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Mini-Sympoisum: Childhood asthma: The fuss and the future

Personalized medicine in children with asthma

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EDUCATIONAL AIMS THE READER WILL COME TO APPRECIATE THAT:

- asthma is a heterogeneous disease with a huge variability in asthma phenotypes, in genetic background of patients, age, severity of asthma, risk factors and co-morbidities which may warrant different and more personalized treatment and monitoring approaches
- several patient characteristics, lung function parameters and biomarkers have been shown to predict treatment response to inhaled corticosteroids (ICS), montelukast or long-acting beta-agonists or to predict successful reduction of ICS
- the number of genes identified for the various asthma drug response phenotypes is small and limits the use of pharmacogenetics in asthma treatment to date
- e-health may allow for personalized treatment and monitoring; studies on the most feasible interventions in individual patients are needed

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SUMMARY

Personalized medicine for children with asthma aims to provide a tailored management of asthma, which leads to faster and better asthma control, has less adverse events and may be cost saving.

Several patient characteristics, lung function parameters and biomarkers have been shown useful in predicting treatment response or predicting successful reduction of asthma medication.

As treatment response to the main asthma therapies is partly genetically determined, pharmacogenetics may open the way for personalized medicine in children with asthma. However, the number of genes identified for the various asthma drug response phenotypes remains small and randomized controlled trials are lacking.

Biomarkers in exhaled breath or breath condensate remain promising but did not find their way from bench to bedside yet, except for the fraction of exhaled nitric oxide.

E-health will most likely find its way to clinical practice and most interventions are at least non-inferior to usual care. More studies are needed on which interventions will benefit most individual children.

INTRODUCTION

Asthma is the leading cause of chronic disease in children in the western world and affects approximately 1 out of 10 children [1]. Although effective medications such as the inhaled corticosteroids (ICS) and updated guidelines on asthma in children are available, a substantial proportion of children (40-70%) has only partly or even poorly controlled disease [2–7]. Guidelines suggest a one size fits all approach with a step up and step down scheme based on asthma control for all patients [3,4]. However, asthma is a heterogeneous disease with a huge variability in asthma phenotypes, in genetic background of patients, age, severity of asthma, risk factors and co-morbidities that may warrant different and more personalized treatment and monitoring approaches [8]. For example, while some children with mild to moderate asthma will benefit from treatment with ICS, others may even deteriorate on ICS and montelukast might be the preferred option. Also, in step 3 asthma treatment it would be very helpful to have more insight on which children will benefit most from the different treatment options in order to manage them with the best possible results and

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the least risk of adverse effects while being cost effective. Although in most children symptom based-management may be sufficient, others will need more intense monitoring programs to achieve better outcomes [9]. Additionally, patient preferences and their individual goals of treatment may play an important role in choosing the most appropriate treatment [10–14].

Therefore the aim of personalized medicine for children with asthma is to provide a tailored treatment and monitoring strategy, which is more safe, leads to faster asthma control, has less adverse events and may be cost-saving. This review aims to summarize the current state and future perspectives on personalized medicine in children with asthma.

PERSONALIZED VERSUS STRATIFIED TREATMENT

Personalized medicine is the customization of health care tailored *to the individual*; it uses new technology or discovery to enable a level of personalization not previously feasible or practical. For example, in cancer therapy, genetic determinants of the tumor determine which chemotherapeutic drugs or which adjuvant therapy should be used for the best survival with the least risk of side effects. In other words personalized medicine aims to identify biomarkers or genetic features of patients most likely to respond to a medication. On the other hand, these biologic markers could be associated with little likelihood of response or even more concerning a likelihood of an adverse effect.

Personalized medicine should be balanced against stratified medicine, which classifies individuals *into subpopulations* that differ in their susceptibility to a particular disease or their response to a particular treatment. For example, in comparison to children of normal weight, obese children are less likely to respond to ICS if lung function and exacerbations are the outcomes [15]. In asthma treatment frequently stratified medicine is used, although pharmacogenetics makes personalized medicine within our reach.

Stratified medicine may be particularly useful in predicting treatment response.

