Author’s response to reviews

Title: Clinical manifestations and anti-TNF alpha therapy of juvenile Behçet’s disease in Taiwan

Authors:
Ya-Chiao Hu (ychu0407@gmail.com)
Yao-Hsu Yang (yan0126@ms15.hinet.net)
Yu-Tsan Lin (yutsanlin@ntu.edu.tw)
Li-Chieh Wang (lcwang5@gmail.com)
Hsin-Hui Yu (hhyu121@gmail.com)
Jyh-Hong Lee (leonid.ljh@gmail.com)
Bor-Luen Chiang (gicmbor@ntu.edu.tw)

Version: 1 Date: 27 Feb 2019

Author’s response to reviews:

Dear Prof Robin L. Cassady-Cain:

Enclosed please find the revised manuscript entitled “Clinical manifestations and anti-TNF alpha therapy of juvenile Behçet’s disease in Taiwan”. We thank the Reviewers for their careful and thoughtful review of our manuscript. We have revised the manuscript according to their specifications and all the changes to the manuscript in text was using track changes. The revisions are detailed as follows and highlighted in the revised manuscript:

1. On page 4 (in Background part), we revise the definition of juvenile Behçet’s disease from “Juvenile BD (JBD) or pediatric BD is diagnosed in patients with symptoms < 16 years old” to “Juvenile BD (JBD) or pediatric BD is diagnosed in patients with symptoms up to the age of 16.” Also, we added two references: reference 3 for the JBD definition and reference 4 for the frequency of JBD.

2. On page 6-7 (in Methods, Study design and enrollment criteria), we change the sentence from “We retrospectively reviewed patients aged <16 years at….” to “We retrospectively reviewed patients with initial BD symptoms at age of 16 years or younger….”. Also, we add “at diagnosis” after the word “laboratory data”. In the same paragraph, we revise the
sentence from “If patients did not satisfy these criteria, but they had oral and/or genital aphthous ulcers and some symptoms and signs associated with BD” to If patients did not satisfy these criteria, but they had oral or genital aphthous ulcers and some symptoms and signs associated with BD.” We also added two sentences for severity score: “The Behçet’s Disease Current Activity Form (BDCAF) scores were also collected to evaluate the change of disease severity. The BDCAF total score was calculated out of 12 and then given as a transformed index score on an interval scale out of 20.” Reference 18 were added for the origin of BDCAF scores.

3. On page 7 (in Methods, statistical analyses), we add a sentence: “Patient data were expressed as counts, percentages or medians with range for quantitative and ordinal data.”

4. On page 9 (in Results, Patients’ characteristics and treatments), we revised the numbers in the sentence from “The median age at the initial onset of symptoms was 11.0 (range 0.1–16.8) years, and the median age at diagnosis was 13.0 (range 0.1–16.9) years” to “The median age at the initial onset of symptoms was 11.0 (range 0.1–16.0) years, and the median age at diagnosis was 13.0 (range 0.1–16.0) years.” We also add two sentences: “Pathergy test was not routinely performed in our cases. Only 5 patients had records of pathergy test and two of them had positive findings.” Another sentence is added in the paragraph about laboratory data: “Thirteen patients received an examination of HLA typing and only one patient had positive HLA-B51.”

5. On page 15-16 (in Results, Anti-tumor necrosis factor-alpha therapy for patients with juvenile Behçet's disease), we revised the phrase from “figure 1” to figure 1A.” We add the phrase “Figure 1A and 1B” after the sentence “The corticosteroid-sparing effects and reductions in the immunosuppression load scores were observed at 6 months after treatment.” Also, we add a paragraph: “Moreover, the serial change of BDCAF scores were depicted in figure 1C, which showed significantly reduction at the 1st month, the 6th month and 1 year after the treatment (P=0.042 at 1st month, P=0.027 at the 6th month, and P=0.026 at 1 year).”

6. On page 18 (in Discussion), we added a brief summary in the beginning of the discussion: “In this single-center retrospective study, we analyzed patients who were diagnosed with JBD and their treatments. We especially reported the favorable response and safety of anti-TNF alpha in those patients with refractory symptoms after conventional treatments. Not only the disease severity scores were significantly reduced, but also the sparing effect on corticosteroid dosage and immunosuppressive drugs were observed.” We delete the paragraph mentioning: “JBD patients have significantly fewer genital ulcers, and more nonspecific gastrointestinal symptoms than adult BD patients. The severity scores are usually lower in JBD.[6] These findings may explain the
differences between JBD and adult BD in relation to the sensitivities of several of the diagnostic criteria.”

