Author’s response to reviews

Title: Effectiveness and Safety of Ferric Carboxymaltose Treatment in Children and Adolescents with Inflammatory Bowel Disease

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To the
Executive Editor
BMC Gastroenterology

RE: MS: 6974930291255436

Title: Effectiveness and Safety of Ferric Carboxymaltose Treatment in Children and Adolescents with Inflammatory Bowel Disease

Authors: Martin W. Laass, Simon Straub, Suki Chainey, Garth Virgin, Timothy Cushway

Dear Editor,

Please find attached a revised version of the manuscript based on the comments made by the two reviewers. We are very grateful to the reviewers for their positive and their insightful comments.

We added an additional file (Table S1) with reference values used in the study. We have also uploaded a pdf file of the manuscript marked with all the changes (in blue) made during the revision process. Appended to this letter is our point-by-point response to the comments raised by the reviewers.

We hope that the revised manuscript is accepted for publication in BMC Gastroenterology.
Yours sincerely,

Martin Laass
(on behalf of all authors)

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Here we give a step by step answer to reviewer's comments:
(Underlined text was added. Our answers are in Italics.)

Reviewer 1
Minor essential revisions:
1. Abstract - Background: It should be 'orally given iron'
   We changed it accordingly.

   2. Abstract - Results: You do not need to say 'diagnosed, concomitant iron
deficiency anemia'. Saying concomitant is sufficient, since it implies diagnosed.
   We changed it accordingly.

   3. Abstract - Results: The sentence about the improved hemoglobin levels was
      unclear to me after I read the paper. I thought the improved levels from 9.5 to
      11.9 was the range of the final (improved) values, and not the change from
      baseline to endpoint. This is clear in the paper, but should be clarified in the
      abstract.
      Indeed this is unclear in the abstract. Therefore, we added in the abstract: "at
      baseline": "...from 9.5 g/dL at baseline to 11.9 g/dL within 5-12 weeks..."
4. Background: In the first three paragraphs, you have used the terms 'iron deficiency' and 'iron deficiency anemia (IDA)' somewhat interchangeably, which they really are not. IDA is one consequence of iron deficiency. The statistics in your first paragraph describe patients who are iron deficient and those who were also anemic. Your focus, and the inclusion criteria for your patient population, is IDA. In the next paragraphs you discuss using hemoglobin to monitor and manage iron deficiency, when I think you really mean IDA, and treating IDA to relieve the acute symptoms of iron deficiency, which is generally asymptomatic until the anemia is manifest. This is a bit of a splitting of hair, but my perspective is as a hematologist, where we do consider iron deficiency without anemia and IDA differently. I would suggest changing the language to IDA to avoid any confusion.

On page 5 we changed iron deficiency into IDA: "Therefore, careful evaluation of iron status, including laboratory parameters like hemoglobin (Hb), mean corpuscular volume, serum ferritin, transferrin saturation, is mandatory to diagnose and treat IDA early during the course of disease."

In other parts of the background section we would like to keep iron deficiency, because IDA and iron deficiency are indeed different as you said (and this is also in our opinion no hairsplitting!). In some of the papers we reference (e.g. Wiskin et al. 2011) there are numbers given for anemia and numbers for iron deficiency. When we talk about ferritin values consistent with iron deficiency, we cannot simply substitute it with IDA. It is known that iron plays a role beyond hemoglobin (myoglobin, for example) and there is an ongoing discussion about treatment of iron deficiency without anemia. That being said, the indication for iron treatment in our study was IDA.

5. Background - Paragraph 2: Good to point out the importance of acute inflammation. I would add one word: '..such as C-reactive protein must 'also' be taken...' It highlights that this is something else to consider.

Done.

6. Methods - Paragraph 6: The definition of baseline is confusing, and it was unclear whether it was a distinct time point from the others. I interpreted it to be either the pre-FCM or the first FCM, which are the two previously defined time points. The graphs don't have a 'baseline', so it isn't a real time point. Might be best to define day of first FCM as baseline, with the comment that the pre-FCM measure was used when first FCM was unavailable.

Yes indeed, baseline definition may be confusing. Normally we used values from day 1 (just before administration, but in a few cases these values were missing, therefore we used pre-FCM values. We tried to make this clearer and added in the method section (paragraph 6):
“This included pre-FCM (any value available from 12 weeks prior to first dose), day of first FCM administration (which is generally referred to as baseline unless missing, in which cases values from pre-FCM were used as baseline) ”

We also added in the figure legend:

“Figure 1-4: FCM day 1 refers to day of first FCM administration, but blood for assessment of laboratory parameters was drawn before FCM administration. This is referred to as baseline (unless values from this day were missing, in which cases Pre-FCM values were used). Additional FCM doses may have been administered after this to achieve iron repletion. Weeks 0-2 comprise days 1 to 14 and weeks 2-4 comprise days 15 to 28.”

7. Results - Paragraph 1: The last sentence needs some grammar correction - '37/72 (51.3%) patients were younger...'

Done.

8. Results - Paragraph 3: Add one word to the second sentence '...from a baseline 'of' 9.5 ...'

Done.

