Journal of Crohn's and Colitis, 2023, **17**, 1579–1586
https://doi.org/10.1093/ecco-jcc/jjad071
Advance access publication 21 April 2023
Original Article

Early Intestinal Ultrasound Predicts Long-Term Endoscopic Response to Biologics in Ulcerative Colitis

Mariangela Allocca[a], Cecilia Dell'Avalle[b], Federica Furfaro[a], Alessandra Zilli[a], Ferdinando D'Amico[a,c], Laurent Peyrin-Biroulet[d,e], Gionata Fiorino[a,f], Silvio Danese[a]

[a]Gastroenterology and Endoscopy, IRCCS Hospital San Raffaele and University Vita-Salute San Raffaele, Milan, Italy
[b]IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy
[c]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; and Division of Colon and Rectal Surgery, Humanitas Clinical and Research Hospital IRCCS, Rozzano, Milan, Italy
[d]Department of Gastroenterology and Inserm NGERE 1256, University Hospital of Nancy, University of Lorraine, Nancy, France
[e]Groupe Hospitalier privé Ambroise Paré – Hartmann, Paris IBD center, 92200 Neuilly sur Seine, France
[f]Gastroenterology and Digestive Endoscopy, San Camillo-Forlanini Hospital, Rome, Italy

Corresponding author: Mariangela Allocca, MD, PhD, Department of Gastroenterology and Endoscopy, IRCCS Hospital San Raffaele and University Vita-Salute San Raffaele, Via Olgettina 60, 20132, Milan, Italy. Tel: +39 026432069; Email: mariangela.allocca@gmail.com

Abstract

Background and Aims: The Milan ultrasound criteria [MUC] is a validated score to assess endoscopic activity in ulcerative colitis [UC]. MUC > 6.2 detects Mayo endoscopic score [MES] > 1. In this study we evaluated the predictive value of MUC for biologic treatment response, using colonoscopy [CS] as a reference standard.

Methods: Consecutive UC patients starting biologic therapy were included, and underwent CS, IUS, clinical assessment and faecal calprotectin [FC] measurement at baseline and within 1 year. In addition, IUS, clinical and FC assessments were performed at week 12. The primary objective was to evaluate whether ultrasound improvement [MUC ≤ 6.2] at week 12 predicted endoscopic improvement at reassessment [MES ≤ 1]. Endoscopic remission was defined as MES = 0.

Results: Forty-nine patients were included [59% under infliximab, 29% under vedolizumab, 8% under adalimumab, 4% under ustekinumab]. MUC ≤ 6.2 at week 12 was the only independent predictor for MES ≤ 1 and MES = 0 at reassessment (odds ratio [OR] 5.80, $p = 0.010$; OR 10.41, $p = 0.041$; respectively). MUC ≤ 6.2 at week 12 showed a negative predictive value of 96% for detecting MES = 0. A ≥2 reduction of the MUC predicted MES = 0 (area under the curve [AUC] 0.816). MUC ≤ 4.3 was the most accurate cut-off value for MES = 0 [AUC 0.876]. Guyatt's responsiveness ratio for the MUC was 1.73 [>0.8].

Conclusion: MUC ≤ 6.2 at week 12 predicts long-term endoscopic response. MUC is accurate in monitoring treatment response and may be used in both clinical trials and routine practice.

Key Words: Ulcerative colitis; intestinal ultrasound; Milan ultrasound criteria

1. Introduction

Ulcerative colitis [UC] is a chronic, relapsing and destructive inflammatory disorder of the colon which can lead to organ damage and impair quality of life.[1] A 'treat-to-target approach' with tight monitoring of intestinal inflammatory lesions is recommended.[2] Colonoscopy [CS] is currently the gold standard to assess disease activity and the response to treatments.[2] However, it is an invasive procedure, is unpleasant to patients, and comes with some risks, especially during severe flares.[3,4] Intestinal ultrasound [IUS] is a patient-friendly, non-invasive, accurate, cheap tool to manage UC patients in clinical practice.[5] Its ability to be performed as a point-of-care ultrasound may drastically change the frequency of assessment of the treatment response, speeding the clinical decision-making process.[6] A recent multicentre study showed that IUS detected a fast and early response to anti-inflammatory treatments, with a high correlation with clinical response at week 12.[7] To our knowledge, only a few studies have evaluated the responsiveness of IUS in comparison with colonoscopy,[8–11] and just one proposed cutoff values for IUS parameters.[12] We have externally validated non-invasive ultrasonography-based criteria (Milan ultrasound criteria [MUC]) to assess and grade endoscopic activity in UC.[13,14] We have also demonstrated that MUC is able to predict a negative course, in terms of treatment escalation, need of corticosteroids, hospitalization or colectomy.[15]

The aim of the present study was to assess the predictive value of IUS and MUC for treatment response in a longitudinal cohort of UC patients under biologic treatments, by using CS as a reference standard.

