Evaluation of false remission in ulcerative colitis and the need for a revised disease activity index

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Aim of the work
To highlight some criteria of remission in ulcerative colitis, to address the issue of false remission, and settle a standard index for its detection.

Patients and methods
Patients with ulcerative colitis in clinical remission were enrolled prospectively and followed for 1 year for evaluation of clinical manifestations, C-reactive protein, fecal calprotectin, and tumor necrosis factor-α, and colonoscopic and microscopic examination for the detection of actual remission, with the exclusion of those who developed clinical relapse during the study.

Results
Out of 36 patients, we had 11 patients (30.5%) with true remission and 25 patients (69.5%) with false remission: 19 patients (52.7%) in false remission group A with abnormal mucosal healing and six patients (16%) in false remission group B with high inflammatory markers. There was a significant positive correlation of inflammatory markers with the ulcerative colitis disease activity index in patients with true remission. There was a significant correlation of the ulcerative colitis disease activity index and histological grades in false remission A and a significant correlation of inflammatory markers with histological grades in false remission B.

Conclusion
About 70% of our patients with ulcerative colitis in clinical remission had an active disease. Clinical remission in ulcerative colitis can be best expressed as true and false remission depending on histological grading in a revised ulcerative colitis disease activity index. Some inflammatory markers can be useful for the detection of true remission.

Keywords:
false remission, revised ulcerative colitis disease activity index, true remission, ulcerative colitis

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Introduction

The natural history of inflammatory bowel disease (IBD) is characterized by repeated episodes of inflammation and ulceration of the intestine, resulting in complications requiring hospitalization, surgery, and escalation of therapy [1,2]. In fact, some patients request dose reduction or treatment withdrawal soon after the resolution of symptoms. A considerable number of patients thus do not take medication as directed. Not only patients but also some physicians instruct patients to decrease or stop drug therapy soon after the resolution of symptoms, often leading to relapse. Frequent divergence between clinical remission and the remission of intestinal lesions in ulcerative colitis (UC) has also been confirmed in previous prospective studies [3,4].

Research has shown that tumor necrosis factor-α (TNF-α) is overexpressed in patients with moderate to severe UC [5]. Biomarkers such as fecal calprotectin (FCP), fecal lactoferrin, serum C-reactive protein (CRP), and fecal S1 00A12 have been shown to correlate with disease activity in UC and Crohn's disease; these biomarkers might be used as surrogate markers for mucosal healing [6]. In a study carried out by Sipponen *et al*. [7], 11 patients achieved a partial or a complete endoscopic response, and showed a significant decrease in FCP and lactoferrin levels. No significant decrease in FCP and lactoferrin concentrations was observed in the three nonresponders.

Newer clinical trials are incorporating mucosal healing as an end point for the evaluation of efficacy. However, before mucosal healing becomes sufficient to guide therapy, clinicians need a standard definition of mucosal healing. Achievement of long-term mucosal healing has been associated with a decreased risk of colectomy and colorectal cancer in patients with UC. Numerous endoscopic indices have been used to assess disease activity in clinical trials of UC. A European Crohn's and Colitis Organization consensus conference on mucosal healing in IBD concluded that mucosal healing is important, but this conference highlighted the need for large, prospective studies assessing the impact of mucosal healing and histological healing on the natural course of this disease [8]. Further, researchers still face the problems associated with the use of different endoscopic assessment scales [6].

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Aim of the work

To date, there is no universal agreement on a validated scale to define remission in UC, and because frequent divergence occurs between clinical and histological intestinal lesions, we attempted to highlight some criteria that may differentiate true and false remission in patients with UC, to address the issue of false remission, and to establish a standard index for its detection.

Patients and methods

Patients with a confirmed diagnosis of UC in clinical remission were prospectively enrolled in this study. Patients were followed every 4 months up to 1 year for the evaluation of clinical, laboratory, and colonoscopy examination with histological examination for the detection of true and false remission, with the exclusion of those who developed clinical relapse at any time during the study. Only 36 patients completed the study. Clinical remission is recognized by the absence of diarrhea and bloody stools. All patients were followed by clinical, laboratory, endoscopic, and histological criteria. Clinical and endoscopic criteria of remission were evaluated according to the ulcerative colitis disease activity index (UCDAI), [9] including stool frequency, rectal bleeding, endoscopic findings, and global assessment, considering the disease in remission to be in the range of 0–2 and active disease in the range of 3–12, with grade 3–6 indicating mild disease, grade 7–10 indicating moderate disease, and more than 10 indicating severe disease.

