

# **TREAT TO TARGET: A PROPOSED NEW PARADIGM FOR THE MANAGEMENT OF CROHN'S DISEASE**

**Short title:** Treat to target in Crohn's disease

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## **Abbreviations used in this paper**

CD, Crohn's disease ; CDEIS, Crohn's Disease Endoscopic Index of Severity ; CRP, C-Reactive Protein ; DAS, Disease Activity Index ; DMARD, Disease-Modifying Anti-Rheumatic Drugs ; MH, Mucosal Healing ; MRE Magnetic Resonance Enterography; MTX, Methotrexate ; PROs, patient reported outcomes ; RA, Rheumatoid Arthritis ; SES-CD, simple endoscopic severity of Crohn's disease ; TNF, Tumor Necrosis Factor

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## **ABSTRACT**

The traditional management of CD, based on progressive, step-wise treatment intensification with re-evaluation of response according to symptoms, does not improve long-term outcomes of CD and places patients at risk for bowel damage. The introduction of novel therapies and the development of new approaches to treatment in rheumatoid arthritis led to better outcomes for patients. Prominent among these is a “treat to target” strategy that is based on regular assessment of disease activity using objective clinical and biological outcome measures and the subsequent adjustment of treatments. This approach is complementary to the concept of early intervention in high risk patients. This review evaluates current literature on this topic and proposes a definition for the concept treating to targets for Crohn's disease.

**Keywords:** Crohn’s disease, therapy, prevention and control, mucosal healing, treat to target

## **INTRODUCTION: WHY A TREAT TO TARGET APPROACH?**

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease that frequently results in progressive segmental damage to the gastrointestinal tract.(1) Population-based studies have demonstrated that the structural and functional bowel damage of CD is a dynamic, yet progressive process such that only 10% of patients experience prolonged remission of symptoms.(2–6) Importantly, even asymptomatic patients often have evidence of active inflammation on endoscopy and structural bowel damage (strictures and/or fistula) identified by imaging are observed in more than 50% of patients after 10 years after diagnosis.(6,7) Consequently, even in the modern era of treatment, the majority of patients undergo surgery as a result of inadequate control of inflammation.(8)

The traditional management of CD features progressive, step-wise treatment intensification with re-evaluation of response according to symptoms. Although clinically sensible, two fundamental problems exist with this approach. First, since it is both an incremental and time-bound paradigm, initiation of highly effective therapy (combined immune-suppression) in patients at the highest risk of disease progression is delayed. Second, given the poor correlation that exists between symptoms and endoscopically defined disease activity, it inherently undertreats substantial proportions of patients.

In rheumatoid arthritis (RA), another chronic and debilitating immune disorder, novel treatment approaches have evolved. A major factor driving this has been the introduction of new therapies, in particular biologic agents such as tumor necrosis factor (TNF) antagonist. The clinical success of new therapies helped alter the goals of treatment, such that discussions of “remission” and achieving the lowest achievable levels of disease activity are increasingly becoming considered both possible and appropriate. It had long been recognized that persistent uncontrolled articular and systemic inflammation resulted in the harmful sequelae of RA, including joint destruction and functional disability, as well as increased morbidity and even accelerated mortality. The efficacy of newer therapies reinvigorated treatment approaches to include older traditional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate in an effort to abrogate inflammation to the greatest extent possible. This included treatment earlier in the disease course, and the use of combinations of agents such as MTX combined with a TNF antagonist.(9) A codification of these developments is the “Treat to Target” (T2T) strategy.(10) The main principles of this strategy are based upon the regular

assessment of disease activity using validated outcome measures and the subsequent adjustment of treatment in case of persistent inflammatory disease activity, preferably following a protocol where therapeutic consequences and targets are predefined (figure 1).(11)

Given some analogies in disease course between RA and CD, the concept of treat-to-target that has evolved in RA can also be adapted to CD. To achieve disease modification and the prevention of structural bowel damage, an effective intervention must occur early in the course of CD (before the development of irreversible bowel damage) and adjusted to control biologic evidence of inflammation.(12,13) While the concept of new treatment goals such as mucosal healing (MH)(14) and deep remission(15,16) are increasingly being considered in CD patients, there is no specific definition of a treat-to-target strategy in CD that would enable these new treatment goals to be achieved. This article reviews the topic of treat-to-target and defines a potential treat-to-target paradigm for CD with help from available evidence and guidelines in RA.

