



REVIEW

Treat-to-target approach in the management of inflammatory Bowel disease



Paulina Nuñez F^{a,*}, Uma Mahadevan^b, Rodrigo Quera^c, Constanza Bay^d, Patricio Ibañez^e

^a Division of Gastroenterology, University of Chile, Hospital San Juan de Dios, Santiago, Chile a Division of Gastroenterology, University of Chile, Hospital San Juan de Dios, Santiago, Chile

^b Division of Gastroenterology, University of California, San Francisco, United States

^c Inflammatory Bowel Disease Program, Gastroenterology Department, Clínica Las Condes, Santiago, Chile

^d Department of Pediatrics, Pontifical Catholic University of Chile, Santiago, Chile

^e Inflammatory Bowel Disease Program, Gastroenterology, Chile

Received 23 May 2020; accepted 29 June 2020

Available online 16 October 2020

KEYWORDS

Crohn's disease;
Ulcerative colitis;
Treat-to-target;
Monitoring;
Biomarkers

Abstract With the advent of biologic and small molecule therapies, there has been a substantial change in the treatment of inflammatory bowel disease. These advances have had a great impact in preventing disease progression, intestinal damage and, therefore, have contributed to a better quality of life. Discordance between symptom control and mucosal healing has been demonstrated. This has led to the search for new disease control targets. The treat to target strategy, based on expert recommendations and now a randomized controlled trial, has determined that clinical and endoscopic remission should be the goal of therapy. Biomarkers (fecal calprotectin) can be a surrogate target. Although histological healing has shown benefits, there is inadequate evidence and inadequate therapy for that to be a fixed goal at this time.

This review will focus on therapeutic goals, according to the evidence currently available, and evaluate strategies to achieve them.

© 2020 Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE

Enfermedad de Crohn;
Colitis ulcerosa;
Tratamiento por objetivos;
Monitorización;
Biomarcadores

Enfoque «Treat to target» en el tratamiento de la enfermedad inflamatoria intestinal

Resumen Con la llegada de las terapias biológicas y moléculas pequeñas, ha habido un cambio sustancial en el tratamiento de la enfermedad inflamatoria intestinal, lo que ha permitido evitar la progresión de la enfermedad, el daño intestinal y, por ende, mejorar la calidad de vida de estos pacientes. Se ha demostrado la discordancia entre el control de los síntomas y la curación mucosa, lo que ha llevado a buscar nuevos objetivos de control de la enfermedad. La estrategia de control por objetivos, definido en base a recomendaciones de expertos, ha determinado que

* Corresponding author.

E-mail addresses: paulinanunez@gmail.com, pnunez@med.uchile.cl (P. Nuñez F).

se debe buscar en un tiempo establecido la remisión clínica y endoscópica. Hay estudios que han sugerido que los biomarcadores (calprotectina fecal) deben ser parte de los objetivos. Aunque la curación histológica ha demostrado beneficios, aún falta evidencia para que sea considerada como tal. Esta revisión se centrará en los objetivos terapéuticos, con la evidencia disponible actualmente, evaluando además las estrategias para alcanzarlos.

© 2020 Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The therapeutic management of Inflammatory Bowel Disease (IBD) has improved in recent years with new therapeutic options including biologic and small molecule therapies. We evolved from the use of repetitive courses of corticosteroids to an early introduction of therapies that can modify the natural history of the disease.¹ Most of the time, the correlation between symptoms and endoscopic disease activity is poor and there is a high risk of reactivation and long-term disease complications. The treat to target approach (T2T) proposes a serial evaluation of disease activity through objective clinical, endoscopic markers and biomarkers. This monitoring will reduce flares and reduce future complications from disease progression. This review will explain the importance of these objectives for Ulcerative Colitis (UC) and Crohn's Disease (CD).

Therapeutic objectives

Historically IBD therapies sought symptom control, however, following the advent of new therapeutic modalities, more stringent goals could be sought.² It is mucosal healing (endoscopic remission) which has been associated with a lower risk of reactivation, hospitalization, colectomy requirements, and in the long term, theoretically, lower risk of progression to colorectal neoplasia.^{3–6}

In 2015, a committee of 28 specialists devised the first IBD management consensus (STRIDE) "Selecting therapeutic targets in IBD", which was based on both clinical and endoscopic objectives.⁷ This is where the concept of "treat to target" (T2T) was born for IBD (a term that was conceived in rheumatology). It involves the identification of a predefined objective which will be pursued with appropriate therapy with strict monitoring and optimization. This approach has led to better long-term results, including clinical, endoscopic, biomarker, and recently histological objectives.^{8,9}

Clinical objectives

It is important to define and clarify certain concepts such as clinical remission, clinical response and quality of life objectives (Fig. 1).^{10–14} IBD patients have a significantly lower QoL compared to the general population.¹⁵ Disease activity associates with poorer QoL; female gender, fatigue, anxiety levels and depression also contribute to decrease it.^{16–18} Regarding the latter, there is a significant associa-

tion between depression symptoms and clinical activity in CD ($p=0.007$) and UC ($p=0.005$).¹⁹ A French national cross-sectional study evaluating PRO showed that 55.1% of CD patients and 37.3% of UC patients had a poor quality of life.²⁰

