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Critical Aspects of Managing Severe Asthma with Biologics

Aspectos críticos del manejo con biológicos del asma grave

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ABSTRACT

Monoclonal antibodies for the treatment of severe asthma with a T2-high phenotype have been a significant therapeutic breakthrough, improving patients' quality of life and reducing severe exacerbations. However, certain aspects remain controversial. The following were chosen to be addressed, in the form of questions: is airway remodeling possible with biologics?; are anti-biologic antibodies a concern?; is complete remission achievable?; when, how, and to which biologic should a "switch" be made?; can biologics be discontinued?; what approach should be taken with a patient who wishes to become pregnant or is already pregnant? and what about lactation? how is adherence to biologic treatments like? Each question was answered based on the review of the scientific evidence of each one.

There is not enough evidence to confirm if biologics prevent long-term airway remodeling, or if they are safe during pregnancy or lactation (with the exception of omalizumab). Currently, there are no established criteria for the concept of complete remission with biologics. Some proposed criteria include the absence of symptoms and exacerbations, not using oral corticosteroids, normal spirometry, suppression of T2 inflammation, and control of comorbidities. However, further research is needed to validate these criteria. Once control is achieved, biologics should not be discontinued. However, it is possible to consider de –escalating other second– or third-line medications, while maintaining regular treatment with inhaled corticosteroids + LABAs (long-acting beta-2 adrenergic bronchodilators) at the lowest possible dose.

Key words: Severe asthma; T2-high phenotype; Biologics; Remission; Pregnancy; Adherence

RESUMEN

Los anticuerpos monoclonales para el tratamiento del asma grave fenotipo T2 alto, han sido un gran avance terapéutico, mejorando la calidad de la vida del paciente y reduciendo las exacerbaciones severas. Sin embargo, persisten aspectos de controversia. Sobre ellos, en formato de preguntas, se eligieron: ¿es posible el remodelamiento de la vía aérea con los biológicos?; ¿son un problema los anticuerpos anti-biológicos?; ¿ae puede alcanzar la remisión completa?; ¿cuándo, cómo y a cuál biológico hacer el "*switch*"?; ¿se pueden discontinuar?;¿qué conducta se debe tomar en una paciente que desea embarazarse, o lo está? ¿y con respecto a la lactancia?; ¿cómo es la adherencia

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con los biológicos?. Se respondieron las preguntas en base a la revisión de la evidencia científica de cada cada pregunta.
No existe suficiente evidencia para asegurar que se evita el remodelamiento de la vía aérea a largo plazo con los biológicos, así como su seguridad en el embarazo o lactancia (a excepción del omalizumab). A la fecha, no hay criterios establecidos para el concepto de remisión completa con biológicos. Se han propuesto algunos criterios como ausencia de síntomas y exacerbaciones y no uso de corticoides orales, espirometría normal, supresión de la inflamación T2 y control de las comorbilidades. Pero para validarlos aún se requieren más investigaciones. Una vez alcanzado el control no se debe suspender el biológico, pero si se puede evaluar desescalar los otros medicamentos de 2° o 3° línea, pero manteniendo siempre el tratamiento regular con corticoides inhalados + LABA, a la menor dosis posible.

Palabras Claves: Asma grave; Fenotipo T2 alto; Biológicos; Remisión; Embarazo; Adherencia

Asthma is a heterogeneous, inflammatory airway disease characterized by recurrent episodes of bronchospasm, bronchial hyperreactivity, and increased bronchial secretions.[1] It affects approximately 340 million people worldwide, with a significant heterogeneity in terms of prevalence across Latin America, ranging from 5% to 24%.[2]

In Argentina, it is estimated that 9.36% of the population (approximately 2.5 million people) has asthma, based on patient records from medical diagnoses.[3] Severe asthma accounts for 3% to 5% of the asthma population, though it has different epidemiological characteristics in Latin America.[1,4] Severe asthma is characterized by persistent symptoms, increased emergency visits, unplanned outpatient appointments, higher rates of hospitalization, and greater use of rescue medications, systemic corticosteroids, antibiotics, and high doses of controller medications (inhaled corticosteroids, long-acting beta-agonists, long-acting anticholinergics, and in some cases, leukotriene inhibitors). This leads to a significant impact on the use of healthcare resources and an increase in mortality rates.[1,5-7] The evaluation carried out in this group of patients for the purpose of classifying them as severe poses a challenge that requires considering some variables, such as ensuring good adherence, proper use of inhalers, and the presence or absence of comorbidities. Patients with severe asthma bear a heavy disease burden, including impacts on their well-being, social life, mental health, and adverse effects.[1,5-7] The concept of difficult-to-control asthma (DCA) focuses on ruling out these variables to clearly define severe asthma. [1,5-8]

Severe asthma represents a heterogeneous syndrome with multiple clinical variants. Over the past two decades, it has been intensely studied, and different phenotypes have been defined.[9-13] Establishing the asthma phenotype in patients with severe uncontrolled asthma is part of the diagnosis and evaluation of these individuals, since it can lead to differential treatment and have prognostic implications.[6] Two inflammatory phenotypic patterns have been defined: T2-high (present in allergic and eosinophilic asthma) and non-T2, also called T2-low.[5-7] Both T2-high phenotypes often show some degree of overlapping. The fraction of exhaled nitric oxide (FeNO), eosinophilia, and IgE are good biomarkers for the T2-high phenotype.[5-7] The T2-allergic phenotype represents 40-50% of severe asthma and has an atopic basis orchestrated by the activation of T helper type 2 cells (Th2), the production of interleukins IL-4, IL-5, and IL-13, and isotype switching in B lymphocytes towards IgE production.[5-7] The T2-eosinophilic phenotype represents more than 25% of severe asthma and is characterized by the presence of eosinophils in bronchial biopsies and sputum. It may be associated with chronic rhinosinusitis and nasal polyps.[5-7] Severe T2-low asthma is characterized by low levels of peripheral blood and sputum eosinophils, a paucigranulocytic or neutrophilic profile, low FeNO levels, and a poor response to glucocorticoids. In some cases, it is associated with chronic airflow limitation, air trapping, and a history of smoking.[5-7]

