February 11, 2013

Dear Editor:

Attached you will find the edited manuscript in World format (#1667)

Title: Expert Opinion: Experience with 6-Mercaptopurine in the Treatment of Inflammatory Bowel Disease

Author: Burton I. Korelitz, M.D.

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript: #1667

**RESPONSE TO REVIEWERS RE MANUSCRIPT #1667 WJG**

Response to Reviewer #1 (The Pharmacologist)

Since it was I (with Dr. Present) who provided the first controlled trial for Crohn’s disease with 6MP, my experience predates the introduction of serological measurements. Subsequently, both Present and I have never had the need to utilize them and indeed we have been able to move along faster and just as safely in management accordingly. This is summarized in Section #2 of the paper which focuses on my clinical experience. Since I do not include references at all, I will now include pertinent papers as recommended reading. Similarly I will include pertinent references on clinical trials. I would love to read separately a paper on recent pharmacological considerations but I do not feel qualified to write it. Perhaps the reviewer will make this contribution. Meanwhile, I will contribute references for appropriate reading.

Response to Reviewer #2

The role of immunosuppressives in Top Down vs. Bottom Up straddles these two approaches to therapy. This is because 6MP has maintenance as well as induction value as opposed to steroids which work quickly but have no maintenance value and infliximab which also works quickly and does have maintenance value. The 6MP, however, is slower in its action than both of the above in most cases. Therefore 6MP will be more appropriate as a Step Up drug unless used from the outset in conjunction with infliximab as done in the Sonic Trial.

I will incorporate the above into Section 3 of the text and again provide references.

I suggest that I omit reference to 5ASA being superior to placebo for Crohn’s disease since the topic is not of specific relationship to this paper.

I am now including references to controlled trials for 6MP/Azathioprine.

My paper is not about Cyclosporine or Methotrexate but limited to 6MP and Azathioprine which were the only drugs fitting the definition of immunosuppressives at the time they were introduced. In addition to the time issue, I still don’t consider these 2 drugs immunosuppressives; the only common denominator for Methotrexate is its role in suppressing antibodies.

I refer to combination therapy in Section 10 and will include reference to the Colombel/Sandborn paper in the New England Journal of Medicine. I will also include the paper by DiSabatino et al as recommended by the reviewer.

I have also made the minor corrections noted by reviewer #2.

Response to Reviewer #3

I am willing to change the title to 6 Mercaptopurine from Immunosuppressives. I had used the term immunosuppressives in the title to refer to 6MP and Azathioprine but not Methotrexate and Cyclosporine. I am perfectly satisfied to make the change to 6MP since the reviewer is absolutely right that most of my experience is related to 6MP rather than Azathioprine and I have made the change.

I will expand on the issue of lymphoma to some extent. The incidence of lymphomas is minimally increased in patients treated with 6MP and as a generality the very small risk should not detract from using the drug if clearly warranted. The prognosis of the lymphoma in general is no different than the lymphoma not treated with 6MP so that the diagnosis of lymphoma is not a death warrant. The exception to this rule is the hepato-splenic lymphoma which carries the worst prognosis of the lymphomas and it occurs in children, particularly male children, who have the most virulent IBD, so that even in this group of patients it is challenging not to use 6MP as well as to using it. Most patients with this type of lymphoma have been on combination therapy (6MP or Azathioprine plus IV infliximab) but the onus is on the immunosuppressives since the lymphoma rarely occurs with infliximab alone. I have included this information in the section on Toxicity.

I am influenced toward using prophylactic therapy after resections for Crohn’s disease since I am impressed with infliximab infusions being more effective than 6MP and the risk of adverse reactions to 6MP including lymphomas is also greater. The results of low dose 6MP have not been as impressive as with IV infliximab.

References for the above statements are now included in recommended reading.

Prophylactic therapy with either drug is indicated for all patients who come to resection since the natural history of Crohn’s disease is recurrent ileitis regardless of the indication for surgery.

I appreciate the comments of the 3 reviewers and agree that the resulting changes enhance the value of my paper.

**Division of Gastroenterology Department of Medicine**

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To the Editor

Dear Professor Ma:

I am pleased that the 3 reviewers find my manuscript satisfactory for publication in the World Journal of Gastroenterology. I have responded to all their comments which I appreciate and I provide you with a corrected paper.

I also now include references which I had omitted previously. Most of the references are my own as would be logical since the submission is based on my personal experience. Nevertheless, I have included many other appropriate references. They are presented in a form so that they are identified according to the titled segment of the paper.

I hope you will like the changes.

With warm regards,

Sincerely,

Burton I. Korelitz, M.D.

BIK:js