CHAPTER 2

FECAL CALPROTECTIN FOR MONITORING RESPONSE TO INDUCTION THERAPY IN PATIENTS WITH ACTIVE INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Fecal calprotectin (FC) is currently the most frequently used biomarker for intestinal inflammation. Whether repeated testing of FC is useful to assess the effect of induction therapy in patients with active inflammatory bowel disease has not been evaluated systematically. We aimed to determine if bringing FC levels back to a predefined target range corresponds with achieving endoscopic remission.

Methods: Medline and Embase were searched from inception to August 2018. We included studies with FC measurements and endoscopy performed before and after induction therapy. Methodological assessment was based on the Quality Assessment of Diagnostic Accuracy Studies checklist. For each study, the positive and negative likelihood ratio of FC were analyzed.

Results: A total of 1516 papers were screened; 332 were retrieved for full text review. Four studies met our strict eligibility criteria for inclusion. A post-induction FC in the target range is 50 (16 to 160) times as likely to be seen in patients with endoscopic remission, as opposed to patients who failed to reach remission.

Limitation: The authors of four potentially relevant papers were contacted but could not release the requested data.

Conclusions: A FC shift into the target range during induction therapy suggests treatment success. A cutpoint of 250 µg/g is the most frequently reported upper threshold of the target range, but a prospective controlled trial in a clinical setting is necessary to confirm whether this is the most appropriate cutpoint in terms of patient outcome and resource use.

INTRODUCTION

Active inflammatory bowel disease (IBD) damages the mucosa of the gastrointestinal tract and causes irreversible bowel damage if disease remission is not restored in a timely fashion.[1] The reference standard to determine therapeutic success in both Crohn's disease and ulcerative colitis is the resolution of ulceration at (ileo)colonoscopy, a state also known as mucosal healing (MH).[2] There is no evidence-based consensus of when best to reassess disease activity after a change in therapy,[3] but frequent endoscopic reevaluation is impractical and patient acceptance for repeated procedures may be low. There is a growing need to replace invasive diagnostics by surrogate non-invasive markers. Calprotectin is a protein released by activated or damaged neutrophils and concentrations measured in stool correlate well with neutrophil migration to the gastrointestinal tract.[4,5] Other neutrophil-derived proteins include elastase, lysozyme, and lactoferrin [6,7], but fecal calprotectin (FC) is currently the most frequently used marker of gastrointestinal inflammation. Several studies have shown that fecal calprotectin (FC) correlates well with colonic inflammation.[8-10] Initial studies suggested that FC may be less sensitive in isolated small bowel disease, but a well-conducted meta-analysis demonstrated that the diagnostic yield of FC is also significant for detection of active disease in the small bowel. [11] Single measurements of FC have been shown to be useful in the initial diagnosis of IBD [12] and repeated measurements of FC facilitate early recognition of disease flares in asymptomatic patients.[13] Whether repeated testing of FC is also useful to monitor the effect of induction therapy has not been evaluated in a systematic review. Since calprotectin is a neutrophil-derived protein, it may not help to determine if the bowel is in the repair phase. The ultimate aim of induction therapy is to achieve MH, or to bring FC levels back to a predefined target range that corresponds with MH.

In the current systematic review we aim to determine if bringing FC levels back to a predefined target range really corresponds with healing of the intestinal mucosa and treatment success.

METHODS

Eligibility criteria

Eligible studies were randomized controlled trials (RCTs), cohort studies and case-control studies, that followed at least 10 patients with active IBD, started with induction therapy and had at least two consecutive FC measurements, including one at the start of induction therapy. We accepted FC test intervals up to 6 months. Studies that did not report the use of a FC target range or cut-point (either predefined or based on Receiver Operating Characteristic curves) were excluded from analysis. We only accepted endoscopy (with or without histopathological confirmation) as reference test. Success of induction therapy was defined as endoscopic remission after induction therapy.

