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Original article

The value of inflammation and coagulation markers for the assessment of the activity and clinical outcome of ulcerative colitis

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SUMMARY

Aim: To investigate the value of various laboratory parameters in assessing the activity (diagnostic accuracy) and predicting the response to treatment (predictive value) of ulcerative colitis (UC). Methodology: Thirty-two patients with active and 12 patients with long standing inactive UC, based on clinical, endoscopic and histologic scores, were included. Laboratory routine variables (haemoglobin, platelets, albumin), inflammation (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], fibrinogen) and coagulation (D-Dimers, prothrombin fragments 1+2, thrombin-antithrombin complex, von Willebrand and VIII factors) indices were measured at baseline and after 12 weeks of treatment. The diagnostic accuracy (sensitivity, specificity, likelihood ratio) and the predictive value of all laboratory variables were calculated. Results: ESR, CRP, fibrinogen, haemoglobin, and von Willebrand factor, showed significant diagnostic accuracy, only when patients with long standing inactive UC, and not those in recent after treatment remission, were included in the calculations. Fibrinogen was the only variable that constantly differed significantly between patients with active and inactive disease (recent or long standing). None of the variables measured at baseline evaluation was effective in predicting the response to treatment. Conclusion: Inflammation variables, especially fibrinogen, are valuable markers of UC activity, while markers of coagulation and fibrinolysis activation are not. Laboratory variables are poor predictors of treatment response in active colitis. Endoscopy seems to be the most accurate and valuable tool for the assessment of colitis activity and monitoring the effect of treatment in UC patients.

Key words: Coagulation, D-Dimers, factor VIII, fibrinolysis, inflammation, inflammatory bowel disease (IBD), prothrombin fragment 1 and 2 (F1+2), thrombin-antithrombin complex (TAT), ulcerative colitis (UC), von Willebrand factor.

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INTRODUCTION

The assessment of disease activity and the monitoring of the effect of treatment are critical issues in ulcerative colitis (UC) management. It is well known that endoscopic and histologic evaluation of the colonic mucosa provide important information about UC inflammatory activity. However, in clinical practice, it is difficult to perform repeated endoscopies for the evaluation of disease activity during a treatment course, because of the cost, the time consuming and the discomfort of the procedure.

Many clinical activity indices[1,2] together with laboratory measurements of biochemical or biological parameters[3] are used for the assessment of UC activity and the monitoring of the response to treatment. The laboratory evaluation

Abbreviations:

SCC: squamous cell cancer;
EUS: endoscopic ultrasonography;
FNA: fine needle aspiration;
TNB: trucut needle biopsy;
PET: positron emission tomography

includes the measurement of the classical markers of acute phase response (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], fibrinogen), the haemoglobin, the platelet count and the serum albumin concentrations. Emerging laboratory disease activity markers include cytokines (interleukins 1, 1ra, 6, 8 and tumor necrosis factor-a [TNF-a]), cell adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]) and antibodies (anti-*Saccharomyces cerevisiae* antibodies [ASCA] for CD).[3] Moreover, since it is well established that UC is characterized by activation of the coagulation and the fibrinolysis cascades,[4] markers of coagulation and fibrinolysis activation (D-Dimers, thrombin-antithrombin complex [TAT], prothrombin fragment 1+2 [F1+2]) were also found to be correlated with disease activity in UC patients in many studies.[4-6]

In the present study we investigated the diagnostic accuracy of routine laboratory, inflammatory and hemostatic variables in assessing the activity of the disease and the predictive value of these variables in determining the response to treatment, in a group of patients with active UC.

MATERIALS AND METHODS

Patients

Forty-four adult patients with ulcerative colitis (28 men and 16 women; mean age, 42.4 years; range 17-73 years) were consecutively included in the study. Recruited patients were hospitalized or followed up at the outpatient clinic of our Department. All patients were of Greek (Caucasian) origin from Northern Greece.

All patients gave their informed consent to participate in the study which was approved by the Hospital's Scientific Committee.

