of exacerbations), but also includes subjective outcomes assessed by the patient, such as symptoms, activity level, quality of life and satisfaction.

Assessments of the therapeutic response could be hampered by disease heterogeneity, comorbidities, complexity of care, and differences in national and regional health systems. The recommendations for assessing the therapeutic response to biologics assumes that the diagnosis of severe asthma is correct and all co-morbidities and factors influencing asthma control are correctly addressed. Baseline asthma severity and duration, dose of oral corticosteroid, atopic status definition, eosinophil cut-off, exacerbation severity and rate history as well as lung function are all important in assessing treatment efficacy or effectiveness[11].

The therapeutic response to biologics should be assessed individually according to pre-defined limits for outcomes focused on the

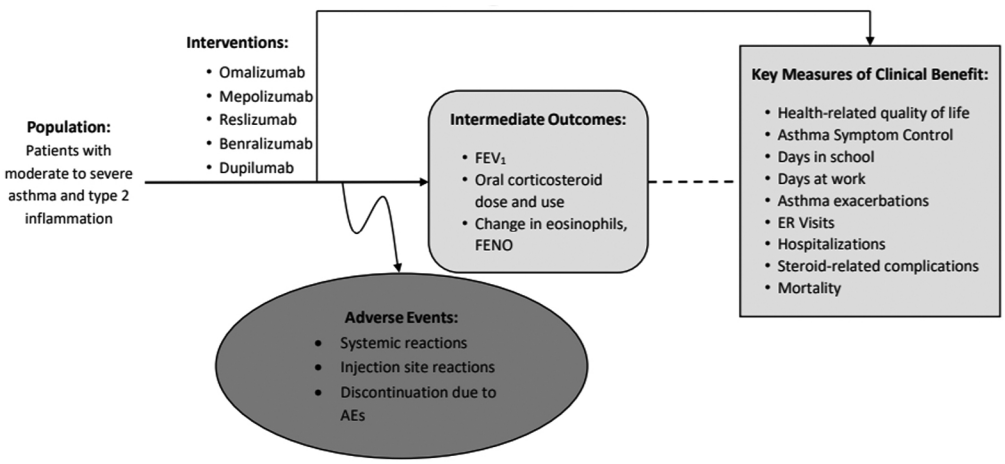


**Figure 1. Monitoring of the therapeutic response after the introduction of biological drugs for severe asthma (10) (Taken with permission from *ICER Rewier 2018).***

Note: AEs: adverse effects; FENO: fractional exhaled nitric oxide; $FEV_1$: forced expiratory volume in one second; SAEs: severe adverse effects

goals of asthma control[11]. All changes since the previous visit should be carefully analyzed in terms of frequency and severity of exacerbations, all elements of asthma symptom control (frequency of symptoms, use of SABA, nocturnal awakening due to asthma, activity limitation), treatment intensity (including OCS dose), quality of life, adherence and inhalation technique, pulmonary function, patient satisfaction, side effects and possible concerns.

GINA and EAACI Guidelines for the treatment of severe asthma with biologics differ slightly about the time period for monitoring the therapeutic response, but agrees that it should be done between 3 and 6 months[1,11]. The GINA 2020 guidelines recommend that the first assessment of the therapeutic response to biologics in severe asthma be made after 4 months. If the response is good, it is recommended to continue treatment with a reassessment every 3-6 months. The GINA 2021 guidelines corrected the recommendation to re-evaluate the therapeutic response every 3-4 months. The EAACI 2021 guidelines recommend an evaluation every 4-6 months.

If therapeutic response to biologics is good and asthma is well controlled, it is recommended to consider reducing and eventually discontinuing oral corticosteroid treatment, then other add-on therapies, and finally inhaled corticosteroids. Oral corticosteroids and all other asthma drugs should be reduced gradually. Inhaled corticosteroids should never be completely ruled out, but at least a moderate dose should be maintained. If after step-down during treatment with biologics there is a loss of symptom control and/or exacerbations reoccur, the therapy should be intensified to the previous dose to re-establish good asthma control[1].

