

Reviewers

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

The manuscript submitted by Yang Lin, et al. has investigated the effects of 24-week tofacitinib therapy on insulin sensitivity in non-diabetic active rheumatoid arthritis patients naïve or exposed to biologic therapy. In this retrospective study, they found reduced insulin resistance was achieved in non-diabetic active RA patients following 24wk of tofacitinib therapy, suggesting JAK/STAT signaling may have the potential in treating diabetic. It's an interesting study, and I have several comments as follows. **Major issues:**

1. Glucocorticoids have a great impact on insulin resistance and glucose metabolism. And even with the same daily dose, the effects of long-term use and short-term use on insulin sensitivity vary greatly. So only analyzing the daily dose of prednisolone is not enough to exclude the impact of glucocorticoids. It is suggested to analyze the total exposure of prednisone in the course of treatment.

Response: As we pointed out at the **Discussion** 2nd paragraph that --- when prescribed

chronically, glucocorticoid (GC) can impair glucose tolerance ---. We agree with the reviewer that only analyzing the daily dosage of prednisolone is not enough to exclude the impact of GC. In 8 (27%) RA patients received chronic GC therapy for more than 6 months in this study, 5 cases were under a long-term follow-up at our hospital; however, the medical records of another 3 patients were only available in our hospital, and we could not obtain the medication profiles from other hospitals. Therefore, we calculated the total exposure of prednisone dosages in six-month period before enrolling into this study. In revised Table 1, the average prednisolone dosages in high-IR and low-IR groups were 887.5 ± 386.5 mg and 843.8 ± 71.8 mg, respectively. There were no statistical significances ($P = 0.913$) between the average total prednisolone dosages in the high-IR and low-IR groups. Furthermore, in those on low-dose prednisolone therapy, significant differences in HOMA-IR levels after TOF therapy were shown in the high-IR group ($n = 4$, 3.993 ± 0.582 to 2.353 ± 0.631 , $P = 0.0286$) but not in the low-IR group ($n = 4$, 1.650 ± 0.149 to 1.595 ± 0.344 , $P = 0.875$), similar to the findings in those patients not receiving the GC treatment. These analyses suggested that there was no significant influence of low-dose prednisolone therapy on the results of this study.

2. In discussion, “A reduction in IR has been identified in RA patients with a

normal weight but not in those with obese status under anti-TNF- α therapy [35]. Despite no identified obesity in the present investigation (all patients had BMI < 27 kg/m²), there were higher BMI levels for patients without IR reduction (n = 7) when compared to those with reduced IR (n = 30) in the high-IR group of patients naïve or exposed to biologic therapy (without vs with IR reduction: 24.53 ± 2.07 vs 22.49 ± 1.91 kg/m², $P = 0.019$), reflecting an influence of increased BMI on IR.” But in present study, improvement of insulin sensitivity is more obvious in high-IR group than in low-IR group. While it is known to all that higher BMI is closely associated with more severe insulin resistance. How to explain this contradiction?

Response: In Table 1, there were no differences in BMI between high-IR and low-IR group ($P = 0.624$), whereas statistical differences were found in the articular activity DAS28 ($P = 0.008$), indicating that IR in RA is driven by the disease activity with higher circulating levels of proinflammatory cytokines in patients with increased IR. In this study, the IR levels in high-IR group were caused primarily by high-grade joint inflammation with higher DAS28 scores, and there was significantly improved insulin sensitivity after TOF therapy with greatly reduced articular inflammation.

In the **Discussion** 1st paragraph, we have pointed out that --- IR is a crucial pathophysiological feature of obesity, with both conditions being characterized by persistent low-grade inflammation ---. In the high-IR group, there were higher BMI

levels for patients without IR reduction when compared to those with reduced IR ($P = 0.019$), suggesting an additional influence of increased BMI on IR.

There is no contradiction in this study. The differences in insulin sensitivity between high- and low-IR group were majorly attributed to high-grade joint inflammation. Furthermore, obesity-related low-grade inflammation was an additional contributing factor to IR.

Minor issues:

1. There is a mistake in legend of Figure 3, “A: Homeostatic model assessment (HOMA)-insulin resistance (IR) levels in all 30 patients at weeks 0 and 24 after tofacitinib (TOF) therapy ($P = 0.016$);”. According to the results, 30 patients should be 26 patients with active rheumatoid arthritis exposed to biologic agents. This should be corrected.

Response: We appreciate the help from the reviewer to point out this typographical error.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript fulfillment all the required criteria stated above but the 74740-Institutional Review Board Approval Form or Document is submitted I think in Chinese language.

Response: Since Mandarin Chinese is the official language in Taiwan, the formal IRB documents and consent forms from patients are in Chinese language. Nevertheless, we have put the English translation on the top of documents as follows.

Title of study: A retrospective chart review study for systemic rheumatology diseases in laboratory examinations and in gastrointestinal, cardiovascular and other clinical manifestations.

Informed consent requirement: The informed consent requirement waived by IRB.