Methods

The diagnosis of UC was based on standard clinical, endoscopic and histologic criteria. A complete medical history was obtained and physical examination was performed in all UC patients. During baseline evaluation, disease activity (active or inactive) was assessed with the Simple Clinical Colitis Activity Index (SCCAI).[7] A SCCAI score ≤2 points was defined as clinical remission. Baseline colonoscopy with biopsy sampling was performed in all patients in order to assess the endoscopic severity and the extent of disease. Endoscopic severity was measured by a modified endoscopic score (EGS) with an 18-point scale.[8] Four grades of activity were considered according to the EGS score: inactive disease (0-3), mild disease (4-7), moderate disease (8-12) and severe disease (13-18). The extent of disease was recorded as proctitis, left-sided colitis, and total colitis.

A grading of the histologic disease activity (HDA)[8] was performed and four grades of histologic activity were considered according to the HDA score: remission (0-3), mild disease (4-6), moderate disease (7-9), severe disease (10-12). The most inflamed site in the colon or rectum was taken into account for the assessment of endoscopic and histologic scores. Ulcerative colitis was considered to be in remission when the combination of clinical, endoscopic and histologic grading was suggestive of inactive disease.

Patients with inherited or acquired bleeding diathesis; recent transfusion of blood products; pregnancy; diabetes mellitus; severe liver, kidney or heart disease; recent cerebrovascular accident (6 months); recent surgery (6 months); infectious, irradiation or ischemic colitis; Crohn's disease; toxic megacolon and malignancy were excluded from the study.

Laboratory studies

Blood samples were collected from UC patients for the routine laboratory measurements and for the quantitative determination of inflammation and coagulation parameters (ESR, CRP, and fibrinogen, TAT, F1+2, D-Dimers, von Willebrand factor [vWF], and coagulation factor VIII [fVIII]).

ESR was measured by standard laboratory technique (normal value <20 mm/h) and CRP was measured with ELISA (normal values <5 mg/L). Plasma fibrinogen concentration was measured by the Claus method using bovine thrombin (bioMerieux sa, France) on OPTION coagulation analyzer (normal values 2-4 g/L).

TAT levels in plasma were measured by sandwich enzyme immunoassay (Enzygnost TAT micro, Dade Behring, Marburg, Germany; normal values 1-4.1 μg/L). F1+2 levels in plasma were measured by sandwich enzyme immunoassay (Enzygnost F1+2 micro, Dade Behring, Marburg, Germany; normal values 0.4-1.1 nmol/L). D-Dimers levels in plasma were measured by immuno-turbidimetric assay (STA-Liatest D-Di, Diagnostica Stago, France; normal value <500 μg/L). von Willebrand factor antigen (vWFAg) plasma levels were measured with an immuno-turbidimetric assay (STA-Liatest vWF, Diagnostica Stago, France; normal values 50-160%). Coagulation factor VIII (fVIII) plasma levels were measured with chromogenic-based photometric method for factor VIII activity (COAMATIC Factor VIII, Chromogenix, Italy; normal values 0.35-1.91 IU/mL).

Treatment and course

Patients with active UC were treated for attenuation of disease activity with high-dose corticosteroids and mesalazine orally and rectally. Azathioprine was continued if already used. Patients were set into a follow up program with regular visits every 2nd week for 12 weeks. Corticosteroids were tapered off with a weekly-based schedule throughout the study period. At the end of the study (12th week) complete clinical, endoscopic and laboratory evaluation (similar to baseline week) was performed in all patients with active colitis.

Complete response (CR) to therapy (treatment-induced remission) was considered if a SCCAI score ≤2 and endoscopic remission were achieved after 12 weeks of therapy. Partial response (PR) was considered if a 50% reduction of SCCAI score was noted together with a reduction of endoscopic activity by at least one grade. No response (NR) to treatment was defined as: (1) failure to improve clinical and endoscopic scores, (2) worsening of the disease activity, (3) need for cyclosporine or colectomy and (4) development of severe disease or treatment complications.