## **CURRENT PROGNOSTIC FACTORS**

CD is a heterogenic condition with a highly variable prognosis. Thus, it is imperative to develop clinical prediction rules that incorporate clinical, laboratory and imaging parameters that accurately predict prognostic risks. Valid prediction rules should be studied across multiple populations that demonstrate changed outcomes in prospective studies. Their ultimate value depends on being simple to implement and remember, and provision of post-test probabilities that lead to a meaningful change in clinical decision making.(17) In RA, predictive models based on combined clinical and laboratory factors have been developed in prospective cohorts that discriminate patients with progressive disease from those who never develop progression.(18,19)

In contrast risk stratification in CD is at an early stage of development. While multiple clinical items have been identified, their utility with regard to predicting outcomes has been variable. In these studies a complicated or disabling disease course has been defined by the need for surgery or the inability to wean from corticosteroids or occurrence of complicated behavior (stricturing and/or penetrating [fistula or abscess]). Cigarette smoking has been consistently identified as a risk factor that is potentially reversible.(20–22) Young age at diagnosis (<40 years old), disease location (foregut, jejunum, ileum, or rectum), anatomic extent of disease, perianal disease, complicated disease behavior, need for corticosteroids to

treat the first flare and deep ulcerations on endoscopy were associated with disabling disease course.(6,20,21,23–29) Conversely elderly-onset CD was associated with less surgery and less complicated behavior.(30) In addition to clinical items, various biologic (immunologic and genetic items) have also been proposed to predict a disabling course of CD.(31) The presence of antibodies to *Saccharomyces cerevisiae* (ASCA), to *Escherichia coli* outer-membrane porin C (OmpC), to CD-related bacterial sequence I2 (anti-I2) and to the CBir1 flagellin are associated with the development of complicated behavior and/or the need for surgery.(32) The prevalence of complications increased in parallel with increasing numbers of positive antibodies.(32) Genetic markers, specifically carriage of *NOD2* variants, *IL23R*, *JAK2*, *TNFS15* and *PRDMI* variants,(33,34) are also associated with complicated CD outcomes such as stenosing or penetrating behavior, perianal disease or surgery. It must be emphasized that despite this extensive literature, there are no validated clinical prediction rules for CD. Prospective cohort studies that integrate all candidate markers into a single predictive model that will facilitate risk stratification at an individual patient level are needed.(35) The lack of adequate data in this area of research makes risk stratification very difficult in clinical practice. Such data are critical to avoid the dual goals of under treating patients with a poor prognosis and over treating patients with a favorable prognosis in the context of a treat to target paradigm.

### **TREAT TO TARGET: WHAT IS THE OPTIMAL TARGET?**

While inducing and maintaining clinical remission of symptoms are vital and explicit goals of therapy that are of unquestionable importance to patients, the use of symptoms alone for management may be insufficient to reduce or prevent long-term bowel damage and disability. The known course of CD ensues from its management in the 1990's(5) when treatment goals were exclusively based on control of symptoms.(36) Corticosteroids were the foundation of management, and were highly effective for control of symptoms in the short term but do not alter the course of CD.(37) Therefore, new treatment targets are needed that feature monitoring of bowel inflammation either through use of biomarkers of inflammation or by direct assessment with endoscopy or cross-sectional imaging modalities.

#### *Defining the target: experience from other chronic diseases*

In many chronic diseases, reaching an objective target improves long term outcomes such as low blood pressure in hypertension, low glycosylated hemoglobin in diabetes, or plaque skin

lesions in psoriasis. Similar to CD, the correlation between symptoms and the presence of active inflammation (synovitis, the main driver of joint destruction) is not always precise in RA. However, in the RA setting not only are patient reported outcomes (PROs) such as pain and functional ability crucially important from the patient's standpoint, PROs are also powerful predictors of long term outcomes. Thus, most RA trials have been based on achieving a composite target that includes both symptoms and more objective assessments of inflammation. The TIGHT Control for Rheumatoid Arthritis (TICORA) trial randomized patients to a strategy of tight control of disease activity based on monthly assessment of a composite disease activity score or routine care.(38) In the experimental group, patients with persistent disease activity had protocol-driven treatment intensification with addition of a new DMARD at 3 month intervals.(38) Conversely, the routine care group was assessed every 3 months, but no formal composite measurement of disease activity was used and treatment decisions regarding modification of the DMARD regimen were made at the discretion of the attending rheumatologist.(38) The trial showed a substantial increase in the rate of remission in the treat-to-target group than in the routine care group.(38) In RA, multiple lines of evidence show a strong relationship between persistence of inflammation and progression of joint destruction, usually assessed with the Sharp score that evaluates the presence of erosions and joint space narrowing on radiographs of the hands and feet. Radiographic outcomes in the TICORA study were also superior at 18 month in the treat-to-target group. These results hint at the potential value of setting specific treatment goals in chronic inflammatory diseases that can impact on long-term outcomes such as disability, longevity, quality of life or pharmacoeconomics.

