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Review article

Utility of serum periostin in combination with exhaled nitric oxide in the management of asthma

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Abbreviations:
FeNO, fraction of exhaled nitric oxide;
FEV_1, forced expiratory volume in 1 s;
ICS, inhaled corticosteroid;
IgE, immunoglobulin E; IL, interleukin;
iNOS, inducible NO synthase; KiHAC, Kinki Hokuriku Airway disease Conference;
TGF, transforming growth factor;
TNF, tumor necrosis factor

ABSTRACT

Type-2/eosinophilic inflammation plays a pivotal role in asthma. The identification of severe type-2/eosinophilic asthma is important for improving the management of patients with asthma. Therefore, efforts to develop non-invasive biomarkers for type-2/eosinophilic airway inflammation have been made during this decade. Currently, fraction of exhaled nitric oxide (FeNO) and serum periostin levels are considered markers of type-2/eosinophilic inflammation in asthma. However, a single-marker approach has limited the ability to diagnose severe type-2/eosinophilic asthma accurately and predict disease outcomes precisely. The present article reviews the utility of FeNO and serum periostin levels in a single-marker approach and in a multiple-marker approach in identifying patients with severe type-2/eosinophilic asthma. Furthermore, based on a sub-analysis of the Kinki Hokuriku Airway disease Conference (KiHAC), geno-endo-phenotypes of patients were stratified into four groups according to the FeNO and serum periostin levels.

Introduction

Asthma has recently been recognized as an umbrella term that encompasses various phenotypes and endotypes rather than a single disease.[1,2] Despite the diversity of endotypes and inflammatory patterns,[3] type-2/eosinophilic inflammation remains a key driver in nearly half of all patients with asthma[4] and has been demonstrated in airway epithelial cells isolated from patients with mild-to-moderate asthma.[5] Therefore, efforts to develop non-invasive biomarkers for type-2/eosinophilic airway inflammation have been made during this decade. Currently, fraction of exhaled nitric oxide (FeNO) and serum periostin levels are considered biomarkers of type-2/eosinophilic inflammation. In the present review article, the strength and weakness of FeNO and serum periostin levels as markers of type-2 inflammation are briefly summarized, which may facilitate improved interpretation of markers in the management of asthma. Studies that compared the utility of two markers to identify severe type-2/eosinophilic airway inflammation or to diagnose pediatric asthma are also reviewed. A single-marker approach may be insufficient to cover the whole range of asthma management, from disease diagnosis to prediction of disease prognosis and response to treatments, even when limited to the prediction of eosinophilic airway inflammation.[6] However, evidence regarding the use of a multiple-marker approach to identify severe type-2/eosinophilic asthma is scarce.[7,8] Herein, the potential utility of a composite marker of FeNO and serum periostin levels is presented based on a sub-analysis of the Kinki Hokuriku Airway disease Conference (KiHAC). Geno-endo-phenotypes with

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either high FeNO levels only or serum perisotin levels only are also described.

FeNO

Currently, FeNO is commonly used in the clinical settings of asthma, and the measurement of FeNO at 50 mL/s of expiratory flow using NIOX VERO® and NObreath® is generally accepted by health insurance systems, including in Japan.[9] The utility of this marker in the management of asthma has been well-established and reviewed elsewhere.[10–12] In brief, NO is predominantly produced by inducible NO synthase (iNOS), which is upregulated in airway epithelial cells, macrophages, and other inflammatory cells in response to the type-2 inflammatory milieu in asthma. Elevated FeNO levels reflect airway eosinophilic inflammation and aid the diagnosis of type-2/eosinophilic asthma in symptomatic patients with cough, wheezes, and dyspnea.[11–13] Elevated FeNO levels predict good responses to inhaled corticosteroid (ICS) treatment, particularly in ICS-naïve patients with asthma.[14,15] Basically, iNOS and FeNO levels are steroid-sensitive, and elevated FeNO levels in patients treated with ICS may indicate poor adherence to ICS.[12,14,16,17] On the other hand, elevated iNOS and FeNO may indicate ICS insensitivity or severe type-2/eosinophilic asthma,[12,18] which reflects a phenotype at an increased risk of future exacerbations.[19,20] Elevated FeNO levels also reflect oxidative/nitrative stress in the airways, which drives fibrosis progression[21] and may represent a marker of excess decline in pulmonary function when sufficiently elevated.[22,23] Thus, FeNO alone may identify severe type-2 predominant asthma in real-world settings. However, there may be a patient group, as discussed later, with high FeNO levels that are asymptomatic and stable for prolonged periods without demonstrating excess decline in pulmonary function. The mechanisms underlying the non-specific raise in FeNO levels remain unknown but may be augmented by several factors other than eosinophilic airway inflammation, such as height and male gender (Table 1). Constitutive NOS, of which sources are steroid insensitive, may also be involved.[24]