We assessed patients clinically using UCDAI. Colonoscopy and histological biopsies were performed for all patients by the same colonoscopist at the time of enrollment and every 4 months for 1 year. All patients were provided with a detailed explanation of the objectives of the examination. Total colonoscopy was performed after standard preparation procedures. The macroscopic endoscopic features of mucosa were evaluated and multiple biopsies were taken from both diseased and healthy areas for histopathological examination. The results of endoscopic mucosal appearance according to UCDAI were classified as follows: grade 0 indicated a normal bowel, grade 1 indicated mild friability, grade 2 indicated moderate friability, and grade 3 indicated exudation, and spontaneous bleeding.

Stool samples for FCP analysis and serum samples for TNF-α and CRP analysis were collected at baseline and every 4 months of the study. FCP was measured using a commercial enzyme-linked immunoassay method (Calprest; Dynex Elisa Eurospital, Trieste, Italy). The FCP results are expressed in mg of calprotectin per kilogram of wet feces with a reference range of less than 50 mg/kg [10]. CRP and TNF-α concentrations were determined using the commercially available enzyme-linked immuno-sorbent assay supplied by Biosource International (Camarillo, California, USA). The assays use the quantitative sandwich enzyme immunoassay technique with a cut-off value of 1.9 pg/ml for TNF-α and 6 mg/l for CRP. All assays were performed according to the manufacturers' instructions.

Multiple biopsies were taken from different sites, embedded in formalin containers, sectioned, and stained with hematoxylin and eosin for conventional histopathological examination. We used Truelove's histological activity index modified by Geboes *et al.* [11], which has six grades ranging from normal mucosa (grade 0) to surface epithelial erosions and ulceration (grade 6).

We divided patients according to the gold standard of activity, that is, histologic findings, into two main groups: true remission group with UCDAI between 0 and 2, plus the normal reference level of inflammatory markers with normal colonic mucosa by both endoscopy and microscopy, and false remission group with UCDAI between 0 and 2, but with abnormal histological findings, further divided as follows: group A with mild to moderate friability of endoscopic mucosal appearance and normal laboratory markers and group B with abnormally high inflammatory markers and a normal mucosal appearance.

Exclusion criteria include: UC patients in clinical relapse, patients with disease complications, those with significant side effects of therapy, those who did not respond to treatment, those who were receiving treatment for other significant conditions, or pregnant patients were excluded. Patients with incomplete colonoscopy, a history of any malignant condition, a history of major gastrointestinal surgical procedures, liver cell failure, coagulopathy, chronic renal failure, smokers, those with drug or alcohol abuse, and NSAID use were also excluded from the study.

The study was carried out after obtaining written informed consent from all the patients, and the protocol was approved by the Ethical Review Board of the hospital.

Statistical analysis

Data were analyzed using the SPSS software (version 17.0, Sofinic International, SA. USA). Quantitative data were expressed as mean ± SD, whereas qualitative data were expressed as number and percentage. Comparisons between the groups were performed

using Student's *t*-test whenever applicable. A value of *P* less than 0.05 was considered statistically significant. Correlations between different variables were evaluated using the Spearman rank correlation coefficient test.

Results

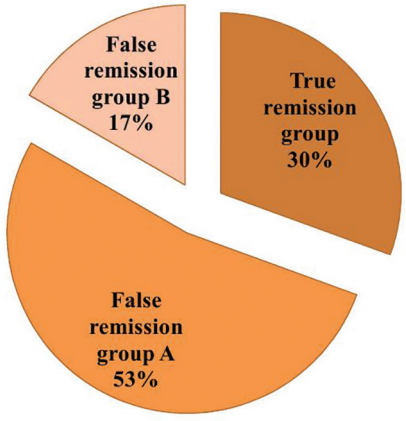
Thirty-six patients in clinical remission, who completed the study, were followed for 1 year. There were 11 patients (30.5%) in the true remission group, five with pancolitis and six with left-sided colitis, versus 25 patients (69.44%) in the false remission group, 10 with pancolitis and 15 with left-sided colitis. There were no significant differences between the two main groups of remission in terms of age, disease duration, and levels of inflammatory markers, including CRP, FCP, and TNF-α. A significantly higher level of UCDAI was found in the false remission group versus the true remission groups (Table 1). We further divided the false remission group into two groups: 19 patients (52.7%) in the false remission group A with an abnormal mucosal appearance and six patients (16%) in the false remission group B with abnormally high levels of inflammatory markers, as shown in Figure 1.

There was a significant increase in UCDAI in the false remission group A versus those in the false remission group B, and a significant increase in inflammatory markers including CRP, FCP, and TNF-α in the false remission group B versus those in the false remission group A (Table 2).

There was a significant positive correlation of inflammatory markers with UCDAI grade in patients with true remission, and a nonsignificant correlation of both groups of false remission (Table 3 and Fig. 2).