Information sources, identification and selection of studies

We searched for studies published in Medline and Embase. The search strategy for Medline was ((“Inflammatory Bowel Diseases”[Mesh] OR inflammatory bowel disease*[tiab] OR IBD [tiab] OR ibd-u [tiab] OR Crohn*[tiab] OR Colitis [tiab]) AND (“Leukocyte L1 Antigen Complex”[Mesh] OR calprotectin [tiab] OR calgranulin [tiab]) AND (monitor*[tiab] OR repeat*[tiab] OR follow-up [tiab] OR follow up [tiab] OR period*[tiab])). For Embase we used ((‘inflammatory bowel disease’/exp OR ‘inflammatory bowel disease*’:ab,ti OR ibd:ab,ti OR ‘ibd-u’:ab,ti OR crohn*:ab,ti OR colitis:ab,ti) AND (‘calgranulin’/exp OR calgranulin:ab,ti OR calprotectin:ab,ti) AND (monitor*:ab,ti OR repeat*:ab,ti OR ‘follow-up’:ab,ti OR ‘follow up’:ab,ti OR period*:ab,ti)).
Available studies were screened using Covidence©, an online screening tool for systematic reviews (www.covidence.org). We restricted our search to studies published in English. Duplicate articles were deleted by Covidence and also manually checked and deleted using RefWorks. For further relevant studies, we checked the reference lists of identified papers. The first selection of studies was carried out by one reviewer (SMH) on the basis of title and abstract. The full paper of each potentially eligible study was then obtained. Two authors (SMH and PvR) independently assessed full manuscripts against the predefined inclusion criteria. Disagreements were resolved by discussion, and consensus was reached with the third author (AH).

Data extraction

The following characteristics were extracted from each selected study: first author, year of publication, country of origin, sample size, age group, type of induction therapy, type of IBD, proportion

of patients that achieved remission after induction therapy, index test with testing interval, and reference standard with testing interval. FC test characteristics per study included the used FC assay and upper limit of the FC target range with the number of true positives, true negatives, false positives, false negatives. Authors were contacted in cases where information was missing to construct a two by two table.

Data analysis
We calculated positive likelihood ratio (LR+, i.e. FC in the target range) and negative likelihood ratio (LR-, i.e. FC out of target range) for each study and presented the data as forest plots, with 95% confidence intervals, and squares with area proportional to study weight. We used LRs instead of sensitivity and specificity because LR is less affected by the pretest probability. We calculated the mean likelihood ratio of LR+ and LR-. Computations were carried out with OpenMetaAnalyst.[14]

Assessment of risk of bias
The QUADAS-2 (QUality Assessment of studies of Diagnostic Accuracy included in Systematic reviews) checklist was used to assess study quality.

RESULTS

Study selection
This review includes results of electronic searches up to 1 August 2018. A total of 1516 papers were screened, of which 332 were retrieved for full text review. Of these, 324 were excluded for not meeting the eligibility criteria. The reasons for exclusion are summarized in the flow diagram (Figure 1). The authors of four probably relevant papers [15-18] were contacted by email for additional information to construct two by two tables, but they could not release the requested data. Four papers were ultimately included in the final analysis.

Study characteristics
The most important study characteristics of the 8 potentially suitable studies are presented in Table 1. Four of these were eventually included in the analysis. All included studies were prospective cohort studies.[19-22] Sample size varied between 15 and 44 patients and all studies included adult participants only.

