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REVIEW ARTICLE

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Pediatric asthma: An unmet need for more effective, focused treatments

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Abstract

Background: Despite remarkable advances in our understanding of asthma, there are still several unmet needs associated with the management of pediatric asthma.

Methods: A two-day, face-to-face meeting was held in London, United Kingdom, on October 28 and 29, 2017, involving a group of international expert clinicians and scientists in asthma management to discuss the challenges and unmet needs that remain to be addressed in pediatric asthma.

Results: These unmet needs include a lack of clinical efficacy and safety evidence, and limited availability of non-steroid-based alternative therapies in patients <6 years

of age. An increased focus on children is needed in the context of clinical practice guidelines for asthma; current pediatric practice relies mostly on extrapolations from adult recommendations. Furthermore, no uniform definition of pediatric asthma exists, which hampers timely and robust diagnosis of the condition in affected patients. **Conclusions**: There is a need for a uniform definition of pediatric asthma, clearly distinguishable from adult asthma. Furthermore, guidelines which provide specific treatment recommendations for the management of pediatric asthma are also needed. Clinical trials and real-world evidence studies assessing anti-immunoglobulin E (IgE) therapies and other monoclonal antibodies in children <6 years of age with asthma may provide further information regarding the most appropriate treatment options in these vulnerable patients. Early intervention with anti-IgE and non-steroid-based alternative therapies may delay disease progression, leading to improved clinical outcomes.

KEYWORDS
asthma management, omalizumab, pediatric asthma, unmet need

1 | INTRODUCTION

Asthma is a chronic airway condition affecting approximately 10% of children in the European Union (EU)[1] and North America,[2,3] with an even higher prevalence observed in some other areas, such as South America.[4] Asthma comprises a serious personal, familial, and global economic burden, including school and employment absences, hospital care, and drug expenditures.[5,6] To an even greater extent than has been observed for adult patients with asthma, considerable variation in pediatric asthma severity, natural disease history, clinical phenotype, and response to therapy can exist between patients, establishing asthma as a condition with significant heterogeneity.[7]

Despite remarkable advances in our understanding of this condition, and the availability and current development of novel medications for the treatment of asthma, many asthma patients remain uncontrolled, which imposes a significant ongoing burden. Uncontrolled pediatric asthma is associated with increased exacerbation rate, impaired quality of life, and persisting bronchial obstruction.[8,9] Current clinical practice guidelines do not always adequately address pediatric asthma, a feature that is probably linked to the limited availability of clinical efficacy and safety data in younger patients, often resulting in an extrapolation of adult recommendations to children. This dearth of evidence may impact on local reimbursement or resourcing policies and therefore on the accessibility of potentially effective medicines for this patient population.[10]

There is an urgent need for an up-to-date assessment of the true burden and unmet needs of asthma patients, and their families, to ensure appropriate support to meet these needs. Provisions to ensure better asthma control at an earlier stage may facilitate improved quality of life and significant long-term cost savings for both asthma sufferers and society.[11] This article is a scoping review of the current unmet needs of children with asthma (Table 1) and the potential role for effective therapies in this vulnerable patient population. Content has been developed from review of the literature and synthesized with expert opinion during a face-to-face, two-day meeting with a group of international expert clinicians and scientists in pediatric asthma management.

TABLE 1 Unmet needs in pediatric patients with asthma

Lack of clinical efficacy and safety evidence of biologics in patients <6 years
Limited availability of non-steroid-based alternative therapies
Lack of available therapies for children with severe asthma
Difficult diagnosis in children
Scarcity of studies on allergen immunotherapy in children
Limited access to specialist pediatric asthma care in some countries
No uniform definition of pediatric asthma or pediatric asthma control
Inadequate pediatric focus in current clinical practice guidelines
Lack of data on asthma endotypes/phenotypes
Lack of well-defined pediatric treatable traits
Lack of molecular studies
Lack of data on personalized treatment strategies based on a phenotype (endotype) approach
Lack of treatment options for comorbidities