2. Methods

2.1. Study design and population

This was a single-centre, prospective observational study. All consecutive adult patients [18 years of age and older] with an established diagnosis of UC [for at least 6 months], seen in a

Figure 1. Design of the study.Abbreviations: CS, colonoscopy; IUS, intestinal ultrasound; PMS, partial Mayo score; FC, faecal calprotectin; CRP, C-reactive protein.

tertiary referral centre [Humanitas Research Hospital, Milan, Italy] between April 2018 and December 2020, requiring investigation by CS for a suspicion of active disease, were enrolled. Inclusion criteria were endoscopic activity, defined by a Mayo endoscopic score [MES] > 1, and a need to start biological therapy. Exclusion criteria were any contraindication to full CS [e.g. intolerance to preparation, severe flare], concomitant participation in clinical trials, disease limited to the rectum, active infections, including *Clostridium difficile* and cytomegalovirus infections, and inability to perform IUS within the time intervals established by the study.

2.1.1. Colonoscopies

Examinations were performed in a blinded fashion by an expert endoscopist, with at least 10 years of experience, using a standard video endoscope [Fujinon] and following the standard protocol used in clinical practice [colonic cleansing by administration of 4 L of polyethylene glycol]. Endoscopic activity was assessed by MES, where endoscopic improvement was defined by MES ≤ 1 and endoscopic remission by MES = 0.[16]

2.1.2. Intestinal ultrasound

A gastroenterologist expert in IUS [20 years of experience] performed all the scanning procedures in a blinded fashion, without having any knowledge of the patient's symptoms or endoscopic findings. Neither preparation nor contrast were used. IUS was performed after 6–8 h of fasting, using an Aloka Arietta V60 with convex [1–5 MHz] and microconvex probes [4–8 MHz], according to an acquisition protocol previously described.[17,18] The entire abdomen was systematically scanned starting from the right iliac fossa. The following parameters were evaluated: bowel wall thickness [BWT] [normal values up to 3 mm], measured in longitudinal and transverse sections, from the interface between the mucosa and the lumen to the interface between the serosa and the muscle layer—a mean of two measurements for each section was calculated; bowel wall pattern [BWP], defined as [0] normal, multilayered, [1] predominantly hypoechogenic, [2] predominantly hyperechogenic, [3] lost; bowel wall flow [BWF], defined as absence [0] or presence [1] of blood signals on colour Doppler; presence of mesenteric lymph nodes; and mesenteric hypertrophy, defined as absence [0] or presence [1]. These parameters were evaluated for each intestinal segment impacted by the disease, and the worst segment was taken into account.

The MUC was measured, as previously described, according to the following formula[17]:

$$\mathrm{MUC} = 1.4 \times \mathrm{BWT}\ [\mathrm{mm}] + 2 \times \mathrm{BWF};\ \text{where BWF} = 1 \text{ if present, or BWF} = 0 \text{ if absent.}$$

Ultrasound improvement was defined as an MUC ≤ 6.2, an maccurate and validated cut-off value for endoscopic improvement [MES ≤ 1].[13,14]

2.2. Study design

All patients underwent CS [reference standard] and IUS at week 0, before starting biologic therapy, and at reassessment, after an average follow-up time of 9.40 months [SD = 3.59]. IUS and CS were performed within a maximum interval of 30 days. Therapies were kept stable in the period between the two procedures. MES and MUC were measured to quantify disease activity and to assess the accuracy of MUC in monitoring UC patients and in detecting therapeutic response to biologic therapy. In addition, at week 0, at week 12 and at reassessment, patients underwent complete clinical assessment and stool samples were obtained for faecal calprotectin [FC] measurements. At week 12, IUS was also performed [Figure 1]. The disease was considered clinically active if the partial Mayo score [PMS] was >2.[16] The Montreal Criteria were used to define disease extent.[19]

2.3. Study aims

The primary objective was to evaluate whether ultrasound improvement [MUC ≤ 6.2] at week 12, during biologic therapy, could predict endoscopic improvement [MES ≤ 1] at reassessment.[2]

The secondary objectives were: [1] to investigate the sensitivity-to-change of MUC in patients treated for active UC, using the MES as a reference standard; [2] to investigate the correlation between MES and MUC at reassessment; [3] to investigate the minimum improvement in MUC able to predict endoscopic improvement and remission at reassessment; [4] to investigate the role of FC < 50 μg/g and PMS ≤ 2 at week 12 as predictors of endoscopic improvement at reassessment; [5] to evaluate whether ultrasound improvement at week 12, during biologic therapy, could predict endoscopic remission at reassessment [MES = 0]; and finally [6] to find the most accurate cut-off value of MUC for endoscopic remission [MES = 0].

