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Review

New markers in ulcerative colitis

Radislav Nakov

Department of Gastroenterology, Tsaritsa Yoanna University Hospital, Medical University of Sofia, Bulgaria

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ABSTRACT

A new target in the treatment of UC is mucosal healing (MH), which is related to long-term remission, reduced rates of hospitalisation, and colectomy. Despite the advantages in the management of UC over the past few decades, much less has been achieved in the diagnosis and monitoring of the disease where colonoscopy remains the "gold standard" method. Therefore, a non-invasive marker correlating with MH is being sought [14]. Non-invasive markers have the potential to avoid invasive diagnostic tests and inhibit potential complications. Although several noninvasive and easily accessible biomarkers for UC are available, their sensitivity and specificity are not adequate to be used as single markers and do not overrule the need for endoscopic evaluation. Consequently, there is still need for new markers of intestinal inflammation in UC. In the current review Based on a literature search using PubMed, we reviewed eight new potential markers in UC studied mainly in the last five years: trefoil factor 3 (TFF3), leucine-rich A-2 glycoprotein (LRG), high mobility group box 1 protein (HMGB1), soluble ST2 (sST2), B cell-activating factor (BAFF), annexin A1 (ANXA1), matrix metalloproteinases (MMP), and neutrophil gelatinase-associated lipocalin (NGAL).

1. Introduction

Ulcerative colitis (UC) is one of the two major subtypes of inflammatory bowel disease (IBD). The prevalence rate of UC is almost 250 cases per 100,000 persons and is increasing worldwide in individuals of all ages [1].

The pathogenesis of UC is not fully elucidated, although environmental and genetic factors, including the microbiome, are thought to be of importance [2]. Typically, UC shows a relapsing and remitting course characterised by periods of active superficial inflammation and ulceration in the colonic mucosa spreading continuously from the rectum and various distances proximal [3].

There is currently no single "gold standard" diagnostic test for UC. Instead, diagnosis is established by a combination of clinical, laboratory, imaging, and endoscopic parameters, including histopathology [4]. Unfortunately, even tests that are conducted by expert clinicians can sometimes result in diagnostic uncertainty [5–7].

A new target in the treatment of UC is mucosal healing (MH), which is related to long-term remission, reduced rates of hospitalisation, and colectomy [8,9]. At present, the most accurate way to assess MH is repeated endoscopy with biopsy [10]. However, this technique has the drawbacks of being invasive, time-consuming, and expensive [11]. Moreover, it is painful and requires both a skilled operator and an uncomfortable preparatory regimen [12]. These limiting factors are often a burden to UC patients and prevent the frequent evaluation of UC activity by endoscopy [13].

Despite the advantages in the management of UC over the past few decades, much less has been achieved in the diagnosis and monitoring of the disease where colonoscopy remains the "gold standard" method. Therefore, a non-invasive marker correlating with MH is being sought [14]. Non-invasive markers have the potential to avoid invasive diagnostic tests and inhibit potential complications [15].

The ability to determine the type of UC, severity, prognosis, and response to therapy using markers has long been the aim of clinical researchers [16–18]. A good biomarker must be accurate, reproducible, standardised, easy to interpret by clinicians, and have a high diagnostic sensitivity and specificity. Unfortunately, no single marker has all of these features.

To date, the most thoroughly studied inflammatory markers are C-reactive protein (CRP) and faecal calprotectin (FC). Despite the reported correlation between endoscopic activity and CRP [19], the data are still insufficient to warrant its broad use in UC. There are many promising results for FC [20,21] demonstrating very good correlation with clinical activity, endoscopic indices, and even MH in UC [7,19,22–24]. [7,19,22–24]. However, more studies are needed to clarify adequate surveillance strategies and cut-off levels before its broad implementation in clinical practise. Although FC is a very sensitive marker for the detection of inflammation in the gastrointestinal tract, it is not a specific marker and increased levels are also found in colorectal cancer, infections, polyps, diverticulitis, and NSAID-induced

E-mail address: radislav.nakov@gmail.com.

