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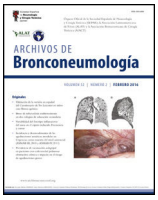

Editorial

The long road to biologic therapies for asthma in pediatric patients☆

El largo camino al tratamiento con biológicos del asma en pediatría

To the Editor,

Pediatricians often face the problem of having fewer therapeutic options in children than in adult patients, and the treatment of severe uncontrolled asthma with biologics is no exception: until a year ago, only omalizumab was available, and although we now also have mepolizumab, other biologics have been approved in adults that are not indicated in children under 18 years of age.[1] Moreover, the 2 biologics approved in pediatric patients are only approved for patients aged 6 years of age and older, and no biologics are available for patients below that age.

Although in many cases allergy plays a key role in the pathophysiology of pediatric asthma, the current level of knowledge of the role of different phenotypes and endotypes in children is limited, in part because their immune system is still in a stage of maturation and adaptation. This generates important differences in the pathophysiology of asthma between children and adults, and even in the different stages of childhood.[2] These differences may limit our ability to extrapolate the design of adult clinical trials and the results obtained to children:

- Differences in the pathophysiology of asthma means that biomarkers used in adults in clinical trials to define indications for use in biologics cannot be directly extrapolated to children: for example, eosinophil or IgE levels are usually higher in children.[3] Consequently, clinical trials performed without the inclusion of pediatric patients may lead to recommendations for biologics that are not applicable to children.
- Differences in the pediatric phenotype also mean that the main variables used in clinical trials in adults are often not the most suitable for use in children: for example, children usually have fewer symptoms between exacerbations and normal lung function.[4,5]
- Finally, differences in the underlying endotype in children and adults may mean that therapeutic targets selected for the development of new drugs based on adult models are not as effective in the pediatric patient.[6]

These circumstances are particularly important if we take into account that biologics are currently approved for different age ranges on the basis of extrapolated data: therefore, approval of a biologic in the pediatric population does not always mean that evidence of efficacy and safety has been obtained in specific clinical trials.

European Medicines Agency (EMA) regulations on the use of medicines in pediatrics have changed in recent years due to this perceived need. Historically, the lack of clinical studies in children still often means that they have to be used outside the age range indication, in other words, "off-label". This approach poses a risk to the pediatric patient because labeling and dosage recommendations are inadequate, and differences between the metabolism of children and adults are well established: children are "not miniature men and women".[7] As a result, drug errors, including dosing errors and adverse reactions to drugs used off-label, are a real issue.[8] The effectiveness of the medication may also be reduced, since the pathophysiology of the disease may be different, as mentioned above with respect to asthma.

Since the 1990s, initiatives have been implemented to improve clinical research in pediatrics, and a set of obligations and rewards have been proposed, including the need to include a pediatric population in the development program of a new drug when it is destined for a disease that occurs in children. In 2007, the Paediatric Medicines Office of the EMA published the European Paediatric Regulation (Article 50[3] No. 1901/2006).[9] One of the strategies of the European Paediatric Regulation was to promote the development of the Paediatric Investigational Plan (PIP), which requires a clinical trial to be conducted in the pediatric population when pharmacokinetic study data are available from the adult population. This regulation has been a challenge, because of the lower incidence of cases, the smaller market, the need to include patients at different stages of development, the involvement of parents and adolescents in decision-making, and the regulatory and ethical aspects of research in children. All these factors hinder the conduct of clinical trials in children. Assessments performed 10 years after the implementation of this regulation show marked contrasts,[10,11] and the same is true for respiratory diseases and allergies in children, although the latest data from the World Health Organization (WHO) indicate that the burden of respiratory disease in children in the EU based on DALY (disability-adjusted life years) lies in third place after mental and behavioral disorders and neonatal pathology.[11] In 2017, areas with the highest number of completed PIPs were immunology/rheumatology (14%), infectious diseases (14%), cardiovascular diseases (10%), vaccines (10%), oncological diseases (7%) and endocrine-metabolic diseases (7%), all ahead of respiratory/allergic or gastrointestinal diseases (around

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5%). This distribution often demonstrates how research priorities are focused on adults rather than children.[11]

So, we currently have two biologics for severe asthma in children aged 6 years of age or older. Both omalizumab and mepolizumab were approved in children under 12 years of age, several years after approval in adolescent and adult patients. However, other treatments approved in adults are not available for use in children under 18 years of age, either due to a lack of clinical trial data or delays in approval, despite the fact that achieving asthma control in children as soon as possible is essential to prevent disease progression and irreversible changes.[12] Early intervention in pediatric patients can improve the prognosis of these patients in adulthood,[5] avoiding the complications of the disease itself and the side effects that could occur with the prolonged use of high-dose oral or inhaled corticosteroids.

However, the lack of specific clinical trials often means that decisions have to be made on the basis of expert opinions, prior clinical experience, or efficacy and safety data extrapolated from other populations. Possible future solutions that could be considered include strengthening the rewards and incentives system for the development of pediatric clinical trials on the one hand, and on the other, accepting the extrapolation of adult safety and efficacy data as an alternative to pediatric clinical trials provided that the necessary premises established by the EMA are met.[13,14] This will enable us to make progress in meeting the therapeutic needs of children.

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Jaime Lozano,[a] Begonya Nafria,[b] Laia Alsina[a,*]

[a] *Servicio de Alergología e Inmunología Clínica, Institut de Recerca Sant Joan de Déu, Hospital Sant Joan de Déu, Barcelona, Spain*

[b] *Patient Engagement in Research Coordinator, Institut de Recerca Sant Joan de Déu, Barcelona, Spain*

* Corresponding author.
E-mail address: lalsina@sjdhospitalbarcelona.org (L. Alsina).