2.4. Statistical analysis

Descriptive statistics of the data are presented as medians [interquartile range], or as percentages when appropriate. A matched-pairs Wilcoxon signed-rank test was used to analyse changes in continuous variables. The McNemar test was used to assess differences in qualitative parameters between baseline and the other time points. A logistic regression analysis was performed to analyse the association between ultrasound improvement at week 12, as defined by an MUC ≤ 6.2, and objective presence of endoscopic improvement assessed by CS and MES ≤ 1 at reassessment. The presence of endoscopic improvement

was the outcome variable [or dependent variable] [i.e. a binomial variable taking the value 1 if MES ≤ 1, and the value 0 if MES > 1]. MUC ≤ 6.2, and other non-invasive parameters, including FC < 50 µg/g and PMS ≤ 2 were used as explanatory variables [or independent variables]. In the univariable analysis, a criterion of $p < 0.10$ was used to identify candidate predictors. A multivariable model was then fitted using a 'backwards elimination procedure'. All variables with $p < 0.05$ were retained in the model. Contingency tables taking into account presence or absence of endoscopic improvement at reassessment, in relation to ultrasound improvement at week 12, were constructed to determine the sensitivity, specificity, positive and negative predictive values, and accuracy of MUC. Correlation between MUC and MES at reassessment was assessed using the Spearman rank correlation test. Reliability between ultrasound improvement at week12 and endoscopic improvement at reassessment was assessed using kappa statistics.

Guyatt's responsiveness ratio, the ratio of the change in the MUC in patients in endoscopic improvement [MES ≤ 1] to the standard deviation of the MUC in patients in endoscopic activity [MES > 1], was calculated. The standardized effect size was also compared: the ratio of the mean change in the MUC in patients in endoscopic improvement to the standard deviation of their baseline scores. For both of these ratios, values >0.8 are indicative of a large effect, indicating that the tool is more responsive to change.

Aiming to investigate the relationship between ultrasound improvement at week 12 and a more stringent target of treatment, such as endoscopic remission [MES = 0] at reassessment, we performed multivariable analysis also using endoscopic remission as a dependent binomial variable taking the value 1 if MES = 0 and the value 0 if MES > 0. The sensitivity, specificity, accuracy, positive predictive value [PPV] and negative predictive value [NPV] of ultrasound improvement at week 12 for detecting endoscopic remission at reassessment were also investigated. A receiver operating characteristic curve was constructed to determine the minimum decrease in MUC for predicting endoscopic improvement and endoscopic remission. Finally, the area under the receiver operating characteristic curve [AUROC] was used to determine cutoff values for MUC for detecting endoscopic remission.

All statistical tests were two-sided. Probability values <0.05 were considered to be statistically significant. Stata software was used for all statistical analyses [Stata Corp.].

We did not perform a power analysis as this is not always feasible in observational studies. Sample size was determined by practical considerations [i.e. time, availability of eligible patients and cost], but also aiming to reach a similar or even higher sample size compared to relevant studies,[12,20–22] in which IUS or other imaging tools, such as magnetic resonance imaging, were shown to assess response to therapy in patients with inflammatory bowel disease. Finally, according to the rules of thumb, for which the sample size should be ten times the number of predictors, we considered that a sample size of at least 40 might have been acceptable. To overcome drop-outs, we aimed to include a total of 49 patients.

2.4. Ethical considerations

The study was performed according to Good Clinical Practice guidelines and was approved by our Institutional Review Board. All patients gave their informed consent for this study. Clinical trial registry website and trial number: https://praticheweb.humanitas.it; ICH1330.

All authors had access to the study data and reviewed and approved the final manuscript.

3. Results

3.1. Study population

A total of 49 patients with UC were included in the study. The characteristics and clinical data of the study population, at week 0, at week 12 and at reassessment, are presented in Table 1. In particular, 59% of the patients were treated with infliximab, 29% with vedolizumab, 8% with adalimumab and 4% with ustekinumab. After treatment, at reassessment, 18 [37%] patients achieved endoscopic improvement [MES ≤ 1] and 20 [41%] achieved ultrasound improvement [MUC ≤ 6.2] [Table 2]. We found a statistically significant, high positive correlation between MUC and MES at reassessment ($r = 0.767$, 95% confidence interval [CI] 0.619–0.862; $p < 0.001$).

3.2. Responsiveness of MUC

We observed a significant change of MUC values before and after treatment, at reassessment (8.7 [7.7–9.5] vs 7.6 [4.2–8.9]; $p < 0.001$). A significant improvement from week 0 was also observed at week 12 (7.5 [4.7–8.5]; $p < 0.001$). Conversely no further significant changes were observed between week 12 and the reassessment (7.6 [4.2–8.9]; $p = 0.18$). It is noteworthy that MUC values were significantly lower at all the time points in the patients with MES ≤ 1 compared to patients without MES ≤ 1 [at week 0, $p = 0.03$; at week 12, $p = 0.003$; at reassessment, $p < 0.001$; Figure 2]. The size of the change in MUC and in MES was significantly correlated [$r = 0.513$, 95% CI 0.271–0.694; $p < 0.001$].

