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REVIEW

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Unanswered questions on the use of biologics in pediatric asthma

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ABSTRACT

The emergence of biologic therapies for the management of asthma has been a revolutionary change in our capacity to manage this disease.

Since the launch of omalizumab, several other biologics have been marketed or are close to being marketed, suggesting that a plethora of monoclonal antibodies can be expected in the coming years. This will facilitate the transition to the paradigm of personalized medicine, but on the other hand will decisively further complicate the choice of the most appropriate treatment, in the absence of reliable enough biological markers.

For these reasons, along with the relatively short time of use with these treatments, there are recurrently arising questions for which there are not even moderately documented answers, and for which the only solution must be based, with all reservations, on the combination of indirect evidence and expertise. In this paper, we attempt to address such questions, providing relevant commentaries and considering the whole width of the evidence base.

Keywords: Severe childhood asthma, Biologics, Omalizumab, Mepolizumab, Benralizumab, Dupilumab, Tezepelumab

INTRODUCTION

The emergence of biologic therapies for the management of asthma has been a revolutionary change in our capacity to manage this disease.

Omalizumab, the first humanized anti-IgE monoclonal antibody, was authorized for use in patients over 12 years of age by the US Food and Drug Administration (FDA) in 2003 and by the European Medicines Agency (EMA) in 2005. Subsequently, the indication was extended to children over 6 years of age by the EMA in 2009 and by the FDA in 2016. Since its launch, considerable experience has been accumulated in the clinical use of this molecule in terms of efficacy, effectiveness, and safety.

More recently, anti-IL5 biologics (mepolizumab, reslizumab, and benralizumab), anti-IL4/13 (dupilumab) have been approved for the treatment of asthma, although only mepolizumab and dupilumab have been authorized for use in children over 6 years of age, so far. On the other hand, the antithymic stromal lymphopoietin tezepelumab is currently approved only for patients over 12 years of age. Moreover, other biologics including anti-

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IL17, anti-IL25, anti-IL33 are in the pipeline, suggesting that a plethora of monoclonal antibodies targeting relevant pathways can be expected in the coming years. This, on the one hand, will facilitate the transition to the paradigm of personalized medicine, but on the other hand will decisively further complicate the choice of the most appropriate treatment(s) for each patient in the absence of sufficiently reliable clinical and/or biological markers. This is especially true in the case of children, given the low prevalence and dynamic nature of severe childhood asthma (SCA), which greatly challenges the recruitment of an adequate number of patients in clinical trials. Furthermore, as all monoclonals target key molecules of allergic inflammation (either IgE-mediated or not), they also affect the multi-morbidities from which patients suffer. Finally, there is considerable overlap between patient populations in whom these treatments are indicated. Consequently, there is considerable heterogeneity in terms of management choices, such as time point at which treatment success is assessed, therapy duration, options and success rate of discontinuation, etc.[1] Several of these questions have not been, and cannot be, assessed through formal clinical trials. There are thus attempts for empirical approaches to differentiate indications based on clinical and biomarker characteristics of the patient.[2]

Real-life studies are providing relevant information on the use of these molecules, particularly omalizumab.[3-5]

However, there are recurrently arising still questions for which there are not even moderately documented answers, and for which the only solution must be based, with all reservations, on the combination of indirect evidence and expertise. In this paper, we attempt to address some such questions, providing relevant commentaries and considering the whole width of the evidence base.

When to start biologics?

SCA is defined as asthma that remains uncontrolled despite adherence to optimized combination of high-dose inhaled corticosteroid and long-acting beta-agonist (ICS-LABA) and despite management of contributory factors and comorbidities, or asthma that worsens when high dose treatment is decreased.[6] Nevertheless, the establishment of the severity of childhood asthma is debated. Added to this, the tools available for calculating severity in children are extrapolations of those for adults, which ignore impact on crucial childhood parameters (school performance, family life, socialization, etc.) and probably weigh inadequately the specific contribution of individual items used in these tools: for example, the impact of asthma on exercise performance is considerably higher in children, while lung function has a lower weight, since there are data suggesting that children with SCA may have lung function within normal limits.[7]

Biologics approved to date for the treatment of SCA are indicated for patients with a "T2"-high profile. The use of certain clinical findings (onset [early/late], atopy [+SPT/-SPT], nasal involvement [Rhinitis/Polyps]), and biomarkers (IgE, Eosinophils, Neutrophils, Periostin, Fractional Exhaled Nitric Oxide [FeNO], IL-17) can help delineate the T2 profile and establish the indication for use, as well as to select the biologic of choice.[8,9]

Obviously, there is a great unmet need regarding the proper use of biologics in children as many of the indications are based on extrapolation of data from adults. Another significant factor in decision-making is the high cost associated with the biologics. Nevertheless, although not clearly demonstrated, it cannot be ruled out that a delay in the initiation of treatment with biologics could lead to prolonged/persistent airway damage.[10]

How to evaluate the response?