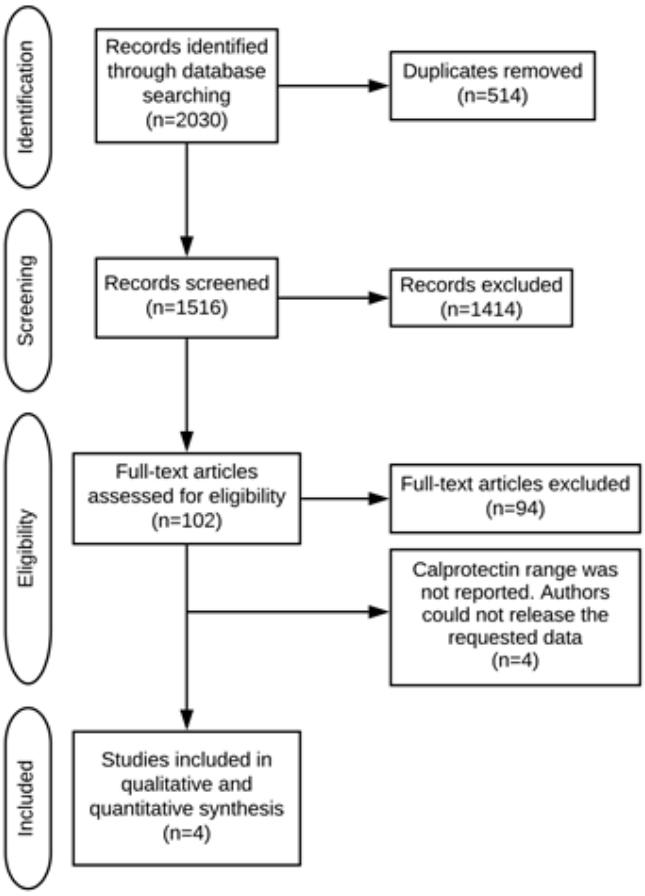

Figure 1. Flow diagram systematic literature search.

In one study patients with CD were followed from the moment of initiating anti-TNF induction therapy.[22] In two other studies patients with UC were followed, from the moment of initiating anti-TNF induction therapy in one ,[19] and from the moment of any kind of induction therapy in the other.[20] In the fourth study a mixture of patients with CD and UC were followed from the introduction of any kind of induction therapy onwards.[21] In all four studies the response to treatment was verified by endoscopy. In two studies endoscopic remission was defined as a Mayo endoscopic subscore of µ1.[19,20] In one study a Crohn's Disease Index of Severity (CDEIS) score < 3 was used[22] and in the fourth study a semi-quantitative four-grade scale was used (normal, mild, moderate and severe), with endoscopic remission defined as return of the endoscopic score to normal [21]. The time interval between the consecutive FC measurements varied from 2 to 12 weeks.

Table 1. Overview of the 4 included and 4 probably relevant studies. The authors of the latter group could not release the requested data.

	N of patients	Age group (range in years)	Study aim	Type of IBD	Proportion of patients that achieved remission after induction treatment	Duration of FC follow-up (in weeks)
Included studies:						
Hassan, 2017 Kuwait	44	A	Monitoring response to treatment with anti-TNF treatment	UC	55% (24/44) clinicial remission and 66% (29/44) mucosal healing	12
Kristensen, 2017	20	A	Monitoring response to treatment with any kind of remission induction therapy	UC	80% (16/20, clinical, biological and endoscopic remission)	16
Sipponen 2008 Finland	15	A (19-44)	Monitoring response to anti-TNF treatment	CD	30% (5/15, clinical and endoscopic response)	12
Wagner, 2008 Sweden	38	A (21-70)	Monitoring response to treatment with any kind of remission induction therapy	UC (27) CD (11)	78% (21/27, UC) and 91% (10/11, CD) complete clinical and endoscopic response	8

Frequency of diagnostic testing (scoring method)			
Fecal calprotectin	**Endoscopy**	**Clinical Activity score**	**CRP and/or BSE**
At baseline and after week 12.	At baseline and at week 12 by colonoscopy with Mayo endoscopic subscore.	At baseline and after week 12 by Clincal Mayo score.	At baseline and after week 12.
3 days after the baseline colonoscopy and then monthly during follow-up .	At inclusion by colonoscopy with Mayo endoscopic subscore and after two consecutive FC measurements <250 µg/g, or one year of follow-up without achieving two consecutive FC measurements <250 µg/g by flexible sigmoidoscopy.	At the time of the first and second endoscopy by Simple Clinical Colitis Activity Index (SCCAI).	At the time of the first and second endoscopy.
At first colonoscopy, and 2, 8 and 12 weeks after the first anti-TNF treatment	At study entry and at week 12 (week 10 for adalimumab patients) by (ileo)colonoscopy with CDEIS.	At first colonoscopy, and 2, 8 and 12 weeks after the first anti-TNFa treatment by CDAI.	At first colonoscopy, and 2, 8 and 12 weeks after the first anti-TNFa treatment.
At inclusion, 4 and 8 weeks.	At inclusion, 4 and 8 weeks by a semi-quantitative four-grade (normal, mild, moderate and severe) scale.	At inclusion, 4 and 8 weeks by HBI.	

