Allergy Asthma Immunol Res. 2021 Mar;13(2):167-170
https://doi.org/10.4168/aair.2021.13.2.167
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Sex and Treatable Traits in Severe Asthma

Han-Ki Park,[1] **Woo-Jung Song** [2*]

[1]Department of Allergy and Clinical Immunology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

▸ See the article "Sex Differences in Severe Asthma: Results From Severe Asthma Network in Italy-SANI" in volume 13 on page 219.

Received: Dec 15, 2020
Accepted: Dec 15, 2020

Correspondence to
Woo-Jung Song, MD, PhD
Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3288
E-mail: swj0126@amc.seoul.kr

ORCID iDs
Han-Ki Park
https://orcid.org/0000-0002-5460-9917
Woo-Jung Song
https://orcid.org/0000-0002-4630-9922

Disclosure
There are no financial or other issues that might lead to conflict of interest.

Severe asthma is a heterogeneous condition with different phenotypes and endotypes.[1] Thus, a simple diagnostic label of severe asthma is not precise enough to guide treatment plans. The concept of "treatable traits" has proposed that a biomarker-directed therapy, based on phenotypes or endotypes, can help personalize treatment plans and finally may lead to better clinical outcomes.[2] Successful clinical trials targeting type 2 (T2) airway inflammation proved that the concept of treatable traits is clinically relevant to severe asthma management, and there is emerging consensus on treatable traits in severe asthma.[3-6]

Sex is a biologic factor, but not a treatable trait. However, it is likely that sex is clinically relevant to asthma evaluation and management. It has consistently been reported that sex is associated with age-related patterns of asthma prevalence.[7] Also, it has been associated with certain asthma parameters indicating more active disease, such as symptom frequency, exacerbation, or disease severity.[8-10] In a cluster analysis of adult asthmatics in the UK, obese non-eosinophilic asthma with high symptom expression was more female predominant, while late-onset eosinophilic asthma was not.[10] Therefore, it is speculated that sex is a determinant for the pattern of treatable traits, or may help to understand the phenotype complexity among patients with severe asthma.

In this issue of *the Allergy Asthma Immunology Research*, Senna *et al.*[11] examined sex differences in clinical, functional, and biologic phenotypes among severe asthmatics in Italy to explore sex-related treatable traits. They analyzed severe asthmatics enrolled in the Severe Asthma Network in Italy—a multi-center real-life registry study with a relatively large sample size (n = 1,123). They confirmed a female predominance (61.8%) and sex differences in several comorbidities of severe asthmatics; female patients had more comorbid obesity and gastroesophageal reflux disease, whereas males more frequently had smoking history and comorbid nasal polyps.

One interesting finding that draws our attention is a sex difference in T2 profile (defined as a combination of blood eosinophils > 300/μL, fractional exhaled nitric oxide [FeNO] > 25 parts per billion and serum total immunoglobulin E (IgE) > 150 U/μL in the study by Senna *et al.*[11]). T2 profile was more frequent in males than in females, although the rate of atopic sensitization was comparable. They attempted multivariate regression analyses, with adjustment for sex, age, asthma onset age, and comorbidities, and then found that T2 profile was significantly associated with late onset of disease (> 40 years) and less body mass index

(< 25 kg/m^2). Male sex showed a positive trend toward T2 profile, but did not reach the level of statistical significance in the multivariate models (adjusted odds ratio: 1.30; 95% confidence interval: 0.97–1.76; $p = 0.087$).[11]

