Peer Review File

Article information: https://dx.doi.org/10.21037/ajo-23-28

Reviewer A

The authors reported the effectiveness of mepolizumab for the CRSwNP and eCRS, and they compared the clinical and disease features between responders and non-responders. They found that responders were likely to have more severe symptomatic disease baseline. The focus point is interesting and suits to the readers of this journal, however, I have several concerns below.

Major comments

1. The impression is that there are many typographical errors and mistakes in figures and wording. Please check carefully.

Reply: These have been checked and corrected throughout the text.

2. The diagnosis of eCRS was unclear, please clarify this.

Reply:

This has been clarified in the methods.

Methods (lines 139-143)

> Adult patients (≥18 years) diagnosed with eCRS (based on sinonasal tissue eosinophilia >10 per high power field [400x magnification] on at least two HPFs, on a biopsy during which all patients had ceased systemic corticosteroid medications at least 4 weeks beforehand)[11] and assessed by a tertiary rhinologist as having disease not controlled by the current standard of care, requiring biologic therapy for management of their disease.[3]

3. Recruitment of subjects was unclear and not unified. The corticosteroid using must affect the diagnoses of eCRS. They should consider the effectiveness for diagnose to eCRS to result and discussion.

Reply:

This has been addressed in both the methods and discussion.

Methods (lines 139-143)

> Adult patients (≥18 years) diagnosed with eCRS (based on sinonasal tissue eosinophilia >10 per high power field [400x magnification] on at least two HPFs, on a

biopsy during which all patients had ceased systemic corticosteroid medications at least 4 weeks beforehand)[11] and assessed by a tertiary rhinologist as having disease not controlled by the current standard of care, requiring biologic therapy for management of their disease.[3]

Methods (lines 168-169)

Current medications (name and dosage) were recorded at screening and reviewed at each treatment visit.

Methods (lines 172-173)

Patients were not permitted to have oral corticosteroid courses for the duration of the study.

Discussion (lines 401-406)

Study participants were defined based on both tissue confirmation of eCRS (based on prior sinonasal biopsy, during which all patients had ceased systemic corticosteroid medications at least 4 weeks beforehand) as well as failure of current standard of treatment for CRS.[1] Defining eCRS based on tissue histopathology (and confirmed on baseline tissue histopathology) allowed this study to assess the effect of mepolizumab on a group of patients with CRS driven by Th2 dominant inflammation at the sinonasal mucosal level, which had not been previously studied.

4. The many tables of results are cumbersome and difficult to understand. Please re-consider or organize the tables for easier understanding and unify the digits in Tables. In addition, the figures in the text and the figures in the charts are not consistent. Please check carefully.

Reply: Tables have been simplified and more detailed results have been included as supplementary tables 1-3. Figures have been checked so that they correctly correlate with the text.

5; Among the responder patients, nNo was low, the reviewer thinks this result is important. Please consider or reflect on the discussion and abstract.

Reply:

The authors have added in the following to the abstract and discussion.

Abstract (lines 80-82)

***Conclusion**: In eCRS, responders were likely to have more severe symptomatic disease at baseline and lower nNO. Cessation of mepolizumab is associated with deterioration of both objective and subjective markers.*

Discussion (lines 493-500)

In this study, baseline nNO was significantly lower in CRS responders than in non-responders. There are multiple contributors to decreased levels of nNO including mucociliary dysfunction, obstructive remodelling changes and anatomical variability in eCRS.[40] Although the mechanism of action is not entirely clear in this study, impaired sinonasal production of nNO (i.e. low nNO levels) may act as a marker of more severe inflammation, which in turn may be more sensitive to IL-5 inhibition by mepolizumab. The usefulness of nNO as a biomarker in inflammatory sinus disease requires further investigation due to the complex variability in and interaction between the anatomical, pathological and physiological contributors to NO production.[41]

Reviewer B

This is an interesting paper on one of the new biologic medications for rhinosinusitis. Although it is pilot study, with limited number of patients (20), the study is well-designed and executed. The information is important and relevant for further studies on the topic. Therefore we suggest accepting it for publication.