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EDITORIAL

Value of colonoscopy for prediction of prognosis in patients with ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by exacerbations and remissions. Some UC patients remain refractory to conventional medical treatment while, in others, the effectiveness of drugs is limited by side-effects. Recently, cyclosporine and leukocyte removal therapy have been used for refractory UC patients. To predict the efficacy of these therapies is important for appropriate selection of treatment options and for preparation for colectomy. Endoscopy is the cornerstone for diagnosis and evaluation of UC. Endoscopic parameters in patients with severe or refractory UC may predict a clinical response to therapies, such as cyclosporine or leukocyte removal therapy. As for the patients with quiescent UC, relapse of UC is difficult to predict by routine colonoscopy. Even when routine colonoscopy suggests remission and a normal mucosal appearance, microscopic abnormalities may persist and relapse may occur later. To more accurately identify disease activity and to predict exacerbations in UC patients with clinically inactive disease is important for deciding whether medical treatment should be maintained. Magnifying colonoscopy is useful for the evaluation of disease activity and for predicting relapse in patients with UC.

Key words: Ulcerative colitis; Colonoscopy; Prediction of outcome

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by diffuse mucosal inflammation of the colorectum with exacerbations and remissions[1-5]. Approximately 15% of patients experience a severe exacerbation requiring hospital admission at some time during their illness[3,6]. The purpose of treatments for patients with ulcerative colitis is achieving remission and maintaining quiescence of the disease. Patients with UC must rely on multiple medications to control their symptoms, including aminosalicylates, corticosteroids and purine analogs. Although decades of clinical experience in the management of UC have allowed the optimization of approaches to the induction and maintenance of remission, some patients remain refractory to conventional medical treatment and the effectiveness of these drugs may be limited by side-effects[7-11]. The use of immunosuppressive agents, including purine analogs, now constitutes a therapeutic modality for the treatment of UC[12]. Although highly effective, a disadvantage of these drugs is the significant delay in their onset of clinical benefit, which limits their utility to the treatment of severe disease.

Although the degree of inflammation as assessed by routine colonoscopy is a reliable parameter of disease activity, discrepancies between colonoscopic appearance and histopathologic abnormalities are sometimes seen in patients with clinically inactive UC (Figure 1). Even when routine colonoscopy suggests remission and a normal mucosal appearance, microscopic abnormalities may persist[13,14] and relapse may occur later[15]. A recently developed high-resolution video-magnifying colonoscope has enabled the observation of pit patterns on the

surface of the colorectal mucosa. This in turn allows an understanding of the morphological relationship between the pit patterns detected colonoscopically and the crypts observed histopathologically[16-20]. As far back as 1980, Poulsen *et al*[21] examined biopsy specimens from the rectal mucosa of UC patients under a stereomicroscope and found microstructural abnormalities in the mucosal surface in almost every patient, as well as a close correlation between stereomicroscopic features and the clinical disease activity, sigmoidoscopic findings, and histologic activity of the disease.

Here, we discuss endoscopic factors predictive of the efficacy of therapies in patients with intractable UC, and endoscopic factors that may predict the probability of subsequent disease relapse in UC patients in remission. We will reconsider the value of endoscopy when we treat UC patients.

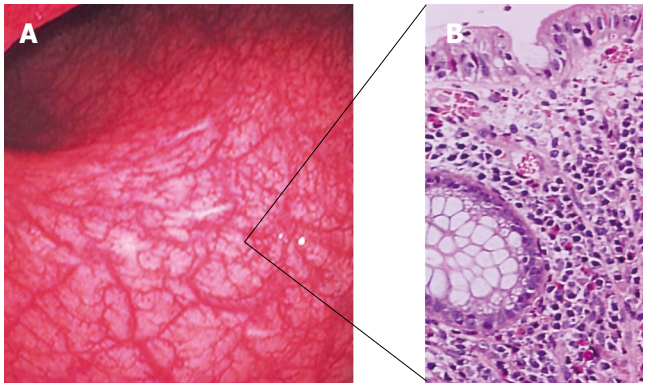

Figure 1 A case of inactive UC. A discrepancy is seen between an endoscopic and a histologic finding. **A**: A routine colonoscopy finding. It shows an almost normal mucosal appearance; **B**: A histologic finding. It shows an intense infiltration of mononuclear cells and neutrophils.

