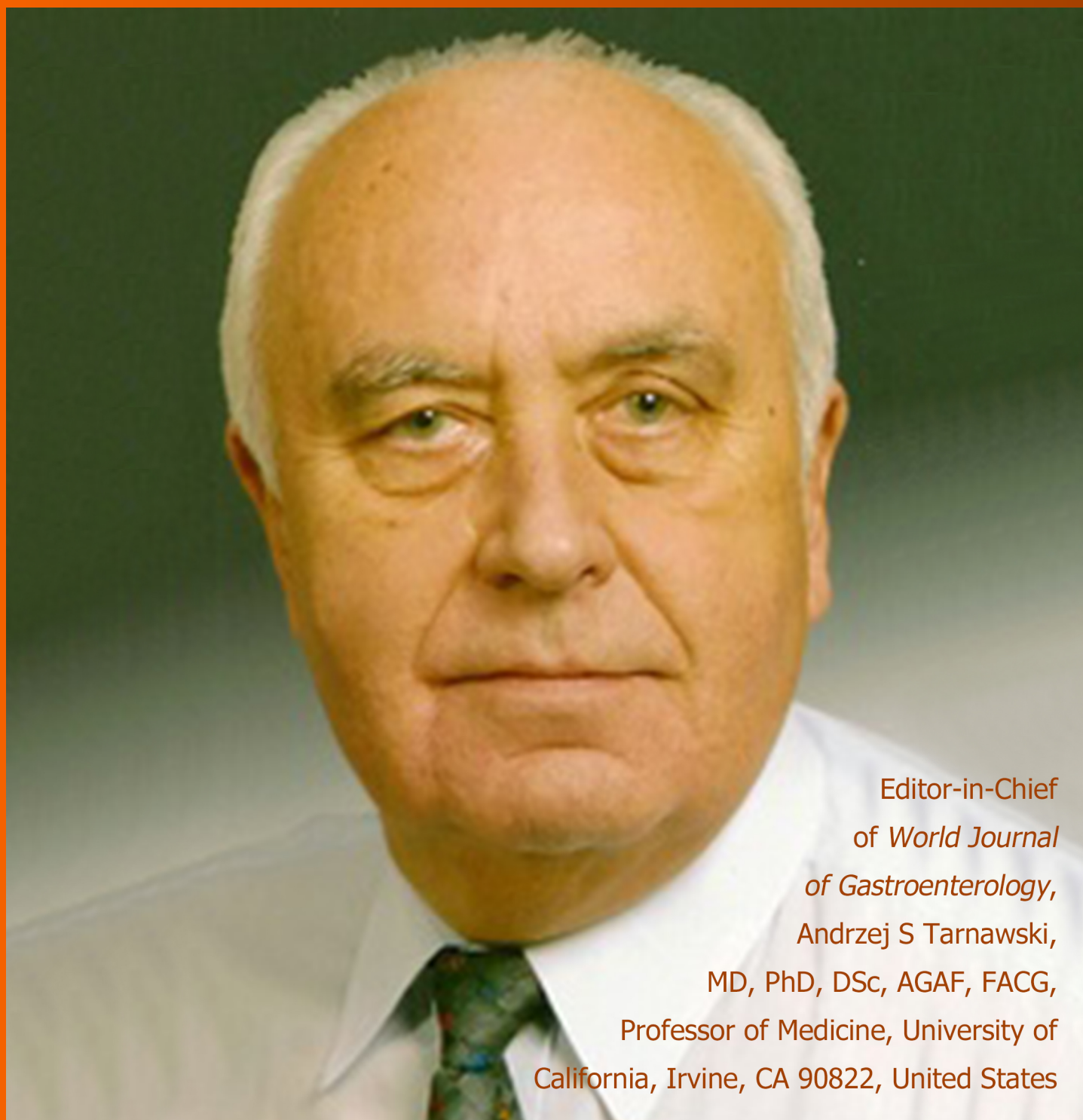


World Journal of *Gastroenterology*

World J Gastroenterol 2024 January 7; 30(1): 1-114



Editor-in-Chief
of *World Journal
of Gastroenterology*,
Andrzej S Tarnawski,
MD, PhD, DSc, AGAF, FACG,
Professor of Medicine, University of
California, Irvine, CA 90822, United States

EDITORIAL

- 1 Editor-in-Chief articles of choice and comments at the year-end of 2023
Tarnawski AS
- 9 2023: A year of accomplishments for the 13 Science Citation Index Expanded- and Emerging Sources Citation Index-indexed *Baishideng* journals
Wang JL, Yan JP, Fan JR, Li X, Guo X, Li JW, Wu YX, Wang JJ, Chen YL, Li L, Lin C, Qu XL, Liu JH, Zhang YL, Yuan YY, Yu HG, Chen YX, Cai YX, Zhang XD, Zhao S, Xu ZH, Ma L, Ma N, Guo DM, Ma LS

EVIDENCE REVIEW

- 17 May ChatGPT be a tool producing medical information for common inflammatory bowel disease patients' questions? An evidence-controlled analysis
Gravina AG, Pellegrino R, Cipullo M, Palladino G, Imperio G, Ventura A, Auletta S, Ciamarra P, Federico A

REVIEW

- 34 Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction: An exploratory proposal based on basic and clinical data
Zhou YW, Ren Y, Lu MM, Xu LL, Cheng WX, Zhang MM, Ding LP, Chen D, Gao JG, Du J, Jin CL, Chen CX, Li YF, Cheng T, Jiang PL, Yang YD, Qian PX, Xu PF, Jin X
- 50 Treat to target in Crohn's disease: A practical guide for clinicians
Srinivasan AR

MINIREVIEWS

- 70 Use of endoscopic ultrasound-guided gallbladder drainage as a rescue approach in cases of unsuccessful biliary drainage
Fugazza A, Khalaf K, Pawlak KM, Spadaccini M, Colombo M, Andreozzi M, Giacchetto M, Carrara S, Ferrari C, Binda C, Mangiavillano B, Anderloni A, Repici A

ORIGINAL ARTICLE

Clinical Trials Study

- 79 Machine learning identifies the risk of complications after laparoscopic radical gastrectomy for gastric cancer
Hong QQ, Yan S, Zhao YL, Fan L, Yang L, Zhang WB, Liu H, Lin HX, Zhang J, Ye ZJ, Shen X, Cai LS, Zhang GW, Zhu JM, Ji G, Chen JP, Wang W, Li ZR, Zhu JT, Li GX, You J

Basic Study

- 91 Mechanistic research: Selenium regulates virulence factors, reducing adhesion ability and inflammatory damage of *Helicobacter pylori*
Qin C, Huang GR, Guan AX, Zhou WT, Chen H, Luo PP, Luo XK, Huang YQ, Huang ZS

LETTER TO THE EDITOR

- 108** Complementary comments on diagnosis, severity and prognosis prediction of acute pancreatitis
Ozturk MO, Aydin S
- 112** Effect of magnetic resonance imaging in liver metastases
Huang XL, Wang XD, Gong ZM, Zheng YF, Mao JX

ABOUT COVER

Editor-in-Chief of *World Journal of Gastroenterology*, Andrzej S Tarnawski, MD, PhD, DSc, AGAF, FACC, Professor of Medicine, University of California, Irvine, CA 90822, United States. atarnawski@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xu Guo*, Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu (Biliary Tract Disease)

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

January 7, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

PUBLISHING PARTNER

Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER's OFFICIAL WEBSITE

<https://www.shca.org.cn>
<https://www.zs-hospital.sh.cn>



Treat to target in Crohn's disease: A practical guide for clinicians

Ashish R Srinivasan

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Duan SL, China; Lakatos PL, Canada; Wang LH, China; Zhu L, China

Received: October 10, 2023

Peer-review started: October 10, 2023

First decision: November 16, 2023

Revised: November 23, 2023

Accepted: December 21, 2023

Article in press: December 21, 2023

Published online: January 7, 2024



Ashish R Srinivasan, Department of Gastroenterology, Austin Health, Victoria, Melbourne 3083, Australia

Ashish R Srinivasan, Department of Gastroenterology, Eastern Health, Victoria, Melbourne 3128, Australia

Ashish R Srinivasan, Department of Medicine, University of Melbourne, Victoria, Melbourne 3052, Australia

Corresponding author: Ashish R Srinivasan, FRACP, MBBS, PhD, Consultant Physician-Scientist, Senior Lecturer, Department of Gastroenterology, Austin Health, No. 145 Studley Road, Heidelberg, Victoria, Melbourne 3083, Australia. ashish.srinivasan1@gmail.com

Abstract

A treat-to-target (T2T) approach applies the principles of early intervention and tight disease control to optimise long-term outcomes in Crohn's disease. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II guidelines specify short, intermediate, and long-term treatment goals, documenting specific treatment targets to be achieved at each of these timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to determining whether current therapy should be continued or modified. Consensus treatment targets in Crohn's disease comprise combination clinical and patient-reported outcome remission, in conjunction with biomarker normalisation and endoscopic healing. Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, or achievable in all patients. This underscores the need to engage patients at the outset in an effort to personalise care and individualise treatment targets. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross-sectional imaging techniques, particularly intestinal ultrasound, holds great promise; as do emerging treatment targets such as transmural healing. Two randomised clinical trials, namely, CALM and STARDUST, have evaluated the efficacy of a T2T approach in achieving endoscopic endpoints in patients with Crohn's disease. Findings from these studies reflect that patient subgroups and Crohn's disease characteristics likely to benefit most from a T2T approach, remain to be clarified. Moreover, outside of clinical trials, data pertaining to the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies. Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake. This highlights the need to describe strategies, processes, and models of

care capable of supporting the integration and execution of a T2T approach in real-world clinical practice. Hence, this review seeks to examine the current and emerging literature to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice for the management of Crohn's disease.

Key Words: Treat to target; Inflammatory bowel disease; Crohn's disease; Treatment targets; Endoscopic remission; Transmural healing; Time to response; Intestinal ultrasound

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: A treat-to-target (T2T) approach applies the principles of early intervention and tight disease control to optimise long-term outcomes in Crohn's disease. This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets, to inform whether current therapy should be continued or modified. Despite its obvious promise, a lack of guidance to support the integration of a T2T approach into clinical practice has the potential to limit its widespread uptake. This review seeks to examine the current and emerging literature, to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice for the management of Crohn's disease.

Citation: Srinivasan AR. Treat to target in Crohn's disease: A practical guide for clinicians. *World J Gastroenterol* 2024; 30(1): 50-69

URL: <https://www.wjgnet.com/1007-9327/full/v30/i1/50.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i1.50>

INTRODUCTION

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee, supported by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), first endorsed the paradigm shifting concept of treat-to-target (T2T) in Crohn's disease and ulcerative colitis in 2015[1]. This paradigm shift was driven by an understanding that even in the absence of clinical symptoms, cumulative insults to the bowel can result in progressive disease complications, highlighting the need for a proactive target driven approach supported by timely clinical assessment and intervention. This is particularly relevant to Crohn's disease wherein uncomplicated inflammatory disease can progress to stricturing (18%) and penetrating/fistulising (70%) disease complications without effective treatment to control inflammation[2].

The modern-day T2T approach in Crohn's disease pursues the goal of optimising long-term outcomes through tight disease control[3]. This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets to determine whether treatment goals have been achieved, and thus whether current therapy should be continued or modified. It also remains important to acknowledge that the treatment goalposts in Crohn's disease have shifted away from targeting clinical remission and quality of life measures alone, toward integrating both clinical and objective assessments of disease activity when appraising treatment response[4]. Consensus treatment targets in Crohn's disease, as defined by the updated STRIDE-II guidelines, comprise combination clinical and patient-reported outcome (PRO) remission, in conjunction with biomarker normalisation and endoscopic healing[4]. These targets prioritise symptom resolution and restoration of quality of life in patients with Crohn's disease, with a view toward reducing long-term disease sequelae and disability.

Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake[5]. Hence, this review aims to provide clinicians with practical guidance regarding the clinical application of a T2T approach in the context of managing patients with Crohn's disease. Evidence supporting current and emerging treatment targets, as well as systems, processes, and models of care necessary to support the integration of a T2T approach into routine clinical practice, will also be examined.

TOWARD A PERSONALISED APPROACH

An essential component of enacting a T2T approach in clinical practice is to ensure that the treatment strategy adopts a shared decision-making model that values input from both the IBD patient and the IBD clinician[6]. Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, or achievable in all patients. This emphasises the need for clinicians to engage patients at the outset in an effort to personalise care and individualise treatment decisions.

Defining treatment goals

Key points: (1) Explain principles and objectives of a T2T approach to patients at Crohn's disease diagnosis; (2) Acknowledge that clinicians and patients may have different goals and objectives; and (3) Define treatment goals that are

acceptable, achievable and clinically meaningful to both parties.

Patient 'buy-in' to the T2T philosophy remains critical in reducing anxiety and cultivating acceptance of therapeutic changes on the basis of scheduled disease assessments, which may not always correspond to patient perceived deterioration in symptoms or wellbeing. A recent study by Selinger and colleagues found that only 66.2% of 298 patients with IBD who were in steroid-free clinical remission, appraised a T2T approach focused on achieving the absence of mucosal inflammation, to be acceptable (Likert scale score $\geq 8/10$)[7]. Instead, patients were more likely to prioritise avoiding clinical flares, hospitalisation, surgery, and colorectal cancer, as acceptable treatment goals. This implies that a third of patients remain unconvinced by the objectives of a T2T approach, highlighting the need for clinicians to spend more time explaining the rationale behind a T2T approach to patients, and appreciate that treatment targets espoused by STRIDE-II may not be acceptable to all patients.

In light of this, it remains important that IBD clinicians consult with patients to discuss and document treatment goals early on in their disease course. These goals need to be acceptable, achievable, and clinically meaningful to both parties. A patient-centric approach may also lead to greater patient 'buy-in' and thereby reduce non-adherence which has been associated with unfavourable outcomes[8-11]. Moreover, the need to personalise treatment goals is exemplified by real-world clinical dilemmas associated with initiating, continuing, and escalating immunosuppression in those with significant comorbidities, polypharmacy, prior malignancy history, older age, and class or dose-specific medication intolerances[12,13]. Thus, prioritising symptomatic relief and quality of life measures with a view towards preserving functional independence may be more appropriate than striving to achieve endoscopic healing in specific IBD populations, such as the elderly and those with significant co-morbidity[14]. Hence, a single treatment target such as endoscopic healing may not be universally applicable across all patients, highlighting the need to personalise treatment goals.