Over the past twenty years, biologics have been developed which now play a central role in the

management of severe T2-high asthma, offering a very acceptable efficacy/safety profile. The first monoclonal antibody developed for the allergic IgE-mediated phenotype was omalizumab, which was approved by the FDA (Food and Drug Administration) in 2003 and by the EMEA (European Medicines Agency) in 2005, and it is widely used in our country.[14] Subsequently, other biologics targeting eosinophilic responses in patients with severe asthma were developed, including inhibitors of IL-4, IL-5, and IL-13.[15-18] Mepolizumab and reslizumab are IL-5 inhibitors. Benralizumab inhibits the IL-5 receptor α. Dupilumab inhibits the IL-4 receptor α subunit, interfering with the actions of both IL-4 and IL-13.[15-18] Mepolizumab, benralizumab, and dupilumab are commercially available in our country. Dupilumab has been developed for the T2-high phenotype and is the only new biologic that does not include eosinophilia. Tezepelumab is the first antibody to inhibit the thymic stromal lymphopoietin (TSLP), an alarmin cytokine originally identified as a lymphocyte growth factor. It binds to the TSLP receptor complex (including the IL-7 receptor α) and activates T-helper 2 lymphocytes, along with a wide variety of immune and non-immune cells.[19] It is being marketed in many developed countries, but not yet in our country.[20-22] While various molecules are under clinical development to treat patients with the T2-low phenotype, none of them has yet progressed to phase III clinical development stages, so none of them is commercially available.

Despite the growing use of biologics in severe asthma for the T2-high phenotype, many critical and challenging aspects persist, where scientific evidence is still limited, and questions remain unanswered. The objective of this review is to critically analyze the most important aspects of the biologics available in our country in the form of questions, based on a review of the published scientific evidence. Basing on their daily practice managing patients with severe asthma with the T2-high phenotype, the authors have selected the most relevant questions to ask on a daily basis:

1. Is airway remodeling possible with the treatment with biologics in severe asthma?
2. Are anti-biologic antibodies a concern?
3. Is complete remission achievable with biologics?
4. When, how, and to which biologic should a "switch" be made? Should biologics be discontinued?
5. What approach should be taken with a patient who wishes to become pregnant or is already pregnant? And what about lactation?
6. How is adherence to treatment and biologics like?

Methodology

Literature search was conducted in the MEDLINE, EMBASE, Cochrane, SciELO, and Lilacs databases until January 31, 2024, using search terms relevant to the respective questions.

1. Is airway remodeling possible with the treatment with biologics in severe asthma?

The consequence of persistent airway inflammation in asthma is the response to diminished innate immunity and to environmental factors. The common final pathway is the development of chronic airflow obstruction due to airway wall remodeling and alterations in biomechanical properties, accompanied by mucus plugs and closure of small airways.[23-25] Structural cells, such as epithelial cells and bronchial smooth muscle cells contribute to the inflammatory response, mediated by chemokines, cytokines, and growth factors.[23-25] Epithelial damage or stress (represented by the increase in epidermal growth factor receptor) triggers cellular activation and releases pro-angiogenic factors (which promote neovascularization) and growth factors such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF). These factors activate subepithelial mesenchymal cells, leading to the proliferation of the extracellular matrix and fibroblasts.[23-25] However, epithelial cells also release chemokines such as IL-8, which is a chemoattractant for neutrophils. The bronchial wall is thicker in severe asthma compared to mild asthma, as is the mass of the bronchial smooth muscle.[23-25] The activation of the bronchial smooth muscle releases chemotactic factors that recruit mast cells and myofibroblasts, as well as extracellular matrix proteins and additional angiogenic factors. Mast cells express Th2 cytokines such as IL-4 and IL-13.[23-25] Fibrocytes also infiltrate the bronchial wall in the most severe forms of asthma. Neutrophils and mast cells located in the glands are associated with mucus plugs in fatal asthma. The thickening of the reticular basement membrane is caused by the extracellular matrix deposition and is a marker of remodeling. Finally,

fibrosis contributes to fixed airflow obstruction in severe asthma.[23-25]

Both airway remodeling and inflammation can begin in childhood (ages 2 to 4) and persist through school age, eventually differentiating in adulthood where inflammation continues, and remodeling remains stable. The implications of this persistence over time in asymptomatic patients, and whether this temporal evolution is independent or not, remain unknown.[23-25]

Interestingly, biologics have been shown to reduce some characteristics of airway remodeling. The first study evaluated the effect of mepolizumab in 24 atopic patients, showing a significant reduction in extracellular matrix proteins, thus suggesting an effect of eosinophils on TGF-β1.[26] At the European Respiratory Society Congress 2023, preliminary results were presented from the ME-SILICO study, where after one year, patients with late-onset severe asthma experienced a reduction in the thickness of the basement membrane.[27] Benralizumab has been shown to reduce the smooth muscle mass of the bronchial wall.[28] Similarly, 13 severe allergic patients treated with omalizumab achieved a 5% reduction in the bronchial wall area.[29] Finally, with tezepelumab, no effect has been determined on basement membrane thickness or epithelial integrity.[30]

