Editorial

Diamant, Zuzana; van den Berge, Maarten; Hanania, Nicola A

Published in:
Current Opinion in Pulmonary Medicine

DOI:
10.1097/MCP.0000000000000650

Publication date:
2020

Asthma: a modifiable disease on a crossroad

Zuzana Diamant[a,b,c], *Maarten van den Berge*[d], *and Nicola A. Hanania*[e]

While asthma is an old disease, we have come a long way to better understanding this syndrome in the last few years. More recently, there has been a substantial increase in our insights into the immunological mechanisms underlying the pathogenesis of asthma which helped define several phenotypes and endotypes [1]. Along with mapping of several endogenous pathways related to asthma which drive the development of targeted therapies, an increasing number of both external and internal factors inducing or modulating these pathways have also been identified. Our better insight and understanding of 'modifiable' factors of asthma will likely improve our approach to its management and thus lead to better outcomes in patients struggling with this disease.

In this issue, Sánchez-García *et al.* [2], discuss the potential risk factors of asthma from in-utero and maternal exposures to infancy and childhood risk factors and point out the role of few preventive strategies that have been studied or need to be examined. Bontinck *et al.* [3] report on the effects induced by the exposome, represented by air pollutants, on human well being in general and, specifically, on airways and lung health. Air pollutants including particulate matter, NO_2 and ozone which arise from road traffic, industries and other human polluting activities, trigger upper and lower airway inflammation and, thus, can both induce and exacerbate airway diseases such as rhinitis and asthma. In close association with this topic, Steelant *et al.* [4] report on the epithelial dysfunction and its consequences on chronic respiratory diseases. Furthermore, interesting new insights on both external and internal disease-modifying factors, that is the environmental and 'endogenous' microbiome, are addressed by Kozik and Huang [5]. They discuss several recent findings underscoring the accumulating evidence that within defined time-windows in life, microbiota have an important (immune) modifying role in asthma pathogenesis and in shaping the asthma phenotype. In addition, they address the interactions of both indoor microbiome (or aerobiome) and 'endogenous' microbiome with environmental factors (e.g. allergens, ozone, etc) and their effects on asthma.

Apart from environmental factors, the clinical expression of asthma in individual patients is composed of multiple, partly overlapping, pathophysiological features and their underlying mechanisms. To implement precision medicine into daily practice, Agusti *et al.* [6] introduced the holistic concept of treatable traits. The bottom line, this approach comes down to proactive identification of all disease-related components within individual patients that can be treated as part of a personalized management plan. It this issue, Ulrik *et al.* [7] provide an update on the treatable traits topic, which is being extended to 'treatable mechanisms' by uncovering underlying molecular pathways and identifying reliable biomarkers to further refine targeted treatments in individual patients. According to Pitzner-Fabricius et al. regular exercise can improve both symptoms and inflammation [8], while both pulmonary and extrapulmonary comorbidities have a major impact on the course of asthma. Bahmer *et al.* [9] discuss the complexity of several aspects of airway remodeling, its changes throughout the life-cycle and the urgent need of adequate biomarkers to monitor treatment respons in clinical daily practice. Rogliani *et al.* [10] discuss the importance of accurately identifying and managing comorbidities especially in patients with uncontrolled disease.

The identification of molecular pathways underlying type 2 asthma has driven the development of several targeted biologics and small molecules. Alarmins [IL25, IL33 and thymic stromal lymphopoietin (TSLP)] act upstream in the inflammatory cascade through activation of dendritic cells and polarizing T cells to produce type 2 cytokines. In addition, they can directly activate several effector cells that play a

[a]Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden, [b]Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic, [c]Department of Clinical Pharmacy & Pharmacology, University Groningen, University Medical Center Groningen and QPS-NL, [d]Department of Respiratory Medicine, University Groningen, University Medical Center Groningen, Groningen, The Netherlands and [e]Section of Pulmonary and Care Medicine, Airways Clinical Research Center, Baylor College of Medicine, Houston, Texas, USA

Correspondence to Prof. Zuzana Diamant, MD, PhD, Department of Clinical Pharmacy & Pharmacology, University Groningen, University Medical Center Groningen and QPS-NL, Hanzeplein 1, Entrance 53, 9713 AG Groningen, The Netherlands. Tel: +31 0 50 3048012; e-mail: z.diamant@gems.demon.nl

Curr Opin Pulm Med 2020, 26:1–2

DOI:10.1097/MCP.0000000000000650

Table 1. Unanswered questions to be addressed for novel-targeted asthma therapies (biologics and small molecules)

Which pathway should be (preferably) targeted (in the first place) by which biologic or SM in an individual patient with an 'overlapping' phenotype/endotype?
What is the optimal duration for a given therapy in an individual patient?
What are the stopping rules for an individual-targeted therapy?
What is the long-term safety of biologics in the general asthma population and selected special populations (e.g. children, pregnant and elderly patients)?
What is the feasibility of administering a combination of biologics and/or SM and will that improve the efficacy and maintain safety of the therapies?
Can chronic use of biologics and/or SM alter the natural course of the disease or come close to actually curing the disease?
Can the use of biologics and/or SM in high-risk individuals prevent the onset of asthma?

