October 27, 2012

Dear Editor,

Thank you for reviewing our manuscript. We appreciate your suggestions and are pleased to resubmit our revised manuscript reflecting the reviewer's comments.

Please find enclosed the edited manuscript in Word format (file name: 518-review.doc).

Title: Clinical outcomes and predictive factors in oral corticosteroid-refractory active ulcerative colitis

Author: Han Ho Jeon, Hyun Jung Lee, Hui Won Jang, Jin Young Yoon, Yoon Suk Jung, Soo Jung Park, Sung Pil Hong, Tae Il Kim, Won Ho Kim, Jae Hee Cheon

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 518

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

COMMENT-1

This paper is well written and the authors highlight the limitation of the study appropriately in their discussion: Retrospective design, not strictly comparative in terms of therapies, and small numbers. Nonetheless, there is an important observation in terms of better management of patients with UC. Some of the findings have been previously reported (eg low HB as a risk factor for refractoriness) but it is valuable to see the principles applied to a different population. 67 patients over a 14 year period in which treatment approaches to acute UC have developed may seem a small number, but the comparative data is compelling and statistically significant using appropriate methods. Duration of oral steroid administration may be a very useful predictor of outcome in these cases. The authors are right to emphasize the need for further

study in this area.

Response: Thank you for your compliment.

COMMENT-2

Review report

Clinical outcomes and predictive factors in oral corticosteroid-refractory active ulcerative colitis

By

Han Ho Jeon, Hyun Jung Lee, Hui Won Jang, Jin Young Yoon, Yoon Suk Jung, Soo Jung Park, Sung Pil Hong, Tae Il Kim, Won Ho Kim, Jae Hee Cheon.

The authors have performed a retrospective study on patients with ulcerative colitis who have received intravenous steroids during the period 1996 – 2010. In the era of biological therapy the primary aim of study may seem a bit off point. However, as biologics are very expensive, evaluation of alternative approaches will certainly be interesting for many readers. The paper is well written, but a few points need clarification before it can be published.

1. Selection of patients should be stated in detail as selection bias is one of the largest problems with retrospective studies.

Response: Reflecting your comment, we have added the following sentences in the methods section (page 4, line 36).

The criteria for eligibility were male or female patients with a diagnosis of UC followed regularly for at least 1 year. The exclusion criteria were patients with a history of corticosteroid therapy at other hospitals, corticosteroid use for diseases other than UC, and a follow-up duration of less than 1 year. All enrolled patients were initiated intravenous corticosteroid therapy after admission after failure of oral steroid therapy which was done at outpatient clinic.

2. Did the doctors treating the patients do the MAYO score routinely? Or have the scores been set retrospectively? Especially the PGA is difficult to do properly from a patient file.

Response: Our study is a retrospective study from a prospectively collected database. At our clinic,

prospective data collection was generally carried out as follows. After a new patient is confirmed to have UC by GI specialists in our clinic, the patient is interviewed by clinical research coordinators and invited to answer the questionnaire concerning all the significant data about UC including lifestyle, and baseline clinical, endoscopic, and laboratory characteristics. The data are stored in a form of Assess file as well as paper form. After then, the questionnaire is updated every visit of the patient to outpatient clinics. We have been constantly carrying this enrollment since 20 years ago. The primary aim of this internal database was to construct the clinical database for clinical research and management of patients among GI specialists in our clinic. Also, GI specialists have checked MAYO or partial MAYO scores including PGA at every OPD visit or hospitalization. Reflecting your comment, we have added the following sentences in the Methods section (page 5, line 17), as following.

Our study is a retrospective study from a prospectively collected database. The data are stored in a form of Assess file as well as paper form. After then, the questionnaire including MAYO or partial MAYO scores including Physician Global Assessment (PGA) is updated every visit of the patient to outpatient clinics.

3. An emerging parameter in IBD management is endoscopic healing. Especially steroid therapy is known to relieve symptoms but do little to promote mucosal healing. Authors should comment on this aspect of steroid therapy.

Response: We agree with your comments. Mucosal healing has emerged as an important treatment goal in UC because evidence is accumulating that it can alter the clinical course of UC. Steroid therapy is frequently initiated on patients with more severe UC or for controlling disease flare. Importantly, evidence of corticosteroid's ability to promote mucosal healing is limited. However, our report was a retrospective design. The period in which corticosteroid treatment to acute UC were given was between January 1996 and 2010 in our study. A considerable portion of this period was at moment before mucosal healing has emerged as an emerging parameter in UC. Then we could not evaluate the mucosal healing as a parameter of clinical outcomes in this study. Reflecting your comment, we have added the following sentences in the discussion section (page 11, line 3), as follows.

Mucosal healing has emerged as an important treatment goal in UC because evidence is accumulating that it can alter the clinical course of UC. However, evidence of corticosteroid's ability to promote mucosal healing is limited. A considerable portion of a period in this study was at moment before mucosal healing has emerged as an emerging parameter in UC. Then we could not evaluate the mucosal healing as a parameter of clinical outcomes in this study.

