[REV. MED. CLIN. CONDES - 2019; 30(5) 339-343]

REVISTA MÉDICA CLÍNICA LAS CONDES
https://www.journals.elsevier.com/revista-medica-clinica-las-condes

Prevention of inflammatory bowel disease complications and recurrence

Prevención de complicaciones y recidiva de la enfermedad inflamatoria intestinal

Jacob E Ollech[a], Roni Weisshof[a], David T Rubin[a]✉.

[a] University of Chicago Medicine, Inflammatory Bowel Disease Center, Chicago, IL, USA.

INFORMACIÓN DEL ARTÍCULO

Historia del Artículo:
Recibido: 10 06 2019.
Aceptado: 12 08 2019.

Key words:
Inflammatory bowel disease, outcome, biomarkers, endoscopy, histology.

Palabras clave:
Enfermedad inflamatoria intestinal, objetivos, biomarcadores, endoscopía, histología.

ABSTRACT

This article describes the need for objective treatment and management goals of inflammatory bowel disease to monitor disease course and progression. We discuss the "treat to target" or "tight control" approach as an evolving treatment strategy in order to prevent future complications. Biochemical, endoscopic, and histologic outcomes are highlighted in this work.

RESUMEN

Este artículo describe la necesidad de utilizar objetivos para el manejo y tratamiento de los pacientes con enfermedad inflamatoria intestinal, para monitorizar el curso y la progresión de la enfermedad. Se discute el enfoque de tratamiento por objetivos (T2T) o control estricto como una estrategia de tratamiento que permitiría prevenir futuras complicaciones. Se destacan en este trabajo marcadores bioquímicos (biomarcadores), endoscópicos e histológicos.

✉ Autor para correspondencia
Correo electrónico: drubin@uchicago.edu

https://doi.org/10.1016/j.rmclc.2019.08.001
e-ISSN: 2531-0186/ ISSN: 0716-8640/

BACKGROUND

Historically, the treatment goal in inflammatory bowel disease (IBD) was symptomatic control of the disease. In the 1960s, the only treatment options that existed for patients with IBD were steroids, sulfasalazine, and surgery, none of which were shown to provide consistent long-term healing of the bowel. Physicians used symptoms to guide the use of available therapies in treating active disease. If patients did not respond to medical treatment or had complications such as bowel obstructions or abscesses, they were referred for surgical management, which not infrequently, resulted in subsequent repeat surgery.

With the introduction of immunomodulators and even more so, tumor necrosis factor (TNF) inhibitors and newer biologic drugs, mucosal healing has become an attainable goal in a substantial number of patients, thus changing the course of disease in IBD. With time, it was recognized that clinical symptoms and disease activity, as defined by endoscopy, are poorly correlated in patients with IBD[1]. Therefore, treatment and management began to focus on more objective, rather than subjective, parameters such as inflammatory biomarkers, mucosal healing as seen by endoscopy and even histologic improvement in order to monitor disease course and progression. Unfortunately, we still do not achieve preferred outcomes in everyone with IBD due to many reasons, including not starting effective treatment after irreversible damage has already happened, or using ineffective or non-optimized therapy to treat patients.

