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Evolving therapeutic goals in Crohn's disease management

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Abstract

The main objectives in Crohn's disease are to avoid disease complications and preserve the patient's quality of life. Early disease control and close monitoring with specific targets to reach might be the only way to change the disease course. In two decades, we have moved from clinical response to full remission (clinical and endoscopic remission) requiring a tight monitoring of both symptoms and objective signs of inflammation. This review summarizes the concepts of tight control and treat-to-target and their potential for disease modification.

Keywords

Tight control, Crohn's disease, treat-to-target

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Clinical case

A 31-years old female with smoking habit presented with chronic diarrhoea and abdominal pain. Diagnosis of moderate ileocaecal Crohn's disease (CD) was made based on the presence of five aphthous erosions at initial colonoscopy. The first line of treatment was oral budesonide. Given the persistence of elevated C-reactive protein (CRP) at 10mg/L and faecal calprotectin (FC) at 350 µg/g at 3 months and despite the absence of symptoms, adalimumab treatment was initiated. Because of the presence of persistent erosions at colonoscopy at 6 months, the treatment was optimized with adalimumab 80 mg every other week. Ten years later, the patient has no disability, normal biomarkers (CRP and FC), no bowel damage at magnetic resonance imaging and did not undergo surgery.

Introduction

CD is a chronic and progressive state of the digestive tract, which can lead to gradual and cumulative bowel damage by altering the parietal architecture resulting in complications such as strictures, fistulae, surgery, intestinal failure and cancer, causing subsequent disability.[1] The Lémann Index is a validated score to assess and quantify bowel damage, which can be used to evaluate the impact of therapeutic strategies on CD course.[2] Historically, the primary objective of treatment in therapeutic trials and clinical practice in CD was to induce and maintain symptomatic remission. This approach failed to clearly modify the natural course of CD.[3] Similar to other inflammatory diseases such as rheumatoid arthritis,[4] new theories such as treat-to-target (T2T) and tight control have emerged. T2T involves identification of a pre-specified target to be reached with therapy, followed by adapted modifications of treatment and repeated monitoring until the target is reached, in a tailored way for the patients regarding their individual needs.[5] With the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus, treatment goals in CD have moved to 'deep remission', which is defined by reaching both symptomatic and endoscopic remission (defined as no ulceration at ileocolonoscopy). There are well known discrepancies between clinical symptoms and endoscopical lesions in CD[6] and clinical evaluation is not a reliable criteria to lead modification of treatment

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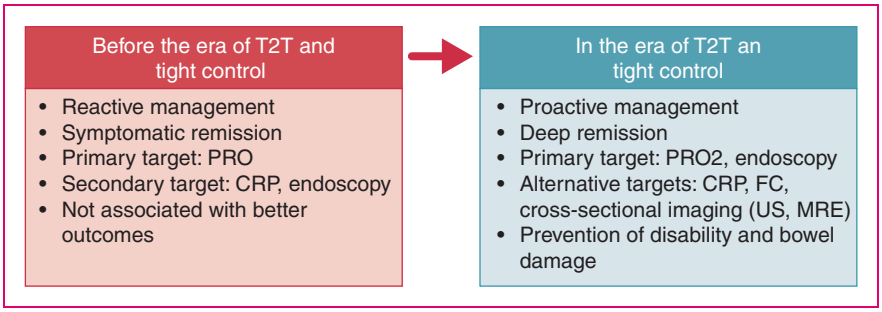

Figure 1. Changes in Crohn's disease management over the past decade.
Before the era of T2T and tight control, patient management was guided by symptoms and only CRP was routinely measured. Other examinations were performed on demand. Residual inflammation could progressively alter the bowel wall and lead to significant damage, with strictures or fistulas requiring disabling surgery.
T2T = treat-to-target; PRO = patient reported outcomes; CRP = C-reactive protein; FC = faecal calprotectin; US = ultrasonography; MRE = magnetic resonance enterography.