The criteria for evaluating the response to biological therapy in children are not well defined. Obviously, exacerbations, control, lung function, adverse events, use of systemic corticosteroids, and patient satisfaction should be considered. Biomarkers have been suggested as potential tools for monitoring treatment, but there are no definitive conclusions.[8,9,11]

Usually, the response to treatment should be evaluated just after the first 4 months.[11-13] The level of response can greatly vary between patients. According to the degree of response patients can be classified into three categories:[13]

- Super-responders: patients who show a great response to biologics or complete asthma control. This definition is an extrapolation from adult data, but the exact definition for children is yet to be identified.
- Partial responders: those who show some improvement but residual asthma manifestations.
- Non-responders: patients who show very little or no improvement or worsen with treatment.

If the response is inconclusive, treatment can be extended for 6–12 months,[11,14–17] since late-responders have been described.[18] However, with an increasing availability of biologics, switching to a different one could be an option, as described below.

When to attempt stopping; how to co-manage with other medications (ICS, OCS)?

The lack of evidence is the main reason for recommendation gaps on these important issues. Among available biologics,[11] omalizumab is the only one with long term clinical experience to allow any evidence on these topics. Real-life studies and metanalyses have demonstrated the efficacy and safety of the use of omalizumab in SCA.[3,4,19–22] However, for cessation of biologics and/or step-down of inhaled treatments, the recommendations are mainly based on expert opinion and scarce evidence from real-life observational data. One French multicentered real-life report in children and adolescents with SCA (n = 100) discontinued omalizumab after 24 months of treatment in 35 patients with good clinical response. The discontinuation was abrupt. Eight (22.8 %) patients had to restart omalizumab for worsening asthma. Based on analysis of patients' characteristics, gender (female), allergic comorbidities (atopic dermatitis, food allergy), lung function (greater airflow limitation) should be considered in the decision to discontinue omalizumab after prolonged treatment.[22] In a Spanish real-life multicentered retrospective observational cohort of SCA patients, 123/484 (25.4 %) patients discontinued the use of omalizumab. In this large cohort with up to 6 years follow-up, in 99/123 (80.4 %) patients the discontinuation of omalizumab was due to good clinical evolution, most of the patients after 24 months of treatment.[4] These two observational studies discontinued omalizumab around 24 months of treatment with good clinical response. The Global Initiative for Asthma (GINA) report suggests in well-controlled cases with medium doses of ICS and with the responsible allergic trigger also controlled, after 1 year of treatment, the possibility of trying to tentatively discontinue omalizumab can be taken into account.[11] Total control of disease, no history of severe exacerbation in the last 12 months and mild lung function abnormalities may be considered the least criteria to indicate cessation of any biologic in SCA.

There is no evidence on step-down approaches of inhaled medications after initiating biologics. There is expert consensus that decreasing or stopping daily oral corticosteroids in the small number of children who receive them, is of paramount importance,[23] always checking for adrenal insufficiency. Then add-on treatments could be removed, including reduction of the dose of ICS. It is advised not to stop ICS treatment.[11]

Is biologic use safe in the short- and long-terms?