7. On page 19 (in Discussion), we revise the sentence from “……, and they were eventually administered anti-TNF-alpha therapy” to “……and she was eventually administered anti-TNF-alpha therapy.” We also delete the paragraph “The age at disease onset in this study was similar to the ages at disease onset described in previous studies, ……… however, our patients presented with fewer skin manifestations.”

8. On page 20 (in Discussion), we revise the sentence from “Hence, the disease in these patients may have been more severe or had a refractory course” to a paragraph: “The BDCAF scores were 7 or 8 out of a total score of 20 before they received anti-TNF alpha therapy. Hence, these patients may not have a very severe disease entity but had a refractory disease course even after multiple conventional treatments.” In the sentence “Intestinal involvement is more frequent in juvenile than in adult BD”, we revise it to “Intestinal involvement is more frequent in juvenile BD.”

9. On page 21 (in Discussion), we revise the sentence from “Our results indicated the effectiveness and safety of anti-TNF-alpha therapy in patients with severe JBD” to “Our results indicated the effectiveness and safety of anti-TNF-alpha therapy in JBD patients whose symptoms were refractory to conventional treatments.” We also revise the sentence form “Although BD activity scores were not available,……” to “The reduced BDCAF scores,……” The paragraph “Several case reports describe anti-TNF-alpha therapy for JBD……. Keneko et al reported dramatic improvements in gastrointestinal symptoms and mucocutaneous manifestations in two JBD patients who were treated with infliximab and etanercept.[16]” is revised to “Several case reports and series reported anti-TNF-alpha therapy for JBD. [15-17, 29-32] The details of the reported cases were listed in Table 5. Use of adalimumab, infliximab and etanercept has been reported respectively. Most of the cases had favorable outcomes after treatment, especially in intestinal and ocular lesions. There were some side effects which were mainly non-serious infection. “

10. On page 24 (in Discussion), we revise the sentence from “Third, there were no serial changes in the severity scores that could quantify the symptom improvements associated with anti-TNF-alpha therapy” to “Third, not all enrolled cases were evaluated by disease severity score.”

11. On page 25 (in Conclusions), we revise the sentence from “We found that patients who were younger at disease onset, had higher serum CRP levels at baseline, and presented with gastrointestinal symptoms tended to have more severe disease” to “We found that patients who were younger at disease onset, had higher serum CRP levels at baseline, and
presented with gastrointestinal symptoms tended to have poor response to our traditional standard treatments.”

12. We revise both Table 1 and Table 3. For more neat and easier reading, we organized the description of median(range) and add a sentence below the table: “For quantitative and ordinal data median and range are presented.” The range of age in Table 1 and Table 3 were revised. We also change the heading of Table 2 from “Systemic treatments” to “Systemic treatments in patients with juvenile Behçet’s disease.” The heading of Table 4 is revised from “Clinical characteristics of patients and response to treatment” to “Clinical characteristics of JBD patients treated with anti-TNF alpha therapy and response of the treatment.” We also add some information in previous treatments column and revise sentence in the content of the reasons for use of aTNF in patient no. 2 from “Steroid-dependent refractory disease status” to “Steroid-dependent disease status with oral ulcers and GI bleeding.”

13. We create a new Table (Table 5) and add several references in the table (Reference 30, 31, 32).

14. We modify the Figure 1 with and add another panel C in it.

15. We modify the abstract according to the revision in the main article.

The point-by-point replies are given in the following pages. We hope that we have addressed satisfactorily all the concerns raised by the Reviewers, and that this manuscript is now acceptable for publication.

Sincerely

Yao-Hsu Yang, MD. PhD.

Department of Pediatrics, National Taiwan University Hospital,

No. 7 Chung-Shan South Road, Taipei, Taiwan.

TEL: 886-2-2312-3456   Ext. 71521

FAX: 886-2-23147450

E-mail: yan0126@ms15.hinet.net
Responses to Reviewer 1

Major points:

1. Anti-TNF use in treatment of juvenile BD is reported in only case series and reports. Thus, the authors could perform a systematic review of the literature and present their own results along with the results from the literature. The results from the literature could be presented in a table for easy reference (their own results could be included in the table as the last line). This will improve this study substantially and provide a nice overview of the subject, as well.

Response: Thanks for the suggestion to make the literature review more clear and concise. We added a table which listed the reported JBD cases receiving anti-TNF alpha therapy (Table 5 in the revised manuscript) to make the discussion easier to read. Since our cases were presented thoroughly in Table 4, the Table 5 did not include these cases.