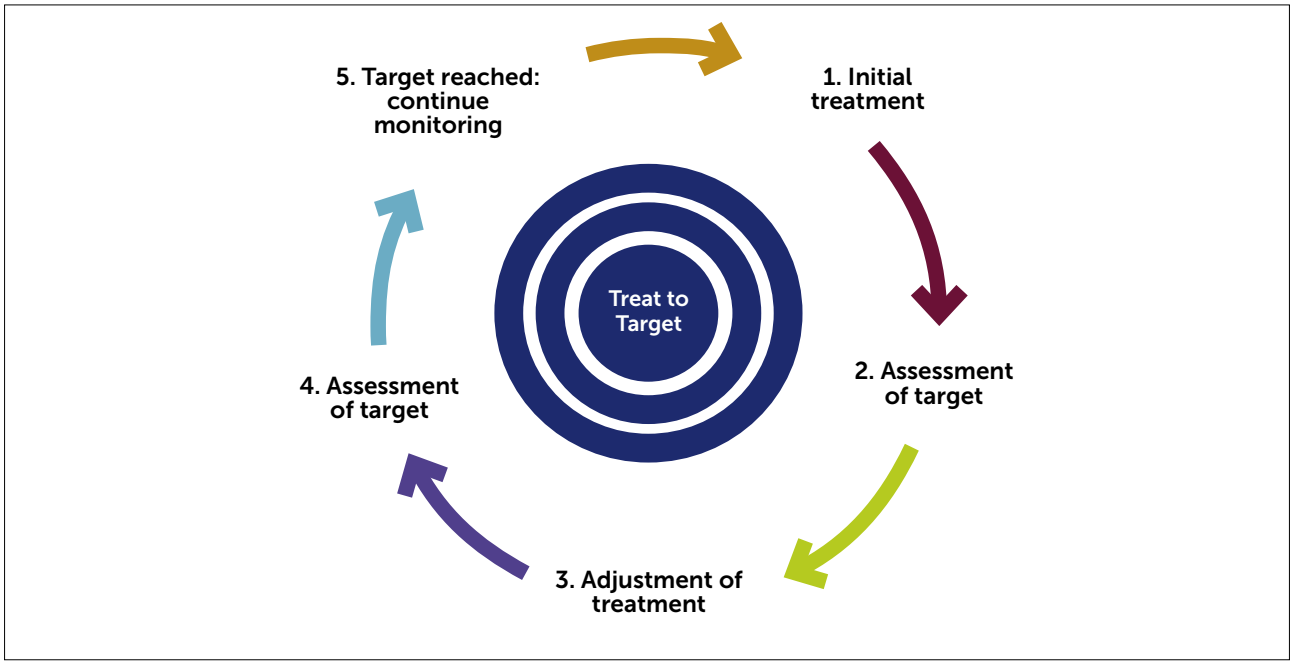
PROACTIVE MANAGEMENT IN IBD

The concept that targeted therapy with the use of objective markers will lead to better treatment outcomes is a relatively new paradigm in IBD. The so-called **"treat to target"** or **"tight control"** approach is becoming the standard of care in the treatment of many chronic conditions including IBD. This treatment strategy is evolving, as it has become more apparent that treatment based on symptomatic response alone is insufficient in preventing future complications and that regular assessment of disease activity via objective endoscopic and biological markers allows for closer monitoring, with the expectation of reducing exacerbations of disease and future complications (Figure 1).

This strategy is not unique to IBD, and indeed such methods have been adopted in other medical disciplines. For example, target goals are used for HbA1c levels for patients with diabetes and blood pressure for patients with hypertension.

On the other hand, targets for complex diseases characterized by a progressive, debilitating inflammatory process with accumulating damage (like IBD) is more challenging. However, the approach of the "treat to target" method may be generalized, and it involves a baseline assessment of the patient's clinical status using subjective and objective data and establishing target goals in respect to these evaluation. Continued assessment then occurs at predetermined time frames, thus allowing the physician to either continue current treatment or make modifications as needed to avoid long term damage and disability.

Figure 1. Schematic of a treat-to-target approach to IBD management



Choosing the correct target goals has been an evolving challenge in IBD. Ultimately the management goal for patients with IBD should be to induce and maintain remission, which is defined by both patient-reported outcomes and objective markers.

Classic clinical assessment scores such as the Crohn's Disease Activity Index (CDAI) and the Mayo Score for ulcerative colitis (UC) were mostly developed for use in the clinical trial setting and do not necessarily reflect what bothers patients in their day to day struggles with IBD. For example, the Mayo Score for UC was initially devised in 1987 for a clinical trial for pH-dependent 5-ASA at the Mayo Clinic[2]. These scores are also subjective and contain some non-clinical data. For example, in the CDAI, laboratory variations of "normal" hematocrit in men and women can often lead to markedly different CDAI scores; similarly, changes in weight can lead to score differences as well. In the Mayo Score the Physician's Global Assessment (sense of well-being), as well as the need for endoscopy, is not patient-reported. Given the different issues alluded to above, a program was initiated by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) for Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)[3]. It examined potential treatment targets for IBD to be used in a "treat to target" clinical management strategy using an evidence-based expert consensus process. The experts agreed that both endoscopic and clinical/patient-reported outcomes (PROs) were important goals in IBD management and these were incorporated into the final recommendations. The target for UC was clinical/PRO remission (defined as resolution of rectal bleeding and diarrhea/altered bowel habit) and endoscopic remission (defined as a Mayo endoscopic subscore of 0-1). Histological remission defined as no active inflammation, such as erosions, crypt abscesses or focal neutrophil infiltration was considered an adjunctive goal. Clinical/PRO remission was also agreed upon as a target for Crohn's disease (CD) and defined as resolution of abdominal pain and diarrhea/altered bowel habits and endoscopic remission, defined as resolution of ulceration at ileocolonoscopy, or resolution of findings of inflammation on cross-sectional imaging in patients who can not be adequately assessed with ileocolonoscopy. Ongoing work at an updated STRIDE paper is occurring.