to control persistent mucosal inflammation, underling the need for an accurate target in order to assess treatment response. Biomarkers (CRP and FC) were not targets in STRIDE but only adjunctive measures of inflammation for monitoring in CD due to insufficient evidence to recommend treatment optimization using biomarkers alone.[5] As it is impossible to repeat colonoscopy, a trial called CALM investigated the effectiveness and safety of two treatment strategies in achieving endoscopical remission in patients with CD by optimizing treatment according to predefined failure criteria: clinical evaluation with adjunctive measures of inflammation (CRP and FC) in the tight control group or clinical evaluation alone in the clinical management group.[7] This trial allowed a prospective validation of tight control strategies based on careful and continuous surveillance of the disease activity by validated composite measurements, and early therapeutic optimization or change of treatment if necessary[7] (Figure 1). This review will discuss four challenging questions: what are optimal targets in CD? Can endoscopy be replaced in the context of tight monitoring? How can the course of CD be modified? Should poor prognostic factors be abandoned in the era of tight monitoring?

What is the optimal target in CD?

Patient reported outcomes. Patient reported outcome (PRO) is the assessment of the patient perception about their symptoms, functional status and well-being. In CD, symptom-based PRO measures (PRO-2) are composed of the two most prominent symptoms, which are abdominal pain and stool frequency.[8] The PRO-2 goal should be resolution of abdominal pain and normalization of bowel habit.[5] The CD Activity Index is commonly used in inflammatory bowel disease (IBD) trials to assess clinical activity of the disease.[9,10] A patient should undergo clinical evaluation every 3 months during active disease and every 6–12 months for quiescent disease.[5] In order to evaluate disability resulting from IBD, the IBD Disability Index (IBD-DI) was developed in 2012[11,12] and validated in a French population-based study with high internal consistency, inter-observer reliability and construct validity, and moderate intra-observer reliability.[13] Disability is a major stake and should be prevented in IBD. Therefore the IBD-DI should be integrated in therapeutic trials and clinical practice as a principal secondary endpoint.[13] However because of the poor reliability of clinical evaluation to guide treatment decisions and the lack of change in the disease course with symptoms-based strategies more objective targets are necessary to prevent bowel damage and resultant disability.

Endoscopy. Endoscopy remains the gold standard to assess disease activity in ileocolonic CD. There are two endoscopic scoring systems used in CD: the CD Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD). SES-CD was developed to respond to the practical limitations of the original score, which is complex and time-consuming to use. The two scores are highly correlated.[14,15] Both scores were found to be responsive to change in a prospective study.[16] The definition of endoscopic remission commonly admitted is a CDEIS <3 or a SES-CD ≤ 2.[17] These scores remain little-used in practice,[18] so STRIDE adopted a simpler goal (resolution of ulceration).[5] Endoscopic evaluation should be made at a minimum of 3 months after initiation of treatment and preferably between 6 and 9 months, because lower rates of mucosal healing have been found with early evaluation.[19,20] Achieving deep remission is the goal in CD[5] because it is associated with better outcomes so endoscopic remission became a major stake. In the ACCENT I trial testing infliximab for moderate to severe CD, there was a trend towards fewer

hospitalizations and surgeries in patients with mucosal healing at weeks 10 and 54.[21] Likewise, the absence of mucosal ulceration at ileocolonoscopy within 1 year of diagnosis or initiating therapy has been associated with reduced corticosteroid use and decreased clinical disease activity, fewer abdominal surgeries related to CD,[22] and predicts sustained steroid-free remission 3 and 4 years after therapy initiation.[23] Endoscopic remission (or mucosal healing) on the first post-treatment endoscopy was associated with a higher rate of sustained clinical remission, maintenance of mucosal healing, and lower risk of CD-related surgery.[24] Endoscopy is the main target but PRO should not be neglected because deep remission was associated with lower risk of major adverse events compared with endoscopic remission alone.[25]

Histology. Data concerning the role of histologic remission on disease outcomes are scare and mainly retrospective. Compared with endoscopic remission, histologic remission was associated with a lower risk of clinical relapse.[26] In the recent trial comparing ustekinumab and placebo in CD, histologic response at week 8 was significantly associated with long-term outcomes of clinical response, clinical remission, mucosal healing, and endoscopic remission at week 44.[27] Given the scant data concerning the predictive role of histological remission in CD, as well as concerns of sampling issues due to the patchy and transmural nature of the disease and the absence of a validated histologic scoring system, histology is not yet recommended as a target in CD.[5]

Can we replace endoscopy in the context of tight monitoring?

