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Short-Acting β_2-Agonist Use Could Be a Confounding Factor for Interpreting Increased IL-6

To the Editor:

The proinflammatory cytokine IL-6 is upregulated approximately threefold during naturally occurring asthmatic attacks (1). Importantly, in relation to overuse of β_2-agonists in the context of asthma exacerbations, IL-6 induction by rhinovirus was further augmented by β_2-agonists (2). *In vitro* studies on bronchial epithelial cells demonstrated that IL-6 is upregulated by β_2-agonists (3).

SARP (Severe Asthma Research Program) enrollment procedures determined that participants maintained medications for asthma as prescribed by their care provider (4). I could not find details on the asthma medications use in the SARP III trials (4, 5). Peters and colleagues (5) did not address the possibility that β_2-agonist use might be confounding the association between plasma IL-6 and higher asthma exacerbation rates. Knowledge about the asthma medication and ideally about the blood levels of β_2-agonists is needed to exclude any influence of β_2-agonists on the increment of IL-6 increase before adopting it as an exacerbation-prone biomarker.

Jevnikar and colleagues (6) recently described a subset of patients with asthma and high IL-6TS. This subset constitutes a novel asthma phenotype associated with frequent exacerbations, eosinophilia, airway inflammation, remodeling, and impaired epithelial integrity. It was noted that 86% of the patients of U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes) cohorts used short-acting β_2-agonists and that 98% of the patients used long-acting β_2-agonists (7), but the authors did not take into account this probable confounding factor.

I would like to alert the authors of both studies that IL-6 could be upregulated by overuse of β_2-agonists. ■

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Systemic IL-6 and Severe Asthma

To the Editor:

We read with interest the findings of Peters and colleagues in patients with severe asthma who reported that an increase in baseline circulating IL-6 levels of 1 pg/μl was associated with a 10% increased risk of an exacerbation over 3 years and was 14% when excluding patients on oral corticosteroids (1). Elevated levels of IL-6 in induced sputum in patients with asthma are related to impaired lung function (2, 3).

IL-6 is also a key component of the cytokine response in viral illness. For example, in hospitalized patients with severe coronavirus disease (COVID-19), circulating levels of IL-6 are the strongest predictor of the need for mechanical ventilation. In the *in vitro* murine model of acute lung

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injury, systemic IL-6 levels are suppressed by both budesonide and formoterol (4). Furthermore, in primary airway epithelial cell cultures, pretreatment with budesonide, formoterol, and glycopyrronium inhibited IL-6 production after infection with the common cold coronavirus (HCoV-229E) (5). Single-inhaler therapy comprising beclomethasone, formoterol, and glycopyrronium reduces exacerbations in patients with uncontrolled asthma with persistent airflow limitation (6). Hence, we would be interested to know whether such patients who have higher levels of circulating IL-6 might benefit more from such triple therapy in terms of protection from viral-induced exacerbations including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). ■

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Reply to Nannini and to Lipworth *et al.*

From the Authors:

Dr. Nannini is concerned that IL-6 could be upregulated by overuse of β_2-agonists (1). This is unlikely because the SARP-III (Severe Asthma Research Program III) protocol included a bronchodilator medication hold for the blood collection visits. Specifically, short-acting β_2-agonists were held for 4 hours, and long-acting β_2-agonists were held for 12 hours (2), but the half-life of IL-6 in plasma is less than 15 minutes (3, 4). In addition, participants could only come in for study visits for blood collection if they had been free of an asthma exacerbation in the previous 4 weeks (2). This protocol feature limited the risk that increased β_2-agonist treatment associated with exacerbations influenced our analysis. Finally, and most importantly, our study focused on plasma IL-6, not airway IL-6, and we have previously reported that patients with IL-6–high asthma do not have high sputum concentrations of IL-6 (5). Instead, the IL-6–high subgroup has clinical features of metabolic dysfunction, including systemic leukocytosis and high frequencies of obesity, hypertension, and diabetes mellitus (5). Thus, we do not consider that high plasma IL-6 concentrations result from spillover from airway IL-6 but instead result from obesity-associated systemic inflammation, which might drive proneness to exacerbation in these patients (6).

Lipworth and colleagues provide important commentary on the links between IL-6 biology and airway viral infections, including coronavirus disease (COVID-19). We agree that IL-6 is a key component of the cytokine response to viral illness, and we believe it relevant that IL-6–high asthma is characterized by obesity and metabolic dysfunction (1, 5), because these comorbidities lead to accelerated immune senescence, which has been linked to poor vaccination responses (7) and impairments in cytotoxic T-lymphocyte function (8). We have reported previously that obesity is associated with decreased airway gene-expression signatures for cytotoxic T lymphocytes (9), so that high plasma IL-6 levels may be marking patients with impairments in airway T-cell responses to viral airway infections, including COVID-19. It is not known whether triple therapy with beclomethasone, formoterol, and glycopyrronium will address this impairment or decrease susceptibility to airway viral illness. Clinical trials will be necessary to determine that. ■

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