INTERASMA Symposium: Clinical diversities in asthma

Phenotypes and Endotypes of Severe Asthma

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Asthma is a heterogeneous clinical syndrome that has differences in clinical features, clinical courses, prognosis, and responsiveness to anti-asthma medications. Despite the heterogeneity, asthma typically shows eosinophilic airway inflammation and in general, the eosinophilic inflammation itself can be well controlled by drugs based on glucocorticoid. In fact, 90-95% of the all asthmatics have been successfully treated by using inhaled corticosteroid (ICS).

However, 5-10% of asthmatic patients, who cannot be controlled with high dose ICS and other currently available anti-asthmatic medications, are considered severe asthma and those patients become a big burden. The severe asthma patients are suffering from not only uncontrolled asthma symptoms but also serious adverse reactions from long-term use of systemic corticosteroids. Therefore, severe asthma is a critical unmet need among asthma patients and the development of new therapeutic strategies are urgently needed.

Unlike management of controllable asthma with ICS, dealing with severe asthma should be differently approached to achieve effective and successful treatment. Given that there is also a clear heterogeneity in severe refractory asthma, it is critical to search for the most appropriate therapies for each subtypes of severe asthma. Why do we have to identify phenotypes and endotypes particularly in severe asthma? Because if we can appropriately classify subtypes of severe asthma, the development of novel drugs for each subtype may be possible and that is the bottom line of precision medicine for severe asthma. Accordingly, identifying phenotypes and endotypes is the first step to overcome severe asthma, a critical unmet need in chronic airway diseases.

When asthmatic patients are treated, 'severe asthma' is the clinically pivotal phenotype and may be identified without difficulties in clinical practice. And in severe asthma, several phenotypes may be suggested based on some clinical characteristics. Firstly, in terms of features of airway inflammation, at least 4 different phenotypes such as eosinophilic, neutrophilic, mixed, and no inflammation exist.

Interestingly, the reason why the eosinophilic inflammation in the airways of severe asthmatic patients is steroid insensitive or resistant is unclear. Furthermore, neutrophilic inflammation in severe asthma has not even clearly characterized. Although vigorous researches have been carried out so far, the precise causes of severe refractory asthma have not been elucidated. In order to clarify the mechanism of steroid insensitive inflammation, it is critical to identify the exact endotypes of severe refractory asthma. Secondly, some asthmatic patients reveal frequent asthma exacerbations and these patients may be a unique phenotype of severe asthma. The precise underlying mechanism why those patients suffer from exacerbation attacks so frequently remains elusive. To solve the problem, finding proper endotypes linked to exacerbation prone factors should be searched. Finally, with regard to pulmonary function in the long run, a unique phenotype may be a rapid decliner in FEV1. Again, there is no endotype clearly related with the characteristic and further investigation should be needed.

Phenotypes in severe asthma substantially overlap and the same is also possible in endotypes. In clinical practice, it would be pragmatic approach that identifying phenotypes should be followed by searching precise endotypes for each phenotype. Although we do not have a perfect new classification of severe asthma based on clear underlying mechanism for each subtype at this moment, recently, several novel biologics targeting eosinophilic airway inflammation by blocking various Th2 cytokines are just about to be launched in clinical practice. It is expected that corticosteroid insensitive eosinophilic inflammation may be controlled with those novel biologics. Nevertheless, there are more severe asthma phenotypes of which the underlying exact pathogenesis has not been elucidated. Further studies to identify right endotypes for each phenotype would be necessary.

In conclusion, a novel classification of severe asthma based on appropriate phenotypes and endotypes can lead to successful precision medicine based treatment for severe asthma.