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Table 1
New markers in ulcerative colitis. Comparison of cut-off levels, area under the curve (AUC), sensitivity, specificity and correlation with endoscopic activity, clinical activity, C-reactive protein (CRP) and faecal calprotectin (FC).

Marker	Ref.	Patients	Cut-off	AUC	Sensitivity	Specificity	Correlation with			
							Endoscopic activity	Clinical activity	CRP	FC
TFF3	Nakov et al. [23]	116	6.74 ng/ml	0.927	87.9%	86.9%	Yes	Yes	Yes	Yes
LRG	Shinzaki et al. [39]	109	n/a	0.849	n/a	n/a	Yes	Yes	No	n/a
HMGB1	Palone et al. [49]	62	n/a	n/a	n/a	n/a	Yes	No	n/a	yes
sST2	Díaz-Jiménez [58]	26	74.87 pg/mL	0.92	83.33%	83.33%	Yes	Yes	n.a	Yes
Faecal BAFF	Zhang et al. [66]	78	334 pg/ml	0.936	88%	100%	Yes	Yes	Yes	Yes
Serum BAFF	Zhang et al. [66]	78	1417 pg/ml	0.749	53%	93%	Yes	Yes	Yes	Yes
ANXA1	Kourkoulis et al. [72]	42	2.043 μg/ml	0.913	88%	93%	Yes	n/a	n/a	n/a
Faecal MMP 9	Buisson et al. [78]	32	900 ng/g	0.870	91%	80%	Yes	Yes	Yes	Yes
Serum MMP 3	Kourkoulis et al. [72]	42	4.743 ng/ml	0.796	100%	67%	Yes	n/a	n/a	n/a
Serum NGAL	Budzynska et al. [88]	41	43.6 ng/ml	0.758	96%	54%	Yes	Yes	Yes	No
Faecal NGAL	Buisson et al. [78]	32	6700 ng/g	0.780	82%	80%	No	No	No	Yes

TFF3 - Trefoil factor 3.
LRG - Leucine-rich A-2 glycoprotein.
HMGB1 - High mobility group box 1 protein.
sST2 - soluble ST2.
BAFF - B cell-activating factor.
ANXA1 - Annexin A1.
MMP - matrix metalloproteinase.
NGAL -Neutrophil gelatinase-associated lipocalin.
n/a - not applicable.

enteropathy. Moreover, the concentrations of FC in stool samples collected during a single day may differ and day-to-day variations can occur [25]. Consequently, new markers of intestinal inflammation in UC are necessary.

Based on a literature search using PubMed, we reviewed eight new potential markers in UC studied mainly in the last five years: trefoil factor 3 (TFF3), leucine-rich A-2 glycoprotein (LRG), high mobility group box 1 protein (HMGB1), soluble ST2 (sST2), B cell-activating factor (BAFF), annexin A1 (ANXA1), matrix metalloproteinases (MMP), and neutrophil gelatinase-associated lipocalin (NGAL) (Table 1).

2. Trefoil factor 3 (TFF3)

Trefoil factors include a family of three mucin-associated peptides secreted by goblet cells in the intestinal mucosa [26]. They play a key role in maintaining mucosal barrier integrity [27] and are upregulated at the site of mucosal damage [28]. TFF3 is also known as intestinal trefoil factor and is predominantly secreted by goblet cells in the small and large intestine [26] and protects the gastrointestinal mucosa from a variety of insults [29].

