DR. SVEN SEYS (Orcid ID : 0000-0002-4399-9892)

PROF. IOANA AGACHE (Orcid ID : 0000-0001-7994-364X)

DR. IRINA BOBOLEA (Orcid ID : 0000-0002-7425-2417)

MR. PAUL BRINKMAN (Orcid ID : 0000-0003-4546-8478)

PROF. MARIANA COUTO (Orcid ID : 0000-0003-4987-9346)

DR. VICTORIA DEL POZO (Orcid ID : 0000-0001-6228-1969)

DR. LIAM HEANEY (Orcid ID : 0000-0003-2063-7992)

PROF. ENRICO HEFFLER (Orcid ID : 0000-0002-0492-5663)

DR. PARAMESWARAN NAIR (Orcid ID : 0000-0002-1041-9492)

PROF. JOAQUIN SASTRE (Orcid ID : 0000-0003-4689-6837)

DR. SUSANNE VIJVERBERG (Orcid ID : 0000-0002-4579-4081)

Article type : Letter to the Editor

Corresponding author mail id : sven.seys@kuleuven.be

Severe asthma: entering an era of new concepts and emerging therapies

Highlights of the 4th International Severe Asthma Forum, Madrid, 2018

Authors

Seys SF[1,*], Quirce S[2,*], Agache I[3], Akdis CA[4], Alvaro-Lozano M[5], Antolín-Amérigo D[6], Bjermer L[7], Bobolea I[8], Bonini M[9,10,11], Bossios A[12], Brinkman P[13], Bush A[14], Calderon M[15], Canonica W[16,17], Chanez P[18], Couto M[19], Davila I[20], Del Giacco S[21], Del Pozo V[22], Erjefält JS[23], Gevaert P[24], Hagedoorn P[25], Heaney L[26], Heffler E[16,17], Hellings PW[27], Jutel M[29], Kalayci O[30], Kurowski M[31], Loukides S[32], Nair P[33], Palomares O[34], Polverino E[35], Sanchez-Garcia S[36], Sastre J[37], Schwarze J[38], Spanevello A[39], Ulrik CS[40], Usmani O[9], Van den Berge M[41], Vasakova M[42], Vijverberg S[13], Diamant Z[7,41,42]

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13843

Affiliations

[1] Laboratory of Clinical Immunology, Department of Clinical Immunology, KU Leuven, Leuven, Belgium

[2] Department of Allergy, Hospital Universitario La Paz, CIBER of Respiratory Diseases (CIBERES), Madrid, Spain

[3] Faculty of Medicine, Transylvania University, Brasov, Romania

[4] Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[5] Pediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues (Barcelona), Spain

[6] Allergy Department, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

[7] Skane University hospital, Lund University Sweden

[8] Allergy Section/ Severe Asthma Unit, Department of Pulmonology and Respiratory Allergy, Hospital Clinic Barcelona, Barcelona, Spain

[9] National Heart and Lung Institute, Imperial College London, UK

[10] Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

[11] Universita' Cattolica del Sacro Cuore, Rome, Italy

[12] Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Huddinge, and Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

[13] Department of Respiratory Medicine, Amsterdam UMC, Amsterdam, The Netherlands

[14] Department of Paediatrics and Paediatric Respiratory Medicine, Imperial College and Royal Brompton Hospital, London, UK

[15] Section of Allergy and Clinical Immunology, Imperial College London, National Heart and Lung Institute, Royal Brompton Hospital, London, UK

[16] Personalized Medicine, Asthma and Allergy - Humanitas Clinical and Research Center – IRCCS - Rozzano (MI), Italy

[17] Department of Biomedical Sciences - Humanitas University - Pieve Emanuele (MI), Italy

[18] Assistance Publique des Hôpitaux de Marseille - Clinique des bronches, allergies et sommeil, Aix Marseille Université, Marseille, France

[19] Allergy Unit, CUF-Porto, Portugal

[20] Department of Biomedical and Diagnostic Sciences, Universidad de Salamanca, Salamanca, Spain

[21] Department of Medical Sciences and Public Health "M. Aresu", University of Cagliari, Cagliari, Italy