Well-defined criteria for assessing the therapeutic response to biological therapy in severe asthma do not currently exist, but

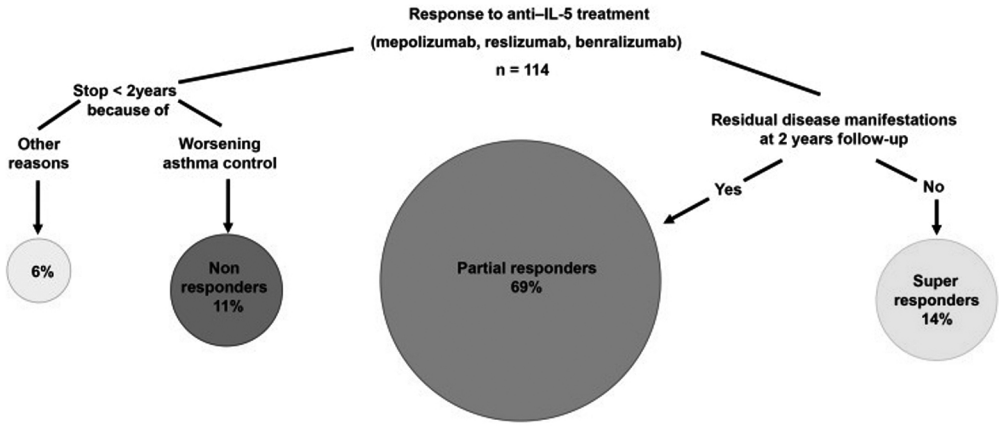


**Figure 2. Response to treatment of severe asthma with biologics (all three anti-IL-5 drugs) after 2 years (26) (Taken from** *Eger K et al. J Alerg Clin Imunol Pract 2021)*

it is clear that not all outcomes are of equal strength and importance. According to the latest EAACI 2021 guidelines, expected outcomes are classified into three groups. The most critical outcomes are considered to be exacerbation of severe asthma, control of asthma symptoms assessed using the ACQ (Asthma Control Questionnaire) or ACT (Asthma Control Test), quality of life measured by the quality of life of the Asthma Questionnaire

(AQLQ) and safety. Lung function, particularly $FEV_1$ (forced expiratory volume in the first second) and dose reduction of OCS and ICS, as well as the use of rescue drugs are considered important outcomes, while FeNO and eosinophils in sputum and blood are considered less important. The EAACI Guidelines Development Group (GDG) for the treatment of severe asthma with biologics has formulated strong recommendations regarding dose reduction of OCS and conditional recommendations with respect to other outcomes[11].

In the observational cohort study by Eger and coworkers, 11% of patients were considered as non-responders, 69% as partial responders, and 14% as super-responders after 2 years of anti–IL-5 treatment for severe eosinophilic asthma[26].

In patients with a good response on biologics to individually predetermined goals, continued treatment is recommended, in accordance with local regulatory authorities and continuous monitoring of effectiveness and safety. The rationale for this recommendation is the evidence that after discontinuation of biologics, their beneficial effect is lost[11]. A few clinical studies to date have shown that in many patients, after discontinuation of biologic therapy, symptom control deteriorates and / or exacerbations recur[27,28]. So far, there are no precise instructions on how long treatment with biologics should last.

If there is no therapeutic response to biologics, the clinicians are advised to find possible reasons. Uncontrolled asthma, after applied biological therapy, requires verification of adherence because some patients, following first few administrations of the biologics, stop taking anti-inflammatory medications without consulting their health care physicians and become non-adherent to the overall management plan.

If there is no satisfactory therapeutic response to the initially introduced biological drug after sufficient time, but the criteria for targeted biological treatment of severe asthma are still met, switching to another biological agent is a rational option.

