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Alimentary Tract

Fecal calprotectin as an alternative to ulcerative colitis endoscopic index of severity to predict the response to corticosteroids of acute severe ulcerative colitis: A prospective observational study

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ABSTRACT

Background: Fecal calprotectin (FC) might be an alternative to ulcerative colitis endoscopic index of severity (UCEIS) to predict the response to corticosteroids (CS) in acute severe colitis (ASC).
Methods: One hundred and seventeen ASC patients were prospectively enrolled. Demographic, clinical, laboratory and sigmoidoscopic data were documented. Multivariate and ROC analyses were performed to identify risk factors for non-response to CS, and the predictive accuracy of possible predictors was assessed.
Results: Totally, 39 (33.33%) patients failed intravenous CS therapy. CS responders among mild (UCEIS 3–4), moderate (UCEIS 5–6) and severe (UCEIS 7–8) groups were 40/44 (90.91%) vs. 36/55 (65.45%) vs. 2/18 (11.11%) ($p < 0.001$). UCEIS (OR = 5.08; 95% CI, 1.93–8.66; $p < 0.001$) and FC (OR = 2.56; 95% CI, 1.17–3.55; $p = 0.022$) were found to be independent risk factors for CS non-responders. Compared with C-reactive protein, platelet, hemoglobin and albumin, baseline FC had the strongest correlation with UCEIS ($r = 0.701$, $p < 0.001$). ROC analysis of UCEIS and baseline FC in predicting CS non-response showed an AUC of 0.85 and 0.76 respectively.
Conclusions: Baseline FC levels correlated significantly with UCEIS in ASC, and both were useful in predicting short-term outcome of CS treatment. Baseline FC levels could be used as an alternative of UCEIS to guide the decision of early salvage therapy or colectomy and reduce the adverse effects of long-term futile CS usage.

1. Introduction

Ulcerative colitis (UC) is a chronic (ongoing) disease of large intestine. The disease is marked by inflammation and ulceration of the colon mucosa, and the causes are still unknown [1]. Approximately 15% of UC patients will develop a severe flare within the disease duration [2]. Acute severe colitis (ASC) is medical emergency, which needs prompt effective treatment on admission. ASC implies that inflammation progresses beyond the mucosa and is associated with systemic symptoms.

For ASC, the cornerstone of management is intravenous corticosteroids (CS) [3]. However, the response to intensive treatment with intravenous CS has remained unchanged for 50 years, and about 30–40% patients required colectomy or salvage therapy due to CS failure [4,5]. The long-term use of CS was associated with high rate of side effects, and concerns about steroid-related infections have also been raised [6,7]. Also, it is clear that delayed colectomy resulted in increased mortality in ASC patients [8,9]. Therefore, a swift change of clinical management is desirable to avoid the deterioration of patients' situation when CS resistance occurs. Evaluation of the degree and prognosis of ASC at an early stage is very important for the caregiver to guide the shift of treatment strategy.

To date, endoscopic assessment using a limited, unprepared sigmoidoscopy and biopsies with minimal air insufflation is still the most objective and effective tool to evaluate the severity of ASC [10], and the ulcerative colitis endoscopic index of severity (UCEIS)

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was introduced as an effective tool to assess the endoscopic severity [11]. UCEIS is valuable in guiding the clinical management, evaluating therapeutic results and predicting mucosal healing [12–15]. It also guides the selection of patients at an early stage that may benefit from second-line therapy [16]. However, as an invasive procedure, sigmoidoscopy is not suitable for all ASC patients, and it increases the risk of bleeding, toxic colitis and even colonic perforations [17]. Therefore, there remains a great need for non-invasive biomarkers to be alternatives for UCEIS that could identify patients who will fail CS therapies at an early stage.

Recently, fecal calprotectin (FC) has aroused interest as an indicator for intestinal mucosal injury. Calprotectin, a 36 kDa calcium and zinc binding protein, represents 60% of cytosolic proteins in granulocytes and about 5% of the total protein [18]. The levels of calprotectin in stools are directly proportional to neutrophil infiltration in the gastrointestinal tract. Recent studies suggested that FC could be used to evaluate disease activity and showed a good correlation with endoscopic and histologic score [19,20]. Failing to reduce FC sufficiently was a subclinical marker of inadequate medical therapy and FC was a strong predictor of relapse in UC. Therefore, endoscopic examinations could be avoided potentially if the colonic mucosa damages can be detected accurately by the changes of fecal markers calprotectin.

It was gradually acknowledged by clinicians that UCEIS score was associated with clinical outcomes in UC patients [15,16], however, more studies are needed to confirm the role of FC in ASC. Also, FC more accurately reflects endoscopic activity assessed by Modified Baron Score than C-reactive protein (CRP), platelets, hemoglobin, and blood leukocytes [21], but its correlation with UCEIS was unknown. In this study, there are two aims: First, to verify the effectiveness of UCEIS in predicting the outcome of CS therapy in ASC; Second, to find the correlation between FC and UCEIS, and to explore the possibility of FC as an alternative to UCEIS in predicting the outcome of CS treatment.

