



Effective Strategies for Managing Asthma Exacerbations for Precision Medicine

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The concept of heterogenous asthma is a cliché now. Although the overall asthma control rate has been remarkably improved since the introduction of inhaled corticosteroids (ICSs) and beta 2 long-acting agonists, asthma control status still varies considerably even among individuals who have received proper antiasthma medications. Responses to treatment, severity of existing symptoms, and prognosis of asthma are all diverse. Among these diversities of clinical courses, acute asthma exacerbation is the most critical and dramatic event that frustrates both patients and physicians. In fact, many asthmatic patients only focus on the occurrence of asthma exacerbations, though physicians are interested in various aspects of asthma, such as daily asthma control status, adherence to medication, and long-term prognosis of the disease. Moreover, patterns of these exacerbations in terms of frequency, severity, provoking factors, and lasting duration of the events are indeed heterogeneous. For example, some patients only occasionally experience mild-to-moderate asthma exacerbations, while others frequently suffer from severe asthma exacerbations that prompt a visit to the emergency departments. Management of asthma exacerbation is important not only because it is a major cause of disease morbidity and increased health care costs^{1,2} but also because it is critically linked to the progressive loss of lung function.^{3,4} Given that the 2 main long-term risk factors for asthma suggested by international guidelines are asthma exacerbation and progressive irreversible airway obstruction, development of effective strategies for controlling asthma exacerbation is an urgent unmet need. A better understanding of the pathogenesis of asthma exacerbation will lead to new strategies for the prevention and treatment of asthma exacerbation.

Why does asthma exacerbation occur and have so heterogeneous clinical features? It is evident that better achievement of daily asthma control leads to less frequent occurrence of asthma exacerbations. In fact, it has been reported that ICS use can substantially reduce asthma exacerbations.⁵ However, since not all asthma exacerbations can be eliminated by achieving asthma

control with appropriate ICS use, it should be noted that asthma exacerbations are not simple natural consequences of untreated asthma or poor compliance with medications. Despite optimal therapies directed by international guidelines, such as Global Initiative Asthma (GINA), asthma exacerbations still occur, and there are many questions regarding the pathogenesis and treatment of asthma exacerbation. In order to investigate the underlying mechanisms of asthma exacerbation, understanding its heterogeneity should be a high priority, because its pathogenesis may differ from one patient to another. Finally, we should consider what are the major causes of asthma exacerbation and its heterogeneity. Intrinsic factors of asthmatic patients contribute to asthma exacerbation in some patients, but various extrinsic environmental factors also strongly contribute to the development of asthma exacerbation episodes. The fact that both intrinsic and environmental factors are closely linked to the events of asthma exacerbation makes a precise understanding of asthma exacerbation even more complicated.

Some asthmatic patients experience exacerbations more frequently than others. Given that asthma is an umbrella term for the clinical syndromes in which many subtypes with various underlying pathogenesis exist, defining the exacerbation-prone subtype of asthma is the first step to elucidate the exact pathogenesis of asthma exacerbation. Kim *et al.*,⁶ conducted a study to characterize and define an 'exacerbation-prone subtype of asthma' through cluster analysis of their asthma cohort and indicated that there are at least 2 different subtypes of exacerbation.

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tion-prone asthmatic showing different clinical features, especially in terms of onset age and atopic status. In addition, they also confirmed that frequent asthma exacerbations are closely related to impaired lung function. Several other studies attempted to characterize exacerbation-prone asthma subtypes;⁷⁻⁹ interestingly, clinical characteristics of each exacerbation-prone asthmatic subtype suggested differed among these studies. In particular, obesity and inflammatory patterns in the airway were not identified as critical factors for frequent aggravation of asthma in the study by Kin *et al.*⁶, while they were in other studies.

The reasons for these different results among studies could be associated with the different ethnic backgrounds and different cohort populations used in the analysis. However, it is also possible that exacerbation-prone asthmatic patients could be more heterogeneous than expected. In fact, it should be considered whether all factors that can possibly have some impact on the development of asthma exacerbations, were included in the analysis. There would be more factors that may exert influence on asthma exacerbations, ranging from diverse intrinsic characteristics of asthmatic patients, including genetic background, atopic status, susceptibility to viral respiratory infections, and airway inflammatory types to various environmental factors in everyday life, such as diet, geographical location, or occupation. Therefore, it may be difficult to say that there are clear-cut subtypes of exacerbation-prone asthmatics when considering all aspects of asthma exacerbation. Taken together, defining and subtyping 'exacerbation-prone asthma' seems to be a much more complicated task than phenotyping and endotyping asthma as a whole.

Meanwhile, there are also various extrinsic factors related to asthma exacerbation that may influence the heterogeneity of frequency, clinical features, and the duration of asthma exacerbation. These extrinsic or environmental factors include viral respiratory infections, allergens, bacterial infections, fungal sensitization, and pollutants, such as tobacco smoke, ozone, and particulate matter, which may differentially contribute to the pathogenesis of asthma exacerbation.¹⁰ Among these diverse factors, viral respiratory infections should first be considered in asthma exacerbation because it is well known that viral infections are responsible for up to 80%-85% of exacerbations in childhood asthma¹¹ and more than 50% in adult asthma.^{12,13} Therefore, investigation into clinical features of viral respiratory infections would be valuable in developing effective strategies for the management of asthma exacerbations.