Guyatt's responsiveness ratio for the MUC was 1.73 (Δ MUC in the group in endoscopic improvement [3.46]/SD of the group not in endoscopic improvement [2.0]), and the standardized effect size ratio was 1.6 (ΔMUC in the group in endoscopic improvement [3.46]/SD of their baseline scores [2.13]). Both these values being >0.8 indicate a large effect of responsiveness for the MUC.

3.3. Early predictors of risk of endoscopic response

Multivariable analysis among all the variables considered at week 12 identified MUC ≤ 6.2 as the only independent predictor of endoscopic improvement [MES ≤ 1] at reassessment (odds ratio [OR] 5.80, 95% CI 1.49–22.47; $p = 0.010$) [Table 3]. Moderate reliability ($k = 0.44$ [0.17–0.71]) was observed between MUC ≤ 6.2 at week 12 and MES ≤ 1 at reassessment. With the aim to investigate the relationship between MUC ≤ 6.2 at week 12 and a more stringent target of treatment, such as endoscopic remission [MES = 0] at reassessment, we performed multivariable analysis also using endoscopic remission as a dependent binomial variable taking the value 1 if MES = 0 and the value 0 if MES > 0. MUC ≤ 6.2 was again the only independent risk factor associated with achieving endoscopic remission [OR 10.41, 95% CI 1.09–99.29; $p = 0.041$] [Supplementary Table S1]. The sensitivity, specificity, accuracy, PPV and NPV [95% CI] of MUC ≤ 6.2 for detecting endoscopic improvement at reassessment were 67% [41–87], 78% [58–91], 73% [58–85], 67% [41–87] and 78% [58–91], respectively. The NPV of MUC ≤ 6.2 increased to 96% [95% CI 81–100] for detecting endoscopic remission [Table 4]. A reduction of ≥2 of the MUC had a sensitivity

Table 1. Characteristics of patients at week 0, at week 12 and at reassessment [*n* = 49]

	Week 0	Week 12	Reassessment
Male	34 [69]		
Age at diagnosis [years]	34 [21–45]		
Disease duration [years]	5.8 [2.8–10.8]		
Disease extent at diagnosis			
Proctitis	2 [4]		
Left-sided	20 [41]		
Extensive	27 [55]		
Disease extent at inclusion			
Proctitis	0		
Left-sided	33 [67]		
Extensive	16 [33]		
Smoking			
Active	8 [16]		
Past	16 [33]		
Never	25 [51]		
Previous use of biologics			
1 biologic	15 [31]		
>1 biologic	9 [18]		
Never	25 [51]		
Use of steroids			
Concomitant	23 [47]	2 [4]	4 [8]
Past	26 [53]	47 [96]	45 [92]
Use of IMM [azathioprine]			
Concomitant	15 [31]	15 [31]	13 [26]
Past	21 [43]	21 [43]	23 [47]
Never	13 [26]	13 [26]	13 [26]
Biological therapy started[a]			
Infliximab	29 [59]	29 [59]	29 [59]
Adalimumab	4 [8]	4 [8]	4 [8]
Vedolizumab	14 [29]	14 [29]	14 [29]
Ustekinumab	2 [4]	2 [4]	2 [4]
Partial Mayo score	4.0 [2.7–6.0]	2.0 [0.0–5.0]	2.0 [0.0–4.5]
PMS > 2	37 [76]	20 [45]	19 [40]
PMS ≤ 2	12 [24]	24 [55]	29 [60]
C-reactive protein, mg/L	4.0 [2.0–6.5]	3.4 [1.5–6.0]	3.5 [1.7–7.3]
CRP ≥ 5	19 [40]	14 [33]	17 [39]
CRP < 5	28 [60]	29 [67]	27 [61]
Calprotectin, µg/g	485 [130–800]	214 [27–673]	101 [26–503]
Calprotectin < 50	3 [7]	15 [35]	14 [33]
Calprotectin 50–250	13 [29]	8 [19]	14 [33]
Calprotectin > 250	28 [64]	20 [46]	15 [34]
Mayo endoscopic score	3.0 [3.0–3.0]	NA	2.0 [1.0–3.0]
0	0		7 [14]
1	0		11 [23]
2	10 [20]		10 [20]
3	39 [80]		21 [43]
Milan ultrasound criteria	8.7 [7.7–9.5]	7.5 [4.7–8.5]	7.6 [4.2–8.9]
MUC ≤ 6.2	3 [6]	18 [40]	20 [41]
MUC > 6.2	46 [94]	27 [60]	29 [59]

Abbreviations: IMM, immunomudulators; PMS, partial Mayo score; CRP, C-reactive protein; MUC, Milan ultrasound criteria.
[a]Biological therapy: a total of ten patients optimized biological dosage, three in adalimumab, two in vedolizumab and five in infliximab, six at week 12 and four after week 12.
Data are presented as medians [interquartile range] or percentages when appropriate.

