

Therapeutic Decisions Often Cannot be Maintained for One Year in Crohn's Disease Patients

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Abstract

Objective: In Crohn's disease (CD) major therapeutic decisions are triggered by failure of medical therapy or by a flare and are based on various diagnostic modalities, the prior clinical course and the patient's perception. We analyzed, whether under real world conditions a therapeutic decision can be maintained over 12 months or needs to be adjusted in this time.

Methods: In 50 patients diffusion-weighted magnetic resonance imaging (DW MRI) studies were used as an indicator for the need to make a therapeutic decision. Decisions were based on the prior clinical course, endoscopy, ultrasound, DW MRI and the patient's perception of the situation and were categorized as surgery (A), no change (B) or intensification of medical therapy (C). The clinical course was analyzed using CDAI and CRP at 3, 6 and 12 months follow up.

Results: 33 of 50 patients had a failure of medical therapy and 17 of 50 had a flare in absence of medical therapy. The median disease duration was 8 years. Group A: In 13 patients surgery for fibro-stenosis or a penetrating complication induced remission lasting for 12 months. Group B: In 17 cases medical therapy initially was kept unchanged. As a group they had a wide range of CDAI values. During 1 year 3 of 17 went on to intensified medication, and 5 of 17 were operated, eventually leading to clinical response or remission. Group C: 20 patients changed to intensified medication, 3 of these 20 were later operated. In group C CDAI improvement lasted longer in those with a disease duration \leq 5 years.

Conclusion: In CD therapeutic decisions often cannot be maintained but need to be adjusted even during 1 year. The likelihood to err is highest if the initial decision is to leave the existing medical therapy unchanged.

Keywords: Crohn's disease; Surgery; Medical therapy; Decision making; DW MRI (diffusion weighted magnetic resonance imaging); CDAI

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) occurring in phases of flares and remission. It is a progressive disease causing cumulative structural damage to the intestine as well as increasing disability with a significant impact on quality of life [1,2]. Within the first 5 years after diagnosis up to one third of CD patients require major abdominal surgery despite of new medical therapeutic options with biological [3], and the cumulative risk of major surgery is about 58% at 20 years after diagnosis [4]. Because of recurrent stenosis many patients need more than one resection with the risk of developing short bowel syndrome [5].

Major therapeutic decisions are mostly triggered by flares or by secondary failure of medical therapy. These decisions are based on the clinical presentation, the prior course of the disease including previous surgery as well as risk factors and on several diagnostic modalities including biomarkers, ultrasound, endoscopy and magnetic resonance imaging (MRI) [6-8]. Importantly, outside an interventional study the patient's perception of the situation and his or her preferences need to be included in any therapeutic decision.

For measuring clinical activity symptom-based scoring systems such as the Crohn's disease Activity Index (CDAI) and the simpler Harvey Bradshaw Index (HBI) have been developed [9,10] and are commonly used. These scores suffer from subjective interpretation, and they do not always correlate with endoscopic lesions. Especially after therapeutic interventions or in the presence of a more advanced medication such as biologicals there may be a higher discrepancy [11,12]. Levels of C-reactive protein (CRP), fecal calprotectin and lactoferrin as biomarkers can be used in addition and correlate with CD partially [13].

Endoscopy is an important diagnostic tool for evaluating luminal mucosal disease activity. However, examination cannot easily be performed proximal to the terminal ileum or distal the ligament of Treitz. For endoscopy several scoring systems are being used in clinical practice to measure disease activity, such as the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simplified Endoscopic Score for Crohn's disease (SES-CD) and the postoperative Rutgeerts Score [14-16].

In addition cross-sectional imaging techniques are the method of choice to evaluate extramural complications and may also be used to characterize intestinal activity [17]. As such the Limberg score is a practicable measurement for routine ultrasound [18].

In CD MRI has a high sensitivity to measure disease activity and to detect complications. The technique has become more widely available and avoids radiation [19,20]. Diffusion weighted MRI (DW MRI) is a recent improvement of the technique [21]. It provides information regarding vascular leakage and water diffusion by measuring changes in water mobility. It has been proposed to have a better discrimination between inflammation and fibrosis in CD [22,23]. There are several complex scores such as Magnetic Resonance Index of Activity (MaRIA) and the Crohn's Disease MRI Index (CDMI) addressing different image features, but at the time of our study none of them had gained wide acceptance. Furthermore, the feature of diffusion weighting is not incorporated in these scores [24]. Until now, data are limited for evaluating DW MRI in a clinical scenario of failure of medical therapy [25].

