Best Practice & Research Clinical Gastroenterology 38-39 (2019) 101599

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Evolution of treatment targets in Crohn's disease

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ARTICLE INFO

Article history:
Received 17 January 2019
Accepted 14 February 2019

Keywords:
Crohn's disease
Treatment targets
Patient reported outcomes
Clinician reported activity indices
Biomarkers
Endoscopy
Imaging
Histology

ABSTRACT

Crohn's disease is a chronic relapsing and remitting inflammatory disorder of the gastrointestinal tract, associated with significantly morbidity due to both symptoms and complications that have a considerable detrimental impact on a patient's quality of life. An early treat to target approach with disease modifying agents has been shown to significantly improve long term outcomes, demonstrated by a number of therapeutic targets in a number of modalities. This review will outline the current treatment targets and measures of disease burden in Crohn's disease.

Introduction

Crohn's disease (CD) is a chronic relapsing and remitting inflammatory disorder of the gastrointestinal (GI) tract with a prevalence of up to 200 per 100,000 [1,2]. The majority of patients require long term medical therapy and almost half of patients will require surgery at 10 years [3]. This can have a significant impact on a patient's quality of life [4].

The traditional management of CD involves a stepwise escalation of treatment but this approach can lead to a delay in those at high risk of disease progression. The correlation between symptoms and endoscopic disease activity is poor so there is a risk of under treatment.

Advances in the treatment of Rheumatoid Arthritis (RA) has led the way to the evolution of treatment targets in CD. The introduction of disease modifying agents, especially anti-tumour necrosis factor (anti-TNFs), in addition to earlier treatment has led to reduction in joint destruction and associated morbidity traditionally associated with RA. This treatment strategy has led to the 'treat to target' approach, which involves regular assessment and treatment adjustment using validated outcomes measures.

In CD intervening at an early stage could also potentially alter disease outcomes but definitions of treatment targets are not well defined [5]. A future 'treat to target' approach would aim to halt the biological progression using histological healing, clinical and surrogate markers of disease activity. Current recommendations are based on the 2015 Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) programme which was developed to determine twelve possible 'treat to target' goals. One such target was the resolution of abdominal pain and change in bowel habit. However, symptom resolution was not sufficient to be recommended as a target and objective evidence of inflammation is required when considering treatment alterations. Another target was the absence of ulceration with objective endoscopic evidence demonstrating this. Histological remission was not recommended as a treatment target. In addition, inflammation resolution on cross sectional imaging was suggested as an alternative to endoscopy. The patient reported outcomes (PRO) recommended were the resolution of abdominal pain and the normalization of bowel movements. The reassessment interval for PROs was recommended every three months until resolution and six to twelve months thereafter. The use of laboratory markers C-reactive protein (CRP)

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https://doi.org/10.1016/j.bpg.2019.02.001
1521-6918/

and faecal calprotectin (FCP) were deemed useful as adjunctive measures to prompt further investigations but not as targets themselves. This programme was the first to suggest composite end-points, including both clinical and endoscopic remission with assessment intervals for these targets [6].

Further prospective work in this area will enable guided, personalised patient therapy with the potential use of tools such as serum drug levels and antibody levels to enable positive treatment modifications to be made [5,6]. This chapter will examine the current evolution of treatment targets and measures of disease burden in CD.

Evolution of primary treatment targets and measures of disease burden

Clinician reported activity indices

Treatment targets are well defined in a number of chronic diseases but there are discrepancies between endoscopic and symptom based disease activity in CD [7]. Clinical remission, therefore, requires a combination of both symptomatic and inflammatory resolution. The Crohn's disease activity index (CDAI) was developed in the 1970's and has been used in a variety of clinical studies to try and provide an accurate, objective and reproducible clinical assessment. Eight variables were selected that correlated with the physician global assessment of CD. The variables used in this equation included: number of stool frequency, abdominal pain, subjective measure of general well-being, presence of complications, use of agents to counteract diarrhoea, abdominal mass, haematocrit and body weight. Scores ranged between 0 and 600: a score <150 is associated with remission, >150 indicative of active disease and >450 signifying severe disease [8,9]. Clinical response using CDAI was defined as a drop in 70 points over two patient visits or a drop of 100 points from baseline [10]. This score, as others, is prone to inter observer variability but this can be minimised by clear instructions [11]. Other problems with this score relate to its complex structure, subjectivity, not always been reproducible and cofounders associated with other GI diseases. The score is also heavily weighted by stool frequency, thus does not adequately reflect disease activity in proximal locations where stool frequency is not a prime symptom [12,13]. However, CDAI still remains very commonly utilised for assessing disease activity in CD clinical trials despite correlating poorly with laboratory, endoscopic and histological markers [10,14–16]. CDAI has been modified over the years with the short CDAI (sCDAI) correlating with the original index [17]. The disease severity can now be further classified as mild active (CDAI 150–220) and moderate-severe (CDAI 220–450) [14]. It is now used as an index clinical response and remission in addition to disease severity.

