Author’s response to reviews

Title: Colon biopsies for evaluation of acute graft-versus-host disease (A-GVHD) in allogeneic bone marrow transplant patients

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PDF covering letter
Response to reviewer’s comments

The changes and related areas are underlined in the copy submitted as additional file.

Reviewer # 1.

Title: Colon biopsies for evaluation of Acute Graft-Versus-Host Disease (A-GVHD) in allogeneic bone marrow transplant patients.
Authors: Shidham et al
Version: 1 Date: 4 Feb 2003
Reviewer: Danielle Canioni
Level of interest: A paper whose findings are important to those with closely related research interests
Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Discretionary revisions:
The lesions described in colon biopsies of acute GVHD are interesting to described mainly for "regular" pathologists since the main histological criteria allowing this diagnosis are already known by pathologists who use to work in teams dealing with bone marrow transplantation. – Modified & highlighted (P3).

Compulsory revisions:
1. There are some typographical mistakes. – Corrected.
2. Since cryptic apoptosis are well known in acute GVHD, we think that it would be interesting to illustrate the other less known histological criteria (like pericryptal apoptosis, crypts abnormalities, decrease of plasma cells comparing to biopsies of control groups...- Added new figures 2 A & B to illustrate these features.
Reviewer # 2.

Title: Colon biopsies for evaluation of Acute Graft-Versus-Host Disease (A-GVHD) in allogeneic bone marrow transplant patients.
Authors: Shidham et al
Version: 1 Date: 4 Feb 2003
Reviewer: Nirag Jhala
Level of interest: A paper of considerable general medical or scientific interest
Advice on publication: Accept after discretionary revisions
This is a timely and well thought out manuscript. It has many strengths and would be important to document features of A-GVHD in the literature and would be of interest to both gastroenterologists as well as pathologists. The study result supports the conclusion and the morphologic features can be used by others to follow.

Discretionary revisions:
One of the concerns is that the authors use colon biopsies in patients who have documented GVHD of skin within 15 days of its detection. It might be also be better to document if the therapy was started or not before obtaining the colon biopsy and following diagnosis of skin GVHD for the present study. – Modified & highlighted (P4 last line)

It may also strengthen the study if cases of colon biopsies from clinically considered GVHD who did not have skin GVHD are included in the study. - Limitation discussed (P6).

Some of the subjective parameters listed in the result section need to be elaborated in the material and method section for better understanding of the reader. - Done

In addition, following are specific comments which need to be considered.

Abstract
Page 2, lines 11 and 12: Does not make sense. The line begins with a number, and suggests that decreased number of lymphocytes are noted when the normal does not contain any.- Modified & highlighted

Page 2, lines 14 and 15: It would be difficult to understand what is outer third of lamina propria a better morphologic definition would be more appropriate.- The point about Plasma cell is deleted altogether from the revised manuscript with reference to the comment by Reviewer# 3, due to lack of proper control.

Page 2 (Conclusions): It would be better if parameters listed in the conclusion are noted to have been studied earlier in the study design or conclusion. Making a statement in conclusion would suggest that these conclusions were drawn from subjective parameters not studied in depth by authors. - Modified

Introduction
Page 3 paragraph 2 last line: The relevance of the statement in context of the present study is unclear. Modified

Competing interests:
None declared.
Reviewer # 3.

Title: Colon biopsies for evaluation of Acute Graft-Versus-Host Disease (A-GVHD) in allogeneic bone marrow transplant patients.
Authors: Shidham et al
Version: 1 Date: 11 Feb 2003
Reviewer: Lisbet Sviland
Level of interest: A paper of limited interest
Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Discretionary revisions:

1. In the introduction the authors state that: "The incidence of intestinal A-GVHD after allogeneic BMT ranges from 30% to 60% and may be associated with or without clinical signs of skin and liver involvement". This is not entirely correct; the incidence of A-GVHD after allogeneic BMT ranges from 30% to 60% with the skin as the most commonly affected organ. - Modified & highlighted (P3)

2. Under methods when the authors describe the negative control groups they state that "the histopathology was negative for diagnostic pathology..." Were these reported as normal? - Specified & highlighted (P5)

3. I would like a comment on the design of the study. Was this a prospective or a retrospective study using archival biopsies? – Retrospective nature (P4)

4. Two negative control groups were included in the study and as the authors say it would have been desirable to have a control group from post BMT patients without GVHD. They state this was impractical due to "obvious ethical limitations". Other similar studies have managed to include autologous BMT recipients as a control group. Was this a possibility? The repopulation of lymphoid cells in the gut will be different in a BMT patient group (see below). - (P6).
Response- This is an excellent point. However, due to limited number of cases in this group we could not include it. Because of the same reason as suggested by the reviewer the point about plasma cells would be difficult to evaluate and so we are deleting that point from the revised manuscript.

Compulsory revision:

1. I would like some more clinical information:
   - What kind of transplant did group A receive? Was it all bone marrow or did the group include patients who received peripheral stem cells or cord blood transplants? - Modified & highlighted (P4).
   - There is no mention of what kind of conditioning the patients received. This is important in the differential diagnosis of A-GVHD in the gut. Although as the authors
state most of the pathology caused by the conditioning regimen will have disappeared by day 21 it should be included in the clinical details.- Modified & highlighted (P4).
- What kind of GVHD prophylaxis did the patients receive?- Modified & highlighted (P4).
- Were the biopsies taken before any treatment for their GVHD was commenced?- Modified & highlighted (P4).

2. It is important to exclude CMV infection as histological features of CMV can be identical to those seen in A-GVHD. There is no mention in the paper how CMV infection was excluded. Serology for CMV is unreliable in the post-BMT setting. For that matter CMV may occur together with GVHD. Did they do immunohistochemistry for CMV on tissue sections and if not why not?- Modified & highlighted (P4).

3. The authors state that plasma cells were more frequent in the negative control groups. They have in this context not discussed the difference in repopulation of lymphoid cells which occurs following a transplant. The control groups they have used are therefore not appropriate and the lack of a "chronic inflammatory response" would be expected in patients post BMT. They would have to include allogeneic BMT recipients with no GVHD or autologous transplant recipients to comment on this finding.

Response- As mentioned above, the point about plasma cells would be difficult to evaluate in the absence of suitable negative control. We are deleting that point from the revised manuscript.

Competing interests:
None declared.