Guidelines recommended that clinical follow-up should be every 3 months in case of active disease and every 6–12 months during remission.⁷

Endoscopic objectives

Recent studies both in clinical trials and in post hoc analysis, have made it possible to recommend endoscopic healing as an objective in patients with IBD. This objective is associated with a better prognosis, lower hospitalization rates, a lower risk of relapse and of surgical interventions.^{21,22}

STRIDE recommends evaluating the resolution of ulcers and mucosal friability within 6–9 months in CD and 3–6 months in UC after starting therapy.⁷ In a recent systematic review, there were no variations in the times suggested to assess endoscopic resolution.^{23,24}

A study that included a 6-month follow-up in 248 UC patients observed a higher percentage risk of relapse in patients who had reached an index of Mayo of 1 vs the group with a Mayo of 0, (36.6% vs. 9.4% with $p < 0.001$).²⁵ Since accumulated evidence would suggest there is a better prognosis, it has been proposed to define endoscopic remission in UC as a UCEIS of 0 or an endoscopic Mayo of 0 points (Fig. 2).^{26–29} Recently, deep remission (clinical and endoscopic) in early, moderate to severe CD patients has been associated with decreased risk of disease progression so endoscopic remission became a major stake in CD.³⁰

Biomarkers

The utility of FC in disease monitoring and as a predictor of relapse has been established.^{31,32} It has a high sensitivity regarding endoscopic activity in both UC and CD, however, in CD the sensitivity changes according to phenotype and location.³³

Using ROC curves, it was possible to determine that in UC patients a $FC < 200 \text{ mcg/g}$ ($AUC = 0.74$) correlated with an endoscopic Mayo of 0, with sensitivity (S), specificity (E), positive predictive value (PPV) and negative (NPV) of 0.75, 0.8, 0.22 and 0.98 respectively. It was also observed that the same FC cut-off point reflected histological remission with an S, E, PPV and NPV of 0.71, 0.76, 0.30 and 0.95 respectively.³⁴ Although the FC threshold that would

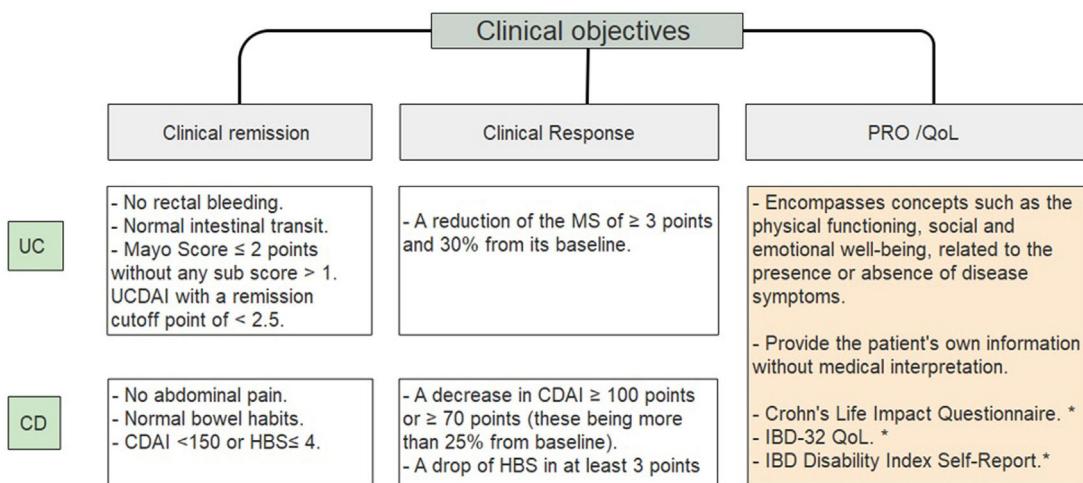


Figure 1 Clinical objectives in IBD.¹⁰⁻¹⁴ UC, ulcerative colitis; CD, Crohn's disease; UCDAI, Ulcerative colitis disease activity index; CDAI, Crohn's disease activity index; HBS, Harvey Bradshaw score; PRO, patient related outcome; QoL, quality of life. * Systematic review showed moderate validation for these scores¹⁴.

