Peer Review File

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Reviewer A

I reviewed the manuscript `` TP-20-482-R1 Title: The Effectiveness of Infliximab for Kawasaki Disease in Children: Systematic Review and Meta-analysis``. with great pleasure. In this manuscript, the author described the effectiveness of infliximab (IFX), inhibitors of tumor necrosis factor (TNF-α), for Kawasaki disease (KD) using Meta-analysis. KD is the leading cause of acquired heart diseases in children. It is an acute, self-limited, systemic vasculitis of unknown etiology that typically presents in early childhood. One of the most widely administered therapies is intravenous immunoglobulin (IVIG), which substantially reduces the incidence of Coronary artery aneurysms (CAA). IFX, a monoclonal antibody, is a selective anti-inflammatory molecule that functions by blocking TNF-α. The pro-inflammatory cytokine TNF-α is elevated in patients with KD, with the highest levels observed in patients with CAA. IFX therapy for KD has been reported to decrease serum soluble TNF receptor 1 and regulate signaling pathways related to KD inflammation and IVIG resistance factors. In a previous study, primary adjunctive treatment with infliximab decreased the duration of fever but was not associated with a decreased risk of non-response to IVIG. The purpose of the study is of interest; however, the study has large limitations.

Major problem.

1. The strategy of KD therapy, primary, and rescue therapy is different because the efficacy of IVIG administered in the acute phase of KD is well established to reduce the prevalence of CAA and the evidence is need to for IVIG non-responders. I think the evidence level of the report from Tremoulet AH, et al, about primary IVIG plus IFX a randomized, double-blind, placebo-controlled trial is high. Please reassessment excluding primary IFX therapy.

Reply 1: Thanks for your professional advice. We reassessed the effect of IFX on the KD patients with CAA in the rescue therapy. The result showed that there was no statistical significance of IFX in the rescue therapy compared with IVIG therapy alone. We also make meta-analysis for the change of Z score (∆Z) of LAD and RCA between IFX and IVIG in the text. Pooled analysis showed that ∆Z score of LAD and RCA was obviously decreased with the IFX as rescue therapy compared with the IVIG alone. We made the conclusion that the therapy of IFX could decrease the score of ∆Z, but not CAA, the detailed analysis data see Figure 4b.

Changes in the text: We have modified our text as advised in result section and discussion section. (see page 11-12, line 239-243; Page 13, line 283-284 and Figure 4b)

2. The definition of CAA is incorrect (ref 12). Please confirm and correct it.

Reply 1: Thanks for your professional advice, we revised the definition of CAA according to "2017 AHA scientific statement."

Changes in the text: We have modified our text as advised (see page 7, line 136-140).

3. Unfortunately, in this manuscript, the conclusion not included new information the IFX therapy for KD. However, the author's approach interest and might be increasing the level of evidence for IFX therapy for KD. For example, it has been pointed out that the prevalence of KD varies among races. Can the author approach this point?

Reply 1: Thanks for your professional advice. We added some data about the effect of IFX either as initial or rescue therapy on treatment response for KD patients in Asian and North American races. Subset meta-analysis for using IFX either as initial or rescue therapy strategy exhibited significant effect on the treatment response compared with IVIG in the Asian group. However, there was no statistical differences in the North American. This outcome showed us that the treatment of IFX was more beneficial to the KD patients in the Asian races on treatment response compared with the North American races.

We also analyzed the effect of IFX therapy on CAA for KD patients in different races, and it was found that IFX therapy has no significant influence either in Asian or North American races compared with IVIG therapy. This outcome was consistent with the overall effectiveness of IFX therapy on CAA.

Changes in the text: We have modified our text as advised in result section and discussion section. (see page 2-3, line 44-46; page 10-11, line 209-222; page 12, line 254-262; page 13, line 284-286 and Figure 3c and 4c).

4. I think it is hard to evaluate the hospital stays in this meta-analysis because the medical systems including a medical cost analysis of each country are too different. Please excluded this analysis or reassessment.

Reply 1: Thanks for your professional advice, we have excluded this analysis of hospital stay in the main body of revised version and included it in the supplement.

Changes in the text: We have modified our text as advised (see supplement).

Minor problem

1. Table and Figure are good however discussion is poor. Please are reassess it.

Reply 1: Thanks for your professional advice, we have revised discussion section.

Changes in the text: We have modified our text as advised (see discussion).