The Harvey Bradshaw Index (HBI) is a much simpler disease activity score used in CD and correlates with CDAI [18]. This score is more suited for routine clinical practice and requires less data for calculation. It comprises of general well-being, abdominal pain, stool frequency, abdominal mass and complications. A score of 5–7 is considered mild, 8 to 15 moderate and >16 severe disease. Clinical remission is considered if score is ≤ 4 points and clinical response if there is $\geq$ 3-point drop [19].

Patient reported outcomes (PRO)

PROs aim to improve the capture of patient's symptoms as objective markers fail to capture this. Also clinician reported activity indices do not always correlate with objective measures of inflammation, therefore, scores which examine bowel, systemic, emotional and social function have been developed [20]. The Food and Drug Administration recommended the development of co-primary endpoints in clinical trials to incorporate objective measures of inflammation with PROs. This is to help achieve more patient-centred management.

CD specific PRO (CD-PRO) is currently under development for use in clinical trials, concentrating on bowel signs, symptoms, quality of life, emotional elements and coping behaviours. Other measures include CD PRO-2 (which consists of the components of abdominal pain and stool frequency) and CD PRO-3 (consisting of abdominal pain, stool frequency and general well-being) [21]. Both performed well when compared to CDAI. Trial data from methotrexate in CD using regression analysis showed that CDAI scores of 150, 220 and 450 correspond with a CD PRO-2 and CD PRO-3 score of 8, 14, 34 and 13, 22, 53 respectively [22]. This outcome measure should be patient-centred and assessed on a regular basis (three monthly) until symptom resolution occurs and then six to twelve monthly afterwards [6]. In addition, patient based HBI (P-HBI) has also been compared with physician based HBI and also showed a good correlation [23].

The main PRO in CD, as in Ulcerative colitis (UC), is the improvement in quality of life (QoL) [24]. The Patient Reported Outcomes Measurement Information System (GI-PROMIS) symptom scale was developed for evaluating physical, mental and social health [25]. GI-PROMIS was recently evaluated on 2378 CD and 1455 UC respondents and was shown to be strongly associated with disease activity and QoL indices [26].

PROs have the potential to act as a therapeutic target in future IBD trials, when combined with clinical features (e.g. absence of abdominal pain/diarrhoea) and resolution of inflammation (on endoscopy/cross sectional imaging) [6] with the ultimate hope to improve patient-centred outcomes.

Endoscopic remission

Distinctive findings of CD include oedema, erythema, nodular mucosa and ulcerations. Friability, spontaneous bleeding in addition to ulceration depth and size correlates with disease severity [27]. The absence of ulceration is the most significant endoscopic target in CD. Where endoscopy is not appropriate or the disease is not within reach of an ileocolonoscopy, cross-sectional imaging is an alternative. Endoscopic scoring (in addition to other objective markers like faecal calprotectin) correlates better with inflammation than CDAI [7,28]. Mucosal healing is associated with reduced corticosteroid use, reduced surgical rates in addition to improved clinical response and lower relapse rates [29].

CD Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD) are validated measures of endoscopic disease activity. CDEIS evaluates four parameters describing the type of ulceration and surface involved in five areas of the lower intestinal tract: the rectum, left and sigmoid colon, transverse colon, right colon and ileum [30]. CDEIS <3 correlates with remission, $\geq$3 active disease and a drop in the total score by > 5 points signifies clinical response [31,32]. SES-CD is more simplified and assesses the size, surface of ulcers, the extension of disease involvement and stenosis. SES-CD <2 correlates with remission, $\geq$3 active disease [33,34].

Rutgeerts score, developed nearly 30 years ago, can be used to monitor post-operative recurrence at the ileo-colonic anastomosis level. This score is used to evaluate recurrence 6–12 months after surgery. Endoscopic examination can detect up to 70% of recurrent disease six to twelve months after. The score consists of five categories (i0, i1, i2, i3 and i4) for describing endoscopic findings at the anastomosis and neo-terminal ileum. Lesions examined for include aphthous ulcers, inflamed mucosa, ulcers, nodular mucosa and stenosis. Low scores (i0, i1) correlate with recurrence rates of 6% in

five years. In higher scores (i3, i4) recurrence was up to 100%. Scores above i2 are considered as disease recurrence. This scores is widely used in clinical practice despite the lack of validation studies [35,36].

