Author's response to reviews

Title: Hepatotoxicity induced by horse ATG and reversed by rabbit ATG: A case report

Authors:

Khalid KA Al-Anazi (khalid_alanazi@yahoo.com)
Mahmoud MD Aljurf (maljurf@kfshrc.edu.sa)
Fahad FZ Al-Sharif (alsharif@kfshrc.edu.sa)
Hamad HM Al-Omar (halomar@kfshrc.edu.sa)
Ahmed A Alami (a_alami2000@yahoo.com)
Fayyaz F Farooq (fayyazrph@hotmail.com)

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Answers to the reviewers

Dear Reviewers:

Happy day to you.

Thank you very much for sending us your valuable comments and suggestions.

Your comments were very valid and fair. We did our best to induce all the modifications requested and to make all the clarifications required:

1-The typing and grammar mistakes were corrected and highlighted.

2-The table was replaced by a figure. We do agree with the reviewer in that the figure is more descriptive than the table.

3-The donor was HLA-identical. This was changed in the text.

4-The generic names of certain drugs were substituted for the trade or brand names eg bactrim and thymoglobulin.

5-Rabbit ATG is a purified IgG product. This has also been mentioned in a number of articles including reference 4 and [reference 6 in the new manuscript ie reference 18 in the old manuscript]. The phrase highly purified was replaced by purified. The horse type of ATG was part of our protocols, but after the development of hepatotoxicity in the patient reported, a substantial shift was made in our section to use rabbit form of ATG instead.
6-No androgen therapy was given to the patient prior to allograft. The patient did have high serum ferritin level prior to transplant due to repeated blood transfusions. The patient did not have any viral hepatitis infections before or after transplant. No liver biopsy was taken in the pre-transplant period. An ultrasound of the liver was done and it was normal. All these were included in the new text. The possible cause of the slight elevation of ALT level prior to ATG therapy could be iron overload caused by previous blood transfusions.

7-The dose of cyclosporine-A, as per our protocol, was mentioned in the new text. The normal range of cyclosporine-A level at our hospital is 150-300 ng/ml. In the early post-transplant period we usually aim at having the levels near the upper limit i.e. around 250 ng/ml.

8-Normal values for bilirubin, ALT and AST were mentioned in the new version of the article.

9-The symbols - and + were used instead of dates when referring to the time before or after the stem cell transplant.

10-The patient did not have any previous medical or surgical illnesses prior to the diagnosis of Fanconi anemia. A new statement regarding this issue was added to the text. The patient remained asymptomatic and hemodynamically stable despite the severe and sudden hepatic dysfunction. This was mentioned even in the old text.

11-The serum bilirubin level became only slightly elevated after the dose of horse ATG given. The normal range of bilirubin at our hospital is 0 to 22 micromole / litre. In our patient the maximum level reached 37 micromole / litre. The conjugated part was predominantly elevated. The horse ATG dose was infused over 10 hours as mentioned in the old and new texts. The patient was not on any medication other than the drugs included in the conditioning protocol. The patient received only one dose of fluconazole and one dose of bactrim prior to the hepatotoxicity. Both medications were resumed 5 days later, when the liver enzymes and bilirubin levels returned to the pre-transplant levels, and no new episodes of hepatotoxicity were encountered. We fully agree with the reviewers in that: fluconazole, bactrim and cyclosporine-A are common causes of drug-induced hepatotoxicity in stem cell transplant recipients.

12-Mild and moderate degrees of hepatotoxicity have been reported with both types of ATG, but these are usually transient and reversible within days.

13-Regarding the statement referring to the multifactorial predisposition for the hepatic impairment. There is a misunderstanding here. We did mean the mild and chronic hepatic dysfunction encountered in the follow up of the patient and not the initial gross hepatic dysfunction encountered following the administration of horse ATG which was part of the conditioning protocol. We actually found and referred to some articles mentioning this long term/chronic liver dysfunction in patients with Fanconi anemia. As this statement may cause further confusion, we preferred to omit it.

14-All the changes you suggested/requested were made and highlighted.
The modifications you made the modified version of the manuscript much better than the originally submitted one. Thank you very much for the excellent reviews you made.

Finally, please do accept the best regards and wishes from my co-authors and myself.

Khalid Al-Anazi