In the current clinical study we retrospectively analyze whether major therapeutic decisions that were made during the clinical course of CD patients and that were based on clinical disease activity measurements (CDAI and HBI), CRP, ultrasound, endoscopy and DW MRI could be maintained over one year or had to be readjusted.

Patients and Methods

DW MRI studies were used as indicators for the potential need to initiate or change therapy for Crohn's disease in individual patients. Thus, all CD patients who had undergone DW MRI at the University Medical Center Rostock between April 2012 and June 2015 were selected for retrospective chart review. 50 DW MRI studies were identified. The study was approved by the institutional research board.

All DW MRI studies were read by a single radiologist (Y. L.), who was aware of the clinical course of the individual patients. The DW MRI was rated as normal, inflammatory, stenotic or inflammatory and stenotic. In relation to the index DW MRI study, the closest endoscopy and ultrasound studies as well as the CDAI and the CRP values were obtained. Endoscopy and ultrasound were rated as normal, inflammatory stenotic or inflammatory and stenotic. In addition, gender, age at MRI, body mass index (BMI), smoking behaviour, disease duration, previous resections, reason for operations, previous medication, and indication for the MRI were recorded.

A clinical decision was made based on the objective data described, the clinical impression of the treating physician and as shared decision with the patient. For purpose of the study this decision was categorized as surgery (Group A), no change (Group B) or intensification of medical therapy (Group C). At the time of the study a strict treat-totarget concept was not applied. CDAI and CRP were used to score disease activity during follow up at 3, 6 and 12 months. Adjustments to the initial decision were made based on the clinical course. If patients had signs of worsening disease activity (indicated by a rise in CDAI) or showed no improvement despite intensified medical therapy the initial decision was revised and changed to either intensification of medical therapy or to surgery.

Remission was defined as a CDAI below 150 [26] and clinical response was defined as a decrease of the CDAI \geq 70 points [27-29]. Normal CRP levels were defined as less than 5 mg/l. Note that CRP values are displayed in the figures on a logarithmic scale.

Statistical analysis

Data were recorded in Access 2010. Statistical analysis was performed with SPSS Statistics version 22. Chi^2 , Friedman and Wilcoxon tests were used for statistical analysis. A p value of ≤ 0.05 was considered statistically significant (Table 1).

Results

50 CD patients underwent DW MRI between April 2012 and June 2015. The DW MRI findings, other imaging studies (endoscopy and ultrasound), and the laboratory values were discussed in an interdisciplinary conference (gastroenterology, surgery, diagnostic radiology), and a therapeutic decision was made and discussed with the patient. The demographic data are summarized in table 1 according to the final therapeutic intervention.

Classification of patients	Group A: Surgery	Group B: No change	Group C: Intensification of MT
Number	13	17	20
Female	12 (92%)	6 (35%)	15 (75%)
Age at MRI (years)	44 (25-72)	46 (24-63)	37 (20-69)
BMI (kg/m²)	25 (16-43)	26 (17-41)	25 (14-33)
Smoker	8 (62%)	8 (47%)	7 (35%)
Disease duration (years)	8 (0-18)	13 (4-33)	9 (0-24)
Previous resections	4 (31%)	11 (65%)	8 (40%)
Surgery because of penetrating complication	4 (31%)	-	-
Indication for initial MRI			
Failure of MT	8	13	11
Acute flare without MT	5	4	9

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Previous medical therapy			
No MT	5 (39%)	3 (18%)	10 (50%)
Budesonid / 5-ASA	2 (15%)	3 (18%)	4 (20%)
Aza / MTX	0	5 (29%)	3 (15%)
Biological	5 (39%)	5 (29%)	3 (15%)
Biological + Aza / MTX	1 (8%)	1 (6%)	0
MRI rating			
Normal	0	5 (29%)	5 (25%)
Inflammatory	11 (84%)	12 (71%)	12 (60%)
Stenotic	1 (8%)	0	2 (10%)
Inflammatory + stenotic	1 (8%)	0	1 (5%)

Table 1: Patients characteristics (n=50).