Table 1 continues on next page

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	N of patients	Age group (range in years)	Study aim	Type of IBD	Proportion of patients that achieved remission after induction treatment	Duration of FC follow-up (in weeks)
Probably relevant studies, but too little information for inclusion:						
Battat, 2017 Canada	27	A	Monitoring response to treatment with ustekinumab	CD	50% (steroid free clinical remission)	-
Colombel 2018 Multiple countries	244	A	Monitoring response to treatment with adalimumab	CD	46% (based on deep remission)	48
D'Haens, 2018 Multiple countries	122	A	Monitoring response to anti-TNF combination therapy	CD	33% (15/45)	54
Frin, 2017 Italy	31	A	Monitoring response to anti-TNF treatment	UC	61% (19/31)	52

Abbreviations: A = adults; CD = Crohn's Disease; HBI = Harvey Bradshaw Index; N = nu
Endoscopic Score for Crohn Disease, CDAI = Crohn's Disease Activity Index; PGA = Ph

Fecal calprotectin	Endoscopy	Clinical Activity score	CRP and/or BSE
Baseline, week 10 and week 26	Prior to treatment and after week 26 by endoscopy with SES-CD	Baseline, week 10 and week 26 by HBI or PGA	Baseline, week 10 and week 26
At week -1, 11, 23 and 35	At 48 weeks after randomization or early termination by ileocolonoscopies with CDEIS.	Every 12 weeks and at unscheduled visits by CDAI	At week -1, 11, 23 and 35.
At baseline and at weeks 2, 4, 6, 12, and 14 of treatment, and then every 4 weeks thereafter until week 54.	At week 0, 12 and 54 by ileocolonoscopies with CDEIS	At weeks 2, 4, 6, 12, and 14 of treatment, and then every 4 weeks thereafter until week 54 by CDAI	At baseline, week 2, 4, 6, 12, and 14 of treatment, and then every 4 weeks thereafter until week 54.
At baseline and at week 2 and 14 of treatment	Before and after induction treatment by rectosigmoidoscopy (if recent colonoscopy was available) or complete colonoscopy with Mayo subscore.	A clinical examination was performed in patients on the day of each anti-TNF infusion.	

umber of participants; CDEIS= Crohn's Disease Index of Severity, SES-CD= Simple
ysicians Global Assessment; UC = ulcerative colitis.

Methodological quality of included studies

The methodological quality of the included studies was assessed using the QUADAS-II checklist and the results are summarized in the risk of bias table (Table 2). All studies used a prospective study design and enrolled consecutive patients with both newly diagnosed or relapsing inflammatory bowel disease. All studies used a commercially available FC assay, and tested FC at baseline and periodically thereafter. In three studies it was unclear whether the endoscopists were blinded for the corresponding calprotectin test results.[20-22] Blinding of the laboratory personnel for the endoscopic or clinical activity outcomes was reported in only one study, but we considered the FC concentration to be a hard outcome measure which is less likely to be affected by prior clinical knowledge. Differences between studies related to FC assay type and predefined FC target range.

Prognostic value

All studies concluded that periodically measuring FC concentrations during induction treatment is a useful method to evaluate whether or not the therapeutic intervention is effective. Details of the FC test characteristics are presented in Table 3. The used FC target ranges varied from 58 to 250 µg/g. Figure 2 presents the forest plots of the positive likelihood ratios and negative likelihood ratios for the 4 studies. Reaching the FC target range during induction treatment corresponded well with endoscopic remission with a positive summary LR of 9 (95% CI