2. Are anti-biologic antibodies a concern?

The incidence of immunogenicity from anti-biologic antibodies (ABAs) and their potential deleterious impact on the efficacy and safety of biologics has been poorly studied.[31] In theory, biologics could be more immunogenic than the small molecules of drugs, as they may directly block the receptors (acting as neutralizing antibodies) and/or increase their clearance via the reticuloendothelial system, or even form autoimmune complexes.[31] Most of the available information on ABAs comes from studies on tumor necrosis factor inhibitors in patients with rheumatoid arthritis, where they have been shown to decrease circulating drug levels and worsen clinical outcomes. However, there is limited data on the use of biologics in asthma. Chen et al conducted a systematic review and meta-analysis of 46 clinical studies, reporting an overall incidence of 2.91% (95% CI [confidence interval], 1.60–4.55). The incidence of ABAs in patients treated with benralizumab was 8.35%; dupilumab, 7.61%; reslizumab, 4.39%; mepolizumab, 3.63%; tezepelumab, 1.12%; and omalizumab, 0%.[31] It has been determined that subcutaneous administration, lower doses, and longer intervals between doses are associated with a higher incidence of ABAs.[31]

In conclusion, since ABAs are not currently available in routine practice, future studies will need to be carried out in order to determine their clinical impact on the management of patients with severe asthma.

3. Is complete remission achievable with biologics?

Asthma remission is defined as the reduction or disappearance of asthma symptoms and a decreased need for medications to control it.[1,8,32,33] In simple terms, it means that asthma is in an inactive or well-controlled state, a concept that has gained renewed interest with the advent of biologic treatments. Remission can occur for several reasons. In some cases, it may result from lifestyle changes, such as avoiding asthma triggers like allergens or irritants, maintaining a clean and smoke-free environment, and following an appropriate treatment plan. A good treatment plan should include the regular administration of asthma medications (commonly inhaled glucocorticoids, with or without LABAs, and biologic therapies in cases of severe asthma). This state is referred to as "clinical remission" and must be sustained for at least twelve months (without symptoms, exacerbations, or the use of systemic steroids, apart from having lung function tests with normal results). On the other hand, the term "complete remission" is used in cases where there is no evidence of bronchial hyperreactivity or bronchial inflammation.[1,6,32,33]

Scientific evidence on asthma remission in both adults and children comes from clinical studies and long-term observations. These studies have shown that a combination of the appropriate medical treatment, the management of triggering factors, and adherence to a personalized care plan can lead to asthma remission in many individuals.

It is important to note that remission does not mean a definitive cure for asthma. In some cases, symptoms may reappear in the future, especially if preventive measures and proper asthma management are not sustained. Therefore, even during remission, it is essential to continue with a regular medical follow-up and maintain a healthy lifestyle to prevent relapses.[2]

Patients with severe asthma bear a heavy disease burden, including impacts on their well-being, social life, mental health, and adverse effects.[34] Cohort studies indicate that approximately 50% of patients with severe asthma have been treated with systemic corticosteroids[2] over extended periods, despite the well-documented adverse reactions.[35]

In 2020, an expert consensus defined asthma remission as the cases of patients without any symptoms, with no exacerbations, no use of corticosteroids, and improved forced expiratory volume in one second (FEV_1), agreed upon by both the patient and physician, for at least twelve months. This was termed clinical remission without treatment.[33] Baseline factors may predict which patients are more likely to achieve remission, as for example shorter disease duration, better lung function, greater asthma control, and earlier age of disease onset.[34] A "super-response" has been observed in approximately one-third of severe asthma patients treated with biologics, which is likely a precursor to achieving remission.[36]

Remission has become the primary treatment goal for other conditions like rheumatological diseases and inflammatory bowel disease. However, in asthma, the concept of remission is still under development (TABLE 1).[33] Recently, asthma remission has been evaluated in a post-hoc analysis of both clinical trials and clinical cohorts, aiming to identify its prevalence in patients receiving biologics (TABLE 2). [37] Between 15% and 37% of the patients achieved remission, though definitions of remission were made independently across studies, leading to heterogeneity.[37] Elevated eosinophil levels and nitric oxide levels were identified as important predictors of remission.[37] Notably, a significant proportion of patients in the placebo arm achieved remission with medium to high doses of inhaled corticosteroids. This shows the anti-inflammatory role of inhaled corticosteroids and

TABLE 1. Clinical remission with and without treatment[33]

Clinical remission with treatment	Clinical remission without treatment
Sustained absence of significant asthma symptoms according to a validated instrument (ACQ <0.75 or ACT >20). Optimization of lung function. Agreement between the patient and the healthcare team regarding the remission of the disease. No use of oral corticosteroids (OC) during treatment and exacerbations, or long-term disease control.	The same criteria as above, sustained without asthma treatment for a period longer than 12 months
Complete remission with treatment	**Complete remission without treatment**
Clinical remission plus the following Current and objective evidence of resolution of inflammation in previously documented asthma (decreased eosinophils in blood/sputum, decrease in FeNO). Negative current bronchial hyperreactivity.	The same criteria as above, sustained without asthma treatment for a period longer than 12 months.