ENDOSCOPIC PREDICTORS OF RESPONSE TO THERAPIES IN PATIENTS WITH REFRACTORY ULCERATIVE COLITIS

In recent years, steroid-refractory cases of UC have been successfully treated by adding intravenous cyclosporine to the glucocorticosteroids. Cyclosporine is a lipophilic cyclic peptide that interrupts the cellular immune response by blocking interleukin 2 productions by T cells. Uncontrolled studies show that approximately 80% of patients with severe UC refractory to glucocorticosteroid treatment respond to cyclosporine therapy[22,23]. The use of cyclosporine is, however, associated with considerable morbidity. Serious complications such as *Pneumocystis carinii* pneumonia and seizures have occurred in as many as 12% of patients in large series, and deaths have been reported[24-26]. Less serious, but nevertheless troubling, side-effects including hypertension, liver and renal impairment, tremor, paresthesia and headache, occur in up to 50% of patients[23,25-27]. It would be useful to define factors predictive of response to cyclosporine treatment for severe flares of ulcerative colitis, to avoid the side effects as well as reduce the risk of subjecting the patients to increased morbidity and mortality due to needlessly delaying colectomy. However, there has been only limited information as to which factors are associated with a response to cyclosporine that leads to possible avoidance of colectomy in such patients. Rowe *et al* demonstrated that a higher percentage of band neutrophils on admission was predictive of patients who were unlikely to respond to cyclosporine and who would require colectomy[28]. On the other hand, McCormack *et al* showed that the *in vitro* cyclosporine sensitivity of proliferating lymphocytes was predictive of the therapeutic response[29]. Genetic factors of the host are also considered to play a role in UC outcomes. The TT genotype of exon 21 multidrug resistance gene 1 polymorphisms is associated with a higher risk of cyclosporine failure in patients with steroid resistant UC[30]. Our prospective analysis with a logistic regression model, colonoscopic findings predictive of response to intravenous cyclosporine in patients with steroid-resistant ulcerative colitis included the presence of deep and extensive ulcerations, and the absence of mucosal bleeding or poor luminal extensibility (Table 1).

Table 1 Colonoscopic finding predictive of response to intravenous cyclosporine in ulcerative colitis patients

	Responders (n = 17)	Non-responders (n = 9)	Relative risk[1] (Odds ratio)
Deep and extensive ulcerations (yes:no)	8:9	0:9	14.20 ($P < 0.005$)
Mucosal bleeding (yes:no)	5:12	7:2	0.12 ($P < 0.05$)
Poor luminal extensibility (yes:no)	4:13	7:2	0.09 ($P < 0.01$)

[1]Logistic regression analysis.

Findings in active UC include the activation and extravasation of large numbers of granulocytes and monocytes/macrophages into the colonic mucosa[31,32]. These infiltrated leukocytes may cause extensive mucosal tissue injury by releasing degradative proteases[32-34], reactive oxygen derivatives[32,34,35], and pro-inflammatory cytokines[36]. Leukocyte removal therapy is recognized as a second novel strategy for the treatment of steroid-refractory UC, based on the assumption that this non-drug therapy attenuates intestinal inflammation by reducing excess and activated granulocytes, monocytes and lymphocytes from the circulating blood before they reach the inflamed mucosa[37]. Adsorption with beads (granulocytapheresis, GCAP) or filters (leukocytapheresis, LCAP) is most commonly used[38,39]. Several studies have reported the beneficial effects of leukocyte removal therapy on both the induction and maintenance of clinical remission in patients with IBD[40-42], suggesting that it may be a useful adjunct to conventional therapy in patients with active severe UC and those refractory to conventional drugs. Further, leukocyte removal therapy might be an effective first line medication[43]. First UC episode and short disease duration are good predictors of response to leukocyte removal therapy[44]. Steroid-naïve patients respond particularly well to this treatment[42,45]. Patients with deep colonic lesions might be less satisfactory[45]. However, our prospective analysis in patients