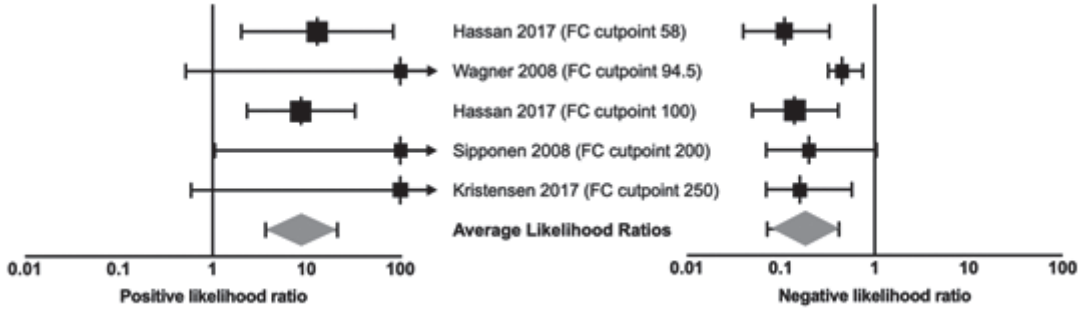

Figure 2. Likelihood ratio (LR) forest plot of the fecal calprotectin test for distinguishing treatment success from treatment failure. The left pane shows the positive LR of included studies (or the prognostic probability that a FC result in the target range corresponds with treatment success), the right pane shows the negative LR (or the prognostic probability that a FC result out of the target range corresponds with treatment success). Error bars represent 95% confidence intervals. Square size is proportional to study weight in meta-analysis. The grey diamonds represent the summary LRs.

4 – 21) and a post-test probability of remission of 90% (88 to 92%). The likelihood of endoscopic remission when post-induction FC values are out of the target range is low with a negative summary LR of 0.17 (95% CI 0.07 – 0.42) and a post-test probability of 15% [13-17]. In other words, a post-induction FC in the target range is 50 (16 to 160) times as likely to be seen in treatment success as opposed to treatment failure.

Table 2. QUADAS-II checklist (n=4)

Study	**Risk of bias**			
	Patient selection	Index test	Reference standard	Flow and timing
■ Hassan 2017	😊	😊	😊	😊
■ Kristensen 2017	😊	😊	?	😊
■ Sipponen 2008	😊	😊	?	😊
■ Wagner 2008	😊	😊	?	😊

	Applicability concerns		
	Patient selection	Index test	Reference standard
■ Hassan 2017	😊	😊	😊
■ Kristensen 2017	😊	😊	😊
■ Sipponen 2008	😊	😊	😊
■ Wagner 2008	😊	😊	😊

😊= low risk of bias; ☹ = high risk of bias; ? = unclear risk of bias

Table 3. Details of fecal calprotectin test results per included study.

			n		
			Remission & FC in target range (TP)	**Active disease & out of target range (TN)**	**Active disease & in target range (FP)**
Study	**FC assay**	**UL target range (µg/g)**	**Concordance**	**Concordance**	**Discordance**
Hassan, 2017	Buhlmann (ELISA)	100 (Clincal remission)	21	18	2
		58 (MH) (by ROC-curve	26	14	1
Kristensen, 2017	Buhlmann (ELISA)	250	16	1	0
Sipponen 2008	PhiCal	200	4	10	0
Wagner, 2008	Calprest (ELISA)	94.5	17	6	0

Abbreviations: FC: fecal calprotectin; CI: confidence interval; UL: upper limit; TP: true positives; TN: true negatives; FP: false positives; FN: false negatives; LR: likelihood ratio

	Post-induction treatment			
Remission & FC out of target range (FN)				
Discordance	**LR (FC in target range) (95%CI)**	**LR (FC out of target range) (95%CI)**	**Post-test probability remission (FC in target range)**	**Post-test probability active disease (FC out of target range)**
3	8.75 (2.33-33)	0.14 (0.05-0.41)	91%	14%
3	13 (2.02-84)	0.11 (0.04-0.33)	96%	18%
3	Infinite (0.59-115)	0.16 (0.07-0.57)	100%	39%
1	Infinite (1.06-257)	0.20 (0.07-1.05)	100%	5%
14	Infinite (0.52-113)	0.45 (0.32– 0.75)	100%	70%

DISCUSSION

Summary of evidence

In this meta-analysis we ultimately included four studies in adults, which were selected for their methodological robustness. In these studies data collection was done prospectively in a series of patients with active IBD. All included studies used a paired design where patients had repeated FC measurements and then endoscopy to evaluate the success of the induction therapy. A decrease of FC values into the target range corresponded well with endoscopic remission, while a failure to reach the FC target range reflected on-going intestinal inflammation.
Patients whose FC values decreased into the target range during induction therapy were 50 [16-160] times as likely to have reached endoscopic remission compared to patients whose FC values decreased but did not actually reach the target.