Diagnostic accuracy of laboratory parameters in assessment of UC activity

The combination of clinical and endoscopic scores was used to distinguish active disease from quiescent disease. Patients with intermediate disease activity (partial response) after 12 weeks of treatment were excluded from analysis. According to the activity of disease laboratory parameters were subdivided in correct positive and correct negative findings, as described in a previous study by Linskens *et al*.[9] The values of the laboratory parameters exceeding the reference range in patients with established active disease at baseline evaluation were considered to be correct positive, whereas the values of the parameters within reference range in patients with established quiescent disease were defined as correct negative. We developed two models of quiescent disease. We calculated the correct negative values of laboratory parameters in UC patients with complete response (CR, treatment-induced remission) after 12 weeks of treatment in "Model 1" and in UC patients found to be in long standing remission at baseline evaluation in "Model 2". Diagnostic accuracy was defined as the ability of the laboratory parameters to establish the activity of disease. The diagnostic accuracy of routine laboratory, inflammatory and hemostatic variables, was determined by means of calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the likelihood ratio.

Clinical value of laboratory parameters in prediction of clinical outcome of active UC

The clinical value of the laboratory parameters was defined as their ability to discriminate between a favorable (complete response to treatment) and unfavorable clinical outcome (no response to treatment, need for cyclosporine administration or colectomy, and manifestation of disease complications). The patients were subdivided in accordance with the clinical response after three months of treatment (CR, PR and NR). Baseline measurements of all variables in patients with no response were compared to patients with complete or partial response in order to assess the clinical value of laboratory parameters.

Statistical analysis

Statistical analyses were performed using the SPSS for Windows package (version 11.0, SPSS, Chicago, IL) and the GraphPad Instat Demo software for Windows (version 3.06, 2003).

Data are presented as mean values along with 95% CI or range (minimum and maximum value). For laboratory parameters, sensitivity, specificity, NPV, PPV, and likelihood ratio were determined. Comparisons of continuous variables between the 3 groups of response to treatment were made by the one-way ANOVA (with Bonferroni test for *post hoc* multiple comparisons) or the Kruskal-Wallis test (non-parametric ANOVA, with Dunn's test for *post hoc* multiple comparisons), when appropriate. Comparisons between two unpaired groups were made by the Student's *t* test or the Mann-Whitney U test, when appropriate. Two-tailed paired Student's *t* test or Wilcoxon's rank test (when non-parametrically distributed) were used to compare baseline and follow-up measurements in patients with active UC. The level of significance was set at 0.05.

RESULTS

Baseline evaluation: clinical and laboratory parameters

During baseline evaluation, 12 patients with ulcerative colitis were found to be in long standing (over 6 months) remission and 32 patients had active disease, according to the criteria set in Patients & Methods section. Demographic, clinical and laboratory data of patients during baseline evaluation are shown in Tables 1 and 2.

There were no differences in sex, age and disease extent between patients with active and inactive UC. Duration of disease was significantly longer in patients with inactive UC. Clinical and laboratory variables differed significantly between the two groups, except for D-Dimers,

Table 1. Demographic and clinical data of ulcerative colitis (UC) patients with active and inactive disease (long standing remission), at baseline evaluation.

	Active UC	**Inactive UC (long standing remission)**
n	32	12
Sex (M/F)	20/12	8/4
Age (range)	42.19 (17-73)	42.83 (18-65)
Duration of disease in years (range)	4 (0.3-18)	7.58 (2-18)
Duration of current symptoms in weeks (range)	4.3 (1-24)	
Extend of disease (n)		
Proctitis	2	1
Left-sided colitis	22	8
Pancolitis	8	3
SCCAI score	8 (3-12)*	0.2 (0-2)
Endoscopic Grading Scale score (EGS)	15.5 (12-18)*	2.3 (0-3)
Histologic Disease Activity score (HDA)	5.4 (1-10)*	1 (0-3)
Treatment (n)		
Oral steroids	14	0
5-ASA compounds	29	12
Azathioprine	11	2
None	1	0
Steroid dependent (n)	15	

Data are expressed as mean (minimum and maximum values).

