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Peer Review File

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Reviewer A

The authors issue a well - documented potential hypothesis.
Reply: Thank you for the kind comment.

Reviewer B

Overall a great summary article. Well-done and well-organized.
Reply: Thank you for the kind comment.

Line 60 - "a group that shares common characteristics" is not needed
Reply 1: the words were removed.
Changes in text: Eosinophilic esophagitis (EoE) is considered to be a type 2 helper cell (Th2) disease. However, EoE, unlike asthma,…..

Line 67 - "diseases." is missing the letter "s"
Reply2: Spelling error was corrected.
Changes in text: markers for other representative Th2 diseases

Lines 156-8 - "The potential significance to the lack of biomarkers is the observation that in asthma the benefit of treatments targeting type 2 cytokines is restricted to patients who have biomarkers of type 2 inflammation" - statement is no longer true, as tezepelumab, which targets TSLP, is effective for asthma regardless of endotype and does not require a biomarker. Please amend.
Reply3: We agree, that these important recent results deserve to be added to the manuscript. However, we interpreted the original statement in reference 2 a little differently from the reviewer. Specifically, that a parenteral anti-TSLP treatment would be efficacious in patients with elevated serum levels of TSLP itself. I have modified the text accordingly.
Changes in text: However, a more recent abstract (new reference 12) has reported that the anti-TSLP antibody, Tezepelumab, has efficacy in asthma that is independent of the serum levels of several biomarkers including IL5, Il13, IgE, periostin, or TARC. Future work will likely examine if elevated serum levels of TSLP, which has been observed in asthmatic cohorts (see table 2) will predict a therapeutic response to

Tezepelumab.

New reference 12: American Journal of Respiratory and Critical Care Medicine 2019;199:A2621
Tezepelumab Treatment Effect on Annualized Rate of Exacerbations by Baseline Biomarkers in Uncontrolled Severe Asthma Patients: Phase 2b PATHWAY Study
J. Corren 4, E. Garcia Gil 2, J.R. Parnes 1, T.-H. Pham 3, J.M. Griffiths 3, https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.
J. Corren [4], **E. Garcia Gil** [2], **J.R. Parnes** [1], **T.-H. Pham** [3], **J.M. Griffiths** [3], https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A2621

Line 165- "Dipulimab" is a spelling error.
Reply: thank you for picking up on that.
Change in text: However, Dupilumab

Line 180-81 "Whereas this could be interpreted as multiple “negative studies” in EoE, the authors propose that a distinct pathophysiology accounts for this incongruity." - I just like this sentence. Nice work.
Reply: Thanks again.

Conclusions section - I'd like a bit more about work examining potential biomarkers as a "future of the field." "Future studies" is good, but what specifically do you think would be valuable? There are small pilot studies on urinary 3-bromotyrosine, for example, that look potentially interesting (PMID 27017558).
Reply: Actually, our intention was the potential for studies that would directly test (hopefully validate, which is the real aim of our manuscript) the hypothesis.
Change in text: . Future work will be able to examine this hypothesis in a more direct fashion with in vitro models and most importantly, with the development of an anti-TSLP agent that can be delivered locally to the inflamed EoE mucosa, analogous to the use of topical, swallowed corticosteroids.

Overall comment - EoE really does respond well to dupilumab. Why? I'd emphasize that somewhere, as we expect approval for EoE in ages 12+ in June 2022.
Reply: agree with that observation (but was unaware of the pending approval)
Change in text (immediately after mention of Dupilumab in line 165—Dupilumab was recently granted orphan status, and because of encouraging results will likely receive approval in the near future.

Table 3 - Three comments.

1) these drugs are not all biologics. Timapiprant (OC000459) is a small molecule inhibitor - it is not a biologic. Please amend.

Reply: Thank you pointing that out.

Change in text: This row has been removed from Table 3

2) RPC4046 did perform well in a real-world extension study (PMID 32205221)

Thank you for bringing that study to our attention. That reference has been added (86) to supplementary bibliography. However, although the authors consistently utilize the words clinical and histologic improvement, Figure 1demonstrates that only about ½ of the patients in the long term extension were able to receive histologic remission (<15 eos/hpf) or symptomatic remission (Eosinophilic Esophagitis Activity Index (EEsAI) score of 20 or less).

Change in text: (In Table 3) Reduced endoscopic (EREFS) and histologic (EoEHSS) disease activity; but after 12 months only ~50% had <15 eos/hpf or symptom remission.

3) Row on RPC4046 - "dysphasia" is an error. Should be "dysphagia." Please amend

Reply: Thank you for picking up on our error. As indicated in the above comment, that word has been removed from table 3.

Change in text: (In Table 3) Reduced endoscopic (EREFS) and histologic (EoEHSS) disease activity; but after 12 months ~50% had <15 eos/hpf or symptom remission

Change in text: In legend to Table 3: The remaining 9 studies failed to show meaningful therapeutic responses, or achieve remission in a substantial portion of patients (IL-13, ref 86).