SM, small molecules.

central role in both allergic and nonallergic asthma. As discussed by van der Veen *et al.* [11], the asthmatic inflammatory process can be shifted towards either a Th2 or a Th1 environment depending on specific macrophage subtypes present within the airway wall. Gauvreau *et al.* [12] discuss the potential of targeting TSLP in the treatment of type 2 asthma, while blocking IL33 and IL25 may help to define their respective role in (the treatment of) asthma. In line with principles of precision medicine and the increased emphasis on targeted therapies in patients with severe asthma, Vijverberg *et al.* [13] discuss the urgent need of clinically reliable biomarkers to guide targeted treatment options in pediatric patients with severe disease. Christenson [14] discusses the use of specific gene signatures representing pathways like Th2 and IL17 to explore the presence of such treatable mechanisms in individual patients.

The development and clinical implementation of targeted drugs into the management of severe asthma allows for the reduction of the overall corticosteroid load in this patient population. Slisz and Vasakova [15] advocate a holistic personalized approach to asthma management, which – apart from pheno/endotyping – should also include the overall (systemic) corticosteroid use with proactive documentation, prophylaxis and treatment of corticosteroid-related adverse events. Timely implementation of the most appropriate targeted treatment options based on adequate biomarkers should be part of the approach.

In summary, our modern understanding of the pathophysiology, triggers and risk factors of asthma have allowed us to 'think differently' about this disease. However, despite great progress in unravelling several molecular mechanisms underlying the pathogenesis of asthma and the development of several effective targeted treatment options, several questions remain unanswered (Table 1). Ongoing and future clinical studies should address these questions with the hope that this will help to further shape the precision medicine approach to asthma.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Z.D. has received honoraria for serving on advisory boards or as a consultant with ALK, Aquilon, AstraZeneca, Boehringer-Ingelheim, CSL-Behring, HAL-Allergy, MSD, Sanofi-Genzyme. Her institution has received research support from Foresee Pharmaceuticals, Novartis and Patara pharma.

M.v.d.B. reports research grants paid to his institution from GlaxoSmithKline, Chiesi, Astra Zeneca and TEVA Pharma.

N.A.H. has received honoraria for serving on advisory boards or as consultant with GSK, Boehringer Ingelheim (BI), Novartis, Sanofi Genzyme, Regeneron, Astra Zeneca and Genentech. His institution has received research support on his behalf from GSK, BI, Astra Zeneca, Novartis and Sanofi.

REFERENCES

1. Diamant Z, Vijverberg S, Alving K, *et al.* Towards clinically applicable biomarkers of asthma – an EAACI position paper. Allergy 2019; 74:1835–1851.
2. Sánchez-García S, Rial MJ, Domínguez-Ortega J. Long and winding road: from infant wheeze to adult asthma. Curr Opin Pulm Med 2020; 26:3–9.
3. Bontinck A, Maes T, Joos G. Asthma and air pollution: recent insights in pathogenesis and clinical implications. Curr Opin Pulm Med 2020; 26:10–19.
4. Steelant B. Epithelial dysfunction in chronic respiratory diseases, a shared endotype? Curr Opin Pulm Med 2020; 26:20–26.
5. Kozik A, Huang YJ. Ecological interactions in asthma: from environment to microbiota and immune responses. Curr Opin Pulm Med 2020; 26:27–32.
6. Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016; 47:410–419.
7. Ulrik CS, Vijverberg S, Hanania NA, Diamant Z. Precision medicine and treatable traits in chronic airway diseases - where do we stand? Curr Opin Pulm Med 2020; 26:33–39.
8. Pitzner-Fabricius A, Toennesen L, Backer V. Can training induce inflammatory control in asthma, or is it symptom control only? Curr Opin Pulm Med 2020; 26:56–61.
9. Bahmer T, Bülow Sand JM, Weckmann M. Lost in transition: biomarkers of remodeling in patients with asthma. Curr Opin Pulm Med 2020; 26:40–46.
10. Rogliani P, Sforza M, Calzetta L. The impact of comorbidities on severe asthma. Curr Opin Pulm Med 2020; 26:47–55.
11. van der Veen TA, de Groot LES, Melgert BN. The different faces of the macrophage in asthma. Curr Opin Pulm Med 2020; 26:62–68.
12. Gauvreau GM, White L, Davis BE. Anti-alarmin approaches entering clinical trials. Curr Opin Pulm Med 2020; 26:69–76.
13. Vijverberg SJH, Brinkman P, Rutjes NWP, Maitland-van der Zee AH. Precision medicine in severe pediatric asthma: opportunities and challenges. Curr Opin Pulm Med 2020; 26:77–83.
14. Christenson SA. The role of genomic profiling in identifying molecular phenotypes in obstructive lung diseases. Curr Opin Pulm Med 2020; 26:84–89.
15. Slisz T, Vasakova M. The burden of corticosteroid overload in severe and difficult to treat asthma: how to reduce this? Curr Opin Pulm Med 2020; 26:90–96.