#### *Targeting mucosal inflammation in CD*

In CD, data from large scale cohort studies and from randomized controlled trials indicate examination of the mucosa to assess for endoscopic or MH indicate that MH is potentially a treatment target. Preliminary support for this relationship came from the first large trial of infliximab, ACCENT-I. Patients who achieved MH, defined as the absence of mucosal ulcers at week 10 and/or week 54, were less likely to have CD-related hospitalizations and surgery.(39) In another recent trial, the Step-Up Top-Down trial, of 133 newly diagnosed and treatment-naïve CD patients who were initially randomized to either corticosteroids or combination therapy with azathioprine and infliximab, 49 underwent ileocoloscopy at the end of the 2 years trial and were followed for an additional 2 years. MH [defined as a simple



endoscopic severity of Crohn's disease (SES-CD) score of 0, meaning no signs of active inflammation in any colonic segment or in the terminal ileum], was predictive of sustained clinical and steroid-free remission through years 3 and 4: 62.5% of patients healed at year 2 remained in steroid-free remission as compared with only 18.5% of patients having a SES-CD above 1 ( $p=0.03$ ).<sup>(40)</sup> These observations are consistent with data from the IBSEN population-based cohort study that prospectively evaluated 843 incident IBD cases from 1990 to 1995.<sup>(41)</sup> One hundred and forty one patients with CD underwent clinical and endoscopic reevaluation within 0.5 and 2 years after diagnosis and 130 cases were followed for 5 years.<sup>(41)</sup> The presence of MH at 1 year, defined as normal or light erythema or granularity without ulcerations, was associated with less inflammatory activity ( $p=0.02$ ), less corticosteroid use and a trend to fewer surgeries ( $p=0.1$ ).<sup>(41)</sup> In a second cohort study of 214 patients treated with infliximab from 1994 to 2008, the presence of MH (defined by the absence of ulcerations) and partial MH (defined as endoscopic improvement but with residual ulceration) predicted both fewer complications and a lower need for hospitalizations and surgeries.<sup>(42)</sup> Additional support for this concept comes from a post-operative recurrence study conducted by Rutgeerts and colleagues who evaluated an inception cohort of 89 patients at a single referral center.<sup>(43)</sup> The 40% of patients with minor endoscopic lesions (normal mucosa or less than 5 aphthous ulcer in the neo-terminal ileum) were at considerably less risk of both symptomatic recurrence and the need for a second resection than those with more severe lesions.<sup>(43)</sup> A post-hoc analysis of the ACCENT 1 trial demonstrated that using MH as an endpoint for decision-making was more cost-effective than a strategy based on clinical symptoms, primarily by decreasing disease related complications that require hospitalization and surgery.<sup>(44)</sup> Collectively these results demonstrate that MH is an attractive potential treatment target for CD but none of them have yet proven that a treatment algorithm based on endoscopic evidence rather than based on symptoms changes outcomes. This issue is complicated in that some patients with symptoms do not have endoscopic evidence of inflammation (and are thus potentially subject to overtreatment in a symptom based treatment paradigm) and other patients without symptoms have residual endoscopic inflammation, leading to an overall accuracy of clinical symptoms, relative to endoscopic inflammation, of 56%.<sup>(45)</sup> It is not yet clear whether patients with clinical remission and residual endoscopic inflammation have a worse prognosis than patients with endoscopic remission. Detailed information from the Accent 1 trial, the Step-Up Top-Down trial, the IBSEN cohort study, and the Leuven cohort study is not available to address this point. A somewhat underpowered

post-hoc analysis of the Extend trial of adalimumab for mucosal healing in CD did not show clear differences in hospitalization and surgery rates between patients who achieved clinical remission as compared with patients who achieved deep remission (combined endpoint of clinical remission and endoscopic remission).(46)

The SONIC trial demonstrated that MH is achievable in up to 44% of patients if highly effective treatment is initiated early in the course of the disease. Among the 325 patients with baseline mucosal ulcerations in the SONIC trial, MH (defined as the absence of mucosal ulcers) occurred at week 26 in 47 of 107 patients (43.9%) who received combination therapy, 28 of 93 patients (30.1%) who received infliximab monotherapy, and 18 of 109 patients (16.5%) who received azathioprine ( $p=0.02$  for infliximab versus azathioprine,  $p<0.001$  for combination therapy versus azathioprine, and  $p=0.06$  for combination therapy versus infliximab).(47) In the Step-Up Top-Down trial, 73% of patients with early-CD assigned to combination therapy achieved MH at week 104.(48) In addition, the preliminary data from a cohort of patients from a referral center with long-standing moderate to severe CD showed that MH was achieved in 50.7% of cases managed by experienced IBD specialists.(49) However large scale clinical trials or cohort studies of sufficient duration will be necessary to link this target to clinically meaningful events such as hospitalization and surgery.