Comparison with previous studies

To the best of our knowledge, this is the first meta-analysis that evaluated the usefulness of repeated FC measurements to monitor response to induction therapy. We are now confident that an FC-based monitoring strategy is valid throughout all phases of IBD monitoring (figure 3). Until recently the FC test was mainly used to decide whether a patient with gastrointestinal symptoms needed to undergo endoscopic evaluation for suspected IBD (phase 1), or to detect an imminent flare in asymptomatic patients (phase 3).[12,13] The use of FC to monitor response to induction therapy has recently gained interest. The majority of studies that were screened for the purpose of this meta-analysis did not use a target range, but interpreted any decrease in FC as a treatment success.[23-31] There is, however, no linear correlation between the level of FC and the severity and extent of the mucosal inflammation. A decrease of FC in phase 2, e.g. from 2000 to 800 µg/g, may seem a significant reduction, but the latter result is still indicating active disease. The difference between the measurements may be explained by an inadequate contact time between stool and inflamed tissue to sufficiently saturate the stool with calprotectin. We are of the opinion that interpreting a decrease of FC in the high range as a treatment success is misleading and leads to overinterpretation of effects in medication trials. We moved away from this potential source of bias by only including studies that used the concept of a target range.

Treat-to-target strategies

The recent gain of interest in calprotectin-based monitoring is synchronous with the introduction of the treat-to-target strategy in IBD. An expert panel (STRIDE) defined the treatment target in IBD as mucosal healing, but did not yet have a practical algorithm to achieve this goal.[2] The treat-to-target approach has been used in many areas of medicine, where treatment targets have been defined to improve quality of life and reduce the risk of end-organ damage (such as joint damage in rheumatoid arthritis and vascular complications in diabetes mellitus).[32,33] Our findings may help to further develop a treat-to-target strategy in IBD. Important steps are to decide on the upper limit of the target range and the test frequency, predefine the therapeutic algorithms, and to evaluate and confirm the cost-effectiveness of the strategy.

Methodological limitations of the review

Since not all studies used histopathological confirmation of disease remission, it is possible that some patients were misclassified because of absence of ulcers on endoscopy, whereas microscopic evaluation would still have shown abnormalities. Secondly, because of the limited number of studies included in this meta-analysis we were not able to identify the ideal upper limit of the target range. The target thresholds in the included studies varied from 58 to 250 µg/g. We assume that picking a low target threshold will lead to earlier treatment escalation and faster depletion of the limited arsenal of medicines.

Clinical Implications

The value of FC as a surrogate for treatment success was evaluated in four studies with adult patients with active IBD. The Fagan plot in figure S1 presents the prognostic values corresponding to this context. With a pre-test probability of treatment success of 50%, a post-induction FC test result in the target range provides a shift in post-test probability of treatment success to 90%, whereas a failure to reach the FC target range reduces the probability of treatment success to 15%.

Although there is no consensus what FC value best demarcates the upper limit of the target range, the authors of this article use a downward trend crossing the 250 µg/g line as an indicator of treatment success. Interpreting any decrease of FC as evidence of effectiveness is probably misleading. It is more appropriate to categorize FC results into clinically meaningful ranges as

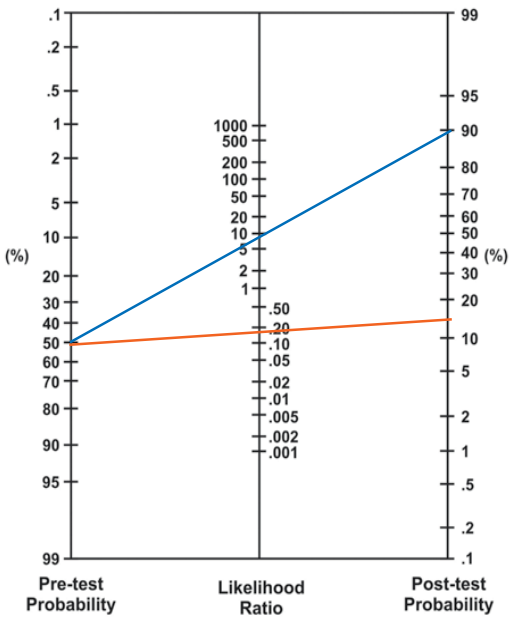

Figure S1. Fagan's nomogram showing post-test probability of treatment success when FC is in the target range (blue line) or FC is still out of the target range (red line).

endoscopic remission (<250 µg/g), active disease (>500 µg/g) and undecisive (250-500 µg/g), as shown in figure 3.

