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Monitoring inflammatory bowel disease activity: Clinical activity is judged to be more relevant than endoscopic severity or biomarkers

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Abstract

Background: There is increasing evidence for the clinical relevance of mucosal healing (MH) as therapeutic treatment goal in inflammatory bowel disease (IBD). We aimed to investigate by which method gastroenterologists monitor IBD activity in daily practice.

Methods: A questionnaire was sent to all board-certified gastroenterologists in Switzerland to specifically address their strategy to monitor IBD between May 2009 and April 2010.

Results: The response rate was 57% (153/270). Fifty-two percent of gastroenterologists worked in private practice and 48% worked in hospitals. Seventy-eight percent judged clinical activity to be the most relevant criterion for monitoring IBD activity, 15% chose endoscopic severity, and 7% chose biomarkers. Seventy percent of gastroenterologists based their therapeutic decisions on clinical activity, 24% on endoscopic severity, and 6% on biomarkers. The following biomarkers were used for IBD activity monitoring: CRP, 94%; differential blood count, 78%; fecal calprotectin (FC), 74%; iron status, 63%; blood sedimentation rate, 3%; protein electrophoresis, 0.7%; fecal neutrophils, 0.7%; and vitamin B12, 0.7%. Gastroenterologists in hospitals and those with ≤10 years of professional experience used FC more frequently compared with colleagues in private practice ($P=0.035$) and those with >10 years of experience ($P<0.001$).

Conclusions: Clinical activity is judged to be more relevant for monitoring IBD activity and guiding therapeutic decisions than endoscopic severity and biomarkers. As such, the accumulating

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1. Introduction

The activity assessment of Inflammatory Bowel Diseases (IBD) is based on a combination of symptoms, clinical findings, and endoscopy.[1–6] Traditionally, the focus of therapeutic IBD trials has been directed towards symptom improvement without the goal of mucosal healing (MH).[1–3] Until the late 1990s there was no clear evidence that MH as a therapeutic goal could be associated with a change in IBD's natural history.[7] The interest in MH as a treatment target was raised when several therapeutic trials evaluating anti-tumor necrosis factor (anti-TNF) medications demonstrated that these drugs were not only capable of inducing but also maintaining MH in a considerable proportion of patients.[1–3] Thereby, the hope of altering the disease course re-emerged. Meanwhile, accumulating evidence exists documenting that treatment with immunomudulators and/or biological agents can achieve long-term healing of the gastrointestinal mucosa and also affect the clinical outcome of both Crohn's disease and ulcerative colitis.[8–11] Although there is some disparity in the literature regarding the definition of MH, it is in the meantime 1) accepted as an important treatment endpoint and 2) also increasingly used in clinical practice.[7] As a consequence of the accumulating evidence, a considerable proportion of gastroenterologists in daily practice would be expected to assess their patients regularly by endoscopy. However, there is a lack of data evaluating IBD monitoring strategies in daily practice. The incorporation of the latest scientific findings into daily practice may need time. Therefore, it is of major interest to evaluate how gastroenterologists in daily practice monitor their IBD patients and also on which findings they base their therapeutic decisions.

When monitoring IBD patients, it has to be kept in mind that there is often an insufficient correlation between clinical activity, endoscopic severity, and biomarkers reflecting endoscopic activity.[12–15] Furthermore, colonoscopies have the disadvantage of being invasive, time-consuming, expensive, and sometimes uncomfortable for the patient which may restrict their wide acceptance by patients.[16] To overcome these limitations, several laboratory markers have been evaluated for the purposes of monitoring IBD activity. Two prominent biomarkers, namely C-reactive protein and fecal calprotectin have been shown in several studies to correlate with endoscopic and also clinical activity.[17–24]

Keeping the increasing evidence of the impact of MH in mind, we performed a nationwide survey among Swiss gastroenterologists to evaluate the following questions:

1. Which parameters are preferred in daily practice for IBD monitoring: clinical activity, endoscopic severity, or biomarkers reflecting intestinal inflammation?
2. On which parameters do gastroenterologists base their therapeutic decisions upon?
3. Which biomarkers are routinely used by gastroenterologists for IBD monitoring?

2. Materials and methods

2.1. Study design

In June 2010, a prospective questionnaire was sent to all board-certified gastroenterologists in Switzerland ($N = 270$).