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; FeNO: fraction of exhaled nitric oxide

TABLE 2. Remission criteria for each biologic[37]

Remission criteria	Dupilumab (QUEST/ TRAVERSE)	Benralizmab (SIROCCO/ANDHI/ XALOC1)	Tezepelumab (NAVIGATOR)	Mepolizumab (REDES)
Absence of symptoms	ACQ 5 < 1.5	ACQ 6 > 1.5	ACQ 6 > 1.5	ACT > 20
Optimization of lung function	Post BD FEV_1 % > 80% or 100 ml	Pre BD 100% increase	Pre BD FEV_1 > 80% Pre BD FEV_1 > 20% (baseline) Pre BD FEV_1 > 95% (baseline)	Didn't include
Non-use of corticosteroids and exacerbations	Yes	Yes	Yes	Yes
Prevalence of clinical remission	32%/36%	26%/28%/43%	28%	37%

ACQ (Asthma Control Questionnaire); FEV_1 (forced expiratory volume in one second); ACT (Asthma Control Test

their impact on disease remission. It is important to say that there are studies where 20% of children with asthma experience spontaneous remission.[37]

In theory, failing to achieve early clinical remission may reduce the likelihood of achieving long-term remission.[38] A post-hoc analysis of the QUEST and TRAVERSE clinical trials demonstrated that at week 52 of the QUEST, 31.7% of patients treated with dupilumab versus 17.7% of those on placebo achieved clinical remission, whereas at week 48 of the TRAVERSE (patients were included in this study once they had completed the QUEST study), clinical remission rates were 36.4% for patients treated with dupilumab/dupilumab and 29.6% for those in the placebo/dupilumab group (placebo in the first trial and dupilumab in the second).[38] This could reflect a "missed opportunity" in the second study arm, as the magnitude of the remission was lower.[38]

There are significant challenges in the clinical assessment of complete asthma remission. Measuring bronchial hyperreactivity is laborious and contraindicated in patients with severe bronchial obstruction. Direct evaluation of airway inflammation through procedures such as bronchoscopy or induced sputum analysis is complex and not widely available.[39] Some patients may have fixed airway obstruction that does not improve with treatment, and their symptoms can be heavily influenced by comorbidities associated with asthma.[39] We are still in the early stages of developing this concept, and more evidence is needed to support it.[39] In the meantime, adopting a therapeutic strategy aimed at modifying the natural course of asthma seems a reasonable approach.

Is remission a realistic goal for the future care of asthma, or are we setting the bar too high?

Achieving remission seems to be a reasonable expectation in asthma because spontaneous remission, commonly referred to as "outgrown" asthma, is considered a frequent occurrence in children with asthma. Studies show that between 5% and 69% of children with asthma experience spontaneous remission during adolescence or adulthood.[40] The wide range of remission rates among these study populations reflects differences in the criteria used to define asthma and remission, including asthma severity, the age of disease onset, and the duration of the follow-up period. When applying the strict criteria for remission mentioned earlier, the proportion of patients achieving complete remission is small.[33] Only 20% of children with well-documented mild to moderate asthma achieved complete remission by the age of 23.[40] Adults with asthma, (with childhood- or adulthood- onset disease) who have been followed over time may show even lower rates of spontaneous remission or complete disease remission. Spontaneous remission does exist, but it is collectively thought that complete remission without relapse is uncommon.

It is unlikely that individuals with moderate to severe asthma, frequent exacerbations, poor lung function, and heightened inflammation driving their disease will experience spontaneous remission. This more symptomatic population is the one that most urgently needs long-term disease modification.

Biologic drugs targeting type 2 pathways reduce exacerbations, hospitalizations, and corticosteroid use while improving lung function and the patient's quality of life.[17] A future goal would be that reducing specific inflammatory pathways could enhance the average airway caliber and modify the course of the disease. Real-world studies show that after the withdrawal of omalizumab or mepolizumab in long-term treated subjects, more than half experienced exacerbations within the following year, similar to control subjects.[41]

Overall, studies to date suggest that discontinuing biologics –even after long-term use– in a large proportion of patients with severe asthma does not reverse the inflammatory mechanisms driving the disease.

How will we know if the disease has subsided or entered remission?

If we continued administering biologics and inhaled preventive medications on a standard schedule, we could not measure the success or identify the characteristics associated with a positive response. Only through careful tapering of preventive medications could we identify this small subset of responders. We should advocate for adopting a personalized tapering approach. Our goal should be good control with the least amount of medication. As we adjust biologic therapies, we may see that some patients can reduce their use of associated preventive medications. Clinical trials on treatment de-escalation will need to be conducted to test these hypotheses. New biologics in clinical development, such as those targeting

epithelial inflammatory signaling, may more permanently reduce the inflammatory signals that drive asthma, and their clinical impact will need to be determined.

As a physician, how does the definition of asthma remission affect the care you provide to each patient?

The short answer is: it shouldn't. This definition is intended solely for clinical research purposes and should not be applied to individual patients, nor should it be used to authorize or withdraw particular therapies. In fact, although asthma guidelines continue to evolve, they still do not include remission as a treatment outcome.[35] Therefore, the goal of the treatment should remain focused on reducing the risk and achieving sustained control, rather than pursuing remission. From a clinical perspective, the relationship between control and remission is not known yet. It is worth noting that the discussed definition of "remission" is a consensus statement from a group of experts.[5] There are no clinical studies demonstrating if this definition leads to better patient outcomes. This definition serves as a starting point to compare therapies, but it will also refine the definition of remission in future studies.[42] Someday, as with other chronic diseases, we may refer to patients whose asthma has entered remission as a real clinical outcome, one that may not represent a cure but can be controlled or even be in a state of dormancy with appropriate treatments.[42] In fact, until more studies are conducted, we will not even know the proportion of adequately treated asthma patients who could meet the criteria for this definition of remission. Therefore, as a physician, it is important to be aware of these discussions and the potential utility of a remission definition, but it is too early to apply this concept to clinical practice.

