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Elevated serum concentrations of soluble selectin and immunoglobulin type adhesion molecules in patients with inflammatory bowel disease

MICHAEL GÖKE,[1]* JÖRG C. HOFFMANN,[2]* JÖRG EVERS,[1] HARTMUT KRÜGER,[2] and MICHAEL P. MANNS[1]

[1] Department of Gastroenterology and Hepatology, and [2] Department of Rheumatology, Medizinische Hochschule Hannover, Carl-Neuberg-Straße 1, 30625 Hannover, Germany

Abstract: Adhesion molecules mediate the extravasation of leukocytes and their accumulation in inflamed tissues. In the present study, serum concentrations of the selectin (sP- and sE-selectin) and immunoglobulin supergene family (sICAM-1 and sVCAM-1) of adhesion molecules were measured in 93 patients with inflammatory bowel disease (Crohn's disease, $n = 65$; ulcerative colitis, $n = 28$) and 58 age-matched normal controls. sP-selectin serum concentrations (mean ± SEM ng/ml) of patients with Crohn's disease (399 ± 33 ng/ml) and ulcerative colitis (385 ± 42 ng/ml) were increased ($P = 0.0067$ and $P = 0.0193$, respectively) compared to controls (251 ± 33 ng/ml). In contrast, E-selectin serum levels of patients with Crohn's disease (58 ± 5 ng/ml) and ulcerative colitis (64 ± 12 ng/ml) were not significantly higher than those of controls (53 ± 5 ng/ml). sICAM-1 serum concentrations of patients with Crohn's disease (420 ± 19 ng/ml) and those with ulcerative colitis (375 ± 40 ng/ml) were elevated ($P = 0.0001$ and $P = 0.0473$, respectively) compared to controls (297 ± 8 ng/ml). Further, sVCAM-1 levels of patients with Crohn's disease (664 ± 43 ng/ml) and ulcerative colitis (963 ± 162 ng/ml) were increased ($P = 0.0222$ and $P = 0.0121$, respectively) compared to controls (510 ± 31 ng/ml). With few exceptions, serum levels of soluble adhesion molecules were not significantly correlated to disease activity indices or disease localization. Elevated circulating selectin and immunoglobulin supergene type adhesion molecules may compete with membrane-bound forms for their cognate ligands and thereby limit the rolling and stable adhesion of leukocytes.

Key words: P-selectin, E-selectin, VCAM-1, ICAM-1, Crohn's disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is characterized by the infiltration of inflammatory cells, including monocytes, neutrophils, and lymphocytes. Migration of leukocytes into tissues is a central event in the inflammatory response. This migration is mediated by adhesion molecules, which can be divided into three groups according to their structural characteristics: the immunoglobulin supergene family, the integrin family of non-covalently linked variable α and β heterodimers, and the selectin family.[1-3]

Intercellular adhesion molecule-1 (ICAM-1, or CD54) and vascular adhesion molecule-1 (VCAM-1, also known as INCAM-110, or CD106) are glycoproteins of the immunoglobulin supergene familiy of adhesion molecules. ICAM-1 is constitutively expressed on fibroblasts, leukocytes, endothelial and epithelial cells, and many tumor cells, and its pression can be upregulated by cytokines such as interleukin (IL) 1-β, tumor necrosis factor (TNF)-α, or interferon (IFN)-γ[1,4,5] as described for lymphocytes, endothelial cells, fibroblasts, biliary epithelial cells, and hepatocytes. ICAM-1 plays a role in adhesion of leukocytes through the β2 (CD18) ligands LFA-1 (CD11a) and Mac-1 (CD11b)[6,7] and mediates transendothelial migration of neutrophils and eosinophils.[1,7-9] Compared to ICAM-1, the expression of VCAM-1 is more limited. It is found on endothelium and dendritic cells.[1,10] VCAM-1 interacts with the integrin ligand very late activation

Address correspondence to: M.P. Manns

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* These two authors contributed equally to this work.