Minimization of the adverse events (AEs) of therapies is a key aim in asthma management. Biologics are generally safe and well tolerated, and their use has reduced the exposure to systemic corticosteroids and their undesirable short- and long-term AEs.[24] A metanalysis identified in children a significantly lower risk of severe AEs with omalizumab compared to placebo (RR 0.40 [95 % CI 0.24; 0.67]).[25] A real-life study of global patterns of biologic use in adults with severe asthma, elucidated that AEs caused by biologics were the reasons underlying stopping or switching biologics in 15.9 % (n = 18/113) and 7.7 % (n = 14/183) respectively.[26] Most frequent AEs were headache, pyrexia, injection site reactions and infections especially of the upper respiratory tract.[27]

Although small, anaphylaxis remains a risk for most biologics and analysis of real-world data from the FDA Adverse Event Reporting System (2004–2020) revealed that the odds ratio was highest for omalizumab. Only dupilumab showed no increased risk for anaphylaxis. For mepolizumab, there is contradiction between clinical trials and real-world evidence but the consensus is that it has

a low but existent anaphylaxis risk.[28] Induction of anti-drug antibodies (ADA) have been demonstrated against various biologics, yet, no apparent correlation has been observed between anaphylaxis and the presence of antibodies of IgE isotype to omalizumab. Furthermore, ADA status had no effect on safety or efficacy of dupilumab.[29] Concerns about potential association of primary malignancies with omalizumab have been cleared by the finding that the incidence rates were similar in treated and non-treated patients (12.3 vs 13.0 per 1000 person years).[30] In a pooled analysis of randomized trials, there was no association between omalizumab intake and risk of malignancy.[31]

Still, the long-term effects of biologics remain unclear and as much as there is an exceptionally robust asthma biologic pipeline, equally robust studies are needed to evaluate the safety and tolerability in children. However, due to the longer time since launch, omalizumab offers the most consistently documented safety profile.

Is there a way to select the "appropriate" biologic for each child?

Data on biomarkers that can efficiently identify the optimal add-on biologic therapy for each child are scant and their role is controversial. Table 1 displays the potential biomarkers in relation to each biologic and their limitations.

T2 biomarkers are limited, namely serum total and specific IgE, peripheral blood eosinophils, and FeNO. Periostin is also associated with T2-high asthma, but its value is influenced by bone metabolism which limits its usefulness in children.[39] Although peripheral blood eosinophil counts do not necessarily parallel airway eosinophilia, the difficulty in obtaining sputum samples makes peripheral blood eosinophils a convenient surrogate marker.[27,39] The relative ease of bedside measurement of FeNO allows it to serve as a biomarker for T2 high inflammation.[32]

Concerning omalizumab, patients with elevated FeNO ($\geq$19.5% ppb) demonstrated 53% reduction in asthma exacerbations compared to only 19% when FeNO was $<$19.5 ppb. Also, exacerbations were reduced by 32% when eosinophil counts exceeded 260 cells/mL, compared to only 9% at lower values.[33] Another report showed that at least 300 eosinophils/μl were linked to a better response to omalizumab with up to 60% decrease in asthma exacerbations.[34] On the other hand, omalizumab add-on therapy was found to reduce exacerbation rates and improve asthma control irrespective of blood eosinophils and FeNO status at baseline.[27] However, these biomarker studies were conducted in populations that include adolescents and adults, and caution should be entertained when applying their results to children.[27,33,34]

In preventing fall season asthma exacerbations, children who were sensitized to 4 or more aeroallergens had a significantly greater response to omalizumab.[35] A large post hoc analysis of 3 randomized controlled studies revealed greater reduction in asthma exacerbations in children with obesity (BMI $\geq$85 % for age), higher eosinophil and FeNO values, hospital admission in the previous 6 months, 3 or more exacerbations in the previous year, and decreased FEV1.[36] Total IgE measurement is not a reliable indicator of response to omalizumab. Although the reduction of serum free IgE to a concentration of $\leq$20.8 IU/mL is likely indicative of a consistent therapeutic response, commercially available assays do not distinguish between the omalizumab–IgE complex and free IgE.[32]

Recent studies recommend IL-5 blockade (mepolizumab or benralizumab) or the anti-IL-4a (dupilumab) therapy for T2 high non-allergic eosinophilic asthma.[40]

According to the recently published VOYAGE study, Dupimumab would reduce the number of exacerbations and improve lung function in children with Th2 asthma, irrespective of evidence of allergy.[44] The response to mepolizumab, may be determined by blood eosinophil count $\geq$300 cells/μL, or $\geq$ 150 cells/μL in children with well characterized eosinophilic asthma, requiring regular oral corticosteroids or urban children with exacerbation-prone eosinophilic asthma.[37,38,41,45]

Dupilumab indirectly lowers IgE levels and hence triggers internalization of FceR1 by blocking the IL-4a receptor and subsequent IL-4/13 signaling. However, a point of-care biomarker that predicts responsiveness is lacking. Elevated FeNO is the most favorable followed by blood eosinophil count.[37,38,40–42] The anti-TSLP