SPECIFIC OBJECTIVE CANDIDATE TARGETS

Biochemical outcomes

There is a definite need for objective and accurate non-invasive markers of disease activity in IBD. Since these do not require invasive interventions, they are easier to perform and are preferred by patients. C-reactive protein (CRP) and fecal calprotectin (FCP) are considered to be helpful biomarkers of disease activity. CRP is an acute phase protein manufactured by the liver as a response to T cells and macrophage activation and subsequent secretion of cytokines interleukin (IL)-6, IL-1, and TNF-α. The correlation between elevated levels of CRP and disease activity is well established[4,5]. However, due to genetic differences, about 15-20% of patients do not raise CRP in response to luminal inflammation[6]. Overall, the mean sensitivity and specificity of CRP for endoscopically active disease in a recent meta-analysis was 0.49 and 0.92, respectively[6].

FCP is a protein released by neutrophils. When there is active inflammation in the gastrointestinal tract, more white blood cells migrate to the gut wall, resulting in more FCP in the lumen and stool. The correlation between FCP values and endoscopic or histologic remission was demonstrated in a recent study. FCP <250 µg/g predicted endoscopic remission with a sensitivity of 67% and a specificity of 77%, while values below 200 µg/g predicted histological remission with a sensitivity of 71% and a specificity of 76%[7].

CRP and FCP can be exploited for several scenarios, specifically for patients who raise these markers with inflammation. In addition, increased CRP at baseline is a predictor for response to infliximab therapy[8]. Consecutive tests with these biochemical markers can be used to assess response to drug therapy with rapid normalization correlated with sustained response, while loss of response is expected in patients who fail to do so[8]. Additionally, an FCP of less than 121 µg/g after induction with anti-TNF medications was predictive for mucosal healing with a negative predictive value of 90%[9]. Of note, FCP had demonstrated lower sensitivity in detecting ileal inflammation in CD patients[9]. Elevated FCP has also been shown to predict endoscopic relapse following ileocecal resection, and most recently is associated with relapse after therapeutic de-escalation defined as any decrease of dose; or increase of interval between two infusions/injections; or medication discontinuation; or replacement by a 'lower' medication (5-aminosalicylic acid [ASA] <thiopurines or methotrexate <biologics)[10,11].

Due to their attractiveness as non-invasive, objective, treatment responsive markers, biochemical markers are used as surrogates in the decision-making algorithm. The STRIDE recommendations also supported this approach[3].

Endoscopic outcomes

Accumulated data in the past several years have established mucosal healing (MH) as an accurate predictor for multiple critical outcomes in IBD. The traditional definition for MH in CD is a relatively normal appearing mucosa, with possible slight erythema or granularity but no ulcerations[3-5]. For UC it is usually defined as an endoscopic Mayo Score of 0 to 13. The difference between complete and partial mucosal healing has not been well established. In a Norwegian population-based

study MH was associated with a low risk of future colectomy (p = 0.02). MH was also associated with a decreased need for future steroid treatment (p = 0.02)[12].

Conversely, the appearance of severe endoscopic disease predicts long-term outcomes in CD as seen in a longitudinal cohort study that followed 102 CD patients. In this study at eight years, the probability for colectomy was 62% in patients with severe endoscopic findings at colonoscopy, versus 18% for patients without ulcerations at colonoscopy[13]. The same is true for ileal CD. Post-hoc analysis of the "Step-up/Top-Down" study including mostly patients with ileal or ileocolonic disease, demonstrated significantly higher steroid-free remission rates by four years for early-stage CD patients with complete MH (p = 0.036; Odds Ratio = 4.3)[14].

The rapid endoscopic response to treatment was also shown to predict long term outcomes. In a post-hoc analysis of the ACT trials, infliximab-treated patients with lower week 8 Mayo endoscopy subscores were less likely to progress to colectomy through 54 weeks of follow-up (p=0.0004)[15].

Histologic outcomes

So far, the data regarding histologic remission as a predictor of significant long-term outcomes are less well defined. In a recent retrospective study from our center describing 646 UC patients, histologic normalization defined as a completely normal mucosa with no features of active or chronic inflammation was independently associated with increased odds of relapse-free survival compared to histologic quiescence in which, despite a lack of active inflammation, features of chronicity including crypt atrophy or branching were still present (P=0.007)[16]. Ultimately, histology may be an even better predictor than endoscopy due to the potential for objective evaluation and the more significant amount of information that can be extracted from the sample. Some earlier data published in 2016 demostrated that histological grade predicted the need for corticosteroid use and acute severe colitis requiring hospitalization, whereas endoscopic grade did not[17]. Similarly, histologic grade of inflammation has been associated with risk of colonic neoplasia[18]. For now, however, a significant limitation in using histologic healing as a target for therapy is the broad diversity in the definition of histologic severity of disease. Currently, histologic remission is only used as an adjunctive goal in treating IBD.