4. When, how, and to which biologic should a "*switch*" be made? Should biologics be discontinued?

Discontinuation of omalizumab therapy

The discontinuation of omalizumab has been evaluated using real-world data.[43] Molimard et al described data from 61 responder patients who discontinued omalizumab after a mean treatment duration of 22.7 ± 13.1 months. They found that 55% of patients lost control of the disease after a median interval of 13.0 months (mean 20.4 ± 2.6 months).[44] A recent study using the French health system database followed 19,203 patients over more than 10 years. It showed that among patients with controlled asthma who discontinued omalizumab for at least 16 weeks, 70%, 39%, and 24% remained controlled without restarting omalizumab 1, 2, and 3 years after discontinuation.[45] Currently, further studies are needed to define the criteria for discontinuing omalizumab therapy.

Switching from omalizumab to other biologics

With the development of other biologics, several real-world studies have addressed this issue.[46-48] In one study, 145 patients on omalizumab who experienced more than two asthma exacerbations per year were switched to mepolizumab for 32 weeks.[46] The study demonstrated improvements in asthma control, exacerbation rates, and lung function. Similarly, another study examined patients with uncontrolled eosinophilic asthma who were receiving omalizumab and were switched to benralizumab.[48] These patients showed improvements in their evolution in terms of exacerbation rates, lung function, IgE levels, FeNO, and eosinophil counts.[47-48] In another study, the most frequent switch was from omalizumab to an anti-IL-5 therapy (49.6%), primarily due to low efficacy and/or adverse effects, in a real-world study involving 3,531 asthma patients.[49]

To conclude, studies related to omalizumab switching have predominantly been conducted in patients with eosinophilic asthma, where anti-IL-5 therapy offers clear advantages. Consequently, prospective studies with structured switching criteria are needed in order to identify patients who could benefit from a broader spectrum of options.

Anti-IL-5 therapy

Switching *from omalizumab to anti-IL-5 therapies*

Several studies evaluated the switch to mepolizumab from omalizumab. The OSMO study assessed the change in asthma control in patients with blood eosinophil counts greater than 150 cells/mL who did not achieve optimal control with omalizumab.[50] Exacerbations decreased from 3.26 to 1.18 events/year, after 32 weeks of treatment. The ACQ-5 (Asthma Control Questionnaire) and SGRQ (St. George's Respiratory Questionnaire) scores improved significantly, regardless of baseline eosinophil levels, comorbidities, exacerbation

history, or oral corticosteroid use. Another retrospective study found that switching to mepolizumab reduced the exacerbation rate, the proportion of patients dependent on oral corticosteroids, and the number of workdays lost.[51]

A real-world study investigated the switch from omalizumab to benralizumab.[48] After one year of benralizumab treatment, significant improvements were noted in exacerbation rates, ACT (Asthma Control Test) scores, FEV_1, and SNOT-22 (Sino-Nasal Outcome Test-22) scores.[48]

Patients with severe eosinophilic asthma who do not respond to omalizumab would benefit from switching to an anti-IL-5 therapy. The primary endotype in these patients is thought to involve eosinophilic inflammation not mediated by the IgE pathway.[52]

Switching to benralizumab from mepolizumab

In cases of insufficient response, switching from an anti-IL-5 monoclonal antibody (mAb) to an anti-IL-5Rα mAb has also been studied.[53] Out of 665 patients treated with anti-IL-5 mAb therapy, 60 switched to benralizumab. The FEV_1 improved from 61% to 68%, and the ACT from 16 to 19 points. Additionally, two retrospective studies demonstrated improvements in exacerbation rates, ACT scores, FEV_1, quality of life (QoL), and oral corticosteroid doses after switching from mepolizumab to benralizumab.[54-55] Even though benralizumab appears more effective than mepolizumab at reducing blood and lung tissue eosinophils, no consistent differences in clinical efficacy have been demonstrated between the two.[55-58] But, if the efficacy of mepolizumab were insufficient, switching to benralizumab would be a validated option.[53,59]

This is based on the fact that several differences have been demonstrated in the mechanism of action of these molecules. Given that basophils express IL-5Rα, their depletion could be induced via benralizumab-mediated cytotoxic activity, as suggested in *in vitro* studies and supported by reductions in circulating basophils.[59-60] Benralizumab also promotes macrophage-mediated phagocytosis of eosinophils.[61] In addition to Th2 and ILC2 as major source of IL-13, eosinophils and basophils expressing IL-5Rα also produce functional IL-13.[62-64] By depleting these cells that aren't a significant source of IL-13 in patients with elevated FeNO, benralizumab would show another difference between it and mepolizumab.

Discontinuation of anti-IL-5 therapy

With regard to the discontinuation of the anti-IL-5 therapy, the COMET study evaluated 155 patients who discontinued mepolizumab after at least three years of use, and compared them to 144 patients who continued treatment. Patients who discontinued anti IL-5 therapy showed a shorter time to first exacerbation, loss of asthma control and increased eosinophil levels. However, cases of severe exacerbations (requiring emergency care or hospitalization) were rare.[41]

Anti-IL-4/IL-13 therapy

Switching *to dupilumab*

There are many cases of switching to dupilumab from other biologics, since it is the most recently approved biologic drug.

In real-world studies from France, the majority of patients who switched biologics (97%) moved from mepolizumab or omalizumab to dupilumab.[65] A study in Japan found that 60% of patients who switched to dupilumab experienced significant reductions in exacerbations and decreased need for oral corticosteroids.[66] In Germany, a study of 38 patients with severe asthma previously treated with anti-IL-5/IL-5Rα mAb or anti-IgE therapies without satisfactory results were switched to dupilumab.[67] 76% of those patients achieved better symptom control, an improved lung function, and reductions in FeNO, IgE levels, use of corticosteroids and exacerbations 3 to 6 months after the switch. Patients with elevated FeNO (>25 ppb) on prior biologic therapies showed greater responses compared to those with non-elevated FeNO levels (<25 ppb). Blood eosinophil levels were reported to increase in these studies switching to dupilumab, but this was not associated with an increase in adverse effects.