2 | UNMET NEEDS IN PEDIATRIC ASTHMA

2.1 | Guidelines that acknowledge the management of different asthma phenotypes

Diagnosing asthma and establishing control as early as possible in childhood are considerable clinical challenges. Clinical practice guidelines are in place to support healthcare practitioners (HCPs) in the management of pediatric asthma[12,13]; however, these may not be totally suitable to ensure optimal management of asthma in the real-life, day-to-day clinical setting. This is largely due to a lack of relevant evidence and different patterns of asthma in children.[13]

Asthma is not a simple, single disease entity; the existence of a variety of clinical presentations (phenotypes) and underlying mechanisms (endotypes), coupled with the presence of symptoms that overlap with other acute and chronic conditions, make the diagnosis of asthma challenging for HCPs.[14] Although the role of allergy in pediatric asthma has been highlighted,[15,16] our current understanding of the role of phenotypes and endotypes is limited in children and is complicated by the fact that the immune system in children is constantly developing and maturing. Therefore, it is likely that differences exist in pathophysiology and inflammatory signaling in asthma in children compared with adults, and even compared with children of different ages.[17,18] It is for this reason that molecular studies are required to provide a much deeper understanding of the immunologic mechanisms underlying allergy and asthma in association with developmental milestones (and indeed underlying each distinct phenotype).[19] Such knowledge may facilitate the development of mechanism- or phenotype-driven treatment options in children to establish control in the early stages of asthma.

The Global Initiative for Asthma (GINA) definition of asthma was recently updated; asthma is proposed to be *"a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"*.[12]

The direct application of this definition to pediatric patients remains restricted, especially in patients <6 years of age. Wheeze, although a hallmark of pediatric asthma, can be a symptom of other conditions too and can be misdiagnosed as asthma in young children, leading to the inappropriate prescription of inhaled corticosteroids (ICS). Furthermore, the relationship between pre-school wheeze and asthma remains debatable.[20] In children, an increase in post-bronchodilator reversibility as measured by forced expiratory volume in one second (FEV_1) of >12% predicted is recommended to fulfill the variable expiratory airflow limitation criterion of the definition of asthma.[12] Outside of an acute exacerbation setting, 12% improvement can be difficult to demonstrate in children with asthma, in whom FEV_1 levels are most often in the normal range.[21] Furthermore, airflow limitation assessment with spirometry or impulse oscillometry can be challenging in young children, making it difficult to conclusively meet the definition of asthma.[22,23] In these cases, asthma diagnosis is essentially based on clinical criteria. Of note, the National Institute for Health and Care Excellence (NICE) guidelines recommend fractional exhaled nitric oxide (FeNO) testing in children (5–16 years) in cases of diagnostic ambiguity.[24]

The inability to reach a robust and universal definition of asthma is not a new phenomenon and is evidenced by the differing approaches currently in existence. These discrepancies have been extensively discussed by the International Consensus on (ICON) Pediatric Asthma group, where they also highlighted a lack of distinction in any current asthma guideline between the definitions of adult versus pediatric asthma.[13] Of note, the Lancet Asthma Commission has recently put forward a new proposal to use "asthma" to describe a collection of overlapping symptoms, rather than as a single disease entity or an indicator for a specific pathophysiology.[25] Interestingly, this approach is similar to the original use of the word "asthma" by Homer more than 2500 years ago.[26]

Furthermore, it is not clear to what extent the severity gradient observed among asthma patients and mentioned in guidelines, that is, mild, moderate, and severe asthma, represents a continuous spectrum or reflects differences in pathophysiology. Such labeling systems are likely to affect future treatment strategies as children with asthma mature. New data on the natural history of asthma may help to inform such therapeutic implications (Figure 1).