Individualising treatment decisions

Key point: (1) Adopting a shared decision-making model that empowers patients to participate in the therapeutic decision-making process should be encouraged.

Once therapeutic goals have been established, it is important to consider which therapy is best suited to achieve agreed-upon treatment targets. While therapeutic effectiveness represents an obvious consideration, several other factors related to the patient, disease, safety, cost, and drug availability, are also likely to influence the choice and sequencing of medical therapies[15]. Therapeutic sequencing, which is the order in which advanced medical therapies are prescribed, represents an emerging concept borne out of the ever-growing therapeutic armamentarium in Crohn's disease, with several newer therapies also on the horizon[16]. This is exemplified by data indicating that second- and third-line biologic therapies may not be as effective as first-line therapies[17]. Although anti-tumour necrosis factor (TNF) therapy remains the consensus first-line medical therapy in perianal Crohn's disease, consensus regarding the sequencing of medical therapies in uncomplicated inflammatory Crohn's disease remains less well-defined[18].

The advent of highly effective biologic medicines, including the recent emergence of small molecules, has proven integral to achieving more favourable clinical outcomes. However, it remains important to acknowledge that the pursuit of more stringent endpoints, such as endoscopic healing, radiologic remission, and normalisation of inflammatory biomarkers, may require early and intensive therapy, which represents an important concept to discuss with patients. This was exemplified by findings of a recent study involving patients with Crohn's disease, who were candidates to receive immunomodulator and/or biologic therapy, which reported that using a shared-decision making model, between the IBD patient and IBD clinician, resulted in more patients (25% *vs* 5%, $P < 0.001$) choosing combination (biologic-immunomodulator) immunosuppression over immunomodulator monotherapy[19]. Additional benefits such as lower decisional conflict ($P < 0.05$) and greater trust in the treatment provider ($P < 0.05$) were also associated with the shared-decision making intervention. This highlights the value of adopting a collaborative approach to therapeutic decision-making that encourages patient participation.

Timing assessments of response

Key points: (1) Assess the right target at the right time for the right therapy; (2) Know time to response of the therapy that you prescribe; and (3) Differentiate between short, medium, and long-term treatment targets per STRIDE-II.

Therapy specific considerations

Once treatment targets have been agreed upon and a specific IBD therapy has been chosen, an awareness and understanding of the anticipated time for the chosen therapy to induce clinical, biochemical, and endoscopic improvement, is vital in determining the optimal timing of clinical follow-up, assessments of response, and defining treatment futility[20]. This is particularly important given that there appears to be significant variability in the time to response between different IBD therapies. In Crohn's disease, therapies such as corticosteroids, exclusive enteral nutrition, anti-TNF therapies, Janus kinase inhibitors (JAK-I), and interleukin 12/23 inhibitors have been associated with clinical improvement within 2 mo, while agents such as methotrexate, thiopurines, and vedolizumab may take longer to demonstrate maximal response[20]. In recognition of this, the STRIDE-II recommendations provide guidance on estimated time to response, albeit based on judgemental estimation of findings from an IOIDC survey and a systematic review[4]. Therapy specific guidance regarding when to undertake assessments of clinical, biochemical, and endoscopic response is summarised in [Figure 1](#) and [Table 1](#).

Treatment target specific considerations

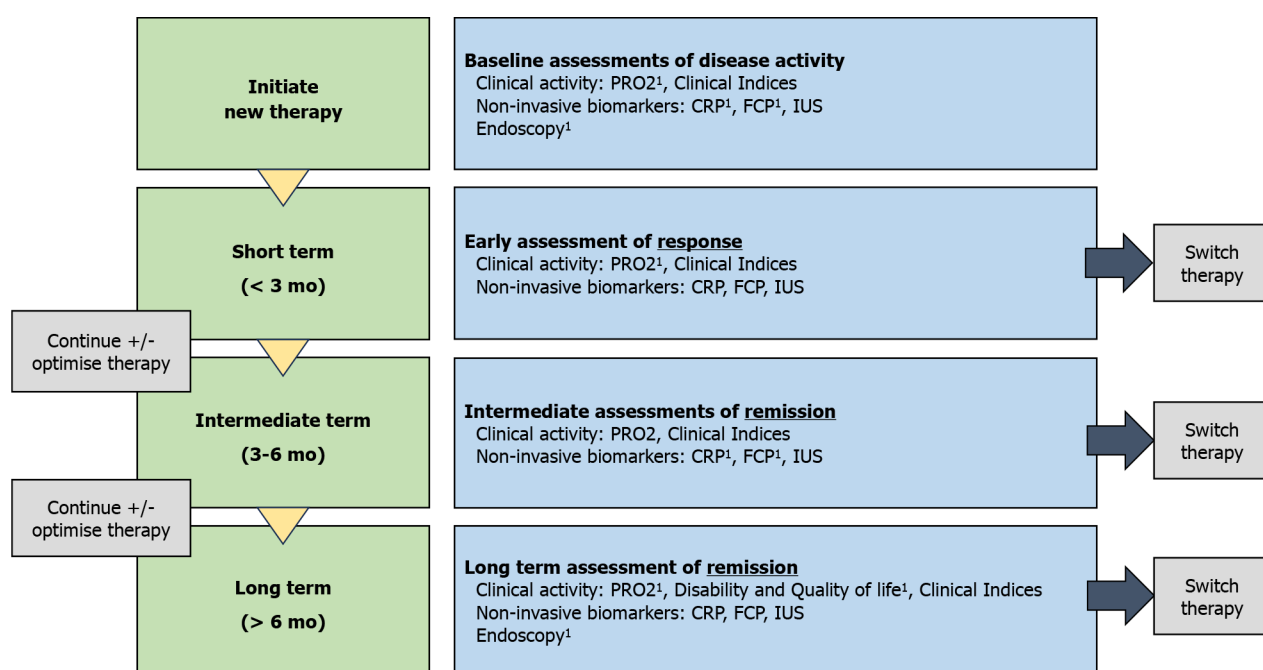
Identifying appropriate treatment targets remain central to a T2T strategy, as is determining suitable timepoints at which

Table 1 Time to treatment targets based on Crohn's disease therapy

	Mean time to treatment target (wk) ¹				
	Clinical response	Clinical remission	Normalisation of CRP	Decrease in calprotectin	Endoscopic healing
Anti-TNF	2-4[4]	4-6[4]	9[4]	11[4]	17[4]
Adalimumab	2-4[114]	4[114]	-	-	12[114]
Infliximab	2-4[115,116]	4-6[4]	-	-	24[117,118]
Exclusive enteral nutrition	2[119]	4-8[119-121]	5[4]	8[4]	4-8[120,121]
Methotrexate	9[122]	22[122]	14[4]	15[4]	24[4]
Oral steroids	2-4[20]	4-7[4,123]	5[4]	8[4]	-
Thiopurine	12[124]	15-18[4,125]	15[4]	17[4]	26[118]
Upadacitinib	2[126]	2-4[126]	-	-	12-16[127]
Ustekinumab	6[128]	6-8[128]	11[4]	14[4]	19[4]
Vedolizumab	6-14[129-132]	10-14[133-135]	15[4]	17[4]	22[136]

¹In the absence of high-quality data, the time to response data should only be used as a guide.

TNF: Tumour necrosis factor; CRP: C-reactive protein.



DOI: 10.3748/wjg.v30.i1.50 Copyright ©The Author(s) 2024.

Figure 1 A practical approach to evaluating response to new therapy using a treat-to-target approach. ¹Selecting Therapeutic Targets in Inflammatory Bowel Disease II endorsed treatment targets: Consider treatment modification if not met. PRO2: Patient reported outcome 2; CRP: C-reactive protein; FCP: Faecal calprotectin; IUS: Intestinal ultrasound.

to evaluate whether or not these targets have been achieved. As an example, if a treatment target were to be evaluated too soon, it remains possible that an inappropriate therapeutic change may be initiated; conversely, if a treatment target were to be evaluated too late, it remains possible that a therapeutic change may be inadvertently delayed. Both of these situations have the potential to lead to adverse patient and disease outcomes. In light of this, the STRIDE-II guidelines distinguish between short, intermediate, and long-term treatment targets[4]. In fact, IBD experts involved in developing the STRIDE-II guidelines identified clinical remission as the most important short-term treatment objective, closely followed by clinical and endoscopic response[4]. Normalisation of inflammatory biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate, and faecal calprotectin were identified as short-to-intermediate treatment targets, while endoscopic healing endures as the consensus long-term treatment target in Crohn's disease[4].

EXAMINING CONSENSUS TREATMENT TARGETS

Several treatment targets have been endorsed by the STRIDE-II committee (Table 2). The following section will review the evidence supporting their recommendations, discuss how to incorporate them into routine clinical practice, and highlight any potential limitations in their real-world application.

Clinical targets

Key points: (1) Clinical symptoms correlate poorly with mucosal inflammation; (2) Patient reported outcome measures (PROMs) should be integrated into routine clinical care; (3a) Short-term (< 3 mo): Clinical response: 50% reduction from baseline PRO2; (3b) Medium-term (3-6 mo): Clinical remission defined by PRO2; and (3c) Long-term (6-12 mo): Absence of disability and normalisation of health-related quality of life.

PROMs

Clinical symptoms have been demonstrated to correlate poorly with mucosal inflammation in Crohn's disease[21]. In fact, it is not uncommon to find substantial mucosal inflammation in the setting of clinical remission. Symptoms have, however, been shown to correlate with patient perceived disease control and quality of life, indicating that symptom control represents an important treatment goal from the patient perspective[22]. PROMs have since become a standard measure of patient wellbeing. As a cheap, inexpensive, and easily reproducible method of evaluating clinical symptoms, PROMs can, and should, be evaluated as part of routine clinical care. The most frequently used PROM is the PRO2 which incorporates two items from the Crohn's disease activity index (CDAI), namely, the weighted daily stool frequency and abdominal pain[23]. The STRIDE-II definition of short-term clinical response and intermediate-term clinical remission is made solely on the basis of PRO2 assessments, with response defined as a 50% reduction from baseline, and remission defined as an abdominal pain score ≤ 1 and stool frequency ≤ 3 . Moreover, at these short (< 3 mo) and intermediate-term (< 6 mo) timepoints, the STRIDE-II guidelines advocate that treatment changes can be made if these targets have not been achieved[4]. Nevertheless, despite the importance of incorporating PROMs such as PRO2 into routine clinical care, they need to be used in conjunction with objective measures of inflammation[4,22].

It would be remiss not to acknowledge the impact that IBD has on a patient's mental and emotional wellbeing[24]. This is also reflected by the STRIDE-II guidelines which endorse improving quality of life and IBD related disability as key long-term treatment targets[4]. Validated questionnaires and tools such as the IBD disability index and the IBD disk should also be utilised to evaluate IBD related disability and quality of life in this context[25,26].

Limitations of clinical targets

Similar to patients, clinicians also value and recognise the importance of symptom control as a treatment target. This was reflected by most experts in the STRIDE-II Delphi group advocating that symptom relief, that is clinical response and clinical remission, represents an important short and intermediate-term treatment goal in Crohn's disease, respectively [4]. However, one of the inherent limitations of using CDAI as a marker of intestinal inflammation in Crohn's disease, is that the CDAI may be similarly elevated in patients with Crohn's disease and irritable bowel syndrome[27]. Moreover, patients who achieve clinical response and remission on the basis of CDAI may not always achieve biomarker normalisation and endoscopic remission, both of which represent intermediate and long-term target targets per the STRIDE-II guidelines, respectively. This was evident in the CALM trial which indicated that treatment escalation on the basis of clinical symptoms alone led to lower rates of endoscopic healing than escalating on the basis of a composite strategy of combined clinical and biochemical (faecal calprotectin plus CRP) activity[28]. Similarly, the SONIC trial found that more than 50% of infliximab-azathioprine treated patients who were in clinical remission had persistent biomarker and/or endoscopic inflammation[29]. In view of the frequent discordance between clinical symptoms and objective assessments of inflammation, the STRIDE-II guidelines do not advocate that clinical response and remission represent long-term treatment targets[4]. Hence, while PROMs such as PRO2 should be integrated into routine clinical care, PROMs are best used in conjunction with objective measures of inflammation to guide therapeutic decision-making[4,22].

Non-invasive biomarker targets

Key points: Medium-term (3-6 mo): (1) Normalisation of CRP < upper limit of normal (ULN) and faecal calprotectin < 250 $\mu\text{g/g}$; and (2) Normalisation of both CRP and faecal calprotectin may be of greater utility in terms of endoscopic outcomes, than normalisation of either biomarker in isolation.

The ideal biomarker to evaluate Crohn's disease activity should be accurate, minimally invasive, inexpensive, and acceptable to patients[30]. Unfortunately, no single biomarker fulfills all of these criteria. Nevertheless, non-invasive biomarkers such as CRP and faecal calprotectin are frequently used in clinical practice. The STRIDE-II consensus guidelines support normalisation of both of these parameters as medium-term treatment targets[4].

CRP

Non-invasive serum biomarkers such as CRP are easily accessible, and thus frequently utilised as part of serial monitoring of disease activity in patients with Crohn's disease. However, in view of CRP being neither disease or bowel specific, limitations in using CRP as the sole basis for treatment decisions must be acknowledged. This is exemplified by findings that up to 20% of patients with active ileal Crohn's disease will have a normal CRP, and that CRP concentrations correlate poorly with clinical symptoms, which can, at times, make its bed-side interpretation challenging[31-33]. Similarly, published data implies that CRP correlates moderately with endoscopic activity in Crohn's disease, with a normal CRP demonstrating a high specificity but low sensitivity for endoscopically active Crohn's disease[34-37].

Table 2 Treatment targets defined by Selecting Therapeutic Targets in Inflammatory Bowel Disease-II for Crohn's disease

Treatment target	Definition
STRIDE-II endorsed treatment targets in adult patients with Crohn's disease	
Clinical response	≥ 50% decrease in baseline Patient Reported Outcomes 2 (PRO2) ¹ ; (abdominal pain and stool frequency)
Clinical remission	PRO2 with abdominal pain score ≤ 1 and stool frequency score ≤ 3 ¹ ; or Harvey Bradshaw Index < 5
Patient reported outcomes	Clinical outcomes evaluated using PRO2; absence of disability and normalisation of health-related quality of life
Biomarker normalisation	C-reactive protein < upper limit of normal; faecal calprotectin < 250 µg/g
Endoscopic response	> 50% improvement in simple endoscopic score-Crohn's disease score; or > 50% improvement in Crohn's disease endoscopic index score
Endoscopic healing	Simple endoscopic score-Crohn's disease ≤ 2; or Crohn's disease endoscopic index score < 3; and absence of ulcers, including aphthous ulcers
Adjunctive treatment targets	
Transmural healing	Adjunct to endoscopic healing to represent a deeper level of healing; assessed using intestinal ultrasound, magnetic resonance (or computed tomography) enterography; however, a consensus definition of transmural healing remains yet to be established

¹Endorsed by Selecting Therapeutic Targets in Inflammatory Bowel Disease-II recommendations.

STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease.

Moreover, although a cut-off of 5 mg/dL is frequently used to differentiate between normal and abnormal CRP concentrations, Falvey and colleagues demonstrated that any CRP above the ULN was associated with a higher risk of endoscopic Crohn's disease activity[38]. This is reflected in the STRIDE-II recommendations which specify that CRP should be normalised to values below the ULN[4].

Faecal calprotectin

Faecal calprotectin has proven useful in predicting disease progression in asymptomatic Crohn's disease, reflecting its utility as a non-invasive biomarker capable of facilitating like-for-like longitudinal comparison of luminal Crohn's disease activity[39-41]. There is also good evidence that calprotectin levels correlate with small bowel and colonic Crohn's disease, although the correlation between faecal calprotectin and endoscopic disease activity has proven more robust in colonic Crohn's disease ($r = 0.73$ to 0.88) compared with isolated ileal Crohn's disease ($r = 0.437$)[42,43].

Faecal calprotectin has also been well described as a surrogate marker for endoscopic lesions in Crohn's disease. In fact, strong correlations have been documented between faecal calprotectin, endoscopic disease activity, and ulcer depth[44-48]. D'Haens and colleagues reported that faecal calprotectin values below 250 µg/g predicted endoscopic healing [Crohn's Disease Endoscopic Index of Severity (CDEIS) ≤ 3] with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 94.1%, 62.2%, 48.5%, and 96.6%, respectively[44]. Conversely, faecal calprotectin values above 250 µg/g were indicative of large ulcers on ileo-colonoscopy with a sensitivity, specificity, PPV, and NPV of 60.4%, 79.5%, 78.4%, and 62.0%, respectively. Similarly, targeting faecal calprotectin threshold below 250 µg/g within 12 mo of Crohn's disease diagnosis has been associated with a reduced risk of composite disease progression, and clinical remission with a sensitivity and specificity of 90% and 76%, respectively[49,50]. While faecal calprotectin cut-offs below 250 µg/g may improve clinical sensitivity for disease remission, higher cut-offs increase specificity for active disease. In light of this, an optimal cut-off for faecal calprotectin has yet to be defined, with the STRIDE-II guidelines designating values between 100-250 µg/g to reflect normalisation of faecal calprotectin.

While several studies have suggested a cut-off value of 250 µg/g to distinguish between active and inactive Crohn's disease, studies have also advocated for lower thresholds depending on the target outcome[40,50-52]. The CALM study showcased the clinical utility of incorporating calprotectin thresholds greater than 250 µg/g to designate active Crohn's disease worthy of adalimumab escalation to achieve higher rates of endoscopic healing at 1 year as part of a T2T approach[28]. Conversely, a study by Noh and colleagues documented that a faecal calprotectin cut-off of 81.1 mg/kg was useful in predicting deep healing reflective of combined endoscopic and radiologic remission in anti-TNF treated patients with Crohn's disease[52]. Thus, faecal calprotectin has the potential to be used to achieve treatment targets reflective of deep remission if lower treatment target cut-offs are designated.

Combined biomarker remission

The CALM study demonstrated that the combination of biomarker remission (faecal calprotectin and CRP) and symptom driven tight disease control was associated with higher 12-mo endoscopic healing and fewer hospitalisations (13.2 vs 28.0 events/100 patient-years; $P = 0.02$) than standard symptom-based management alone in early Crohn's disease (adjusted risk difference = 16.1%, 95%CI: 3.9-28.3, $P = 0.01$)[28]. Moreover, follow-up out to 3 years (range: 0.05-6.26 years) suggested that achieving tight disease targets such as endoscopic remission, with or without associated clinical remission (*i.e.*, deep remission), was associated with significantly reduced rates of adverse disease sequelae after adjusting for age,

disease duration, prior stricture or surgery, and intervention group. These findings support STRIDE recommendations of deep remission as the target of choice, with CALM also providing clinical justification to support treatment intensification to facilitate biomarker normalisation to achieve these targets.

Endoscopic targets

Key points: (1) Endoscopic healing remains the designated long-term treatment target per STRIDE-II; (2a) Short to medium-term (0-6 mo): Endoscopic response: > 50% reduction in SES-CD or CDEIS; and (2b) Long-term (> 6 mo): Endoscopic remission, SES-CD ≤ 2 or CDEIS < 3, without ulcers.

Favourable associations between endoscopic healing and long-term disease related complications, flares, and surgeries in both Crohn's disease and ulcerative colitis, support the pursuit of endoscopic healing as a long-term treatment target[4, 53,54]. With this in mind, the STRIDE guidelines recommend that endoscopic assessment be undertaken 6-9 mo after initiation of medical therapy. However, endoscopic healing may not always be achievable within this timeframe. This was addressed in the STRIDE-II guidelines which acknowledged that endoscopic response may suffice as a short-term target following initiation of a new therapy[4]. However, a lack of consistency in the definitions of endoscopic response and remission in Crohn's disease, led the STRIDE-II panel to develop definitions to align with their proposed endoscopic endpoints[4]. Endoscopic response was defined as > 50% decrease in the SES-CD or CDEIS, from baseline while endoscopic remission was defined as achieving SES-CD ≤ 2 or CDEIS < 3 without any ulcers, including aphthous ulcers [4].

Endoscopic response

Preliminary data suggests that early endoscopic assessment within 6 mo of biologic initiation may be associated with fewer disease-related complications (adjusted hazard ration (aHR) = 0.35, $P < 0.01$) and a reduction in 24-mo risk of disease-related complications (aHR = 0.87, $P = 0.02$), including corticosteroid use, emergency presentations, hospitalization, and surgery[55]. Moreover, the benefit of early endoscopy in Crohn's disease was suggested to be greatest when performed within 4 mo of biologic initiation, with early endoscopic assessment also associated with an increased likelihood of changing biologic (aHR = 1.15, $P < 0.01$)[55]. Interpreted together, these findings may reflect that the benefits of early endoscopic assessment may relate to proactive disease monitoring capable of facilitating early treatment optimisation, and discontinuation of futile therapy. Nevertheless, further studies are required to clarify the generalisability of these findings given that unmeasured confounders may have accounted for, and influenced the selection of patients who underwent early endoscopic assessment, which was the minority (12.8% 2, 279/17, 807) in this studied cohort[55].

Endoscopic healing

Endoscopic healing in Crohn's disease is generally defined as the absence of ulceration of the bowel mucosa[56]. Recalibrating towards this treatment target in Crohn's disease has been driven by studies indicating that achieving endoscopic healing may be associated with more favourable long-term outcomes[57-60]. A systematic review with meta-analysis of 673 Crohn's disease patients across 12 studies, 7 of which included anti-TNF therapies, highlighted the long-term benefits of medically induced endoscopic healing, with more than two-thirds (69%) of patients who achieved endoscopic healing within the first 6 mo maintaining long-term clinical remission[61]. Early documented endoscopic healing was also associated with high rates (94%) of long-term endoscopic healing relative to comparatively low rates (18%) amongst those with active disease at their first endoscopic re-assessment. In addition to favourable associations with long-term clinical symptoms, endoscopic healing has also been associated with lower rates of Crohn's related surgery and hospitalisation [58,61,62]. Baert *et al*[59] also demonstrated that endoscopic healing in patients with early-stage Crohn's disease was associated with significantly higher rates of steroid-free remission rates at 4 years, further emphasising the long-term benefits of achieving this treatment target. Schnitzler *et al*[58] showed that endoscopic healing, induced by maintenance infliximab therapy, was associated with improved long-term disease outcomes, most notably, lower rates of abdominal surgery. Ananthakrishnan and colleagues also demonstrated, through the use of a decision analysis model, that striving for endoscopic healing as an endpoint was a cost-effective strategy in Crohn's disease patients initiating infliximab[60]. Taken together, these studies suggest that striving to achieve endoscopic healing in the era of biologics is achievable, worthwhile, and cost-effective.

Mirroring STRIDE recommendations, the concept of "deep remission", reflective of both clinical and endoscopic remission, has emerged as the ultimate treatment target. The was reflected by the EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing trial which documented lower rates of hospitalisation and disease related surgery across Crohn's disease patients who demonstrated deep remission at 12 mo[63].

Limitations associated with endoscopic healing

One of the drawbacks associated with targeting endoscopic healing is its reliance on ileo-colonoscopy which is invasive, resource intensive, and does not allow for mucosal assessment of small bowel segments proximal to the terminal ileum. Similarly, endoscopic evaluation may be limited by the presence of Crohn's disease associated strictures which can lead to under-estimation of disease activity in up to 50% of patients[64]. Hence, STRIDE-II guidelines specify that cross-sectional imaging techniques such as magnetic resonance enterography (MRE), computed tomography (CT) enterography (CTE), and intestinal ultrasound (IUS), can be employed to monitor small bowel segments not readily accessible by ileo-colonoscopy[4].

The STRIDE-II guidelines also recommend that endoscopic assessment be undertaken 6-9 mo following initiation of any therapy[4]. However, repeated ileo-colonoscopy over this timeframe to assess both short-term endoscopic response

and longer-time endoscopic healing, is unlikely to be favoured by patients and healthcare payers alike, particularly in light of emerging data to support the use of non-invasive endoscopic surrogates[4]. These challenges highlight the need for accurate non-invasive disease monitoring strategies that are deemed acceptable by patients, considered cost-effective by healthcare payers, and deemed clinically useful and comparable to ileo-colonoscopy by clinicians. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross-sectional imaging techniques, particularly IUS, holds great promise in this regard.

T2T IN CLINICAL TRIALS

Key points: (1) The CALM and STARDUST trials evaluated the efficacy of a T2T guided approach in achieving endoscopic endpoints in patients with Crohn's disease treated with adalimumab and ustekinumab, respectively; and (2) On the basis of these studies, we have yet to identify which patient and Crohn's disease characteristics are likely to benefit most from a T2T approach.

To date, two randomised clinical trials, namely, CALM and STARDUST, have evaluated the efficacy of a T2T guided approach to therapeutic decision-making focused on achieving endoscopic endpoints, relative to symptom directed treatment adjustments alone, in patients with Crohn's disease.

The clinical efficacy of therapeutic decision-making based on tight disease control, based on pre-defined clinical and inflammatory biomarker targets, *vs* standard clinical disease activity alone, was evaluated by the CALM study as part of a multi-centre international randomised trial of Crohn's disease patients treated with adalimumab[28]. The CALM study concluded that a clinical approach favouring tight disease control led to improved clinical and endoscopic outcomes compared to a symptom driven management approach alone. Despite using an aggressive top-down approach across a Crohn's disease cohort with relatively uncomplicated disease of short duration, only 46% of patients in the CALM study achieved the primary endpoint of mucosal healing with absence of deep ulcers at 48 wk[28]. More recently, the multicentre, randomised STARDUST trial evaluated the efficacy of a T2T approach in Crohn's disease patients treated with ustekinumab, relative to a clinically driven dose-adjustment strategy, in achieving endoscopic response at week 48 ($\geq 50\%$ decrease from baseline SES-CD score)[65]. The T2T strategy involved using week 16 endoscopy to inform ustekinumab dosing decisions, following which further dosing adjustments were made on the basis of regular clinical and biomarker assessments over the ensuing 32 wk. Week 48 endoscopic response, which was the primary endpoint, was not significantly different between the two groups (38% *vs* 30%, $P = 0.087$). Notably, the T2T cohort in the STARDUST trial had very low rates of endoscopic remission (11%) and mucosal healing (14%), with comparable clinical and biomarker outcomes between the T2T and clinically-directed treatment groups, apart from clinical response which was significantly lower in the T2T group ($P = 0.020$).

It is, however, important to acknowledge differences in patient, disease, and treatment characteristics between the Crohn's disease populations of the CALM and STARDUST trials. Patients recruited to CALM tended to have early Crohn's disease and be naïve to immunosuppressive therapies. The study also applied different criteria for treatment step-up, and used different endoscopic endpoints to those used in the STARDUST trial. By comparison, patients recruited to STARDUST typically had a longer duration of Crohn's disease and were more likely to have failed advanced medical therapies, potentially reflective of a more treatment refractory cohort. While these differences should caution against direct comparison between both studies, they do highlight several important points: (1) The need to identify which patients stand to benefit most from a T2T approach, such as those with a complex Crohn's disease phenotype and/or high inflammatory burden; and (2) Whether a T2T strategy may be more effective when enacted in Crohn's disease patients with a shorter duration of disease, and minimal or no prior exposure to advanced immunosuppressive therapies.

EMERGING TREATMENT TARGETS

On the basis of current evidence, treatment targets such as transmural healing and histologic remission have not yet been endorsed by the STRIDE-II guidelines. Similarly, treatment targets specific to complex Crohn's disease phenotypes such as stricturing Crohn's disease have yet to be clearly defined. Nevertheless, these endpoints may represent future treatment targets and this section will briefly explore the current and emerging literature on these topics.

Transmural healing

Key points: (1) Transmural healing was not endorsed as a treatment target by STRIDE-II; and (2) Evidence based consensus definitions of transmural response and healing are required before transmural endpoints can be integrated into clinical trials and subsequent clinical practice.

Crohn's disease is a transmural disease process, highlighting potential limitations associated with simply using ileo-colonoscopy to assess disease activity, including response to therapy, at a mucosal level[66]. This is supported by data from several studies indicating that transmural healing is associated with favourable disease-related outcomes in patients with Crohn's disease. In fact, Castiglione and colleagues compared long-term outcomes following transmural healing and endoscopic healing, reporting that transmural healing was superior to endoscopic healing in predicting steroid-free clinical remission ($P = 0.01$), clinical relapse at 1 year ($P = 0.03$), hospitalisation rate at 1 year ($P = 0.004$), surgery at 1 year ($P = 0.009$), and need for therapeutic dose escalation ($P = 0.005$) in patients with Crohn's disease[67].