To sum up, this therapeutic approach is supported by published data regarding the switching of biologics in approximately 1,527 patients with severe asthma. The data came from various sources, as for example the information gathered from different clinical trials (OSMO, post-hoc analyses of MENSA and SIRIUS, ANANKE), various real-world studies and case reports.

Should other controller drugs be discontinued?

The current goal of asthma treatment includes the concept of clinical remission, which could

ideally lead to discontinuing treatment. Recent consensus guidelines have proposed several definitions of clinical remission, complete remission, and super-responders in severe asthma patients.[33] These definitions encompass several aspects of the disease, such as symptoms, exacerbations, lung function, and inflammation. Several studies have demonstrated that biological treatments attain many of these goals.[68] For this reason, it might be feasible to consider discontinuation of a biological treatment. Several studies have been published on the discontinuation of biologics in severe asthma, some of which have been discussed earlier.[41,43-45,69] Most of these studies report that after discontinuation, symptoms worsen, and the frequency of exacerbations increases. However, in selected patients, this discontinuation strategy might be feasible. For that purpose, it is important to identify the characteristics of these patients. First, patients shouldn't have any exacerbations, and they should have adequate symptom control and stable lung function with the biological treatment at the time treatment discontinuation is considered. According to multiple reports, suppression of T2 inflammation is necessary to achieve clinical remission.[70] Similarly, comorbidities should also be controlled. As mentioned earlier (TABLE 1), currently there are no established criteria for the concept of complete remission free of biologics. However, further research is still needed to validate these criteria. Regarding the de-escalation of the rest of the baseline controller treatment once asthma control (or remission) is achieved, the SHAMAL study shows that patients who met clinical remission criteria during biological therapy face a risk of accelerated lung function decline due to uncontrolled inflammation when inhaled corticosteroids are discontinued as part of maintenance therapy.[71] For this reason, if treatment de-escalation is considered for these patients, it is recommended that they discontinue only second- or third-line medications (leukotriene receptor antagonists, LAMAs [long-acting muscarinic antagonists]), while always maintaining regular baseline treatment with inhaled corticosteroids + LABAs at the lowest possible dose.

5. What approach should be taken with a patient who wishes to become pregnant or is already pregnant? And what about lactation?

Pregnancy and lactation are generally significant concerns within the medical community, particularly due to the need for medication and the potential teratogenic effects on the fetus.

It is now well established that good asthma control has a very positive impact on pregnancy development, on the fetus, and on childbirth.

However, managing severe asthma remains a challenge for physicians, undoubtedly, both pregnancy and lactation add complex issues that must be addressed through clear guidelines, approved medications, and, in many cases, decisions should be jointly made and defined by a multidisciplinary team, since there are limited studies of level A evidence regarding the use of monoclonal antibodies (biologics) during pregnancy. There are no specific clinical trials involving pregnant women; human teratogens are usually identified through case reports. In the United States, the frequency of congenital defects is approximately 3% of live births, the stillbirth rate is 0.625%, preterm births account for 10.1%, and low birth weight occurs in 8.24% of cases. However, it is unclear how much of this can be solely attributed to medications.[72]

In the future, we will likely have more concrete safety data, as emerging publications begin to explore the treatment of asthma during pregnancy based on treatable traits.[73]

To establish practical recommendations for pregnant women and women who are breastfeeding, general observational studies are typically used. These include pregnancy registry studies, cohort studies, case-control studies, and database analyses (including data from adverse event reports).[74] One of the primary registries used for biological products is MotherToBaby (last updated in November 2022 for biologics), which has ongoing studies limited to the U.S. and Canada but currently lacks sufficient data for the scenarios previously described.[75] The Food and Drug Administration (FDA) also maintains a list of open registries for various medications, which is updated as new data and outcomes become available.[76]

Studies conducted in animals have shown that most of the current biologics cross the placenta and are concentrated in breast milk, but do not have adverse effects; however, these findings remain experimental. Other published studies rely primarily on case reports.

Based on the most recently published data regarding safety during pregnancy from the first to the third trimester, the following recommendations are proposed (Table 3).[77]

TABLE 3. Safety of biologics during pregnancy from the first trimester[77]

OMALIZUMAB	Probably safe
MEPOLIZUMAB	Probably safe, without studies to support it
BENRALIZUMAB	Probably safe, without studies to support it
DUPILUMAB	Probably safe, without studies to support it
TEZEPELUMAB	Probably safe, without studies to support it
RESLIZUMAB	Probably safe, without studies to support it

Omalizumab

The safety profile of omalizumab is well-established, with data from more than 9,500 patients in clinical trials and over 400,000 patient-years post-marketing. This has provided safety data since its approval by the FDA in 2003 and the European Medicines Agency (EMA) in 2005. Additionally, like other IgG molecules, omalizumab crosses the placenta during the second and third trimesters of pregnancy.[78]

The observational study of the use and safety of Xolair (omalizumab) during pregnancy (EXPECT), conducted in the United States from 2006 to 2018, is the largest prospective study on this topic. It reported results from 230 pregnant women with asthma exposed to omalizumab either eight weeks before or at any time during pregnancy.[79-80] The study identified a congenital anomaly rate of 8.1%, a live birth rate of 99.1%, a stillbirth rate of 0.9%, and a preterm birth rate of 15.0% in this cohort.[79-80] The findings from the registry were compared with a cohort of pregnant women with asthma who had not been exposed to omalizumab. This comparison group, called the Quebec External Comparator Cohort (QECC), included 1,153 women, matched by age and disease severity.[80] This comparison showed that the live birth rate and the prevalence of major congenital malformations were similar to those of the EXPECT sub-cohort.[80] A higher rate of low birth weight was found in babies born to patients who had been treated with omalizumab (13.7% in EXPECT vs. 9.8% in QECC).[80] However, 64.9% of women in the EXPECT sub-cohort had severe asthma, compared to 21.2% in the QECC group, which makes it difficult to determine whether the low birth weight was caused by the exposure to the medication or the severity of the disease.[80] There are other studies, primarily case reports, that didn't find any difference with regard to the data reported above.