9. Results - Paragraph 7: You don't need the parenthesis to explain that oedema is swelling. Just say oedema of the palms and fingers of both hands. Your readers should know what that means.

We deleted the parenthesis and the word "swelling".

10. Results - Paragraph 7: You have a confusing double negative in the discussion of the slow rate and high volume administered, which was not in accordance with the instructions not to dilute below 2 mg/mL. It's much clearer in the discussion that dilution went beyond manufacturer's recommendations.

We would like to keep the double negative, because in the instruction there is this statement to have a maximum dilution. Wording has been slightly adapted to try to make clearer.

11. Results - Paragraph 7: After changing your dilutions, only one further event (not events) occurred.

We deleted the "s"

12. Discussion - Paragraph 2: The paragraph ends with 'suggest a need for additional iron to avoid repeat deficiency respectively anemia'. I don't know what that is. I think you mean to say 'recurrent IDA', which is what you discuss in
Paragraph 4.

Yes, indeed this is clearer, we changed to: "... additional iron to avoid recurrent IDA."

13. Discussion - Paragraph 6 - Same comment about oedema that I made in the results section.

We deleted the parenthesis and the word “swelling” also here.

Discretionary revisions:

1. Results - Paragraph 2: I would suggest starting with a sentence stating the total number of administrations. You've done this in the abstract, and it would introduce the content of the paragraph well.

We added: "The total number of FCM administrations was 147 and the mean number per patient was 2.0. The mean cumulative dose of intravenous FCM was 821 mg iron given in two single infusions (median dose: 500 mg iron diluted in 100mL saline over 66 minutes, max. dose: 1000 mg)."

2. Results - Table 2: I don't think you need the first row, showing the indication for 100% was IDA. You've stated that clearly in the text, and it doesn't add to the table.

We deleted this row.

3. Results - Paragraph 4: I wonder if you aren't overinterpreting the changes in the WBC and platelet count. Both of these rise transiently and then fall, and the changes are fairly minor. This may actually represent changes in myelopoeisis with the management of the IDA. We often see increased platelet counts with IDA because of increased bone marrow activity, which then increases further when iron is provided for hematopoeisis. As the anemia improves, marrow function returns to baseline, which may explain the drop in the counts. I don't know for sure, and that doesn't address the CRP, but it's something to consider.

In the discussion we recommend to interpret this changes with caution: "Further to anemia management, the administration of iron also appeared to result in decreases respectively normalization of white cell count, platelets and C-reactive protein. These observations might suggest a role of iron therapy also in reducing inflammation and normalization of secondary thrombocytosis in IBD, however should be interpreted with caution, as medication changes were not captured as part of this study."

4. Discussion - Paragraph 5 - Given my previous comments about the falling WBC and platelets, I found your reference to similar findings in other studies
interesting. It might be helpful to add one sentence describing their interpretation of that finding.

We added: "However, similar reductions have been seen in other studies using FCM, where a decrease of platelets was observed independent of inflammation markers such as C-reactive protein [16]. Therefore, decreases in platelet count in our study may reflect normalized bone marrow activity rather than reduced inflammation."

Reviewer 2

In their retrospective study entitled “Effectiveness and Safety of Ferric Carboxymaltose; Treatment in Children and Adolescents with Inflammatory Bowel Disease” the authors presented for the first time important data on the use of FCM in the pediatric population. The paper is well written, however some points are too imprecisely formulated. In general, more references should be cited.

We added references 4, 6 and 7 and changed counting accordingly.


Background:

Page 5, Line 11: this is incorrect; there three different forms of iron deficiency anaemia in IBD: IDA, ACD, and combined IDA/ACD, which is not uncommon (see Stein et al. Nat Rev. Gastroenterol Hepatol 2010, Blumenstein et al. J Crohn #s Colitis 2014)

That is just what we say here: “In IBD usually two forms of anemia coexist: iron-deficiency anemia (IDA) and anemia of chronic disease.” Usually neither IDA
nor ACD exist alone.

Page 6, line 4: ...aggravating intestinal inflammation: please cite reference

We added the following reference:


Methods:

Definition of Anaemia: What do the authors mean by “defined by the local laboratory”? What are the exact values? Are these values different from the WHO classification?

Classification of IDA: What is meant by “below the lower reference of the lab”? Precise values should be defined according to recently described algorithms (Weiss G, Goodnough LT. N Engl J Med 2005) as done by Blumenstein et al. J Crohn #s Colitis 2014 or Voegtlin et al. J Crohn #s Colitis 2010.

The values of our local lab are indeed slightly different to the WHO reference values. In an additional file (Table S1) we give now exactly the reference values we used for the study. Reference values vary in different populations. Therefore, we used these values instead of WHO values.

Anemia was defined as Hb below the lower reference value (according to age and gender) of the local laboratory (Additional file 1: Table S1). Anemia was classified as IDA when the following values were below the lower reference value of the laboratory: mean corpuscular volume of the erythrocytes, transferrin saturation and ferritin (<20 µg/L). Anemia was also classified as IDA when the soluble transferrin receptor or the soluble transferrin receptor/ log ferritin ratio was elevated (Additional file 1: Table S1).