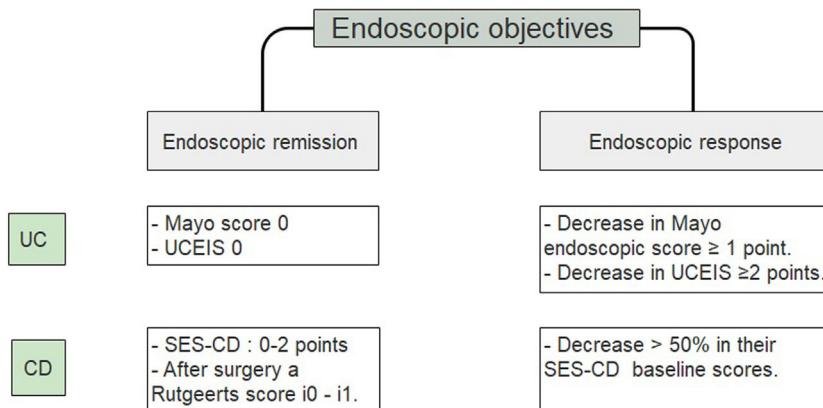


Figure 2 Endoscopic objectives in IBD.²⁶⁻²⁹ UC, ulcerative colitis; CD, Crohn's disease; UCEIS, ulcerative colitis endoscopic index of severity; SES CD, simple endoscopic score for Crohn's disease.

indicate mucosal healing is still in validation.³⁵ In a recent update on T2T management of UC, AGA proposes a cut point of 100 mcg/g to consider remission of the disease,²³ this being confirmed by other authors.³⁶ FC concentration can vary depending on the location of the disease, being lower at the ileal level. However, an altered value of this parameter can help to make treatment decisions.³⁷ Thus, in patients with asymptomatic CD, two measurements of elevated FC can predict a higher risk of relapse in the following 3 months.³⁸ Therefore, it is recommended to carry out a FC 2–3 months after starting therapy.³⁹

FC is also used to monitor post-surgical CD, with values $< 100 \mu\text{g/g}$ suggestive of remission.⁴⁰ In turn, FC could also be used in those patients who are scheduled to withdraw drugs. In a prospective study of 160 patients with IBD, FC levels $> 100 \mu\text{g/g}$ at 8 weeks after therapeutic de-escalation was the best threshold to predict clinical relapse in these patients with a HR = 3.96 [2.47–6.35]; $p < 0.0001$.⁴¹

Radiological objectives

Imaging is a very attractive non-invasive monitoring option. However, to date, studies only support its use in patients with CD.^{23,42} In a retrospective study of 150 patients with CD observed for 9 years, those with resolution of the inflammation by either computed tomography enterography or magnetic resonance enterography were associated with a decrease in hospitalizations (HR = 0.28, 95 CI –0.15 to 0.50) and surgery (HR = 0.34, 95 CI 0.18–0.63).⁴³ Other studies have also shown that achieving radiological remission would be associated with a lower probability of requiring therapy optimization, hospitalizations and surgery at one-year term (HR = 0.27, 95% CI 0.13–0.56; $p = 0.001$).⁴⁴

Diffusion resonance modalities have shown high sensitivity in detecting mucosal lesions. They could have potential applicability in the future, with the Magnetic Resonance Index of Activity (MaRIA) and the Nancy Index being the most widely used.⁴⁵⁻⁴⁷

In perianal CD, studies have evaluated the percentage of remission with anti-TNF by magnetic resonance imaging (MRI), with a good inter-observer correlation ($p < 0.001$). To date new scores are sought to achieve greater precision.^{48,49}

Ultrasound (US) is another low-cost, widely available, non-invasive method that allows evaluating patients with IBD. This technique is widely used in Europe. It can determine wall thickening, fat compromise, masses, abscesses, or fistulas, and Doppler can help assess the increase in local vasculature indicating inflammation. Although there are activity scores, none have yet been validated.^{50,51} The European guidelines for Crohn's and Colitis conclude that both MRI and US have similar performance in evaluating activity in ileocolonic CD.⁵² A recently published study including 80 CD patients treated with anti-TNF for at least one year, confirmed the usefulness of ultrasonography as a non-invasive method in the follow-up and management of patients with CD.⁵³

In STRIDE, it was recommended to evaluate the resolution of the inflammation by images in CD when it was not possible by endoscopy, but not in UC.⁷ To date, there are still no changes in these objectives.

Histological objectives

Histological remission was not recommended as a therapeutic objective in the AGA systematic review in 2019.²³ However, different studies have suggested that achieving histological remission in UC may be associated with a better long-term prognosis, regarding relapse-free periods, use of corticosteroids and hospitalizations.⁵⁴ Danese et al., recently published that complete remission should be considered as one of the main therapeutic objectives in UC since it is possible to find histological alterations even in endoscopically healthy mucosa.⁵⁵

Patients who achieve complete remission (clinical, endoscopic and histological remission), had a lower risk of clinical relapse than the group that persisted with histological activity.^{56,57} The presence of inflammatory activity in biopsies in patients with endoscopic mucosal remission would be associated with an increased risk of clinical relapse at 18 months.⁵⁸ Even though only complete histologic normalization of the bowel (non segmental normalization) was associated with improved relapse-free survival (HR 0.23; 95 CI 0.08–0.68; $p = 0.008$).⁵⁹