A recent systematic review identified 17 studies that evaluated transmural healing in Crohn's disease using any of MRE, CTE, or bowel sonography, reporting that transmural healing was achieved in 14.0% to 42.4% of patients[68]. Moreover, the good correlation between transmural healing and endoscopic healing across these studies highlighted the potential of using radiologic assessments in lieu of ileo-colonoscopy in select cases. This was also acknowledged by the STRIDE-II guidelines wherein imaging was recognised to play a complementary role in the assessment of small bowel Crohn's disease, specifically in patients whose disease may not easily and repeatedly be assessed *via* ileo-colonoscopy[1]. Despite the documented utility of using cross-sectional imaging to identify therapy related response and remission, the clinical application and uptake of this strategy have been hampered by significant heterogeneity in the definitions of transmural healing across published studies thus far[68]. On this basis, the IOIBD Delphi group recommended imaging targets be considered adjuvant treatment targets until validated consensus evidence-based definitions of transmural response and transmural healing have been established[1].

Examining the utility of IUS in T2T

IUS represents a safe, non-invasive, inexpensive, and clinically useful method of evaluating transmural Crohn's disease activity[69,70]. These qualities are particularly valuable in the context of a T2T approach that requires frequent assessments of disease activity, with IUS capable of being repeated at short-intervals to evaluate treatment response in a manner that is acceptable to patients and healthcare payers alike[69,71]. Similarly, IUS also offers unique advantages over endoscopy and magnetic resonance imaging (MRI) for the assessment of Crohn's disease activity in pregnant and paediatric IBD populations[72-74]. It is also favoured by patients, exemplified by a recent study in which 98/121 (81%) IBD patients who had an IUS ranked it as their preferred modality to monitor disease activity[71]. These attributes support positioning IUS ahead of endoscopy and other cross-sectional imaging modalities such as CT and MRI in several clinical scenarios, including early assessments of treatment response.

The STRIDE-II guidelines define short, intermediate, and long-term treatment targets, with IUS capable of being repeated at all of these timepoints. In addition to serial disease monitoring, IUS also has the potential to facilitate early assessments of response to newly initiated therapies, and/or immediately prior to treatment changes[70]. This was exemplified by the IUS-sub study of the STARDUST trial which demonstrated that sonographic response to ustekinumab in patients with Crohn's disease could be detected as early as week 4[75]. Similarly, de Voogd *et al*[76] reported that a reduction in bowel wall thickness as early as 4-8 wk following initiation of anti-TNF therapy predicted future endoscopic response and remission. This highlights the potential of using early sonographic assessment to differentiate between responders and non-responders in a manner capable of facilitating early therapeutic optimisation, and discontinuation of ineffective therapy. Hence, serial IUS assessments at early, intermediate, and later timepoints following initiation or changes to IBD therapy may hold merit, and thus be incorporated into existing T2T algorithms.

Imaging features of intestinal inflammation such as bowel wall thickness, hyperaemia, and mesenteric inflammatory changes, all of which represent important parameters in the evaluation of transmural disease activity in Crohn's disease, can also be evaluated by IUS[66-68]. Meta-analyses have also documented that IUS has comparable sensitivity and specificity to MRE and CT in the diagnosis and identification of Crohn's disease related complications[77,78]. In light of this, the joint European Society of Gastrointestinal and Abdominal Radiology and European Crohn's and Colitis Organisation committees have endorsed IUS as a suitable diagnostic and monitoring tool in Crohn's disease[79]. The METRIC study also reported that both MRE and IUS have high sensitivity for detecting small bowel Crohn's disease, concluding that both investigations represent suitable first line investigations, and alternatives to ileo-colonoscopy in the diagnosis and monitoring of Crohn's disease[80]. It is, however, important to acknowledge that uniform reporting of IUS disease activity represents a key issue to be addressed before sonographic response and transmural endpoints can be routinely used as surrogate endpoints in clinical trials. This is exemplified by a lack of validated and consensus IUS disease activity scores, with a recent systematic review documenting the use of 21 ultrasound indices in 26 studies[81]. To date, bowel wall thickness represents the most studied and reliable measure of sonographic disease activity and has been shown to correlate well with future clinical and objective outcomes[75,76,82,83].

Histologic healing

Key points: (1) Histologic healing was not endorsed by STRIDE-II as a treatment target in Crohn's disease; and (2) Further studies are required to clarify the clinical significance of histologic disease activity in the setting of endoscopic remission in Crohn's disease.

Despite achieving endoscopic remission, patients with Crohn's disease may have evidence of persisting histologic inflammation. In contrast to ulcerative colitis wherein persistent histologic activity has been shown to predict subsequent relapse, the significance of histologic activity in determining outcomes in Crohn's disease remains less clear. A recent systematic review and meta-analysis identified only one study that reported adequate data to evaluate the value of histologic ileocolonic activity on future relapse in Crohn's disease, finding that histologic activity did not predict future relapse in the setting of endoscopic healing[84,85]. In light of this, the authors concluded that there was no discernible association between histologic activity and relapse in Crohn's disease, acknowledging that further data is needed. Hence, despite the questionable benefit of histologic activity in a patchy transmural disease, additional high-quality studies are required to more definitively evaluate the incremental value, if any, that histologic activity may add in the setting of endoscopic healing in patients with Crohn's disease.

Structuring Crohn's disease

Key points: (1) Treatment targets specific to Crohn's disease associated strictures remain to be defined; hence, STRIDE-II does not provide specific guidance on the management of strictures; and (2) To date, only one clinical trial, the

STRIDENT study, has applied the principles of T2T to Crohn's disease strictures.

Up to 50% of patients with Crohn's disease develop clinically significant strictures over long-term follow-up, with stricturing complications representing one of the most frequent indications for Crohn's disease related surgery[2,86]. The advent of biologic therapies capable of effectively treating bowel inflammation, a known precursor to the development of Crohn's disease related strictures, has been associated with a decrease in the frequency of surgical resections over the past two decades[87,88]. This was exemplified by findings of a recent systematic review which documented that up to 50% of patients treated with anti-TNF therapy avoided surgery over 4 years of follow-up[89].

In view of the inflammatory nature of Crohn's disease strictures, applying a T2T approach focused on treating stricture associated inflammation using anti-TNF therapy was recently investigated by the STRIDENT study[90]. This study remains the first and only randomised controlled study of both drug therapy and treatment strategy, using a T2T approach, in patients with Crohn's disease complicated by symptomatic *de novo* or anastomotic strictures[90]. In this single-centre open-label study, Schulberg and colleagues compared the efficacy of standard adalimumab monotherapy ($n = 25$), with combination high-dose adalimumab and thiopurine co-therapy ($n = 52$) dose intensified on the basis of a T2T approach. The study's primary endpoint, a decrease in the 14-d obstructive symptom score at 12 mo by one or more points from baseline, was achieved in 41/52 (79%) and 16/25 (64%) of the high-dose and standard adalimumab dosing groups [odds ratio (OR) = 2.10, 95% CI: 0.73-6.01, $P = 0.17$], respectively[90]. Notably, the combination of intensive immunosuppression with adalimumab-thiopurine co-therapy and T2T dosing adjustments on the basis of objective non-invasive measures of inflammation, was associated with fewer episodes of treatment failure, more favourable structural stricture characteristics, and less stricture-related inflammation; however, these differences were not significantly different from standard adalimumab monotherapy. The STRIDENT study did, however, unequivocally demonstrate the efficacy of anti-TNF therapy for the treatment of Crohn's disease strictures, with the authors postulating that the efficacy of anti-TNF therapy, irrespective of the dose applied, may have reduced anticipated advantages associated with the combination of intensive dosing and a T2T approach.

Despite the findings of the STRIDENT study, a lack of agreement regarding the definition of a stricture, an absence of validated stricture-specific PROMs, and ambiguity surrounding clinical, radiologic, and endoscopic definitions of response, may reflect why stricture specific targets have not been included in the most recent iteration of STRIDE recommendations. Nevertheless, an interdisciplinary expert panel of gastroenterologists and radiologists recently met with the objective of standardising the assessment of Crohn's disease strictures and defining clinically consequential treatment targets[91]. Hence, a validated suite of treatment targets specific to Crohn's disease strictures that are capable of being used in clinical practice are eagerly awaited.

INTEGRATING T2T INTO CLINICAL PRACTICE

To date, much of the focus has been on adopting STRIDE-II recommendations, with comparatively less focus on the systems and processes required to support their integration into routine clinical practice. Significant gaps between STRIDE-II recommendations and real-world clinical practice emphasise the need to define a reproducible and cost-effective model of care that embodies the principles of T2T in Crohn's disease. This represents an important first-step in reducing variability in IBD care which has been identified as a significant barrier to high-quality care[92]. Second, the cost and resource implications of executing a T2T approach, particularly in low resource healthcare settings, represents another potential obstacle to real-world uptake; highlighting the need to ensure that a T2T approach is not simply the domain of well-resourced healthcare settings. Physician familiarity with the concepts of T2T are also likely to influence their real-world application, highlighting the need for initiatives focused on improving knowledge and understanding of T2T principles. Collectively, these challenges highlight the need to devise strategies that promote uptake of a T2T approach in real-world clinical practice, and will be the focus of the following section.

Defining a suitable model of care

Key points: (1) The complex care needs of patients with Crohn's disease highlight the need for a disease-specific model of care that includes systems and processes capable of supporting a T2T approach; and (2) The optimal model of care remains yet to be defined, and should thus be the focus of future research.

Several models of IBD care have been proposed, including participatory, integrated, and values-based healthcare (VBHC) models. A participatory model of care encourages active collaboration and communication between the patient and their treating team of doctors, nurses, and allied health practitioners[92]. The integration of e-health decision support tools that encourage patients to participate in their IBD care may be useful in this context[93]. An integrated model of IBD care actively involves the patient in aspects of service development, encompasses an action plan for patient follow-up that includes care co-ordination, and prioritises strategies that optimise biopsychosocial wellbeing[94]. This approach has been shown to reduce rates of hospitalisation (48% to 30%) and healthcare costs in an Australian IBD setting[95].

More recently, the concept of VBHC has been described. This model focuses on delivering cost-effective, patient focused IBD care based on quantification and continuous measurements of health value[96]. A pilot study that evaluated the impact that a VBHC approach had on healthcare utilisation, demonstrated that a VBHC approach was able to reduce the number of endoscopies (10%, $P = 0.01$), while numerically reducing the number of surgeries (25%, $P = 0.49$), hospitalisations (28%, $P = 0.71$), emergency presentations (37%, $P = 0.44$), radiological studies (25%-86%), and IBD-related costs (16%, $P = 0.24$) [97]. Regueiro *et al*[98] similarly described the concept of a Patient Centred Medical Home that prioritised open access scheduling, remote disease monitoring, and telemedicine, demonstrating this approach to be associated with reduced hospital presentations and improved quality of life in patients with IBD within the first year of operation.

However, a Dutch study, which evaluated the efficacy of a self-managed telemedicine system (myIBDcoach) in terms of health-care utilisation and patient-reported quality of care, found that despite reducing outpatient visits ($P < 0.001$) and hospitalisations ($P = 0.046$) relative to standard IBD care, this strategy did not impact the mean number of flares ($P = 0.819$), need for surgery ($P = 0.786$), or patient reported quality of care scores ($P = 0.411$) [99]. Importantly, several aspects of a VBHC model, including those centered on care co-ordination and improving patient-reported quality of life metrics, remain central to enacting a T2T approach, highlighting the potential utility of this model of care in IBD[4]. Nevertheless, the optimal model of care, in both low and high resource settings, remains yet to be defined, highlighting the need for further research in this area.

Multi-disciplinary care co-ordination

Key points: (1) A multi-disciplinary approach remains central to both the management of Crohn's disease and the implementation of a T2T approach; and (2) Care co-ordination represents a crucial, yet potentially overlooked, aspect of executing a T2T strategy in clinical practice.

Fragmentation of care has long been associated with less favourable clinical outcomes, highlighting the importance of a co-ordinated multidisciplinary approach that values input from medical, surgical, nursing, and allied health members of the IBD team[100]. Patients also perceive a multidisciplinary approach to improve their quality of life and contribute towards a positive patient-physician relationship, with recent data also indicating that IBD patients value access to multidisciplinary care[101,102]. In light of this, a multidisciplinary approach has fast become standard of care in Crohn's disease, and has been shown to be of particular value in the management of complex phenotypes such as stricturing and perianal Crohn's disease[103,104]. Moreover, a multidisciplinary approach to chronic diseases such as IBD has been shown to improve continuity and cost-effectiveness of care, as well as the health and quality of life of patients[105,106].

In the context of a T2T approach, a multidisciplinary approach also requires that the patient and their treating IBD team identify, document, and agree upon treatment goals, highlighting that the patient represents an integral member of the multidisciplinary team (Figure 2). Moreover, the STRIDE-II guidelines require frequent assessment of disease activity, even more so in the setting of active disease, highlighting the need to schedule and follow-up investigations in a manner capable of supporting timely clinical decision-making. Hence, co-ordination of care represents a crucial, yet potentially overlooked, aspect of executing a T2T approach as part of routine clinical practice. Studies have also highlighted the utility of virtual models of care as a vehicle to help co-ordinate care and support clinical decision-making in this context. A virtual perianal clinic, inclusive of surgeons, IBD specialists, and nursing staff, was demonstrated to facilitate more timely biologic initiation and surgical intervention, than standard IBD care[107]. Similarly, a virtual biologic clinic, designed specifically to reduce heterogeneity associated with the management of loss of response to anti-TNF therapy, was shown to more frequently achieve tight disease control reflective of a T2T approach compared to standard outpatient IBD care alone in patients with Crohn's disease[108]. These findings highlight the potential utility of integrating non-traditional models such as 'virtual care' into traditional models of IBD care.

Cost and resource utilisation

Key points: (1) The cost and resource implications of implementing a T2T approach, particularly in resource poor settings, remain important; and (2) A hybrid approach that combines non-invasive disease monitoring with endoscopic assessments may be the most cost-effective T2T strategy, but requires prospective real-world validation.

In addition to being clinically important, treatment endpoints such as endoscopic remission must also be cost-effective. A decision analytic model demonstrated that a strategy focused on achieving mucosal healing, that is targeting the absence of mucosal ulceration, rather than clinical remission, was more cost-effective over 2 years in patients with Crohn's disease initiating infliximab[60]. This was also corroborated by *post hoc* analysis of data from the CALM study which indicated that a T2T approach in Crohn's disease was more cost-effective than standard care from a United Kingdom and Canadian healthcare payer perspective[109,110].