TREATING TO A PRESPECIFIED TARGET

The question of whether a "treat to target" management strategy leads to better outcomes in IBD is being actively studied. In 2018, a landmark study (CALM) showed the superiority of a "treat to target" approach when treating IBD.

CALM was an open-label, randomized controlled trial, done in 22 countries, which evaluated 244 adult patients with active CD. The patients were randomly assigned to - a "clinical management" group and a "tight control" group. In each group, management could be escalated from no treatment to adalimumab, which could be increased in frequency, and then finally to combination therapy with adalimumab plus daily azathioprine.
In the "clinical management" group, decisions to escalate were based on the patient's symptoms, whereas in the "tight control" group, these were also driven by biomarkers of inflammation (FCP and CRP) and treatment was escalated even if these patients were in clinical remission.

At the end of the year-long study, a significantly higher proportion of patients in the tight control group had endoscopic healing (46% versus 30% in the clinical management group). These results provide compelling evidence that treatment based on biomarkers, rather than symptoms alone, does a better job at controlling CD[19].

The same concept is valid in the post-operative setting where a large prospective trial (POCER) clearly showed a benefit to a proactive colonoscopy at six months post-ileo-cecal resection, followed by treatment optimization based on the Rutgeerts score regardless of symptoms[20].

CONCLUSIONS

In the past ten years, we have moved beyond symptom improvement in the management of IBD and into disease control to prevent IBD related complications and recurrence. This is done by incorporating objective measures of inflammation into our treatment algorithm. The strategy of treating to achieve specific targets has true benefits in multiple long-term critical outcomes. It is essential to employ strategies of continuous disease and drug monitoring to keep patients under optimal control. Emerging data demonstrate that this treat to target approach is both feasible and practical.

Declaración conflicto de intereses
Potential Competing Interests: JEO and RW have no relevant disclosures. DTR is a consultant and has received grant support from Abbvie, Merck & Co., Janssen, Takeda and Pfizer.
Funding: The present investigation has not received specific grants from agencies of the public sector, commercial sector or non-profit entities.

REFERENCES

1. *Modigliani R, Mary JY, Simon JF, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990;98(4):811-818.*
2. *Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-1629.*
3. *Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015;110(9):1324-1338.*
4. *Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481-517.*
5. *Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114(3):384-413.*
6. *Mosli MH, Zou G, Garg SK, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2015;110(6):802-819; quiz 820.*
7. *Mak WY, Buisson A, Andersen MJ, et al. Fecal Calprotectin in Assessing Endoscopic and Histological Remission in Patients with Ulcerative Colitis. Dig Dis Sci. 2018;63(5):1294-1301.*
8. *Jürgens M, Mahachie John JM, Cleynen I, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(5):421-427.e1.*
9. *Guidi L, Marzo M, Andrisani G, et al. Faecal calprotectin assay after induction with anti-Tumour Necrosis Factor α agents in inflammatory bowel disease: Prediction of clinical response and mucosal healing at one year. Dig Liver Dis. 2014;46(11):974-979.*
10. *Wright EK, Kamm MA, De Cruz P, et al. Measurement of Fecal Calprotectin Improves Monitoring and Detection of Recurrence of Crohn's Disease After Surgery. Gastroenterology. 2015;148(5):938-947.e1.*
11. *Buisson A, Mak WY, Andersen MJ Jr, et al. Faecal calprotectin is a very reliable tool to predict and monitor the risk of relapse after therapeutic de-escalation in patients with inflammatory bowel diseases. J Crohns Colitis. 2019;13(18):1012-1024.*
12. *Frøslie KF, Jahnsen J, Moum BA, Vatn MH, IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412-422.*
13. *Allez M, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97(4):947-953.*
14. *Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138(2):463-468.*
15. *Colombel JF, Rutgeerts P, Reinisch W, et al. Early Mucosal Healing With Infliximab Is Associated With Improved Long-term Clinical Outcomes in Ulcerative Colitis. Gastroenterology. 2011;141(4):1194-1201.*
16. *Christensen B, Hanauer SB, Erlich J, et al. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. Clin Gastroenterol Hepatol. 2017;15(10):1557-1564.e1.*
17. *Bryant R V, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over six years of follow-up. Gut. 2016;65(3):408-414.*
18. *Colman RJ and Rubin DT. Histologic inflammation increase the risk of colorectal neoplasia in ulcerative colitis: a systematic review. Intest Res. 2016;14(3):202-210.*
19. *Colombel J-F, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomized, controlled phase 3 trial. Lancet (London, England). 2018;390(10114):2779-2789.*
20. *De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomized trial. Lancet. 2015;385(9976):1406-1407.*