

Dear Editor:

Thank you very much for your decision letter and advice on our manuscript, entitled "Immunotherapies application in ASLE in pregnancy: a case report and literature review" We also thank the reviewers for their constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by MedSci Bioscience Limited.

We hope that the revision is acceptable for publication in your journal, and we look forward to hearing from you soon.

Yours sincerely,

Huiling Zheng

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

1. The information in the case report is confusing. I suggest starting with the pre-pregnancy evaluation. Subsequently, present the evolution during the pregnancy, including relevant laboratories and activity indexes at each evaluation time. The form of presentation "24 +3 weeks of pregnancy" is difficult to understand. Describe the clinical course of the episode of care during follow-up visits, including weeks of pregnancy, relevant clinical data, relevant laboratory studies, activity indices, indications for discontinuation, or medication modification.

Response: The patient's condition was stable from pre pregnancy to 21 + weeks of gestation, because the activity of lupus was induced by cold after 21 + weeks of pregnancy. Therefore, in the History of present illness, the description of the disease started from 21 + weeks. The changes of the patient's condition during pregnancy have been adjusted one by one according to the reviewer's opinions (see table 2).

2. Change "Medrol" to methylprednisolone.

Response: We have changed "Medrol" to methylprednisolone and marked it in red.

3. I suggest changing the presentation of Table 2 and Figure 1. The authors should include an activity index in each of the evaluations carried out (SELENA-SLEDAI or BILAG).

Response: We have changed the presentation of Table 2 and Figure 1 (see Table 2)

4. The pregnancy was planned or accidental. Why was the patient not prescribed chloroquine/hydroxychloroquine from the beginning of the pregnancy? Why was tacrolimus or low-dose glucocorticoids not maintained to maintain remission during pregnancy?

Response: Although the urine protein of the patient was around 3g before pregnancy, she still had a strong desire for pregnancy and changed the medication regimen before pregnancy. Because of the fundus lesions, the patient did not take hydroxychloroquine during pregnancy (ocular fundus lesion is the contraindication of hydroxychloroquine). However, after transferring to Zhejiang No.1 Hospital, he began to take hydroxychloroquine, which may be due to different doctors' understanding of the disease. During the stable period of the disease, the patient had been maintained with low-

dose glucocorticoids. (Line 177-178)

5. What are the indications for immunoglobulin in the treatment of systemic lupus erythematosus during pregnancy? What is the recommended dose in pregnancy? What is the appropriate time interval between the first and second doses of intravenous immunoglobulin? Based on their clinical case, do the authors consider that IVIG administration was successful?

Response: IVIG has immunotherapeutic effect on SLE itself, and has non-specific anti infection effect. It can significantly improve the success rate of treatment of various lupus crisis. It is suitable for patients with severe thrombocytopenic purpura, severe thrombocytopenia with severe infection, high activity of lupus with severe infection and poor response to hormone immunosuppressive agents. Some studies have confirmed that IVIG can achieve good therapeutic effect only when it is used periodically (every 2-4 weeks) at a high dose (75-100g). I think the use of immunoglobulin in this clinical case was successful because of the significant improvement in clinical indicators.

6. If the response to the 1st cycle of immunoglobulin was good, what is the indication of plasmapheresis? Why did you not receive a second IVIG dose three weeks after the 1st dose?

Response: After using 1st cycle of immunoglobulin, the indication of

plasmapheresis were significantly improved (liver function: AST 56U / L, AST 39u / L; renal function: Cr 102mol / L; complement C3 0.52g/l, complement C4 0.10g/l; hemoglobin 93g / L, etc.) The patient did not receive a second IVIG dose three weeks after the 1st dose, it's because the patient has a lot of proteinuria, which is more than 19g at the highest. IVIG treatment is a double-edged sword for the kidney, it has the toxic effect of causing renal tubular necrosis.

7. The azathioprine dose used is less than 2 mg / Kg / d, in an outbreak patient, because a suboptimal dose was used.

Response: Because the patient was a multi-target therapy with a combination of multiple drugs, the dosage of each drug will be reduced to reduce the side effects of the drug.

8. What was the reason for the suspension of tacrolimus? Why was cyclosporine or tacrolimus not used as the initial medications for treating lupus activity?

Response: The reason for the suspension of tacrolimus was the deterioration of renal function, and the reason why cyclosporine or tacrolimus was not used as the initial medication for treating lupus activity was also due to the high creatinine.

9. Was glucocorticoid use only in pulses and high doses? Why was a maintenance dose not used?

Response: Glucocorticoids represent the corner-stone of treatment in SLE, they are not only used in high-dose shock therapy, but also gradually reduced and maintained during the remission period (see line 131,157~162) .

10. After cesarean section, a two-cycle of intravenous immunoglobulin was administered, because if there was no clinical response; since the authors used plasma adsorption therapy.

Response: Immunoglobulin is used in lupus activity during pregnancy. Clinical indicators show that the effect is good, but in the subsequent lupus activity (see table 2), considering a large amount of proteinuria, so we used plasma adsorption therapy.

11. One week after the cesarean section, rituximab 100mg was indicated. Why 100mg? Why was the second dose of rituximab not considered? Why combine sub-therapeutic doses of rituximab and cyclophosphamide?

Response: Although the effect of rituximab has been significantly improved in the treatment of lupus activity, the adverse reactions still exist, which restrict the development of clinical technology to a certain extent. Some studies have found that, on the basis of conventional treatment and immunotherapy, the total effective rate of patients was achieved by the integration of low-dose

rituximab (100mg intravenous drip, once a week, for four weeks). Moreover, the whole clinical effect has been significantly improved, and at the same time, it can significantly improve and control the occurrence of adverse reactions in patients, playing a comprehensive and balanced role in the whole treatment environment.

