Author's response to reviews

Title: Colectomy rate in steroid-refractory colitis initially responsive to cyclosporin: A long-term retrospective cohort study

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Dear Editor:

We are herein including the responses to the arguments raised by the two referees as per your message dated November 8.

One of the referees deemed that our work was well done; however, she raised a number of issues that we have tried to respond to in the enclosed point-by-point document.

The other referee concentrated onto the English form, and required us a complete re-writing of the paper. We are including a detailed response to this referee also.

We hope to have met your requirements but are ready for further revision work, should anything be missing or need changing. In the hope to ease your revision, major changes have been underlined in this version.

RESPONSES TO REFEREE S. VERMEIRE

The referee deems that our work was well done and the results relevant; however, a number of pivotal issues are raised.

1. Table 1, now added in the present version, contains the information required by the referee.

2. The referee is correctly concerned with the possibility that Fig. 1 "masquerades" the very fact, highlighted in other series, that for the specific cohort of steroid-refractory UC patients who flare and require CsA while they are already on active AZA, continuation on this drug after CsA induction will have short-lived benefits. The referee suggests stratification to account for these patients, a suggestion that we considered; however, in this particular series the AZA-pretreated subjects were a relative minority (11%) and our statistician (MF), based on a specific reference (Peto R et al, British J Cancer, 1976; 34:585-612), warned us that these numbers would prevent a statistically correct stratification. On the other hand, we dare to add that it is just this low proportion that reduces the risk of Fig. 1 to be misleading on these premises. Nevertheless, we emphasize that the message in Fig. 1 is tempered by the numbers in Table 4 that witness a worse prognosis for those already on AZA in our series. Table 4 is further commented on in the Discussion by stating that higher proportions of such AZA resistant patients would have led us to the same conclusions of Moskowitz report; the relative absence of such difficult patients may have favored our higher rate of
colectomy avoidance at the 7th yr: 35% vs 12%.

3. The wide CsA window of 60-240 ng/ml that we quote in this paper is the legacy of the historical work that founded the kidney transplant program at our hospital in the early 1980’s (ref. 10). In fact we state in the Methods that we tended to maintain all patients in the higher areas of the window, as correctly emphasized by the referee. Table 2 now enlists CsA levels together with a number of other variables and found no differences between responders and failures.

4. The decision to include the NEORAL treated subset must carefully be justified, and we agree that the frequency of left-sided disease is not a criterion. As noted in the text, the stools/day, the ESR, and the HB concentrations of these patients yielded a score in the range of 10 to 11. All of the NEORAL treated patients relapsed, similarly to the IV treated ones.

The final colectomy rate was 46% vs 78% in the IV group, a difference, however, that is not significant (p=0.07 by Fisher’s exact test). Anyway, it is worth noting that the NEORAL patients fell into the most favorable part of our learning curve and received AZA more frequently (66%) than those treated before 1996 (26%), a fact that per se might explain their better outcome. In agreement with our findings, one very recent literature report claims that for patients with full-blown refractory UC, NEORAL can perform as well as IV CsA (Inflamm Bowel Dis 2006; 12: 1131-1135).

5. Following the referee’s suggestion, the final sentence has been replaced. Again we emphasized that the problem of the AZA-refractory patients is pivotal in stating whether CsA is a real rescue drug or just a bridge to colectomy. In so doing, we were guided by the considerations contained in the Editorial by Simon Travis on "Infliximab and Azathioprine: Bridge or Parachute" which on page 1355 of the April 2006 issue of Gastroenterology deals with the issue of thiopurine refractory and naive patients, and we trust to have interpreted the referee’s thinking.

6. As to the minor points: a) All of the patients currently followed up who are colectomy-free are also steroid-free; b) the drop-outs were patients who either moved away from town or were unreliable as to the visit calendar.

RESPONSE TO REFEREE D. O’DONOGHUE

This referee called for a complete re-writing of the paper insofar he deemed that the message, although good and relevant, was lost due to the poor English presentation. In agreement with him, we moved some information from the Method section to the Result section where it found a better place. The Patient and Method section was almost totally re-written, as well as the conclusion paragraph, which was criticized by the referee. Also because of the changes required by the other referee, altogether these alterations led to a total revising of the text.

Finally, we had the manuscript read through by a native English-speaking MD and, wherever possible, his suggestions were incorporated.