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antigen-4 (VLA-4 = $\alpha_4\beta_1$) and is involved in adhesion of monocytes, lymphocytes, and eosinophils to activated endothelium.[1,9,11–14]

E-selectin (formerly ELAM-1 or LECAM-2) and P-selectin (also known as GMP-140, CD62, LECAM-3, or PADGEM) are transmembrane cell surface glycoproteins of the selectin class of adhesion molecules.[1–3,15–18] E-selectin is expressed on cytokine-stimulated vascular endothelium and mediates the adherence of neutrophils, monocytes, and a subpopulation of memory T-cells to activated endothelium.[2,3,15,16,19,20] Known ligands for E-selectin include the sialyl Lewis^x antigen, Lewis^a antigen, related fucosylated N-acetyl-lactosamines, the recently described high affinity ligand E-selectin ligand-1, and also the P-selectin glycoprotein ligand-1 on circulating white blood cells and on certain tumor cells.[2,3,21–24] P-selectin is present in the α-granules of platelets and Weibel-Palade bodies of endothelial cells.[17,18,25] After stimulation with thrombin, histamine, or leukotrienes, P-selectin is translocated to the cell surface within minutes and mediates adhesion of neutrophils and monocytes to activated platelets and endothelial cells.[2,3,26–28] Ligands for P-selectin are, in part, the same as those for E-selectin.[2,3,24,29–31]

While selectins (L-, P, and E-selectins) are thought to control the initial attachment and rolling of leukocytes, integrins and immunoglobulin supergene family adhesion molecules mediate stable adhesion to the endothelium and extravasation.[1–3,30–32]

In recent years, soluble forms of several adhesion molecules, including sICAM-1/2, sVCAM-1, sE-selectin, and sP-selectin, have been identified in human serum or plasma.[33–38] Elevated serum concentrations of circulating adhesion receptors have been described in inflammatory, infectious, and malignant diseases.[39,40] Increased expression of adhesion molecules in the inflamed intestine may lead to elevated serum levels of these molecules, which, conversely, may compete with membrane-bound forms for binding to their cognate ligands, thereby modulating leukocyte migration. Measurement of these soluble receptors might permit monitoring of inflammatory diseases such as IBD and improve understanding of their immunopathogenesis. Therefore, it was the objective of this study to measure these circulating adhesion molecules in sera of patients with Crohn's disease (CD) and ulcerative colitis (UC) in comparison to healthy (normal) controls and evaluate correlations between serum levels and clinical and laboratory markers of disease activity.

Patients and methods

Blood samples were collected after overnight fasting from a total of 93 patients with IBD (CD, $n = 65$; UC, $n = 28$) defined according to standard clinical, histological, and radiological methods. Exclusion criteria were chronic liver or kidney disease, previous transplantation, malignancy, acute or chronic infection, and other

Table 1. Characteristics of patients with inflammatory bowel disease and normal controls

	Normal controls	Crohn's disease (CD)	Ulcerative colitis (UC)
Patients/controls (men/women)	58 (33/25)	65 (27/38)	28 (14/14)
Mean age in years (range)	32.7 (22–58)	35.1 (17–60)	37.4 (16–65)
CDAI (mean ± SE)	—	127.5 ± 12.8	—
van Hees index (mean ± SE)	—	145.2 ± 6.1	—
Colitis score (mean ± SE)	—	—	5.7 ± 0.9
Patients with active/inactive CD (mean CDAI)	—	28/37 (182.4/116.2)	—
Patients with active/inactive UC (mean colitis score)	—	—	9/19 (11.8/3.2)
Localization of CD (percentage of patients)			
Small intestine only	—	16.9	—
Small and large intestine	—	52.3	—
Large intestine only	—	30.8	—
Localization of UC (percentage of patients)			
Proctitis	—	—	32.1
Left colon	—	—	21.4
Pancolitis	—	—	46.5
Medication (percentage of patients)			
None	100	23.4	21.4
Prednisone	0	42.2	21.4
Sulfasalazine	0	25.0	35.7
Mesalazine	0	40.6	35.7

CDAI, Crohn's disease activity index

chronic inflammatory disease (e.g., psoriasis, systemic lupus erythematosus, rheumatoid arthritis). Disease activity indices were calculated for all IBD patients. In CD patients, disease activity was evaluated using the Crohn's disease activity index according to Best et al. (CDAI)[41] and the van Hees activity index.[42] For all UC patients, the colitis score according to Gomes et al.[43] was calculated. CD was considered active if the van Hees index was more than 150; UC was considered active in patients with a colitis score of more than 6. Sera obtained from 58 healthy persons served as controls. The characteristics of patients and controls are shown in Table 1.