**p<0.001, SCCAI score active UC vs. inactive UC, EGS score active UC vs. inactive UC, HDA score active UC vs. inactive UC*

Table 2. Laboratory data of ulcerative colitis (UC) patients with active and inactive (long standing remission) disease, at baseline evaluation.

	Active UC (n=32)	**Inactive UC (n=12)**	**P**
ESR (mm/hr)	40.5 (33-48)	15.6 (8-23)	<0.001
CRP (mg/L)	25.7 (10.8-40.5)	4.1 (3-5.1)	0.002
Fibrinogen (g/L)	4.9 (4.5-5.4)	3.5 (2.8-4.2)	0.001
Haemoglobin (g/dL)	12.5 (11.8-13.2)	14.7 (13.9-15.4)	0.001
Platelets (X109/L)	332 (294-369)	254 (209-299)	0.011
Albumin (g/L)	4.5 (4.3-4.7)	5 (4.9-5.2)	0.003
von Willebrand factor (%)	146 (123-169)	99 (71-127)	0.025
VIII factor (IU/mL)	1.72 (1.47-1.96)	1.19 (0.8-1.58)	0.03
D-Dimers (μg/L)	921(440-1402)	608 (-122 – 1338)	0.278
F1+2 (nmol/L)	3.89 (1.63-6.14)	3.72 (-0.35 –7.79)	0.153
TAT (μg/L)	7.21 (1.59-12.84)	3.99 (1.32-6.67)	0.254

Data are expressed as mean (95% CI).

F1+2, and TAT (Tables 1 and 2). None of the UC patients in long standing remission was on corticosteroids.

Treatment and outcome

After 12 weeks of therapy 12 patients with active UC showed complete response and 10 patients showed partial response to the treatment, while 10 patients did not show any significant improvement of disease activity (non-responders). There was not any withdrawal due to severe adverse events, disease complications, worsening of dis-

ease, or need for colectomy. No relapse of disease was observed in patients with inactive UC during the study period.

Post-treatment clinical and laboratory values

Only patients with complete response showed a significant improvement in clinical, endoscopic and histologic scores at week 12 compared to baseline values (Table 3). Patients with complete response to therapy showed a significant reduction of clinical, endoscopic and histologic scores compared to patients with partial or no response (Table 3).

Analyses of routine laboratory and inflammation parameters revealed that patients with complete response had a significant improvement only in fibrinogen and albumin serum values after 12 weeks of treatment, while patients with partial or no response had no significant improvement in all these parameters (Table 4). Analyses of coagulation parameters showed that only patients with complete or partial response had significant improvements in some of these parameters (Table 4).

Clinical scores (SCCAI, EGS, HDA), fibrinogen, D-Dimers and factor VIII plasma values differed significantly between complete responders after 12 weeks of treatment and patients with active disease at baseline evaluation (Table 5).

Diagnostic accuracy

Diagnostic accuracy of all laboratory parameters is shown in Tables 6 and 7, for Models 1 and 2 of disease remission respectively, as described in Patients & Methods section. The diagnostic accuracy in discriminating active from inactive disease, as expressed by Likelihood Ratio, was improved in Model 2 (UC in long standing remission) for most of the variables compared to Model 1 (treatment-induced remission).

Clinical value

We did not find any significant differences in clinical and laboratory baseline measurements in patients with complete response to therapy compared to partial or to no responders after 12 weeks of treatment.

DISCUSSION

In this study we found, during baseline evaluation, significantly increased values of ESR, CRP, fibrinogen, platelets, von Willebrand factor, VIII factor and significantly decreased values of haemoglobin and albumin in UC patients with active disease compared to those with long standing remission. Additionally, we did not find significant differences in the values of coagulation activation parameters (D-Dimers, F1+2, and TAT) between UC patients with active disease and those with long standing remission.

