COMMENT ON ALBOGAMI ET AL.

Glucagon-Like Peptide 1 Receptor Agonists and Chronic Lower Respiratory Disease Exacerbations Among Patients With Type 2 Diabetes. Diabetes Care 2021;44:1344–1352

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We read with interest the article by Albogami et al. (1) on the association of glucagon-like peptide 1 receptor agonists (GLP-1RAs) and respiratory exacerbations among patients with asthma and/or chronic obstructive respiratory disease (COPD). In particular, the main conclusion that GLP-1RA initiation may be associated with a subsequent decrease in respiratory exacerbations echoes our findings recently published in the *American Journal of Respiratory and Critical Care Medicine* (2). Using electronic health records (EHR) of patients with asthma and comorbid type 2 diabetes, we found new initiators of GLP-1RAs had fewer asthma exacerbations than initiators of alternative step-up diabetes therapies in the 6 months following drug initiation. Albogami et al. extend these findings (compared to dipeptidyl peptidase 4 inhibitors and sulfonylureas) to 12 months of follow-up and additionally examine a COPD population, broadening the clinical relevance of GLP-1RAs to respiratory disease.

While our study did not examine a COPD-only population, our findings were consistent among patients with moderate and severe asthma, including asthma and comorbid COPD, a population included in the study by Albogami et al. but not examined in the stratified analysis. It is unsurprising that, for the primary outcome (hospitalizations) among the asthma-only population, results did not reach statistical significance. Hospitalizations for asthma are relatively rare, particularly in a population with a mild asthma phenotype and with the advent of biologics. We would, however, expect to see a more significant effect for the study's secondary outcome (e.g., corticosteroid prescriptions) and were wondering if this outcome was examined in a stratified analysis by the authors.

As Albogami et al. discuss, claims data are limited by the lack of obesity data as well as access to relevant laboratory values; these variables are present in the EHR. We found that even when accounting for baseline HbA_{1c}, baseline BMI, and changes in both parameters over the study period, GLP-1RAs were associated with fewer exacerbations than comparator drugs. This aligns with the authors' efforts to adjust for obesity in their sensitivity analyses and supports their findings. Conversely, a strength of claims data is pharmacy fill confirmation, which the EHR lacks. The findings by Albogami et al. increase our confidence in the strength of the observed associations between GLP-1RA initiation and the range of different respiratory-related outcomes in both studies.

Finally, a growing body of preclinical data demonstrates GLP-1RA impact on allergic airway inflammation (3), specifically type 2 biomarkers of airway inflammation, including the interleukin-13 pathway in mice and humans (4). Therefore, agonizing the GLP-1 receptor may have both direct and indirect actions on airway smooth muscle via inflammatory pathways, uniquely impacting airway inflammation in asthma versus COPD. Similarly, obesity and metabolic dysfunction may have distinct impacts on asthma and COPD phenotypes. Future studies of GLP-1RAs in COPD should include assessments of airway inflammation (i.e., eosinophil counts), spirometry, and BMI.

We welcome the addition of the findings by Albogami et al. and believe that, together with our previously published work, they present a convincing case for prospective examination of GLP-1RA use in patients with comorbid type

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2 diabetes and obstructive respiratory disease, a population in great need of novel approaches to intervention (5).

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