In a Cochrane review it was established that Nancy Index and Robarts Histopathology Index (RHI) are the his-

tological indices with the highest validity. However, until now none of them have been fully validated to determine the cut-off point to define histological cure.⁵⁹ This can be observed in the VARSITY study, which is the first study comparing "head to head" two biologic therapies (adalimumab vs. vedolizumab) in patients with moderate to severe UC. Geobes and RHI scores were used to define histological cure. The remission values at 52 weeks for Geobes were 10% for vedolizumab and 3% for adalimumab and for RHI 38 and 20% respectively.^{60,61} The role of histological remission in CD is less clear and what is known is mainly based on retrospective studies. However, in a recent study comparing ustekinumab vs placebo, histological response at 8 weeks was associated with a lower risk of relapse both clinically and endoscopic at 44 weeks.⁶² Furthermore, in patients with ileal CD, histological rather than endoscopic remission was associated with a lower risk of clinical relapse (HR 2.05; $p = 0.031$), need to scale up in therapies (HR 2.17; $p = 0.011$) and use of corticosteroids (HR 2.44; $p = 0.018$).⁶²

Currently, studies that validate scaling up therapy or de-escalation are still lacking.⁶³

How do we achieve those goals?

The introduction into clinical practice of pharmacological monitoring of anti-TNFs, determining their serum levels or the presence of antibodies against the drug, has allowed personalized therapy and thus a better strategy to achieve therapeutic objectives, definitions in Table 1.⁶⁴ However, pharmacological monitoring has not currently been suggested for clinical practice for other biologics (vedolizumab or ustekinumab) nor small molecule therapy (tofacitinib).^{65,66} It must be considered that 30% of patients may have a primary failure despite optimization of therapy. Up to 50% of those who achieve endoscopic and clinical remission goals may have a loss of response.⁶⁷ The CALM study showed a 48-week endoscopic remission rate of 45.9% in tight control (the one that uses objective markers of inflammation, which allows them to optimize therapies if necessary) vs 30.3% in routine clinical control (based only on achieving clinical objectives) with $p = 0.010$.⁶⁸ In a follow-up study of the CALM study with a mean of 3 years, those who achieved early (at 12 weeks) and deep remission had a lower risk of disease progression regardless of being followed with a conventional or strict approach.⁶⁹

In turn, in subsequent analyzes of the TAILORIX study showed that more than the strategy used, it was the high

Table 1 Definitions and concepts in therapeutic goals in IBD⁶⁴.

Therapeutic drug monitoring: measurement of drug levels and antibodies, evaluating the effectiveness of the drug, its metabolism and immunogenicity. This management allows guiding therapies to adjust or change.

1) Proactive: is the approach of empirically measuring drugs levels and antibodies in order to improve response rates and prevent loss of response by looking for drug concentrations that are considered in an optimal therapeutic range.

2) Reactive: is the approach of measuring drugs levels and antibodies in patients that show inflammatory activity.

a) **Non-responder (primary):** patient in biologic therapy who does not achieve remission or response after optimization of therapy.

b) **Loss of response (secondary):** a patient who achieves a response with a biological or small molecule drug but loses response over time.

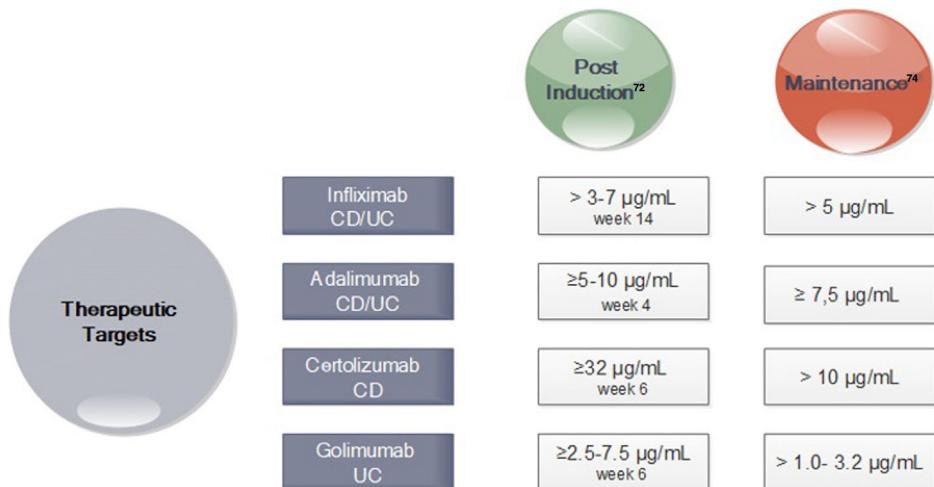


Figure 3 Drug Concentration Targets for Anti-TNF agents after Induction and during Maintenance⁷¹⁻⁷⁴. *CD Crohn's disease; UC ulcerative colitis. *In perianal disease would be necessary high levels of anti-TNF.