4. Extended pre-operative use of steroids increase surgical complications. Authors should discuss this in relation to the outlined treatment regimen.

Response: An extended pre-operative use of steroids might increase the risk of surgical complications. In the review of literature, emergent colectomy surgeries performed more than 14 days after admission were associated with more than 3 fold increased risk of any postoperative complications and postoperative infections[1]. Moreover, UC patients undergoing an elective surgery have been shown to be at an increased risk of postoperative infectious complications in patients treated with corticosteroids[2]. In our study, a total of 9 patients underwent elective proctocolectomy within 1 year. Among of them, one patient died of pneumonia and sepsis after proctocolectomy.

These results have been added in the discussion section (page 10, line 14), as follows

An extended pre-operative use of steroids might increase the risk of surgical complications[1,2]. UC patients undergoing an elective surgery have been shown to be at an increased risk of postoperative infectious complications in patients treated with corticosteroids. In our study, a total of 9 patients underwent elective proctocolectomy within 1 year. Among of them, one patient died of pneumonia and sepsis after proctocolectomy.

1 Faiz O, Warusavitarne J, Bottle A, Tekkis PP, Clark SK, Darzi AW, Aylin P. Nonelective excisional colorectal surgery in English National Health Service Trusts: a study of outcomes from Hospital Episode Statistics Data between 1996 and 2007. *J Am Coll Surg* 2010; **210**: 390-401.

2 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003; **125**: 320-327.

5. Typo p 8: "exacervation"

Response: We rewrote it in the revised manuscript.

6. Discussion p 9 – authors should avoid repeating the results too extensively – second paragraph can be shortened.

Response: Based on your comments, we shortened the sentence (page 9, line 5) as following.

One month after the initiation of intravenous corticosteroid therapy, 78.5% of patients (32.1% with complete response and 46.4% with partial response) showed clinical improvement, whereas 42.6% were dependent on steroids at one year.

COMMENT-3

The authors evaluated the clinical outcomes and prognostic factors after intravenous corticosteroids following oral corticosteroid failure in active ulcerative colitis patients, demonstrated that the duration of oral corticosteroid therapy (> 14 days, P = 0.049) and lower hemoglobin level (≤ 11.0 mg/dL, P = 0.02) were found to be poor prognostic factors for response at two weeks. These findings are interesting but seem to be somewhat surface.

7. Some previous papers indicated the significance of cytomegalovirus infection in steroid-refractory ulcerative colitis. It should be recommended to include data of cytomegalovirus infection in this paper.

Response: Recent studies have shown that cytomegalovirus (CMV) infection in patients with active UC was associated poor outcomes[1-3]. However, due to a high prevalence of CMV immunohistochemical positivity in the intestine, the clinical impact of CMV infection is still difficult to evaluate in patients with active UC. In our study, CMV infection was detected in 5 patients. All were diagnosed by histologic examinations and were treated with ganciclovir. Of these, one patient underwent proctocolectomy within 14 days after the treatment. The rest of them responded to ganciclovir treatment. Finally, three patients were in partial remission and one patient was steroid dependent at one year. These results have been added in the results section (page 7, line 22), as following.

In our study, CMV infection was detected in 5 patients. All were diagnosed by histologic examinations and were treated with ganciclovir. Of these, one patient underwent proctocolectomy within 14 days after the treatment. The rest of them responded to ganciclovir treatment. Finally, three patients were in partial remission and one patient was steroid dependent at one year.

1 Wada Y, Matsui T, Matake H, Sakurai T, Yamamoto J, Kikuchi Y, Yorioka M, Tsuda S, Yao T, Yao S, Haraoka S, Iwashita A. Intractable ulcerative colitis caused by cytomegalovirus infection: a prospective study on prevalence, diagnosis, and treatment. *Dis Colon Rectum* 2003; **46**: S59-65.

2 Domenech E, Vega R, Ojanguren I, Hernandez A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabre E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379.

3 Cottone M, Pietrosi G, Martorana G, Casa A, Pecoraro G, Oliva L, Orlando A, Rosselli M, Rizzo A, Pagliaro L. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. *Am J Gastroenterol* 2001; **96**: 773-775.

8. In addition, are there any data evaluated predictive factors (including dose and duration of corticosteroid use) in intravenous corticosteroid therapy one month, 3 months, or 1 year after oral corticosteroid therapy in

corticosteroid-refractory active ulcerative colitis?

Response: Our corticosteroid treatment policy was as the following, as referred to description in the methods section.