Over the last few years, it has been suggested that serum levels of TFF3 measured by ELISA can predict disease activity [30,31] and reflect MH in UC patients [23,32]. Grønbaek et al. [33] found that serum TFF3 levels correlated with disease activity indices in patients with UC and noted a trend toward reductions in TFF3 levels with clinical improvement after therapy with steroids. In a recent study, Srivastava et al. [32] showed that serum TFF3 could identify with reasonable sensitivity and specificity patients with MH in a group of UC patients in clinical remission or with mild activity. In our studies, we showed that the mean levels of TFF3 in active UC were significantly higher than those identified in patients with quiescent UC, which were similar to those of healthy controls [30,31]. Furthermore, TFF3 demonstrated a strong correlation with clinical activity, endoscopic indices, and FC, indicating its potential for use as a marker for disease activity and complete MH in UC patients [23]. Our recent study demonstrated that a TFF3 cut-off level of 6.74 ng/ml had AUC of the ROC curve 0.927, sensitivity of 87.9%, and specificity of 86.9% for predicting complete MH defined as both UC endoscopic index of severity (UCEIS) and Mayo endoscopic subscore (MES) values of 0 [23].

Interestingly, TFF3 correlates well with CRP levels in UC patients and its combination with CRP has comparable predictability of complete MH to FC, enabling UC patients to avoid stool sampling and be followed-up using only blood tests [23]. This could be beneficial for patients reluctant to handle faecal material.

TFF3 can predict disease activity in those with UC in real clinical practise and correlates well with FC levels and endoscopic activity, so it could be used as a non-invasive marker to predict disease activity in these patients.

3. Leucine-rich A-2 glycoprotein (LRG)

In inflammatory diseases, proinflammatory cytokines such as IL-6, IFNs, TNF-a, IL-1b, and IL-22 are upregulated. Among them, IL-6 plays a key role in the induction of acute phase proteins (APPs) such as CRP and serum amyloid A (SAA) by stimulating hepatocytes in the liver [34]. UC is a disease that is IL-6-independent in nature, given that CRP and SAA often remain at normal levels. Therefore, there is a need for a new inflammatory marker that is upregulated independently of IL-6.

Serada et al. obtained sera from rheumatoid arthritis patients, analysed the samples using a proteomic approach, and identified LRG, a 50-kD protein [35]. LRG is produced by neutrophils, macrophages, hepatocytes, and intestinal epithelial cells and its concentrations can easily be measured by commercially available ELISA [36–38]. LRG can serve as a new marker to evaluate disease activity in UC because serum LRG shows high levels in UC patients with active disease and decreases promptly when disease activity declines [38].

Serada et al. also showed that serum LRG concentrations were significantly elevated in active UC patients compared with those in remission and healthy controls and correlated with disease activity in UC better than CRP [38]. Shinzaki et al. demonstrated that serum LRG levels were significantly increased and correlated with clinical and endoscopic activities in patients with UC [39]. LRG levels were associated with both clinical and endoscopic activities even in patients with normal serum CRP levels. Moreover, LRG levels were significantly lower in patients with complete MH and deep remission. Serial measurements of LRG levels in a subset of patients demonstrated that LRG was significantly elevated during the endoscopically active stage compared with that during the MH stage [39].

Western blotting analysis confirmed that LRG is upregulated markedly in inflamed colonic tissues compared to non-inflamed colons

[38]. This demonstrates that LRG is released from inflamed tissues in the intestinal tract and may explain why LRG correlates well with the endoscopic scores of the disease.

In summary, LRG is potentially more effective than CRP as a marker for detecting endoscopic activity in UC patients, can predict MH, and could be used for follow-up.

4. High mobility group box 1 protein (HMGB1)

HMGB1, a damage-associated molecular pattern (DAMP) prototype, is presently considered a potent inflammatory mediator involved in multiple adult and paediatric disorders including infectious diseases, ischaemia, immune disorders, neurodegenerative diseases, metabolic disorders, and cancer [40–42]. Therefore, HMGB1 has been considered a new therapeutic target, particularly for the treatment of chronic inflammation [43,44], including gut inflammation [45].

HMGB1 was recently identified as a potent proinflammatory mediator when present extracellularly. Secreted HMGB1 acts as a cytokine by signalling via the receptor for advanced glycated end-products and by members of the Toll-like receptor family triggering inflammatory response that includes the production of multiple cytokines, induction of vascular adhesion molecules, and impaired function of intestinal epithelial cells [46,47].