2.2 | Timely and appropriate referral from primary care providers

Systems of care for pediatric asthma patients vary between countries. In some countries, asthma is mainly diagnosed and cared for by general practitioners and primary care physicians (GPs/PCPs), while in other countries, children have more access to specialist care. This may have an important impact upon asthma control and access to advanced therapies. In systems where the GP/PCP plays a dominant role, referral of certain asthma patients for specialized care is often necessary. Table 2 describes a number of potential roles of the specialized care center for pediatric asthma. Although patient referral recommendations are addressed in clinical practice guidelines, failure to promptly refer a patient from primary to specialist care is a potential barrier to the effective management of pediatric asthma.[14]

In countries where a significant portion of asthma management is delivered in busy primary care clinics, GPs/PCPs are in an important position to identify uncontrolled or difficult-to-treat asthma. The importance of local factors in the primary care setting should not be overlooked; local environmental triggers of symptoms and the ability to adapt global strategy documents to suit local needs should also be considered.[27] An extensive overview of guideline recommendations for the referral of adults with asthma is available.[14] Similar guideline-defined recommendations are relatively limited for children, although the Canadian pediatric guidelines do recommend referral in the case of diagnostic uncertainty or uncontrolled asthma on medium-dose ICS.[28] It is critical that local healthcare systems have clear guidance in place to support GPs/PCPs in the referral of such patients to a specialist in appropriate instances, but this is not always available. This guidance is important as it is not feasible to expect a GP/PCP to have the time or resources to optimize treatment in difficult cases, owing to the very broad range of conditions and patients presenting to primary care facilities.[29] The use of electronic diaries and mobile health technology may significantly improve the management of pediatric asthma, and the communication between the GP/PCP and the specialist.[30,31]

Increased awareness of effective referral strategies and improved communication between GPs/PCPs and specialists may improve the rate of appropriate referrals.[29] The time to referral will ultimately depend on local healthcare regulations and resources of GPs/PCPs.[14] Local implementation of strategies to support GPs/PCPs in the delivery of pediatric asthma care and appropriate