2. Materials and methods

2.1. Patients

Consecutive patients with a confirmed diagnosis of ASC between January 2014 and February 2016 were enrolled in this prospective observational study (follow-up from January 2014 to September 2016). The study was approved by the Ethics Committee of Jinling Hospital and registered at ClinicalTrials.gov (NCT02922374).

Diagnosis of UC was made based on clinical signs, lab tests and endoscopic examination. The extent of colon involvement was evaluated by abdominal CT. The significant mural pathology of ASC on CT scan included bowel wall thickening, mucosal hyperenhancement, pericolonic stranding, and mural stratification. According to Patel et al. [22], the colon could be divided into six anastomotic segments (rectum, sigmoid colon, descending colon, transverse colon, ascending colon, and cecum) on contrast-enhanced CT. When the lesion was confined to left colon or distally, it was defined as E2, or otherwise as extensive colitis (E3). ASC was defined by the Truelove & Witt's criteria as presence of more than 6 bloody stools/d along with any one of the follows: tachycardia >90 bpm, fever >37.8 °C, Hb <10.5 gm/dL, CRP and/or ESR >30 mm/h [10]. The inclusion criteria was: (1) age 18 or over, (2) a confirmed diagnosis of ASC, (3) patients were generally able to tolerate the flexible sigmoidoscopy within one week before CS treatment, (4) fecal specimens have been collected for test before sigmoidoscopy.

Patients with incomplete sigmoidoscopy, inadequate fecal sample, indeterminate diagnosis of ASC (colorectal cancer, Crohn's disease), infectious colitis, *Clostridium difficile* and cytomegalovirus (CMV) infection, and primary immunodeficiency were excluded. Patients with ulcerative proctitis, history of bowel resection, intestinal anastomosis, and ileostomy were also excluded.

2.2. UCEIS

Sigmoidoscopy was performed using an Olympus-CF-H260 endoscopy (9.8 mm diameter; Tokyo, Japan) without fluoroscopic guidance. The UCEIS consisted of the following three descriptors and calculated as a simple sum [11]: vascular pattern (scored 0–2), bleeding (scored 0–3), erosions and ulcers (scored 0–3). Score range was from 0 to 8 points as shown in Supplementary Table 1. Two gastroenterologists unaware of the outcome were involved in image analysis work with disagreement resolved by a senior physician. Since this was a pragmatic study, vascular pattern (scored 0–2), erosions and ulcers (scored 0–3) were analyzed according to sigmoidoscopic images, bleeding (scored 0–3) was analyzed according to sigmoidoscopic images reports, which contains the colonoscopy performer's description during bleeding situation. The degree of endoscopic activity of ASC was stratified into three grades: mild (2–4), moderate (5–6) and severe (7–8).

2.3. Fecal calprotectin

After admission, stool was collected before sigmoidoscopy since bowel cleaning could affect the results of FC. Each participant was provided with a sterile fecal specimen tube and morning single fecal samples (5–10 g) were collected. The sample was mixed by the proportion of 1:49 with extractant and then fully stirred, the supernatant was collected after high speed centrifugation (10,000 × *g*, 5 min) and stored frozen at −20 °C for test. FC was measured using the instruction of the kits (PhiCal, NovaTec Immunodiagnostica GmbH, Germany). The extraction liquid was thawed at room temperature and diluted with a 1:50 dilution. Using double antibody sandwich ELISA method, the FC levels were quantitatively assessed, and the technologists performing the analysis were blinded to patients' details.

2.4. Management

Inpatient management algorithm followed the standard protocol, and all treatment details were collected. Intravenous CS was started with methylprednisolone 60 mg/d or hydrocortisone 400 mg/d. Malnourished patients received nutritional support, and enteral nutrition was preferred over parenteral nutrition. For patients with hypoalbuminemia (<25 g/L), intravenous albumin was given. Subcutaneous low molecular heparin as thromboembolic prophylaxis was routinely used. Data on duration of intravenous steroid therapy and response were recorded, as well as salvage therapy.

The primary endpoint was efficacy of intravenous steroid therapy and the response of intravenous steroid therapy was judged at day 3–5 according to Travis criteria. Failure of intravenous steroid therapy included patients who needed salvage therapy with infliximab or cyclosporine, colectomy, or death. Patients with deterioration in general condition or adverse prognostic characters underwent emergent colectomy within 24–48 h. Patients who were refractory or had incomplete response to steroid were colectomized, switched to salvage therapy with intravenous infliximab 5 mg/kg/d or cyclosporine at 2 mg/kg/d, or maintained under intravenous corticosteroids for several additional days (7–10 days maximally). Those who had complete response were switched to oral prednisolone. All patients were followed up until September 2016.