2. von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, *et al*. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. *JAMA* 2013;309:2457–2464.
3. Iwashita T, Yasuda I, Doi S, Kato T, Sano K, Yasuda S, *et al*. The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy* 2008;40:400–405.
4. Reich JM, Brouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest* 1998;113:147–153.
5. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, *et al*. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e26–e51.

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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Luis J. Nannini, M.D.*
Neumonología Hospital "E Perón"
Granadero Baigorria, Argentina

and

Universidad Nacional de Rosario
Rosario, Argentina

ORCID ID: 0000-0002-9868-9883 (L.J.N.).

*Corresponding author (e-mail: ljnannini@hotmail.com).

References

1. Yokoyama A, Kohno N, Fujino S, Hamada H, Inoue Y, Fujioka S, *et al*. Circulating interleukin-6 levels in patients with bronchial asthma. *Am J Respir Crit Care Med* 1995;151:1354–1358.
2. Ritchie AI, Singanayagam A, Wiater E, Edwards MR, Montminy M, Johnston SL. β_2-agonists enhance asthma-relevant inflammatory mediators in human airway epithelial cells. *Am J Respir Cell Mol Biol* 2018;58:128–132.
3. Johnston SL, Edwards MR. Mechanisms of adverse effects of β-agonists in asthma. *Thorax* 2009;64:739–741.
4. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, *et al*. Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;6:545–554, e4.
5. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, *et al*., NHLBI Severe Asthma Research Program. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. *Am J Respir Crit Care Med* 2020:202:973–982.
6. Jevnikar Z, Östling J, Ax E, Calvén J, Thörn K, Israelsson E, *et al*.; Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes study group. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. *J Allergy Clin Immunol* 2019;143:577–590.
7. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, *et al*.; U-BIOPRED Study Group. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;46:1308–1321.

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

Originally Published in Press as DOI: 10.1164/rccm.202006-2297LE on July 20, 2020

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202006-2354LE on July 20, 2020