Potential alternatives to MH as a treatment target exist to assess for mucosal inflammation. Assessment of intestinal inflammation by non-invasive imaging techniques, especially magnetic resonance enterography (MRE), is attractive given the opportunity to reduce discomfort, and complications relative to ileocolonoscopy. Furthermore MRE avoids the radiation exposure associated with computed tomography.(50) The overall sensitivity of MRE for the detection of disease activity is 80% (95% CI 77–83%) and specificity is 89% (95% CI 93–96%).(51) However long-term data regarding the outcomes of patients stratified by disease activity based on MRE assessment are, for the most part, lacking.(52) In a recently published abstract, in which 27 patients were assessed before and after treatment with either corticosteroids or adalimumab, the magnitude of reduction in a MRE activity index closely paralleled improvement in CDEIS scores.(52)

Since both ileocolonoscopy and MRE are costly, their repeated use to monitor patients for the presence of intestinal inflammation is constrained. Considerable attention has been placed on the development of surrogate markers of mucosal disease activity such as fecal biomarkers or CRP. Data showing a relationship between fecal biomarkers (calprotectin or lactoferrin) and clinically meaningful events are sparse necessitating further validation.(53–55) Elevated

concentrations of CRP correlate well with both endoscopic and histologic evidence of inflammation. In contrast a poor correlation exists between CRP concentrations and symptoms.(56,57) A prospective longitudinal study that evaluated 101 patients with CD showed that CRP was reproducible and reliable, CRP concentrations decreased as the disease went into clinical remission.(58) A higher rate of clinical relapse was observed in patients with a persistently elevated CRP. However, up to one third of patients with intestinal inflammation do not have an elevated CRP concentration.(58–60) In several studies assessing biologics such as TNF antagonists or ustekinumab, normalization of CRP concentrations reflected objective evidence of decreased inflammation and increased the likelihood of sustained remission on maintenance therapy or the likelihood of clinical relapse in case of a persistently elevated CRP.(61–63) In the ACCENT 1, 75% of patients with normalization of the CRP (<0.5mg/dL) at week 22 maintained remission over the study period.(64) Thus, changes in CRP concentrations provide useful information in monitoring response to treatment and the risk of further relapse in the two third of CD patients who have a raised CRP concentration in the presence of active disease.(58)

In summary, MH defined endoscopically by the disappearance of ulceration is currently the most established marker of intestinal inflammation and should be the testable target for use in a CD treat-to-target treatment algorithm in the near term, because it has been demonstrated to be achievable, monitorable and associated with better outcomes. However, MH as the target should be viewed as a starting place, and it is likely that the target will evolve over time to other less invasive objective measures of inflammation. In the intermediate term, MRE may prove to be an attractive alternative in locations where the technology is available and cost-effective. Identification and development of surrogate biomarkers, while currently insufficient for making therapeutic decisions, remains a priority. The International Organization on Inflammatory Bowel Disease (IOIBD) is leading a consensus effort that will further consider Selection of the Therapeutic taRget in Inflammatory bowel DiseasE (STRIDE).

## **MONITORING THE TARGET AND THERAPEUTIC ADJUSTMENT**

Data from both RA and CD indicate that early introduction of highly effective therapy in patients at high risk for disease related progression or complications is an attractive treatment paradigm. Beyond early management, development of a successful treat-to-target algorithm requires pre-definition of the optimal timeframe for re-assessment and subsequent therapy

adjustment. On the one hand, too short a time frame may not allow the efficacy of a treatment approach to be fully defined; on the other hand, too long a time frame allows persistent inflammation to potentially evolve to medically intractable bowel damage.