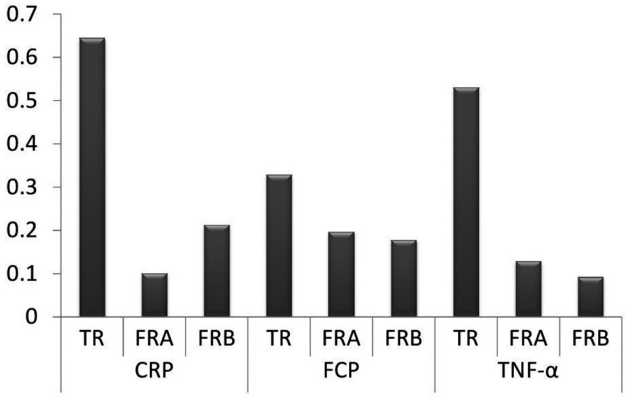
In the false remission group A, there was a significant correlation of UCDAI with histological grade and a nonsignificant correlation of inflammatory markers with histological grade. In the false remission group B, there was a significant correlation of inflammatory markers with histological grades and a nonsignificant correlation of UCDAI with histological grade (Table 4).

Figure 1



Number of patients in different groups of remission.

Figure 2



Correlation of inflammatory markers with UCDAI. CRP, C-reactive protein; FCP, fecal calprotectin; FR, false remission; TNF-, tumor necrosis factor-α; TR, true remission; UCDAI, ulcerative colitis disease activity index.

Table 1 Baseline demographic characteristics

	True remission group	False remission group	*T*	*P*
Number of patients [*n* (%)]	11 (30.55)	25 (69.44)	—	—
Age (years)	33.81 ± 7.960	39.08 ± 7.54	1.9	0.066
Duration of the disease (months)	6.18 ± 2.457204	5.64 ± 2.09	0.67	0.501
Disease extent				
Pancolitis	5	10	—	—
Left-sided colitis	6	15	—	—
UCDAI	1 ± 0.85	1.5 ± 0.54	2.04	0.048*
CRP (mg/l)	6.190 ± 4.202726	17.8 ± 19.33	1.95	0.058
FCP (mg/kg feces)	43.36 ± 14.15	72.4256 ± 70.05	1.35	0.18
TNF-α (pg/ml)	1.393 ± 1.92	8.859 ± 14.73	1.661	0.105

CRP, C-reactive protein; FCP, fecal calprotectin; TNF-α, tumor necrosis factor-α; UCDAI, ulcerative colitis disease activity index; *Significant.

Table 2 Comparison of clinical, laboratory, and endoscopic parameters in false remission groups

Parameters	False remission group A	False remission group B	*T*-test	*P*-value
Number of patients	19	6		
UCDAI	1.94 ± 0.22	0.86 ± 0.37	2.43	0.023*
CRP	9.105 ± 4.56	36.66 ± 14.56	3.69	0.0001*
FCP	46.57 ± 16.51	91.01 ± 38.06	4.129	0.0004*
TNF-α	1.688 ± 1.948	20.33 ± 5.89	9.055	0.0001*

CRP, C-reactive protein; FCP, fecal calprotectin; TNF-α, tumor necrosis factor-α; UCDAI, ulcerative colitis disease activity index; *Significant.

Table 3 Correlation of inflammatory markers with UCDAI

Inflammatory markers	Correlation coefficient (*r*)	*P*-value	Significance
CRP			
TR	0.644	0.032	Significant
FR A	0.100	0.683	Nonsignificant
FR B	0.212	0.686	Nonsignificant
FCP			
TR	0.328	0.324	Significant
FR A	0.196	0.421	Nonsignificant
FR B	0.177	0.737	Nonsignificant
TNF-α			
TR	0.530	0.093	Significant
FR A	0.128	0.601	Nonsignificant
FR B	0.091	0.863	Nonsignificant

CRP, C-reactive protein; FCP, fecal calprotectin; FR, false remission; TNF-α, tumor necrosis-α; TR, true remission; UCDAI, ulcerative colitis disease activity index.

Table 4 Correlation of UCDAI and inflammatory markers with histological grades

Parameters	Histologic grade					
	FRA			FRB		
	r	*P*	Significance	*R*	*P*	Significance
UCDAI	0.714	0.0006	Significant	0.521	0.289	Nonsignificant
CRP	0.264	0.274	Nonsignificant	0.864	0.026	Significant
FCP	0.0216	0.93	Nonsignificant	0.82	0.045	Significant
TNF-α	0.038	0.077	Nonsignificant	0.901	0.014	Significant

r, correlation coefficient; UCDAI, ulcerative colitis disease activity index; TR, true remission; FR, false remission; CRP, C-reactive protein; FCP, fecal calprotectin; TNF-α, tumor necrosis alpha.