Table 2. Percentages of patients achieving ultrasound and endoscopic outcomes at reassessment, among the different groups of treatment

Biologics	MUC ≤ 6.2 *N* [%]	MES ≤ 1 *N* [%]	MUC > 6.2 *N* [%]	MES > 1 *N* [%]
Infliximab	10/29 [34]	10/29 [34]	19/29 [66]	19/29 [66]
Adalimumab	3/4 [75]	2/4 [50]	1/4 [25]	2/4 [50]
Vedolizumab	6/14 [43]	5/14 [36]	8/14 [57]	9/14 [64]
Ustekinumab	1/2 [50]	1/2 [50]	1/2 [50]	1/2 [50]
All patients	20 [41]	18 [37]	29 [59]	31 [63]

Abbreviations: MUC, Milan ultrasound criteria; MES, Mayo endoscopic score.

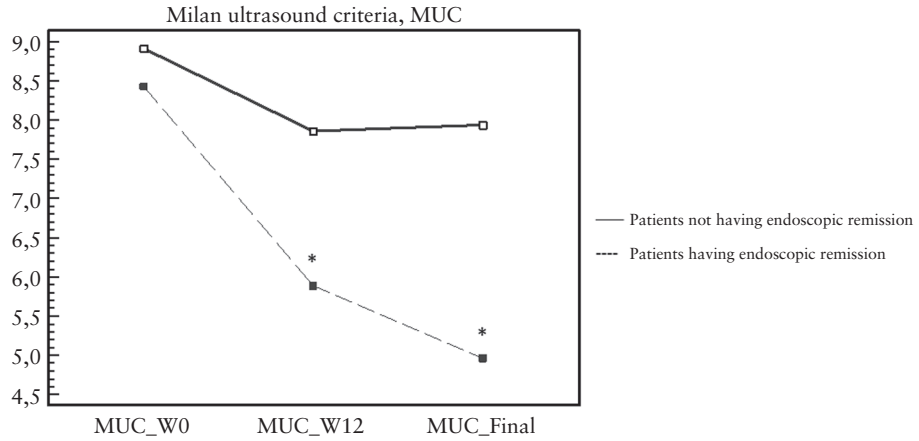

Figure 2. MUC changed significantly over time [$p < 0.001$], with the largest drop at week 12 [$p < 0.001$]. MUC values were significantly lower at all time points in patients with MES ≤ 1 [dashed line] compared to patients without MES ≤ 1 [continuous line] at reassessment [$p < 0.05$].Abbreviations: MUC, Milan ultrasound criteria; MES, Mayo endoscopic score.

Table 3. Influence of non-invasive tools at week 12 on the risk of endoscopic improvement [MES ≤ 1] at reassessment

Parameter	Univariable analysis		Multivariable analysis	
	OR [95% CI]	*p*	OR [95% CI]	*p*
MUC ≤ 6.2	7.0 [1.84–26.61]	***0.0043***	5.80 [1.49–22.47]	***0.010***
FC, µg/g	6.0 [1.52–23.67]	***0.010***	—	—
<50	0.44 [0.07–2.51]	0.35		
50–250	0.30 [0.08–1.12]	0.074		
>250				
CRP < 5 mg/L	2.03 [0.51–8.00]	0.31	—	—
PMS ≤ 2	3.54 [0.97–12.90]	0.054	—	—

Abbreviations: MES, Mayo endoscopic score; MUC, Milan ultrasound criteria; FC, faecal calprotectin; CRP, C-reactive protein; PMS, partial Mayo score. Significant *p*-values are highlighted in bold and italics.

Table 4. Diagnostic accuracy of MUC ≤ 6.2 at week 12 in detecting endoscopic improvement [MES ≤ 1] and endoscopic remission [MES = 0] at reassessment

	Sensitivity, % [95% CI]	Specificity, % [95% CI]	Accuracy, % [95% CI]	PPV, % [95% CI]	NPV, % [95% CI]
Endoscopic improvement [MES ≤ 1]					
MUC ≤ 6.2	67 [41–87]	78 [58–91]	73 [58–85]	67 [41–87]	78 [58–91]
Endoscopic remission [MES = 0]					
MUC ≤ 6.2	86 [42–100]	68 [51–82]	71 [56–84]	33 [13–59]	96 [81–100]

Abbreviations: MUC, Milan ultrasound criteria; MES, Mayo endoscopic score; PPV, positive predictive value; NPV, negative predictive value.

of 89% [95% CI 65–98] and a specificity of 77% [95% CI 59–90] [AUROC 0.806, 95% CI 0.667–0.904], and a sensitivity of 100% [95% CI 59–100] and a specificity of 62% [95% CI 46–76] [AUROC 0.816, 95% CI 0.680–0.912], in predicting patients who achieved MES ≤ 1 and MES = 0, respectively [Figure 3].