Considering MH as the target, from large scale cohort and the step-up/top-down trials, MH resulted in a beneficial effect on the longer term course of CD when assessed over periods of 6 months to 2 years.(40–42) Data from numerous controlled trials demonstrate that the timeframe for MH to occur under treatment with immunosuppressives, TNF antagonists or combination therapy ranged from 10 to 26 weeks, with higher rates of MH seen at later time points (Supplementary Table 1).(39,47,65–70) In the EXTEND trial, that evaluated MH in patients randomly assigned to either adalimumab or placebo, MH was defined as absence of mucosal ulceration at week 12.(69) Recently, a small cohort study observed more MH among patients with repeated procedures within 26 weeks.(49) In a small trial utilizing a treat-to-target approach, infliximab administered postoperatively was discontinued in 12 consecutive patients without endoscopic evidence of disease recurrence 3 years after the surgery and, in case of recurrence 4 months after, was restarted at 1 mg/kg. Prescheduled, repeated endoscopic assessment was performed every 16 weeks followed by infliximab dose increment by 1 mg/kg if mucosal lesions persisted until MH (i0 or i1).(71) Following the algorithm, all 10 patients with endoscopic recurrence achieved MH, with 2 patients on infliximab 2 mg/kg and 8 patients on infliximab 3 mg/kg.(71) Despite the small size of this trial (requiring colonoscopy up to every 16 weeks), it demonstrates the potential of adjusting therapy on the basis of an objective treatment target according to a predefined timeframe.

These results underlined that mucosal changes occurred relatively rapidly with anti-TNF therapy after therapeutic adjustment. In the absence of MH, several therapeutic choices are available including: increasing the dose or decreasing the dosing interval of the ongoing drug; switching treatment to another drug within the class or switching treatment to another drug outside the class; or, adding a drug to the ongoing treatment regimen to improve outcomes.(72–74) Close repeated assessment and subsequent therapeutic adjustment based on endoscopic findings, irrespective of symptoms, may ultimately ensure adequate control of intestinal inflammation and avoid long-term bowel damage.

## **PRACTICAL IMPLEMENTATION**

Although trials in RA suggest that a treat-to-target strategy could be beneficial, additional confirmatory large-scale effectiveness studies are still needed to determine whether this strategy is translatable into practice. A recent cohort study performed in 6 Dutch hospitals that assessed feasibility of treat-to-target in daily care demonstrated high adherence to treat to target recommendations in RA, including the frequency of disease assessment and the prevalence of appropriate changes in therapy.(75) It should be noted that any therapeutic algorithm must be reasonable and implemented taking into account both the risks and benefits. In diabetes mellitus, another chronic disease, intensive therapy to reach a tight predefined target improves several microvascular outcomes but was shown to increase overall mortality.(76)

Beyond the therapy related risks related to any use of medication for chronic disease, the need of repeated colonoscopy is a particular issue in CD. Contrary to a blood pressure or a blood sample, patient discomfort, direct and indirect costs, and the potential for rare but serious complications relative to ileocolonoscopy could decrease adherence of patients to the strategy. A clear and open communication around the benefit and risk of alternative management strategies, the various therapeutic options, and the desired disease outcomes are essential for achieving a physician-patient relationship that creates the possibility for a patient to participate in his or her health and share decision making maximizes the likelihood that the patient will adhere to the agreed upon treatment strategy.(77)

Analyses of a large administrative data base in Manitoba (Canada) indicated that early access to specialty care by a gastroenterologist was a predictor of surgery-free survival that was associated with a higher rate of immunosuppressive therapy within the first years after diagnosis. These results underscore the potential of specific follow-up and the introduction of more intensive treatment, introduced early in the course of the disease to improve CD outcomes.(78)

In summary, the limitations of a treat to target strategy include the lack of validated prediction rules in CD that would allow risk stratification in individual patients, feasibility issues regarding patient acceptance of serial colonoscopy examinations, and feasibility issues regarding the ability of currently available treatment regimens to achieve mucosal healing.

## **PROPOSAL FOR A DEFINITION OF TREAT TO TARGET IN CROHN'S DISEASE**

### *Lessons from rheumatoid arthritis*

Ten statements were established by an international task force based on 4 overarching principles(10): 1) shared decision making between the patient and the rheumatologist; 2) measuring disease activity; 3) treatment to target by adjusting therapy to suppress disease activity; and 4) maximizing long-term health-related quality of life through control of symptoms, prevention of structural damage, and normalization of function and social participation. Control of disease activity and achievement of these treatment goals is done mainly through the abrogation of inflammation.(10) The 10 statements are summarized in the table 1.

Based on this preliminary experience from RA, a proposal for specific recommendations can be made regarding the structure of a treat to target algorithm for CD as follow. (Table 1 and Figure 2)

#### *Patient Selection*

Pending the availability of a validated prediction rule of disease outcomes, clinical markers (disease location, extent and behavior, age, severity of endoscopic ulceration, tobacco use), and possibly serologic and genetic markers should be considered for use in therapeutic decision making after patient selection and triage of high versus low “risk” groups. Importantly, the addition of these predictors may increase the individual risk for disabling CD course and should increase the urgency for the patient to receive effective treatments.