Faecal HMGB1, measured by Western blotting analysis, has been shown to significantly correlate with endoscopic activity (assessed by MES) but not with clinical activity (partial Mayo score) both in paediatric and adult UC patients [48]. Faecal HMGB1 expression is significantly increased in paediatric and adult patients with UC and strongly correlates with disease severity. HMGB1 has a strong correlation with FC both in paediatric and adult UC patients [49]. Moreover, in UC patients with clinical and endoscopic remission, faecal HMGB1 shows a strong match with the degree of Geboes histological score of inflammation [46,47]. Therefore, HMGB1 can be used as a non-invasive biomarker of clinically overt and subclinical gut inflammation and of MH, suggesting its use to monitor disease course and assess therapy outcomes [50].

Faecal HMGB1 can be used in clinical practise as a reliable biomarker of intestinal inflammation in both paediatric and adult UC patients and also to reveal histological changes in patients with clinical and endoscopic remission.

5. Soluble ST2 (sST2)

ST2 belongs to the IL-1R super-family and is expressed as two splice variants: one membrane bound, ST2L, which is a receptor of IL-33, and a soluble protein, sST2 [51–53]. In 2010, Beltran et al. described for the first time increased levels of sST2 in serum and total ST2 in the colonic mucosa in IBD patients and its distribution in epithelial and infiltrating cells from the colonic mucosa [54]. They also showed that serum sST2 levels correlated significantly with total ST2 levels in the colonic mucosa [54]. Since then, several groups have shown evidence that the ST2/IL-33 system may participate in the development of IBD [55,56].

Serum sST2 values are significantly higher in patients with active rather than inactive IBD as well as compared with non-IBD patients and controls [57]. Diaz-Jimenez et al. showed that a cut-off level of 74.87 pg/mL discriminates active from inactive UC with sensitivity, specificity, ability to correctly classify UC according to activity, and AUC of the ROC curve of 83.33%, 83.33%, 83.33%, and 0.92, respectively. The serum levels of sST2, measured by ELISA, in patients with UC significantly correlated with endoscopic and histopathological scores and with the pro-inflammatory cytokine tumour necrosis factor-α [57].

Díaz-Jiménez et al. showed that both serum and mucosal ST2 correlate significantly with FC [58]. They performed consecutive sST2 measurements to follow changes in the inflammatory activity of UC patients who responded or not to treatment and demonstrated that sST2, similar to FC, is a useful biomarker for monitoring relapse and predicting clinical outcomes in UC patients [58].

In summary, sST2 levels demonstrate effective differentiation between the endoscopic activity degrees of UC, which strongly suggests its usefulness in monitoring relapse and outcomes. Determining whether sST2 levels can monitor the treatment impact on endoscopic MH and whether they can predict the risk of complications in UC or need for surgery are some of the questions that should be answered by further studies.

6. B cell-activating factor (BAFF)

BAFF, a member of the tumour necrosis factor (TNF) superfamily predominantly produced by myeloid cells (monocytes, macrophages, and dendritic cells) [59,60] and neutrophils, is critical for the maintenance of normal B cell development and homeostasis [61]. BAFF binds to three separate receptors: B cell maturation antigen (BCMA), transmembrane activator and calcium modulating and cyclophilin ligand interactor (TACI), and BAFF-receptor (BAFF-R) [62,63]. These three main receptors have distinct expression patterns based on the B cell development stages related to their separate functions [64]. BAFF action is not restricted only to B lymphocytes because it also regulates the activation of T lymphocytes [65]. BAFF can enhance the in vitro response of CD4+ and CD8+ T cells as well as naive and effector T cells [65].