Although the STRIDE guidelines advocate for endoscopic remission, the integration of more cost-effective non-invasive disease monitoring strategies such as faecal calprotectin have also been proposed. The potential utility of this approach was exemplified by a microsimulation model which sought to evaluate the cost-effectiveness, over a 5-year horizon, of a biomarker *vs* endoscopy-driven approach to T2T disease monitoring in Crohn's disease to optimise quality adjusted life years at a pre-specified willingness to pay threshold[111]. This study concluded that a hybrid model that prioritised upfront biomarker-based monitoring on a 6-mo basis, reserving endoscopic disease monitoring for cases where endoscopic remission was not achieved by 1 year, and returning to biomarker-based monitoring once endoscopic remission was achieved, represented the most cost-effective approach. The emerging utility of non-invasive disease monitoring strategies such as point-of-care IUS also promise to make scheduled assessments of Crohn's disease more accessible and cost-effective than routine ileo-colonoscopy in the context of a T2T framework.

It is also important to acknowledge the potential challenges, often related to cost and resource limitations, associated with implementing a T2T approach in low resource healthcare settings, where practicality and cost-effectiveness often need to be prioritised. This emphasises the need to integrate cost-effective non-invasive surrogates of endoscopic endpoints to ensure that the potential benefits of a T2T approach are not limited to patients managed in well-resourced IBD centres.

Interventions to increase uptake of T2T

Key points: (1) Significant gaps between STRIDE-II recommendations and their real-world application exist; (2) Clinician familiarity with T2T principles may influence their real-world application; and (3) Clinician directed quality improvement and collaborative learning interventions have been shown to increase uptake and application of a T2T

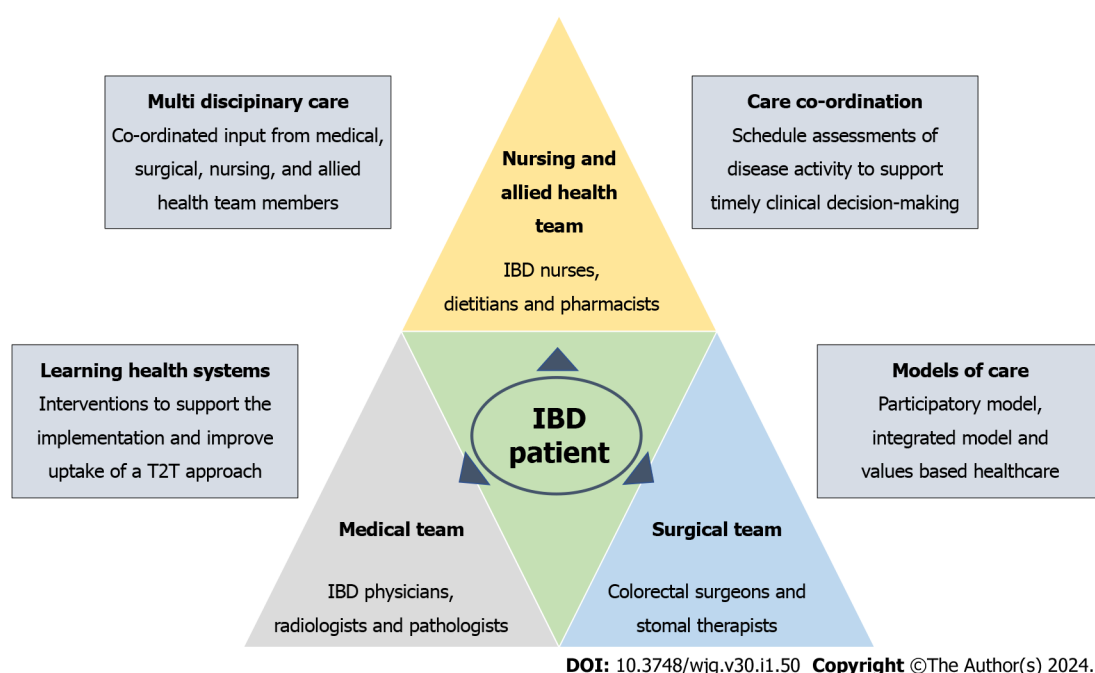


Figure 2 A treat-to-target approach requires multidisciplinary care. IBD: Inflammatory bowel disease; T2T: Treat-to-target.

approach.

Several factors, including clinician familiarity, patient acceptance, and access to healthcare resources, have contributed toward a significant gap between STRIDE-II recommendations and clinical practice[5,7]. Bryant and colleagues highlighted the significance of clinician familiarity with T2T principles, finding that familiarity with the concept was associated with the perception of it being relevant to clinical practice (OR = 5.5, 95%CI: 1.5–20.4, $P = 0.01$)[5]. The patient perspective was evaluated by Selinger and colleagues who reported that only two-thirds of IBD patients appraised a T2T approach targeting endoscopic endpoints to be acceptable, illuminating potential gaps between patient perceptions and STRIDE-II recommendations[7]. Finally, the need to undertake frequent investigations, including ileo-colonoscopy, is resource intensive and inconvenient to patients, potentially impacting the execution of a T2T approach outside of well-resourced IBD centres.

This highlights the need for interventions to support the implementation, and improve uptake, of a T2T approach. The Treat to target in RA: Collaboration To Improve adOption and adhereNce (TRACTION) cluster randomised trial sought to increase uptake of a T2T approach in rheumatoid arthritis through the use of a group-based learning collaborative focused on training and educating clinicians on how to apply a T2T approach in clinical practice[112]. This intervention was able to increase the mean T2T implementation score from 11% to 57% compared to only 25% in the control group ($P < 0.004$). Moreover, increased uptake of a T2T approach following the group-based learning collaborative intervention was not associated with a disproportionate increase in resource use, or adverse events. A similar intervention, using a 12-mo breakthrough series collaborative, sought to improve the implementation of T2T amongst IBD clinicians, using monthly report cards, webinars, an active listserv, and two learning sessions[113]. This quality improvement initiative led to a clinically significant increase in rates of 'intention to T2T' from 23% to 49% over 12 mo. Importantly, this initiative was also associated with increased rates of steroid-free clinical and endoscopic remission.

OVERVIEW OF CURRENT PRACTICE AND EMERGING CONCEPTS

The STRIDE-II guidelines specify short, intermediate, and long-term treatment goals (Figure 3), and document specific treatment targets to be achieved at each of these timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to enacting a T2T approach. It is, however, also important that the timing of these assessments parallels therapy-specific time to response, to ensure that the results of these investigations can be reliably used to inform clinical decision-making (Table 1)[114–136]. Although frequent endoscopic evaluation is recommended in the pursuit of endoscopic treatment targets, this approach is quite resource intensive, emphasising the need for comparable non-invasive assessments such as faecal calprotectin and IUS, which can be more easily, inexpensively, and acceptably repeated at multiple timepoints. Moreover, a hybrid approach that prioritises non-invasive biomarkers to undertake background disease monitoring, reserving more frequent endoscopic assessments for high-risk patients or those who do not achieve endoscopic endpoints within 12 mo, may hold promise, but requires real-world validation[111].

Although the CALM study highlighted the utility of a T2T strategy in maintaining tight disease control to achieve improved clinical and endoscopic outcomes in patients with early Crohn's disease treated with adalimumab, the

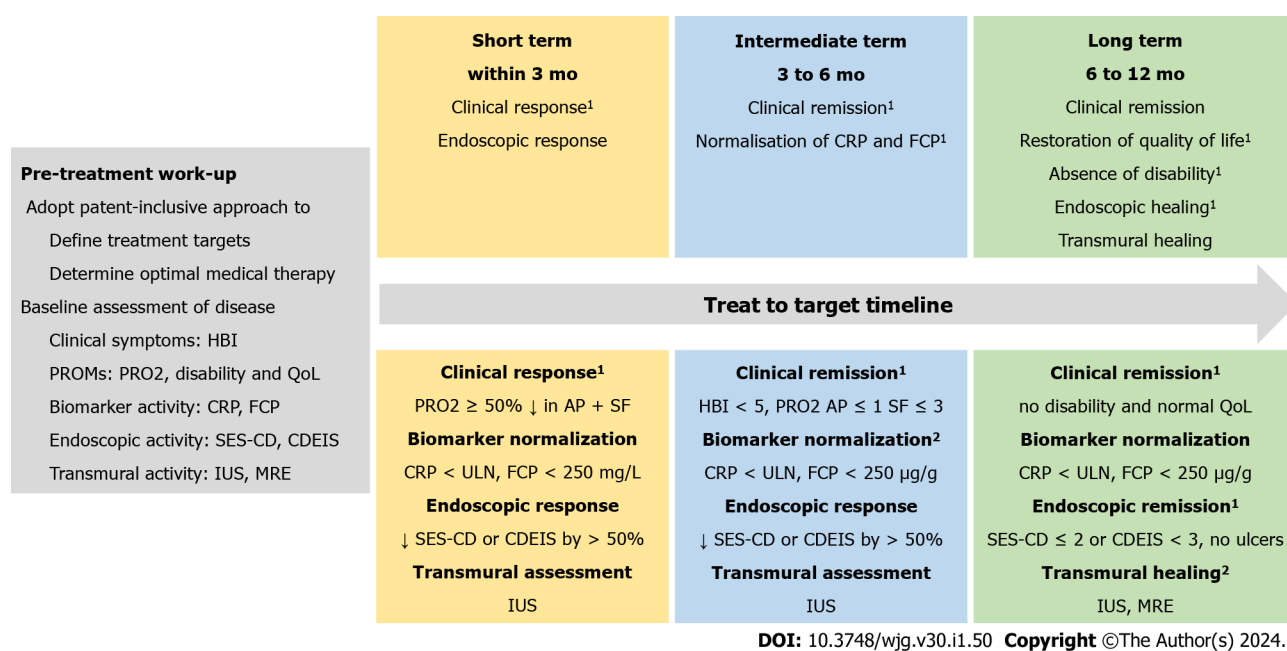


Figure 3 A practical approach to the clinical application of a treat-to-target strategy in clinical practice. ¹Selecting Therapeutic Targets in Inflammatory Bowel Disease II endorsed treatment target: Consider changing therapy if not met. ²Transmural healing is an adjuvant to endoscopic remission. HBI: Harvey Bradshaw Index; PROM: Patient reported outcome measure; PRO2: Patient reported outcome 2; QoL: Quality of life; AP: Abdominal pain; SF: Stool frequency; CRP: C-reactive protein; ULN: Upper limit of normal; FCP: Faecal calprotectin; SES-CD: Simple Endoscopic Score for Crohn's Disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; IUS: Intestinal ultrasound; MRE: Magnetic resonance enterography.

STARDUST trial did not demonstrate a T2T approach to be superior to symptom guided care in achieving endoscopic response in ustekinumab treated patients[28,65]. While differences in patient, disease, and treatment characteristics make direct comparison between these two studies difficult, they highlight that we have yet to identify which patients and disease characteristics are likely to benefit most from a T2T approach. Moreover, outside of clinical trials, evidence of the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies that not only evaluate the clinical effectiveness of this strategy, but also provide practical guidance regarding how to implement the principles of T2T into real-world clinical practice.

Emerging treatment targets such as transmural healing have also demonstrated good correlation with endoscopic outcomes[68]. However, in the absence of consensus definitions of transmural response and healing, including a lack of well-designed studies comparing endoscopic and transmural outcomes, guidelines advise that transmural outcomes remain an adjuvant target at the present time. Similarly, treatment strategies and targets specific to complex disease phenotypes such as stricturing, penetrating, and perianal Crohn's disease remain to be well-defined on the basis of current data, highlighting another area of unmet need.

CONCLUSION

In conclusion, a T2T approach provides clinicians and patients with clear treatment goals and objectives. This alone has been transformative, providing much needed clarity and direction to IBD care. However, despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its widespread uptake. This highlights the need to develop models of care, inclusive of systems and processes, that are capable of meeting the specific care needs of patients with Crohn's disease. These models must be cost-effective and easily reproducible in both high and lower resource healthcare settings. The utility of non-invasive and cost-effective disease monitoring strategies such as point-of-care IUS also warrants strong consideration in this context as they promise to make scheduled assessments of Crohn's disease more achievable than routine endoscopy or MRI. Patient 'buy-in' to, and clinician familiarity with, the principles of T2T have also been shown to greatly influence the uptake of a T2T approach, emphasising the need for interventions focused on engaging and educating both parties. Hence, several challenges remain to be addressed before the promise of a T2T approach can be fully realised in the context of managing the complex care needs of patients with Crohn's disease.

FOOTNOTES

Author contributions: Srinivasan AR conceptualised the study, reviewed the literature, and composed the manuscript.

Conflict-of-interest statement: Dr. Ashish Srinivasan has received speaker fees from Arrotex Pharmaceuticals and advisory fees from AstraZeneca and AbbVie.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Australia

ORCID number: Ashish R Srinivasan 0000-0001-5952-1570.

