Title: Treatment of children and adolescents with ulcerative colitis by adsorptive depletion of myeloid lineage leucocytes as monotherapy or in combination with low dose prednisolone after failure of first-line medications

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Version: 3 Date: 27 June 2013

Author's response to reviews: see over
The Editor,
BMC Gastroenterology 27 June 2013

Dear Editor,

Subject, revised MS: 4413307339698979, Treatment of children and adolescents with ulcerative colitis by adsorptive depletion of myeloid lineage leucocytes as monotherapy or in combination with low dose prednisolone after failure of first-line medications.

The authors thank you for your communication of 4 June 2013 in connection with the above manuscript. Likewise, we thank our reviewer colleagues for their time and courtesy in evaluating our manuscript. We were please to receive the evaluation reports and have spared no effort to revise our manuscript and factor their suggestions. In the manuscript, our revisions are shown in blue and are itemized below.

Reviewer 1, and the Editor’s notes regarding the English language.

The final version of our manuscript has been edited by a British academic who has published a large number of articles including on inflammatory bowel disease. Also has edited several articles which have appeared in BMC Gastroenterology. We can assure the Editor and our reviewer colleague that this issue has been thoroughly addressed.

Reviewer 2

Please be assured that we valued your comments and have revised the manuscript to the best of our ability to address your concerns.

1. The text now refers to corticosteroids.
2. The objective of the study has been stated in the Abstract
3. Setting and time line of the study are now stated in the manuscript Abstract.
4. The statement, “initial GMA sessions” has been revised to read “the first 5 GMA sessions”.
5. In this study, 17 patients received GMA and 12 of them responded without adding another medication, while 5 responded after adding prednisolone. Therefore the majority responded. The 7 patients who did not receive GMA could not be considered as GMA non-responders. In response to your concern, we have omitted the word “most” and wrote “majority”
6. The tapering schedule for prednisolone was 5mg per week.

Minor issues

1. In British English “an” often appears before a number, like an 11 year old boy or an 80% of people .....To address you concern, “an” has been omitted.
2. Prednisolone does now is shown as “mg/kg/day.
3. Comma after “Factors” has been removed.
4. Similarly, comma after “children” has been omitted.
5. The sentence has been revised. Thank you.
6. In British English, “venepuncture” is the correct spelling, although, venipuncture often appears in the literature. Please verify this. However, to be in line with your thinking, we changed venepuncture to “venipuncture”
7. The misprint “Analyse” now reads “Analyses”. Thank you.

Major Compulsory Revisions.

1. In Japan, GMA with the Adacolumn is an established and officially approved by the Japan Ministry of Health for the treatment of patients with active IBD. This treatment is included in the national health reimbursement scheme. GMA is widely used to treat IBD. The text is correct and is stated further under the Ethics statements. In the Methods section we have revised the text to indicate Japan and not worldwide. Additionally the Adacolumn is CE marked and therefore, in the countries of the European Union, its clinical application is based on the CE mark [reference 14].
2. In this study, assessment of CAI was according to Rachmilewitz D. Br Med J 1989; 298:82-86, while the assessment of DAI (mucosal healing) was according to Sutherland LR, et al. Gastroenterology 1987; 92: 1894-1898. Both index systems are published in reputable journals and we are not the first authors to use these indices. These scoring systems appear in several papers which we have cited. We do understand these are not widely used in contemporary literature, but they are not invalidated by any subsequent study. Both these sources are cited in this manuscript [references 23, 24].
3. As stated in the text under “Objective” and explained for Reviewer 3, the major objective in this study was to induce remission in young patients who either had not responded to first-line medications or had relapsed while receiving first-line medications. Nonetheless, we did add a paragraph on the maintenance of remission and follow to the results section giving clinically relevant data. We have now added the average follow up time and ranges. We hope this can alleviate your concern.
4. Yes, salicylates were continued by patients who were with active UC and received GMA therapy. Your concern has been addressed in the text, Table 1 and Figure 1.
5. The number of UC patients who have received GMA at our IBD unit during the past 12 years is well over 200 [references 25, 27]. In this study, we have included children and adolescents who were steroid naïve and had a short duration of UC (12 month or less).
6. In Figures 2 and 3, the annotations have been amended precisely in line with your suggestion.
7. Subgroup analysis. In the text, we have commented that in our previous studies involving GMA, age or gender was never found to be a marker of response or otherwise. However,
duration of UC and the extent of mucosal damage are strongly associated with response to GMA [reference 25]. However, in these young patients, the duration of UC was very short as compared to those reported in reference 25 (our study).

8. The text has been revised to address your concern. Although GMA carriers adsorb a large fraction of granulocytes and monocytes from the blood which passes through the Adacolumn, but the level of these leucocytes in the systemic circulation does not fall significantly [reference 14] due to an influx of naïve leucocytes (CD10 negative neutrophils) from the marginal pools including the bone marrow into the circulation [reference 26]. The naïve neutrophils are thought to be less inflammatory [reference 26]. Therefore, neither in this study nor in previous GMA studies [references 10,14-22, 25,28], patients showed opportunistic infection.

9. Table 1 does show age, weight and baseline medications as mg/kg/day.

Reviewer 3
Major revisions,
The authors thank you for your valued comments. Yes, we have used two different scoring systems to evaluate UC activity or improvements, but one of these is according to Rachmilewitz D. Br Med J 1989, 298:82-86 and was used to assess CAI. The other system is according to Sutherland LR, et al. Gastroenterology 1987, 92:1894-1898 and was used to evaluate endoscopic index (DAI). Both index systems are published in reputable journals and we are not the first authors to use these indices. Mucosal healing in 9 of 17 GMA group (52.9%) is not a low rate. For biologics, mucosal healing rate in UC patients is very much lower than this (please verify).

Regarding PUCAI, we are aware of this indexing system, but most of our patients were teenagers with bodyweight between 33 – 55.5kg which is very close to adult Japanese patients. In this study, we did not use the Mayo scoring system, but will give this option serious consideration in the future.

Regarding your comments on the maintenance of remission, please see the methods section, we have stated that our major objective in this study was to induce remission in young patients who either did not respond to first-line medications or had relapsed while on first-line medications. We hope you will graciously agree that maintenance of remission, although reported, but was not the main objective of this study.

In Table 1, demographic variables of all 24 patients including CAI and DAI were presented in the original submission. This Table is updated in line with the comments from Reviewer 2.

Minor points
The misprint “was” on page 10 has been deleted. Thank you.
As you may have noticed in the discussion section, we have commented on the limitation of our study including sample size. We are aware of the RCT outcome reported by Sands et al.,
and had referred to that paper in the discussion section. Our patients were all steroid naïve with a relatively short duration of UC which are known responder features. Please see an earlier publication: Cohen RD. Treating ulcerative colitis without medications – “Look Mom, No Drugs!” Gastroenterology 2005; 128: 235-236.

At the end of the discussion section, we have added a statement indicating the need for an RTC in paediatric UC patients.

Yours sincerely
Tomotaka Tanaka, MD, PhD
(on behalf of all authors)