Currently, there is no evidence-based consensus when best to reassess disease activity after a change in therapy. The recently published ECCO-ESGAR guideline for diagnostic assessment in IBD advises to re-evaluate disease activity approximately 12 to 26 weeks after treatment initiation. [3]

CONCLUSION

This meta-analysis shows that a decrease of FC values into the target range corresponds with endoscopic remission, whereas a failure to reach the FC target range reflects on-going intestinal inflammation. A FC shift into the target range can be used as a surrogate marker for treatment success in clinical trials in IBD when endoscopy is impractical or poorly tolerated. The upper limit of the target range is yet to be discussed.

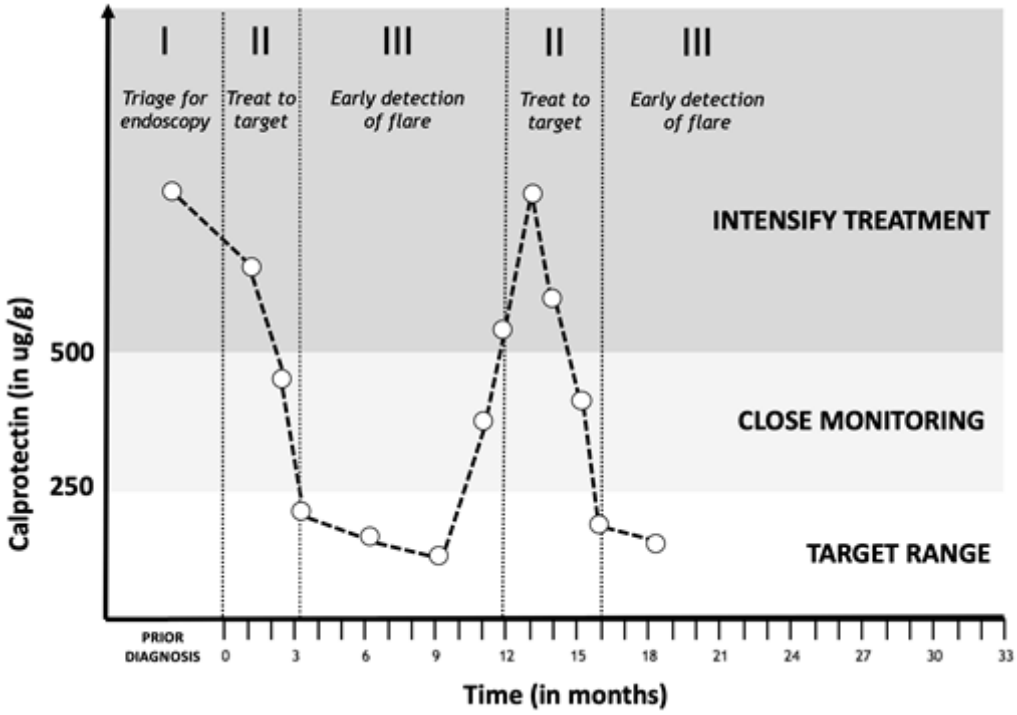

Figure 3. The phases of calprotectin-based IBD monitoring. In phase 1 ("pretreatment") the fecal calprotectin (FC) test is used to decide whether a patient with gastrointestinal symptoms should be exposed to endoscopy. In phase 2 ("treat-to-target"), induction therapy is introduced and the patient's response is periodically assessed. Phase 3 starts when induction therapy is successfully completed and FC values are in the target range (<250 µg/g). This phase involves a schedule of regular calprotectin measurements with a larger interval and a strategy what to do when a sequence of measurements suggests a drift away from the target range. Phase 2 and 3 alternate in the further course of the disease.

Figure adapted from "Do Not Read Single Calprotectin Measurements in Isolation When Monitoring Your Patients with Inflammatory Bowel Disease" by P.F. van Rheenen, Inflammatory Bowel Disease, 20:1416-7. Copyright 2014 by the Wolters Kluwer Health, Inc. Adapted with permission.

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