DOI: 10.1111/all.13188

CORRESPONDENCE

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

# Asthma management: A new phenotype-based approach using presence of eosinophilia and allergy

Dear Editor,

We read with great interest the report of Terl et al. Authors have prepared a national asthma guideline which reflects asthma heterogeneity, eases the use of biological markers and the management of asthma and foregrounds the phenotype-targeted treatment approach in the framework of their review titled as: "Asthma management: A new phenotype-based approach using presence of eosinophilia and allergy." Starting with a pragmatic concept evaluating whether every asthma patient has allergy and eosinophilia, the guideline has been classified under three asthma phenotypes: (i) eosinophilic allergic asthma, (ii) eosinophilic nonallergic asthma and (iii) noneosinophilic nonallergic asthma.[1]

Introduction of such phenotyping system for asthma, which is easy to understand and applicable, will quite simplify and organize the patient management and treatment options. The use of the current biological agents (omalizumab, mepolizumab, reslizumab) will be particularly clarified according to these phenotypes and biological markers. The phenotyping system will also help to designate the use other biological agents which have the potential to appear in the guidelines in the upcoming years such as Dupilumab and Lebrikizumab.

We have also been using similar asthma phenotyping classification in our clinic (Table 1). However, we think that the use of the term "atopic" can be more convenient instead of "allergic" in phenotypical asthma classification in order not to cause confusion in terminology. As eosinophilic inflammation is also an allergic reaction, when the term "atopic asthma" is used, the specific IgE response formed against general aeroallergens would be reflected better.[2]

In addition to these phenotypes, we think that adding two more phenotypes would be more appropriate in terms of asthma management and especially the use of new biological agents. We use five different phenotypes in our clinic at asthma diagnosis and treatment management: (i) atopic noneosinophilic, (ii) atopic eosinophilic, (iii) nonatopic eosinophilic, (iv) eosinophilic, comorbid chronic rhinosinusitis with nasal polyposis (atopic or nonatopic) and (v) nonatopic noneosinophilic.

Phenotyping with this methodology eases management of both severe and nonsevere asthma patients. For example, in Group 2, where the patient has pure atopic eosinophilic severe asthma, omalizumab treatment is expected to be more efficient than anti-IL-5 treatment even though the patient has eosinophilia because in this case the real responsible mechanism for type 2 inflammation and

**TABLE 1** Classification of asthma phenotypes and treatment based on phenotypes

| Groups of Phenotype | Treatment methods[a] | Biologicals for severe asthma patients |
|---|---|---|
| Atopic, noneosinophilic | Low-dose budesonide/formoterol or low-dose beclomethasone/formoterol maintenance and reliever therapy | Anti-IgE |
| | Immunotherapy | |
| | LTRA | |
| Atopic, eosinophilic | Low-dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy | Anti-IgE, Anti-IL-4/IL-13 |
| | Immunotherapy | |
| | LTRA | |
| Nonatopic, eosinophilic | Fine particles ICSs | Anti-IL-5, Anti-IL-13 |
| | LTRA | |
| Eosinophilic, comorbid chronic rhinosinusitis with nasal polyposis (atopic or nonatopic) | Fine particles ICSs | Anti-IL-5 |
| | LTRA | |
| Nonatopic, noneosinophilic | Tiotropium | ? |
| | Theophylline | |
| | Azithromycin | |

ICSs, inhaled corticosteroids; LTRA, Leukotriene receptor antagonists.

[a]In our clinic, treatment regimes suggested by GINA are applied in stepwise approach in order to control symptoms and minimize future risks. However, some treatment methods might be more effective at patients with appropriate phenotypes and steps.

 © 2017 EAACI and John Wiley and Sons A/S. Published by John Wiley and Sons Ltd. 

eosinophilia would be allergen-specific IgE and mast cell degranulation. If the level of blood periostin is high in this group, it might be suitable candidate for dupilumab. Because where there is no atopy, there is no IL-4, and if there is no IL-4, there is no atopy.[3-5] For Group 3, if exhale NO or periostin levels are too high, anti-IL-13; and if blood eosinophil level is too high, then anti-IL-5 will be a more appropriate option.[5] However, anti-IgE or anti-IL-4/IL-13 will not be as effective as these two biological agents. Group 4 patients will have much more benefit from anti-IL-5 treatment even though they have atopies, since their blood eosinophil levels are higher. Therefore, anti-IL-5 treatment should be the preferred choice for biological agent at severe asthma cases with atopy and eosinophilic, comorbid chronic rhinosinusitis with nasal polyposis. We hope that new biological agents targeting nonatopic noneosinophilic severe asthma group, the orphan group, will also emerge as new therapeutic options for type 2 inflammation become routinely administered in clinical practice,

In conclusion, we would like to thank Terl and his colleagues for their contribution to the literature with such a good review. We also wanted to share our view about this review and to share our clinical approach to asthma management based on asthma phenotypes.