Radiologic targets. Cross-sectional imaging techniques are not primary targets in CD but are complementary tools to endoscopy, especially if the diseased segment cannot be accessed.[5] Radiological assessment is less invasive, can evaluate the small bowel, and provide information about the transmural nature of inflammation. Ultrasonography (US), computed tomography enterography (CTE), and magnetic resonance enterography (MRE) can be used according to the patient situation with an equivalent accuracy.[28] CTE has shown high accuracy in the assessment of disease but exposes subjects to ionizing radiation[29] and should be abandoned outside the emergency setting. MRE is a non-ionizing technique that has been found to be predictive for disease outcomes in CD. In a prospective study including 214 patients with inactive disease on MRE, rates of therapy optimization, hospitalization and surgery at 1 year were significantly lower.[30] The Nancy score is an MRE score that has been shown to accurately detect endoscopic healing in CD, and was found to be responsive to change after treatment.[31] It showed good accuracy with 80% specificity and 70% sensitivity for the diagnosis of endoscopic healing.[31] Mucosal healing on MR after treatment corresponding to a Nancy score <6 was also associated with lower risk of surgery.[31] The Nancy score is usable in practice for tight monitoring as it does not require fasting or colonic preparation. The simplified MaRIA score (Magnetic Resonance Index of Activity) is another score that strongly correlates with endoscopical findings[32] but requires bowel preparation and its predictive value is pending. US is a widely available, cheap, non-invasive, time-efficient and well-tolerated technique. It was found to be highly correlated with MRE, and US-guided strategies showed good concordance with both cross-sectional imaging and colonoscopy, demonstrating its decision-making relevance for CD patients.[33] Several US scores are available for CD but most of them have been developed through suboptimal processes or their predictive value has not been demonstrated.[34]

CRP. CRP is a broadly used and studied biomarker in CD. When CD patients have raised CRP levels at diagnosis, variation of CRP concentration may help to monitor response to treatment. In CD, elevated CRP is correlated with clinically active disease and endoscopic and histologic inflammations.[35] CRP was found to be predictive of relapse in CD patients with elevated levels at diagnosis[36] but approximately 20% of CD patients do not have increased CRP during flares[37] and an elevated CRP level may be provoked by an extra-intestinal cause.[37] A CRP level $\geq$5 mg/L was found to have a 92% specificity for predicting active endoscopic CD but only 49% sensitivity.[38] A decrease of CRP might be a better predictor of long-term outcomes than the baseline level. In a post hoc analysis of the ACCENT I randomized controlled trial (RCT), patients with CRP $\geq$5 mg/L at week 14 had a probability of sustained response of 37.2% compared with 56.6% in patients with CRP <5 mg/L.[39] In another study, CRP normalization <10 mg/L at week 12 was also predictive of endoscopic response at week 52 with a positive predictive value of 79%.[40] However, CRP is not indicative of CD as it reflects systemic inflammation and is poorly correlated with endoscopical healing, but remains a complimentary tool to endoscopy and FC.

Faecal calprotectin. In CD an FC level <250 µg/g is predictive of mucosal healing (corresponding to CDEIS < 3) with a sensitivity of 94% and a specificity of 62%.[41] Conversely, an FC concentration >250 µg/g has a positive predictive value of 78.4% for the presence of ulcers in CD patients with colonic

involvement.[41] After surgery, available evidence showed that FC values <100 µg/g strongly suggest no recurrent disease.[42] In CD asymptomatic patients, two consecutive elevated FC levels were associated with a higher risk of relapse within 3 months.[43] In a cohort of patients with CD treatment with tumor-necrosis factor (TNF) antagonists, a concentration of FC ≤100 µg/g after induction therapy was highly associated with clinical remission at 1 year.[44] FC concentration may vary with disease location with FC levels lower in patients with ileal disease compared with those with colonic involvement[45]; however, any abnormal FC value must guide treatment decision regardless of ileal or colonic involvement, and initial investigations in CD should include FC at the first colonoscopy.[46] FC might also guide decisions for de-escalation.

