Personalised medicine in paediatric asthma

Dr. Marielle Pijnenburg
Erasmus MC, Sophia Children's Hospital
University Medical Centre
Dr Molewaterplein 60
3015 GJ Rotterdam
NETHERLANDS
m.pijnenburg@erasusmc.nl

AIMS

After this presentation participants

- recognize what patients/ caregivers expect from personalized medicine
- are able to name the potentials and limitations of systems biology for precision medicine in children with asthma

SUMMARY

Personalized medicine may be a misleading term. In this presentation a mother of a child with asthma will talk about her expectations on personalized medicine. For patients and parents personalized medicine is often ‘personal medicine’, care targeted on the individual, taking into account the specific expertise of patient and/or parents on his/ her disease. This might be achieved by ‘patient and family centred care’.

To avoid misunderstandings nowadays the term ‘precision medicine’ is more commonly used. Precision medicine is the customization of health care tailored to the individual; it uses some kind of technology or discovery enabling a level of personalization not previously feasible or practical. The NIH defines precision medicine as an ‘emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person’.

Precision medicine should be discerned from stratified medicine, which classifies individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a particular treatment.

Why do patients need precision medicine?

Asthma is a highly heterogeneous disease with, amongst others, large variations in genetic background, severity, inflammatory patterns, triggers and risk factors. Many different phenotypes and endotypes have been identified, e.g. the preschool child with viral wheezing may need a completely different approach than an adolescent with severe therapy resistant asthma. Asthma guidelines advocate a one size fits all approach in all patients, which may be beneficial in most children, but may be not in others. Response to treatment, necessity of frequent monitoring and prognosis may differ substantially between children with asthma. Therefore the aim of precision medicine for children with asthma is to provide a tailored treatment and monitoring strategy for the individual, which is more safe, leads to faster asthma control, has less adverse events and may be cost-saving.

Systems biology and precision medicine

Numerous environmental, genetic, microbial, epigenetic factors interact to lead to signs and symptoms of ‘asthma’. The study of systems of biological components, which may be molecules, cells, organisms or entire species is called systems biology.
In this presentation examples are given on how genetics, metabolomics and exposomics may be used in personalized medicine for children with asthma.

**Genetics**

Genetic information may be helpful in prediction, monitoring and in treatment (pharmacogenetics) of patients with asthma. Genes involved in asthma development may be different from those involved in asthma severity and lung function decline. Several loci have been identified in GWAS with the 17q21 locus the most highly replicated. However, genes found in GWAS only explain a small degree of the heritability of asthma and a multigenetic approach is necessary for prediction of asthma, although high sensitivity and specificity may not be expected.

A recent study by Bonnelycke and co-workers showed an example how genetics can be used for risk assessment. In this study GWAS in 2-6 year old children with recurrent severe exacerbations CDHR3 was identified as a susceptibility locus, and patients with 2 risk alleles were at a 1.7 higher risk of hospitalization and severe exacerbations.

Although current asthma treatment is effective in most patients, response to treatment is heterogeneous. For the three main asthma therapies (ICS, beta-2 agonists and LTRA) response is partly genetically determined, although the number of genes identified for the various asthma drug response phenotypes remains small. Pharmacogenetics is the study of the genetic basis for interindividual differences in the response to drugs with the goal to identify patients with good response and reduce side effects and cost of medications. The Arg16Gly single nucleotide polymorphism is the best studied SNP and the Arg16Arg polymorphism has been associated with an impaired therapeutic response to LABA.

**Metabolomics**

Current monitoring strategies for respiratory diseases are mainly based on clinical features, lung function and imaging. As airway inflammation is the hallmark of many respiratory diseases in childhood, biomarkers that assess the presence and severity of airway inflammation might be helpful in both diagnosing and monitoring paediatric respiratory diseases. Biomarkers may play a role in prediction of asthma, risk management, assessing or predicting response to treatment and in the identification of new pathways and possible therapeutic targets.

Eosinophils in blood may be the most simple biomarker in asthma and are associated with an increased risk of later asthma in preschool children, and predict response to omalizumab, mepolizumab and reslizumab. Therefore, they may be particularly useful in identifying patients who will benefit from these expensive biologicals.

The analysis of volatile organic compounds (VOCs) in exhaled breath (EB) and biomarkers in exhaled breath condensate (EBC) may be helpful in diagnosing and monitoring asthma in children. A recent review on EBC in asthma showed that pH in EBC is lower in asthmatics, and even lower if asthma is poorly controlled. Higher levels of aldehydes are generally found and reduced glutathione levels during exacerbations. For eicosanoids and TH2 cytokines results were more variable. VOC profiles are able to discern asthma from healthy with high predictive value and predict response to treatment. There is some correlation with asthma control, less with asthma severity.

Lack of standardization of collection methods and analysis techniques, lack of longitudinal studies and validation studies hampers the introduction of EB and EBC in clinical practice.

**Exposomics**

Fifty percent of worldwide mortality is attributable to a few environmental factors: air pollution, smoking and diet. Therefore, the ‘exposome’ plays an extremely important role in health and disease.
Most studies on exposure are however not very accurate, not measured at real-time and measure only 1 exposure. New technologies may enable to measure multiple exposures more accurately.

Integrating genome, epigenome, exposome, transcriptome, microbiome and metabolome in a system-wide approach may lead to new insights in asthma, lead to more accurate disease endotypes and ultimately to precision medicine. However, several challenges have to be overcome. Handling of large, complex data sets and integration of data sets and analysis is a huge computational challenge. Translation in a format which is appropriate for clinical decision making in individual patients is another challenge. Then, cost-benefit of these approaches is not known.

Conclusions

- For patients ‘personal medicine’, which may be attained with patient and family centered care is very important
- ‘Personalized medicine’ for children with asthma is a developing field
- Treatment and monitoring on genomics/ metabolomics/exposomics may benefit selected children with asthma
- Pharmacogenetics may help in choosing the right medication for the right child, preventing adverse effects
- Metabolomics in EB and EBC remain promising but still a research tool
- Exposomics is a new dimension which has to be developed

REFERENCES