Schnitzler et al. investigated mucosal healing rates and the need for surgery. They demonstrated that mucosal healing was associated with a fifty-percentage reduction in surgery rates during the follow up period. After the follow up period, 42.2% of patients with mucosal healing required hospitalisation when compared to 59.3% without mucosal healing ($p = 0.0018$) [37]. Subjects with endoscopic remission are associated with significantly higher corticosteroid-free remission rates when compared with those without (70.8% vs 27.3% $p = 0.036$) [38]. Allez et al. described the probability of surgery with severe endoscopy features at 1, 3 and 8 years as 31%, 42% and 62% respectively [39]. Mucosal healing leads to better long-term remission rates and improved quality of life [40–42]. Endoscopic post-operative recurrence within 12 months of resection is a good predictor of clinical recurrence [35]. Mucosal healing is also associated with reduced colorectal cancer in UC but no data is available for CD [43].

A prospective cohort study using 740 Norwegian patients (both UC and CD) described improved clinical outcomes with mucosal healing on long-term follow up. Patients were assessed at year 1 and 5. Those in endoscopic remission by year 1 had significantly lower resection rates (11% vs 20%) at 5 years. Mucosal healing was associated with reduced inflammation at 5 years ($p = 0.02$) and reduced corticosteroid use ($p = 0.02$). Endoscopic mucosal healing is a major therapeutic target in CD, associated with both clinical and corticosteroid-free remission, reduced hospitalisation and surgery [29,44].

However, symptoms and mucosal healing do not always correlate in CD. Deep remission is the term used when clinical remission is also associated with mucosal healing. It is not completely clear as to whether achieving deep remission is an effective way to monitor disease progression or whether this target always needs to be achieved before stepping down treatment [45]. Few studies have examined mucosal healing in CD as a therapeutic endpoint. Two such studies investigating mucosal healing induction with infliximab and adalimumab, showed that the pooled rate of healing when compared with placebo were 29% and 7% respectively. Anti-TNFs were more effective in inducing mucosal healing with an odd ratio 3.93 (95% CI 0.77–20.10) [41,46] when compared to placebo. The SONIC trial reported mucosal healing rates for azathioprine, infliximab and combination therapy of infliximab and azathioprine of 17%, 30%, and 44% respectively. Combination therapy showed statistically significant higher mucosal healing rates than azathioprine or infliximab alone [47]. These results were similar Lemann et al. report comparing azathioprine with combination therapy [48,49]. It is important to note that corticosteroids, do not achieve mucosal healing [50,51] and hence do not positively affect long term outcomes.

In addition, risk of clinical relapse is reduced when endoscopic remission is achieved [52]. Thus, mucosal healing is a very important endpoint in routine clinical practice and in clinical trials. However, there are some important limitations with mucosal healing. Firstly, the time period required for endoscopic follow up is not completely clear. Secondly, mucosal healing is dependent on endoscopist interpretation and subject to observer variability. Thirdly, endoscopic assessment is costly and can be associated with significant risks. In addition, it remains unclear what degree of mucosal healing is required to alter disease course [53]. Finally, mucosal healing and clinical features do not always correlate which has led to the requirement of a combination of endpoints to monitor disease activity [54].

Cross sectional imaging

Cross sectional imaging (magnetic resonance imaging (MRI), computer tomography (CT) and ultrasound (US) are underutilised tools in CD activity assessment. At present imaging is useful to assess areas not easily accessible by colonoscopy.

Although endoscopy remains the gold standard for assessing the mucosa in CD, magnetic resonance enterography (MRE) shows good correlation with the presence and severity of mucosal lesions. MRE measurements are based on bowel wall thickening, enhancement of the bowel wall after administration of intravenous contrast with gadolinium, presence of ulcers, mural oedema, regional enlarged lymph nodes (>10 mm), peri-enteric vascularization, peri-enteric fluid, fat stranding, and fibro-fatty proliferation. At present, it is unclear whether changes assessed by MRI are adequate to measure response to biologic therapy in comparison to endoscopy and clinical scores. Ordás et al. measured the accuracy of MRE in measuring response to therapy. The accuracy of MRE to determine ulcer healing and endoscopic remission was 90% and 83% respectively. There was also good correlation of CDEIS with the magnetic resonance index of activity (MaRIA score) which grades wall thickness, oedema, contrast enhancements and ulceration ($r = 0.51$; $p < 0.001$). MRE is minimally invasive, but further studies are needed to study the response during therapy [55].

