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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