3.4. Cut-off value for endoscopic remission

A receiver operating characteristic curve set an enquiry MUC ≤ 4.3 as the best cut-off value to determine endoscopic remission [MES = 0]. Sensitivity and specificity were 100% [95% CI 59–100] and 76% [61–88], respectively [AUROC 0.876, 95% CI 0.750–0.952].

4. Discussion

A 'treat-to-target' strategy with close monitoring of the response to treatment is recommended in UC.[2] Colonoscopy is the mainstay of this approach and patients often undergo numerous colonoscopies during therapy. However, this procedure is not well accepted by patients.[23] IUS is a non-invasive technique which does not require specific preparation and contrast media and is welcomed by patients. In addition, IUS can be performed in real time, at the point of the care, speeding the clinical decision-making process.[6] We have developed and externally validated the MUC to assess disease activity in UC.[13,14] It correlates very well with endoscopic grading of inflammation; in particular, a MUC > 6.2 is an indicator of endoscopic activity [MES > 1] with a specificity of 100%. Furthermore, MUC is very easy to calculate, as it consists of only the sum of BWT and BWF. These two parameters are the most reliable and reproducible among the ultrasound parameters,[12,24] thus overcoming the limit that sees bowel US as an operator-dependent procedure.

In this study we have demonstrated, using colonoscopy and MES as a reference standard, that MUC responds to treatment, the minimal decrease for MUC [a delta MUC reduction of 2 points] able to predict endoscopic improvement [MUC ≤ 1] and remission [MUC = 0] at reassessment, and in particular that an MUC ≤ 6.2 at 12 weeks is the only predictor for endoscopic improvement and remission at the reassessment. Furthermore, we have shown that an MUC ≤ 6.2 at week 12 has an NPV of 96% for endoscopic remission at reassessment, thus allowing an early adjustment of treatment in cases where this early ultrasound target has not yet been reached. Indeed, a multicentre large study showed a normalization of most ultrasound parameters within 12 weeks from the beginning of the treatment and, in particular, a high correlation between the normalization of BWT and clinical response at 12 weeks.[7] Our study confirms that IUS response occurs within 12 weeks, and in addition shows that it is the only predictor of endoscopic response at reassessment.

To our knowledge, this is the first study that demonstrates that a validated ultrasound-based score may be used for monitoring the response to treatment in UC patients. Recently a study of 27 UC patients treated with tofacitinib showed that BWT, but not BWF, was accurate in detecting endoscopic improvement and remission at 8 weeks.[12] BWT seems to normalize earlier than BWF,[7] and an early endoscopic assessment may have masked the response of BWF, as suggested by the same authors.[12] In the development study, we employed multivariable modelling, using MES as a reference standard, to build the MUC and converted the beta coefficient from the final model of each relevant variable [among bowel ultrasound parameters only BWT and BWF resulted in independent predictors for endoscopic activity] into a weighted score, magnifying the weights of the individual ultrasound parameters. In fact, a prediction tool from the multivariable model performs better than the univariable ones.[13] A previous longitudinal prospective study compared bowel US and CS for the assessment of response to steroids in UC patients. The authors found a consistent concordance. However, they used a non-standardized ultrasound scale of activity.[25] Finally, in this study, we have determined that an MUC ≤ 4.3 was the most accurate cut-off value for MES = 0 [AUROC 0.876], showing that a non-invasive ultrasound-based approach may also be feasible when we want to achieve more ambitious treatment targets.

Standardized metrics to communicate disease activity and therapeutic response are crucial to implement the use of IUS for the management of patients with UC, both in clinical practice and in clinical trials. In this direction, a simple and easy score, such as MUC that includes only two parameters, BWT and CDS, and is highly reproducible and reliable, may be helpful. Additionally, the use of a rigorously built score has a higher accuracy compared to the use of single parameters.

This study has several strengths: [1] we used the only existing validated ultrasound-based score; [2] response to treatment was assessed in comparison to colonoscopy, the current gold standard; [3] IUS and colonoscopy were performed in a blinded fashion; [4] treatment was kept stable between the