2.2. Questionnaires

Swiss gastroenterologists were identified using the members' database of the Swiss Gastroenterology and Hepatology Association. The gastroenterologists were sent a one-page introduction containing the description of the study design and goals. Of note, the introduction page did not include informations on the increasing evidence of the clinical impact of MH on IBD's disease course in order to avoid a selection bias. Included was also a one-page questionnaire consisting of 20 questions, 8 of which were designed to assess demographic information and 12 were designed to address IBD monitoring habits. The gastroenterologists were asked to answer the questions reflecting on their clinical habits during the last 12 months (time period from May 1st 2009 to April 30th 2010). The questionnaire was developed by consensus rounds among the co-authors after having performed a literature search on IBD monitoring strategies.

The questionnaire (provided as supplemental material) addressed the following parameters:

1. Demographic information: name, age, gender, and years of gastroenterologic practice from the time of board examination.
2. Different aspects of IBD monitoring and diagnosis over the period of the last 12 months: the number of patients in which FC test was used; the percentage of IBD patients in which FC was used for activity monitoring; the type of biomarkers used for IBD activity monitoring; the most important factor for assessment of IBD activity (ranking of the following items from 1 to 3, where 1 has the highest and 3 the lowest priority: clinical activity, endoscopic activity, and biomarkers measuring inflammation); the most important factor for therapeutic decisions in IBD (ranking from 1 to 3 of the following items: clinical activity, endoscopic activity, and biomarkers measuring inflammation); an assessment of patient's compliance for fecal sampling; an estimation of whether FC vs CRP testing accurately reflects endoscopic IBD activity; an estimation of whether more frequent use of FC could decrease the endoscopy load; and an estimation whether $70 USD is an appropriate fee for a quantitative FC test.

A pilot questionnaire was given to 10 gastroenterologists. As a direct result of the pilot trial, minor modifications to the questionnaire were introduced in August 2010. The finalized questionnaires were distributed in English to all Swiss gastroenterologists in September 2010. An English questionnaire was

chosen in order to circumvent validating a German, a French, and an Italian version of the questionnaire among each other. Within the questionnaire package, an envelope with stamps was enclosed. After completion, the questionnaire was sent back to the study center at University Hospital Basel. The deadline for questionnaire submission was the end of October 2010. Questionnaires were then validated and entered into a database. In the case of missing information, queries were sent (by phone and/or email) until the issues were resolved.

2.3. Inclusion and exclusion criteria

All Swiss board-certified gastroenterologists treating patients were eligible for inclusion. The only exclusion criterion was unwillingness to participate in the study, in which the gastroenterologist did not return the questionnaire.

2.4. Statistical analysis

The data were entered into a database (Microsoft® Office, Access 2000, Redmond, Washington, USA). All statistical analysis was performed with a statistical package program (Stata® 9, College Station, Texas, USA). Data distribution was analyzed using normal Q–Q plots. Results of quantitative data are presented either as median plus interquartile ranges (for nonparametric data) or mean ± standard deviation (SD) and range (for parametric data). Categorical data were summarized as the percentage of the group total, and analysis between groups was performed using the Pearson's chi-square test. Nonparametric quantitative data in 2 unpaired groups were analyzed using the Wilcoxon rank sum test. A Bonferroni adjustment was performed in case of multiple testing. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of participating gastroenterologists

A total of 153 Swiss board-certified gastroenterologists participated in the survey (response rate 153/270 = 57%). Table 1 provides an overview of their demographic characteristics. A higher percentage of gastroenterologists in private practice had more than 10 years of gastroenterologic practice experience (from the time of board examination) than their colleagues in hospitals (52/73 vs 34/66, $P = 0.017$).

3.2. Priority items for assessing IBD activity: clinical activity, endoscopy, or biomarkers

We evaluated which parameters are perceived by individual gastroenterologists to be best suited to reflect IBD activity. The 3 categories for monitoring of IBD activity are as follows: clinical activity, endoscopic activity, and biomarkers measuring inflammation. These categories were ranked from 1 to 3, where 1 had the highest priority and 3 had the lowest priority. The results of this ranking are depicted in Fig. 1. Seventy-eight percent chose clinical activity as having the most impact on IBD activity assessment. Endoscopic activity and biomarkers were perceived to be best suited for IBD activity

Table 1 Demographic characteristics of participating gastroenterologists.

| Item	Frequency
Number of gastroenterologists participating	153
Females/males	11/142
Age (years, mean ± SD)	45 ± 9
	(range, 32–66)
Years of practice from the time of board	14 ± 8
certification	(range, 1–33)
Setting of practice	
Private practice	52%
Private hospital	2%
District hospital	14%
Large non-university hospital	14%
University hospital	18%
Number of IBD patients treated in the last year	
1–40	51%
41–100	41%
>100	8%

assessment by 15% and 7% of gastroenterologists, respectively. As a second priority option, 52% of gastroenterologists chose biomarkers. Endoscopic activity and clinical activity were perceived to be second best for IBD activity assessment by 36% and 12% of gastroenterologists, respectively. As a least priority option, endoscopic activity, biomarkers measuring inflammation, and clinical activity were chosen by 52%, 36%, and 12% of gastroenterologists, respectively.

