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Invited review article

Recent developments regarding periostin in bronchial asthma

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ICS	inhaled corticosteroids
ILC2	group2 innate lymphoid cells
FeNO	fractional exhaled nitric oxide

ABSTRACT

Although it is currently recognized that bronchial asthma is not a single disease but a syndrome, we have not yet made use of our new understanding of this heterogeneity as we treat asthma patients. To increase the efficacy of anti-asthma drugs and to decrease costs, it is important to stratify asthma patients into subgroups and to develop therapeutic strategies for each subgroup. Periostin has recently emerged as a biomarker for bronchial asthma, unique in that it is useful not in diagnosis but in categorizing asthma patients. We first found that periostin is a novel component of subepithelial fibrosis in bronchial asthma downstream of IL-13 signals. Thereafter, it was shown that periostin can be a surrogate biomarker of type 2 immune responses, the basis of the notion that a detection system of serum periostin is potentially a companion diagnostic for type 2 antagonists. Furthermore, we have recently shown that serum periostin can predict resistance or hyporesponsiveness to inhaled corticosteroids, based on its contribution to tissue remodeling or fibrosis in bronchial asthma. Thus, serum periostin has two characteristics as a biomarker for bronchial asthma: it is both a surrogate biomarker of type 2 immune responses and a biomarker reflecting tissue remodeling or fibrosis. We can take advantage of these characteristics to develop stratified medicine in bronchial asthma.

Introduction

It is now recognized that bronchial asthma is not a single disease but a syndrome.[1] Clinicians have empirically been aware of the heterogeneity of bronchial asthma for a long time. Many factors—age of onset, obesity, types of inflammatory cells, IgE-dependency, and responsiveness to inhaled corticosteroids (ICS)—lead to the heterogeneity of bronchial asthma. But as we consider treatments for asthma patients, we have not yet taken into account the heterogeneity of the disease; severity has been the most important factor in deciding on treatment.[2] For example, we increase the ICS dose according to severity, and for the most severely ill patients, we have other options such as oral steroids or anti-IgE antibodies. But it is now questionable whether this is the best strategy.

ICS is recognized as a very effective therapeutic agent for bronchial asthma, significantly decreasing the number of asthma deaths. However, 5–10% of asthma patients are resistant to ICS treatment.[3,4] Although the percentage is relatively small, these patients account for about 50% of the total medical cost of treating asthma patients. It has been reported that the effectiveness of anti-IgE antibodies for severe asthma patients is at most 60%.[5] Although anti-IgE antibodies recognize IgE, serum IgE levels cannot predict responsiveness. Moreover, biologics including anti-IgE antibodies are very expensive. So it is important to stratify patients into subgroups showing good or poor responsiveness to ICS or anti-IgE antibodies and to develop a strategy to administer ICS as the first-line agent and oral corticosteroids or anti-IgE antibodies as second-line agents. Development of stratified medicine in bronchial asthma would both increase the efficacy of anti-asthma drugs and decrease treatment costs.

Periostin has recently emerged as a biomarker for bronchial asthma.[6] Biomarkers have been mainly developed to diagnose diseases. However, periostin is a unique biomarker in that it is not used for diagnosis but for categorizing asthma patients. Diagnostics to predict the efficacy of drugs are now called “companion

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diagnostics." So it is reasonable to expect that a periostin detection system would have the potential to be a companion diagnostic for anti-asthma drugs. In this article, we focus on the characteristics of periostin as an inflammatory mediator of bronchial asthma and the usefulness of measuring periostin in the treatment of bronchial asthma. We recommend another review article for the overall characteristics of periostin and the functional roles of periostin in allergic diseases.[7]