[22] Department of Immunology, IIS-Fundación Jiménez Díaz, and CIBERES, Madrid, Spain

[23] Unit of Airway Inflammation, Department of Respiratory Medicine, Lund University, Lund, Sweden

[24] Department of Otorhinolaryngology, Ghent University, Ghent, Belgium

[25] Pharmaceutical Technology and Biopharmacy, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

[26] Centre for Experimental Medicine, Queen's University of Belfast, Belfast, UK

[27] Department of Otorhinolaryngology, UZ Leuven, Leuven, Belgium

[28] ALL-MED Medical Research Institute; Wroclaw, Poland

[29] Department of Clinical Immunology, Wroclaw Medical University, Wrocław, Poland

[30] Hacettepe University School of Medicine, Ankara, Turkey

[31] Department of Immunology and Allergy, Medical University of Łódź, Łódź, Poland

[32] 2nd Respiratory Medicine Dept National and Kapodistrian University of Athens, Medical School

[33] Department of Medicine, St Joseph's Healthcare & McMaster University, Hamilton, Ontario, Canada

[34] Dpt. Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid, Madrid, Spain

[35] Respiratory Disease Dept, Hospital Universitari Vall d'Hebron (HUVH) Institut de Recerca Vall d'Hebron (VHIR) Passeig Vall d'Hebron, CIBERES, Barcelona, Spain

[36] Allergy Unit. Hospital Infantil Universitario Niño Jesús, Madrid, Spain

[37] Department of Allergy, Fundación Jiménez Díaz, CIBER of Respiratory Diseases (CIBERES), Madrid, Spain

[38] Child Life and Health and Centre for Inflammation Research, The University of Edinburgh, Edinburgh, UK

[39] University of Insubria, Varese, and ICS Maugeri, IRCCS, Italy

[40] Respiratory Research Unit, Department of Respiratory Medicine, Hvidovre Hospital and Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[41] University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen Research Institute for Asthma and COPD Research Institute, Groningen, Netherlands

[42] Department of Respiratory Medicine, First Faculty of Medicine of Charles University and

Thomayer Hospital, Prague, Czech Republic

*: shared first authorship

To the Editor

In the past decades, new insights into molecular mechanisms of severe asthma have further unveiled its heterogeneous nature prompting the need for personalised and targeted approaches. These and several other hot topics related to severe asthma were addressed in the 4th International Severe Asthma Forum, organized by the Asthma, ENT, Immunology and Pediatric sections of the European Academy of Allergy and Clinical Immunology in collaboration with the Spanish Society for Allergy and Clinical Immunology.

Severe asthma is currently defined as asthma that requires treatment with high-dose inhaled corticosteroids combined with a second controller ± systemic corticosteroids to maintain control or, asthma that remains "uncontrolled" despite this therapy (1). While severe asthma affects 5-10% of the entire asthma population, it accounts for >80% of the total healthcare costs related to asthma. Of note, severe asthma should be distinguished from difficult-to-treat asthma for which (re)evaluation of diagnosis, precipitating triggers, treatment adherence, as well as treatment of comorbidities is recommended. To improve treatment adherence, patient education on sustained use of controller medications in combination with a proper inhalation technique is mandatory. eHealth, comprising of a variety of tools and applications, including mobile devices (mHealth), can support patient awareness, improve adherence and support disease self-management (2).

Sensitizing agents at the workplace can cause occupational asthma. Irritants are often related to work-exacerbated asthma but at high concentrations may also elicit occupational asthma. A detailed occupational history including the insight into potential sensitizers at work is an integral, but often under-emphasized, part of the evaluation of patient with severe asthma. Patients with occupational asthma due to high-molecular-weight (HMW) agents commonly present with rhinitis, conjunctivitis, atopy and early asthmatic reactions following specific inhalation challenge, while asthma exacerbations are more frequently associated with occupational asthma induced by low-molecular-weight (LMW) agents. Interestingly, the inflammatory profile triggered by HMW and LMW agents is similar (3).