#### *The Patient-Physician Relationship*

Patients with CD need to be able to trust their physician, to maximize the chance that they will adhere to an agreed upon treatment strategy. Thorough discussion about the risk of the drugs versus the risks of the disease, the applicability of any prognostic markers for the individual patient, consideration of the time horizon for an individual patient, costs associated with the medications and follow-up evaluation with laboratory studies, endoscopy, and imaging studies that might be employed in a treat to target strategy are needed.

#### *Definition of the target and the treatment*

As previously described, the achievement of symptomatic remission is essential for the patient’s wellbeing, but as a therapeutic goal, it alone does not provide optimal long-term outcomes or prevent disability. Therefore a decrease in objective markers of inflammation, particularly MH, that can improve long-term outcomes and reduce disability, should be

selected as the therapeutic target. The use of validated markers of inflammation in addition to symptoms is also important since there is a high rate of concomitant functional gastrointestinal disorders and co-morbidities such as irritable bowel syndrome (IBS), bile acid diarrhea, small intestinal bacterial overgrowth, short bowel syndrome with fat malabsorption and steatorrhea, and mechanical obstruction due to strictures in patients with CD.(79)

Among the currently available objective markers of inflammation, endoscopic assessment with resolution or near-resolution of ulcer lesions is the preferred treatment target. Nevertheless, the definition of MH and the value of achieving complete MH (deep remission), in distinction to partial healing, are debated and, from a practical standpoint, many studies have defined MH as the absence of ulcers.(80) In some instances MRE (or possibly ultrasound) may be an alternative to endoscopy. Therapeutic targets (e.g. remission versus clear improvement) may be different in patients without or with pre-existing bowel damage.

#### *Establishing a timeframe to assess the target and to institute treatment optimization*

Based on a review of data from controlled trials, the mean time to maximum symptomatic response was broadly similar for corticosteroids, antimetabolites and TNF antagonists, ranging from 10 to 26 weeks. Surrogate marker normalization between 6 and 14 weeks were associated with better outcomes. MH is likely best assessed by endoscopy after 3-6 months.

Collectively, these data suggest that an ideal treat-to-target strategy should follow the patient every 3-6 months for assessment of MH (disappearance of ulcers) with colonoscopy (or MRE or ultrasound in patients who cannot be adequately assessed with colonoscopy). In the case of persistent significant endoscopic ulceration, treatment should be further optimized to reach the predefined target of MH. Six month intervals between colonoscopy procedures may be a reasonable compromise between selecting a time after which additional mucosal healing is unlikely to occur and a time interval between procedures that would be acceptable to patients. Finally, such targets may be useful in patients with pre-existing bowel damage who have residual non-inflammatory based symptoms, to maximize long-term quality of life while minimizing worsening of disability.

Once the predefined treatment target of MH is reached, treatment should be maintained with regular monitoring of clinical symptoms and biomarkers every 6 months, and among patients for whom other treatment options or optimization of ongoing therapy are available, regular monitoring for sustained MH every 1-2 years. A final consideration is what to do with patients who received combination therapy with a TNF antagonist and azathioprine, achieved

MH, and in who several interval colonoscopies have shown persistent MH. Can and should such patients under therapy de-escalation, removing either the azathioprine or the TNF antagonist? Preliminary data raise the possibility that therapy de-escalation may be possible, but the existing studies are too small to inform clinical practice.(81,82) Additional data are needed to address this important issue.

## **CONCLUSION**

In spite of available effective treatments, the development of complications such as stricture, fistula, and abscess that result in surgery and lead to a disabling course of CD, remain common. This “natural history” is not likely to improve unless the overall, symptom-based, therapeutic strategy for CD is changed. A change in strategy for patient management will lead towards optimal use of Disease-Modifying Anti-Inflammatory bowel disease Drugs.(83) Evolving evidence indicates that intensive care that aimed at abrogating intestinal inflammation might improve long term outcome of CD. The definition of the present proposed concept needs inevitably to evolve as far as treatment and assessment of mucosal inflammation will evolve over time. As part of this new way of thinking, the International Organization on Inflammatory Bowel Disease is leading a consensus effort on selecting the therapeutic target in inflammatory bowel Disease. However the principles of the treat-to-target strategy that employs both systematic follow-up of patients and therapy optimization focusing on inflammation and damage may persist. These evolving concepts need further evaluation and the REACT II trial in which strategies of treating the patients to the target of MH will be compared to conventional symptoms-based approach is going to start and will provide support to such approach.(84)



