

Format for ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7869-review.doc).



Title: Clinical Characteristics and Management of Corticosteroids Therapy for Patients with Autoimmune Hepatitis-induced Liver Failure

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Review A

(1) In fact the study is retrospective. Please change the first sentence in "patient population"

Response:

The "prospective study" was changed to "retrospective study" in the revised manuscript.

(2) A diagnosis of AIH was made based on the presence of anti-nuclear (ANA) and/or smooth muscle antibody (ASMA). Although the results of autoantibody testing are often helpful, they can be misinterpreted. Positive results for testing of antinuclear antibodies (ANA) can be detected quite commonly in patients with liver diseases unrelated to AIH. Data on specific antibodies for Autoimmune hepatitis type 1 (anti-actin) or type 2 (anti LKM-1) or anti-soluble liver antigen are not specified. Other conditions that can lead to liver failure such as Wilson disease are not rule out. A comment about these facts should be included.

Response:

A diagnosis of AIH was made based on the criteria defined by the International

Autoimmune Hepatitis Group, not only based on the presence of autoantibody. Other conditions that can lead to liver failure such as Wilson disease were excluded in our study. A comment was added to “patient population” in the revised manuscript.

(3) I would like more clarity about the concept of acute on chronic liver failure. These patients had been previously diagnosed of AIH? Which was the original hepatopathy? They have received immunosuppressive therapy previously?

Response:

Acute on chronic liver failure (ACLF) is defined as acute liver decompensation on the basis of chronic liver disease with mandatory jaundice (TBil >171.0 μ mol/L or a rapid rise >17.1 μ mol/L/day), coagulopathy (PTA < 40%) and recent development of complications. There were 13 patients who were diagnosed as ACLF in the study. For these patients, they had been previously diagnosed of AIH. AIH was the original hepatopathy.

Corticosteroid therapy was used very carefully in AIH patients in our center. The clinical symptom of the patients were improved when using Ursodeoxycholic acid (URSO) and supportive therapy. They haven't received immunosuppressive therapy previously.

(4) Corticosteroid therapy: A comment about the dose. Habitually the dose for the acute liver failure used by other authors is higher. Why is used the low dose? The reason for combination therapy with azathioprine should be also noted. This drug has the action after 2 months of therapy.

Response:

The initial dose of prednisolone for AIH therapy was 60 mg/day suggested by the International Autoimmune Hepatitis Group. Different initial dose of corticosteroids was used in severe and fulminate AIH in the previous studies. Prednisolone ranged from 30 to 60 mg/day was used in Yasui's study (Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. J Gastroenterol. 2011; 46(3):378-90.); prednisolone 1mg/kg body weight/day was initiated in Ichai's study (Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl. 2007; 13(7): 996-1003.). In China, we don't have a guideline for AIH-induced liver failure therapy. In our study, all of patients receiving corticosteroid therapy were women and had lower weight. Considering the clinical conditions of patients, we use low dose of corticosteroid (20-50 mg/day) to reduce the side effect.

In order to improve treatment efficiency, azathioprine was added (cases 1, 12 and 16). Other patients were not provided due to hemocytopenia. Usually, the therapeutic actions of azathioprine emerge slowly. It was still used in the patients with fulminate AIH previously (Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl. 2007; 13(7): 996-1003.). However, the effect of azathioprine in AIH-induced liver failure needed to be further determined.

(5) The authors compare survivors and non-survivors and found a significant difference in the sense of lower MELD score and corticosteroid therapy which were associated to survivor. The authors also describe the characteristics of the seven patients that have received corticosteroids. However, they have not analyzed the differences between the four survivors and the three non-survivors that have received corticosteroid therapy.

Response:

The comparison of clinical characteristics between the four survivors and the three non-survivors that have received corticosteroid therapy was analyzed statistically previously (shown as below). However, we are not sure whether included the table in the manuscript since the number of patients was small.

Table 5 Corticosteroid treatment associated with survivors and non-survivors

| Variables | Survivor (n = 4) | Non-survivor (n = 3) | p-value |
|-------------------------------------|---------------------|-------------------------|---------|
| Age (years) | 40.0 0± 8.37 | 64.00 ± 16.52 | 0.077* |
| SIRS (yes), n (%) | 0 (0) | 0 (0) | |
| Cirrhosis (yes), n (%) | 2 (50) | 3 (100) | 0.429** |
| subacute/ACLF | 2/2 | 0/3 | 0.429** |
| Total Bilirubin (mg/dl) | 20.75 ± 6.67 | 18.00 ± 6.26 | 0.724* |
| Alanine aminotransferase (IU/L) | 195.75± 74.09 | 524.67 ± 194.31 | 0.034* |
| Prothrombin activity (%) | 30 .50± 5.26 | 30.67± 8.02 | 0.858* |
| MELD score | 21.50 ± 2.08 | 27.00 ± 7.81 | 0.212* |
| Hepatic encephalopathy (yes), n (%) | 1 (25) | 1 (33.33%) | 1.000** |
| IgG (mg/dl) | 2483.50 ± 901.45 | 2760.00 ± 747.49 | 0.724* |
| Duration(days)* | 24.50±8.10 | 91.00±20.88 | 0.034* |

* Mann-Whitney U test, ** Fisher's Exact test

Duration: Days from diagnosis to corticosteroid therapy

(6) In the Tables please specify all abbreviations

Response:

All abbreviations were specified in Tables.

Review B

(1) Page 1. Military Hospital, please provide city. Conflict of interest, change people to authors. In the abstract, give results with numbers including p values, also present details regarding MELD scores in numbers and p values.

Response:

City of military hospital was added. In the abstract, the details regarding MELD scores in numbers and p values were added in revised manuscript.

(2) Page 2. Para 2 should start with: Although there is 5 lines below, correct to 2-5%.

Response:

It was corrected in the revised manuscript.

(3) Page 3. survey of Ichai, not from... Under Patient population, it should read The retrospective study, not the prospective study.

Response:

The "prospective study" was changed to "retrospective study" in the revised manuscript.

(4) Page 5, under 2, first sentence should start with the imm., not The Immun... And 6 lines below, please correct to globulins.

Response:

It was corrected in the revised manuscript.

(5) Page 7, Discussion. Para 3: Our study has...

Response:

It was corrected in the revised manuscript.

(6) Page 8. Yasui et al have...

Response:

It was corrected in the revised manuscript.

(7) Table 2, Top. Correct to Corticosteroid. Bottom of this table: globulins.

Response:

It was corrected in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,
Bing-zhu

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