On the other hand, the results from UC patients in complete response after 12 weeks of therapy (treatment-induced remission) showed significant improvement only in fibrinogen, D-Dimers and factor VIII values compared to patients with active disease at baseline evaluation. Moreover, only complete responders' group showed significant

Table 3. Improvement of disease activity clinical, endoscopic and histologic indices in active UC patients according to response after 12 weeks of treatment

	Weeks of Follow Up Wilcoxon Signed Ranks Test	Complete Responders (CR) n=12	Partial Responders (PR) n=10	Non Responders (NR) n=10
SCCAI	Baseline	9 (7.5-10.5)	7.7 (5.8-9.6)	6.9 (4.6-9.2)
	12th week	0.3 (0.02-0.6)	0.5 (0.12-0.9)	2.4 (0.5-4.28)
	P	0.002	0.005	0.005
EGS	Baseline	15.8 (14.8-16.9)	15.5 (14.1-16.9)	15.2 (13.9-16.5)
	12th week	2.7 (2.4-3)	8.8 (7.2-10.4)	14.2 (13.1-15.3)
	P	0.002	0.005	0.172
HDA	Baseline	5.33 (3.8-6.9)	4.8 (3.2-6.4)	6 (4.7-7.3)
	12th week	0.67 (0.1-1.2)	3.6 (1.4-5.8)	5 (3.7-6.3)
	P	0.002	0.348	0.258

Data are expressed as mean (95% CI).
*SCCAI score mean differences (week 12-week 0): **CR vs. PR, **CR vs. NR (One-way ANOVA)*
*EGS score mean differences (week 12-week 0): **CR vs. PR, **CR vs.NR (Kruskal-Wallis non-parametric ANOVA)*
*HDA score mean differences (week 12-week 0): **CR vs. PR, **CR vs. NR (One-way ANOVA)*

Table 4. Improvement of laboratory, inflammation and coagulation parameters in active UC patients according to response after 12 weeks of treatment

	Weeks of Follow Up Paired test	Complete Responders (CR) n=12	Partial Responders (PR) n=10	Non Responders (NR) n=10
ESR (mm/hr)	Baseline	37 (23-51)	51 (34-68)	34 (26-43)
	12th week	28 (18-38)	36 (22-51)	28 (19-36)
	P	0.347	0.054	0.206
CRP (mg/L)	Baseline	25.5 (4-47)	29.3 (-8 – 66.8)	22.2 (-7.2 –51.7)
	12th week	14.8 (-9 – 38.7)	6.7 (4.6-8.7)	11.42 (1.9-20.92)
	P	0.117	0.093	0.674
Fibrinogen (g/L)	Baseline	4.83 (4.1-5.6)	5 (4.2-5.8)	4.98 (3.9-6)
	12th week	3.7 (3.33-4.2)	4.39 (4-4.8)	4.6 (4-5.1)
	P	0.009**	0.092	0.372
Haemoglobin (g/dL)	Baseline	12.4 (10.9-14)	12.7 (11.1-14.2)	12.5 (11.5-13.6)
	12th week	12.2 (11.2-13.1)	13 (11.8-15.9)	12.9 (11.7-14)
	P	0.671	0.455	0.142
Platelets ($X10^9$/L)	Baseline	330 (277-383)	343 (257-430)	322 (239-465)
	12th week	283 (246-320)	303 (234-371)	281 (243-318)
	P	0.125	0.062	0.185
Albumin (g/L)	Baseline	4.2 (3.7-4.6)	4.7 (4.3-5)	4.8 (4.4-5.1)
	12th week	4.8 (4.7-5)	4.5 (4.3-4.8)	4.8 (4.6-5)
	P	0.017*	0.235	0.704
von Willebrand factor (%)	Baseline	149 (110-278)	160 (102-219)	129 (93-165)
	12th week	107 (88-120)	116 (92-139)	105 (82-129)
	P	0.034*	0.091	0.153
				0.153
VIII factor (IU/mL)	Baseline	1.85 (1.37-2.3)	1.77 (1.6-2.4)	1.5 (1.28-1.74)
	12th week	1.05 (0.8-1.3)	0.89 (0.51-1.25)	0.88 (0.58-1.19)
	P	0.021*	0.007*	0.003*
D-Dimers (μg/L)	Baseline	945 (48-1842)	1510 (319-2702)	302 (66-538)
	12th week	126 (64-187)	402 (139-665)	608 (-237 – 1602)
	P	0.062	0.022*	0.678
F1+2 (nmol/L)	Baseline	1.31 (0.67-1.96)	6.65 (1.2-12.1)	4.2 (-1.2 –9.6)
	12th week	0.95 (0.47-1.4)	1.56 (0.54-2.6)	0.71 (0.53-0.9)
	P	0.034*	0.241	0.214
TAT (μg/L)	Baseline	3.91 (1.24-6.6)	4.97 (1.22-8.7)	13.43 (-5.84 – 32.7)
	12th week	3.91 (0.28-7.5)	7.22 (-6.2 – 20.7)	1.97 (0.84-3)
	P	0.583	0.203	0.114