Mepolizumab

The Mepolizumab Pregnancy Exposure Study is a prospective, observational exposure cohort study that investigates pregnancy outcomes in women exposed to mepolizumab during pregnancy, in comparison with the results of women who didn't use mepolizumab during pregnancy but did use other asthma medications (the "treated disease" comparison group), and the results of women exposed to non-teratogenic agents (the "non-asthmatic" comparison group).[82-83] This study was initiated after the approval and marketing authorization of the European Medicines Agency (EMA). The objective of the study is to monitor planned and unplanned pregnancies exposed to mepolizumab and assess its potential teratogenic effects, focusing on major congenital defects as the primary outcome, and the secondary outcomes, including preterm birth, newborns who are small for the gestational age, spontaneous abortion, and stillbirth.[83] The study is conducted by the Research Center of the Organization of Teratology Information Specialists (OTIS), located at the University of California, San Diego.[83] The target sample size is: 200 women in the mepolizumab-exposed cohort, 300 women in the treated disease cohort, and 300 women in the non-asthmatic cohort.[83] The study is expected to run for 6.5 years from the start of recruitment, which began in 2016-2017.[76,82-83]

Benralizumab

Like its predecessor, the anti-IL-5 agent, benralizumab, which has been approved for use in 2017, is not approved for use in pregnant women. There is only one ongoing study regarding its safety in this group (ClinicalTrials.gov Identifier: NCT03794999)[84]. This study began on March 20, 2019, and its estimated primary completion date is February 27, 2026. Its primary objective is to monitor both planned and unplanned pregnancies

in order to assess potential teratogenic effects (congenital defects) associated with exposure to benralizumab.[84] This exposed group will be compared to two unexposed reference groups. It is estimated that 800 pregnant women with asthma who have been exposed to benralizumab at any time during their pregnancy or within 8 weeks prior to their last menstrual period will participate.[84] As control group, the study will include pregnant women with asthma who haven't been exposed to benralizumab during pregnancy or within the 8 weeks prior to their last menstrual period, along with a third group of pregnant women without an asthma diagnosis, who have not been exposed to any known human teratogen and have not taken benralizumab during pregnancy. This study aims to provide information about the potential risks associated with the use of benralizumab during pregnancy and contribute to scientific knowledge regarding its safety in this population.

Dupilumab

Currently, there are no specific studies addressing the relationship between asthma and pregnancy-lactation. However, research is underway in North America (USA-CANADA) focusing on evaluating the safety of using dupilumab during pregnancy and its impact on newborns. A notable example of these studies is the "Post-Authorization Safety Study in North America" (ClinicalTrials.gov NCT04173442), which has been ongoing since October 24, 2018, and is scheduled to conclude on July 9, 2026.[85] This study is organized into three distinct cohorts: 1. Women who have used dupilumab for an indication other than asthma or atopic dermatitis; 2. Those who have been exposed to dupilumab within 10 weeks following the last menstrual period or at any time during the current pregnancy; 3. Comparison cohort without disease: women exposed to dupilumab within 10 weeks before the first day of the last menstrual period, women diagnosed with any approved indication for dupilumab, and those who have had the first contact with the study after receiving a prenatal diagnosis of any major structural defect. The primary purpose of this study is to provide valuable information about the safety of dupilumab during pregnancy, with special attention to possible effects on maternal health and child development.[85]

Tezepelumab-reslizumab

There are no safety studies regarding pregnancy and lactation.[86]

Conclusions on the use of biologics during pregnancy and lactation

In the first place, it is essential to strengthen the doctor-patient relationship to understand and plan future pregnancies in patients with severe asthma who are receiving biologics.

It is important to understand the benefit of having controlled asthma compared to uncontrolled asthma during pregnancy and the risks associated with this situation.

While it is often difficult to differentiate the side effects that occur in pregnant women and in the fetus in this group of patients with severe asthma receiving various medications, exacerbations may also occur alongside other comorbidities.

At present, given the practical and ethical challenges of intervention studies in this patient group, we emphasize the importance of basing the use of biologics on the limited publications available. Currently, the only biologic considered safe for use during pregnancy is omalizumab, and future results from ongoing studies are still awaited for other biologics.