Studies have shown that switching to another biologic drug can have a significant effect on improving FEV1, controlling asthma symptoms, and reducing OS in patients with an initially poor response to a previous biologic drug[25,29,30]. The exact time and manner of switching from one biological drug to another have not yet been defined. More precise recommendations in this regard are expected from large ongoing studies aimed at switching biologic drugs. In a report by Numate et al, an analysis of switching from one biological drug to another in randomized studies (omalizumab to mepolizumab, mepolizumab to benralizumab, all three biologics from the IL5 / IL-5 receptor group to dupilumab) showed efficacy. Most reports suggested switching to another drug after approximately 4 months. In real-life studies, the effectiveness of biologics stabilized after 16 weeks in 80% of cases and within 24 weeks in 90% of cases. The median time to change the first biologic in subjects who did not respond to treatment was after 8.6 months and for the second after 2.7 months. In clinical practice, if justified, the large number of different biologics available for severe asthma makes it possible to reduce switching interval to each subsequent biologic treatment[25].

A sustained suboptimal therapeutic response to a biological drug requires re-phenotyping and re-examination of biomarkers and immune response pathways. Exacerbations in patients who do not respond to biologic therapy do not necessarily have to be eosinophilic and the type of exacerbation cannot be inferred without confirmation. The inflammatory phenotype of asthma exacerbations may be distinguished using FeNO[31], but induced sputum is a more desirable option for reassessing whether airway inflammation is eosinophilic or neutrophilic. If the response to treatment is unsatisfactory and a reassessment shows that there is no airway eosino-

philia, biologics should be discontinued and T2 low asthma treatment measures should be considered[11].

It is important to keep in mind that biologics may induce the production of antibodies against drugs (ADAs) that may affect the loss of a therapeutic response or hypersensitivity reaction. The measurement of ADA in everyday clinical practice has not yet been implemented. As the detection of ADAs is essential for immunogenicity assessment, future tasks is to determine how and when to routinely measure them in clinical practice[32]. If the reason for non-response is the development of neutralizing anti- drug antibodies[33,34] or other dysfunctions and autoimmune response, it is justified to switch to another biological drug following the specific characteristic[35]. Possibilities of combining two biological drugs with different mechanisms were also considered but the rationale for such use is still lacking.

## Effect of biologics on exacerbations

Asthma exacerbations are the most undesirable adverse event that can occur during illness and that can be life-threatening to the patient. Such exacerbations in patients with severe asthma are frequent and significantly impair their quality of life. According to EAACI 2021 recommendations, the impact on exacerbations of severe asthma during biologic treatment are among critical, the most important outcomes for assessing treatment success[11]. Most studies, including a number of new ones, report that biologics significantly reduce the number and severity of exacerbations in patients with severe asthma[15–20,23,24,28,36–39]. The results of a recently published MEX study call into question the routine use of oral corticosteroids to treat all asthma exacerbations without recognizing an inflammatory phenotype of asthma exacerbations which are not always eosinophilic[31].

The effect of biologic therapy on exacerbations should be closely monitored during the therapy with biologics. In some patients, exacerbations may not decrease significantly in a short period of time, so the other endpoints should be used to define a therapeutic response[11,40].

## Effects of biologics on symptoms and quality of life

Symptoms of patients with severe asthma that remain uncontrolled despite the maximum intensity of treatment are the most obvious indicator of the severity of the disease if all other measures are taken to exclude the factors responsible for uncontrolled disease. Given the subjectivity, they need to be assessed with questionnaires. A clinically significant smallest difference in the ACT score is considered to be three points[41]. The sum of symptoms in severe asthma is usually very low, and it is difficult to assess the actual improvement based on differences in the ACT score. ACT has known limitations in severe asthma. It is recommended to reduce the ACT cut-off for uncontrolled asthma in severe asthma to score 16[42]. Improvement of symptoms during the treatment of severe asthma should be assessed by their qualitative and quantitative characteristics as well as by their timing, location, aggravating or alleviating factors, and associated manifestations. Of particular importance is the assessment and treatment of co-morbidities as they may contribute to poor disease control by aggravating or mimicking symptoms of asthma[4].

