

Point to point Response:

Round 1

Reviewer#03646555:

Several English-language errors Abstract line 5= "inhalatives" should be "inhalers" Introduction line 3= "histopathologically" should be "histopathologically" Introduction line 22= "like for example" should be "such as" Introduction line 30= "Esophageal Eosinophilia" should be "Esophageal eosinophilia" Introduction line 35= "(dysphagia-)" should be "dysphagia" Treatment objectives in EoE line 26= "exact extend" should be "exact extent" Treatment objectives in EoE line 34= "thorough patient information" should be "through patient information" Treatment objectives in EoE line 36= "therapy-adherence" should be "therapy adherence" Fluticasone line 27= "The succeeding phase 2b study" should be "The subsequent phase 2b study" Fluticasone line 31= "1.5mg HS"- what does this mean? HS is not a common abbreviation. Fluticasone line 37= "EoE-treamtent" should be "EoE treatment" Budesonide line 1= this sentence is too long. I suggest removing the words "sweet and easy to swallow", which are largely self-evident. Budesonide line 28= "szintigraphically" should be "scintigraphically" Long-term-treatment= paragraph title should be "Long term treatment" Long term treatment line 27= "showed significant higher" should be "showed significantly higher" Long term treatment line 36= "afore mentioned" should be "aforementioned" Long term treatment line 50= "comparable low" should be "comparably low" Long term treatment line 53= "already mentioned" should be "aforementioned" Possible side effects of STCs line 3= "averagely" should be removed (it is not an appropriate word) and "8,7%" should be "8.7%". Possible side effects of STCs line 14= "most of esophageal candidiasis-cases" should be "most esophageal candidiasis cases" Possible side effects of STCs line 17= "microabszesses" should be "microabscesses" Practical management line 28= "no biomarker was" should be "no biomarker has been" Practical management line 30= "unspecific" should be "non-specific" Practical management line 37= "there's" should be "there is" Practical management line 42= "don't have to be expected" should be "rarely occur". Other issues: In table 1, the column mean age expresses numbers in the European manner (9,6) instead of the standard scientific manner (9.6). In the final row, the mean age is 11-55- what does this mean?

- Thank you for your excellent corrections. Suggested changes were done in the text/table

I think reference 78 should be expanded upon in the text (adrenal suppression in 10% of children). How was this measured? Did this improve upon cessation of steroids in these children? This is a potentially very concerning side effect.

- Thank you for your remark. We expanded reference 78 accordingly in the text.

I think after reference 31, more should be done by the authors to explain the potential mechanisms of actions of glucocorticoids at the cellular level. A few more sentences would suffice.

- We added the information to our manuscript.

In the Fluticasone section, it is stated "All these studies used fluticasone as a nebulized preparation, which may explain lower response rates compared to budesonide, which has

been usually administered as a viscous suspension or as an esophagus-specific targeted formulation [58]". However this sentence does not belong in this section, as the authors have not yet discussed budesonide, and not presented any of the limited data yet about head-to-head comparisons. This sentence should just be omitted.

- We agree, the sentence was removed.

In the Long term treatment section, it is stated "treatment was stopped, which was only possible in 9.4% of patients after averagely 89 weeks". Please rephrase: averagely is not an appropriate word. Is this a median or mean time to treatment cessation?

- changed

In the Long term treatment section it is stated "Recently, results of an open-label extension study with the afore mentioned budesonide oral suspension (BOS) have been published. 82 EoE-patients who completed 12 weeks of either budesonide (2mg twice daily) or placebo therapy received another 24 weeks budesonide (2 mg once daily for 12 weeks, with optional dose increase (1,5-2 mg twice daily) for 12 weeks thereafter). 42% of the therapy responders maintained a histologic remission during the open-label extension and 4% of non-responders gained response [45]."

However these findings do not actually support the premise of this paragraph, which is that long term treatment is important. This extension period did not involve some patients taking placebo as a comparison group. Therefore it is unclear whether the 42% who maintained a histologic remission did so as a function of ongoing therapy or not.

- In our opinion, the study mentioned supports the potential success of long term STC-treatment, although a placebo group is lacking which is rather a limitation of the study than a complete negation of the therapeutic effect.

The following sentence "Although an esophagus targeted oral suspension was used, initial histological remission has already been comparable low with only 39% [43]" is grammatically incorrect, and it is unclear what the significance of this sentence is in the context of discussion of long term therapy. It could probably be omitted.