Data are expressed as mean (95% CI).

improvement in fibrinogen, albumin, von Willebrand, factor VIII, and F1+2 values after 12 weeks of therapy compared to baseline values.

Analyses for diagnostic accuracy of laboratory variables revealed that for patients with recent remission (treatment-induced remission, Model 1) only fibrinogen showed a considerable value as may be concluded from the sensitivity, the specificity and the likelihood ratio. On the contrary, for patients with long standing remission (Model 2) the diagnostic accuracy was improved for many laboratory variables. The most valuable parameters in Model 2 included ESR, CRP, fibrinogen, haemoglobin, and von Willebrand factor.

Evidence suggest that a hypercoagulable state may be an important contributory factor in the pathogenesis of ulcerative colitis.[4,10] The hypercoagulable state has been

Table 5. Clinical, routine laboratory, inflammatory and coagulation parameters in active UC at baseline measurements and disease in complete remission after 12 weeks of treatment

	Active UC at baseline (n=32)	**UC in complete remission after 12 weeks (n=12)**	**Mann-Witney U test P**
SCCAI	8 (3-12)	0.3 (0.02-0.6)	<0.001
EGS	15.5 (12-18)	2.7 (2.4-3)	<0.001
HDA	5.4 (1-10)	0.67 (0.1-1.2)	<0.001
ESR (mm/hr)	40.5 (33-48)	28 (18-38)	0.08
CRP (mg/L)	25.7 (10.8-40.5)	14.8 (-9 – 38.7)	0.063
Fibrinogen (g/L)	4.9 (4.5-5.4)	3.7 (3.33-4.2)	0.002
Haemoglobin (g/dL)	12.5 (11.8-13.2)	12.2 (11.2-13.1)	0.474
Platelets (X109/L)	332 (294-369)	283 (246-320)	0.186
Albumin (g/L)	4.5 (4.3-4.7)	4.8 (4.7-5)	0.224
von Willebrand factor (%)	146 (123-169)	107 (88-120)	0.08
VIII factor (IU/mL)	1.72 (1.47-1.96)	1.05 (0.8-1.3)	0.002
D-Dimers (μg/L)	921(440-1402)	126 (64-187)	0.008
F1+2 (nmol/L)	3.89 (1.63-6.14)	0.95 (0.47-1.4)	0.075
TAT (μg/L)	7.21 (1.59-12.84)	3.91 (0.28-7.5)	0.195

Data are expressed as mean (95% CI).

found to exist both in active and inactive ulcerative colitis since previous studies have shown persistent activation of coagulation and fibrinolysis both in active and quiescent UC after treatment.[6,11-14] Previous studies by van Bodegraven *et al.*[12,13] showed persistent hemostatic imbalance and hypercoagulation in patients with ulcerative colitis who were in remission after treatment. Furthermore, Kjeldsen *et al.*[6] found that clinical response to treatment with corticosteroids in UC patients was accompanied by a decrease in fibrin degradation products (FbDPs) plasma concentrations but not in F1+2. However, numerous other studies have shown that coagulation and fibrinolysis activation markers are valuable for the diagnosis and prognosis of deep vein thrombosis, cardiovascular disease and stroke.[15-20] In accordance with previous data, in the present study we did not find any striking differences in markers of coagulation and fibrinolysis activation (D-Dimers, TAT, F1+2) between patients with active ulcerative colitis and patients with ulcerative colitis in remission (recent or long standing), although some of these parameters improved after treatment in complete responders' group. The results in our study suggest that a continuous high or low grade coagulation activation exists in UC patients irrespective of disease activity status and strongly support that hemostatic variables of coagulation activation show poor diagnostic accuracy in identifying patients with active disease.