3.3. Items determining therapeutic decisions

We further assessed the parameters that gastroenterologists rely on when making therapeutic decisions in IBD patients. The results of this ranking process are depicted in Fig. 2. Seventy percent of gastroenterologists chose clinical activity as the parameter having the most impact on their therapeutic decisions. The endoscopic activity and biomarkers measuring inflammation were chosen by 24% and 6% of gastroenterologists, respectively. As a second priority option, 44% of gastroenterologists chose
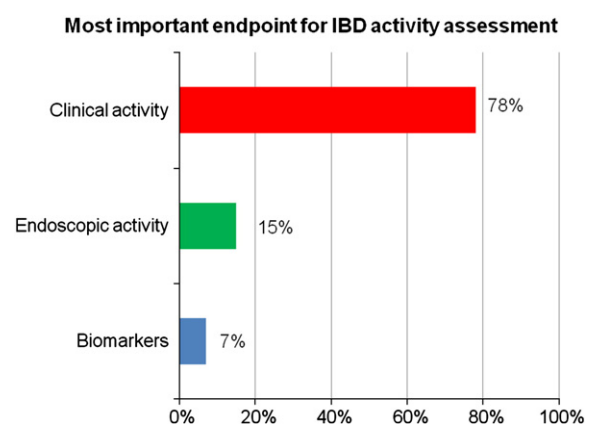
Figure 1 Most important endpoint for IBD monitoring (only one answer possible). IBD, inflammatory bowel disease.
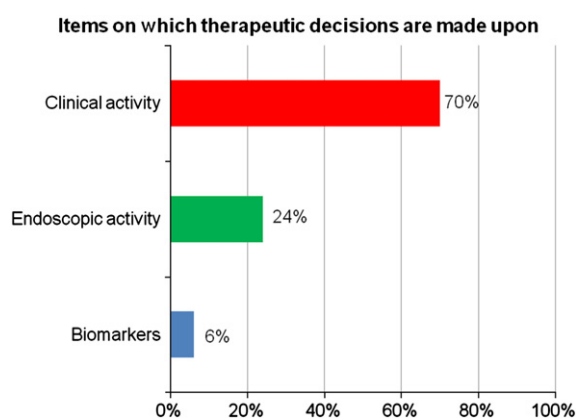
Figure 2 Items on which gastroenterologists base their therapeutic decisions upon (only one answer possible).

biomarkers. Endoscopic activity and clinical activity were perceived to be second best for IBD activity assessment by 39% and 17% of gastroenterologists, respectively. As a least priority option, biomarkers measuring inflammation, endoscopic activity, and clinical activity were chosen by 46%, 38%, and 16% of gastroenterologists, respectively.

3.4. Biomarkers of choice for monitoring IBD activity

We asked the participating gastroenterologists about their preferences for using different biomarkers for the purposes of monitoring IBD activity. The results are depicted in Fig. 3. Ninety-four percent of gastroenterologists used CRP for IBD activity assessment. Differential blood count and FC were also used for monitoring IBD activity by 78% and 74% of gastroenterologists, respectively.

3.5. Use of fecal calprotectin for IBD monitoring

The data on the use of FC for IBD monitoring are depicted in Table 2. Eighty-six percent of the participating gastroenterologists have used FC for IBD monitoring. In order to obtain more detailed data on the use of FC testing, we asked the gastroenterologists to categorize their FC testing practice.
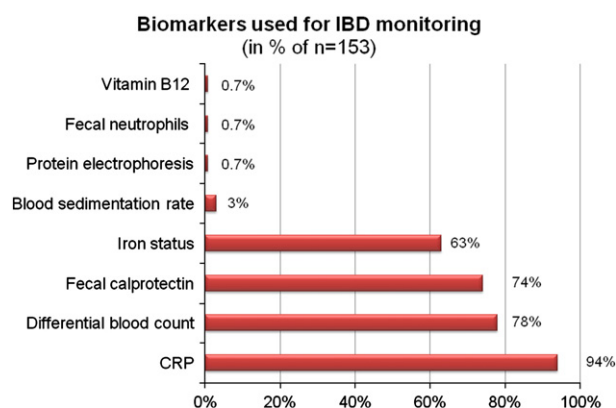
Figure 3 Biomarkers used for monitoring IBD activity. Several answers were possible; therefore, the total exceeds 100. CRP, C-reactive protein; IBD, inflammatory bowel disease.