6. How is adherence to treatment and biologics like?

The WHO defined adherence in 2003 as "the degree to which a patient's behavior, in terms of medicine-taking, following a diet, or making lifestyle changes, corresponds with the recommendations of the healthcare provider."[87]

It is well known that non-adherence is very common among asthma patients, and it is due to several factors: psychosocial aspects of the patient, factors inherent to the disease itself, doctor-patient relationship, and even access to medications, all of which have been widely determined in several studies.[88] Non-adherence has been reported in 30-70% of patients. Busby et al determined in patients with severe asthma that the factors associated with poor adherence were the fact of belonging to ethnic minorities (OR 3.10, 95% CI 1.68–5.73) and having two or more changes in preventive medication (OR 2.77, 95% CI 1.51–5.10).[89] In the SAPPHIRE study, it was estimated that 75% adherence to inhaled corticosteroids resulted in a 49% reduction

in exacerbations.[90] In the different definitions of "poorly controlled asthma", assessing adherence problems and addressing them before labeling a patient as having severe asthma is a mandatory step in the recommendations of different international and national guidelines. Almost a quarter of the exacerbations and two-thirds of asthma-related hospitalizations are linked to poor adherence to the preventive treatment.[90-91] It is assumed that patients enrolled in clinical studies also adhered to the treatment. As per protocol, in clinical studies, it is necessary to ensure treatment adherence more than 80% of the time, and this is achieved not only through patient self-reporting of medication intake but also by counting the doses of the drugs under investigation and using electronic dosing devices during each visit or through telemedicine. Therefore, probably better asthma control can be achieved in these patients solely by improving adherence. As a common factor in almost all clinical development studies of new biologics, a "clinical study effect" has been observed in the placebo arms, in the reduction of severe exacerbations (between 30-50%), improvement in FEV_1 (less than 200 ml), asthma control, and quality of life (both with improvements greater than the clinically significant minimal differences).[92] It is striking to see how the three studies investigating biologics in corticosteroid-dependent patients (SIRIUS, ZONDA, and VENTURE) achieved significant reductions in corticosteroid use (35-65% reduced the dose by half), and even complete discontinuation (8-25%).[92] The hypothetical reasons for this result could be based on the idea that the patients enrolled in the studies were probably undertreated or poorly adherent, with poor asthma control; and it was observed in the study that by improving treatment adherence, standardizing the treatment regimen, and ensuring proper follow-up, asthma control was achieved, leading to the previously detailed results.[92] In the placebo arms of phase III studies, the real impact of adherence has been demonstrated.[92] Ensuring good adherence is always the first step for a patient with poorly controlled asthma, and improving it has a beneficial impact on quality of life, asthma control, reduction of exacerbations, and systemic corticosteroid use, and also saves healthcare system resources.[93]

Pre-filled autoinjector devices (AIDs) and adherence

AIDs are simple to use, practical, and enable effective home management with a low risk of critical errors.[94] Potential candidates include children, adolescents, and adults of working age.[94] Elderly patients with neurological, psychiatric, or rheumatological conditions affecting the upper limbs may not be suitable. Proper education of the patient is critical. The first dose should be administered in a specialized center for severe asthma or in a physician's office. Instructions on timing, storage, and cleaning of the AID are essential for successful use. A suitable doctor-patient relationship is essential.[88,94] It is important to note that not all dosing regimens for the biologics available in our country are the same. All are administered subcutaneously. Omalizumab and mepolizumab are administered every four weeks. Benralizumab is administered every four weeks for the first three doses, and starting from the fourth dose, every eight weeks. Dupilumab is administered every two weeks.

In Argentina, reslizumab is not commercially available. Among the other four biologics, there are pre-filled autoinjector devices that have improved treatment adherence. Their correct administration and adherence have been confirmed by measuring the concentration of the biologic in the blood in optimal levels.[94-97]

Adherence and FeNO suppression test

The FeNO Suppression Test (FST) was described more than ten years ago to evaluate non-adherence to asthma treatment.[98] Using a device adapted to a dry powder inhaler, data are recorded for one week simultaneously with the inhalation of baseline preventive medication. A 42% decrease in FeNO between the average values of days 0/1 and days 4/5 is considered positive.[98-99]

More recently, Couillard et al have used the FST to identify adherent patients with T2 corticosteroid-resistant phenotypes, determining that FeNO and eosinophils provide complementary and different information: FeNO reflects airway inflammation, while eosinophilia reflects systemic inflammation.[100]

Butler et al determined in a study of 135 patients that those with a negative FST were more likely to be treated with biologics (39 out of 54 patients, 72%) compared to those with a positive

FST (35 out of 81 patients, 43%, p=0.001). High maintenance doses of corticosteroids (CS) and previous admission to the ICU were identified as predictors. An increase in FeNO correlates with better asthma control and adherence to high doses of ICS/LABA.[101]

CONCLUSIONS

Treatment with biologics for patients with severe, uncontrolled T2-high phenotype asthma has been a major advance in the last twenty years, with proven efficacy and safety, improving the patient's quality of life by reducing severe exacerbations and hospitalizations. However, controversial aspects still exist. There is not enough evidence to confirm if biologics prevent long-term airway remodeling, or if they are safe during pregnancy or lactation (with the exception of omalizumab). Currently, there are no established criteria for the concept of complete remission with biologics. Some proposed criteria include the absence of symptoms and exacerbations, not using oral corticosteroids, normal spirometry, suppression of T2 inflammation, and control of comorbidities. However, further research is needed to validate these criteria. Once control is achieved, biologics should not be discontinued. However, it is possible to consider de-escalating other second- or third-line medications (leukotriene receptor antagonists, LAMAs), always maintaining regular base treatment with inhaled corticosteroids + LABAs at the lowest possible dose.

Conflict of interest

Dr. Fernando Saldarini has participated in medical conferences on asthma for AstraZeneca, GlaxoSmithKline, ELEA, TEVA Chile, Janssen, and SANOFI for continuing medical education programs.

Dr. Diego Litewka has participated in conferences and continuing medical education programs on asthma for Novartis, Sanofi, and GlaxoSmithKline.

Dr. Martin Sívori has participated in conferences and continuing medical education programs on asthma for AstraZeneca, ELEA, and GlaxoSmithKline.

Dr. Daniel Pascansky has participated in conferences, consultations on asthma for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Elea, Casasco, as well as continuing medical education programs on asthma for Novartis.

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