Biologic	Criteria for prescription[a]	Limitations	References
Omalizumab (anti- IgE)	• Serum IgE >30, <1500 IU/m • Sensitization to perennial aeroallergens • FeNO ≥19,5 ppb [b] • Eosinophils ≥260/mm^3 [b] • Periostin ≥50 ng/mL [b] • Decreased FEV1	• IgE assays are not able to distinguish between the omalizumab-IgE complex and free IgE • Eosinophil levels are influenced by infections, allergen exposure, and steroid therapy • FeNO levels are transiently influenced by exercise and prior spirometry. Inhaled and systemic steroids, and leukotriene-receptor antagonists reduce FeNO, and high nitrate food may increase it. It increases at a rate of 5 % per year of age due to increased height. • Periostin level is influenced by bone metabolism	17,27,32-38
Mepolizumab (*Anti*-IL5)	Blood eosinophil count ≥300 cells/µL, or blood eosinophil count ≥150 cells/µL in patients with well characterized eosinophilic asthma or requiring regular OCS	• Peripheral blood eosinophil counts do not always reflect airway eosinophilia • Eosinophil levels are influenced by infections, allergen exposure, and steroid therapy	17,27,37-41
Benralizumab (anti-IL5 Ra)	Blood eosinophil ≥300/µL		
Dupilumab (*Anti*-IL4R)	Peripheral eosinophilia (≥150 cells/µL), and/or FeNO >25 ppb	• Peripheral blood eosinophil counts do not always reflect airway eosinophilia	17,37-42
Tezepelumab (anti-TSLP)	• Blood eosinophil ≥300/µL • FeNO ≥25 ppb	• Eosinophil levels are influenced by infections, allergen exposure, and steroid therapy • FeNO levels are transiently influenced by exercise and prior spirometry. Inhaled and systemic steroids, and leukotriene-receptor antagonists reduce FeNO, and high nitrate food may increase it. It increases at a rate of 5 % per year of age due to increased height.	32,43

Table 1. Biomarkers for biological therapies *FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 s; ppb: part per billion; TSLP: thymic stromal lymphopoietin. [a]In addition to the diagnosis of severe asthma. [b]Would predict better response.*

tezepelumab reduces Th2 biomarkers suggesting an influence on IL-4, IL-5, and IL-13 pathways. Blood eosinophilia and elevated FeNO are also potential biomarkers.[32,43]

There are still unmet needs for head-to-head comparison studies of biologics and search for new biomarkers that would guide treat-to-target biological therapy in pediatric asthma. The results

of the TREAT study, a 52-week non-inferiority trial comparing omalizumab and mepolizumab in children with severe asthma may help to shed some light on this situation.[46]

There have been several attempts to develop algorithms for biologic selection in severe asthma, almost always based on adults.[47–50] In several patients, more than one biologic may be considered. Following detailed phenotypic characterization and evaluation of specific indication, treatment priorities and expectations should be discussed with the patients and their carers.[47,51] For several years, based upon its longer term experience and extensive safety record for children with allergic sensitization and severe asthma, omalizumab has been an initial biological treatment of choice.[39] However, this is changing with increasing use of the other agents. Multimorbidities are also an important consideration, as discussed below; eg, concomitance with atopic dermatitis (AD) can justify a trial with dupilumab.[2] In any case, asthma trials demonstrate that the effectiveness of dupilumab in asthma was independent of Atopic Dermatitis comorbidity.[42,44,52]

When to consider switching?

Different biologics target specific pathways, but it is often difficult to identify the ideal treatment for a particular patient, as there is frequently overlap between different endotypes. Suboptimal clinical responses and drug discontinuations are not so rare in biologic treatment; however, there are no head-to-head comparative trials,[47,53] while assertions of superiority of one agent over the other made by indirect comparisons have important limitations.[51,54–57] This makes the timing or criteria for switching between biologics, a dilemma. We still hope that response biomarkers may emerge,[51] but we are still far from the identification of accurate enough discriminative biomarkers. At present, the minimum time for assessing efficacy of a biologic is 4 months.[11] The first data from the Severe Paediatric Asthma Collaborative in Europe (SPACE) registry, a prospective, non-interventional, European observational database, showed that 79% of children who were prescribed a biologic had suboptimal control, and of those about 80% were eligible to switch to another approved biologic.[58]