S-Editor: Qu XL

L-Editor: Wang TQ

P-Editor: Yuan YY

REFERENCES

- 1 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Geary R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]
- 2 **Cosnes J**, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250 [PMID: 12131607 DOI: 10.1097/00054725-200207000-00002]
- 3 **Gonczi L**, Bessissow T, Lakatos PL. Disease monitoring strategies in inflammatory bowel diseases: What do we mean by "tight control"? *World J Gastroenterol* 2019; **25**: 6172-6189 [PMID: 31749591 DOI: 10.3748/wjg.v25.i41.6172]
- 4 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021; **160**: 1570-1583 [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]
- 5 **Bryant RV**, Costello SP, Schoeman S, Sathananthan D, Knight E, Lau SY, Schoeman MN, Mountfield R, Tee D, Travis SPL, Andrews JM. Limited uptake of ulcerative colitis "treat-to-target" recommendations in real-world practice. *J Gastroenterol Hepatol* 2018; **33**: 599-607 [PMID: 28806471 DOI: 10.1111/jgh.13923]
- 6 **Rubin DT**, Krugliak Cleveland N. Using a Treat-to-Target Management Strategy to Improve the Doctor-Patient Relationship in Inflammatory Bowel Disease. *Am J Gastroenterol* 2015; **110**: 1252-1256 [PMID: 25848924 DOI: 10.1038/ajg.2015.86]
- 7 **Selinger C**, Carbonell J, Kane J, Omer M, Ford AC. Acceptability of a 'treat to target' approach in inflammatory bowel disease to patients in clinical remission. *Frontline Gastroenterol* 2021; **12**: 30-38 [PMID: 33493249 DOI: 10.1136/flgastro-2019-101366]
- 8 **Viswanathan M**, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012; **157**: 785-795 [PMID: 22964778 DOI: 10.7326/0003-4819-157-11-201212040-00538]
- 9 **Jackson CA**, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 2010; **105**: 525-539 [PMID: 19997092 DOI: 10.1038/ajg.2009.685]
- 10 **Selinger CP**, Robinson A, Leong RW. Clinical impact and drivers of non-adherence to maintenance medication for inflammatory bowel disease. *Expert Opin Drug Saf* 2011; **10**: 863-870 [PMID: 21548837 DOI: 10.1517/14740338.2011.583915]
- 11 **Fenton C**, Al-Ani A, Trinh A, Srinivasan A, Marion K, Hebbard G. Impact of providing patients with copies of their medical correspondence: a randomised controlled study. *Intern Med J* 2017; **47**: 68-75 [PMID: 27616436 DOI: 10.1111/imj.13252]
- 12 **Castle SC**. Clinical relevance of age-related immune dysfunction. *Clin Infect Dis* 2000; **31**: 578-585 [PMID: 10987724 DOI: 10.1086/313947]
- 13 **Lahaye C**, Tatar Z, Dubost JJ, Soubrier M. Overview of biologic treatments in the elderly. *Joint Bone Spine* 2015; **82**: 154-160 [PMID: 25553833 DOI: 10.1016/j.jbspin.2014.10.012]
- 14 **Román AL**, Muñoz F. Comorbidity in inflammatory bowel disease. *World J Gastroenterol* 2011; **17**: 2723-2733 [PMID: 21734780 DOI: 10.3748/wjg.v17.i22.2723]
- 15 **Laredo V**, Gargallo-Puyuelo CJ, Gomollón F. How to Choose the Biologic Therapy in a Bio-naïve Patient with Inflammatory Bowel Disease. *J Clin Med* 2022; **11** [PMID: 35160280 DOI: 10.3390/jcm11030829]
- 16 **Dunleavy KA**, Pardi DS. Biologics: how far can they go in Crohn's disease? *Gastroenterol Rep (Oxf)* 2022; **10**: goac049 [PMID: 36196255 DOI: 10.1093/gastro/goac049]
- 17 **Garcia NM**, Cohen NA, Rubin DT. Treat-to-target and sequencing therapies in Crohn's disease. *United European Gastroenterol J* 2022; **10**: 1121-1128 [PMID: 36507876 DOI: 10.1002/ueg2.12336]
- 18 **Torres J**, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020; **14**: 4-22 [PMID: 31711158 DOI: 10.1093/ecco-jcc/jjz180]

- 19 **Zisman-Ilani Y**, Thompson KD, Siegel LS, Mackenzie T, Crate DJ, Korzenik JR, Melmed GY, Kozuch P, Sands BE, Rubin DT, Regueiro MD, Cross R, Wolf DC, Hanson JS, Schwartz RM, Vrabie R, Kreines MD, Scherer T, Dubinsky MC, Siegel CA. Crohn's disease shared decision making intervention leads to more patients choosing combination therapy: a cluster randomised controlled trial. *Aliment Pharmacol Ther* 2023; **57**: 205-214 [PMID: [36377259](#) DOI: [10.1111/apt.17286](#)]
- 20 **Vasudevan A**, Gibson PR, van Langenberg DR. Time to clinical response and remission for therapeutics in inflammatory bowel diseases: What should the clinician expect, what should patients be told? *World J Gastroenterol* 2017; **23**: 6385-6402 [PMID: [29085188](#) DOI: [10.3748/wjg.v23.i35.6385](#)]
- 21 **Laterza L**, Piscaglia AC, Minordi LM, Scoleri I, Larosa L, Poscia A, Ingravalle F, Amato A, Alfieri S, Armuzzi A, Cammarota G, Gasbarrini A, Scaldaferrì F. Multiparametric Evaluation Predicts Different Mid-Term Outcomes in Crohn's Disease. *Dig Dis* 2018; **36**: 184-193 [PMID: [29514146](#) DOI: [10.1159/000487589](#)]
- 22 **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 Diseases: A Systematic Review. *Clin Gastroenterol Hepatol* 2018; **16**: 648-663.e3 [PMID: [29074448](#) DOI: [10.1016/j.cgh.2017.10.019](#)]
- 23 **Khanna R**, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, Rolleri RL, Bortey E, Paterson C, Forbes WP, Levesque BG. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther* 2015; **41**: 77-86 [PMID: [25348809](#) DOI: [10.1111/apt.13001](#)]
- 24 **Sudhakar P**, Wellens J, Verstockt B, Ferrante M, Sabino J, Vermeire S. Holistic healthcare in inflammatory bowel disease: time for patient-centric approaches? *Gut* 2023; **72**: 192-204 [PMID: [36171081](#) DOI: [10.1136/gutjnl-2022-328221](#)]
- 25 **Ghosh S**, Louis E, Beaugier L, Bossuyt P, Bouguen G, Bourreille A, Ferrante M, Franchimont D, Frost K, Hebutterne X, Marshall JK, O'Shea C, Rosenfeld G, Williams C, Peyrin-Biroulet L. Development of the IBD Disk: A Visual Self-administered Tool for Assessing Disability in Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2017; **23**: 333-340 [PMID: [28146002](#) DOI: [10.1097/MIB.0000000000001033](#)]
- 26 **Tadibiri S**, Nachury M, Bouhnik Y, Serrero M, Hébuterne X, Roblin X, Kirchgessner J, Bouguen G, Franchimont D, Savoye G, Buisson A, Louis E, Nancey S, ABitbol V, Reimund JM, DeWit O, Vuitton L, Matthieu N, Peyrin-Biroulet L, Gilletta C, Allez M, Viennot S, Trang-Poisson C, Dib N, Brixi H, Boualil M, Plastaras L, Boivineau L, Fumery M, Caillo L, Laharie D, Amiot A; GETAID-IBD-disk study group. The IBD-disk Is a Reliable Tool to Assess the Daily-life Burden of Patients with Inflammatory Bowel Disease. *J Crohns Colitis* 2021; **15**: 766-773 [PMID: [33246337](#) DOI: [10.1093/ecco-jcc/jjaa244](#)]
- 27 **Lahiff C**, Safaie P, Awais A, Akbari M, Gashin L, Sheth S, Lembo A, Leffler D, Moss AC, Cheifetz AS. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2013; **37**: 786-794 [PMID: [23432394](#) DOI: [10.1111/apt.12262](#)]
- 28 **Colombel JF**, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, Danalioglu A, Novacek G, Armuzzi A, Hébuterne X, Travis S, Danese S, Reinisch W, Sandborn WJ, Rutgeerts P, Hommes D, Schreiber S, Neimark E, Huang B, Zhou Q, Mendez P, Petersson J, Wallace K, Robinson AM, Thakkar RB, D'Haens G. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2017; **390**: 2779-2789 [PMID: [29096949](#) DOI: [10.1016/S0140-6736\(17\)32641-7](#)]
- 29 **Peyrin-Biroulet L**, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, Rutgeerts P, Tang LK, Cornillie FJ, Sandborn WJ. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63**: 88-95 [PMID: [23974954](#) DOI: [10.1136/gutjnl-2013-304984](#)]
- 30 **Ikhtaire S**, Shajib MS, Reinisch W, Khan WI. Fecal calprotectin: its scope and utility in the management of inflammatory bowel disease. *J Gastroenterol* 2016; **51**: 434-446 [PMID: [26897740](#) DOI: [10.1007/s00535-016-1182-4](#)]
- 31 **Jones J**, Loftus EV Jr, Panaccione R, Chen LS, Peterson S, McConnell J, Baudhuin L, Hanson K, Feagan BG, Harmsen SW, Zinsmeister AR, Helou E, Sandborn WJ. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008; **6**: 1218-1224 [PMID: [18799360](#) DOI: [10.1016/j.cgh.2008.06.010](#)]
- 32 **Boirivant M**, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. *J Clin Gastroenterol* 1988; **10**: 401-405 [PMID: [3418087](#) DOI: [10.1097/00004836-198808000-00011](#)]
- 33 **Vermeire S**, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2006; **55**: 426-431 [PMID: [16474109](#) DOI: [10.1136/gut.2005.069476](#)]
- 34 **Morris MW**, Stewart SA, Heisler C, Sandborn WJ, Loftus EV, Zello GA, Fowler SA, Jones JL. Biomarker-Based Models Outperform Patient-Reported Scores in Predicting Endoscopic Inflammatory Disease Activity. *Inflamm Bowel Dis* 2018; **24**: 277-285 [PMID: [29361090](#) DOI: [10.1093/ibd/izx018](#)]
- 35 **Chen JM**, Liu T, Gao S, Tong XD, Deng FH, Nie B. Efficacy of noninvasive evaluations in monitoring inflammatory bowel disease activity: A prospective study in China. *World J Gastroenterol* 2017; **23**: 8235-8247 [PMID: [29290660](#) DOI: [10.3748/wjg.v23.i46.8235](#)]
- 36 **Bodelier AG**, Jonkers D, van den Heuvel T, de Boer E, Hameeteman W, Masclee AA, Pierik MJ. High Percentage of IBD Patients with Indefinite Fecal Calprotectin Levels: Additional Value of a Combination Score. *Dig Dis Sci* 2017; **62**: 465-472 [PMID: [27933473](#) DOI: [10.1007/s10620-016-4397-6](#)]
- 37 **Nakurai A**, Kato J, Hiraoka S, Inokuchi T, Takei D, Morito Y, Akita M, Takahashi S, Hori K, Harada K, Okada H, Yamamoto K. Slight increases in the disease activity index and platelet count imply the presence of active intestinal lesions in C-reactive protein-negative Crohn's disease patients. *Intern Med* 2014; **53**: 1905-1911 [PMID: [25175121](#) DOI: [10.2169/internalmedicine.53.2627](#)]
- 38 **Falvey JD**, Hoskin T, Meijer B, Ashcroft A, Walmsley R, Day AS, Garry RB. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflamm Bowel Dis* 2015; **21**: 824-831 [PMID: [25738372](#) DOI: [10.1097/MIB.0000000000000341](#)]
- 39 **Kennedy NA**, Jones GR, Plevris N, Patenden R, Arnott ID, Lees CW. Association Between Level of Fecal Calprotectin and Progression of Crohn's Disease. *Clin Gastroenterol Hepatol* 2019; **17**: 2269-2276.e4 [PMID: [30772585](#) DOI: [10.1016/j.cgh.2019.02.017](#)]
- 40 **De Suray N**, Salleron J, Vernier-Massouille G, Grimaud J, Bouhnik Y, Laharie D, Dupas J-L, Pillant H, Picon L, Veyrac M. P274 Close monitoring of CRP and fecal calprotectin levels to predict relapse in Crohn's disease patients. A sub-analysis of the STORI study. *J Crohns Colitis* 2012; **6** Suppl 1: S118-119 [DOI: [10.1016/s1873-9946\(12\)60294-3](#)]
- 41 **Zhulina Y**, Cao Y, Amcoff K, Carlson M, Tysk C, Halfvarson J. The prognostic significance of faecal calprotectin in patients with inactive inflammatory bowel disease. *Aliment Pharmacol Ther* 2016; **44**: 495-504 [PMID: [27402063](#) DOI: [10.1111/apt.13731](#)]
- 42 **Kawashima K**, Ishihara S, Yuki T, Fukuba N, Sonoyama H, Kazumori H, Yamashita N, Tada Y, Kusunoki R, Oka A, Oshima N, Mishima Y, Moriyama I, Kinoshita Y. Fecal Calprotectin More Accurately Predicts Endoscopic Remission of Crohn's Disease than Serological Biomarkers

Evaluated Using Balloon-assisted Enteroscopy. *Inflamm Bowel Dis* 2017; **23**: 2027-2034 [PMID: 28817462 DOI: 10.1097/MIB.0000000000001202]