On the contrary, laboratory markers reflecting acute phase response due to inflammation in ulcerative colitis (ESR, CRP, fibrinogen, haemoglobin, albumin) are valuable in discriminating patients with active disease from patients with quiescent disease. However, as demonstrated in our study, this advantage is lost when we have to deal with patients in recent remission after treatment. Even for CRP, which has a short half-life and is considered as a useful tool in monitoring the course of treatment,[3,21-23] we could not prove its diagnostic accuracy validity for patients with complete response to treatment. We do not think that our results were biased by the disease extent and severity, nor by any medication, since in the majority of patients with active disease, including the steroid-dependent patients, the disease at baseline evaluation was

Table 6. Diagnostic accuracy of laboratory variables to discriminate active from inactive UC (Model 1: treatment-induced remission)

Laboratory parameter	UC 1 (n=32)	UC2 (UC=12)	Sens	Spec	PPV	NPV	LR
ESR	27	3	0.84	0.25	0.75	0.37	1.125
CRP	19	8	0.59	0.66	0.83	0.38	1.781
Fibrinogen	23	9	0.72	0.75	0.88	0.50	2.875
Haemoglobin	20	1	0.63	0.083	0.65	0.07	0.682
Platelets	5	12	0.16	1	1	0.3	
Albumin	3	12	0.09	1	1	0.16	
von Willebrand factor	12	12	0.38	1	1	0.38	
VIII factor	10	12	0.31	1	1	0.30	
D-Dimers	12	12	0.38	1	1	0.38	
F1+2	15	8	0.47	0.67	0.79	0.32	1.406
TAT	11	9	0.34	0.75	0.78	0.3	1.375

Sens: sensitivity; Spec: specificity; NPV: negative predictive value; PPV: positive predictive value; LR: likelihood ratio. The numbers in columns UC1 and UC2 are the actual number of correct test results for patients with active disease at baseline evaluation (UC1) and patients with inactive disease after 12 weeks of treatment (recent remission) (UC2), respectively.

Table 7. Diagnostic accuracy of laboratory variables to discriminate active from inactive UC (Model 2: long standing remission)

Laboratory parameter	UC 1 (n=32)	UC3 (UC=12)	Sens	Spec	PPV	NPV	LR
ESR	27	7	0.84	0.58	0.84	0.58	2.025
CRP	19	9	0.59	0.75	0.86	0.41	2.375
Fibrinogen	23	10	0.71	0.83	0.92	0.52	4.313
Haemoglobin	20	11	0.63	0.92	0.95	0.48	7.5
Platelets	5	12	0.16	1	1	0.30	
Albumin	3	12	0.09	1	1	0.29	
von Willebrand factor	12	11	0.38	0.92	0.92	0.35	4.5
VIII factor	10	10	0.31	0.83	0.83	0.31	1.875
D-Dimers	12	9	0.38	0.75	0.80	0.35	1.5
F1+2	15	8	0.47	0.67	0.79	0.32	1.406
TAT	11	8	0.34	0.67	0.73	0.28	1.031

The numbers in columns UC1 and UC3 are the actual number of correct test results for patients with active disease (UC1) and inactive disease (UC3) at baseline evaluation, respectively.