A reliable indicator for clinical success of a biologics therapy is OCS discontinuation in patients with steroid-dependent asthma.[59,60] Failure to achieve OCS-sparing in such patients is a switching signal.[51] Only a small number of reports describing successful switching between biologics in severe asthma patients have been published, almost all in adults.[61–66] In a large cohort including adults with severe asthma treated with biologics for more than 6 months, 79% continued their first biologic, 10% stopped and 11% switched; insufficient efficacy and/or AEs were the most frequent reasons for stopping or switching.[26] On the other hand Numata et al, studied 97 severe asthma adults treated with biologics, of which 35% switched the biologic mainly due to lack of control; only one-third of those improved.[67]

Other circumstances for the consideration of switching one biologic for another, can be the occurrence of adverse events, the patient's preferences, and other special safety consideration in case of comorbidities, incidental opportunistic infections,[68] patients with high risk of helminths infestation,[69] and more infrequently in adolescents pregnancy[70] and lactation.[71] Regarding the potential teratogenic effect of biologic treatments for asthma, there are only data on omalizumab that demonstrate the absence of risk of congenital abnormalities in the offspring of pregnant women treated with this biologic.[70]

The OSMO (omalizumab switch to mepolizumab) study proves that neither efficacy, nor safety and tolerability data were compromised by proceeding with such a change without a previous washout period.[72,73]

Even though algorithms for switching among biologics based on biomarkers and some particular patients' characteristics have been proposed,[51] the available evidence regarding biologic switching in pediatric patients is very limited, so information on this subject should be evaluated with caution.

In children who remain uncontrolled, the use of combined biological therapy could also be considered, but no data exist in this age group.[53]

How to include comorbidities in the algorithm for selection and effectiveness evaluation?

It seems reasonable to assume that, apart from asthma, other diseases in which IgE or eosinophilia may play a predominant role could also benefit from the use of biologics. Thus, apart from the impact on comorbidities in patients with asthma treated with biologics, some clinical trials, pragmatic studies, and case reports or case series document the use of biologics in other diseases. Epidemiological data suggest that rhinitis/rhinoconjunctivitis, asthma, and AD form a multimorbidity cluster, attributed to shared genetic polymorphisms and pathogenetic mechanisms, more so in the pediatric population.[74,75] In fact, 1 study suggests that the presence of multiple comorbidities in SCA may be indicative of a good response to omalizumab, insofar as it suggests a strong allergic background.[76]

The beneficial effect of omalizumab on allergic rhino-conjunctivitis (AR) has been extensively studied and verified for different outcomes, such as nasal symptom score, ocular symptom score, and nasal medication symptom score, both in children and adults.[77] The efficacy of dupilumab has been shown in adult AR patients with comorbid severe asthma;[78] no compelling studies of the IL-5 pathway-targeting biologics have been performed in AR.[79]

The presence of T2 immunity and comorbid asthma are common in AD, although important differences between the two diseases translate to different therapeutic approaches.[80] Dupilumab is approved for infants (6 months and older), children and adolescents with moderate to severe AD,[81,82] with confirmed high efficacy and safety profile.[83,84] Based on the available data a conditional recommendation based on expert's opinion on the efficacy of dupilumab in patients with asthma and AD has been issued,[16] although, as we have mentioned, the absence of concomitant AD does not impair efficacy in asthma.

Anti-IgE, anti-IL5, IL-5Rα and IL-4R, have shown safety and efficacy in reducing nasal polyp mass and symptom scores in chronic sinusitis with nasal polyps (CRSwNP) However, studies on the efficacy of biologicals in children are still lacking,[85] because the prevalence of this condition is lower in children than in adults,[86] although recent data suggest that it may be higher than the estimated.[87] In any case, the presence of CRSwNP in this context should prompt the search for ciliary dyskinesia or fibrocystic disease.

CAN BIOLOGICS MODIFY THE NATURAL HISTORY OF ASTHMA?