with steroid resistant ulcerative colitis did not find any colonoscopic findings predictive of response to leukocyte removal therapy[46]. Further study with a larger population of patients needs to be conducted to define predictors of response to cyclosporine or leukocyte removal therapy, including prolonged outcome, for more appropriate selection of treatment options with these therapies in patients with severe ulcerative colitis.

PREDICTION OF RELAPSE IN PATIENTS WITH QUIESCENT ULCERATIVE COLITIS

Severity in ulcerative colitis is generally assessed using symptoms, laboratory data[47], colonoscopic findings[48-55] and histologic degree of inflammation in the biopsy specimens[15,56-59]. Histopathologic assessment is considered the standard for evaluation of disease activity in patients with ulcerative colitis[60]. The observation under conventional colonoscopy has been regarded as useful for the evaluation of disease activity, since it offers direct observation of mucosal changes, but it still remains controversial whether colonoscopic grade correlates with histopathologic findings. It has been reported that the degree of histologic inflammation within biopsy specimens did not necessarily correlate with endoscopic abnormalities[48,49,61,62]. It is not unusual for routine colonoscopy performed to assess the stage of UC to show quiescent colitis despite the histological persistence of inflammation[48,61,63], which later results in the relapse of colonic inflammation[15]. Hurlstone DP *et al* reported high-frequency ultrasound is a valid adjunctive 'tool' for the trans-mural assessment of the colorectal wall in UC[64]. This technique may aid in the initial diagnosis, and ongoing chronic management of disease.

Matsumoto *et al* reported usefulness of magnifying chromoscopy for the assessment of severity in UC patients[65]. In their study, magnifying colonoscopy was performed in 41 patients with ulcerative colitis, and the findings in the rectum were graded according to network pattern (NWP) and cryptal opening (CO). The clinical, endoscopic and histologic grades of activity were not different between groups divided by the presence or absence of each finding. However, when the two features were coupled, patients with visible NWP and CO had a lower clinical activity index and lower grade of histologic inflammation than those in whom both findings could not be visualized. Furthermore it has been suggested that the presence of branches in surface epithelium may be a factor that predicts future disease relapse[15], and they suggested that altered pattern as defined by magnified colonoscopic views may be predictive of the course of ulcerative colitis[65].