As for comorbidities, chronic rhinosinusitis with nasal polyps is a prevalent upper airway comorbidity in severe asthma, responding to corticosteroids and type 2 immune response (T2)-targeted therapies. Likewise, obesity, a key component of the metabolic syndrome, is linked to severe

asthma. Asthma patients with metabolic syndrome experience worse respiratory symptoms resulting from both lung function impairment and increased airway inflammation. Obviously, proper advice on dietary intake, lifestyle adjustments and/or bariatric surgery should be part of severe asthma management.

Bronchiectasis is present in approximately 30% of patients with severe asthma. Although both diseases share overlapping features, such as symptoms, neutrophilic inflammation and airway hyperresponsiveness, common underlying pathways require further research.

Furthermore, a significantly higher prevalence of mental disorders, especially depression and anxiety, has been reported in patients with severe asthma. Patients with psychological comorbidities often present with low treatment adherence, smoking, inactivity and obesity. Hence, for severe asthma, psychological support is recommended as part of daily clinical practice.

Coinciding with a reduced response to standard treatment, severe asthma patients are often exposed to an overload of (combinations of nasal, cutaneous, inhaled and oral) corticosteroids causing adverse events which impose substantial health care costs. This clearly underscores the need for alternative treatment options enabling reduction of the overall corticosteroid dose.

Reflecting its heterogeneous nature, severe asthma comprises several different phenotypes, distinguishable by age of onset, allergy status, airway inflammatory pattern and response to treatment (4). Eosinophilic asthma is the most commonly studied inflammatory phenotype, driven by T2 cytokines and present in approximately 50% of asthmatics, with both allergic and non-allergic triggers initiating or aggravating the disease. In contrast, the relevance and driving factors in non-T2 asthma, including neutrophilic asthma, are less well-defined and often precipitated by various factors including pathogens, air pollutants, cigarette smoke, cold air or exercise (5). Finally, the pauci-granulocytic phenotype may reflect either well-treated airway inflammation or symptomatic severe asthma driven by episodic inflammatory or non-inflammatory events, e.g., airway smooth muscle (ASM) hypertrophy (6). More recent data showed that different inflammatory signatures may be present at different anatomic sites within the airways of individual severe asthma patients.

Recent insights into molecular pathways underlying the inflammatory phenotypes helped to define distinct endotypes. Presently, the sub-endotype(s) of T2 asthma are best defined. T2-driven mechanisms are involved in epithelial barrier dysfunction, airway eosinophilia, mucus hypersecretion and airway hyperresponsiveness. In these patients, biologicals targeting T2-pathways, *i.e.*, IgE, IL-4, IL-5, and IL-13, showed an overall 50-60% reduction in severe exacerbations

(7). Future studies will establish if biologicals to more upstream targets will safely deliver additional benefits, e.g. tezepelumab (anti-TSLP), which suppresses both IL4/13, IL5 pathways and also impacts non-T2 inflammatory events. However, targeted interventions so far did not achieve any disease-modifying effects and there is significant heterogeneity in treatment response due to the complexity of the T2 endotype. Additionally, recent health-economic evaluation showed that the cost of currently registered biologics for severe asthma exceeds the recommended maximal cost per quality-adjusted life-year by far.

Treatments targeting the following pathways: alarmins (e.g. TSLP, IL-25, IL-33), kinases (e.g. JAK, Pi3K), and other pro-inflammatory mediators (e.g. PGD2) are currently under clinical development while their long-term effectiveness remains to be seen. While bronchial thermoplasty may be considered for patients with severe asthma with predominant chronic airway obstruction due to ASM hyperplasia, non-T2 asthma and mixed endotypes still represent unmet needs.

Further understanding of the molecular pathways will help to elaborate accurate algorithms matching the right biological to the right patient. To this end, simple and reliable biomarkers are indispensable, which adequately reflect the underlying pathophysiology and the treatment response, as well as predict the long-term outcomes. In connection with the T2-signature, blood or sputum eosinophils and FeNO are presently the best validated biomarkers. While eosinophils can best be used to predict treatment response in eosinophilic (severe) asthma, FeNO proves useful in identifying T2 inflammation, partly unrelated to eosinophils and mainly IL13-driven.