Evidence in adults suggests that many of the clinical benefits of biologics begin to dissipate when therapy is discontinued. However, it is plausible that early interruption of pathways in the allergic asthma march may have lasting benefits, presuming a young child's immune system may be modifiable, possibly in a critical time window at the early onset of disease.[88,89]

Inhalant allergen sensitization is not only the norm in children with asthma, but is also associated with an increased risk of severity, persistence, and progression of the disease. Respiratory viral infections during the first years of life potentiate the effect of aeroallergens.[89–91] In addition, it has been shown that sensitization to inhalant allergens may precede the development of virus-induced wheezing.[92] Actually, in most cases, sensitization to inhalant allergens begins around the age of 1–3 years and becomes more pronounced during the following years.[93] In this sense, early allergic sensitization also plays an important role in this regard, since people who develop a precocious allergic sensitization are more likely to have more persistent forms of asthma, as well as more severe exacerbations.[94,95]

But, beyond its role in triggering the allergic response, the coupling of IgE to its receptors on the cell membrane induces an impairment of antiviral responses, mainly mediated by Type I interferons,[96,97] This could lead to an increase in viral infections, which in turn could contribute to the progression and chronification of asthma. In fact, experimental studies also show that IgE, in addition to promoting Type 2 allergic responses, is capable of suppressing the production of protective T-reg lymphocytes.[98,99] The result of this early Th2 switch would induce in children an increased risk of viral respiratory infections, as well as an increased propensity to develop asthma.

Given the importance of type 2 pathways in the progression and persistence of asthma, it is of interest to consider immune based therapies administered early in life to determine whether they may modify the course of the disease.[100] In order to justify biologic therapy in young children in prevention, targeting high risk children who have not yet demonstrated firmly established disease is necessary, also to ample real-world safety data. This premise involves administering the therapy in a controlled, blinded-placebo controlled fashion with enough time to conceive an impact, and follow the natural history off therapy to compare disease progression with control. The Preventing Asthma in High Risk Kids (PARK) study,[101] funded by the US National Institute of Allergy and Infectious Diseases (NIAID), is evaluating omalizumab in high risk 2–3 year old children, treating them for 2 years plus a follow up until age 6–7 for asthma and allergic disease outcomes, compared to control. This is the first study of its kind to definitively evaluate the role of interrupting IgE in early life and its long-term effect on disease modification in children (ClinicalTrials.gov Identifier: NCT02570984). If the hypothesis was confirmed, treatment with omalizumab (anti-IgE) would be the first intervention capable of significantly preventing the development of asthma in children with early wheezing. Besides, potential positive results could strengthen rationale for IgE targeted interventions by not only antibody-based mechanisms but further development of small molecule therapeutics, which are currently in the early stages of development and provide significant insights into the pathobiology of asthma and other IgE-mediated allergic diseases and pave the way for additional utility in many of the Type 2 targeted biologics.

Off-label uses

As with other medicines, off-label use of biologics can only be considered in exceptionally severe/debilitating or "quoad vitam" situations, for which other therapeutic alternatives have failed, and for which there is a well-founded assumption of potential efficacy, subject to the corresponding informed consent and local legal compassionate procedures. In the recent past, published reports and anecdotal data have explored the limits of omalizumab, as it was the only available biological agent. These included the use outside the indicated IgE range (30–1500kU/L),[4,10,102,103] without exceeding the maximum dose (600 mg every 2 weeks), or using more frequent dosing, based on specific IgE/Total IgE ratio.[104] Omalizumab has also been used in cases of apparently non-allergic asthma, where local IgE is suspected,[105] "intrinsic" asthma,[106–109] and seasonal asthma.[110,111] The PROSE study showed that adding omalizumab to regular care before return to school, reduced viral-induced asthma exacerbations.[112] The ANCHORS study has included 16 children under 6 years of age, with a reduction in the rate of severe exacerbations of 95 %, and no relevant side effects.[4] The ongoing PARK study is currently formally exploring the use in toddlers.[100]

Obviously, in these cases the cost/benefit ratio must be adequately assessed; therefore, its consideration would be limited to certain very severe cases. Several of these uses would not be necessary with the availability of alternative agents to switch to.

A summary of the questions raised in this article is shown in Table 2.

