Padua, April 19, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word Format (file name 2475-review.doc.

Title: 5-ASA colonic mucosal concentrations resulting from different pharmaceutical formulations in ulcerative colitis

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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 the reviewers as follows:

1. The format has been updated. The title has been slightly changed.

2. A summary of less than 100 words outlines the most innovative and important arguments and core contents

3. a point-by-point answer has been provided to the reviewers' questions.

In this study, we enrolled consecutive patients needing a colonoscopy for surveillance purposes or clinical activity. All of the patients were being chronically treated with mesalamine and were receiving comparable doses of 5-ASA (i.e., 2.4 g of a pH-dependent formulation, 3 g of a pro-drug, or 3 g of a time-dependent-release formulation). No selection has been made on the type of mesalamine and this accounted for the different number of patients treated with each drug.

In Italy, mesalamine is usually administered 3 times per day, so it is assumed that pills are taken at breakfast, lunch, and dinner. We recorded a large degree of variation in the adherence to taking the pills during the day, but no correlation was found between the time since the last time the drug was taken and the drug's mucosal concentration. The mean time since last pill assumption of the group receiving the time-dependent-release formulation have been corrected due to an error in the calculations. It is now apparent that there were no differences in the last time since a pill was taken among the 3 groups. We apologise for the mistake.

Topical therapy consisted of either 2 or 4 g of a drug, and we assumed that either amount could increase the drug mucosal concentrations; indeed, the concentrations were significantly higher in the combo-treated patients compared with patients receiving oral mesalamine alone. We only examined 28 patients receiving combo therapy.

The more frequent use of pH-dependent-release mesalamine indeed reflects our practice. Time-dependent formulations do not represent the first choice in ulcerative colitis treatment because the release begins proximal to the colon, which is reflected in the fact that all of the patients included in this group had pancolitis. We should have included patients with Crohn's disease to increase the number of samples, but we did not want to add the variability of a different type of disease. The use of pro-drugs in amounts that were comparable to the dose of the pH-dependent formulation was limited to a smaller number of patients. Salazopyrin is still used by approximately 15% of the ulcerative colitis patients who we follow, especially if they have articular symptoms, but the amount of drug taken per day varies widely.

Moreover, the study was carried out under rather stable assay conditions, which was demonstrated by the low inter-assay coefficient of variation (< 4%).

We agree with the assertion that the mucosal mesalamine concentrations varied widely. The absolute mucosal concentration was quite low in many patients receiving pH-dependent formulations even though they had significantly higher values on average than the other groups. Variability in the mucosal concentration may have several potential causes. However, our results showed that the degree of variability was similar in the 3 groups of patients, and despite all of the study limitations, it was clear that two factors affected the mucosal concentration of the drug, the type of formulation and the presence of active inflammation.

Corrections and new parts are highlighted in the text.

4. English language has been revised by NPG Language Editing as suggested by the editor and certificate is provided.

We thank you very much the reviewers for the opportunity to revise our paper and hope that in the present form it is now suitable for publication.

Sincerely yours,

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