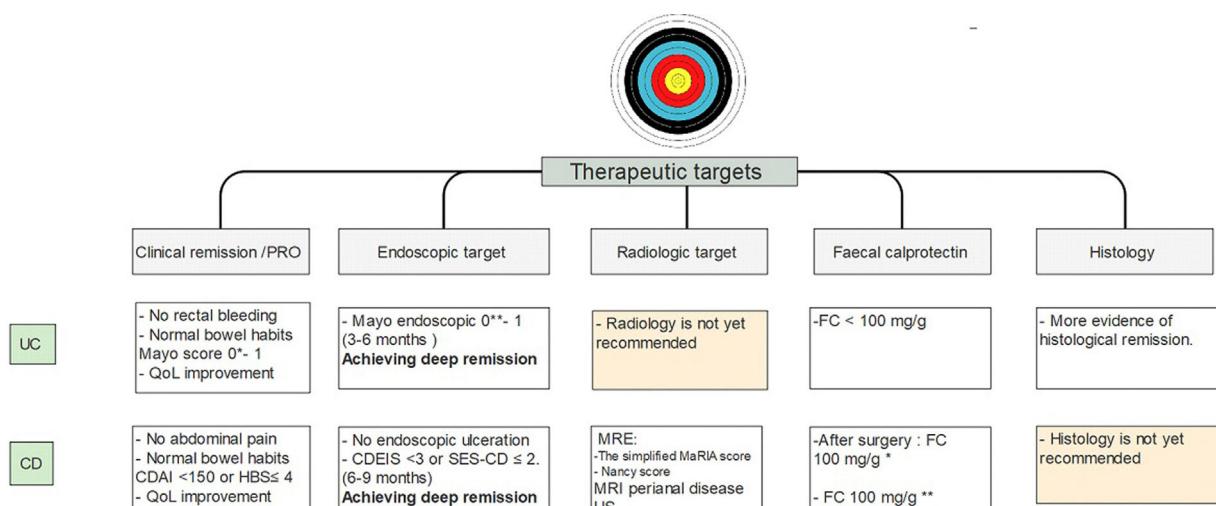


Figure 4 Treat to target approach in IBD patients^{10-14,26-28,37-40,54-58,62}. UC, ulcerative colitis; CD, Crohn's disease; MRE, magnetic resonance enterography; US, ultrasonography; FC, fecal calprotectin. * Strongly suggest no recurrent disease. ** Highly associated with clinical remission at 1 year.

levels of infliximab in week 2 (>23.1 mg/ml) and week 6 (>10 mg/ml) that were associated with mucosal healing at 12 weeks.⁷⁰ Optimal therapeutic ranges of anti-TNF that ensure an optimal response have been established for both induction and maintenance (Fig. 3).⁷¹⁻⁷⁴

The AGA therapeutic monitoring guidelines recommend a reactive approach,⁷³ meaning testing in those patients who present with activity, without making a recommendation about the proactive strategy. Others, however, recommend following a reactive strategy (in those non-responders or secondary loose response) as well as a proactive one (testing to maintain a desired level or to titrate induction therapy).⁷⁴ An expert consensus, using the Delphi method, recommends checking levels of anti-TNF at the end of induction, once during maintenance and in primary failure or loss of secondary response. This strategy is not recommended with other biological therapies.⁷⁵ In addition, the proactive strategy would allow

for a more rational confrontation when considering therapy retreat.^{76,77}

Is T2T practiced in "the real" world?

Although the need for objective management is clear, studies have shown differences in adherence to these. A study carried out in the United States found that in 56.4% of patients with CD and in 67.8% of the patients with UC, proactive management was performed in a 24-month follow-up, with colonoscopy being the instrument most widely used (87.9%).⁷⁸ A survey in New Zealand showed that 93% of gastroenterologists (40/43) measured levels of anti-TNF in the follow-up of patients treated with anti-TNF. The main reason for measuring them was lack of primary response or loss of response (87%).⁷⁹

Conclusion

Early disease control, with close monitoring and pre-established goals may be the best way to change the course of the disease.⁸⁰

Over the years, the therapeutic objectives of IBD have changed, advancing from clinical remission to deep remission (which includes clinical and endoscopic remission). Today, it is even more stringent, including quality of life indicators (PRO) and biomarkers, such as FC, in the follow-up of patients with IBD and may soon include histologic remission.

It is important to emphasize that there is more and more information that close monitoring of these objectives may change the course of the disease. These would indicate that achieving early histological remission, may avoid the long-term risks of colorectal cancer.⁸¹ Current therapeutic goals are described in Fig. 4.

Considering the current therapeutic objectives, the question that must be answered is what to do in those patients who are in clinical and endoscopic remission but maintain histological activity. Do we need to optimize? In this, we must undoubtedly consider each patient's risk factors and decide on a case-by-case.

Conflict of interests

The authors declare that they have no conflict of interest.