More innovative biomarker techniques*, i.e.* breathomics, require specific expertise including metabolomic analysis of exhaled air through mass spectrometry or eNose technology. Other emerging approaches include transcriptomics, genomics and micro-RNA analysis. Recent data showed that nasal epithelium gene profiling reflects bronchial gene expression and hence may serve as a future biomarker to guide asthma treatment. Alternatively, further classifying biomarkers may arise from new imaging techniques and advanced physiology. Future pragmatic biomarker strategies, combining innovative methods for decoding the molecular, immunological, anatomical and physiological complexity, will further improve (sub)phenotyping, endotyping and personalized treatment.

Pulmonary rehabilitation is an alternative, effective but often overlooked treatment strategy (8). However, patients should be informed on potentially detrimental effects of exposure to irritants such as chlorine by-products or cold air in specific training environments.

In childhood, the increased asthma risk after severe viral bronchiolitis may be due to long-lasting epithelial and innate immune changes, resulting in diminished antiviral immunity and enhanced pro-inflammatory T2 responses. Most children with T2 asthma respond well to low-dose ICS ± additional controller, but there are currently no predicting biomarkers for step-up to LABA, LTRA or increased ICS dose. Rather than increasing pharmacotherapy in the non-responsive child, co-morbidities, social and environmental factors should be addressed, especially poor adherence. In addition to omalizumab, at least 3 additional biologicals (mepolizumab, benralizumab, dupilumab) should become available soon for childhood severe asthma (9). To enable personalised treatment approaches further research into response predictors is key.

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–73.

2. Sleurs K, Seys S, Bousquet J, Fokkens W, Gorris S, Pugin B, et al. Mobile health tools for the management of chronic respiratory diseases. Allergy. 2019. doi: 10.1111/all.13720. [Epub ahead of print]

3. Vandenplas O, Godet J, Hurdubaea L, Rifflart C, Suojalehto H, Wiszniewska M, et al. Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma? Allergy. 2018. doi: 10.1111/all.13542. [Epub ahead of print]

4. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783–800.

5. Seys SF, Lokwani R, Simpson JL, Bullens DMA. New insights in neutrophilic asthma. Curr Opin Pulm Med. 2019;25(1):113–20.

6. Ntontsi P, Loukides S, Bakakos P, Kostikas K, Papatheodorou G, Papathanassiou E, et al. Clinical, functional and inflammatory characteristics in patients with paucigranulocytic stable asthma: Comparison with different sputum phenotypes. Allergy. 2017;72(11):1761–7.

7. McGregor MC, Krings JG, Nair P, Castro M. Role of Biologics in Asthma. Am J Respir Crit Care Med. 2018. doi: 10.1164/rccm.201810-1944CI. [Epub ahead of print]

8. Rochester CL, Spanevello A. Heterogeneity of pulmonary rehabilitation: like apples and oranges - both healthy fruit. Eur Respir J. 2014;43(5):1223–6.

9. Abrams EM, Becker AB, Szefler SJ. Current State and Future of Biologic Therapies in the Treatment of Asthma in Children. Pediatr Allergy Immunol Pulmonol. 2018;31(3):119–31.

Legends to figures

Figure 1. Pathogenesis and targeted biological therapies of T2 asthma.

Epithelial activation by allergens, viruses and pollutants leads to activation of epithelial cells and release of TSLP, IL-25 and IL-3, which lead to the activation of type 2 innate lymphoid cells (ILC) and dendritic cells. ILC2 play a role in T and B cell activation and recruitment and are early providers of Th2 and T cell recruitment cytokines. A T2 type of an immune environment is characterized by IL-4, IL-5, IL-9, IL-13, IL-25, IL-33 production coming from Th2 cells, ILC2 and tissue cells. T2 environment is characterized by tissue eosinophilia, epithelial barrier defects, local IgE production, tissue migration of T2 related cells. Biologicals block several molecular aspects of these pathways such as omalizumab-IgE, dupilumab-IL4Ralpha, tezepelumab-TSLP, mepolizumab and reslizumab-IL-5 and benralizumab-IL5Ralpha. IL: interleukin, TSLP: thymic stromal lymphopoietin, TNF: tumor necrosis factor, Th2: Thelper 2 cell, ILC2: innate lymphoid cell type 2, Eos: eosinophil, MC: mast cell, VLA-4: very late antigen-4.