Symptoms greatly impair quality of life associated with health status (HRQoL) in patients with severe asthma, and the use of biologics has proven promising in this sense. More than 60% studies, dealing with the treatment of severe asthma included a HRQoL questionnaire as a primary, secondary, or research outcome[43]. Research has shown that improving overall quality of life is the most important outcome for most patients with severe asthma (44).

## Safety

The results of randomized and real-life studies as well as experience in everyday clinical practice confirms that the safety profile of all five biologics is very good. Side effects during treatment with biologics in clinical studies were mild in most cases for all approved biologics. Sometimes they did not differ from the side effects seen in patients receiving placebo. The most common side effects were lower respiratory tract infection, nasopharyngitis, sinusitis, worsening of asthma, headache, pain or reaction at the injection site and arthralgia[14–21,36–39].

Common immediate side effects after administration are local pain and discomfort at the injection site. Very rarely, anaphylactic reactions occur during administration, which is why drugs should be given under the supervision of health professionals and patients should be monitored for some time after administration[14]. Reports of such adverse reactions state that they have been successfully treated.

## Effects of biologics on corticosteroids treatment

One of the most important effects of biologic therapy is the possibility to exclude or reduce the dose of corticosteroids in patients who need them for disease control. The consequences of long-term of systemic corticosteroids use are widely recognized. Price and coworkers recently investigated that patients with asthma prescribed oral corticosteroid (OCS) had a significantly increased risk of osteoporosis and osteoporotic fracture, pneumonia, cardio and cerebrovascular diseases, cataract, sleep apnea, renal impairment, depression and anxiety, type 2 diabetes and weight gain[45]. The short courses of systemic corticosteroids are much safer, but are still associated with increased risk of adverse events[46]. In project ROSA the majority physicians have a favorable perception towords using biological agents whenever patients are eligible and the most of them are more willing to accept some degree of lung function deterioration compared to other outcomes (worsening of symptoms, quality of life) when reducing OCS dose[47]. If the patients show a good response to biologics, it is recommended to consider reducing OCS carefully and gradually. Reduction of corticosteroids in cases of a good response to biologics should be gradually assessed at intervals of several months. Studies have shown that it sometimes takes a long time for a dose of corticosteroids to be significantly reduced or completely ruled out[48].

Allowing a reduction in OCS therapy by half or complete exclusion is the main criterion for response to treatment. It is also recommended to try to stop taking other additional medicines, but to maintain a medium dose of inhaled corticosteroid at all times.

According to the new GINA guidelines, the introduction of a biologic is recommended before the use of systemic corticosteroids in order to prevent their side effects. In patients with uncontrolled severe asthma who are not eligible for biologics or those who do not respond to biologic therapy, OCS treatment is still an important alternative to achieving control. Patients who do not respond to biologics may also not respond to systemic corticosteroids[1].

## Effects of biologics on lung function

Severe asthma that is refractory to treatment usually significantly affects lung function and the use of biologic drugs often significantly improves it. In some patients, the changes may be permanent due to airway remodeling and result in fixed airway obstruction.

Pulmonary function in patients with severe asthma is very important, but during biologic treatment a certain degree of impairment of pulmonary function is considered more acceptable compared to other outcomes such as exacerbations, symptoms and quality of life if oral corticosteroids may be excluded or reduced[47].

According to EAACI Guidelines, the effect of biologic drugs on the improvement of lung function is an important but not critical outcome for assessing the effectiveness of treatment[11].