PREDICTING TREATMENT RESPONSE

Inhaled corticosteroids versus montelukast

Several studies addressed the question whether response to treatment may be predicted by clinical markers, lung function, biomarkers and/or genetic polymorphisms. Anticipating treatment response may improve symptoms more quickly and prevent side effects of treatment in susceptible individuals. However, one should be aware that phenotypic or genetic predictors of long-term treatment response depend on the definition of outcome, like Forced Expiratory Volume in 1 second (FEV1) or asthma control days [16,17].

In children with persistent asthma who require step 2 asthma treatment all guidelines prefer ICS over leukotriene receptor antagonists (LTRA), however, some children might benefit more from a LTRA [18]. In a cross over trial in 126 children with mild-moderate asthma, where response to ICS or LTRA was defined as an improvement of at least 7.5% predicted in FEV1, most children had a differential response [19]. Children were more likely to respond better to fluticasone than to montelukast if they used more bronchodilators, had higher bronchodilator response, higher fractional exhaled nitric oxide (FeNO) levels, higher eosinophil cationic protein (ECP) levels or lower methacholine PC_{20} and pulmonary function values. Younger age and shorter duration of asthma were associated with a more favorable outcome on montelukast [19]. With asthma control days as a primary outcome, FeNO was both a predictor and a response indicator in discriminating the difference in treatment response between fluticasone and montelukast [20]. In a second study, parental history of asthma, elevated FeNO, low PC_{20} values, or a history of ICS use predicted better long-term clinical and lung function outcomes with ICS compared to LTRA [21]. In contrast, the ratio between urinary leukotriene E4 to FeNO predicted a better response in FEV1 and asthma control days of montelukast over fluticasone in children with mild-moderate asthma [22]. (Table 1)

Table 1
Step 2 treatment: ICS vs montelukast

Favors ICS response	Favors LTRA response
FEV1 as outcome: - Higher SABA use - higher bronchodilator response - higher FeNO - higher ECP levels - lower methacholine PC(20) - lower pulmonary function values Asthma control days as outcome: - higher FeNO Asthma control and lung function as outcome: - parental history of asthma - higher FeNO - low PC_{20} values - history of ICS use	FEV1 as outcome: - Younger age - Shorter duration of asthma Asthma control and lung function as outcome: - urinary leukotriene E4/ FeNO ratio

As needed versus daily ICS

Four studies assessed whether daily ICS is superior to as needed ICS use in children with mild asthma, however none of them studied predictors of successful response to as needed treatment as compared to daily ICS [23–26].

Step 3 treatment

In children who are not well controlled on low dose ICS, step up in treatment may be required and 3 potential options are available: doubling the dose of ICS, adding a long acting beta-2 agonist (LABA) or adding a LTRA. If we were able to pick out the best option for each individual child, over – and under-treatment might be avoided and asthma control established quicker. In a crossover study in 182 children with uncontrolled asthma, the 3 treatment options were compared and the vast majority of patients showed a differential response to the treatment options [27]. Neither methacholine PC_{20} values, or FeNO, or genotype at position 16 of the β_2-adrenergic receptor, nor FEV1 or bronchodilator response (post-hoc analysis) predicted to which treatment option patients would respond best. (Table 2) However, higher baseline scores on the Asthma Control Test (ACT) or childhood Asthma Control Test (C-ACT) predicted a greater probability that the best response would be to LABA step-up [27]. In a post hoc multivariate analysis higher impulse oscillometry reactance area predicted higher FEV1 response to LABA add on compared to ICS step up

Table 2
Predictive factors for step 3 treatment (doubling ICS, adding LABA, adding LTRA)

Predictor	Effect
- baseline FEV1	Not predictive
- bronchodilator response	Not predictive
- baseline FeNO	Not predictive
- (C-) ACT > 19	Favors LABA
- methacholine PC_{20} values	Not predictive
- genotype at position 16 of the β_2-adrenergic receptor	Not predictive
- no history of eczema	
- higher IOS reactance area	Favors LABA
- race	Favors LABA Not predictive*

* In children with eczema, black children responded better to LABA step-up, white Hispanics to LTRA step-up.