highly active and extensive. One explanation could be the fact that in UC patients with recent remission the inflammatory activity is still maintained in some degree compared to patients with long standing remission. It is also known that active UC has only a modest or even absent CRP response compared to the strong CRP response in CD,[3,21] and for that reason CRP is not considered as a robust biomarker for UC activity. However, although some studies have shown poor correlation of CRP levels and endoscopic or histologic severity of disease, other studies have shown the opposite results.[23-30] In a recent study, Zilberman *et al.* suggested that although UC patients present lower high-sensitivity CRP (hs-CRP) serum levels compared to CD patients, a similar degree of correlation exists between hs-CR and the disease activity index in both diseases.[29]

In our study, fibrinogen was the only laboratory variable that constantly differed significantly between patients with active disease and disease in remission (recent or long standing) and showed significant diagnostic accuracy in both models we analyzed. Fibrinogen is a hemostatic factor that is considered as an acute phase reactant[31] and several studies reported elevated fibrinogen levels in IBD patients with both active or inactive disease.[32-34] In a previous study, similarly to our findings, Linskens et al.[9] reported a significant diagnostic accuracy for fibrinogen (likelihood ratio 2,3). Furthermore, numerous prospective studies have demonstrated a strong and independent ef-

fect of raised plasma fibrinogen on both the onset and the progression of coronary heart disease (CHD), stroke and peripheral arterial disease.[35,36]

Another important finding in our study was the observation that von Willebrand and factor VIII plasma levels showed a significant correlation with UC activity and a considerable diagnostic accuracy (especially von Willebrand factor in model 2). As previously documented, these coagulation factors behave as acute-phase reactants.[31,37] We have previously reported that elevated plasma vWF levels in active ulcerative colitis correlate with increased acute-phase proteins and possibly reflect an acute-phase response of the perturbed endothelium due to inflammation.[38]

Recent data showed that increased CRP levels are associated with better response rates and normal CRP levels predict high placebo response rates in clinical trials with biologicals.[39-43] In a Belgian study, a baseline CRP >5 mg/l before the start of therapy was associated with a higher response (76%) compared with CRP <5 mg/l (46%) in CD patients treated with infliximab.[39] Moreover, CRP has been shown to be a good marker for predicting disease course and outcome in a number of diseases, beyond IBD. Most well known is its association with cardiovascular disease and poor outcome after myocardial infarction.[44-46] Also, high serum CRP levels in multiple myeloma were associated with worse survival.[47] Finally, there is strong evidence that elevated D-Dimers plasma levels are strong predictors of cardiovascular events in the general population and in patients with cardiovascular disease and are associated with poor outcome and prognosis.[20] In accordance with the study by Linskens *et al.*,[9] our analysis of data has shown that none of the variables measured at baseline evaluation in patients with active disease was effective in predicting the response (favourable or not) after 12 weeks of treatment.

In this study we used the combination of clinical and endoscopic indices for discriminating patients with complete, partial or no response. The clinical score (SCCAI) was significantly improved in all patients with active disease after 12 weeks of treatment, while the endoscopic score (EGS) was significantly improved only in patients with a favourable response (complete or partial). However, significant histologic improvement was noted only in complete responders' group. These results suggest that, in contrast to the clinical score, endoscopy with or even without biopsies was the most important tool for the assessment of the disease severity and for monitoring the response to treatment in UC patients. Although there are conflicting aspects about the necessity of endoscopy in assessing the activity of UC, the vast majority of data suggest that endoscopy is an important and valuable tool for the diagnosis and the assessment of ulcerative colitis activity.[48-51]

In conclusion, in the present study we found that acute phase reactants (inflammation indices including ESR, CRP, fibrinogen, von Willebrand factor and VIII factor) are valuable markers of UC activity. In particular, fibrinogen could be an emerging laboratory activity marker for ulcerative colitis. On the other hand, the markers of coagulation and fibrinolysis activation (D-Dimers, TAT, F1+2) have poor diagnostic accuracy. The inflammatory and hemostatic variables we studied were poor predictors of the treatment outcome of active ulcerative colitis. The endoscopic evaluation, with or without biopsy sampling, together with the clinical assessment are the most accurate and valuable tools in the management of UC patients.

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