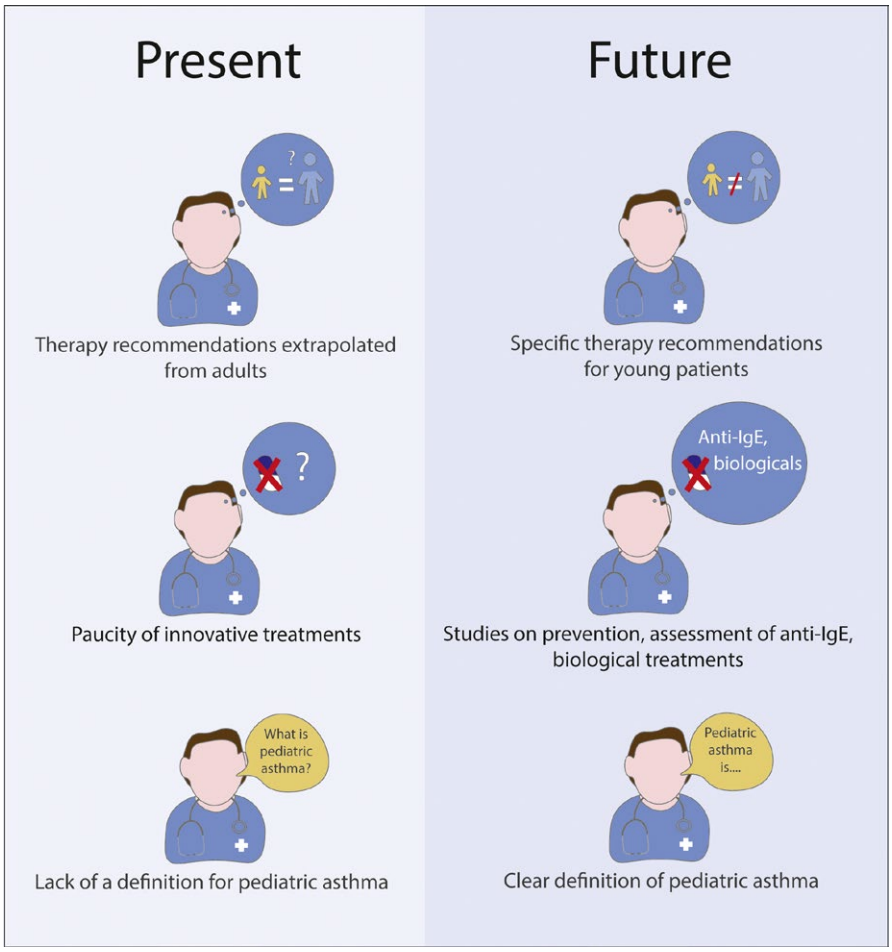

FIGURE 1 Present inadequacies and potential future realities of pediatric asthma management

referral guidelines may improve clinical outcomes for children with asthma. Referral of pediatric patients with severe asthma to a specialist should be considered with high-priority status, even if the condition is controlled.[32] This expert panel suggests the following algorithm for when referral may be considered: 3–4 courses of oral corticosteroids in a year, or a severe exacerbation requiring hospitalization, or atypical symptoms suggesting an alternative diagnosis *(unpublished)*.

TABLE 2 The roles of the specialized care center for pediatric patients with asthma

Diagnosis, including differential diagnosis
Managing severe asthma
Phenotype/endotype approaches
Personalized treatments
Clinical trials
Educational programs
Treatment-related adverse event surveys
Transition to adulthood and adult asthma services
Implementation of cooperative strategies between GPs/PCPs and asthma specialists
Biologic and other therapies reserved for severe asthmatics
Cohort studies

GPs, general practitioners; PCPs, primary care physicians

2.3 | Effective treatment options

As with adults, the ultimate goals of pediatric asthma management include adequate symptom control and reduced future risks.[12] Natural history modification and possible disease prevention are also of high importance in children.[33] Achieving asthma control usually requires pharmacological intervention, including controller medication, rescue medication, and add-on therapy, in the case of severe asthma.[12] Equally as important are the non-pharmacological treatment approaches, which are frequently underestimated. These include patient education and trigger avoidance (eg, minimizing exposure to pollutants and allergens to reduce asthma-associated morbidity).[34,35]

Corticosteroids play a central role in the pharmacological management of asthma. Over the last six decades, the clinical effectiveness of corticosteroid treatment in asthma has been demonstrated.[36-38] The mainstay controller medication used in pediatric asthma to limit airway inflammation is an ICS, as it has been shown to significantly improve lung function[39] and reduce exacerbations.[40] However, ICS dose regimens that are suitable for the pediatric population vary across different guidelines, as do the thresholds used to define low-, medium-, and high-dose ICS. There is also high variability of dose delivered according to device choice.[41] The need for guidelines to be updated according to ICS dose responses has also been highlighted previously.[42]

Furthermore, delivery via the inhaled route can be ineffective in children <5 years in whom drug deposition to the lungs may be compromised by improper inhalation technique or anatomic factors.[43] Potential side effects of their use remain an important issue in relation to parents' adherence and should always be considered by HCPs.[44] Although ICS use in children is important and effective, there are non-frequent, but potentially serious, adverse effects associated with their use. These include possible height deficits, increased susceptibility to infection, and hypothalamic-pituitary-adrenal (HPA) axis suppression, potentially leading to adrenal crisis or growth retardation in children.[44-47] As the incidence of adverse events is often dose-dependent, the minimum effective dose in order to achieve uncompromised asthma control should always be considered.[44]