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## Tables

Tables 1 Recommendations of an international task force for the definition of treat-to-target in RA and proposal view for Crohn's Disease <sup>10</sup>	
Recommendation in Rheumatoid arthritis	<p>(1) The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.</p> <p>(2) Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.</p> <p>(3) While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.</p> <p>(4) Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.</p> <p>(5) Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.</p> <p>(6) The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.</p> <p>(7) Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.</p> <p>(8) The desired treatment target should be maintained throughout the remaining course of the disease.</p> <p>(9) The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.</p> <p>(10) The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.</p>
Proposal recommendation for Crohn's disease	<p><u>Relationship :</u></p> <ul style="list-style-type: none"> <li>- The gastroenterologist should appropriately inform the patient about the treatment target and the strategy planned to reach this target</li> </ul> <p><u>Target &amp; Treatment :</u></p> <ul style="list-style-type: none"> <li>- The primary target for treatment of Crohn's disease should be absence of endoscopic ulceration</li> <li>- The level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.</li> <li>- The desired treatment target should be maintained throughout the remaining course of the disease.</li> <li>- The use of both clinical symptoms and objective measures of inflammation (endoscopic or imaging) is required in routine clinical practice to guide treatment decisions</li> <li>- Objective inflammation of the bowel (endoscopic, imaging) should be considered when making clinical decisions, in addition to assessing clinical disease activity.</li> </ul> <p><u>Time to assessment :</u></p> <ul style="list-style-type: none"> <li>- Until the desired treatment target is reached, mucosal healing should be assessed every 6 months until the disappearance of ulceration, and every 1-2 years thereafter. Drug therapy should be adjusted accordingly</li> </ul>



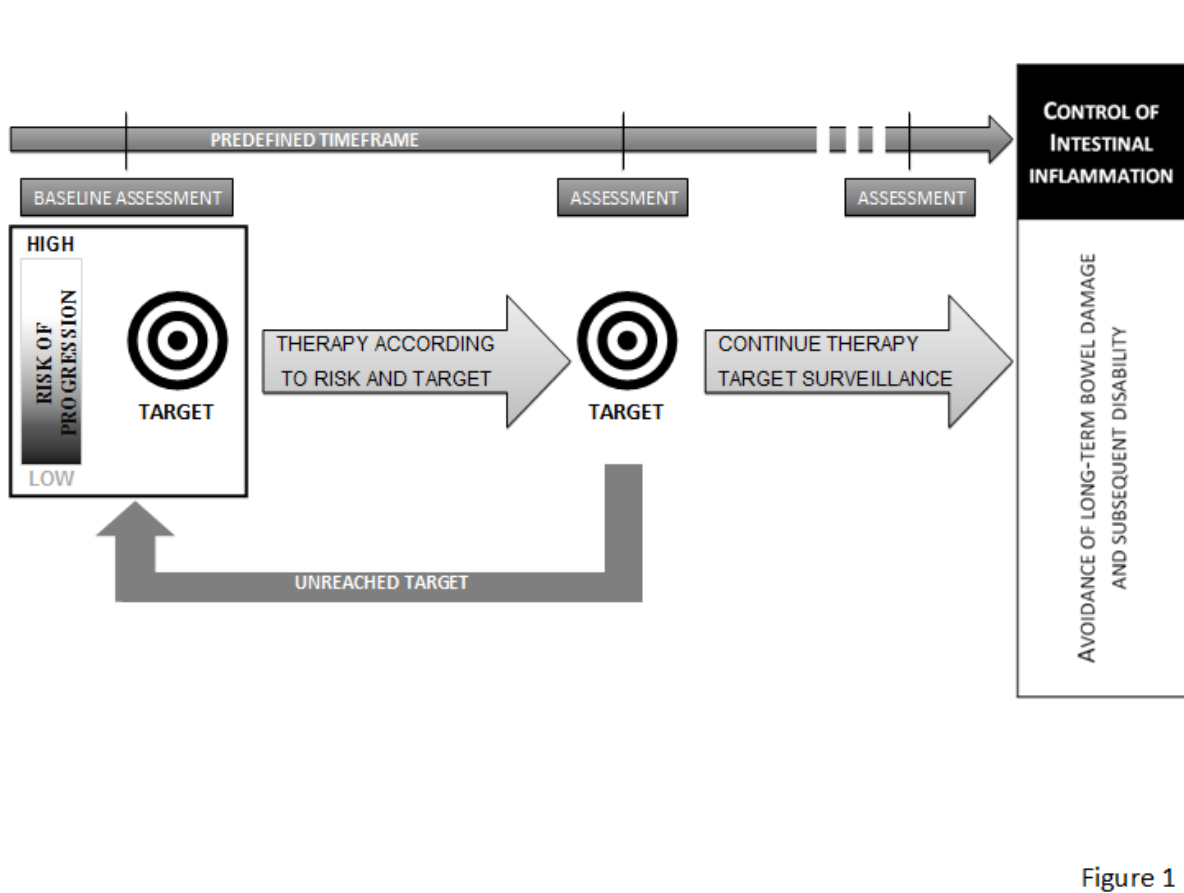
**Supplementary Table 1:** Results of prospective trials that assessed mucosal healing according to treatment and time.