Another important issue is related to the cost-effectiveness of biologics. In some studies carried out in developed countries, this continues to be the subject of debate,[113–120] and more pharmacoeconomic studies, particularly in children are needed. However, due to their high nominal cost, the use of biologics in children with SCA in low- and middle-income countries (LMICs) constitutes a great limitation that can eventually condition the adequate control of these patients. Differences in burden of disease are likely to be attributable to suboptimal asthma treatment due to socioeconomic deprivation and factors related to it (poverty, air pollution, climate change, exposure to indoor allergens, urbanization, diet, etc), as well as social, financial, cultural, and healthcare barriers. Therefore, in these countries, the reduction of the burden and severity of asthma, in principle, would require the solution of these previous problems before considering other alternatives. In any case, the cost of medicines is still a major challenge particularly for LMICs, because not only newer asthma treatments and approaches are often unavailable and unaffordable, but there is also a lack of research on their effectiveness and implementation feasibility in

QUESTION	ANSWER	COMMENTS
1. WHEN TO START?	As soon as possible, once a clear diagnosis of SCA has been established and conventional treatment has failed	delaying treatment too long can have prolonged/ irreversible consequences?
2. HOW TO EVALUATE THE RESPONSE?	Outcomes to consider • Exacerbations • control symptoms • lung function • adverse events • use of systemic CS • patient satisfaction Evaluate at 4 months. Some cases of late responders (OMZ) can justify the evaluation of the response up to 1 year	Level of response can vary from super-responders to partial and non-responders
3. HOW TO ATTEMPT STOPPING; HOW TO CO-MANAGE WITH OTHER MEDICATIONS (ICS, OCS)?	2–6 years depending on clinical response (OMZ) Try to stop/reduce concomitant treatment (particularly OCS)	Consider to reduce/stop OMZ if: • total control of disease • no history of severe exacerbation in the last 12 months • mild lung function abnormalities No evidence with Mepo or Dupi
4. IS BIOLOGIC USE SAFE IN THE SHORT- AND LONG-TERMS?	To date, yes Rare cases of anaphylaxis with omalizumab and mepolizumab	Omalizumab the most well documented safety profile in children (13 years)
5. IS THERE A WAY TO SELECT THE 'APPROPRIATE' BIOLOGIC FOR EACH CHILD?	OMZ: • Allergic Phenotype • Eosinophilic Phenotype if *Anti*-IL-5 has failed + IgE >30 kU/L • severe symptoms to seasonal allergens MEPO • Eosinophilic Phenotype • Allergic Phenotype if OMZ failed + ↑ Eosinophil count. Concomitance with atopic dermatitis → OMZ or DUPI	OMZ: initial biological treatment of choice for patients with allergic sensitization and SCA because of: • longer experience • extensive safety record
6. WHEN TO CONSIDER SWITCHING?	See questions 2 and 5 Evaluate the response at 4th month, particularly on the discontinuation of oral CS	Also evaluate: • AEs • Patient's preferences • Comorbidities (see question 6)

(continued)

QUESTION	ANSWER	COMMENTS
	Combined biological therapy feasible, but affordability must be carefully evaluated	• Pregnancy • Lactation • incidental opportunistic infections • High risk of helminth infestation Wash-out not needed
7. CAN WE USE BIOLOGICS TO MODIFY THE NATURAL HISTORY OF THE DISEASE?	No data to date. Pending results of the PARK study with OMZ	No planned studies with MEPO and DUPI in this respect
8. HOW TO INCLUDE COMORBIDITIES IN THE ALGORITHM FOR SELECTION AND EFFECTIVENESS EVALUATION?	Multiple allergic comorbidities suggest a good response to OMZ	Allergic rhinitis/rhinoconjunctivitis • OMZ +++ • DUPI +++ • MEPO + Food allergy • OMZ +++ • DUPI: ? • MEPO: ? Atopic dermatitis • OMZ: ++?[a] • DUPI: +++ • MEPO: 0[a] CRSwNP (adults) • OMZ ++ • DUPI +++ • MEPO ++ Cystic Fibrosis with ABPA • OMZ: +/++ • DUPI: +/++ • MEPO: +/++ Eosinophilic Esophagitis • DUPI: +[b]
9. USE BIOLOGICS OUT OF LABEL?	Only when: • high functional or "quoad vitam" severity and, • alternative therapeutic alternatives failed and, • well-founded assumption that the biologic could be useful and, • local legal regulations allow compassionate use	

Table 2. Key points *OMZ: Omalizumab MEPO: Mepolizumab DUPI: Dupilumab. [a]Has not been approved for atopic dermatitis due to the lack of robust evidence proving its efficacy. [b]Approved for adults.*