References

- Palmela C, Torres J, Cravo M. New trends in inflammatory bowel disease. *GE J Gastroenterol.* 2015;22:103–11.
- Peyrin-Biroulet L, Reinisch W, Colombel J, Mantzaris G, Kornbluth A, Diamond R, et al. Clinical disease activity. C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut.* 2014;63:88–95.
- Baars JE, Nuijti VJ, Oldenbug B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. *Inflamm Bowel Dis.* 2012;18:1634–40.
- Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology.* 2010;138:463–8.
- Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology.* 2011;14:1194–201.
- Shah SC, Colombel JF, Sands BE, Narula N. Mucosal healing is associated with improved long-term outcomes of patients with ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2016;14:1245–55.
- Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324–38.
- Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol.* 2015;13:1042–50.
- Battat R, Duijvestein M, Guizzetti L, Choudhary D, Boland B, Dulai P, et al. Histologic healing rates of medical therapies for ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2019;114:733–45.
- Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol.* 2009;7:1081.
- Thia KT, Sandborn WJ, Lewis JD, Loftus EV Jr, Feagan BG, Steinhart AH, et al. Defining the optimal response criteria for the Crohn's disease activity index for induction studies in patients with mildly to moderately active Crohn's disease. *Am J Gastroenterol.* 2008;103:3123–31.
- Jairath V, Khanna R, Zou GY, Stitt L, Mosli M, Vandervoort MK, et al. Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. *Aliment Pharmacol Ther.* 2015;42:1200–10.
- De Jong MJ, Huibregtse R, Masclee AAM, Jonkers DMAE, Pierik MJ. Patient-reported outcome measures for use in Clinical trials and clinical practice in inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol.* 2018;16:648–63.
- Van Andel EM, Koopmann BDM, Crouwel F, Noomen CG, de Boer NKH, van Asseldonk DP, et al. Systematic review of development and content validity of patient-reported outcome measures in Inflammatory Bowel Disease: do we measure what we measure? *J Crohns Colitis.* 2020, pii:jjaaa057.
- LeBlanc K, Mosli MH, Parker CE, MacDonald JK. The impact of biological interventions for ulcerative colitis on health-related quality of life. *Cochrane Database Syst Rev.* 2015. CD008655.
- Gibson PR, Vaizey C, Black CM, Nicholls R, Weston AR, Bampton P, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study. *J Crohns Colitis.* 2014;8:598–606.
- Parra RS, Chebli JMF, Amarante HMBS, Flores C, Parente JML, Ramos O, et al. Quality of life, work productivity impairment and healthcare resources in inflammatory bowel diseases in Brazil. *World J Gastroenterol.* 2019;25:5862–82.
- Van Assche G, Peyrin-Biroulet L, Sturm A, Gisbert JP, Gaya DR, Bokemeyer B, et al. Burden of disease and patient-reported outcomes in patients with moderate to severe ulcerative colitis in the last 12 months – multicenter European cohort study. *Dig Liver Dis.* 2016;48:592–600.
- Mikocka-Walus A, Pittet V, Rossel JB, von Känel R, Swiss IBD, Cohort study group. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2016;14:829–35, e1.
- Williet N, Sarter H, Gower-Rousseau C, Adrianjafy C, Olympie A, Buisson A, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *J Crohns Colitis.* 2017;11:165–74.
- Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology.* 2011;141:1194–201.
- Colombel JF, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, et al. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2014;12:414–22.
- Ungaro R, Colombel J, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a system review. *Am J Gastroenterol.* 2019;114:874–83.
- Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc.* 2006;63:433–42.

25. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, Uribarri L, Baston I, Ferreiro-Iglesias R, et al. Evaluation of the risk of relapse in ulcerative colitis according to the degree of mucosal healing (Mayo 0 vs 1): a longitudinal cohort study. *J Crohn's Colitis*. 2016;10:13–9.
26. Vuitton L, Peyrin Birolet L, Colombel JF, Pariente B, Pineton de Chambrun G, Walsh AJ, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. *Aliment Pharmacol Ther*. 2017;45:801–13.
27. Negreanu L, Voiosu T, State M, Voiosu A, Bengus A, Mateescu B. Endoscopy in inflammatory bowel disease: from guidelines to real life. *Ther Adv Gastroenterol*. 2019;12:1–10.
28. Daperno M, Comberlato M, Bossa F, Biancone L, Bonanomi AG, Cassinotti A, et al. Inter-observer agreement in endoscopic scoring systems: preliminary report of an ongoing study from the Italian Group for Inflammatory Bowl Disease (IG-IBD). *Dig Liver Dis*. 2014;46:969–73.
29. Vuitton L, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut*. 2016;65:1447–55.
30. Ungaro RC, Yzet C, Bossuyt P, Baert FJ, Vanasek T, D'Haenes GR, et al. Deep remission at 1 Year prevents progression of early Crohn's disease. *Gastroenterology*. 2020, <http://dx.doi.org/10.1053/j.gastro.2020.03.039>, pii:S0016-5085(20)30390-5.
31. Lasson A, Öhman L, Stotzer PO, Isaksson S, Überbacher O, Ung KA, et al. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: a prospective, randomized, controlled study. *United Eur Gastroenterol J*. 2015;3:72–9.
32. Kostas A, Siakavellas SI, Kosmidis C, Takou A, Nikou J, Maropoulos G, et al. Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease. *World J Gastroenterol*. 2017;23:7387–96.
33. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, 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;110:802–19.
34. Mak WY, Buisson A, Andersen MJ Jr, Lei D, Pekow J, Cohen RD, et al. Fecal calprotectin in assessing endoscopic and histological remission in patients with ulcerative colitis. *Dig Dis Sci*. 2018;63:1294–301.
35. Boon GJ, Mulder CJ, Gearry RB. Are faecal markers good indicators of mucosa healing in inflammatory bowel disease? *World J Gastroenterol*. 2015;21:11469–80.
36. Dulai PS, Jairath V. How do we treat inflammatory bowel disease to aim for endoscopic remission? *Clin Gastroenterol Hepatol*. 2019, pii:S1542-3565(19)31500-9.
37. Gecse KB, Brandse JF, van Wilpe S, Löwenberg M, Ponsioen C, van den Brink, et al. Impact of disease location on fecal calprotectin levels in Crohn's disease. *Scand J Gastroenterol*. 2015;50:841–7.
38. Ma C, Battat R, Parker CE, Khanna R, Jairath V, Feagan BG. Update on C-reactive protein and fecal calprotectin: are they accurate measures of disease activity in Crohn's disease? *Expert Rev Gastroenterol Hepatol*. 2019;13:319–30.
39. Gonczi L, Bessisow T, Lakatos PL. Disease monitoring strategies in inflammatory bowel diseases: what do we mean by "tight control"? *World J Gastroenterol*. 2019;25:6172–89.
40. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology*. 2015;148:938–47.
41. Buisson A, Mak WY, Andersen MJ, Lei D, Kahn SA, Pekow J, 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;13:1012–24.
42. Manetta R, Capretti I, Lelleggia N, Marsecano C, Viscido A, Bruno F, et al. Magnetic resonance enterography (MRE) and ultrasonography (US) in the study of the small bowel in Crohn's disease: state of art and review of the literature. *Acta Biomed*. 2019;90:38–50.
43. Deepak P, Fletcher JG, Fidler JL, Barlow JM, Sheedy SP, Kolbe AB, et al. Radiological response is associated with better long-term outcomes and is a potential treatment target in patients with small bowel Crohn's disease. *Am J Gastroenterol*. 2016;111:997–1006.
44. Fernandes SR, Rodrigues RV, Bernardo S, Cortez-Pinto J, Rosa I, da Silva JP, et al. Transmural healing is associated with improved long-term outcomes of patients with Crohn's disease. *Inflamm Bowel Dis*. 2017;23:1403–9.
45. Ordas I, Rimola J, Alfaro I, Rodriguez S, Castro-Poceiro J, Ramírez-Morros A, et al. Development and validation of a simplified magnetic resonance index of activity for Crohn's disease. *Gastroenterology*. 2019;157:432–9.
46. Laurent V, Naudé S, Vuitton L, Zallot C, Baumann C, Girard-Gavanier M, et al. Accuracy of diffusion-weighted magnetic resonance colonography in assessing mucosal healing and the treatment response in patients with ulcerative colitis. *J Crohns Colitis*. 2017;11:716–23.
47. Thierry ML, Rousseau H, Puillon L, Girard-Gavanier M, Baumann C, Lopez A, et al. Accuracy of diffusion-weighted magnetic resonance imaging in detecting mucosal healing and treatment response, and in predicting surgery, in Crohn's disease. *J Crohns Colitis*. 2018;12:1180–90.
48. Van Assche G, Vanbekevoort D, Bielen D, Coremans G, Aerden I, Noman M, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gast*. 2003;98:332–9.
49. Van Rijn K, Lansdorp C, Tielbeek J, Nio Y, Buskens C, D'Haens G, et al. Evaluation of the modified Van Assche index for assessing response to anti-TNF therapy with MRI in perianal fistulizing Crohn's disease. *Clin Imaging*. 2020;59:179–87.
50. Kucharzik T, Kannengiesser K, Petersen F. The use of ultrasound in inflammatory bowel disease. *Ann Gastroentrol*. 2017;30:135–44.
51. Bots S, Nylund K, Löwenberg M, Gecse K, Giljia OH, D'Haens G. Ultrasound for assessing disease activity in IBD patients: a systematic review of activity scores. *J Crohns Colitis*. 2018;12:920–9.
52. Panes J, Bouchnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis*. 2013;7:556–85.
53. Zorzi F, Ghosh S, Chiaramonte C, Lolli E, Ventura M, Onali S. Response assessed ultrasonography as target of biological treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2019, pii:S1542-3565(19)31244-3.
54. Christensen B, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. *Clin Gastroenterol Hepatol*. 2017;15:1557–64.
55. Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. *Nat Rev Gastroenterol Hepatol*. 2020;17:1–2.
56. Lobatón T, Bessisow T, Ruiz-Cerulla A, De Hertogh G, Bisschops R, Guardiola J. Prognostic value of histological activity in patients with ulcerative colitis in deep remission: a prospective multicenter study. *United Eur Gastroenterol J*. 2018;6:765–72.
57. Jauregui-Amezaga A, Geeritis A, Das Y, Lemmens B, Sagaert X, Bessisow T, et al. A Simplified Geboes score for ulcerative colitis. *J Crohns Colitis*. 2017;11:305–13.

