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Name of Journal: ***World Journal of Gastrointestinal Pharmacology and Therapeutics***

ESPS Manuscript NO: 21751

Manuscript Type: REVIEW

October 5, 2013

Shui Qiu, Science Editor, Editorial Office,
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA

Dear Dr.Qiu:

Thank you for your insightful review of our manuscript entitled "Recent discoveries and emerging therapeutics in eosinophilic esophagitis". We have addressed the issues raised by the Reviewer, and we have incorporated the suggested changes into our manuscript.

Response to Reviewer 1:

Point 1. …. *I would suggest adding some information on role of long-term topical steroid therapy (maintenance therapy) in eosinophilic esophagitis (EoE) to make it more complete.*

In response to the reviewer's suggestion we have added the following in our manuscript. In children, both fluticasone and oral viscous budesonide (OVB) have demonstrated histological remission after 3 months of intervention in double blind randomized placebo controlled trials which correlated to symptom improvement. Subepithelial fibrosis was seen to improve with OVB therapy. In adults, fluticasone induced histological remission in 62% of adults, however the response was not accompanied by a relief of symptomatic dysphagia.

Long-term data on budesonide as a maintenance therapy was assimilated by Straumann et al. Patients who took low dose swallowed budesonide for 50 weeks achieved partial remission (i.e. reduced eosinophilia) compared to placebo. In addition, mucosal remodeling was attenuated in the treatment group without signs of epithelial atrophy.

Point 2. …. *Page 11 CRTH2 typed as CHTH2*

It has been modified as suggested to CRTH2 in the following sentence- Therefore, CRTH2 is an appealing target for Th2-type inflammatory disorders.

Point 3. …. *Page 12 - randomize should be randomized*

It has been modified as suggested to randomized in the following sentence - A randomized controlled trial demonstrated a modest improvement in eosinophilic inflammation and clinical symptoms in 26 severe, steroid-refractory EoE adults compared to placebo

Point 4. …. *Page 13 - show"ed" significant improvement*

It has been modified as suggested - A randomized controlled trial conducted in children and adolescents did not show statistically significant symptomatic improvement with reslizumab compared to placebo, but did show significant improvement in esophageal eosinophilia compared to placebo.

Response to Reviewer 2:

Point 1. …. *Introduction needs to be edited. Several sentences are not clear, such as "Despite 20 years, EoE is relatively a newly recognized disease".*

It has been modified as per the suggestion as- EoE was first recognized almost 20 years ago as a distinct entity. EoE is relatively a newly recognized disease.

Point 2. …. *Please edit carefully. -Throughout the paper punctuation is placed before references .(4)I believe this is incorrect and should be as follows(4).*

The references have been modified as per the suggestion and placed before the punctuation mark throughout the manuscript. Example- Adolescents and adults are more likely to present with dysphagia, food impaction, heartburn, and strictures[1].

Point 3. …. *Please discuss literature on how many biopsies are adequate from the mid and distal esophagus, this is an important clinical question. Are 4 biopsies needed? Any data to support 2 versus 4?*

In the manuscript we have discussed about a study by Nielsen et al. who examined biopsy fragments in 102 adult EoE cases and determined that a minimum of 4 biopsy fragments from the mid and/or proximal esophagus submitted in separate containers would optimize diagnostic yield for EoE. We did not come across any study in literature which per se has looked at any data comparing the diagnostic yield of two versus four biopsies.

Point 4. ….*Page 7 Line 2, replace "are evidence" with "is evidence"*

It has been modified as- While EoE involves an eosinophil-predominant inflammation, there isevidence to suggest that other immune cells, such as mast cells, basophils, and invariant natural killer T cells also mediate inflammation.

Point 5. ….*Please expand the section on steroid use. Please discuss dosing, length of treatment, recurrence rate, outcomes. These are critical pieces of information for a clinician about one of the most common drug treatments for EoE.*

As per the suggestion of the reviewer the recommended dosages of fluticasone and budesonide, length of treatment, recurrence rates and outcomes have been added in the manuscript as follows.

Currently, the American College of Gastroenterology (ACG) guidelines recommend Fluticasone 880-1760 mcg per day in a divided dose for adults and 88-440mcg/day for children. The dosage of OVB is 1mg per day for children and 2mg per day in divided doses for adults. The recommended duration is 8 weeks for topical steroid therapy.

In children, both fluticasone and oral viscous budesonide (OVB) have demonstrated histological remission after 3 months of intervention in double blind randomized placebo controlled trials which correlated to symptom improvement. Subepithelial fibrosis was seen to improve with OVB therapy. In adults fluticasone induced histological remission in 62% of adults, however the response was not accompanied by a relief of symptomatic dysphagia.

Long term data on budesonide as a maintenance therapy was assimilated by Straumann et al. Patients who took low dose swallowed budesonide for 50 weeks achieved partial remission (i.e. reduced eosinophilia) compared to placebo. In addition, mucosal remodeling was attenuated in the treatment group without signs of epithelial atrophy.

Overall, the disease typically relapses within 2–9 months after discontinuation of steroids.

Point 6. ….*Please expand on the indications for dilation, and any literature on the long term success of dilation without medical treatment.*

In the manuscript we have added finding from randomized blinded controlled trial which evaluated response to dilatation as an early treatment strategy in adults with dysphagia (without severe strictures) and esophageal eosinophilia. The subjects treated with medications (PPI and fluticasone) and randomized to dilation procedures did not have any better dysphagia score outcomes compared to subjects treated with medical therapy alone. We did not come across any study which looked the success of dilatation without use of medications in the absence of fibrostenotic complications of EoE.

We thank the editors and reviewer for their helpful suggestions. The incorporation of

the suggested changes and clarifications has strengthened our report, and we hope that you now find it acceptable for publication. We look forward to hearing from you.

Sincerely yours,

Edaire Cheng, M.D

Aakash Goyal, M.D