In 2016, Zhang et al. demonstrated increased BAFF expression in both the serum and colon of patients with IBD as measured by ELISA [66]. Furthermore, serum BAFF levels correlated with disease activity, CRP, TNF-a, and IL-1b in patients with UC. Faecal BAFF concentrations of 334 pg/ml significantly discriminated UC patients from IBS or healthy controls with sensitivity, specificity, and AUC of 88%, 100%, and 0.936, respectively. In addition, both serum and faecal BAFF serve as sensitive and specific markers for detecting chronic inflammation, although the sensitivity and specificity of faecal BAFF is better compared with those of serum BAFF [66].

Fu et al. showed that faecal BAFF is a promising non-invasive biomarker for discriminating UC from IBS. Moreover, faecal BAFF levels showed stronger correlation with endoscopic inflammatory scores compared to FC in UC patients [67].

In summary, patients with UC have elevated BAFF levels in their serum, colon tissue, and faeces, indicating a potential role of BAFF in the pathogenesis of the disease. Faecal BAFF may be considered an excellent non-invasive marker of disease activity of UC.

7. Annexin A1 (ANXA1)

ANXA1 is a calcium- and phospholipid-binding protein with potent anti-inflammatory activities. It is particularly abundant in the cells of the host immune system, including monocytes, macrophages, and PMNs [68]. Functionally, ANXA1 attenuates leukocyte recruitment by inhibiting cell adhesion and transmigration [69]. It has been reported that ANXA1 plays an important role in the regulation of mucosal regeneration and healing [70].

It is documented that there is a significant increase in ANXA1 expression in colonic biopsies from patients with active UC or those in medically induced remission compared to controls. Moreover, ANXA1 serum levels are significantly different between controls and UC patients, implying that it could be used as a diagnostic marker of UC [71]. The best cut-off value reported by Kourkoulis et al. was 2.043 μg/ml with 88% sensitivity and 93% specificity [72].

Serum ANXA1 shows good potential for use as a marker for diagnosis and even MH of UC; however, more data are needed to confirm its use in everyday practise.

8. Matrix metalloproteinases (MMP)

Matrix metalloproteases (MMPs) are a family of Zn-containing endopeptidases that degrade the extracellular matrix. In addition to playing a central role in extracellular matrix turnover, MMPs activate or degrade a variety of non-matrix substrates including chemokines, cytokines, growth factors, and junctional proteins [73]. MMPs are mainly secreted by neutrophils but also by various cell types, such as fibroblasts, mesenchymal cells, tumour cells, and several inflammatory cells such as monocytes or lymphocytes.

It was previously reported that MMP-9, a gelatinase generally absent from the surface epithelium, was highly expressed in inflamed IBD mucosa by macrophages and neutrophils [74,75]. Annahazi et al. suggested that the MMP-9 level was higher in UC patients than in those suffering from IBS with predominant diarrhoea [76]. Farkas et al. reported an increased faecal MMP-9 level in UC patients with endoscopic activity, suggesting that faecal MMP-9 could be an interesting biomarker in UC [77].

Buisson et al. showed that faecal MMP-9 values, measured by ELISA, correlated well with clinical activity, CRP concentration, FC values, and MES in UC patients [78]. MMP-9 values were higher in the UC patients with MES of 2 or 3 than in those with MH defined as MES < 2. In this study, MMP-9 values had better efficacy to detect endoscopic activity in UC patients than FC and lipocalin-2. The best MMP-9 cut-off to detect UC endoscopic activity was 900 ng/g with sensitivity and specificity of 91.0% and 80.0%, respectively [78].

Kofla-Dłubacz et al. demonstrated that median serum concentrations of MMP-3 and MMP-9 were higher in children with UC than in healthy controls. MMP-3 with a threshold of 5.4 ng/mL had the highest discriminative value (AUC = 0.9, $p < .001$, sensitivity = 71%, and specificity = 92%) in distinguishing patients with UC from healthy individuals [79]. The cut-off value of 2.46 ng/mL of serum MMP-9 had AUC of 0.69, 61% sensitivity, and 73% specificity [79]. Kourkoulis et al. reported that serum MMP3 concentrations correlate well with MES and a cut-off value of 4.743 ng/ml could discriminate MES 0 from MES 1 with 100% sensitivity and 67% specificity [72].