All patients and controls gave their informed consent for blood sampling and evaluation of their data. The study was preformed in accordance with the World Medical Association Helsinki Declaration.

Measurement of soluble adhesion molecules in sera of patients and controls

Serum samples were prepared within 30 min of venipuncture by centrifugation at 2500 *g* for 20 min. Samples were stored at −70°C until analysis. Serum concentrations (ng/ml) of circulating sICAM-1, sVCAM-1, sE-selectin, and sP-selectin were measured with enzyme linked immunosorbent assay (ELISA) systems (British Bio-Technology, Abingdon, UK). Inter- and intra-assay coefficients of variation for all ELISAs were less than 10%.

Detection of human anti-mouse antibodies

To avoid false positive results in the ELISA measurements of soluble adhesion molecules, sera of all patients and controls were analyzed for the presence of nonspecific human anti-mouse antibodies (HAMA). The detection assay was performed as previously described.[44] Only those patients and controls without detectable HAMA were included in this study.

Other laboratory tests

At the time of blood sampling, a complete blood count was conducted and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin concentration, and serum protein electrophoresis, including α_2- and γ-globulin levels, were measured in all IBD patients.

Statistics

Values are expressed as means ± SE. The Mann-Whitney *U*-test (two-tailed) was used to assess differences between different groups. Differences were considered significant if the *P* value was less than 0.05. Spearman's rank coefficient *r* was calculated for linear correlation of values. Statistical calculations were made using the SPSS program (version 5.0, SPSS, Chicago, IL, USA) on an IBM compatible 486 DX PC.

Results

Soluble selectins in sera of patients with IBD

P-selectin serum levels of patients with CD (399 ± 33 ng/ml; $n = 43$) and UC (385 ± 42 ng/ml; $n = 23$) were significantly increased ($P = 0.0067$ and $P = 0.0193$, respectively) compared to levels in the healthy controls (251 ± 33 ng/ml, $n = 23$) (Fig. 1a).

E-selectin serum concentrations of patients with CD (58 ± 5 ng/ml; $n = 31$) and UC (64 ± 12 ng/ml; $n = 13$) were also higher than those of controls (53 ± 5 ng/ml; $n = 9$) as shown in Fig. 1b. However, these differences were not significant as assessed by Mann-Whitney *U*-test.

Soluble immunoglobulin supergene family adhesion molecules in sera of patients with IBD

As shown in Fig. 2a, the concentrations of sICAM-1 in sera of patients with CD (420 ± 19 ng/ml; $n = 56$) and UC (375 ± 40 ng/ml; $n = 25$) were significantly elevated ($P = 0.0001$ and $P = 0.0473$, respectively) compared to concentrations in normal controls (297 ± 8 ng/ml; $n = 42$).

sVCAM-1 serum levels of patients with CD (664 ± 43 ng/ml; $n = 35$) and even more in those with UC (963 ± 162 ng/ml; $n = 15$), were significantly increased ($P = 0.0222$ and $P = 0.0121$, respectively) compared to controls (510 ± 31 ng/ml; $n = 15$) as shown in Fig. 2b.

Serum levels of soluble adhesion molecules in relation to laboratory and clinical markers of IBD activity, localization, and medication

For evaluation of the associations between soluble adhesion molecule levels and clinical or laboratory markers of IBD activity, correlations between sP-selectin, sE-selectin, sICAM-1, and sVCAM-1 serum concentrations and several laboratory parameters of inflammation, including ESR, complete blood count, CRP, albumin, α_2- and γ-globulins, were examined. Overall, there was no strong correlation between the soluble adhesion receptors studied and these laboratory markers. However, sICAM-1 serum levels were significantly correlated with CRP in UC patients ($r = 0.63$; $P = 0.001$) and with α_2-globulins in CD patients ($r = 0.37$; $P = 0.007$) and sE-selectin concentrations in patients