58. Kevans D, Kirsch R, Dargavel C, Kabakchiev B, Riddell R, Silverberg MS. Histological markers of clinical relapse in Endoscopic quiescent ulcerative colitis. *Inflamm Bowel Dis.* 2019; pii:izz308.
59. Christensen B, Hanauer S, Gibson P, Turner J, Hart J, Rubin D. Segmental histologic normalisation occurs in ulcerative colitis but does not improve clinical outcomes. *J Crohns Colitis.* 2020; <http://dx.doi.org/10.1093/ecco-jcc/jja068>.
60. Mosli M, Parker C, Nelson S, Baker K, MacDonald J, Zou GY, et al. Histologic scoring indices for evaluation of disease activity in ulcerative colitis. *Cochrane Database Syst Rev.* 2017; CD011256.
61. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törnér M, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med.* 2019;381: 1215–26.
62. Novak G, Parker CE, Pai RK, MacDonald JK, Feagan BG, Sandborn WJ, et al. Histologic scoring indices for evaluation of disease activity in Crohn's disease. *Cochrane Database Syst Rev.* 2017;7; CD012351.
63. Li K, Friedman JR, Chan D, Pollack P, Yang F, Jacobstein D, et al. Effects of ustekinumab on histologic disease activity in patients with Crohn's disease. *Gastroenterology.* 2019;157:1019–31, e7.
64. Chateau T, Peyrin- Biroulet L. Evolving therapeutic goals in Crohn's disease management. *United Eur Gastroenterol J.* 2020;8:133, 139.
65. Strik As, Bots SJ, D'Haens G, Löwenberg M. Optimization of anti-TNF therapy in patients with inflammatory bowel disease. *Expert Rev Clin Pharmacol.* 2016;9:429–39.
66. Agrawal M, Colombel JF. Treat-to-target in inflammatory bowel diseases. What is the target and how do we treat? *Gastrointest Endosc Clin N Am.* 2019;29:421–36.
67. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicenter, randomised, controlled phase 3 trial. *Lancet.* 2018;390:2779–89.
68. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther.* 2011;33:987–95.
69. Danese S, Sandborn WJ, Colombel JF, Vermeire S, Glover SC, Rimola J. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. *Gastroenterology.* 2019;157:1007–18.
70. Dreesen E, D'Haens G, Baert F, et al. Infliximab exposure predicts superior endoscopic outcomes in patients with active Crohn's disease: pharmacokinetic–pharmacodynamic analysis of TAILORIX. *J Crohns Colitis.* 2018;12:S063–4.
71. Papamichael K, Cheifetz AS. Use of anti-TNF drug levels to optimise patient management. *Frontline Gastroenterol.* 2016;7:289–300.
72. Fine S, Papamichael K, Cheifetz A. Etiology and management of lack or loss of response to anti-tumor necrosis factor therapy in patients with Inflammatory Bowel Disease. *Gasteroenterol Hepatol (NY).* 2019;15:656–65.
73. Egan C, Doherty G. Why do we need to improve monitoring of patients with inflammatory bowel disease (IBD) on biologic treatment? *Expert Opin Biol Ther.* 2019;19: 907–18.
74. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytler Y, Singh S. American Gastroenterological Association institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology.* 2017;153:827–34.
75. Mitrev N, Vande Castele N, Seow CH, Andrew JM, Connor SJ, Moore GT, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther.* 2017;46:1037–53.
76. Papamichel K, Cheifetz AS, Melmed GY, Irving PM, Van de Castele N, Kozuch PL, et al. Appropriate therapeutic drug monitoring of biological agents for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2019;17: 1655–68.
77. Papamichael K, Vogelzang E, Lambert J, Wolbink G, Cheifetz. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory disease. *Expert Rev Clin Immunol.* 2019;15:837–48.
78. Shah R, Hoffman GR, El-Dallal M, Goldowsky AM, Chen Y, Feuerstein JD. Is therapeutic drug monitoring for anti- tumor necrosis factor agents in adults with inflammatory bowel disease ready for standard care? A systematic review and meta-analysis. *J Crohns Colitis.* 2020 Feb 17, pii:jjaa029.
79. Limketkai BN, Singh S, Jairath V, Sandborn W, Dulai PS. US practice patterns and impacts of monitoring for mucosal inflammation after biologic initiation in inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;25:1828–37.
80. Le Berre C, AnanthakrishnanA, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative colitis and Crohn's disease have the same burden and goals for treatment. *Clin Gastroenterol Hepatol.* 2020;18:14–23.
81. Samaan MA, Arkir Z, Ahmad T, Irving PM. Wide variation in the use and understanding of therapeutic drug monitoring for anti-TNF agents in inflammatory bowel disease: an inexact science? *Expert Opin Biol Ther.* 2018;18:1271–9.