There have been numerous studies exploring the role of various viral respiratory infections in asthmatic patients. Considering the significant impact of viral infections on the development and exacerbations of asthma it is critical to answer important questions concerning the precise diagnosis and control of viral infections by using novel techniques and therapeutic modalities, such as anti-infectives or immunomodulators. Re-

cently, based on the importance of respiratory infections, a position paper entitled, 'the potential of anti-infectives and immunomodulators as therapies for asthma and asthma exacerbations,' was published by EAACI Anti-infectives in Asthma and Asthma Exacerbations Task Force.¹⁴ In the paper, the authors highlighted the importance of controlling respiratory infections in asthma exacerbations and suggested the potential effectiveness of several anti-infective agents, such as pavilizumab and motavizumab, for RSV infections, pleconaril for picornaviruses, vapendavir for enteroviruses and rhinovirus (RV), intranasal recombinant soluble ICAM-1, tremacamra for RV, favipiravir for influenza virus, interferons for influenza viruses, and other various anti-viral agents under development for various viruses.¹⁴ In addition, some experimental vaccines for RSV and RV, which are major triggers for asthma exacerbation, are also ongoing clinical trials.¹⁵ More work is needed to prove the efficacy of drugs and vaccines for controlling virus-induced asthma exacerbation before introducing them to clinical practices.

Despite the importance of viral infections as causative factors for asthma exacerbations, there have been few reports discussing the precise diagnosis of viral respiratory infections during asthma exacerbations in Korea. Because diversity in the kinds of respiratory viruses is expected to exist across different areas and countries, identifying Korea-specific patterns of various respiratory viruses during asthma exacerbations may be useful for understanding and managing Korean patients with asthma exacerbations. In a prospective cohort study, Seo *et al.*¹⁶ reported the prevalence of viral respiratory infections in Korean adult asthmatics with acute exacerbations. They demonstrated that respiratory viruses were identified in approximately 20% of lower respiratory tract infection, irrespective of the presence of asthma exacerbation, and that RV and influenza virus (IFV) A/B were most frequently detected. In addition, seasonal variations were also noted in the detection rates of RV (September to December), IFV (January to April), parainfluenza virus (May to September), and RSV A/B (September to April) in Korea. Despite some methodological limitations, that study is expected to provide a basis for future research into the development of novel anti-infective therapeutic agents and ensuring clinical trials. The importance of correctly detecting causative viruses for asthma exacerbation will continue to increase in clinical practice with the development of novel anti-viral agents; thus, clinical studies with a larger scale are needed for future clinical practices utilizing precision medicine for asthma.

Collectively, it becomes clear that different preventive and therapeutic approaches should be employed for each episode or subtype of asthma exacerbations. Defining useful and applicable subtypes of asthma exacerbations should be based on intrinsic factors that induce exacerbation-prone traits among asthmatic patients as well as extrinsic environmental factors, including respiratory infections. Thus, the following fundamen-

tal questions are raised: What should be considered in precision medicine for asthma exacerbation? What is the value of precision medicine in asthma care? What are the pragmatic approaches for the management of asthma exacerbations from the viewpoint of precision medicine in daily practice? Indeed, a prerequisite for clinically useful precision medicine for asthma is that patients should first be treated with optimal asthma medications. Then, various effective therapeutic options should be employed in clinical practice for targeting different causes of asthma exacerbation, such as microorganisms, allergens, and host aberrant immunologic status. If asthma exacerbations occur in well-characterized asthmatic patients, optimal precision medicine will perform precise subtyping of asthma exacerbations and search for the best treatment for each particular patient. For instance, an asthmatic patient with intrinsic immunologic abnormalities showing high risk of exacerbation by RV infection would be treated with anti-RV vaccines in advance. Future precision medicine for asthma requires comprehensive approaches to subtype asthma exacerbations with consideration of all contributing factors causing asthma exacerbations. Even so, more consideration should be given to how drug discovery programs are best implemented to exploit these aspects.

REFERENCES

- Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol* 2012;129:1229-35.
- Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol* 2011;127:145-52.
- O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19-24.
- Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007; 30:452-6.
- Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *Jama* 2004;292:367-76.
- Kim MA, Shin SW, Park JS, Uh ST, Chang HS, Bae DJ, et al. Clinical Characteristics of Exacerbation-Prone Adult Asthmatics Identified by Cluster Analysis. *Allergy Asthma Immunol Res* 2017;9:483-90.
- Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS One* 2012;7:e36631.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181:315-23.
- Amelink M, de Nijs SB, de Groot JC, van Tilburg PM, van Spiegel PI, Krouwels FH, et al. Three phenotypes of adult-onset asthma. *Allergy* 2013;68:674-80.
- Castillo JR, Peters SP, Busse WW. Asthma Exacerbations: pathogenesis, Prevention, and Treatment. *J Allergy Clin Immunol Pract* 2017;5:918-27.
- Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005;11:21-6.
- Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;359:831-4.
- Atmar RL, Guy E, Guntupalli KK, Zimmerman JL, Bandi VD, Baxter BD, et al. Respiratory tract viral infections in inner-city asthmatic adults. *Arch Intern Med* 1998;158:2453-9.
- Edwards MR, Walton RP, Jackson DJ, Feleszko W, Skevaki C, Jartti T, et al. The potential of anti-infectives and immunomodulators as therapies for asthma and asthma exacerbations. *Allergy* 2017.
- Glanville N, McLean GR, Guy B, Lecouturier V, Berry C, Girerd Y, et al. Cross-serotype immunity induced by immunization with a conserved rhinovirus capsid protein. *PLoS Pathog* 2013;9:e1003669.
- Seo KH, Bae DJ, Kim JN, Lee HS, Kim YH, Park JS, et al. Prevalence of Respiratory Viral Infections in Korean Adult Asthmatics With Acute Exacerbations: Comparison With Those With Stable State. *Allergy Asthma Immunol Res* 2017; 9:491-8.