Reviewer B

Dr. Li Dan et al. conducted a systematic review and meta-analysis to report the efficacy of infliximab as an initial or adjunctive therapy for patients with acute KD. They concluded that initial, but not additional, IFX therapy led to improved treatment response. In addition, the use of IFX therapy improved CAAs Z score and reduced hospital stays without severe ADEs.

This report is of interest and value, as IFX may provide stronger evidence for the future KD patients.

Comments

-Author stated that IFX therapy is effective in responding to KD patients with either initial or additional administration. However, risk stratification such as Kobayashi score in Japan before the start of treatment was not discussed. The authors also need to describe which types of patients requires IFX as initial treatment.

Reply 1: Thanks for your professional advice. We have made subgroup analysis of the effect of

using IFX as initial treatment on the treatment response between the group of KD patients who were predicted to have high risk of IVIG resistance and the group of normal KD patients. The result manifested that IFX therapy was more effectiveness in the group of high-risk KD patients than IVIG therapy alone. However, it is a problem to stratify patients with risk. So far, there are at least 4 different scoring systems, such as Kobayashi score, Egami score, Sano score and Formosa score, for the risk stratification of IVIG resistance have been developed. These models played useful predictive ability in the early identification of high-risk IVIG resistance patients before the start of treatment.

Changes in the text: We have modified our text as advised in result section and discussion section. (see page 2, line 36-39 and line48-49; page 11, line 223-235; page 14, line 287-293 and Figure 3d).

- Table 1b needs to be completely modified. "Duration of IFX Therapy, d" and "Incidence of CAA in each group, No (%)" could not be understood. Please correct it precisely.

Reply 1: Thanks for your professional advice, we have excluded "Duration of IFX Therapy, d" because of limited information in the 9 studies, and we have changed "Incidence of CAA in each group, No (%)" to "Incidence of CAA in each study, N (%)"

Changes in the text: We have modified our text as advised (Table 1b).

- The author is also discussing other drug options such as prednisolone, cyclosporine, and plasmapheresis. These factors should be considered as confounding factors.

Reply 1: Thanks for your professional advice. We have reassessed the 9 studies, of which 4 studies did not discuss other drugs except for IVIG and IFX therapy, and the other 5 studies included not only IFX and IVIG, but also prednisolone, cyclosporine, and plasmapheresis. These drugs were used for the IVIG-resistance after IFX or IVIG treatment, and these drugs considered as confounding factors of analysis the efficacy of IFX, which is effective for the IVIG-resistance KD patients, and might influence the results.

Changes in the text: We have modified our text as advised in the section of limitation (see page16, line 332-338).

Reviewer C

The authors conduct a systematic review to investigate the efficacy and safety of infliximab (IFX) as an intensification therapy with intravenous immunoglobulin (IVIG) ore rescue therapy in patients with Kawasaki disease (KD). This manuscript followed the standard methods but there are some room for improvement for several issues. The authors may wish to consider the following comments should they choose to revise their manuscript.

General comments

The most important concern of this manuscript is the studies the authors included in the meta-analysis.

The following two therapies are completely different in the treatment strategy of patients with KD:

1. IFX+IVIG as an initial therapy
2. IFX as a second therapy in patients who did not respond to initial therapy

The reviewer does not rebut to performing systematic review for them. However, it may not be

a good idea to perform meta-analysis for these two different treatments:
1. IFX+IVIG vs. IVIG at initial therapy
2. IFX vs. IVIG at rescue therapy

Other issues

- There is a systematic review of TNF-alpha blockers for children with KD in the Cochrane Library (Yamaji N et.al. 2019). What is unclear by this Cochrane review and what does the present study aim to clarify?

Reply 1: Thanks for your professional advice. Yamaji N et al reported that TNF-α blockers including IFX and etanercept in 5 RCTs that compared TNF-α blockers to placebo or other drugs in children with KD. However, RCT studies are rigorously designed, whether such results are appropriate for other clinical conditions remains unclear. The present study aims to evaluate IFX in all studies not only RCTs, but also observational studies and case-control studies in the KD patients.

Changes in the text: We added it in the introduction section (see page 4, line 76-82)

- It is a little confusing that the author mentioned they included all the relevant studies published until July 2020 in P. 2, and Dec 31, 2020 in P. 3.

Reply 1: We have changed this mistake.

Changes in the text: We have modified our text as advised (Page 2, Line 31).