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Review

New insights into the treatment of severe asthma in children

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EDUCATIONAL AIMS THE ARTICLE WILL ASSIST THE READER TO:

- Be aware of the definition of severe, therapy-resistant asthma and the need to distinguish this from difficult-to-treat asthma
- Be aware of the intensive development in new classes of inhaled corticosteroids and bronchodilators
- Increase their knowledge of biological therapies targeting inflammation and impaired immunity
- Discuss the fact that the majority of studies have been conducted in adults and be critical concerning extrapolation to paediatric populations.

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SUMMARY

Severe asthma accounts for 0.5% of the general paediatric population and 4.5% of children with asthma, representing the major burden of asthma-health-care-associated costs. After ensuring a diagnosis of asthma and excluding difficult-to-treat patients with co-morbidities and non-adherence profiles, there remains children with real therapy-resistant asthma for whom the recommendations are to treat beyond guidelines. We describe new insights into the treatment of severe asthma in children, regarding both "classic drugs" (corticosteroids, bronchodilators) and innovative biological therapies targeting airway inflammation and impaired innate immunity. All of these new avenues remain to be studied and validated in children and will require fine clinical and biological phenotyping.

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Abbreviations: ATS, American Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; ACT, asthma control test; FEV1, forced expiratory volume in one second; FeNO, fraction of exhaled nitric oxide; BMPRII, bone morphogenetic protein receptor type II; GLCCI1, glucocorticoid-induced transcript 1; GRα, glucocorticoid receptor α; GRβ, glucocorticoid receptor α; GRE, glucocorticoid-responsive elements; HDAC2, histone deacetylase 2; IL-, interleukin; ADRB2, adrenoceptor beta 2; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; HFA, hydrofluoroalkane; MMAD, mass median aerodynamic diameter; CIC, ciclesonide; BUD, budesonide; FLUT, fluticasone propionate; PEF, peak expiratory flow; MAPK, mitogen-activated protein kinases; Nrf2, nuclear erythroid 2-related factor 2; COPD, chronic obstructive pulmonary disease; SAL, salmeterol; ICAM-1, intercellular adhesion molecule 1; FDA, Food and Drug Administration; EMA, European Medicines Agency; TSLP, thymic stromal lymphopoeitin; NEJM, New England Journal of Medicine; AQLQ, Asthma Quality of Life Questionnaire; DREAM study, Mepolizumab for severe eosinophilic asthma; IFN-, interferon; AZISAST study, Azithromycin for prevention of exacerbations in severe asthma; RSV, respiratory syncitial virus; AIR study, Asthma Intervention Research; HRQL, health-related quality of life.

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INTRODUCTION

Severe asthma accounts for 0.5% of the general paediatric population and 4.5% of children with asthma [1]. Unlike in adults [2], severe asthma in childhood is strongly associated with atopy [3], with up to 93.5% of children in the TENOR study showing atopy [4]. Severe asthma represents the major source of asthma-health-care-associated costs [5]. We sought to review new insights, both in traditional asthma treatments (corticosteroids, bronchodilators) and in new avenues which have been studied primarily in adults, such as biological, antiviral therapies and thermoplasty, and their potential transfer to severe, therapy-resistant paediatric asthma.

DEFINITION, PHYSIOPATHOLOGY

The ATS/ERS definition of severe asthma for patients ≥6 years old is asthma which, during the previous year, required treatment with medications according to GINA guidelines steps 4-5, or with

systemic corticosteroids for ≥50% of the time, to prevent it from becoming "uncontrolled", or which remains "uncontrolled" despite these interventions [6]. Severe asthma actually comprises two sub-groups: difficult-to-treat (but treatable) patients in whom control can be achieved by ensuring adherence, the avoidance of adverse psycho-social or environmental exposures and co-morbidities; and severe, therapy-resistant asthma in which treatment above and beyond standard guidelines may be considered [7–9].

In the difficult-to-treat group, it would be difficult to justify high-cost therapies such as omalizumab unless the primary goals of environmental control (exposure to smoke, allergens...) and adherence have been achieved. Indeed, after strict management of co-factors during nurse-led home visits in a group of 71 children with problematic asthma, potentially modifiable factors were identified in 79% and the interventions recommended led to control without further escalation of treatment in 55% [10]. The frequency of treatable, difficult-to-treat asthma is probably underestimated. In an ancillary study of the Childhood Asthma Management Program, adherence < 80% was proven for 75% of 140 children when measured objectively, but was self-reported for only 6% [11].