## Effects of biologics and biomarkers

According to the Working Group of the National Institute of Health (NIH), a biomarker is defined as "… a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". Simply, a biomarker indicates an alteration in physiology from normal[49]. Ideally, a biomarker might be the pathophysiological therapeutic target itself. Identification of specific biomarkers such as peripheral blood absolute eosinophil count, total IgE, specific IgE and fractional exhaled nitric oxide (FeNO) in biological materials allowed precise treatment of patients with severe T2 high asthma. Biomarkers indicate certain asthma endotypes and predict responses to biological therapies[5]). During treatment with biologics, a reduction or complete eosinophil depletion is observed which is usually accompanied by a good clinical response to treatment, but this response to biomarkers is considered a less important outcome than other clinical outcomes. Routine monitoring of IgE levels is not recommended during omalizumab treatment[1,9]. In many patients with T2 high asthma, known biomarkers overlap as shown in Figure 2. Overlapping of biomarkers often leads to doubts about drug choice and existing biomarkers are often considered insufficient for a precise decision about the best biologic to administer. In the current situation, the overlapping of known biomarkers, in case of poor response to the initial biological drug allows switching to another biologic that targets another capture point, which often results in a good response. In studies that looked at the association between the efficacy of biological therapy and predictive biomarkers, there was a significant difference in response rate between the groups of biologics depended on the biomarker on which the drug was selected. When the biologics were selected based on peripheral blood eosinophil counts (PBEC), IgE and FeNO the response rate was 33% (PBEC), 36% (IgE) and 50% (FeNO) for omalizumab, 65% (PBEC), 67% (IgE) and 64% (FeNO) for mepolizumab/benralizumab and 64% (PBEC), 50% (IgE) and 73% (FeNO) for dupilumab[25]. One of the goals of future research is to identify better clinically relevant biomarkers in terms of patient selection and prognosis of therapeutic response to biologics, and which will better reflect the clinical response during treatment.

## Conclusion

All previous clinical studies as well as experiences from everyday practices have shown that biologics in severe asthma are highly efficient and safe in precisely selected patients with severe T2 high asthma. However, all patients treated with biologics are not good responders and there are still many doubts and unknowns regarding the treatment.

It is estimated that the effectiveness of biologics on severe asthma in real world settings is about 60%[11]. For now, there are no clearly defined criteria for assessing the effectiveness of biologics in everyday practice. Patients treated with biologics should be closely monitored and evaluated against baseline and against pre-defined treatment outcome goals. The critical outcomes of treatment with biologics are considered to be the impact on reducing exacerbation, improving symptoms and quality of life as well as the safety of biological therapy. Important treatment outcomes are considered to be the effect on reducing the intensity of treatment (oral and inhaled corticosteroids, recue medications) and the effect on improving lung function[11].

Biologic drugs allow specific inhibition of certain asthma pathways, which does not always meet all set treatment goals equally suc-

cessfully[51]. Previous reports on therapeutic responses have not provided accurate answers to a number of questions about long-term biological treatment in daily clinical practice. Precise definition of therapeutic response, criteria for optimal and suboptimal response, criteria for continuation or discontinuation of biologics, duration of biological treatment in patients who responded to therapy, rules for switching to other biological drugs in patients who did not respond to therapy, rules for combining biological drugs and the biological treatment of allergic comorbidities are just some of the questions that need to be answered.

It is also necessary to clarify issues related to the identification of factors associated with treatment failure and the possibility of increasing the therapeutic response rate. In particular, there is a great need to identify new molecular targets in order to offer effective treatments for those patients who do not respond to currently available biologics[11].

### *Literature*


1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention [Internet]. [place unknown]: Global Strategy for Asthma Management and Prevention; c2022 [cited September 10, 2021]. Available from: http://www.ginasthma.org.
2. Bagnasco D, Passalacqua G, Caminati M, et al. Evolving phenotypes to endotypes: is precision medicine achievable in asthma? Expert Rev Respir Med. 2020 Feb;14(2):163-72.
3. Schoettler N, Strek ME. Recent Advances in Severe Asthma: From Phenotypes to Personalized Medicine. Chest. 2020 Mar;157(3):516-28.
4. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. Respirology. 2017 May;22(4):651-61.
5. Albendiz VJ, de Castro FJ, Gutierrez IG et al. Characteristics of patients with severe asthma in our population. J Allergy Clin Immunol. 2018 Feb;141(suppl 2):AB101. doi:10.1016/j.jaci.2017.12.323
6. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007 Feb;119(2):405-13.
7. Jin HJ. Biological treatments for severe asthma. Yeungnam Univ J Med. 2020 Oct;37(4):262-8.
8. Porzsolt F, Rocha NG, Toledo-Arruda A, et al. Efficacy and effectiveness trials have different goals, use different tools, and generate different messages. Pragmat Obs Res. 2015 Nov 4:6:47-54.
9. Menzies-Gow A, Szefler SJ, Busse WW. The Relationship of Asthma Biologics to Remission for Asthma. J Allergy Clin Immunol Pract. 2021 Mar;9(3):1090-8.
10. Institute for Clinical and Economic Review. ICER Final Evidence Report 2018: Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation; Effectiveness, Value, and Value-Based Price Benchmarks. Boston, MA: Institute for Clinical and Economic Review; 2018.
11. Agache I, Akdis CA, Akdis M, et al. EAACI Biologicals Guidelines-Recommendations for severe asthma. Allergy. 2021 Jan;76(1):14-44.
12. Busse W, Spector S, Rosén K, et al. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. J Allergy Clin Immunol. 2013 Aug;132(2):485-6.e.11.
13. Bourgoin-Heck M, Amat F, Trouvé C, et al. Omalizumab could be effective in children with severe eosinophilic non-allergic asthma. Pediatr Allergy Immunol. 2018 Feb;29(1):90-9.