Their findings are straightforward and descriptive rather than mechanistic because T2 profile was assessed only using rather convenient surrogate markers (such as the combinations of FeNO, total IgE, or blood eosinophils) and no parameters were given to explain the basis of T2 inflammation.[11] Atopic sensitization to conventional aeroallergens was less likely to explain T2 phenotype.[11] Type 2 innate lymphoid cells (ILC2s) may play a role in T2 inflammation, as they are capable to induce persistent airway eosinophilia in severe asthmatics.[12] *Staphylococcus aureus* (SA) may be one of the triggering factors for host T2 immune responses even in non-atopics.[13] SA is a frequent colonizer in the nasal mucosa,[14] and staphylococcal serine protease-like proteins (Spls) can shift toward T2 inflammation (including eosinophilia and Spl-specific IgE sensitization) via inducing IL-33 and ILC2 responses from the airway epithelium.[15] IgE sensitization to SA enterotoxins is associated with nasal polyps and asthma severity, which is also more prevalent in older males.[16,17] Thus, it has been suggested that host immune responses to SA may underlie a subphenotype of late-onset severe eosinophilic asthma.[13] This hypothesis is now being evaluated in different cohorts of severe asthmatics to see if there are certain molecular endotypes related to SA exposure.

Another question is how to further phenotype T2-low severe asthma. Although several treatable traits have been suggested through cluster analyses and randomized clinical trials with monoclonal antibodies, there are limited options for patients with T2-low severe asthma.[1,3,18] An omics-based approach may help understand potentially different immune pathways across asthma phenotypes.[19] The U-BIOPRED cohort study integrated sputum transcriptomic signatures and suggested 3 transcriptomic-associated clusters (TACs) among moderate-to-severe asthmatics: TAC1 (T2-high phenotype, enriched by IL-13/Th2 and ILC2 gene signatures), TAC2 (neutrophilic phenotype, enriched by ILC1, neutrophil activation and inflammasome signatures) and TAC3 (pauci-granulocytic or moderately eosinophilic phenotype, enriched by ILC3, Th17, OXPHOS and ageing signatures).[20] Omics-based approach will broaden our understanding of molecular pathways underlying non-T2 severe asthma.

While it is utmost important to understand immune mechanisms underlying asthma severity, it is equally important to well characterize patients, particularly for symptomatology. A subgroup of severe asthmatic patients (such as female-predominant, obese, non-eosinophilic asthma) show little evidence of T2 inflammation or airflow obstruction but are reportedly highly symptomatic.[10] However, to our knowledge, there is little evidence as to which symptom components are particularly uncontrolled and why such sex differences occur in severe asthmatics.[21] Female patients may have a greater perception of symptoms, such as cough or breathlessness, despite better lung functions than male patients.[22] Cough and breathlessness were tipped as key symptoms causing distress severe asthmatic patients during acute exacerbation.[23] In functional brain imaging studies for cough (but not asthma), a greater activation of the somatosensory cortex was observed in response to tussigen inhalation challenge among females, suggesting a sex difference in the central processing of cough sensation.[24] Sensory neuropathy is also suggested to underlie certain common comorbidity, such as laryngeal dysfunction,[25] and is less likely to respond to conventional anti-asthmatic treatments. Neuro-phenotyping with proper characterization of symptomatology and comorbidity may help further understand mechanisms of severe asthma.

https://doi.org/10.4168/aair.2021.13.2.167

The study by Senna *et al.*[11] is a large-scale, real-world evidence to confirm sex differences in phenotypes or treatable traits that were identified in previous studies of severe asthmatic patients. More work is warranted to further understand the role of sex in asthma phenotypes and endotypes, but their study suggested several clues that we should seek in further characterization of severe asthmatics. The newly discovered treatable mechanisms would not only provide new pathobiological insights but also help develop novel treatment options. System biology and novel phenotyping could be promising options to bring advances in precision medicine for severe asthma.