Discussion

Assessment of disease activity in IBD is a challenging aspect; however, there is no consensus on a validated scale to define disease activity, and combinations of endoscopy and clinical disease activity indices have been used [12].

There is no validated definition of what constitutes mucosal healing in IBD. An International Organization of IBD task force proposed defining mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of gut mucosa [13]. Nevertheless, endoscopy may not show mucosal damage when microscopic inflammation is present and it has been reported that endoscopy contributes little additional information toward scoring clinical activity [14].

In some patients who achieved mucosal healing with biological treatment, endoscopy on relapse showed exactly the same pattern and location of the disease as before mucosal healing [5]. Microscopic (histological) healing may be a better predictor for relapse than the macroscopic appearance (or clinical criteria). Histological assessment showed that indicators of acute mucosal inflammation, including crypt abscesses, mucin depletion, or an acute inflammatory cell infiltrate, were associated with a two- to three-fold increase in the risk of UC relapse during 12 months' follow-up [15]. The presence of basal plasmacytosis (i.e. dense infiltration of plasma cells in the lower third of the mucosa) in patients with quiescent UC has also been associated with a 4.5-fold increased risk of relapse [16]. Using a novel six-point histological scoring system, Rubin *et al.* [17] reported that an increased level of histological inflammation can predict both colectomy and hospitalization in patients with UC. A prospective study has shown only modest agreement between clinical, endoscopic, and histological measures of remission, with complete agreement in just 58 and 89% agreement between endoscopy and histopathology, although a third, 36% of those with histological remission, had clinical symptoms of activity [18].

In a study carried out by Yokoyama *et al.* [19], active intestinal lesions were found in 29 patients in clinical remission (76%), despite the absence of diarrhea or bloody stools. In our group of patients, we found intestinal lesions in 19 patients in clinical remission (53%), despite the absence of clinical symptoms of activity, 11 patients (30.5%) with true remission, where there was complete agreement between clinical, endoscopic findings and histopathology, and six patients (17%) in the false remission group with agreement between clinical and endoscopic findings, but with high inflammatory markers. These data probably indicate that UCDAI as well as most of the UC evaluation criteria, which lack the gold standard criteria of true remission, that is histological normalization cannot define actual remission in UC accurately, and it classified 70% of our patients with active disease as showing remission. Thus, we recommend a revised UCDAI classification system with the addition of histological grades to include five categories:

(a) stool frequency,
(b) rectal bleeding,
(c) mucosal appearance,

(d) physician's rating of disease activity, and
(e) histological findings.

The use of surrogate markers for periodic monitoring of inflammation could be valuable as a sensitive, noninvasive screening tool to identify asymptomatic patients who could benefit from endoscopy. A combination of stool markers, CRP, and activity index may increase the accuracy of measuring endoscopic inflammation and may be an important avenue for improving noninvasive monitoring of intestinal inflammation. Such an assessment may also indicate the risk of relapse after achieving clinical remission if CRP and or FCP are elevated [20]. However, several other internal and external factors affecting the serum level of inflammatory markers minimize their detection ability and their use in UC patients. In this study, only 16% of our patient group were detected to be in false remission depending on inflammatory markers as an initial test with a normal UCDAI grade and were proven to have abnormal histological findings.

We found a significant correlation of histological grade with UCDAI in patients under false remission with abnormal mucosal appearance and this correlation was actually present between abnormal mucosal appearance and histological grades because the patient was in clinical remission. Also, histological grades are correlated to inflammatory markers in the false remission group with abnormal inflammatory markers; thus, we conclude that patients with clinical remission either have an abnormal mucosal appearance, which is correlated to histological grade, or they have abnormal inflammatory markers, which are correlated to histological grades.

This study highlighted the need for large studies assessing a novel UC evaluation scale with the impact of mucosal and histological healing and its effects on the course of the disease. Furthermore, researchers still face the problems associated with the use of different endoscopic assessment scales.

Conclusion

About 70% of our patients with UC in clinical remission have an active disease. Clinical remission in UC can be best expressed as true and false remission depending on histological grading in a new revised UCDAI. This improved its ability to detect cases with false remission and may be a sufficient guide to therapy. Even if the UCDAI grade is 0 and the mucosa appears healthy, it is better to include both microscopic and macroscopic criteria of remission as factors of mucosal healing. Thus, we need a new clinical scale for evaluation of UC including both endoscopic mucosal healing parameters and standardized histological findings. Inflammatory markers such as CRP, FCP, and TNF-α are somewhat useful in the detection of true remission.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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