MRI characteristics have shown fair to good interobserver variability (kappa = 0.62 to 0.66) across all observers in other studies. The interobserver variability for length of disease, pattern of enhancement, oedema and wall thickness has been shown to be 0.62, 0.62, 0.66 and 0.69 respectively [56]. Measuring bowel peristaltic motion with MRI also enables quantification of bowel function [57]. Bowel motility is reduced during active disease, with extent of reduction correlating with the severity of inflammation [58]. Also MRI motility has been shown to improve with anti-TNF treatment (median = 73.4% increase from baseline vs non-responders median = 25% reduction, $p < 0.001$), thus MRI motility has the potential to predict long-term response to biologic therapy [59].

With regards to other imaging modalities, a retrospective CT enterography study revealed that 60% patients had a radiological response to infliximab. Due to the nature of this study it is difficult to obtain the true accuracy of this modality [60]. US is an easily available, non-invasive tool and has a sensitivity and specificity for disease activity of 0.84 and 0.98 respectively. A disadvantage of this technique is a lower accuracy for disease proximal to the terminal ileum and that it is examiner dependent [61]. US findings associated with CD include a bowel wall thickness greater than 4 mm, reduced compressibility, stenosed lumen and presence of fistulas or abscesses. US is useful as a first approach tool but needs confirmation by other modalities [62].

The 'Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease' (METRIC) multicentre trial assessed the diagnostic accuracy of MRE and small bowel US for the extent and activity of disease in individuals with CD. The primary outcome was the difference in per patient small bowel sensitivity. A total of 284 patients completed the study. Sensitivity for extent and presence for MRE was 80% (95% CI 72–86) and 97% (95% CI 91–99) respectively. The sensitivity for US for disease extent and presence was 70% (95% CI 62–78) and 92% (95% CI 84–96) respectively. The difference between MRE and US was significant: extent 10% (95% CI 1–18, $p = 0{\cdot}027$) and presence 5% (1–9, $p = 0{\cdot}025$). The specificity for MRE for disease extent and presence was 95% (95% CI 85–98) and 96% (95% CI 86–99) respectively. Using US, the specificity for extent and presence was 81% (95% CI 64–91) and 84% (95% CI 65–94). There was a significant difference between MRE and US for

extent and presence of 14% (1–27, p = 0·039) and 12% (0–25, p = 0·054). Both modalities were accurate at detecting disease but MRE performed significantly better [63].

Horsthuis et al. compared the accuracy of US, MRI and CT in diagnosing IBD in a meta-analysis but found no significant different in each modality with sensitivity ranging from 84% to 93% and specificity from 93% to 96%. CT involved radiation exposure and was less accurate when compared to MRI [64]. All modalities are sensitive for the detection of abscesses but detection is dependent on the anatomical location.

Cross sectional imaging has an advantage over endoscopy in its ability to assess the entire luminal wall, to examine the small bowel and diagnose penetrating complications. In research settings, MRI screening examinations would allow for the selection of patients with active disease without complicated penetrating disease that are more likely to respond to therapy. Cross sectional imaging is also unable to detect mild disease. At present, there is only weak correlations with cross sectional imaging and clinical activity indices and biomarkers [62].

Histology

Ongoing inflammation in CD leads to a significantly increased risk of relapse, surgery and the development of colorectal cancer [38,65]. Scoring systems are limited in CD due to the transmural or discontinuous nature of disease and the absence of a standard definition of histological remission. Baars et al. investigated the prognostic value of histological inflammation and found it was not associated with adverse outcomes such as relapse rates and surgery as a large proportion of patients in clinical remission had histological evidence of inflammation. The inconsistent and patchy distribution of inflammation did make interpretation difficult [66], with other studies also showing microscopic inflammation in quiescent disease [67,68]. Few trials to date have used histological remission as a therapeutic end-point in CD. D'Haens et al. investigated response to infliximab and showed an improvement in inflammatory infiltrate but architectural changes remained after 28 days of infliximab treatment [69]. Due to the present lack of convincing data histological remission should not be treatment target in CD [6].