Out of 50 CD patients 33 patients were female (66%); their mean age was 42 years (range 20-72), and their mean disease duration was 10 years (range 0-30). Patients underwent DW MRI because of failure of medical therapy (33/50; 66%), or because of an acute episode of CD (including initial clinical manifestation) in the absence of medical therapy (17/50; 34%).

The number of patients at the different time points along the follow up decreases in some cases because the initial decision was changed or because CRP values were not available for all time points.

Surgery

In 13 patients with a mean disease duration of 8 years (range 0-18) surgery was performed with an intestinal resection (Group A, Figure

1), 4/13 (31%) of them had undergone surgery before. 4/13 (31%) underwent an intestinal resection because of an acute complication. 6 (46%) received additional postoperative medical therapy. In the entire group the mean CDAI decreased significantly from 346 to 106, 126, 133 after 3, 6 and 12 months ($p \le 0.01$).

Initially all patients had a CDAI above 150. After 3 months 10 patients (77%) were in remission, the remaining 3 (23%) had a response. After 6 months CDAI indicated remission in 9 of 11 patients (82%), 18% had an increase of their CDAI above the response value. After 12 months 8 of 10 (80%) were in remission.

Mean CRP levels decreased from 112 to 9, 10 and 5 mg/l; after 3, 6 and 12 months; after 3 and 6 months this reduction was statistically significant ($p \le 0.05$) (Figure 1)



Figure 1: Group A patients with the initial decision to operate; Surgery resulted in remission and a strong decrease in the CRP values in the majority of patients in whom the initial decision was to operate (n=13).

4 of 13 patients (31%) in Group A had to be operated because of a penetrating complication. These patients went into remission and

remained in remission for the entire follow up. The remaining 9 patients (69%) were operated for a stenosis. At the initial follow up

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they also were in remission but during the ensuing months their CDAI increased again and they developed mild active disease based on mean CDAI values of 153 after 6 months and 163 after 12 months. Nevertheless these patients still had a response based on a decrease in CDAI compared to base line of more than 70 points (Figure 2).

keep medical therapy unchanged was modified in the remaining 8 patients: 5 of 17 (29%) underwent surgery, 2 because of a complication, and 3 because of a stenosis. 3 of 17 (18%) had their medical therapy intensified, two of them to biologicals, one to Azathioprine (Figure 4).





Prophylactic postoperative medical therapy to prevent early relapse is indicated in high risk patients, but the details of risk stratification and of how to initiate and adjust such therapy were under debate at the time of our study [30-33]. Thus, we did not follow a formal clinical pathway including scheduled endoscopy but initiated postoperative medical therapy with a TNF α antagonist or Azathioprine based on the preoperative clinical course and on the risk factors penetrating complication and repeated surgery. Figure 3 show that during 12 months follow up both subgroups went into remission after intestinal resection (Figure 3).



Figure 3: Clinical course after resective surgery depending on additional medical therapy; CDAI and CRP levels of 13 Group A patients decreased with and without medical therapy after surgery at all-time points during follow up.

No change in medical therapy

Group B included 17 patients with the decision to keep medical therapy unchanged. Their mean disease duration was 13 years (range 4-33). 11 patients in this group (64%) had been operated in the past, 5 (29%) received Azathioprine or Methotrexate and 6 (35%) TNF α blockade or dual immune-suppression. Only 9 of 17 patients (53%) remained on their unchanged medical therapy. 4 of these patients received Methotrexate or Azathioprine, 3 TNF α blockade and 1 Azathioprine plus TNF α blockade, 1 patient did not receive any MC medication. During the follow up of 12 months the initial decision to



Figure 4: Clinical course of patients with the initial decision to keep medical therapy unchanged (Group B); In the entire group of 17 Group B patients with the initial decision to keep their medical therapy unchanged the average CDAI and CRP levels remained constant.

In the entire group the average CDAI and the CRP levels remained constant (Figure 4). CDAI and CRP values had a wide distribution including the normal range in this group of patients (7/17 patients, 41%, had a CDAI below 150), both initially when the decision was made not to change medical therapy, and during follow up (Figure 4).

For further analysis we divided the group into those patients, in whom the initial decision was changed to surgery (n=5) or intensified medical therapy (n=3) and in those in whom the decision not to change medical therapy could be maintained over 12 months follow up (n=9), and compared the course of their CDAI and their CRP over time (Figure 5). 5 patients underwent surgery 3 months after the initial decision. Their CDAI was low initially but high at the time of surgery, but they had elevated CRP levels both initially and at the time of surgery. Surgery resulted in a drop of the CDAI (CDAI<150 in 3 of 5 patients, 60%) and the CRP to near normal values.