Table 2 Use of FC for IBD monitoring within the past 12 months. Abbreviations: FC, fecal calprotectin; IBD, inflammatory bowel disease.

Item	Frequency (*n*=153)
Use of FC for monitoring IBD activity, *n* (%)	
>70% of patients with IBD	43 (28%)
30−70% of patients with IBD	34 (22%)
<30% of patients with IBD	54 (36%)
Never	22 (14%)

The results of this analysis are shown in Table 2. This analysis demonstrates that only 28% of gastroenterologists used FC testing in more than 70% of their patients with IBD to monitor disease activity.

We were also interested in the potential differences with respect to the use of FC testing in IBD patients by gastroenterologists in private practice and their colleagues working in hospitals. The results of this analysis are presented in Table 3. Gastroenterologists in hospitals used FC testing for the purposes of monitoring IBD activity more frequently than their colleagues in private practice ($P=0.035$).

We further evaluated whether the gastroenterologists with more than 10 years of practical experience differed with respect to their FC testing practices from their colleagues with up to 10 years of experience. The results of this analysis are depicted in Table 4. We identified a trend that gastroenterologists with more than 10 years of gastroenterologic practice experience treated a higher number of IBD patients per year compared to their colleagues with up to 10 years of experience ($P=0.061$). The gastroenterologists with more than 10 years of practice experience used FC testing for IBD monitoring significantly less often compared with colleagues with 10 years or less of gastroenterologic practice experience ($P<0.001$).

3.6. Fecal calprotectin test accuracy, costs, and compliance with fecal sampling

Eighty-nine percent (133/150) of gastroenterologists considered FC to be more accurate than CRP in discriminating IBD

Table 3 Comparison of the use of FC for IBD monitoring according to the professional setting (private practice vs hospital). Abbreviations: FC, fecal calprotectin; IBD, inflammatory bowel disease.

Item	Private practice, *n* (%)	Hospital, *n* (%)	P value
>40 IBD patients treated in the last 12 months	41/79 (51.9%)	33/73 (45.2%)	$P=0.409$
FC used in >20 patients in the last 12 months	44/79 (55.7%)	34/74 (45.9%)	$P=0.228$
FC used in ≥30% of patients for IBD monitoring	33/79 (41.8%)	43/73 (58.9%)	$P=0.035$

Table 4 Comparison of the use of FC testing stratified according to the years of professional experience from the time of board examination (≤10 years of experience vs >10 years). Abbreviations: FC, fecal calprotectin; IBD, inflammatory bowel disease.

Item	Experience ≤10 y	Experience >10 y	P value
>40 IBD patients treated in the past 12 months	20/53 (37.7%)	46/85 (54.1%)	P=0.061
FC used in >20 patients in the past 12 months	29/53 (54.7%)	42/86 (48.8%)	P=0.501
FC used in ≥30% of patients for IBD monitoring	36/53 (67.9%)	31/86 (36%)	P<0.001

from irritable bowel syndrome (IBS), and 78% (114/146) of gastroenterologists considered FC to be more accurate than CRP for monitoring IBD activity.

Sixty percent of gastroenterologists estimated that the use of FC could reduce their endoscopy load. Fifty-one percent of gastroenterologists considered the fee for FC testing ($70 USD) to be appropriate, whereas the other 49% considered the fee to be too high. Eighty-seven percent of gastroenterologists judged the patient's compliance with fecal sampling to be good.

4. Discussion

The results of our nationwide survey demonstrate that clinical activity is regarded as the most relevant factor for the assessment of IBD activity by the majority of gastroenterologists. Furthermore, therapeutic decisions are primarily based on the assessment of clinical activity, whereas endoscopic activity and biomarkers measuring inflammation appear to play a minor role.

Motivated by the increasing scientific evidence supporting MH as a therapeutic goal in IBD management, we aimed to assess the status of IBD monitoring strategies among Swiss gastroenterologists. Indeed, our study reveals a certain gap between the mounting scientific evidence demonstrating the benefit of MH as a therapeutic endpoint and the daily practice of IBD monitoring.