As per clinical guideline recommendations, short courses of oral corticosteroids (OCS) are used to effectively treat exacerbations.[12] However, frequent OCS use for exacerbations, especially at higher doses, is associated with a wide range of adverse effects in children including growth impairment,[48] reduced bone density,[46] and behavioral effects.[49] Also, the association between OCS and bone fractures has been highlighted in a recent multivariate analysis which demonstrated a 17% increased risk of bone fracture in pediatric patients after one OCS prescription compared with none.[50] It is therefore important to monitor level of control regularly and adjust the preventative treatment accordingly. If the severity of asthma requires increasing the regular dose of ICS (or combination therapy), or OCS bursts beyond an acceptable level, it is important to consider corticosteroid-sparing strategies in this particular patient population. To this end, long-acting β_2-agonists (LABAs) are indeed available for the treatment of asthma in school-aged children and older, and they are frequently prescribed in combination with an ICS. Of note, the black box warning on medicines containing both an ICS and a LABA was recently removed by the US Food and Drug Administration, presumably affording more "peace of mind" to HCPs and caregivers of children receiving these medications. Tiotropium is a long-acting muscarinic antagonist (LAMA) recently approved for children with severe asthma ≥6 years of age, providing another treatment option for GINA step 4 and 5 patients. Furthermore, in patients ≥6 years of age with severe asthma, add-on anti-IgE therapy with omalizumab has shown clinical efficacy and also reduces OCS use.[51] Similar efficacy data are still unavailable for patients <6 years due to a lack of appropriate studies.

3 | POTENTIAL FOR BIOLOGICS AS NON-STEROID-BASED TREATMENTS IN PEDIATRIC ASTHMA

An important question in the era of stratified medicine is what can be done beyond corticosteroids. Stratified or personalized medicine recognizes that the underlying mechanisms of asthma can vary significantly between patients, and it is widely acknowledged that there is a need for non-steroid-based treatment approaches in the management of asthma, especially in children.[52]

With the rapid emergence of many biologics for the treatment of adult asthma (including anti-IgE, anti-interleukin [IL]-5, anti-IL-5Rα, anti-IL-13, and anti-thymic stromal lymphopoietin monoclonal antibody approaches),[53] there is increased interest in their potential use in pediatric patients. Establishing disease control as early as possible in pediatric asthma is critical, as is the prevention of asthma or disease progression; however, asthma management in very young patients is based largely on clinical judgment, expert opinion, and cost of medications owing to the lack of clinical evidence in this particular patient population.[54] As described previously by Szefler and colleagues, "*the younger the child, the less information there is available to guide clinicians*".[33] We would also add that the younger the child, the later he/she can benefit from medical progress.

Omalizumab is currently the only anti-IgE monoclonal antibody with an approved indication in children ≥6 years (EU). In the EU, omalizumab is approved as add-on treatment in patients ≥6 years of age with severe persistent allergic asthma that is not sufficiently controlled with ICS plus LABA therapy[55] and in the United States (US) for patients ≥6 years with moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are not sufficiently controlled with ICS monotherapy.[56] This labeling excludes asthma patients <6 years who might benefit from anti-IgE therapy and limits the add-on therapy options available to physicians. Studies demonstrating the efficacy and safety of omalizumab in pre-school children and milder patients are currently in planning, while similar studies involving other biologics are urgently required. Mepolizumab is an anti-IL-5 monoclonal antibody approved for the treatment of patients ≥18 years (≥12 years in some countries) with eosinophilic asthma, and it is encouraging to note that other anti-IL-5Rα and anti-IL-4Rα therapies are currently under investigation in patients ≥12 years.[53] Although the results of studies of these biologics, including mepolizumab[57,58] and benralizumab,[59,60] are a very positive step forward for patients with asthma, it is disappointing that only a limited number of adolescents were included in these initial trials.[61] Furthermore, the efficacy of these promising therapies in patients below this age threshold (<12 years) is entirely unknown. It would be unfortunate if today's pediatric patients reach adulthood without getting the opportunity to experience the potential benefits that any of these biologic therapies may have had on their asthma and quality of life. For this reason, more studies of longer duration that include children of all age groups are urgently needed to provide additional data on the efficacy of these biologics. However, the authors acknowledge that the relatively low prevalence of severe refractory asthma in younger children may impede the recruitment of these patients for such studies.

