Asthma Exacerbations in Individuals on Glucagon-like Peptide-1 Receptor Agonists for Type 2 Diabetes

To the Editor:

We welcome the finding by Foer and colleagues (1) of a statistically significant reduction in asthma exacerbations after the initiation of GLP-1 (glucagon-like peptide-1) therapy versus other medications for type 2 diabetes mellitus. Whereas earlier work had hypothesized that GLP-1 therapy might lead to improved exacerbation frequency and Asthma Control Questionnaire (ACQ) scores if weight loss above the median was achieved (2), the current work points to an effect of GLP-1 therapy independent of its weight loss–promoting properties.

The authors acknowledge that established atherosclerotic cardiovascular disease (ASCVD) could be a confounder where the secondary outcome, asthma symptoms, is concerned but omitted to state whether this may also be true in the case of the primary outcome (asthma exacerbations). Could the authors clarify whether the inclusion of ASCVD in the propensity score affects the primary outcome?

An analysis limited to the human-analog GLP-1R (GLP-1 receptor) agonists (lixisenatide, dulaglutide, and exenatide) may also be useful in excluding any confounding effect by ASCVD, as the authoritative guidelines cited by the authors favor these agents over the exendin-based GLP-1 receptor agonists (exenatide and liraglutide) when treatment considerations such as ASCVD or weight management (promoting loss or limiting gain) exist.

Pooling GLP-1 analogs and exendin-based GLP-1 agents in the analysis may limit the study, as it is possible that these two subclasses have slightly different actions, particularly where nonincretin effects (which are less well understood) are concerned. For example, some actions of GLP-1 may be receptor independent; this has been proposed to occur in the liver by transmembrane transport of GLP-1 degradation products GLP-19–36, GLP-128–360, or GLP-132–36 where adenyl cyclase and Wnt signaling is consequently activated (3).

The authors selectively note that Asthma Control Test (ACT) and ACQ use symptoms of “shortness of breath” and “wheeze” to measure symptom control and that patients on GLP-1R agonists had fewer associated encounters coded with these symptoms compared with basal insulin and sulfonylurea users. One could equally note that both ACQ and ACT contain an item measuring rescue bronchodilator use, and the exploratory analyses identified no differences across groups compared with GLP-1R agonist users for short-acting β2-agonist prescriptions during the study period, thus underlining the need for a prospective trial to assess whether GLP-1 therapy results in improvements exceeding the minimal clinically important difference in composite scores, such as the ACT and ACQ, as well as in objective asthma outcomes preferred for regulatory approval, such as FEV1.

We also observe that this study does not allow for patients to be phenotyped as type 2 high or low. Most of the preclinical studies have focused on the effect of GLP-1 on T-helper type 2 (Th2)-type inflammation—for example in BALB/c mice (4)—and none have modeled obesity. Yet those with the unmet need cited by the authors (i.e., those with asthma unresponsive to inhaled corticosteroids) tend to have a Th2 gene expression signature similar to that of healthy control subjects (Th2-low) (5), the proposed “late-onset nonallergic” phenotype, affecting primarily middle-aged women with obesity. Prospective studies are needed to investigate whether the benefits demonstrated in this study are evenly distributed among those with evidence of type 2 high inflammation and those without. A benefit in this latter group is plausible, as GLP-1 is known to ameliorate both dysregulated arginine metabolism and advanced glycation end-product–mediated inflammation—pathways common to both obesity and asthma pathophysiology (6)—and would begin to address their currently unmet need.

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We appreciate the insightful comments by Watchorn and colleagues in response to our report on the association between asthma exacerbations and GLP-1RA (glucagon-like peptide-1 receptor agonist) use in patients with comorbid asthma and type 2 (T2) diabetes mellitus (T2DM). The intersection of metabolic disease and asthma is a complex and compelling area of study with direct implications for treatment strategies and clinical outcomes aligned with regulatory approval metrics—we absolutely agree, and we look forward to this unfolding area of investigation.

In conclusion, Watchorn and colleagues’ letter highlights the need for prospective studies of GLP-1RA therapy using single agents within the class (e.g., GLP-1 analogs or exendin-based therapies) in well-phenotyped asthma populations with outcomes aligned with regulatory approval metrics—we absolutely agree, and we look forward to this unfolding area of investigation.

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