nature portfolio

Peer Review File

Inflammasome-targeted therapy might prevent adverse perinatal outcomes of recurrent chronic intervillositis of unknown etiology

Editorial Note: This manuscript has been previously reviewed at another journal. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

REVIEWER COMMENTS

Reviewer #2 (Remarks to the Author):

The current study involved administering an inflammasome pathway blockade to three consecutive pregnant patients with a history of recurrent chronic intervillositis. Although the approach taken by the clinicians to avoid chronic intervillositis seems to be very promising, it is based on too few patients and, thus, no solid conclusions cannot be made based on this limited clinical experience. I recommend publishing this small series of cases in obstetrics journal, where this finding could get potentially more attention by specialists. Moreover, the safety aspects of the medications used on pregnant women is not properly discussed in the current manuscript.

Reviewer #3 (Remarks to the Author):

This revised paper is only very marginally improved. Concerns related to inadequate sample size and lack of information of maternal immune cell parameters still limit the overall impact. At a very minimum, the authors should include the negative data for maternal blood immune analysis that in the response to reviewers indicates "did not reveal any anomalies before, during, or after pregnancy in the treated patients".

In the point by point below our responses to the reviewers are in blue:

Reviewer #2
(Remarks to the Author)

The current study involved administering an inflammasome pathway blockade to three consecutive pregnant patients with a history of recurrent chronic intervillositis. Although the approach taken by the clinicians to avoid chronic intervillositis seems to be very promising, it is based on too few patients and, thus, no solid conclusions cannot be made based on this limited clinical experience. I recommend publishing this small series of cases in obstetrics journal, where this finding could get potentially more attention by specialists. Moreover, the safety aspects of the medications used on pregnant women is not properly discussed in the current manuscript.

Thank you for your comments. While we understand your concern regarding the limited number of patients involved in our study, we believe that the unique approach of administering an inflammasome pathway blockade to pregnant patients with a history of recurrent chronic intervillositis presents valuable insights and potential implications for clinical practice.
We firmly believe that our manuscript will be of great interest to the readership of Nature Communications due to the groundbreaking nature of our results for a recurrent condition that has thus far defied effective treatment.

Thank you for your feedback regarding the safety aspects of the medications used in our study on pregnant women. We acknowledge that our manuscript primarily discussed safety aspects related to anakinra, and we appreciate the opportunity to provide additional clarification on the safety profiles of the other medications used in our study. For colchicine, a systematic review and meta-analysis involving 550 pregnancies of women, primarily with familial Mediterranean fever (FMF), found no significant increase in the incidence of fetal malformations or miscarriages when the drug was taken during pregnancy at doses of 1–2 mg per day (Reference 1). Low-dose aspirin (LDA) has been extensively studied in high-risk pregnancies and shown to improve outcomes. A Cochrane review comprising 77 trials involving 40,249 women and their babies provided high-quality evidence that antiplatelet agents, mostly LDA up to 150 mg/day, reduced the incidence of pre-eclampsia and its complications, with a favorable safety profile (Reference 2). Regarding hydroxychloroquine, the systematic literature review supporting the 2022 British Society for Rheumatology (BSR) guidance consistently found no statistically significant difference in outcomes, including congenital malformations, across various studies (Reference 3). We believe that these findings, coupled with the safety data discussed in our manuscript related to anakinra, provide a comprehensive overview of the safety profiles of the medications used in our study on pregnant women.
[1] *Indraratna PL, Virk S, Gurram D et al. Use of colchicine in pregnancy: a systematic review and meta-analysis. Rheumatology 2018;57:382–7.*
[2] *Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2007;CD004659*
[3] *Russell MD, Dey M, Flint J, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology 2022; 62: e48–88.*

In the revised manuscript, we included this additional information to address your concerns regarding the safety aspects of the medications used (lines 219-228 and lines 384-390).

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We regret that the revisions did not fully address your concerns. We understand the importance of providing comprehensive data to enhance the impact of our study.

In response to the reviewer's suggestion for enhanced impact in our publication, we have incorporated detailed data on post-treatment maternal immune parameters. Specifically, we present comprehensive analyses of the blood immune status of the three treated patients at multiple time points: before, during, and after pregnancy. Through this analysis, we aimed to investigate the potential impact of the treatment on maternal immune parameters.

Our findings reveal that the treatment administered did not exert discernible effects on maternal immune parameters across the observed time points. By comparing the immune profiles before and after treatment, we observed consistency in the immune status of the patients, indicating the stability of their immune systems throughout the study period.

These results are significant as they suggest that the treatment under investigation does not elicit notable alterations in maternal immune parameters, thereby addressing an important aspect of safety and efficacy (lines 173-176 and supplementary appendix).

REVIEWERS' COMMENTS

Reviewer #3 (Remarks to the Author):

I remain concerned that this small case series will have limited impact, and agree with reviewer 2, and as I have suggested previously, is more appropriate for a specialized journal.

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Reviewer #3:
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We firmly believe that our manuscript will be of great interest to the readership of Nature Communications due to the groundbreaking nature of our results for a recurrent condition that has thus far defied effective treatment.