Fujiya *et al* proposed the classification of magnifying colonoscopic findings in patients with ulcerative colitis which is useful for the evaluation of disease activity and for the prediction of periods of remission[66]. The classification was devised as follows: regularly arranged crypt opening, villous-like appearance, minute defects of epithelium (MDE), small yellowish spots (YS), and coral reef-like appearance. The colonoscopic findings by classification were compared with histopathologic findings in 61 patients and the usefulness of the classification for predicting relapse was prospectively analyzed in 18 patients. Under conventional colonoscopic examinations, all areas evaluated as Matts grade 1 had a corresponding histopathologic grade 1. In contrast, most areas assessed as Matts grade 3 or 4 were diagnosed as histopathologic grade 3 or higher. However, grade 2 mucosa had histopathologic findings that varied from quiescent to active disease. These suggest that normal and diseased mucosas are easily recognized by conventional colonoscopy, but it is difficult for conventional colonoscopy to assess the minute mucosal changes that reflect smoldering histopathologic inflammation[48,49,61]. In contrast, under magnifying colonoscopic examinations, 37 (82.2%) of the 45 areas in which regularly arranged crypt openings or a villous-like appearance was detected had a corresponding histopathologic grade 1, and all areas in which MDE, SYS, or the coral reef-like appearance was observed had a corresponding histopathologic grade 2 or higher. In this study, the correlation between histopathologic grade and magnifying colonoscopic findings ($r^2 = 0.807$) was better than that for histopathologic grade versus conventional colonoscopy ($r^2 = 0.665$). This study found that patients in whom MDE was observed during clinical remission frequently had a relapse within short periods (6 mo) compared with patients without these findings, and 50% of patients who underwent clinical remission still had active inflamed mucosa with MDE, which correlates with the results of previous studies in which 30% to 60% of patients in remission, as determined by clinical symptoms, were still in the active stage of ulcerative colitis based on histopathologic findings[49,62]. In our study we found that magnifying colonoscopy (MCS) grade was associated with the degree of histological inflammation in quiescent patients with ulcerative colitis, and might predict the probability of subsequent disease relapse in patients with ulcerative colitis in remission. Magnifying colonoscopy was performed in 112 patients with ulcerative colitis in remission. The relationship between pit patterns and histological disease activity was evaluated. Pit patterns in the rectal mucosa were classified into three MCS grades on the basis of size, shape, and arrangement (Figure 2). The patients were followed until relapse or a maximum of 12 mo. A positive correlation was identified between MCS grade and histological grade (Figure 3). Multivariate proportional hazard model analysis showed that MCS grade was a significant predictor of relapse. Kaplan-Meier estimate of relapse during 12 mo' follow up was found to increase with increasing MCS grade, with a percentage of 0 for grade 1, 19% for grade 2, and 43% for grade 3 (Figure 4). Although MCS grade positively correlated with histological grade, histological grade was less accurate predictors of disease relapse. One reason may be that they are assessed in biopsy specimens derived from a specific and limited area, whereas magnifying colonoscopy allows the observation of a more extended and representative area of colorectal mucosa, and accordingly greater accuracy by MCS grading.