			TIME OF ASSESSMENT AND RATE OF MUCOSAL HEALING Number of Patients with MH/Number of patient assessed (%)		
TREATMENT	REF	YEAR	MH wks 10-12	MH wks 26	MH wks 50-54
METHOTREXATE	66	1989	5/14 (35.7)	-	-
AZATHIOPRINE	65	1995	3/6 (50)	-	-
	67	1999	-	-	10/20 (50)
	68	2009	-	-	25/30 (83)*
	47	2010	-	18/109 (16.5)	-
	47	2010	-	47/107 (43.9)	-
AZATHIOPRINE + IFX	47	2010	-	47/107 (43.9)	-
INFLIXIMAB	39	2004	4/18 (22)	-	5/17 (29)**
	47	2010	-	28/93 (30.1)	-
ADALIMUMAB	69	2012	17/62 (27.4)	-	15/62 (24.2)**
CERTOLIZUMAB PEGOL	70	2013	1/11 (4)	-	3/16 (8)
Abbreviation: MH, Mucosal Healing; IFX, Infliximab; WKS, weeks					
* baseline endoscopy results unavailable					
** Patients evaluated at weeks 10 and 54 for mucosal healing					

**FIGURE LEGENDS:**

**Figure 1:** Overview of the treat-to-target concept. According to risk stratification, highly effective disease modifying therapy should first be administered to high risk patients. Treatments should be then monitored and adjusted using a predefined objective target.

**Figure 2:** Schematic representation for a treat-to-target based strategy for Crohn's disease. Based on preliminary experience from RA, proposal algorithm for CD include careful selection of patients to active treatment, use of mucosal healing as the optimal target and a timeframe to assess treatment efficacy.



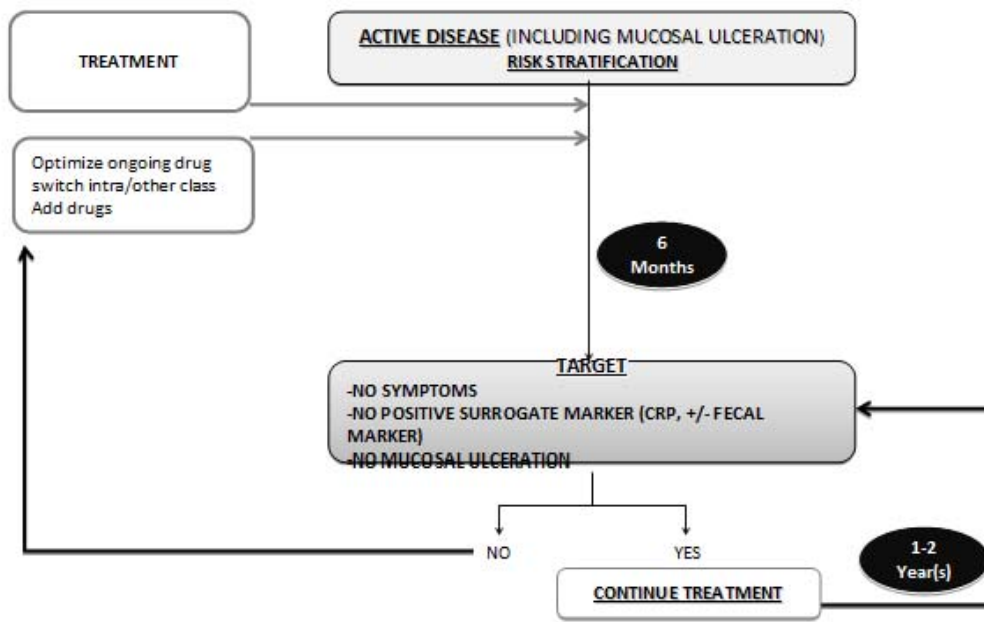


Figure 2