First, clinical activity indices do not strongly correlate with endoscopic severity, which is regarded as the "gold standard" for IBD activity monitoring.[14,15,25,26] We have recently demonstrated in a cohort of 140 patients with CD that the correlation of the simplified endoscopic severity index with the CDAI was weaker ($r=0.38$) than with either CRP ($r=0.53$) or FC ($r=0.75$).[25] The correlation of clinical activity indices with endoscopic severity may be weakened in part due to the presence of IBS symptoms in IBD patients.[27,28] However, Keohane et al. have recently demonstrated that FC was elevated in patients with CD and UC fulfilling the Rome II criteria, which indicates that occult inflammation may be responsible for symptom generation rather than coexistent IBS.[29,30]

Second, the monitoring of IBD in daily practice using symptom indices may not be the appropriate strategy in light of the accumulating evidence emphasizing the importance of MH as a therapeutic endpoint. The interest in MH arose from the findings of van Dullemen et al. that infliximab not only improved symptoms in patients with refractory luminal CD but also induced marked healing of ileocolonic lesions by week 5 after intravenous administration.[31] So far, several clinical trials have demonstrated that MH can be achieved by corticosteroids, azathioprine, methotrexate, infliximab, adalimumab, and certolizumab in a subset of IBD patients.[1–3,7]

Mucosal healing is developing into an increasingly important study endpoint in clinical trials, as accumulating evidence demonstrates the association of MH with improved long-term outcomes in both CD and UC. One of the most important outcomes is the reduced need for hospitalizations. Schnitzler et al. followed 214 patients with CD for a median duration of 5 years. In that study, 64.8% (83/128) of patients who achieved MH were in clinical remission until the end of the follow-up period compared with 39.5% (34/86) of patients who did not achieve MH ($P=0.0004$).[32] Furthermore, patients who achieved MH during infliximab therapy required significantly fewer hospitalizations during their follow-up (42.2%, 54/128) compared with patients who did not achieve MH (59.3%, 51/86, $P=0.001$). Another study highlighted the potential benefit of MH in reducing need for surgical intervention. Froeslie et al. observed 458 patients with IBD with clinical and endoscopic evaluation at baseline, 1 year, and 5 years after the diagnosis of IBD.[11] In patients with CD, 11% (6/53) of patients with MH at 1 year underwent surgical resection by 5 years compared with 20% (18/88) of patients without MH at 1 year ($P=0.10$).[11] In patients with UC, 2% (3/178) with MH at 1 year underwent colectomy by 5 years compared with 7% (13/176) of patients without MH at 1 year ($P=0.02$). Reaching MH as a therapeutic endpoint may also have the benefit of reducing the risk of IBD-associated colorectal cancer. A study by Gupta et al. demonstrated that prolonged histologic inflammation was a risk factor for progression to advanced neoplasia in patients with long-standing UC (hazard ratio, 3.0; 95% confidence interval, 1.4–6.3).[33]

Our study has several methods–inherent strengths and limitations. We present the first nationwide survey evaluating how IBD monitoring is performed in daily practice. We were able to demonstrate that the latest evidence supporting the advantages of MH for IBD monitoring has not yet translated into the way IBD is monitored in daily practice. Therefore, this survey can serve as a basis for the status quo of IBD monitoring. We are curious to evaluate whether additional evidence supporting the benefit of MH as a therapeutic endpoint is going to change the current IBD monitoring strategies. As more evidence for the benefit of striving for MH becomes available, we expect to see a gradual shift from IBD monitoring strategies relying mainly on clinical activity to those assessing the endoscopic activity or biomarkers reflecting gastrointestinal inflammation.

One of the possible limitations of our study may lie in the method-inherent selection bias. It is possible that gastroenterologists who frequently monitor IBD patients were more likely to participate in our survey. However, considering the 57% response rate, we believe this study accurately reflects current IBD monitoring practices among Swiss gastroenterologists.

In summary, this survey demonstrates that clinical activity is perceived as the dominant factor for both IBD activity assessment and for serving as the basis for therapeutic decisions. Endoscopic activity and biomarkers reflecting gastrointestinal inflammation play a more minor role. This practice neither reflects the existing knowledge that there is only a moderate correlation between clinical symptoms and endoscopic severity, nor the scientific evidence supporting MH as a therapeutic goal. Therefore, it appears that mounting evidence on the benefit of MH does not yet influence IBD monitoring habits in daily practice. A future survey is planned to evaluate whether IBD monitoring strategies among gastroenterologists will change as additional evidence lending support to the benefits of MH becomes available.

Conflict of interest

Acknowledgments

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