In the severe, therapy-resistant-asthma, or refractory-asthma, group, we can identify several avenues for treatment failure. Corticosteroid resistance is evaluated, after a directly observed parenteral or oral steroid trial, by ACT, FEV1, sputum eosinophil count, or FeNO improvement or normalization, with no consensual paediatric definition in terms of dose, route, length and degree of response [12]. Congenital corticosteroid resistance linked to mutations in the glucocorticoid receptor remains exceptional [13], and to date no mutations in glucorticoid receptors nor single nucleotide polymorphisms have been associated with corticosteroid resistance in airways diseases. Genetic susceptibility within asthmatic families has been studied through microarray and genome-wide association studies, indicating two genes, BMPRII and GLCCI1, associated with steroid responsiveness. Acquired steroid resistance in asthma is mainly due to Th2 pro-inflammatory cytokines and oxidative stress [14]. This resistance can, in theory, be overcome with high doses of corticosteroids at the expense of a major risk of side effects. IL-4 and IL-2 over-expressed in the airways of corticosteroid-resistant asthma, combined with IL-13, reduce glucocorticoid-receptor-α (GRα) function through phosphorylation, altering its nuclear translocation and binding to Glucocorticosteroid Responsive Elements (GRE). Nitrosylation through NO donors can also alter GRα binding affinity for corticosteroids. A second mechanism of acquired resistance, also induced by pro-inflammatory cytokines and microbial super-antigens, is the increased expression of a negative inhibitor (GRβ). A third mechanism, induced by oxidative and nitrative stress, is insufficient histone deacetylation (by HDAC2 inactivation and degradation), which is normally involved in inflammatory gene repression by corticosteroids.

Resistance to bronchodilators has also been studied. Genetic variation in the β-2 adrenergic receptor gene [15] and the IL-6 and IL-6R genes [16] has been associated with modification of the acute bronchodilator response to short-acting β-agonists, but these effects have not been demonstrated with long-acting beta-agonists [17]. Moreover, the ADRB2 genotype does not predict the pattern of response in step-up therapy when comparing LABA step-up with LTRA step-up, or to ICS step-up in children with uncontrolled asthma, despite using low-dose inhaled corticosteroids [18].

Another pitfall is to consider severe, therapy-resistant asthma as one disease [9,19]. Refractory asthma includes several clinical, biological, and probably molecular, phenotypes. The exacerbating child, obstructive or brittle asthma, fungal sensitization, eosinophilia, neutrophilia, cortico-resistance, or cortico-sensitivity, are not likely to respond equally to treatment. The second-line management of severe asthma, after confirming that a child is therapy resistant, is to explore the phenotype in order to tailor the treatment properly. Few new drugs are yet available, but many phase II/III studies are ongoing.

NEW CORTICOSTEROIDS

Inhaled corticosteroid (ICS) remains the gold-standard therapy, even for severe asthma. However, side effects linked to the high doses needed in this group of patients increase the risk of adrenal suppression and growth retardation [20].

Three pathways of development aim at providing safer inhaled corticosteroids, with the highest activity and lowest side effects. First, a pro-drug such as ciclesonide that is only converted to its active form, C21-des-methylpropionyl-ciclesonide, in the lungs, leads to the lowest oro-pharyngeal absorption. Once-daily administration, available with ciclesonide, fluticasone furoate and mometasone furoate [21] due to their high affinity to GR and slow efflux rates, may improve adherence. The development of drugs such as beclometasone HFA-134a with low MMAD might favour a maximal distal bronchial deposition of the drug [22]. Ciclesonide combines these three features and is available for children of ≥12 years in Europe. In the recent Cochrane review, an improvement in asthma symptoms, exacerbations and side effects of ciclesonide (CIC) versus budesonide (BUD) and fluticasone propionate (FLUT) was neither demonstrated nor refuted in children, but the studies were short (three months) and the maximal ciclesonide dose was 320 μg q.d. [23]. In studies focused on severe asthma in patients aged 12-75 years, 320 μg b.i.d. CIC had lower side effects than 500 μg b.i.d. FLUT in a 24-week trial [24]. In the same age group, 320 μg b.i.d. for 12 weeks was superior to 160 μg q.d. for time-to-first-exacerbation, % predicted FEV1, morning PEF, asthma-symptom score and rescue-medication use [25].

A second approach would be to add a second drug in order to overcome cortico-resistance and to reduce doses. Several drugs decrease GR phosphorylation, notably long-acting β-agonists (LABA) but also new molecules currently in clinical development, such as inhaled p38-MAPK inhibitors. Others have been demonstrated *in vitro*, in mice, and in adult COPD patients, to improve HDAC2 activity, notably theophylline which can act as an epigenetic modulator [26]. Antioxidants such as Nrf2 activators are also in development [14].

The last approach is the development of dissociated corticosteroids which are, *in vitro* and in mouse models, more effective in the trans-repression than the trans-activation of inflammatory genes [27]. Trans-activation causes the expression of anti-inflammatory genes, but also concurrently that of genes responsible for side effects (e.g., osteocalcin).

NEW BRONCHODILATORS

Long-acting bronchodilators, such as the long-acting anti-cholinergic (tiotropium) and ultra-LABAs (indacaterol, vilanterol), have recently been authorized in adult COPD. They can be administered once daily.

Studies have been conducted with tiotropium, available with the Handihaler® and Respimat® devices, in adults with severe asthma of fixed, obstructive phenotype. Despite an increase in cardiovascular disease and mortality in adults with the Respimat 5 and 10 μg device in COPD [28,29], studies in asthma have been conducted with both devices. A phase III clinical trial using 5 μg Respimat® for 48 weeks demonstrated better bronchodilation (pre- and post-dose FEV1) and delay-to-first-exacerbation when added to the usual treatment [30]. After a run-in period with 80 μg b.i.d. beclometasone-HFA, in a triple-crossover study with 14-week periods, the pre-dose FEV1 was higher when adding 18 μg