Serum periostin

Serum periostin is considered another promising biomarker of type-2/eosinophilic inflammation. Periostin expression is increased by stimulation with interleukin (IL)-4, IL-13, and transforming growth factor β mainly in airway fibroblasts and epithelial cells.[25–27] The utility of serum periostin in asthma management is also reviewed elsewhere.[27–31] Periostin, a matricellular protein, is a downstream product of the type-2 pathway; promotes eosinophil adhesion and recruitment to the airways[32]; and activates functions of eosinophils, including O_2^- generation.[33] Thus, high serum periostin levels are considered a marker of type-2/eosinophilic asthma and airway remodeling that results in an accelerated decline in pulmonary function.[34] Similar to FeNO,[35] high serum periostin levels are often accompanied by eosinophilic chronic rhinosinusitis-like conditions[29,36] and may predict treatment failure while tapering ICS doses[37] and good responses to biologics against type-2 pathway in patients with asthma.[38,39] In contrast with FeNO, serum periostin levels are stable with a small coefficient of variation[40,41] and may have a feature of ICS insensitivity.[29,42] These similar but different characteristics/modifiers indicate that high serum periostin levels may imply a more static disease process, while FeNO levels reflect more dynamic disease activity in patients with type-2/eosinophilic asthma on ICS treatment.[29] Although the precise mechanisms are unknown, elevated serum periostin levels are less frequently observed in obese patients with asthma,[43] which is also reported in a recent epidemiological study on serum periostin levels.[44] Possibly reflecting its fibrosis-prone nature,[45] serum periostin levels are elevated in fibrotic diseases, such as idiopathic interstitial pneumonia[46] and scleroderma[47] (Table 1).

Table 1
Characteristics of FeNO and serum periostin.

	FeNO	Serum periostin
Relevant cytokines	IL-4,[60,61] IL-13[60,62] IL-1β,[63] TNF-α[63]	IL-4,[25–27] IL-13[25–27] TGF-β[26,27]
Modifiers	Height ↑[64–66] Male gender ↑[66,67] Nitrate-rich diet ↑[68] Airway viral infection ↑[69] Current smoking ↓[70] Spirometric manoeuvers ↓[71] Atopic predisposition ↑[64,65,67] Allergic rhinitis ↑[65,72]	Idiopathic pulmonary fibrosis ↑[46] Scleroderma ↑[47] Bone marrow fibrosis ↑[73] Proliferative diabetic retinopathy ↑[74] Non-alcoholic fatty liver disease ↑[75] IgG4-related diseases ↑[76] Atopic dermatitis ↑[77]
Responsiveness to ICS	++[29]	+[29]
Pulmonary function decline	+[23] (when high enough)	+[34]

Comparisons between FeNO and serum periostin in the prediction of airway eosinophilia and diagnosis of pediatric asthma

Efforts to identify the best single marker with sufficient sensitivity and specificity to predict airway eosinophilia is clinically important. Although direct comparisons between FeNO levels and serum periostin levels are rarely reported (Table 2), serum periostin levels have been found to be the best predictor of airway eosinophilia among FeNO, blood eosinophil counts, serum IgE, and serum periostin in adult patients with severe asthma who remained symptomatic despite receiving high doses of ICS treatment (BOBCAT study) (n = 67; 32 males; mean age, 46 years; FEV_1, 60%; daily ICS doses >1000 μg fluticasone propionate equivalent; Asthma Control Questionnaire score, 2.7).[41] These results were not observed in another study of patients with mild-to-moderate asthma (n = 110; 54 males; mean age, 49 years; FEV_1, 100%; daily ICS doses, 500 μg fluticasone propionate equivalent).[48] However, the potential mechanisms underlying this discrepancy may be attributable to differences in periostin assay systems and disease severity among studied patients.[49] A recent study of Japanese pediatric patients with asthma reported a similar predictability of serum periostin and FeNO in distinguishing children with asthma from controls.[50] Thus, results from a single-marker approach may often depend on patient characteristics and the periostin assay kits used. Thus, a multiple-marker approach is expected to improve the accuracy in predicting severe type-2/eosinophilic asthma.

Combination of FeNO and serum periostin in the management of severe asthma

In several diseases, such as pancreatic adenocarcinoma,[51] Alzheimer's disease,[52] and severe graft-versus-host disease,[53] the superiority of a multiple-marker approach in terms of diagnostic accuracy over a single-marker approach has been reported. In mild-to-severe asthma, combinations of FeNO levels, blood eosinophil counts, and serum total IgE levels demonstrated no greater utility in predicting airway eosinophilia in asthma than single markers.[54] However, no studies of a composite marker of FeNO and serum periostin in predicting severe eosinophilic asthma have been reported.

In a sub-analysis of the Kinki Hokuriku Airway disease Conference (KiHAC) study, the utility of a composite marker of high FeNO and high serum periostin levels were examined. FeNO levels at a constant exhalation flow rate of 50 mL/s were measured using a