Furthermore, safety is an urgent, outstanding issue when treating children with asthma—there is a serious lack of safety information regarding biologics (with the exception of omalizumab) for patients below the age of 18 years. While over 10 years of omalizumab use has suggested a favorable long-term safety profile in children and adolescents,[62] all other biologic therapies need to demonstrate the

same as soon as possible. Results of such studies may allow better informed treatment recommendations to be disseminated by guideline committees in the future.

An unmet need that is particularly relevant for young children (particularly those <6 years) with asthma (where significant impact could be made on the course of disease at this early stage of life) is the possibility of preventing (or delaying) the progression of asthma severity using effective therapeutic intervention at a young age.[63] Although we have observed some promising data with immunotherapy in children (5–12 years) to date,[64] studies assessing current asthma therapies in infants have been sparse. It is possible that omalizumab can modify disease or prevent disease progression, which are characteristics that will be evaluated in the Preventing Asthma in high Risk Kids (PARK) study in the United States (https://clinicaltrials.gov/ct2/show/NCT02570984). In this study, which is due to commence in 2018, children aged 2–3 years with a history of 2–4 wheezing episodes in the previous year and positive aeroallergen allergy will receive omalizumab or placebo for 2 years and will be followed for an additional 2 years. The co-primary outcomes of the PARK study are (a) active asthma diagnosis and (b) asthma severity assessed by the validated composite asthma severity index (CASI),[65] which combines symptoms, medication use, and lung function into the score (time frame: final 12 months, during the 2-year observation period off the study drug). If this study demonstrates a significant benefit of anti-IgE therapy in infants, its use in younger asthma patients will be worth considering in the future.

Ultimately, owing to the known heterogeneity that exists among children with asthma, it stands to reason that a personalized treatment rather than a universal "one-size-fits-all" approach should be developed. The promising results of the recent Individualized Therapy for Persistent Asthma in Young Children (INFANT) study support this, wherein 74% of children showed clinically relevant responses to one treatment over others, and blood eosinophils and aeroallergen sensitization status were shown to be useful and clinically accessible biomarkers to guide response to treatment.[66]

4 | UNANSWERED QUESTIONS FOR OMALIZUMAB THERAPY IN THE PEDIATRIC ASTHMA POPULATION

Considerations for omalizumab therapy in pediatric patients are listed in Table 3. Viruses, particularly rhinoviruses, are associated with the majority of asthma exacerbations in children, which occur frequently during the autumnal season upon the recommencement of the school year.[67] Interestingly, reduced susceptibility to virus-induced asthma exacerbations with omalizumab in children (6–17 years) has been demonstrated.[67,68] Mechanistically, this exacerbation reduction is believed to be linked to enhanced interferon (IFN)-α responses.[67] A similar impact on anti-viral responses in children has not yet been demonstrated with another biologic agent, but the results of such studies would be important additions to our scientific knowledge on exacerbation prevention and reduction in children. The true potential impact of early-life IgE blockage on the future development of asthma remains to be further investigated. The results of the PARK and EXPECT[69] (discussed later) studies may add further insights.

TABLE 3 Considerations for omalizumab use in the pediatric asthma population

Reduction of viral-induced exacerbations
Potential to treat multi-morbidities, including allergic rhinitis and food allergy
Limitations of the dosing table
Potential for home administration
Good safety profile

Pediatric asthma patients often suffer significant multi-morbidity, including allergic rhinitis and food allergy.[70,71] Importantly, omalizumab has been shown to be effective in allergic rhinitis (by significantly improving total Rhinitis Quality of Life Questionnaire score).[72] Furthermore, the efficacy of omalizumab in patients with food allergy is encouraging; omalizumab decreased or eliminated food allergy symptoms upon accidental exposure to foods against which they were sensitized.[73] However, there is still a paucity of evidence for similar therapeutic action in affected patients <6 years of age. This suggests an unmet need to investigate the efficacy of omalizumab, and other anti-IgE therapies, in young children with multi-morbid asthma.