Intravenous corticosteroid therapy was initiated with intravenous administration of 100 mg of hydrocortisone every eight hours. Intravenous corticosteroid therapy was continued for 1−2 weeks, with the treatment duration depending on the individual patient conditions, followed by gradual tapering of corticosteroids. After clinical improvement of UC, the dose of intravenous hydrocortisone was reduced to 200 mg daily. If the patients had no clinical exacerbation of UC, they were administered 30 mg/day of oral corticosteroid therapy before discharge. Our oral corticosteroid tapering policy was to reduce prednisolone by 5 or 10 mg weekly for patients with improved clinical symptoms but to sustain the current dose of prednisolone for one week for patients with lasting clinical symptoms. Therefore, we thought that there was little difference in terms of the dose and duration of intravenous corticosteroid therapy one month, 3 months, or 1 year after oral corticosteroid therapy in corticosteroid-refractory active ulcerative colitis. Moreover, oral steroid dose is not different much among patients because we strictly use the fixed protocols. Then, unfortunately, we did not have to evaluate the dose and duration of corticosteroid use in intravenous corticosteroid therapy one month, 3 month or 1 year after oral corticosteroid therapy in corticosteroid-refractory active ulcerative colitis

9. Specific comments:

1. The authors demonstrated that the duration of oral corticosteroid therapy and lower hemoglobin level were found to be poor prognostic factors for response at two weeks. But, they never explain the relationship between corticosteroid-refractoriness and the duration of oral corticosteroid therapy and anemia. In this paper, it is essential to explain them including steroid resistance.

Response: We demonstrated that the duration of oral corticosteroid therapy and lower hemoglobin level were strongly associated with poor outcome at two weeks. Lower hemoglobin level as a risk factor for poor response in our study is in accordance with an earlier reports, which reflects that initial severity of disease might be a significant predictor of poor clinical outcome after steroid treatment[1-3]. Also, anemia is a common and important complication of IBD with a prevalence rate ranging from 8.8% to 66.6% in UC patients[4,5]. The quality of life, an ability of work, and cognitive function can be impaired because of anemia in IBD patients[6,7]. Impaired quality of life by anemia in UC patients could influence patient well-being sense and Physician Global Assessment (PGA). For this reason, a lower hemoglobin level could be a risk factor for

poor response in our study.

In this study, the duration of oral corticosteroid therapy (> 14 days *vs.* ≤ 14 days, $P = 0.049$) was found to be another poor prognostic factor for response at two weeks. This finding indicates that patients with UC with more severe disease activity achieved remission less often than those who tended to achieve remission earlier[8]. The duration of oral corticosteroid therapy was likely to reflect the severity nature of UC in these non-responding patients. Additionally, prolonged oral corticosteroid therapy might be associated with mortality and morbidity such as infection and sepsis in UC patients undergoing surgery.

With regard to the duration of intravenous corticosteroid treatment, the limit of 7-10 days for certifying the criteria of steroid resistance was based on historical series, which show that the median time of remission of UC was 7.5 days and that prolonged treatment beyond 10 days did not increase the remission rate[8]. In contrast with this point of view, a large retrospective study of single experienced hospital was in favor of more conservative approach, which entered into remission within the 21 days of treatment[9]. Therefore, it is difficult to define resistance to corticosteroids which day after treatment is used as a limit marker. However, none of the previous studies have shown that duration of oral corticosteroid administration was an independent predictor of non-response to intravenous corticosteroid therapy. Our study was the first attempt to explain this situation.

These results have been added in the discussion section (page 9, line 24) and (page 9, line 35).

1 Carbonnel F, Gargouri D, Lemann M, Beaugerie L, Cattan S, Cosnes J, Gendre JP. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. *Aliment Pharmacol Ther* 2000; **14**: 273-279.

2 Park BJ, Lee KJ, Hwang JC, Sin SJ, Chung JY, Cho SW. Relapse Rates of Ulcerative Colitis in Remission and Factors Related to Relapse. *Korean J Gastroenterol* 2008; **52**: 21-26.

3 Seo M, Okada M, Yao T, Matake H, Maeda K. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol* 2002; **37**: 29-34.

4 Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med* 2004; **116 Suppl 7A**: 44S-49S.

5 Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004; **53**: 1190-1197.

6 Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2006; **12**: 123-130.

7 Gisbert JP, Bermejo F, Pajares R, Perez-Calle JL, Rodriguez M, Algaba A, Mancenido N, de la Morena F, Carneros JA, McNicholl AG, Gonzalez-Lama Y, Mate J. Oral and intravenous iron treatment in inflammatory bowel disease: hematological response and quality of life improvement. *Inflamm Bowel Dis* 2009; **15**: 1485-1491.

8 Meyers S, Lerer PK, Feuer EJ, Johnson JW, Janowitz HD. Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective, randomized, double-blind clinical trial. *J Clin Gastroenterol*

1987; **9**: 50-54.

9 Daperno M, Sostegni R, Scaglione N, Ercole E, Rigazio C, Rocca R, Pera A. Outcome of a conservative approach in severe ulcerative colitis. *Dig Liver Dis* 2004; **36**: 21-28.

3 References and typesetting were corrected

Thank you again for your review and all your valuable comments. We believe the reviewer's comments have significantly improved the quality of our manuscript. We look forward to your response.

Sincerely yours,

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