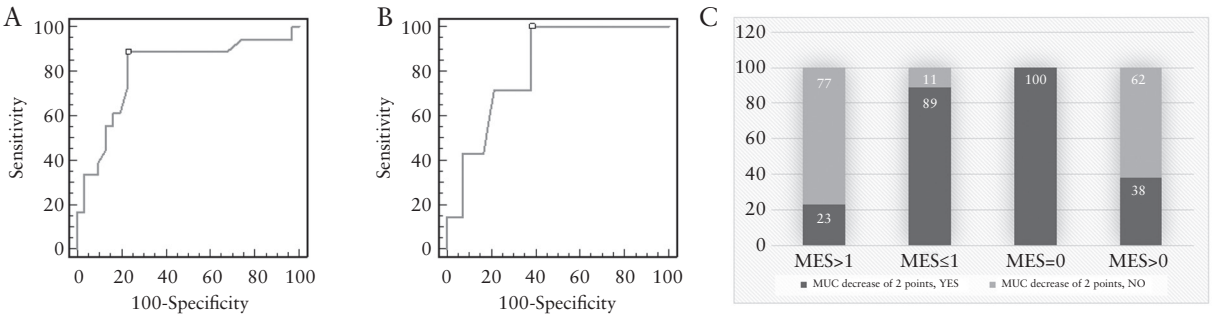

Figure 3. ROC curve analysis measuring sensitivity and specificity of the delta MUC decrease: a decrease of 2 points had a sensitivity of 89% and specificity of 77% in predicting patients who achieved MES ≤ 1 [A]; sensitivity 100% and specificity 62% in predicting patients who achieved MES = 0 [B]. Percentages of patients with an MUC decrease of 2 points achieving endoscopic outcomes at reassessment [C].Abbreviations: MUC, Milan ultrasound criteria; MES, Mayo endoscopic score; ROC, receiver operating characteristic.

different procedures; and [5] we performed a prospective longitudinal study in a real-world setting. This study has also same limitations: [1] it is a single-centre study; [2] the sample size, although in line other similar studies, is modest; [3] we did not use a central reading for endoscopic and ultrasound findings; [4] the interval between IUS and colonoscopy was up to 30 days. To overcome limits due to the large interval between the two procedures, patients maintained stable therapies. [5] The inter-rater variability was not assessed. However, the reliability of the two ultrasound parameters [BWT and BWF] to build the MUC is now well known. [6] Finally, large international multicentre studies are warranted to confirm the validity of these data.

In conclusion, we have demonstrated that IUS and MUC are highly accurate for assessing a response to treatment already at week 12, and for predicting endoscopic remission at reassessment, in a prospective, longitudinal cohort of UC patients under biologics. In particular, patients who fail to achieve an MUC ≤ 6.2 at 12 weeks have a high likelihood of not achieving endoscopic remission at reassessment [<1% change in false negative results].

Our findings could lead to non-invasive, early and tight control in the monitoring of patients with a well-timed assessment of response to treatment aimed at achieving the target.

Funding

No funding was obtained for this project.

Conflict of Interest

MA received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie, Ferring, Galapagos and Pfizer; FF received consulting fees from Amgen, Abbvie, Janssen and Pfizer; LP-B declares personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher; grants from Abbvie, MSD, Takeda and Fresenius Kabi; stock options: CTMA; GF received consultancy fees from Ferring, MSD, AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis and Celltrion; SD served as a speaker, consultant and advisory board member for Schering-Plough, Abbott [AbbVie] Laboratories, Merck, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson and Johnson. The other authors have no conflicts of interest to declare.

Author Contributions

Mariangela Allocca is guarantor of the article, she conceived and designed the study; Cecilia Dell'Avalle, Federica Furfaro, Alessandra Zilli and Ferdinando D'Amico collected all the data; Mariangela Allocca performed the data analysis and drafted the manuscript; Gionata Fiorino, Laurent Peyrin-Biroulet and Silvio Danese critically revised the manuscript; all authors approved the final version of the manuscript.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