Cyclophosphamide is a non-specific cell cycle inhibitor. It kills cells by cross-linking with DNA and inhibits DNA synthesis to inhibit cell division. The treatment of SLE with high-dose shock therapy can lead to the decline of ovarian function in women of childbearing age, and even cause the risk of amenorrhea. Studies have used a small dose of cyclophosphamide at 200 mg every 3 weeks combined with immunoadsorption to reduce its toxicity. After 8 courses of treatment, the results of the study showed that the efficacy of the combined drug group was significantly better than that of the immunoadsorption method alone. It can be seen that low-dose cyclophosphamide can still exert its efficacy (see line 158~159).

12. The drugs' efficacy is difficult to understand because multiple treatments were used in subtherapeutic doses (i.e., azathioprine, rituximab, cyclophosphamide), the recommended IVIg dose during pregnancy in some studies is every three weeks. It is not clear if the pregnancy was planned if the patient was in remission at the time of pregnancy, and the reason why she did not maintain hydroxychloroquine, tacrolimus, or low doses of glucocorticoids

to decrease the possibility of lupus flare-up during the pregnancy is not specified.

Response: Multi target therapy has a significant effect on lupus activity with less adverse reactions and high safety. In recent years, clinical studies have confirmed the effectiveness of multi-target therapy. In the multi-target therapy, the dose of various drugs will be reduced by 50%, which can reduce the adverse reactions of various drugs, but its curative effect is improved because of the synergistic effect. It is an effective method to treat lupus activity.

The patient's pregnancy was planned, and the immunoglobulin was not used periodically in the lupus activity for three reasons: 1. A large amount of proteinuria, which the highest reached more than 19g, if immunoglobulin is used again, it may cause the toxic effect of renal tubular necrosis. 2. At 24+ weeks of gestation, the condition deteriorates and the patient is transferred to another hospital for treatment. Different doctors have different views on the treatment of the disease.

The main reason for not using hydroxychloroquine and tacrolimus was that the patient had fundus lesions and high creatinine levels, so there were drug contraindications. And glucocorticoids are maintained throughout pregnancy.

13. The discussion is limited to the review of immunosuppressants used in the treatment of lupus erythematosus. The discussion of the case, instead of a

review of the medications used, mainly discusses the risks and benefits of the treatments used. Why stop or change the dose of a drug; at what time should its effectiveness be evaluated? Why use sub-therapeutic doses of many of them? Why use plasmapheresis?

Response: Use of immunosuppressive agents during pregnancy is an issue that needs to be considered. Immunosuppression is needed to prevent flares of activity, but questions remain about the safety and long-term mutagenic effects of some drugs. According to the reviewer's opinion, we have revised the corresponding part of the paper (see line 242~250, 264~266, 273~276, 367~373, 377~380).

14. The authors propose as objective: "provide some guidance for the clinical use of immunotherapies in pregnancy." With what was previously indicated and reported with the clinical practice guidelines. What should be the treatment of choice in patients with SLE activity during pregnancy? How is it considered to be refractory to treatment? What should be the treatment of patients refractory to treatment? Do you consider that the use of multiple drugs at suboptimal doses is better than using 1 or 2 drugs at optimal doses? What would be the justification for employing?

Response: Currently, there is no radical cure for SLE activity in pregnancy, but standardized treatment can make most of the patients' condition relieved. Early diagnosis and treatment are emphasized to avoid or delay irreversible

pathological damage of tissues and organs. SLE is a highly heterogeneous disease. Clinicians should master the indications and contraindications of drugs, and measure the risk and benefit of treatment during pregnancy according to the severity of the disease.

This patient can not obtain the expected curative effect after traditional drug treatment, and the degree of organ damage of the patient is aggravated after treatment, which can be called refractory systemic lupus erythematosus.

Heterogeneity is a significant characteristic of lupus. Multiple parts of the immune system are involved in systemic and renal autoimmunity at the same time. It is not effective to treat refractory lupus by intervening single pathway or consuming single cell type. Bao et al. first put forward the concept of multi-target therapy internationally and combined the use of immunosuppressants with different targets to reduce the dose of each immunosuppressant at the same time, which not only ensures the effect of the drug, but also reduces the risk of adverse reactions. A large number of studies have shown that for refractory lupus, multi-target combination therapy is more effective and safer than single use of 1 or 2 drugs.

Therefore, based on a large number of studies, it can be seen that, for refractory lupus, the use of multiple drugs at suboptimal doses is better than using 1 or 2 drugs at optimal doses.

15. Being a case report, I find no justification for considering emerging

therapies. Alternatively, the authors consider that some of the drugs under investigation would be useful for the case presented.

Response: In my opinion, a typical clinical case is an epitome of clinical treatment of diseases, especially pregnancy complicated with lupus. How to achieve a good pregnancy outcome is a challenge for rheumatologists and obstetricians. Therefore, it is the common responsibility of rheumatologists and obstetricians to find a reasonable treatment plan. In addition, through the analysis of this clinical case, we can also get some experience and understanding of the deficiencies.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript is interesting and well written. However, I suggest to briefly discuss the role of vaccines including flu and pneumococcal vaccinations to decrease the risk of infections and, thus, of developing SLE flares (see and add as references papers by Murdaca et al concerning vaccinations)

Response: We have discussed briefly the role of vaccines in lines 380-387.