- The sentence was erased

In the Practical management section: "Best results still exist for the easy and cheap to measure but rather unspecific absolute eosinophilic count (AEC), which thus might be helpful for therapy monitoring in some EoE patients [80]."

This needs further clarification. If the authors state that no biomarker is reliable enough to replace endoscopy, what is the evidence for using absolute eosinophilic count? Can they expand more on reference 80? Furthermore, can the authors clarify if this refers to serum eosinophils?

- We edited this section accordingly and added additional citations.

In the Practical management section: The section discussing PPI's is overly long and ultimately irrelevant to the main article topic, which is steroids. I think it should be summarised in just one or two lines, and moved up to the section "Short-term treatment: induction of remission".

- We agree, we removed the entire paragraph.

The structure of the article can also be improved. The paragraphs "Fluticasone" and "Budesonide" are very long and therefore somewhat difficult to follow. Furthermore, discussion of Dellon's head-to-head trial of budesonide vs fluticasone should be discussed

after these paragraphs, not in lines 10-23 of the much lower paragraph entitled "Practical management". Therefore I suggest the authors subdivide their work into the following small paragraphs, with appropriate headers, from "Fluticasone" onward:

1. Fluticasone inhalers versus placebo 2. Oral fluticasone preparations versus placebo 3. Oral budesonide slurry versus placebo 4. Oral budesonide tablets and oral suspension versus placebo 5. Fluticasone inhalers versus esomeprazole/ prednisolone 6. Head-to-head comparisons between steroid doses and routes of administrations (this can incorporate lines 10- 23 of Practical management)

- Thank you for your suggestions, however, we intended to first describe the different STCs and according therapeutic studies. In the practical management section we then critically compared STC treatment-options. Therefore, we would prefer to keep our chosen structure of the article.

Reviewer#00504545:

It is a very interesting paper with a broad review of the "state of the art" of the efficacy of the swallowed topical corticosteroids (mainly fluticasone and budesonide) in the short term evolution of the patients with Eosinophilic Esophagitis that are very well done comparatively with placebo in RCTs. There are less experience in the long-term treatment of these patients. It is an excellent review of this subject and is very well written.

- Thank you

Reviewer#03473965:

I salute the authors for scrutinizing the literature for EoE treatment. As this manuscript has the ambition of a review, I would like a method section describing the selection of the referred articles in the text. I think it is important to mention in the concluding chapter that Jorveza is the only approved brand on the European market, and that long-term treatment only is recommended within a research setting. You mention in brief the PPI-treatment. A short segment on food restrictions would be nice. Infants are not 3-15 years old;) (page 9).

- Thank you for your comment. In the practical management section we stated, that the budesonide orodispersible tablet (Jorveza) is the only approved medication for EoE in Europe. As suggested by reviewer 1, we completely deleted the PPI section, because this was not the scope of our review, focusing on PPI-treatment. Therefore, we also do not include a section on food restriction diets. "Infants are not 3-15 years old" -> we corrected this.

Reviewer#02542970:

This paper reviewed Treatment of Eosinophilic Esophagitis with Swallowed Topical Corticosteroids. it would bring some new information in this area.

- Thank you

Round 2

Excellent. Thank you for answering all my previous extensive comments. Only a few small grammatical comments, apologies if I missed some of these at my last revision. It is otherwise ready to publish.

1. in the abstract, the sentence "So far, mainly asthma inhalors containing either budesonide or fluticasone have been administered to the esophagus by swallowing these inhalatives "off label". "Inhalors" should be spelt "inhalers". "these inhalatives" should probably be reworded "medications".

Done

2. In the sentence "Recently, a phase 1/2a safety and tolerability study found very promising clinical, endoscopical and histological response rates in 22 patients", the word "endoscopical" should be "endoscopic".

Done

3. In the sentence "In addition, an orally administered powder formulation of fluticasone (500-1000 µg BID) was recently described as another possibility for EoE treamtent", the word "treamtent" should be "treatment".

Done

4. In the sentence "Another retrospective study which evaluated the long-term efficacy of STC in 229 adult EoE patients over four years showed significant significantly higher proportions of patients on STCs in clinical remission (31.0%)", the word "significant" should be removed, instead of just having a strikethrough line through it.

Done

5. In the sentence "A post-hoc analysis of the EOS-1 trial with these criterias", "criterias" should be "criteria".

Done