Medical therapy was intensified in 3 patients after 6 months. Of note these patients initially had high CDAI values, only one of them had a CDAI indicating remission. Intensification of their medical therapy was associated with a drop in the CDAI only at 12 months (remission in 2 patients, response in none more).

In those patients whose medication was maintained unchanged the mean CDAI and CRP remained stable (Figure 5).

Intensification of medical therapy

In 20 patients the decision was made to intensify their existing medical therapy (Group C). The mean disease duration in this group was 9 years (range 0-24). 8 patients (40%) had been operated in the past, 3 (15%) received Azathioprine and 3 (15%) TNFa blockade. Intensification of medical therapy included initiation of specific medical therapy in patients without prior CD medication (10 patients; 50%; 1 to 5-ASA, 1 to Azathioprine, 5 to biologicals, 3 to a combination of an immunosuppressant with TNFa antagonist) or escalation from Budesonide or 5-ASA to Azathioprine (n=2), to a biological (n=1), to a combination of an immunosuppressant with TNFa antagonist (n=1) or from Azathioprine or Methotrexate to a TNFa antagonist (n=2) or a switch from one to another TNFa antagonist

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(n=3). In addition 2 of 8 patients without prior surgery and 1 patient with prior surgery were operated during the follow up of 12 months, 2 because of a symptomatic stenosis and 1 because of a penetrating complication. In those 3 (15%) the initial decision to intensify medical therapy had to be revised because it did not lead to a sufficient improvement. In none of the patients of Group C intensified medical therapy was de-escalated.



Figure 5: Clinical course of Group B patients according whether initial decision not to change therapy could be maintained; Note that Group B patients (n=17) who required intensification of medical therapy during follow up had high CDAI but low CRP values and that patients who required surgery during follow up had moderately elevated CRP values initially.

In those 17 patients (85%) who received intensified medication but who did not undergo surgery the CDAI decreased significantly ($p \le 0.05$) at 3 and 6 months follow up to remission in average. Initially in 18 of 20 (90%) CDAI indicated active disease (CDAI \ge 150); after 3 months 8 of 20 (40%) had active disease, 10 of 20 (50%) had a CDAI indicating remission, 2 of 20 (10%) had a CDAI indicating response; after 6 months 9 of 17 (52%) were in remission, 5 of 17 (29%) had a response; and after 12 months still 7 of 16 (44%) were in remission, and 2 of 16 (13%) had clinical response with escalated medication. CRP level decreased at 3 and 6 months follow up without reaching normal values but at 12 months the CRP level numerically rose again. The increase in the CDAI and the CRP at 12 months follow up suggests that the effect of intensified medical therapy was not sustained at least in some of the patients in Group C (Figure 6).





Recurrent or ongoing sub-clinical inflammation may over time lead to structural damage to the intestine that is not amendable to medical therapy [31,32]. To this end, we compared the clinical response of group C patients with disease duration of less or more than 5 years (Figure 7). CDAI values after 12 months were significantly lower in patients with disease duration of less than 5 years compared with patients with longer disease duration. After 12 months 5 of 7 (71%) patients with disease duration of 5 or less years had a CDAI below 150, indicating remission, in 1 of 7 (14%) CDAI indicated a response. In contrast in the patients with a disease duration longer than 5 years only 2 of 9 (22%) were in remission and in 1 of 9 (11%) CDAI indicated a response (Figure 7).



Figure 7: Clinical course of patients with intensified medical therapy (Group C) according to their disease duration; CDAI levels decreased and remained low in patients with disease duration of less than 5 years, while CDAI initially decreased but increased at 12 months in patients with disease duration of more than 5 years.

Discussion

The current study addresses whether clinically triggered therapeutic decisions in the scenario of a flare, a complication or secondary failure of medical therapy can be maintained for 12 months i.e. prove to be correct or need to be modified. Because cross-sectional imaging techniques are recommended for complete staging, we used DW MRI studies as an indicator for a situation when a major therapeutic decision was searched along the disease course of Crohn's patients [17]. Cases were recruited from our tertiary care IBD clinic, and the MRI study was triggered by clinical symptoms in all cases. This explains why some patients had a CDAI within the range considered to indicate remission. About half the patients had been operated before, a situation, when the CDAI loses sensitivity. In addition, the cohort had a wide range of pre-existing medical therapies of various intensity and duration [34]. Thus, this study represents a real-world single center cohort of significantly impaired CD patients.