REFERENCES

1. Chung KF, Adcock IM. Precision medicine for the discovery of treatable mechanisms in severe asthma. Allergy 2019;74:1649-59.
PUBMED | CROSSREF
2. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016;47:410-9.
PUBMED | CROSSREF
3. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55:1900588.
PUBMED | CROSSREF
4. McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. Eur Respir J 2019;53:1802058.
PUBMED | CROSSREF
5. McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J 2020;55:1901509.
PUBMED | CROSSREF
6. Song WJ, Lee JH, Kang Y, Joung WJ, Chung KF. Future risks in patients with severe asthma. Allergy Asthma Immunol Res 2019;11:763-78.
PUBMED | CROSSREF
7. Shah R, Newcomb DC. Sex bias in asthma prevalence and pathogenesis. Front Immunol 2018;9:2997.
PUBMED | CROSSREF
8. Sohn KH, Song WJ, Park JS, Park HW, Kim TB, Park CS, et al. Risk factors for acute exacerbations in elderly asthma: what makes asthma in older adults distinctive? Allergy Asthma Immunol Res 2020;12:443-53.
PUBMED | CROSSREF
9. Park SY, Kim JH, Kim HJ, Seo B, Kwon OY, Chang HS, et al. High prevalence of asthma in elderly women: findings from a Korean National Health Database and adult asthma cohort. Allergy Asthma Immunol Res 2018;10:387-96.
PUBMED | CROSSREF
10. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
PUBMED | CROSSREF
11. Senna G, Latorre M, Bugiani M, Caminati M, Heffler E, Morrone D, et al. Sex differences in severe asthma: results from severe asthma network in Italy-SANI. Allergy Asthma Immunol Res 2021;13:219-28.
CROSSREF
12. Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O'Byrne PM, et al. Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. J Allergy Clin Immunol 2016;137:75-86.e8.
PUBMED | CROSSREF
13. Bachert C, Humbert M, Hanania NA, Zhang N, Holgate S, Buhl R, et al. *Staphylococcus aureus* and its IgE-inducing enterotoxins in asthma: current knowledge. Eur Respir J 2020;55:1901592.
PUBMED | CROSSREF
14. Kim YC, Won HK, Lee JW, Sohn KH, Kim MH, Kim TB, et al. *Staphylococcus aureus* nasal colonization and asthma in adults: systematic review and meta-analysis. J Allergy Clin Immunol Pract 2019;7:606-615.e9.
PUBMED | CROSSREF

https://doi.org/10.4168/aair.2021.13.2.167

15. Teufelberger AR, Nordengrün M, Braun H, Maes T, De Grove K, Holtappels G, et al. The IL-33/ST2 axis is crucial in type 2 airway responses induced by *Staphylococcus aureus*-derived serine protease-like protein D. J Allergy Clin Immunol 2018;141:549-559.e7.
PUBMED | CROSSREF

16. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 2016;137:1449-1456.e4.
PUBMED | CROSSREF

17. Song WJ, Sintobin I, Sohn KH, Kang MG, Park HK, Jo EJ, et al. Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly. Clin Exp Allergy 2016;46:411-21.
PUBMED | CROSSREF

18. Kim BK, Park SY, Ban GY, Kim MA, Lee JH, An J, et al. Evaluation and management of difficult-to-treat and severe asthma: an expert opinion from the Korean Academy of Asthma, Allergy and Clinical Immunology, the Working Group on Severe Asthma. Allergy Asthma Immunol Res 2020;12:910-33.
PUBMED | CROSSREF

19. Park HW, Weiss ST. Understanding the molecular mechanisms of asthma through transcriptomics. Allergy Asthma Immunol Res 2020;12:399-411.
PUBMED | CROSSREF

20. Kuo CS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al. T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED. Eur Respir J 2017;49:1602135.
PUBMED | CROSSREF

21. Pattinson K. Functional brain imaging in respiratory medicine. Thorax 2015;70:598-600.
PUBMED | CROSSREF

22. McCallister JW, Holbrook JT, Wei CY, Parsons JP, Benninger CG, Dixon AE, et al. Sex differences in asthma symptom profiles and control in the American Lung Association Asthma Clinical Research Centers. Respir Med 2013;107:1491-500.
PUBMED | CROSSREF

23. Song WJ, Won HK, Lee SY, Park HK, Cho YS, Chung KF, et al. Patient's experience of asthma exacerbation and management: a qualitative study of severe asthma. ERJ Open Res. Forthcoming 2020.

24. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J 2014;44:1149-55.
PUBMED | CROSSREF

25. Lee JH, An J, Won HK, Kang Y, Kwon HS, Kim TB, et al. Prevalence and impact of comorbid laryngeal dysfunction in asthma: a systematic review and meta-analysis. J Allergy Clin Immunol 2020;145:1165-73.
PUBMED | CROSSREF