How to modify the course of CD? From early intervention to early disease control

Two RCTs (RAPID and AZTEC) studied early initiation of azathioprine in CD (before 6 months compared with conventional management and before 8 weeks compared with placebo respectively), but neither of these trials showed a clear benefit.[47,48] Early introduction of combined immunosuppression (before 12 weeks) was studied in the RCT REACT, including 1819 patients first treated with corticosteroids.[49] In this study, combination therapy with adalimumab or infliximab associated with an immunosuppressant (thiopurine or methotrexate) did not result in a better clinical remission (corticosteroid-free remission, defined by the Harvey–Bradshaw Index ≤4) at 1 year compared with conventional management,[49] however, many patients in the trial had had CD for several years. Conversely, patients treated with early combination therapy had a significant reduction in serious adverse events such as surgery,[49] suggesting that early initiation of potent agents might change the natural history of CD. Other trials showed that patients with recent disease reached remission more frequently than patients with longstanding disease whether treated with adalimumab alone,[50] certolizumab[51] or vedolizumab.[52] As already shown in rheumatology,[53] these studies underline the importance of early intervention in CD. More importantly, in the light of the CALM results, early control of disease activity more than early intervention might be the key to changing the natural history of CD. The results were consistent across studies regardless of the mechanism of action of the treatments administered, suggesting that the nature of the first treatment might no be determinant. Ten to twenty percent of patients with mild to moderate CD will have an uncomplicated evolution,[54] and tight control might prevent overtreatment in this population. These patients, who are more likely to remain quiescent after treatment for the first flair, might, for example, be treated with one course of budesonide for mild ileitis or one course of prednisolone for mild colitis associated with close monitoring.

Should we abandon poor prognostic factors in the era of tight monitoring?

Current guidelines in CD identified four poor prognosis factors: perianal involvement, ileocolonic and jejunal location, diagnosis of CD before the age of 40 years, and the need to treat the initial flare with steroids.[46] Current smoking and penetrating or stricturing disease behaviour are also risk factors for surgery in CD.[55] Patients with more than one poor prognosis factor could benefit from early introduction of biologics.[46] This is a field of active research because reliable risk factors might individualize patients that need intensive therapy in order to prevent complications and, conversely, avoid overtreatment in patients with good disease prognosis. More prognosis factors (such as serologic or genetic factors) were identified, especially in children[56] but were never implemented in clinical practice mainly due to their insufficient predictive value. These prognostic factors appear to be even less significant if patients are closely monitored; exempting patients with multiple risk factors, tight monitoring with a rapid step-up strategy should be recommended with the ultimate aim of preventing disabilities and bowel damage.

Discussion

The primary goal of CD management should be the prevention of long-term disability and bowel damage. In the past decade patients have been undertreated because of strategies targeting only the symptoms. In 2010 the concepts of early CD and the window of opportunity emerged,[57,58] leading broadly to the early use of potent agents (mainly anti-TNF therapy) in a top-down strategy. However, this strategy might lead to overtreatment in the 10–20% of patients with a benign natural history,[54] and raises both economic and safety concerns. Early disease control based on close monitoring using non-invasive radiologic and/or biological markers might be the answer to altering the natural course of CD and maximizing the risk–benefit ratio of such a strategy. Proactive therapeutic drug monitoring was also recently validated in a prospective study and appears to be associated with better long-term outcomes.[59] It might be a useful complementary monitoring tool. We refer the readers to recent review articles on the clinical utility of drug monitoring in IBD.[60] Many poor prognostic factors have been

described in CD,[61–63] which may guide treatment decisions in an attempt to avoid complications or overtreatment; however, this approach appears less relevant if there is tight control of disease activity, except in patients with multiple risk factors who should benefit from early introduction of biologics. Some factors may restrain the applicability and acceptance of T2T in everyday practice. The ongoing REACT2 study (ClinicalTrials.gov NCT01698307)[64] comparing clinical remission associated with endoscopical healing versus clinical remission alone using objective outcomes may allow prospective validation of T2T in the future. In the years to come we might be even more ambitious by achieving transmural and histological healing given the increase in our armamentarium. The ongoing CURE trial (Clinical Trial NCT03306446),[65] for example, will explore whether drug de-escalation can be considered in CD patients who benefited from early disease control with anti-TNF therapy and tight monitoring.

Declaration of conflicting interests

Thomas Chateau has no conflicts of interest to disclose. Peyrin-Biroulet reports personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen; grants from AbbVie, MSD and Takeda; and stock options: CTMA.

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