MMPs have high diagnostic potential in UC severity evaluation. Faecal MMP-9 and serum MMP-3 measurement can be reliable assays to assess endoscopic activity in UC in clinical practise.

9. Neutrophil gelatinase-associated lipocalin (NGAL)

A promising new marker of IBD activity is NGAL (known also as lipocalin-2) measured in serum or faeces. NGAL is an acute phase glycoprotein covalently bound to MMP-9 [80]. Under physiological conditions, it is secreted in small amounts by neutrophils, macrophages, epithelial cells, smooth muscle cells, hepatocytes, adipocytes, and neurons [81]. Increased NGAL concentrations in serum is associated with injury to epithelial cells in the gastrointestinal tract, respiratory tract, or renal tubules [81,82]. A number of studies have demonstrated the role of NGAL as a diagnostic and prognostic biomarker for acute or chronic kidney disease, sepsis, and acute pancreatitis as well as gastric, colorectal, pancreatic, and biliary cancer [80,83,84].

Increased concentrations of urinary MMP9/NGAL complex and NGAL in stool have been reported in IBD patients [81,85]. In two studies, serum NGAL concentrations were significantly higher in UC and CD patients than in healthy individuals or patients with IBS [86,87].

Budzynska et al. demonstrated that serum NGAL, measured by ELISA, significantly rose with increasing clinical and endoscopic activity assessed by Mayo score [88]. On clinical grounds, NGAL levels significantly differentiated patients with active disease from those in complete remission. Serum NGAL levels correlated with CRP, ESR, and iron concentrations, but not with FC. An optimal cut-off level of 43.6 ng/ml demonstrated the ability to distinguish endoscopically active from inactive UC with AUC of 0.758 (sensitivity of 96% and specificity of 54%) [88].

Buisson et al. reported that faecal NGAL values correlated with FC values but not with clinical activity, CRP, or MES in UC patients [78]. The mean concentrations of NGAL were higher in UC patients with MES of 2 or 3 than in those with MH defined as MES < 2. The best NGAL cut-off to detect UC endoscopic activity was 6700 ng/g with AUC, sensitivity, and specificity of 0.78, 82.0%, and 80.0%, respectively [78].

In summary, NGAL is a valuable biomarker of inflammatory activity in UC patients, complementary to commonly used laboratory tests. NGAL can discriminate UC patients with endoscopic and clinical remission. However, its diagnostic efficacy especially in the context of non-invasive monitoring of therapy effects must be confirmed in larger studies.

10. Conclusion

UC is a highly heterogeneous disease for the onset, course, and progression of the disease and the response to therapies. Furthermore, the diagnosis of UC remains difficult, especially in the early stages of the disease, and the prompt and accurate diagnosis of UC patients is pivotal. Therefore, it is important to identify predictors of the disease course, complications, probability of response to therapy, and any adverse events to enable a targeted therapeutic process.

Several studies have suggested promising biomarkers in stools and serum, demonstrating the presence of new UC markers. Some of these non-invasive indicators have shown high sensitivity and specificity for disease activity in UC and good correlation with clinical activity, endoscopic activity, and FC levels, which could improve their utility in disease diagnosis and monitoring of UC in the near future. However, the currently available data for all of the reviewed new UC markers are not sufficient and their diagnostic efficacy must be confirmed in larger studies. Although some of the new UC markers demonstrate better potential to diagnose intestinal inflammation than CRP and correlate well with FC levels, none show the potential of being superior to FC. Studies evaluating the combined diagnostic activity of new potential markers of UC and traditional markers as CRP and FC will be valuable for clinical practise.

In conclusion, to better understand the role of new UC markers in different disease phases and optimally use them in everyday practise, it is crucial to increase studies, the number of IBD centres and patients involved in trials, and standardise diagnostic kits and single-marker cut-offs.

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