2. One of the major flaws of this study is the lack of structured outcome scores for evaluating the effect of anti-TNF treatment. The authors should use IBBDAM or BDCAF scores to report the objective outcomes of the treatment.

Response: Thanks for your comments. We agree that lacking an objective disease severity score to evaluate the outcomes is truly one of the drawbacks in the study. We tried to apply the Behçet’s Disease Current Activity Form (BDCAF) respectively for the 6 patients who had anti-TNF alpha therapy to make a more objective evaluation of the treatment response. The application of BDCAF was described in the method part. The results were added in the results part and as one new figure in the Figure 1 as figure 1C. There was significantly reduction of severity score at the 1st month, the 6th month and 1 year after starting anti-TNF therapy.

3. The authors compared the juvenile BD patients who received anti-TNF treatment with the ones that did not receive anti-TNF, and they concluded that patients with younger at disease onset, higher CRP at baseline, and gastrointestinal symptoms at presentation tended to have more severe disease course. This is not reflecting the real situation here. Receiving anti-TNF agents does not mean having a more severe disease in every case. To make such conclusion, the patients should be grouped according to the disease severity which could be achieved by using structured scores.

Response: Thanks for the comments. We agree that receiving anti-TNF agents does not mean having a more severe disease in every case. Our cases receive the therapy because they had refractory disease course after conventional treatments. After applying BDCAF scoring as your suggestion, it shows that before anti-TNF alpha therapy, their disease severity scores were not
high (7 or 8 out of 20) even though they had refractory symptoms in particular one or two involved organ, such as GI tract, eyes or CNS. We make some modification to our discussion and conclusion. Our experience of JBD patients receiving anti-TNF alpha therapy can apply to those refractory cases but can’t extend to those with severe cases.

4. Discussion is disorganized. It should be revised: It could start with a brief summary (1-2 sentences) of the salient results of this study. Then these results could be discussed with the results of previous studies in a neat order. The unnecessary parts should be deleted (such as parts about the comparison of juvenile and adult BD which is not the focus of this article).

Response: Thanks for the comments and the discussion is modified as your suggestions.

Minor points to consider:

For points 5 to 7

5. In the background part, the authors should provide reference to the sentence about the frequency of juvenile BD.

6. In the methods, the authors indicated that they involved several patients as with possible JBD if they did not satisfy the ICBD or PEDBD criteria but they had oral aphthosis and/or genital aphthosis. Here, they should change "and/or" to "or" since patients with oral AND genital aphthosis are classified as having BD according to the ICBD.

7. The normality tests and the expression type of numerical variables (as median and range) should be indicated in the statistical methods.

Response: Thanks for the comments. The detail of the points mentioned above was modified in the revised manuscript in the background part and method part.

8. The patients are defined as having juvenile or pediatric BD, if both disease onset and disease diagnosis are before or at 16 years of age. The authors also wrote that they depended on this definition. However, the maximum range of age at disease onset and diagnosis is 16.8 and 16.9 years, respectively in their results.

Response: Thanks for the comments. We revised the definition of JBD as patients with symptoms up to the age of 16 as the reference no. 3. in the background and method parts.
Besides, we rechecked the records and confirmed the maximum range of disease onset (initial symptoms) was 16 years, which was corrected in the text and tables.

9. The time period when the acute phase reactants were checked should be mentioned clearly (at disease onset? Or at diagnosis, etc.).

Response: Thanks for the comments. The laboratory data including acute phase reactants were checked at diagnosis and we will describe it in the methods part.

10. Did the authors have the results for HLAB51 and pathergy test? Or did they not perform these? This should be indicated clearly.

Response: Thanks for the comments. Although the data was limited but some of the patients did receive the tests. The results were added in the results part.

11. Table headings should be more informative and include the disease name (e.g. the heading of Table 2).

Response: Thanks for the suggestions. We did some modification and revised the heading of Table 2 and Table 4 to make them more informative.

Responses to Reviewer 2

Major comment: Why etanercept was given for eye and GIS involvement instead of adalimumab or infliximab?

Response: Thanks for the comments. For patients with eye involvement, we used adalimumab and it could be applied based on the regulation in Taiwan. However, for patients with GI tract involvement, adalimumab can be applied for patients with inflammatory bowel disease for free but not Behcet’s disease and infliximab was not available then in Taiwan. Etanercept was the biologic agent we can get more easily and the cheaper choice for these patients.