Patients with allergic multi-morbidities are more likely to be sensitized to a multitude of allergen molecules as a consequence of the so-called "molecular spreading" process.[74] These patients are easily identifiable by serum IgE testing with microarray technology, are less responsive to allergen immunotherapy, and would probably benefit from a more comprehensive anti-IgE treatment.[75] Specific trials of the impact of anti-IgE therapy in extremely polysensitized asthma patients are still lacking.

Although omalizumab is available for certain asthma patients aged 6–17 years, there is still room to improve accessibility to this drug. The omalizumab dosing table is an important consideration, whereby serum IgE levels and body weight must be taken into account when calculating drug dose. However, patients in whom pretreatment serum IgE levels exceed the upper limits of the dosing table are deemed ineligible for this therapy,[76] even though it is not uncommon for patients with severe disease to show such excessively high IgE levels. This is particularly frustrating for families and physicians of children for whom there are no alternative anti-IgE therapies currently licensed. Studies assessing omalizumab in patients with total IgE >1500 IU/mL, new protocols with decreasing doses, or less frequent administration after omalizumab initiation in controlled patients are needed. Moreover, growth curves of "normal" total IgE levels throughout childhood have been recently reported[77] and may help in revising and expanding the criteria for eligibility for omalizumab treatment. Finally, the fact that there are two parameters (serum IgE and body weight) involved in the dosing table may be an added complication for some physicians.

As omalizumab is a treatment that is administered every 2 or 4 weeks, the opportunity to administer the medication at home would be of great benefit for both patients and busy parents/guardians. Home administration is currently performed in France by a nurse or GP. However, the convenience of home use must be balanced with the risk of omalizumab-associated anaphylaxis, a serious, albeit very rare occurrence, affecting 0.1%–0.2% of patients receiving this biologic agent.[78]

Alternative biologic options with safe and flexible dosing regimens are welcome. As new biologics such as anti-IL-5 and anti-IL-4/-13 therapies are emerging, it will become increasingly important to ensure that physicians have optimal educational support when choosing the appropriate biologic for the appropriate patient to maximize the clinical outcomes for the pediatric patient. This may include the identification of an easily accessible biomarker to distinguish between inflammatory phenotypes in children. Further studies of the safety and efficacy of these biologics in younger patients will certainly help to fill current gaps in our knowledge.[33]

5 | OMALIZUMAB AND PREGNANCY

An observational study assessing the safety of omalizumab during pregnancy is also currently underway. The EXPECT omalizumab pregnancy registry (https://clinicaltrials.gov/ct2/show/NCT00373061) records the incidence of congenital anomalies in babies born to asthmatic mothers who were exposed to ≥1 dose of omalizumab 8 weeks before conception or at any time during pregnancy. Interim analysis of the EXPECT study has revealed no increase in the prevalence of major anomalies in babies of asthmatic mothers who were exposed to omalizumab (via the feto-maternal barrier) compared with the general asthma population.[69] Observational data for the newborn are also collected at birth, and at 6 and 12 months post-delivery (and up to 18 months post-delivery if the infant is being breastfed). Therefore, when completed, this study is expected to provide much-needed safety information on the use of omalizumab during pregnancy, while also facilitating the assessment of longer-term preventative and safety outcomes in these children. Similar studies involving the assessment of other biologic therapies would be highly beneficial.

6 | FINAL CONSIDERATIONS

Asthma is a condition that often begins in young children. If asthma is adequately treated to establish control early in life, it is possible that these young patients will experience improved quality of life, improved lung function, reduced morbidity and asthma severity as adults, coupled with potential cost savings for healthcare systems. This hypothesis is supported by the recent Finnish experience, in which improved asthma control resulted in significant cost savings through reduced healthcare utilization.[79] In order to achieve this globally, the unmet needs in the management of asthma must be addressed.

