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## Reply to Lipworth et al.

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## Don't Forget about Facilitatory Effects of Corticosteroids on $\beta_2$ -Adrenoceptors in Acute Asthma

To the Editor:

We read with interest the findings of Moran and colleagues showing equally rapid reductions in blood eosinophils with oral prednisolone and subcutaneous benralizumab (1) in patients with poorly controlled asthma. The authors go on to suggest that benralizumab might be used as an alternative to corticosteroids for the treatment of acute exacerbations of eosinophilic asthma. Their data was not obtained in the setting of acute severe airflow obstruction, where airway smooth muscle constriction also plays a key role in airflow limitation in addition to endobronchial inflammation. Pointedly, they did not comment on whether the acute fall in eosinophils was accompanied by a commensurate improvement in airway geometry as FEV<sub>1</sub>. In this regard, the findings of Moran and colleagues do not take into account the acute facilitatory effect of systemic corticosteroids such as prednisolone on airway smooth muscle in terms of rapid upregulation and resensitization of  $\beta_2$ -adrenoceptors in patients with acute asthma, especially those who have been taking inhaled corticosteroids with long-acting  $\beta_2$ -agonists (2). Moreover, benralizumab exhibits antiinflammatory activity by suppressing eosinophils alone, whereas corticosteroids have more broad-spectrum activity on a variety of inflammatory cells in asthma. Notably, benralizumab is also considerably more expensive than oral prednisolone. Hence, although we would advocate for benralizumab as a suitable long-term treatment for reducing exacerbations in severe eosinophilic asthma, we would not endorse its routine use for treatment in acute asthma. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Reply to Lipworth *et al*.

From the Authors:

We thank Dr. Lipworth and colleagues for their interest in our work published recently in the *Journal* (1). They rightly point out that the biology of asthma attacks is more complex than blood eosinophils alone and that corticosteroids have a wide range of other potentially relevant antiinflammatory effects. However, local treatment with inhaled corticosteroids (ICS) is usually the mainstay of patients with frequent eosinophilic exacerbations, and therefore in the great majority of patients, the key question is what oral corticosteroids (OCS) add to ICS in an acute attack (2) and whether this effect is seen with benralizumab. We suggest that depletion of circulating eosinophils is the only effect OCS are likely to have that are not shared with ICS (3).

Because OCS are known to have severe side effects, and in noneosinophilic exacerbations of chronic obstructive pulmonary disease they are actually harmful (4), it would be a significant advance to determine whether a combination of ICS and rapidly acting anti-IL-5 treatment would cover all the benefits of OCS in acute asthma while mitigating the harms of OCS. With respect to this, we recently published a case report (5) that showed the addition of benralizumab to ICS resulted in a dramatic improvement of peak flow and FEV<sub>1</sub> within 6 hours when given to treat an asthma attack in a patient in whom systemic corticosteroids were contraindicated. We believe that these findings support the idea that systemic targets of benralizumab that express the IL-5 receptor (such as eosinophils and basophils) play a pivotal role in sustaining the nonbronchodilator responsive airflow limitation seen in asthma attacks.

The use of benralizumab in acute asthma may also provide other benefits. Treatment failure is a major issue in

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the current acute asthma treatment paradigm (6). The longer half-life of benralizumab and the harms of systemic corticosteroids may tip the cost–benefit assessment in favor of benralizumab.

We agree that more work is needed before benralizumab becomes an option for the management of asthma attacks. Nevertheless, the rapidity of eosinophil depletion certainly makes it an exciting prospect. We look forward to the results of our clinical trial to examine this idea (clinicaltrials.gov ID: NCT04098718). ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Erratum: COVID-19–related Genes in Sputum Cells in Asthma: Relationship to Demographic Features and Corticosteroids

Our article, published in the July 1, 2020, issue of the *Journal* (1), contained an error in the number of healthy control subjects. The paper reported on 330 asthma participants in the SARP-3 (NHLBI Severe Asthma Research Program-3) cohort and 79 healthy control subjects (57 recruited by the University of California San Francisco [UCSF] Airway Clinical Research Center and 22 recruited by SARP-3). We recently discovered that a coding error resulted in sputum cell RNA from 47 mild asthma patients being included in the UCSF healthy subject group. To correct the error, we removed the 47 mild asthma patients and reanalyzed the data. After performing the reanalysis including the 22 healthy subjects from SARP and 10 healthy subjects from UCSF (total of 32 healthy controls) (revised Table 1), we found that our study conclusions remain the same. As illustrated in revised Figures 1 and 2, sputum cell gene expression for COVID-19–related genes (ACE2 [angiotensin-converting enzyme 2] and TMPRSS2 [transmembrane protease serine 2]) are not significantly different in asthma and health (revised Figure 1A and 1B), and sputum cell gene expression for ACE2 and TMPRSS2 are significantly correlated with one another (revised Figure 2A). The reanalysis shows that the *P* value for the increase in asthma for sputum cell ICAM1 expression (a comparator/control gene) compared with health increased from 0.005 to 0.09 (revised Figure 1C). The main data for the paper, as originally presented in Figures 3 and 4 and which relied on data analyses that were restricted to the asthma cohort, do not need correction.

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