References

1. Gordon IO, Agrawal N, Willis E, *et al*. Fibrosis in ulcerative colitis is directly linked to severity and chronicity of mucosal inflammation. *Aliment Pharmacol Ther* 2018;**47**:922–39. doi:10.1111/apt.14526.
2. Turner D, Ricciuto A, Lewis A, *et al*; International Organization for the Study of IBD. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;**160**:1570–83. doi:10.1053/j.gastro.2020.12.031.
3. Damore LJ, Rantis PC, Vernava AM, Longo WE. Colonoscopic perforations: etiology, diagnosis, and management. *Dis Colon Rectum* 1996;**39**:1308–14. doi:10.1007/BF02055129.
4. Eckardt VF, Gaedertz C, Eidner C. Colonic perforation with endoscopic biopsy. *Gastrointest Endosc* 1997;**46**:560–2. doi:10.1016/S0016-5107(97)70017-8.
5. Smith RL, Taylor KM, Friedman AB, Gibson RN, Gibson PR. Systematic review: clinical utility of gastrointestinal ultrasound in the diagnosis, assessment and management of patients with ulcerative colitis. *J Crohns Colitis* 2020;**14**:465–79. doi:10.1093/ecco-jcc/jjz163.
6. Allocca M, Furfaro F, Fiorino G, Peyrin-Biroulet L, Danese S. Point-of-care ultrasound in inflammatory bowel disease. *J Crohns Colitis* 2021;**15**:143–51. doi:10.1093/ecco-jcc/jjaa151.
7. Maaser C, Petersen F, Helwig U, *et al*; German IBD Study Group and the TRUST&UC study group. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: Results from the TRUST&UC study. *Gut* 2020;**69**:1629–36. doi:10.1136/gutjnl-2019-319451.
8. Maconi G, Ardizzone S, Parente F, Bianchi Porro G. Ultrasonography in the evaluation of extension, activity, and follow-up of ulcerative colitis. *Scand J Gastroenterol* 1999;**34**:1103–7. doi:10.1080/003655299750024904.
9. Parente F, Molteni M, Marino B, *et al*. Bowel ultrasound and mucosal healing in ulcerative colitis. *Dig Dis* 2009;**27**:285–90. doi:10.1159/000228562.
10. Yamaguchi T, Yoshida S, Tanaka S, *et al*. Predicting the clinical response to cytapheresis in steroid-refractory or -dependent ulcerative colitis using contrast-enhanced ultrasonography. *Scand J Gastroenterol* 2009;**44**:831–7. doi:10.1080/00365520902839659.
11. Socaciu M, Ciobanu L, Diaconu B, Hagiu C, Seicean A, Badea R. Non-invasive assessment of inflammation and treatment response in patients with Crohn's disease and ulcerative colitis using contrast-enhanced ultrasonography quantification. *J Gastrointest Liver Dis* 2015;**24**:457–65. doi:10.15403/jgld.2014.1121.244.chr.
12. de Voogd F, van Wassenaer EA, Mookhoek A, *et al*. Intestinal ultrasound is accurate to determine endoscopic response and remission in patients with moderate to severe ulcerative colitis: a longitudinal prospective cohort study. *Gastroenterology* 2022;**163**:1569–81. doi:10.1053/j.gastro.2022.08.038.
13. Allocca M, Fiorino G, Bonovas S, *et al*. Accuracy of humanitas ultrasound criteria in assessing disease activity and severity in ulcerative colitis: A prospective study. *J Crohns Colitis* 2018;**12**:1385–91. doi:10.1093/ecco-jcc/jjy107.

14. Allocca M, Filippi E, Costantino A, *et al*. Milan ultrasound criteria are accurate in assessing disease activity in ulcerative colitis: external validation. *United Eur Gastroenterol J* 2021;**9**:438–42. doi:10.1177/2050640620980203.
15. Allocca M, Dell'Avalle C, Craviotto V, *et al*. Predictive value of Milan ultrasound criteria in ulcerative colitis: A prospective observational cohort study. *United Eur Gastroenterol J* 2022;**10**:190–7. doi:10.1002/ueg2.12206.
16. Schroeder K, Tremaine W, Ilstrup D. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**:1625–9. doi:10.1056/NEJM198712243172603.
17. Allocca M, Fiorino G, Bonovas S, *et al*. Accuracy of humanitas ultrasound criteria in assessing disease activity and severity in ulcerative colitis: A prospective study. *J Crohns Colitis* 2018;**12**:1385–91. doi:10.1093/ecco-jcc/jjy107.
18. Allocca M, Filippi E, Costantino A, *et al*. Milan ultrasound criteria are accurate in assessing disease activity in ulcerative colitis: external validation. *United Eur Gastroenterol J* 2021; **9**:438–42. Doi: 10.1177/2050640620980203.
19. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. *Gut* 2006;**749**:53. doi:10.1136/gut.2005.082909.
20. Ordás I, Rimola J, Rodríguez S, *et al*. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. *Gastroenterology* 2014;**146**:374–82.e1. doi:10.1053/j.gastro.2013.10.055.
21. Thierry ML, Rousseau H, Pouillon L, *et al*. Accuracy of diffusion-weighted magnetic resonance imaging in detecting mucosal healing and treatment response, and in predicting surgery, in Crohn's disease. *J Crohns Colitis* 2018;**12**:1180–90. doi:10.1093/ecco-jcc/jjy098.
22. Laurent V, Naudé S, Vuitton L, *et al*. Accuracy of diffusion-weighted magnetic resonance colonography in assessing mucosal healing and the treatment response in patients with ulcerative colitis. *J Crohns Colitis* 2017;**11**:716–23. doi:10.1093/ecco-jcc/jjw211.
23. Buisson A, Gonzalez F, Poullenot F, *et al*. Comparative acceptability and perceived clinical utility of monitoring tools: a nationwide survey of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:1425–33. Doi: 10.1097/MIB.0000000000001140.
24. Novak KL, Nylund K, Maaser C, *et al*. Expert consensus on optimal acquisition and development of the International Bowel Ultrasound Segmental Activity Score [IBUS-SAS]: a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's disease. *J Crohns Colitis* 2021;**15**:609–16. doi:10.1093/ecco-jcc/jjaa216.
25. Parente F, Molteni M, Marino B, *et al*. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis: A prospective study. *Am J Gastroenterol* 2010;**105**:1150–7. doi:10.1038/ajg.2009.672.