As asthma is one of the most common conditions affecting children,[1] both primary care providers and specialists play important roles in diagnosis and management.[29] Furthermore, dissemination and implementation of evidence-based guidelines to ensure efficient and appropriate escalation of therapy are critical.

There is still a paucity of clinical evidence available, or being generated, to support specific treatment (including biologic) recommendations in all children, especially those <6 years of age, as well as a lack of non-steroid-based treatment options indicated for or assessed in this age group. More adolescents and young children must be accommodated in ongoing and future planned clinical trials of biologic therapies. Through studies like these, clinical data may be used to support guideline committees in making informed recommendations for all patients with asthma. Studies exploring the potential for asthma prevention or disease modification are urgently needed also. The inclusion of tools to support the prevention of long-term effects of childhood asthma should be considered by committees for future asthma guidelines; these could include recommendations for continuous monitoring of spirometry over time to map lung function during childhood, the use of the CASI (as is being employed in the PARK study), and an increased emphasis on the use of technology to monitor treatment adherence.[80] Further biomarker studies in children to build upon current evidence for stratified treatment approaches are also encouraged, to ensure timely and early therapeutic intervention to maximize clinical outcomes.

An increased focus on children in the context of asthma guidelines would be welcome; current pediatric practice often relies on extrapolations from adult recommendations due to a lack of available clinical trial data in young children and adolescents. Uniform and conclusive definitions of pediatric asthma and pediatric asthma control are needed. Studies assessing safety and efficacy of biologics with outcomes that are relevant to pediatric asthma patients are warranted, including the impact on the quality of life of the child and caregiver as composite end-points. The outcomes of these studies may then be used as evidence to support specific treatment recommendations in clinical practice guidelines, which are directly relevant for younger patients, and which would resonate with parents/guardians and healthcare practitioners. Findings may also facilitate label modifications of certain therapies to include use in younger patients. Emerging therapies with novel targets and mechanisms of action also need to be studied in the pediatric patient population to ensure that therapy can be optimized for individual patients, regardless of age, disease severity, or endotype.

Since the approval of omalizumab over ten years ago, there have been many studies demonstrating its benefits in children ≥6 years of age; however, the biologic therapeutic options available to younger asthma patients are limited. With more evidence of efficacy and safety in this vulnerable patient population, there is considerable potential for early intervention with omalizumab in these very young patients to improve clinical outcomes and possibly reduce disease progression and/or severity. Studies that demonstrate efficacy of omalizumab in younger patients are needed and are planned. Evidence of disease-modifying and/or disease prevention potential

of omalizumab in pediatric asthma is needed to support the use of omalizumab in younger patients with uncontrolled disease who may significantly benefit from such therapy, but who are currently excluded. This unmet need may be addressed in part by the PARK study. Earlier intervention with omalizumab in appropriate patients may reduce or prevent the use of corticosteroids, inhaled or systemic, to maintain control in a patient population that is particularly vulnerable to adverse events associated with ICS or OCS.

Optimal management of pediatric asthma also involves the critical step of specialist referral of uncontrolled or difficult-to-treat patients in countries where asthma treatment is largely delivered by the GP/PCP.[14] An increased understanding of the potential benefits of anti-IgE therapy in multi-morbid asthmatic children is also needed to ensure that patients are optimally treated, with specific label changes implemented where appropriate.

Finally, it is widely acknowledged that there are many unmet needs which remain to be addressed in the management of pediatric asthma patients. Prevention measures, biomarker analyses, and age-specific treatment recommendations are just some of the ways in which the management of this condition may be driven forward in order to benefit as many patients and families as possible.

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DISCLOSURE

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AUTHOR CONTRIBUTION

All authors were involved in the conception, drafting, and critical review of this article. All authors approved the final version to be published and agree to be accountable for all aspects of this work.

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