Decisions were based on the interdisciplinary interpretation of the clinical course, the current imaging studies (diffusion-weighted MRI, endoscopy, and ultrasound) and biochemical markers (CRP) by a team of gastroenterologists, surgeons, and radiologists, all of whom were aware of the patient's clinical course and of the available set of diagnostic data. The suggested therapeutic approach was finalized in a process of shared decision-making with the patient.

The CDAI was used to measure disease activity. Because the CDAI has decreased sensitivity and specificity with longer disease duration and after surgery, we also analysed CRP values [35]. Decisions were categorized as surgery (Group A), as keeping the current medical therapy unchanged, because there was no discernible manifestation of disease (Group B), or as to intensify medical therapy base on a discernible disease manifestation (Group C).

In the presence of a penetrating complication surgery was straight forward and proved to induce remission that lasted over the entire follow up. This was also in the case, when surgery was performed for fibro-stenotic lesion. These data confirm the previously described good outcomes after intestinal resection [36,37]. Interestingly, surgery was also highly effective measured both by CDAI and by CRP in 5 of 17 patients (29%) in whom the initial decision was to keep medical therapy unchanged, but in whom this decision could not be maintained, and in 3 of 20 patients (15%) in whom the initial decision was to escalate medical therapy, but who had to be operated because of an insufficient response.

There was no difference in the course of the CDAI or the CRP whether patients received postoperative medical therapy or not. This is most likely due to the small number of patients and to the short observation period, similar to the observation in the PREVENT trial [38].

Patients, in whom the initial decision was to keep their medical therapy unchanged (Group B), were notable for their wide range of CDAI and CRP values at base line. 41% (7 patients) even appeared to be in remission based on their CDAI. In only 9 of 17 patients (53%) medical therapy could indeed be kept unchanged. This subgroup initially had near normal CDAI scores and CRP values, which remained stable during follow up, indicating that the initial decision was correct. In contrast, 5 of 17 patients (29%) went on to surgery. This subgroup also initially had near normal CDAI values, even suggesting remission in 40%, but had moderately elevated CRP values. Surgery resulted in remission in 60% and also in reduced CRP values. In 3 of 17 patients (18%) their preexisting medical therapy was intensified. Interestingly they initially had high CDAI scores but normal CRP values. CRP values remained low and the CDAI got better at the 12 months follow up after intensification in 2 of 3 patients. Thus, these patients apparently have been highly symptomatic, had not discernible manifestation of their disease, and had no systemic biomarkers of inflammation. Somewhat unexpectedly two of these three patients profited from intensification of medical therapy and even went into remission by CDAI.

Taken together the decision to keep medical therapy unchanged in the clinical scenario, when a decision is warranted, must be made very careful, because it cannot be maintained in about 50% of patients. This decision may most likely err in patients with a low CDAI but may be guided by CRP, with elevated CRP values suggesting the need of surgery.

Intensification of medical therapy-including initiation of any Crohn's specific medication-proved to result in a significant reduction of the CDAI and the CRP, also reflected in clinical remission and response. After 6 months CDAI indicated remission or response in 82% of these patients, and after 12 months this outcome was still achieved in 56%. Patients in this group tended to have a less intense preexisting medical therapy and a shorter disease duration than those in Group B, but this was not significant. Naturally it is easier to intensify therapy from a low than from a high level. Furthermore, structural damage to the intestine, that is not or merely amendable to medical therapy is more likely with longer disease duration. This is reflected by the lower effectiveness of TNFa blockers in long standing disease [39,40]. Consistent with that there was a trend for shorter effect of intensified medical therapy eventually requiring surgery in patients with a disease duration for longer than 5 years.

In summary our data show that under real world conditions there is a relevant chance that a therapeutic decision may not be sustainable over the course of the following 12 months even if this decision is based on multiple diagnostic modalities and is made by an interdisciplinary team including a shared decision process with the patient. The likelihood to err appears to be highest if the initial decision is to leave the existing medical therapy unchanged because there appears to be no discernible disease manifestation and despite the presence of an elevated CRP level.

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