- 43 **Lobatón T**, López-García A, Rodríguez-Moranta F, Ruiz A, Rodríguez L, Guardiola J. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. *J Crohns Colitis* 2013; **7**: e641-e651 [PMID: 23810085 DOI: 10.1016/j.crohns.2013.05.005]
- 44 **D'Haens G**, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224 [PMID: 22344983 DOI: 10.1002/ibd.22917]
- 45 **Goutorbe F**, Goutte M, Minet-Quinard R, Boucher AL, Pereira B, Bommelaer G, Buisson A. Endoscopic Factors Influencing Fecal Calprotectin Value in Crohn's Disease. *J Crohns Colitis* 2015; **9**: 1113-1119 [PMID: 26351383 DOI: 10.1093/ecco-jcc/jjv150]
- 46 **Schoepfer AM**, Beglinger C, Straumann M, Trummel M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: 19755969 DOI: 10.1038/ajg.2009.545]
- 47 **Sipponen T**, Kärkkäinen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther* 2008; **28**: 1221-1229 [PMID: 18752630 DOI: 10.1111/j.1365-2036.2008.03835.x]
- 48 **E Penna FGC**, Rosa RM, da Cunha PFS, de Souza SCS, de Abreu Ferrari ML. Faecal calprotectin is the biomarker that best distinguishes remission from different degrees of endoscopic activity in Crohn's disease. *BMC Gastroenterol* 2020; **20**: 35 [PMID: 32054445 DOI: 10.1186/s12876-020-1183-x]
- 49 **Plevris N**, Fulforth J, Lyons M, Siakavellas SI, Jenkinson PW, Chuah CS, Lucaci L, Pattenden RJ, Arnott ID, Jones GR, Lees CW. Normalization of Fecal Calprotectin Within 12 Months of Diagnosis Is Associated With Reduced Risk of Disease Progression in Patients With Crohn's Disease. *Clin Gastroenterol Hepatol* 2021; **19**: 1835-1844.e6 [PMID: 32798706 DOI: 10.1016/j.cgh.2020.08.022]
- 50 **Dhaliwal A**, Zeino Z, Tomkins C, Cheung M, Nwokolo C, Smith S, Harmston C, Arasaradnam RP. Utility of faecal calprotectin in inflammatory bowel disease (IBD): what cut-offs should we apply? *Frontline Gastroenterol* 2015; **6**: 14-19 [PMID: 25580205 DOI: 10.1136/flgastro-2013-100420]
- 51 **Diederer K**, Hoekman DR, Leek A, Wolters VM, Hummel TZ, de Meij TG, Koot BG, Tabbers MM, Benninga MA, Kindermann A. Raised faecal calprotectin is associated with subsequent symptomatic relapse, in children and adolescents with inflammatory bowel disease in clinical remission. *Aliment Pharmacol Ther* 2017; **45**: 951-960 [PMID: 28138990 DOI: 10.1111/apt.13950]
- 52 **Noh SM**, Oh EH, Park SH, Lee JB, Kim JY, Park JC, Kim J, Ham NS, Hwang SW, Yang DH, Byeon JS, Myung SJ, Yang SK, Ye BD. Association of Faecal Calprotectin Level and Combined Endoscopic and Radiological Healing in Patients With Crohn's Disease Receiving Anti-tumour Necrosis Factor Therapy. *J Crohns Colitis* 2020; **14**: 1231-1240 [PMID: 32157278 DOI: 10.1093/ecco-jcc/jjaa042]
- 53 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]
- 54 **Ungaro RC**, Yzet C, Bossuyt P, Baert FJ, Vanasek T, D'Haens GR, Joustra VW, Panaccione R, Novacek G, Reinisch W, Armuzzi A, Golovchenko O, Prymak O, Goldis A, Travis SP, Hébuterne X, Ferrante M, Rogler G, Fumery M, Danese S, Rydzewska G, Pariente B, Hertervig E, Stanciu C, Serrero M, Diculescu M, Peyrin-Biroulet L, Laharie D, Wright JP, Gomollón F, Gubonina I, Schreiber S, Motoya S, Hellström PM, Halfvarson J, Butler JW, Petersson J, Petralia F, Colombel JF. Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. *Gastroenterology* 2020; **159**: 139-147 [PMID: 32224129 DOI: 10.1053/j.gastro.2020.03.039]
- 55 **Limketkai B**, Singh S, Sandborn WJ, Dulai PS. Early Endoscopic Evaluation After Initiation of Biologic Therapy Reduces Disease-Related Complications in Inflammatory Bowel Disease, Supporting the Concept of Treat-to-Target: 574. *Am J of Gastroenterol* 2018; **113**: S330-331 [DOI: 10.14309/0000434-201810001-00574]
- 56 **Daperno M**, Castiglione F, de Ridder L, Dotan I, Färkkilä M, Florholmen J, Fraser G, Fries W, Hébuterne X, Lakatos PL, Panés J, Rimola J, Louis E; Scientific Committee of the European Crohn's and Colitis Organization. Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. *J Crohns Colitis* 2011; **5**: 484-498 [PMID: 21939926 DOI: 10.1016/j.crohns.2011.07.003]
- 57 **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**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]
- 58 **Schnitzler F**, Fidler H, Ferrante M, Noman M, Arijis I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301 [PMID: 19340881 DOI: 10.1002/ibd.20927]
- 59 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-8; quiz e10 [PMID: 19818785 DOI: 10.1053/j.gastro.2009.09.056]
- 60 **Ananthakrishnan AN**, Korzenik JR, Hur C. Can mucosal healing be a cost-effective endpoint for biologic therapy in Crohn's disease? A decision analysis. *Inflamm Bowel Dis* 2013; **19**: 37-44 [PMID: 22416019 DOI: 10.1002/ibd.22951]
- 61 **Shah SC**, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317-333 [PMID: 26607562 DOI: 10.1111/apt.13475]
- 62 **Reinink AR**, Lee TC, Higgins PD. Endoscopic Mucosal Healing Predicts Favorable Clinical Outcomes in Inflammatory Bowel Disease: A Meta-analysis. *Inflamm Bowel Dis* 2016; **22**: 1859-1869 [PMID: 27206015 DOI: 10.1097/MIB.0000000000000816]
- 63 **Colombel JF**, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, Thakkar RB, Robinson AM, Chen N, Mulani PM, Chao J. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 414-22.e5 [PMID: 23856361 DOI: 10.1016/j.cgh.2013.06.019]
- 64 **Bruining DH**, Zimmermann EM, Loftus EV Jr, Sandborn WJ, Sauer CG, Strong SA; Society of Abdominal Radiology Crohn's Disease-Focused Panel. Consensus Recommendations for Evaluation, Interpretation, and Utilization of Computed Tomography and Magnetic Resonance Enterography in Patients With Small Bowel Crohn's Disease. *Radiology* 2018; **286**: 776-799 [PMID: 29319414 DOI: 10.1148/radiol.2018171737]
- 65 **Danese S**, Vermeire S, D'Haens G, Panés J, Dignass A, Magro F, Nazar M, Le Bars M, Lahaye M, Ni L, Bravata I, Lavie F, Daperno M, Lukáš M, Armuzzi A, Löwenberg M, Gaya DR, Peyrin-Biroulet L; STARDUST study group. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. *Lancet Gastroenterol Hepatol*

- 2022; **7**: 294-306 [PMID: [35120656](#) DOI: [10.1016/S2468-1253\(21\)00474-X](#)]
- 66 **Varyani F**, Samuel S. "Can Magnetic Resonance Enterography (MRE) replace ileo-colonoscopy for evaluating disease activity in Crohn's disease?". *Best Pract Res Clin Gastroenterol* 2019; **38-39**: 101621 [PMID: [31327407](#) DOI: [10.1016/j.bpg.2019.05.008](#)]
- 67 **Castiglione F**, Imperatore N, Testa A, De Palma GD, Nardone OM, Pellegrini L, Caporaso N, Rispo A. One-year clinical outcomes with biologics in Crohn's disease: transmural healing compared with mucosal or no healing. *Aliment Pharmacol Ther* 2019; **49**: 1026-1039 [PMID: [30854708](#) DOI: [10.1111/apt.15190](#)]
- 68 **Geyl S**, Guillo L, Laurent V, D'Amico F, Danese S, Peyrin-Biroulet L. Transmural healing as a therapeutic goal in Crohn's disease: a systematic review. *Lancet Gastroenterol Hepatol* 2021; **6**: 659-667 [PMID: [34090579](#) DOI: [10.1016/S2468-1253\(21\)00096-0](#)]
- 69 **Luber RP**, Petri B, Meade S, Honap S, Zeki S, Gecse KB, Griffin N, Irving PM. Positioning intestinal ultrasound in a UK tertiary centre: significant estimated clinical role and cost savings. *Frontline Gastroenterol* 2023; **14**: 52-58 [PMID: [36561789](#) DOI: [10.1136/flgastro-2022-102156](#)]
- 70 **Kucharzik T**, Wittig BM, Helwig U, Börner N, Rössler A, Rath S, Maaser C; TRUST study group. Use of Intestinal Ultrasound to Monitor Crohn's Disease Activity. *Clin Gastroenterol Hepatol* 2017; **15**: 535-542.e2 [PMID: [27856365](#) DOI: [10.1016/j.cgh.2016.10.040](#)]
- 71 **Rajagopalan A**, Sathananthan D, An YK, Van De Ven L, Martin S, Fon J, Costello SP, Begun J, Bryant RV. Gastrointestinal ultrasound in inflammatory bowel disease care: Patient perceptions and impact on disease-related knowledge. *JGH Open* 2020; **4**: 267-272 [PMID: [32280776](#) DOI: [10.1002/jgh3.12268](#)]
- 72 **van Wassenae EA**, de Voogd FAE, van Rijn RR, van Der Lee JH, Tabbers MM, van Etten-Jamaludin FS, Gecse KB, Kindermann A, De Meij TGJ, D'haens GR, Benninga MA, Koot BGP. Diagnostic Accuracy of Transabdominal Ultrasound in Detecting Intestinal Inflammation in Paediatric IBD Patients-a Systematic Review. *J Crohns Colitis* 2019; **13**: 1501-1509 [PMID: [31329839](#) DOI: [10.1093/ecco-jcc/jjz085](#)]
- 73 **Flanagan E**, Wright EK, Begun J, Bryant RV, An YK, Ross AL, Kiburg KV, Bell SJ. Monitoring Inflammatory Bowel Disease in Pregnancy Using Gastrointestinal Ultrasonography. *J Crohns Colitis* 2020; **14**: 1405-1412 [PMID: [32343768](#) DOI: [10.1093/ecco-jcc/jjaa082](#)]
- 74 **Andrew B**, Vasudevan A, Srinivasan A. The Role of Intestinal Ultrasound During Pregnancy in Patients With Inflammatory Bowel Disease. *Am J Gastroenterol* 2023; **118**: 2096-2097 [PMID: [37916754](#) DOI: [10.14309/ajg.0000000000002402](#)]
- 75 **Kucharzik T**, Wilkens R, Maconi G, Agostino M, Le Bars M, Nazar M, Sloan S, Lahaye M, Li N, Ercole E. Intestinal ultrasound response and transmural healing after ustekinumab induction in Crohn's disease: Week 16 interim analysis of the STARDUST trial substudy. *Z Gastroenterol* 2020; **58**: e77 [DOI: [10.1093/ecco-jcc/jjz203.049](#)]
- 76 **de Voogd F**, Bots S, Gecse K, Gilja OH, D'Haens G, Nyland K. Intestinal Ultrasound Early on in Treatment Follow-up Predicts Endoscopic Response to Anti-TNF α Treatment in Crohn's Disease. *J Crohns Colitis* 2022; **16**: 1598-1608 [PMID: [35639823](#) DOI: [10.1093/ecco-jcc/jjac072](#)]
- 77 **Horsthuis K**, Bipat S, Bennis RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008; **247**: 64-79 [PMID: [18372465](#) DOI: [10.1148/radiol.2471070611](#)]
- 78 **Panés J**, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, Mendoza JL, Paredes JM, Quiroga S, Ripollés T, Rimola J. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 125-145 [PMID: [21615440](#) DOI: [10.1111/j.1365-2036.2011.04710.x](#)]
- 79 **Maaser C**, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annesse V, Calabrese E, Baumgart DC, Bettenworth D, Borralho Nunes P, Burisch J, Castiglione F, Eliakim R, Ellul P, González-Lama Y, Gordon H, Halligan S, Katsanos K, Kopylov U, Kotze PG, Krustinš E, Laghi A, Limdi JK, Rieder F, Rimola J, Taylor SA, Tolan D, van Rheeën P, Verstockt B, Stoker J; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019; **13**: 144-164 [PMID: [30137275](#) DOI: [10.1093/ecco-jcc/jjy113](#)]
- 80 **Taylor SA**, Mallett S, Bhatnagar G, Baldwin-Cleland R, Bloom S, Gupta A, Hamlin PJ, Hart AL, Higginson A, Jacobs I, McCartney S, Miles A, Murray CD, Plumb AA, Pollok RC, Punwani S, Quinn L, Rodriguez-Justo M, Shabir Z, Slater A, Tolan D, Travis S, Windsor A, Wylie P, Zealley I, Halligan S; METRIC study investigators. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. *Lancet Gastroenterol Hepatol* 2018; **3**: 548-558 [PMID: [29914843](#) DOI: [10.1016/S2468-1253\(18\)30161-4](#)]
- 81 **Goodsall TM**, Nguyen TM, Parker CE, Ma C, Andrews JM, Jairath V, Bryant RV. Systematic Review: Gastrointestinal Ultrasound Scoring Indices for Inflammatory Bowel Disease. *J Crohns Colitis* 2021; **15**: 125-142 [PMID: [32614386](#) DOI: [10.1093/ecco-jcc/jjaa129](#)]
- 82 **Smith RL**, Taylor KM, Friedman AB, Gibson DJ, Con D, Gibson PR. Early sonographic response to a new medical therapy is associated with future treatment response or failure in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2022; **34**: 613-621 [PMID: [35352696](#) DOI: [10.1097/MEG.0000000000002367](#)]
- 83 **Maaser C**, Petersen F, Helwig U, Fischer I, Roessler A, Rath S, Lang D, Kucharzik T; German IBD Study Group and the TRUST&UC study group; German IBD Study Group and TRUST&UC study group. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. *Gut* 2020; **69**: 1629-1636 [PMID: [31862811](#) DOI: [10.1136/gutjnl-2019-319451](#)]
- 84 **Hu AB**, Tan W, Deshpande V, Ananthakrishnan AN. Ileal or Colonic Histologic Activity Is Not Associated With Clinical Relapse in Patients With Crohn's Disease in Endoscopic Remission. *Clin Gastroenterol Hepatol* 2021; **19**: 1226-1233.e1 [PMID: [32360823](#) DOI: [10.1016/j.cgh.2020.04.050](#)]
- 85 **Gupta A**, Yu A, Peyrin-Biroulet L, Ananthakrishnan AN. Treat to Target: The Role of Histologic Healing in Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2021; **19**: 1800-1813.e4 [PMID: [33010406](#) DOI: [10.1016/j.cgh.2020.09.046](#)]
- 86 **Rieder F**, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut* 2013; **62**: 1072-1084 [PMID: [23626373](#) DOI: [10.1136/gutjnl-2012-304353](#)]
- 87 **Rungoe C**, Langholz E, Andersson M, Basit S, Nielsen NM, Wohlfahrt J, Jess T. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut* 2014; **63**: 1607-1616 [PMID: [24056767](#) DOI: [10.1136/gutjnl-2013-305607](#)]
- 88 **Ma C**, Moran GW, Benchimol EI, Targownik LE, Heitman SJ, Hubbard JN, Seow CH, Novak KL, Ghosh S, Panaccione R, Kaplan GG. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol* 2017; **112**: 1840-1848 [PMID: [29087396](#) DOI: [10.1038/ajg.2017.394](#)]
- 89 **Schulberg JD**, Wright EK, Holt BA, Wilding HE, Hamilton AL, Ross AL, Kamm MA. Efficacy of drug and endoscopic treatment of Crohn's