14. Di Bona D, Fiorino I, Taurino M, et al. Long-term "real-life" safety of omalizumab in patients with severe uncontrolled asthma: A nine-year study. Respir Med. 2017 Sep:130:55-60.
15. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep 25;371(13):1198-207.
16. van Toor JJ, van der Mark SC, Kappen JH, et al. Mepolizumab add-on therapy in a real world cohort of patients with severe eosinophilic asthma: response rate, effectiveness, and safety. J Asthma. 2021 May;58(5):651-8.
17. Caminati M, Cegolon L, Vianello A, et al. Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response. Expert Rev Respir Med. 2019 Dec;13(12):1205-12.
18. Harrison T, Canonica GW, Chupp G, et al. Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis. Eur Respir J. 2020 Oct 15;56(4):2000151. doi: 10.1183/13993003.00151-2020.
19. Jackson DJ, Korn S, Mathur SK, et al. Safety of Eosinophil-Depleting Therapy for Severe, Eosinophilic Asthma: Focus on Benralizumab. Drug Saf. 2020 May;43(5):409-25.
20. Virchow JC, Katial R, Brusselle GG, et al. Safety of reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from 6 trials. J Allergy Clin Immunol Pract. 2020 Feb;8(2):540-8.e.1.
21. Halling AS, Loft N, Silverberg JI, et al. Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis. J Am Acad Dermatol. 2021 Jan;84(1):139-47.
22. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. N Engl J Med. 2021 May 13;384(19):1800-9.
23. Kavanagh JE, d'Ancona G, Elstad M, et al. Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. Chest. Aug 2020;158(2):491-500.
24. Kavanagh JE, Hearn AP, Dhariwal J, et al. Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma. Chest. 2021 Feb;159(2):496-506.
25. Numata T, Araya J, Miyagawa H et al. Effectiveness of Switching Biologics for Severe Asthma Patients in Japan: A Single-Center Retrospective Study. J Asthma Allergy. 2021 Jun 3:14:609-618.
26. Eger K, Kroes JA, ten Brinke A, et al. Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma- A Real-Life Evaluation. J Allergy Clin Immunol Pract. Mar 2021;9(3):1194-200.
27. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol. 2014 Mar;133(3):921-3.
28. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. J Allergy Clin Immunol. 2017 Jul;140(1):162-9.e2.
29. Pepper AN, Hanania NA, Humbert M et al. How to Assess Effectiveness of Biologics for Asthma and What Steps to Take When There Is Not Benefit. J Allergy Clinin Immunol Pract. 2021 Mar;9(3):1081-8
30. Drick N, Milger K, Seeliger B, et al. Switch from IL-5 to IL-5-Receptor α Antibody Treatment in Severe Eosinophilic Asthma. J Asthma Allergy. 2020 Nov 11:13:605-614..
31. McDowell PJ, Diver S, Yang F, et al. Medical Research Council: Refractory Asthma Stratification Programme (RASP-UK Consortium). The inflam-

matory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. Lancet Respir Med. 2021 Oct;9(10):1174-84.