Population	Clinical trials, Real-Life studies, Pragmatic trials, Case reports, Case series[a]			Guidelines, Reviews, Editorials, Comments[a]		Systematic Reviews, Meta-analysis[a]
	References			References		References
Children	1 3 (O) 4 (O) 5 (O) 7 10 (O) 19 (O) 20 (O) 22 (O) 35 (O) 36 (O)	42 (D) 44 (D) 45 (M) 52 (D) 58 61 83 (D) 84 (D) 89 91 92	93 94 95 96 (O) 99 (O) 100 (O) 101 (O) 102 (O) 111 (O) 112 (O) 119 (O)	2 8 24 37 40 44 46 53 74 76 81	87 88 90 121 122	
Children, Adolescents, Adults	21 (O) 74 75			6, 16 17 23 27 28 31 (O)	38 39 50 82 90 117	25
Adolescents, Adults	29 (D) 30 (O) 33 34 (O) 43 69 (O) 72 110 (O)			56 57 115 (M) 118 (D)		54 55 86
Adults	18 (O) 59 (M) 60 (B) 62 63 64 65 66	67 68 (B) 70 (O) 71 78 (D) 103 (O) 104 105 (O)	106 (O) 107 (O) 108 (O) 109 (O) 113 (O) 119	13 26 49 51 79		77 (O)
NA/ND				9, 11 12 14 15 32 (O) 41 47 48	50 73 80 85 97 98 (O) 114 (O) 116 120	

Table 3. Categorization of the studies included in this paper *NA/ND: Not applicable, Not done.In parentheses, the biologic involved in the study: (O) Omalizumab, (D) Dupilumab, (M) Mepolizumab, (B) Benralizumab.The rest of the studies either do not refer to any specific biologic or are comparisons between several biologics. [a]Based on studies in ….*

these populations.[121–123] Since this may vary considerably from country to country our paper has focused on questions that arise when one or more of these medications are available/accessible. For this reason, these questions should be analyzed at a local level.

CONCLUSIONS

The use of biologics in severe asthma is new to many pediatric specialists and many pragmatic questions about their clinical use remain unanswered. But, in order to adequately contextualize the conclusions of this review, it is necessary to highlight several limitations that should be considered:

1. The title of our paper, "Unanswered questions on the use of biologics in pediatric asthma" responds to a need derived from the frequency with which certain topics arise among physicians treating pediatric asthma. And its "unanswered" status is a consequence of the absent/inexistent evidence available in this regard. Therefore, an answer to these questions necessarily requires the use of a low level of evidence (expert opinions, together with the personal experience of the signatories).
2. As can be seen in Table 3, many of the studies included are conducted in adult populations. Therefore, in the absence of specifically pediatric data, extrapolation to children should be made with caution.
3. In the case of studies with biologics in children included in this review (Table 3), these include double-blind randomized controlled clinical trials (DBRCT),[42,44,45,52,83,112] in vitro studies based on DBRCT data,[97] DBRCT design,[101] DBRCT reviews,[2,35,36] open randomized studies,[84] real-life studies,[3–5,10,19,20,22,100,103,113,120] and case reports or case series.[61,102]

Real-life multicenter studies in children and adolescents with asthma are needed to better evaluate the aspects discussed in this paper. Until then the only solution available, with all reservations, is based on expert opinion, with the understanding that some current answers may not be applied in the future with the emergence of new evidence.

Abbreviations

AD, Atopic Dermatitis; ADA, Anti-Drug Antibodies; AEs, Adverse Events; AR, Allergic Rhinoconjunctivitis; BMI, Body Mass Index; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; DBRCT, Double-Blind Randomized Controlled clinical Trials; EMA, European Medicines Agency; FDA, Food and Drug Administration; FeNO, Fractional Exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in 1 s; GINA, Global Initiative for Asthma IL: Interleukin; ICS, Inhaled Corticosteroids; IgE, Immunoglobulin E; LABA, Long-Acting Beta Agonist; LMICs, Low- and Middle-Income Countries; NIAID, National Institute of Allergy and Infectious Diseases; OCS, Oral Corticosteroids; ppb, parts per billion; SCA, Severe Childhood Asthma; SPT, Skin Prick Test; TSLP, Thymic Stromal Lymphopoietin

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Declaration of competing interest

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