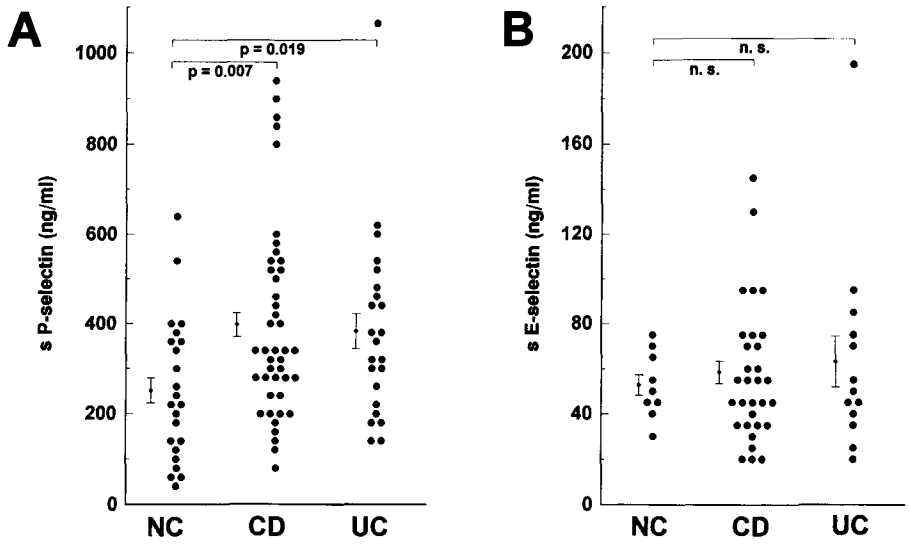

Fig. 1A,B. Serum concentrations (means ± SE) of **A** soluble P-selectin and **B** soluble E-selectin of normal controls (*NC*) and patients with Crohn's disease (*CD*) and ulcerative colitis (*UC*). Differences between patient and control groups are indicated (*P*, Mann-Whitney *U*-test value; *n.s.*, Not significant)

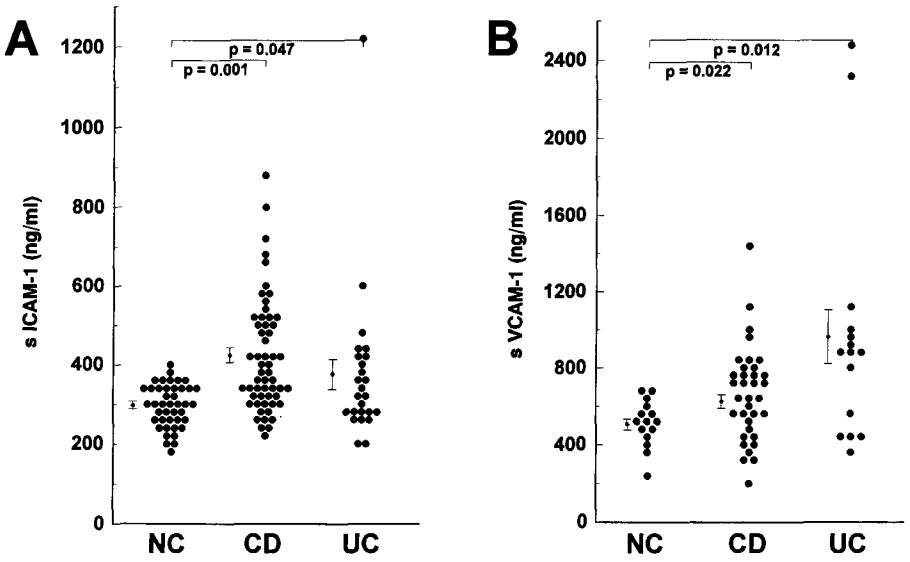

Fig. 2A,B. Serum concentrations (means ± SE) of **A** soluble immunoglobulin supergene family adhesion molecules soluble intercellular adhesion molecule-1 (*sICAM*-1) and **B** soluble vascular adhesion molecule-1 (*sVCAM*-1) of normal controls (*NC*) and patients with CD and UC. Differences between patient and control groups are indicated (*P*, Mann-Whitney *U*-test value)

with CD were significantly correlated with platelet counts ($r = 0.41$; $P = 0.029$) and CRP levels ($r = 0.41$; $P = 0.03$).