32. Matucci A, Nencini F, Vivarelli E, et al. Immunogenicity-unwanted immune responses to biological drugs – can we predict them?, Exp Rev Clin Pharmacol. 2021 Jan;14(1):47-53.
33. Mukherjee M, Bulir DC, Radford K, et al. Sputum autoantibodies in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2018 Apr;141(4):1269-79.
34. Mukherjee M, Lim HF, Thomas S, et al. Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy. Allergy Asthma Clin Immunol. 2017 Jan 6:13:2. doi: 10.1186/s13223-016-0174-5.
35. Rup B, Pallardy M, Sikkema D, et al. Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: recommendations of the Innovative Medicines Initiative ABIRISK consortium. Clin Exp Immunol. 2015 Sep;181(3):385-400.
36. Busse WW, Bleecker ER, FitzGerald JM, et al: BORA study investigators. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med. 2019 Jan;7(1):46-59.
37. Korn S, Bourdin A, Chuupp G et al. Integrated Safety and Efficacy Among patients Receiving Benralizumab for Up 5 Years. J Allerg Clin Immunol Pract. 2021 Dec;9(12):4381-92.e4.
38. Wechsler ME, Peters SP, Hill TD, et al. Clinical Outcomes and Health-Care Resource Use Associated With Reslizumab Treatment in Adults With Severe Eosinophilic Asthma in Real-World Practice. Chest. 2021 May;159(5):1734-46.
39. Halling AS, Loft N, Silverberg JI, et al. Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis. J Am Acad Dermatol. 2021 Jan;84(1):139-47.
40. Fitzpatrick AM, Szefler SJ, Mauger DT, et al. Development and initial validation of the Asthma Severity Scoring System (ASSESS). J Allergy Clin Immunol. 2020 Jan;145(1):127-39.
41. Schatz M, Kosinski M, Yarlas AS, et al. The minimally important difference of the asthma control test. J Allergy Clin Immunol. 2009 Oct;124(4):719-23. doi:10.1016/j.jaci.2009.06.053
42. Korn S, Both J, Jung M et al. Prospective evaluation of current asthma control using ACQ and ACT compared with GINA criteria. Ann Allergy Asthma Immunol. 2011 Dec;107(6):474-9.
43. Lanario JW, Burns L. Use of Health Related Quality of Life in Clinical Trials for Severe Asthma: A Systematic Review. J Asthma Allergy. 2021 Aug 12:14:999-1010.
44. Hossny, E., Caraballo, L., Casale, T. et al. Severe asthma and quality of life. World Allergy Organ J. 2017 Aug 21;10(1):28. doi: 10.1186/s40413-017-0159-y.
45. Price DB, Trudo F, Voorham J et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy. 2018 Aug 29:11:193-204. doi: 10.2147/JAA.S176026.
46. Price D, Castro M, Bourdin A et al. Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety. Eur Respir Rev. 2020 Apr 3;29 (155):190151. doi: 10.1183/16000617.0151-2019.
47. Loureiro CC, Ferreira MB, Ferreira J et al. Reducing oral corticosteroids in severe asthma (ROSA Project): a nation-

wide Portuguese consensus. Pulmonology. 2021 Jul-Aug;27(4):313-27.
48. Khurana S, Brusselle GG, Bel EH et al. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study. Clin Ther. 2019 Oct;41(10):2041-56.e5.
49. Jain KK. Role of Biomarkers in Personalized Medicine. In: Jain KK. Textbook of Personalized Medicine. Cham, Switzerland: Springer;2021. p. 110-13.
50. Wangberg H, Woessner K. Choice of biologics in asthma endotypes, Curr Opin Allergy Clin Immunol. 2021 Feb 1;21(1):79-85
51. McCracken JL, Tripple JW, Calhoun WJ. Biologic therapy in the management of asthma. Curr Opin Allergy Clin Immunol. 2016 Aug;16(4):375-82.