History of the development of stratified medicine in bronchial asthma

Anti-IL-5 antibodies

Trials for development of stratified medicine in bronchial asthma began with anti-IL-5 antibodies, although it is doubtful that the present strategy involving these antibodies was intended from the beginning. IL-5 is a signature cytokine of type 2 immune responses produced mainly in Th2 cells and group2 innate lymphoid cells (ILC2).[8,9] IL-5 primarily induces the development and expansion of eosinophil lineage cells. Its importance in the pathogenesis of bronchial asthma was established in the 1990s mainly through analyses of IL-5–deficient mice.[10] Based on these findings, anti-IL-5 antibodies were developed as anti-asthma drugs, and these agents were used in several clinical trials. However, the initial results were disappointing; although peripheral eosinophils decreased, lung functions were not improved by administering anti-IL-5 antibodies.[11,12] These results seem reasonable now because asthma patients are known to be heterogeneous, and molecularly targeted drugs such as anti-IL-5 antibodies would be effective only for some fraction of asthma patients, not for all. However, no stratification was performed in those trials. Thereafter, the strategy for development of an anti-IL-5 antibody called mepolizumab as an anti-asthma drug was changed, targeting steroid-resistant asthma patients showing high eosinophil numbers in sputum or blood, because it was assumed that sputum or blood eosinophils reflected IL-5 levels as a surrogate marker of IL-5. This strategy was successful, demonstrating that mepolizumab decreased exacerbation of asthma in stratified patients.[13,14] A phase III study of mepolizumab has recently been reported, showing that mepolizumab has a glucocorticoid-sparing effect, reduces exacerbations, and improves asthma symptoms.[15,16] This study is the first example of development of stratified medicine in bronchial asthma.

IL-4/IL-13 antagonists

The importance of IL-4 and IL-13, other signature cytokines of type 2 immune responses, in the pathogenesis of bronchial asthma was established in the 1990s using model mice, as had been done with IL-5.[17–19] In particular, IL-13 plays a central role in pathogenesis because compared with IL-4, it is abundantly expressed in inflamed lesions.[20] IL-4 and IL-13 are related cytokines sharing a receptor (type II IL-4 receptor/IL-13 receptor) and signal pathways via the receptor. Based on these findings, antagonists against IL-13, or both IL-13 and IL-4, have been developed as anti-asthma drugs. However, some antagonists have shown satisfactory results, whereas others were withdrawn for low efficacy (Fig. 1).[21–26] This can again be explained by the heterogeneity of asthma patients; some patients are responsive to IL-4/IL-13 antagonists, whereas others are not. Among several clinical trials, the Roche/Genentech group adopted a fruitful strategy.[21] They applied serum periostin as a surrogate biomarker of *in vivo* IL-13 production and examined the efficacy of an anti-IL-13 antibody called lebrikizumab for stratified patients. They found that lebrikizumab showed good efficacy for high periostin patients, whereas it did not for low periostin patients. This study should be appreciated as a milestone in the development of stratified medicine for bronchial asthma.

A Sanofi group has recently published the results of a clinical trial of an anti-IL-4 receptor α chain antibody called dupilumab using peripheral or sputum eosinophils for stratification of asthma patients.[23] Hanania and colleagues have shown the usefulness of peripheral eosinophil number, fractional exhaled nitric oxide (FeNO), and periostin to predict the efficacy of anti-IgE antibodies (omalizumab).[27] More than half of the anti-asthma drugs under development are antagonists against type 2 immune responses (Fig. 2). Therefore, it is a very important issue in the establishment of stratified medicine for bronchial asthma to identify which biomarker is the most useful to reflect type 2 immune responses

Ongoing

Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Status
Anti-IL-13 Ab (Lebrikizumab)	Roche/Genentech	-	+	phase III ongoing
Anti-IL-13Ab (Tralokinumab)	AstraZeneca/Medimmune	-	+	phase IIa finished
Anti-IL-13/IL-4 Ab (QBX258)	Novartis	-	+	phase II ongoing
Anti-IL-4Rα Ab (Dupilumab)	Sanofi/Regeneron	+	+	phase II finished

Withdrawn

Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Final Evaluation
IL-4 mutein (Pitrakinra)	Bayer/AEROVANCE	+	+	phase IIa
Anti-IL-4Rα Ab (AMG 317)	Amgen	+	+	phase II
Anti-IL-13 Ab (IMA-638)	Pfizer	-	+	phase II

Fig. 1. The status of IL-4/IL-13 antagonists as anti-asthma agents. IL-4/IL-13 antagonists that are under development (upper panel) or were withdrawn (lower panel) are depicted.