In CD patients, no significant correlations between soluble adhesion molecule serum concentrations (sP-selectin, sE-selectin, sICAM-1, and sVCAM-1, respectively) and activity indices were found as summarized in Table 2. Of note, sICAM-1 serum levels in CD patients with van Hees index values >150 (471 ± 35 ng/ml; $n = 24$) were higher than those of patients with van Hees index values ≤ 150 (381 ± 17 ng/ml; $n = 32$). However, this difference was not significant ($P = 0.071$). In UC patients, a moderate correlation was found between sICAM-1 serum concentrations and the colitis score according to Gomes et al.[43] ($r = 0.43$; $P = 0.036$). No significant correlations were found between sP-selectin, sE-selectin, or sVCAM-1 serum levels and colitis index values as shown in Table 2.

Table 2. Correlations between serum concentrations of soluble adhesion molecules and IBD activity indices in patients with Crohn's disease and those with ulcerative colitis

	CD-CDAI[41]	CD-van Hees index[42]	UC Colitis score[43]
sICAM-1	−0.04 (0.78)	0.01 (0.99)	0.43 (0.036)
sVCAM-1	0.014 (0.94)	−0.198 (0.58)	0.13 (0.65)
sE-selectin	0.2 (0.3)	0.11 (0.57)	−0.28 (0.38)
sP-selectin	−0.17 (0.29)	−0.35 (0.2)	−0.13 (0.56)

r, Spearman's correlation coefficients are shown. *P*, values are shown in parentheses. sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1

To evaluate associations between soluble adhesion receptor levels and the type of IBD medication, adhesion molecule serum concentrations in different treatment groups (no therapy; steroids only; steroid plus 5-aminosalicylic acid/5-aminosalicylic compound alone) were compared. Overall, no significant differences in serum levels of adhesion molecules were found in patients in different treatment groups. Interestingly, IBD patients receiving 5-aminosalicylic acid (40 ± 4 ng/ml; $n = 18$) had significantly lower sE-selectin serum levels compared to levels in IBD patients receiving no medication (64 ± 6 ng/ml; $n = 10$; $P = 0.005$) or a combination of steroids and 5-aminosalicylic acid (74 ± 12 ng/ml; $n = 14$; $P = 0.012$).

No significant differences in serum levels of soluble adhesion molecules were found in patient groups with different localizations of IBD (involvement of small intestine, large intestine, or both small and large intestine) in either CD or UC patients (data not shown).

Discussion

Before their extravasation, leukocytes need to interact with the vascular endothelium in the following sequential steps, mediated by adhesion molecules: (1) margination (i.e., displacement of leukocytes from the axial blood stream); (2) attachment to and rolling along the endothelium; (3) formation of a firm stable adhesion to the blood vessel wall; and finally (4), diapedesis and further migration into the extravascular tissue upon activation by chemotactic agents.

Serum levels of soluble immunoglobulin supergene and selectin types of adhesion molecules have been reported to be elevated in inflammation, infection, and cancers.[39,40,45,46] Only few studies have examined serum alterations of soluble adhesion molecules in patients with IBD;[47–49] most attention has been paid to serum levels of the soluble immunoglobulin supergene family adhesion molecule sICAM-1, which has been found to be elevated in patients with CD and those with UC.[47–49] sVCAM-1 serum levels have also been found to be elevated in IBD patients.[49] However, little information existed about soluble selectins in IBD. sE-selectin serum concentrations have been studied in one recently published report in which median values for both IBD patient groups were slightly higher than in controls.[49] To our knowledge, data about sP-selectin serum levels in IBD patients have not previously been reported.

The present study confirms earlier reports of increased serum levels of sICAM-1 and sVCAM-1 in patients with IBD. Furthermore, the findings presented here add new information about two different circulating molecules of the selectin class of adhesion molecules in sera of IBD patients. Selectins are of particular interest because these molecules, in contrast to immunoglobulin supergene type adhesion receptors, are involved in the rolling of leukocytes, an early event within the cascade of leukocyte extravasation and subsequent accumulation in the inflamed tissue. The present data indicate that sP-selectin serum concentrations are substantially increased in patients with CD and those with UC compared to normal controls. In contrast, sE-selectin levels in sera of IBD patients were not found to be significantly higher than those of controls.