CONCLUSION

Endoscopic parameters in patients with severe or refractory

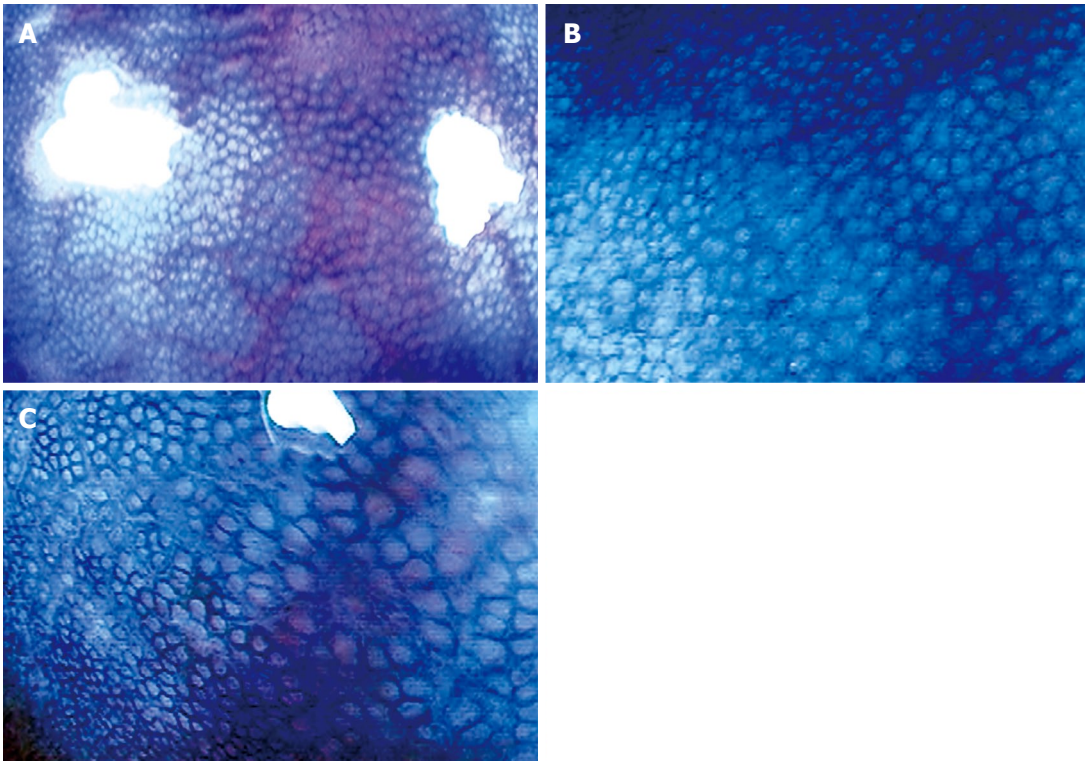

Figure 2 Grading of pit structures in the colorectal mucosa of patients with inactive UC. **A**: MCS grade 1, pits small, round, and regularly arranged; **B**: MCS grade 2, pits rather large, oval, and somewhat irregular in arrangement; **C**: MCS grade 3, pits of various shapes and sizes, and irregularly arranged.

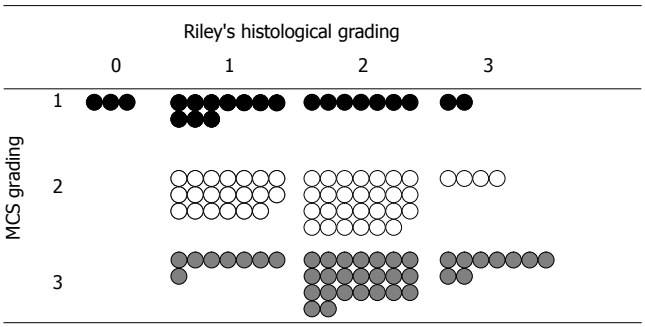

Figure 3 Correlation between grading of pit structures and histological findings ($P < 0.001$, Spearman's rank test). The number of colored ring indicates the number of the patients performed magnifying colonoscopy ($n = 112$).

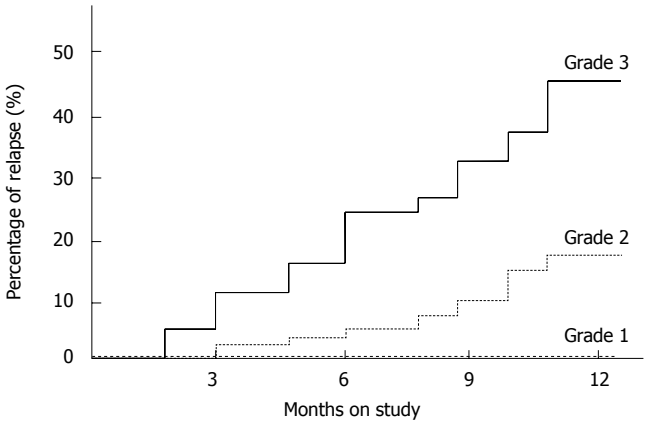

Figure 4 Kaplan-Meier survival analysis showing the cumulative proportion of patients who had a relapse according to MCS grade group.

UC may predict a clinical response of the therapies, such as cyclosporine or leukocyte removal therapy. Magnifying colonoscopy is useful for the evaluation of disease activity and for predicting relapse in patients with ulcerative colitis. Endoscopy is the cornerstone for diagnosis and evaluation of UC, and advanced imaging techniques, including chromoendoscopy, magnification endoscopy, confocal endomicroscopy, and spectroscopy, may aid in this field. Further studies remain to be done to define endoscopic predictors of response to therapy or outcome of UC patients.

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