## CONFLICT OF INTEREST

The author has no conflict of interest.

I. Yilmaz
*Department of Chest Diseases, Division of Immunology and Allergy, Erciyes University School of Medicine, Kayseri, Turkey*
*E-mail: insu2004@yahoo.com*

Edited by: Thomas Bieber

## REFERENCES

1. Terl M, Sedlák V, Cap P, et al. Asthma management: a new phenotype-based approach using presence of eosinophilia and allergy. *Allergy*. 2017;72:1279-1287.
2. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832-836.
3. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy*. 2012;67:835-846.
4. Pavord ID, Hilvering B, Shrimanker R. Emerging Biologics in Severe Asthma. *Immunol Allergy Clin North Am*. 2016;36:609-623.
5. Muraro A, Lemanske RF Jr, Hellings PW, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis-RACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2016;137:1347-1358.

# Reply

We would like to thank Dr. Yilmaz and his team for their valuable comments on our paper, in addition to the information on their "in-house" classification of asthma phenotypes and decision-making protocol.

We are pleased to learn that they follow a generally similar phenotypic classification in clinical practice as our team. Indeed, their classification appears to be more detailed with regard to the first two phenotypes mentioned in our paper, with illustrative examples and considerations for anti-IL-5, anti-IL-4 and/or anti-IL-13 therapy. These considerations clearly highlight the complicated and heterogeneous nature of the disease.

Of important note, even at our centres for severe asthma, the diagnostic process is not limited to only the three phenotypes mentioned in our paper, particularly in severe and/or problematic patients.[1,2] In such patients, we use a more detailed classification aimed at individualized therapy. Besides the characterization of inflammation, we also take into account the predominant localization and the final pattern of bronchial obstruction (lung function testing with a particular interest in the presence of small airways disease and indication for fine-particle ICS or soft-mist tiotropium inhalers; significant reversibility of bronchial obstruction as an indirect marker of smooth muscle hypertrophy/hyperplasia indicated for bronchial thermoplasty).

However, we believe that in daily clinical practice (i.e, outside specialized centres), the three phenotypes discussed in our classification are sufficient as the starting point for consecutive management; furthermore, this classification is easy to use and its adoption as the initial approach in all patients might avoid confusion or management mistakes.

We agree with Dr. Yilmaz's recommendation to refer to our first asthma type as simply atopic asthma. In fact, we also use this term quite often in our "in-house" terminology. However, we find it quite confusing to divide allergic asthma into atopic noneosinophilic and atopic eosinophilic types. We believe that virtually "all IgE allergic asthma are eosinophilic by nature of its pathogenesis."[3] Only the difference in the degree of allergic reaction, which is determined mostly by the sensitization intensity and spectrum, together with actual exposure to causative allergens, leads to the absence of systemic eosinophilia in milder forms of allergic asthma. Eosinophilia, or eosinophilic inflammation, in such cases presents exclusively in the bronchial wall and promptly disappears after initiation of ICS treatment. Based on our clinical experience, a vast majority of patients receiving anti-IgE therapy initially showed mono- or oligosensitization to some aeroallergens without any signs of systemic eosinophilia. Only years or decades later, due to the significant polysensitization or dominant sensitization to the permanent massive

exposure, which is typically noted in SAFS, systemic eosinophilia occurs. If such a patient does not undergo allergologic examination, he/she could be misdiagnosed as having eosinophilic, nonallergic asthma. This might also be the case with even a standard allergy evaluation without detailed mould testing.

Once again, we would like to thank Dr. Yilmaz and his team for their practical remarks, proposal of a decision-making protocol and mind-provoking/stimulating ideas.

## CONFLICT OF INTEREST

The authors report no potential conflict of interest relevant to this letter.

M. Terl

*Department of Pulmonary Medicine, University Hospital and Faculty of Medicine in Pilsen, Charles University, Prague, Czech Republic*

*E-mail: terl@fnplzen.cz*

## REFERENCES

1. Sedlak V, Chlumsky J, Teřl M, Novotna B. Doporučený postup diagnostiky a léčby obtížně léčitelného bronchiálního astmatu. 2011. Available from: http://www.pneumologie.cz/guidelines. Accessed date 05 April 2017.
2. Bel EH, Sousa A, Flemming L, et al. on behalf of the members of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax*. 2011;66:910-917.
3. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008;454:445-454.