Serum elevations of soluble selectin and immunoglobulin supergene adhesion molecules may be involved in altered leukocyte rolling along and subsequent adhesion to the endothelium of blood vessels in the inflamed intestine. The mechanism by which soluble adhesion molecules are released, their biological half-time in the blood, their ligand affinity, and the physiological role of these circulating adhesion molecules are largely unknown. Therefore, the pathophysiological importance of the elevations of soluble adhesion molecules in sera of IBD patients described here remains to be elucidated. It is possible that increased circulating adhesion molecules compete with the membrane-bound receptors for binding to their cognate ligands, thereby limiting leukocyte adhesion and subsequent extravasation into the inflamed intestine. Alternatively, soluble adhesion molecules may modulate the activation of signal transduction pathways after binding to ligand-bearing cells.[46]

The cellular source of elevated circulating sICAM-1 and sVCAM-1 in IBD patients is undefined. Among

others, vascular endothelial cells may be a possible source. For circulating sP-selectin and sE-selectin it appears even more likely that vascular endothelial cells that are activated by cytokines such as IL-1β, TNF-α, and IFN-γ are cellular sources. Whether increased circulating soluble selectin and immunoglobulin supergene adhesion molecules merely reflect increased local tissue expression is unknown at present.

E-selectin, which was not or was weakly detected in normal colonic mucosa, was found to be expressed on endothelial surfaces in association with active inflammation in patients with either UC or Crohn's colitis.[49–51] Expression of endothelial P-selectin has also been found to be increased in veins, venules, and capillaries in patients with active CD and those with UC.[52] Because of the restricted expression of P-selectin in endothelial cells, as well as in α-granules of platelets, it is possible that platelet-derived sP-selectin contributes to serum elevations of this molecule. This may even add further evidence for a pathogenic role of platelets in IBD, which has been discussed in a recent review.[53] Since P-selectin has previously been shown to have anti-inflammatory activity and to down-regulate CD18-dependent neutrophil adhesion and respiratory burst,[38,54] the increased presence of sP-selectin may be important for preventing the inappropriate activation of neutrophils in the circulation.

Vascular endothelia also showed higher expression of ICAM-1 in inflamed tissue sections from patients with CD and those with UC compared to expression in control specimens, whereas endothelial staining for VCAM-1 was not strikingly different in sections from UC and CD patients compared to staining in controls.[49] Interestingly, anti-α_4 integrin antibodies have been demonstrated to attenuate colitis in the Cotton-top model of ulcerative colitis.[55] This may indicate the possible importance of the VLA-4/VCAM-1 pathway in the pathophysiology of IBD, although VLA-4 also binds ligands other than VCAM-1, including fibronectin.[12,13]

Collectively, the present data clearly show that serum concentrations of sP-selectin and the immunoglobulin supergene family adhesion molecules sICAM-1 and sVCAM-1 are elevated in patients with CD and patients with UC compared to concentrations in normal controls. Increased leukocyte adhesiveness and aggregation has recently been shown to be a useful indicator of disease activity in patients with IBD.[56] Therefore, it appears plausible that elevation of soluble adhesion molecules may be involved in altered leukocyte migration and the inflammatory response in IBD. Furthermore, medication may influence the measured adhesion molecule concentration, as shown in this report for E-selectin serum levels in IBD patients. This finding is supported by in vitro studies indicating a dose-dependent inhibition of E-selectin expression in lipopolysaccharide-stimulated human umbilical vein endothelial cells after the addition of sulfasalazine.[57] Since elevated serum levels of the soluble adhesion receptors described here have also been found in other inflammatory and infectious illnesses, as well as in cancers of various organs,[34,43,45,46] they do not appear to be specific indicators of intestinal inflammation in patients with IBD. Further studies will be needed to elucidate serum levels of soluble adhesion receptors in other intestinal diseases (i.e., infectious diarrhea, diverticulitis, and gluten-sensitive enteropathy).

With the exception of sICAM-1 in UC patients, serum levels of soluble adhesion receptors did not show significant correlations to clinical and laboratory markers of disease activity, or to the localization of IBD. Therefore, routine serum measurement of these soluble adhesion molecules for clinical monitoring of patients with UC or CD does not appear to be justified.

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