- disease strictures: A systematic review. *J Gastroenterol Hepatol* 2021; **36**: 344-361 [PMID: 33150989 DOI: 10.1111/jgh.15330]
- 90 **Schulberg JD**, Wright EK, Holt BA, Hamilton AL, Sutherland TR, Ross AL, Vogrin S, Miller AM, Connell WC, Lust M, Ding NS, Moore GT, Bell SJ, Shelton E, Christensen B, De Cruz P, Rong YJ, Kamm MA. Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures (STRIDENT): an open-label, single-centre, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 318-331 [PMID: 34890567 DOI: 10.1016/S2468-1253(21)00393-9]
- 91 **Rieder F**, Bettenworth D, Ma C, Parker CE, Williamson LA, Nelson SA, van Assche G, Di Sabatino A, Bouhnik Y, Stidham RW, Dignass A, Rogler G, Taylor SA, Stoker J, Rimola J, Baker ME, Fletcher JG, Panes J, Sandborn WJ, Feagan BG, Jairath V. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther* 2018; **48**: 347-357 [PMID: 29920726 DOI: 10.1111/apt.14853]
- 92 **Jackson BD**, De Cruz P. Quality of Care in Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019; **25**: 479-489 [PMID: 30169698 DOI: 10.1093/ibd/izy276]
- 93 **Jackson BD**, Con D, De Cruz P. Design considerations for an eHealth decision support tool in inflammatory bowel disease self-management. *Intern Med J* 2018; **48**: 674-681 [PMID: 29136332 DOI: 10.1111/imj.13677]
- 94 **Mikocka-Walus AA**, Andrews JM, Bernstein CN, Graff LA, Walker JR, Spinelli A, Danese S, van der Woude CJ, Goodhand J, Rampton D, Moser G. Integrated models of care in managing inflammatory bowel disease: a discussion. *Inflamm Bowel Dis* 2012; **18**: 1582-1587 [PMID: 22241699 DOI: 10.1002/ibd.22877]
- 95 **Mikocka-Walus AA**, Turnbull D, Holtmann G, Andrews JM. An integrated model of care for inflammatory bowel disease sufferers in Australia: development and the effects of its implementation. *Inflamm Bowel Dis* 2012; **18**: 1573-1581 [PMID: 22179943 DOI: 10.1002/ibd.22850]
- 96 **Ahmed Z**, Sarvepalli S, Garber A, Regueiro M, Rizk MK. Value-Based Health Care in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019; **25**: 958-968 [PMID: 30418558 DOI: 10.1093/ibd/izy340]
- 97 **van Deen WK**, Spiro A, Burak Ozbay A, Skup M, Centeno A, Duran NE, Lacey PN, Jatulis D, Esrailian E, van Oijen MG, Hommes DW. The impact of value-based healthcare for inflammatory bowel diseases on healthcare utilization: a pilot study. *Eur J Gastroenterol Hepatol* 2017; **29**: 331-337 [PMID: 27926663 DOI: 10.1097/MEG.0000000000000782]
- 98 **Regueiro M**, Hashash JG, McAnallen S, Ramalingam S, Perkins S, Manolis C, Kogan J, Watson A, Binion DG, McGowan M, Anderson A, Click B, Bell-Temin H, Weaver E, Fultz J, Graziani M, Smith-Seiler D, Szigethy E. Decreased Emergency Room Utilization and Hospitalizations, and Improved Quality of Life in the First Year of an Inflammatory Bowel Disease (IBD) Patient Centered Medical Home (PCMH): 579. *Am J Gastroenterol* 2016; **111**: S266 [DOI: 10.14309/00000434-201610001-00579]
- 99 **de Jong MJ**, van der Meulen-de Jong AE, Romberg-Camps MJ, Becx MC, Maljaars JP, Cilissen M, van Bodegraven AA, Mahmmod N, Markus T, Hameeteman WM, Dijkstra G, Masclee AA, Boonen A, Winkens B, van Tubergen A, Jonkers DM, Pierik MJ. Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial. *Lancet* 2017; **390**: 959-968 [PMID: 28716313 DOI: 10.1016/S0140-6736(17)31327-2]
- 100 **Ghosh S**. Multidisciplinary teams as standard of care in inflammatory bowel disease. *Can J Gastroenterol* 2013; **27**: 198 [PMID: 23616956 DOI: 10.1155/2013/710671]
- 101 **Phan VH**, van Langenberg DR, Grafton R, Andrews JM. A dedicated inflammatory bowel disease service quantitatively and qualitatively improves outcomes in less than 18 months: a prospective cohort study in a large metropolitan centre. *Frontline Gastroenterol* 2012; **3**: 137-142 [PMID: 28839654 DOI: 10.1136/flgastro-2011-100086]
- 102 **Feeney M**, Chur-Hansen A, Mikocka-Walus A. People Living with Inflammatory Bowel Disease Want Multidisciplinary Healthcare: A Qualitative Content Analysis. *J Clin Psychol Med Settings* 2022; **29**: 570-577 [PMID: 34185254 DOI: 10.1007/s10880-021-09801-4]
- 103 **Duncan J**, Caulfield S, Clark A, Anderson S, Sanderson J, Irving P. PTH-071 A multidisciplinary virtual biologics clinic: is it worthwhile? *BMJ Publ Group* 2010 [DOI: 10.1136/gut.2009.209064]
- 104 **Gasparetto M**, Angriman I, Guariso G. The multidisciplinary health care team in the management of stenosis in Crohn's disease. *J Multidiscip Healthc* 2015; **8**: 167-179 [PMID: 25878504 DOI: 10.2147/JMDH.S38729]
- 105 **Odes S**, Vardi H, Friger M, Wolters F, Russel MG, Riis L, Munkholm P, Politi P, Tsianos E, Clofent J, Vermeire S, Monteiro E, Mouzas I, Fornaciari G, Sijbrandij J, Limonard C, Van Zeijl G, O'morain C, Moum B, Vatn M, Stockbrugger R; European Collaborative Study on Inflammatory Bowel Disease. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006; **131**: 719-728 [PMID: 16952541 DOI: 10.1053/j.gastro.2006.05.052]
- 106 **Cohen RD**, Larson LR, Roth JM, Becker RV, Mummert LL. The cost of hospitalization in Crohn's disease. *Am J Gastroenterol* 2000; **95**: 524-530 [PMID: 10685762 DOI: 10.1111/j.1572-0241.2000.01779.x]
- 107 **Yarrow H**, Irving P, Williams A, Hibberts F, Koumoutsos I, Darakhshan A, Westcott E, Duncan J. Improving care for patients with perianal Crohn's disease: review of a perianal virtual clinic. *J Crohns Colitis* 2017; **11** Suppl 1: S492 [DOI: 10.1093/ecco-jcc/jjx002.926]
- 108 **Srinivasan A**, van Langenberg DR, Little RD, Sparrow MP, De Cruz P, Ward MG. A virtual clinic increases anti-TNF dose intensification success via a treat-to-target approach compared with standard outpatient care in Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 1342-1352 [PMID: 32379358 DOI: 10.1111/apt.15742]
- 109 **Panaccione R**, Colombel JF, Travis SPL, Bossuyt P, Baert F, Vaňásek T, Danalıoğlu A, Novacek G, Armuzzi A, Reinisch W, Johnson S, Buessing M, Neimark E, Petersson J, Lee WJ, D'Haens GR. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. *Gut* 2020; **69**: 658-664 [PMID: 31285357 DOI: 10.1136/gutjnl-2019-318256]
- 110 **Lakatos PL**, Kaplan GG, Bressler B, Khanna R, Targownik L, Jones J, Rahal Y, McHugh K, Panaccione R. Cost-Effectiveness of Tight Control for Crohn's Disease With Adalimumab-Based Treatment: Economic Evaluation of the CALM Trial From a Canadian Perspective. *J Can Assoc Gastroenterol* 2022; **5**: 169-176 [PMID: 35919766 DOI: 10.1093/jcag/gwac001]
- 111 **Dulai PS**, Jairath V, Narula N, Wong E, Kochhar GS, Colombel JF, Sandborn WJ. A Microsimulation Model to Determine the Cost-Effectiveness of Treat-to-Target Strategies for Crohn's Disease. *Am J Gastroenterol* 2021; **116**: 1709-1719 [PMID: 34587127 DOI: 10.14309/ajg.0000000000001263]
- 112 **Solomon DH**, Losina E, Lu B, Zak A, Corrigan C, Lee SB, Agosti J, Bitton A, Harrold LR, Pincus T, Radner H, Yu Z, Smolen JS, Fraenkel L, Katz JN. Implementation of Treat-to-Target in Rheumatoid Arthritis Through a Learning Collaborative: Results of a Randomized Controlled Trial. *Arthritis Rheumatol* 2017; **69**: 1374-1380 [PMID: 28512998 DOI: 10.1002/art.40111]
- 113 **Singh S**, Oliver B, Hou J, Lum D, van Deen W, Weaver A, Siegel C, Melmed G. Real World Implementation of Treat-To-Target In Patients With Ibd in a Learning Health System: An Ibd Qorus Collaborative Study. *Inflamm Bowel Dis* 2023; **29** Suppl 1: S41-42 [DOI: 10.1093/ibd/izac247.076]

- 114 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-33; quiz 591 [PMID: 16472588 DOI: 10.1053/j.gastro.2005.11.030]
- 115 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035 [PMID: 9321530 DOI: 10.1056/NEJM199710093371502]
- 116 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]
- 117 **Tursi A**, Elisei W, Giorgetti GM, Penna A, Picchio M, Brandimarte G. factors influencing mucosal healing in Crohn's disease during infliximab treatment. *Hepatogastroenterology* 2013; **60**: 1041-1046 [PMID: 23803367 DOI: 10.5754/hge11514]
- 118 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
- 119 **Giaffer MH**, North G, Holdsworth CD. Controlled trial of polymeric versus elemental diet in treatment of active Crohn's disease. *Lancet* 1990; **335**: 816-819 [PMID: 1969560 DOI: 10.1016/0140-6736(90)90936-y]
- 120 **Fell JM**, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, Kitching P, Donnet-Hughes A, MacDonald TT, Walker-Smith JA. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2000; **14**: 281-289 [PMID: 10735920 DOI: 10.1046/j.1365-2036.2000.00707.x]
- 121 **Yamamoto T**, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. *Inflamm Bowel Dis* 2005; **11**: 580-588 [PMID: 15905706 DOI: 10.1097/01.mib.0000161307.58327.96]
- 122 **Chong RY**, Hanauer SB, Cohen RD. Efficacy of parenteral methotrexate in refractory Crohn's disease. *Aliment Pharmacol Ther* 2001; **15**: 35-44 [PMID: 11136276 DOI: 10.1046/j.1365-2036.2001.00908.x]
- 123 **Modigliani R**, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. 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**: 811-818 [PMID: 2179031 DOI: 10.1016/0016-5085(90)90002-i]
- 124 **Present DH**, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987 [PMID: 6102739 DOI: 10.1056/NEJM198005013021801]
- 125 **Ardizzone S**, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; **35**: 619-627 [PMID: 14563183 DOI: 10.1016/s1590-8658(03)00372-4]
- 126 **Loftus EV Jr**, Panés J, Lacerda AP, Peyrin-Biroulet L, D'Haens G, Panaccione R, Reinisch W, Louis E, Chen M, Nakase H, Begun J, Boland BS, Phillips C, Mohamed MF, Liu J, Geng Z, Feng T, Dubcenco E, Colombel JF. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2023; **388**: 1966-1980 [PMID: 37224198 DOI: 10.1056/NEJMoa2212728]
- 127 **Sandborn WJ**, Feagan BG, Loftus EV Jr, Peyrin-Biroulet L, Van Assche G, D'Haens G, Schreiber S, Colombel JF, Lewis JD, Ghosh S, Armuzzi A, Scherl E, Herfarth H, Vitale L, Mohamed MF, Othman AA, Zhou Q, Huang B, Thakkar RB, Pangan AL, Lacerda AP, Panes J. Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients With Crohn's Disease. *Gastroenterology* 2020; **158**: 2123-2138.e8 [PMID: 32044319 DOI: 10.1053/j.gastro.2020.01.047]
- 128 **Feagan BG**, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johans J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI-IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2016; **375**: 1946-1960 [PMID: 27959607 DOI: 10.1056/NEJMoa1602773]
- 129 **Shelton E**, Allegretti JR, Stevens B, Lucci M, Khalili H, Nguyen DD, Sauk J, Giallourakis C, Garber J, Hamilton MJ, Tomczak M, Makrauer F, Burakoff RB, Levine J, de Silva P, Friedman S, Ananthakrishnan A, Korzenik JR, Yajnik V. Efficacy of Vedolizumab as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort. *Inflamm Bowel Dis* 2015; **21**: 2879-2885 [PMID: 26288002 DOI: 10.1097/MIB.0000000000000561]
- 130 **Amiot A**, Grimaud JC, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, Buisson A, Stefanescu C, Trang-Poisson C, Altwegg R, Marteau P, Vaysse T, Bourrier A, Nancey S, Laharie D, Allez M, Savoye G, Moreau J, Gagniere C, Vuitton L, Viennot S, Aubourg A, Pelletier AL, Bouguen G, Abitbol V, Bouhnik Y; Observatory on Efficacy and of Vedolizumab in Patients With Inflammatory Bowel Disease Study Group; Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2016; **14**: 1593-1601.e2 [PMID: 26917043 DOI: 10.1016/j.cgh.2016.02.016]
- 131 **Baumgart DC**, Bokemeyer B, Drabik A, Stallmach A, Schreiber S; Vedolizumab Germany Consortium. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice--a nationwide consecutive German cohort study. *Aliment Pharmacol Ther* 2016; **43**: 1090-1102 [PMID: 27038247 DOI: 10.1111/apt.13594]
- 132 **Pulusu SSR**, Srinivasan A, Krishnaprasad K, Cheng D, Begun J, Keung C, Van Langenberg D, Thin L, Mogilevski T, De Cruz P, Radford-Smith G, Flanagan E, Bell S, Kashkooli S, Sparrow M, Ghaly S, Bampton P, Sawyer E, Connor S, Rizvi QU, Andrews JM, Mahy G, Chivers P, Travis S, Lawrence IC. Vedolizumab for ulcerative colitis: Real world outcomes from a multicenter observational cohort of Australia and Oxford. *World J Gastroenterol* 2020; **26**: 4428-4441 [PMID: 32874055 DOI: 10.3748/wjg.v26.i30.4428]
- 133 **Sandborn WJ**, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933 DOI: 10.1056/NEJMoa1215739]
- 134 **Sands BE**, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; **147**: 618-627.e3 [PMID: 24859203 DOI: 10.1053/j.gastro.2014.05.008]
- 135 **Dulai PS**, Singh S, Jiang X, Peerani F, Narula N, Chaudrey K, Whitehead D, Hudesman D, Lukin D, Swaminath A, Shmidt E, Wang S, Boland BS, Chang JT, Kane S, Siegel CA, Loftus EV, Sandborn WJ, Sands BE, Colombel JF. The Real-World Effectiveness and Safety of Vedolizumab for Moderate-Severe Crohn's Disease: Results From the US VICTORY Consortium. *Am J Gastroenterol* 2016; **111**: 1147-1155

[PMID: 27296941 DOI: 10.1038/ajg.2016.236]

- 136 **Vivio EE**, Kanuri N, Gilbertsen JJ, Monroe K, Dey N, Chen CH, Gutierrez AM, Ciorba MA. Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice. *J Crohns Colitis* 2016; **10**: 402-409 [PMID: 26681763 DOI: 10.1093/ecco-jcc/jjv226]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