Treat-to-target studies

The 'treat to target' approach is based on international IBD expert consensus and describes a variety of targets. These included: patient reported outcomes, remission using endoscopic standards and the laboratory markers CRP and FCP. The use of cross-sectional imaging was suggested as an alternative to endoscopy and composite end-points. A number of treat to target studies have been completed. Colombel et al. recently conducted a multi-centre, randomised controlled open label trial entitled 'Effect of tight control management on Crohn's disease' (CALM study). They compared endoscopic and clinical outcomes of patients with active CD. Patients with endoscopic evidence of active disease, CDEIS >6 and CDAI 150–450, who were naïve to immunomodulators or biologics were recruited. Patients were randomised to a tight control algorithm using biomarkers and clinical symptoms or a clinical management algorithm using solely clinical symptoms in a 1:1 depending on smoking status, disease duration and weight after an 8-week induction period with prednisolone therapy. Treatment was intensified in a controlled manor for both groups. The options were either no treatment, induction with adalimumab then two weekly, weekly or weekly with the addition of daily azathioprine. Treatment failure criteria for the tight control group was defined as: faecal calprotectin (FCP) ≥250 μg/g, C-reactive protein (CRP) ≥5 mg/L, CDAI ≥150, or prednisone use. In the clinical management group this was considered as a CDAI decrease of <70 points compared with baseline or CDAI >200. Patients were reviewed every 12 weeks for 24 months and treatment was escalated if clinical remission was not achieved. The primary endpoint was mucosal healing (CDEIS <4) without ulceration at 48 weeks. The investigators compared endoscopic and clinical outcomes in moderate to severe CD. 244 patients were recruited and there was a significant difference in achieving the primary outcome in the tight control group when compared to the clinical management group 46% vs 30% adjusted risk difference of 16·1% (95% CI 3·9–28·3; p = 0·010). Better clinical and endoscopic outcomes occurred in participants exposed to controlled escalation guided by clinical and biomarker parameters in early CD patients. This study was the first treat to target study measuring objective markers of inflammation [70]. Decision-making based on objective biochemical markers of disease activity is effective in CD management [70] and enhances mucosal healing rates.

The 'Randomised evaluation of an algorithm for Crohn's Disease treatment' (REACT) study compared the effectiveness of the conventional 'step up' treatment with early combined immunosuppressive (ECI) 'accelerated step up' treatment with adalimumab and an immunomodulator (anti-metabolite). This open label cluster randomised controlled trial assigned patients 1:1 to either therapy. Over 800 patients were recruited to each arm. The primary endpoint was corticosteroid-free remission at 52 weeks (HBI <4). The secondary endpoint was adverse events at 24 months. ECI was not shown to be more effective than conventional therapy in symptom control but there was a major reduction in adverse outcomes such as surgery rates and hospital admissions with a hazard ratio of 0·73, 95% CI 0·62 to 0·86, p = 0·0003 for the ECL arm [71]. The use of corticosteroid-free remission as a primary endpoint could explain the negative results in this trial. This study highlighted the limitations of using clinical symptom-based scores. There was no difference between the clinical scores but a clear difference in adverse events, therefore, suggesting clinical symptoms are not good predictors of important disease outcomes.

'The enhanced algorithm for Crohn's treatment incorporating early combination therapy' (REACT 2) study is currently underway investigating CD related complications at 6 and 12 months and the proportion of patients in deep remission without progression of disease. It investigates whether the use of enhanced algorithm with ECI and endoscopic assessment improves patient management when compared with conventional step wise care. 1200 CD patients treated with adalimumab and immunomodulator will be randomised into a symptom-based treatment (standard care) or endoscopy-based escalation. This study will provide evidence to help determine whether the achievement of mucosal healing as a treat to target is achievable and whether mucosal healing improves outcomes [72].

Up to 90% CD patients who have undergone surgery, develop recurrence at the anastomosis site within 12 months [35,73]. Risk factors associated with recurrence of disease includes smoking, perforating disease, previous resection and primary anastomosis [74,75]. 'The post-operative Crohn's endoscopic recurrence study' (POCER) conducted by De Cruz et al. aimed to identify the optimal strategy to prevent post-operative recurrence. This randomised controlled trial conducted was in Australia and New Zealand. CD patients who underwent intestinal resections received 12 weeks of therapy with metronidazole. High risk patients also received a thiopurine or adalimumab depending on individual tolerance. Patients were randomised to a colonoscopy at 6 months (active practice) or no colonoscopy (standard practice) in a 2:1 allocation. Patients with endoscopic recurrence (Rutgeerts score ≥ i2) at 6 months received stepped up treatment: thiopurine, two weekly

adalimumab with thiopurine or weekly adalimumab. The primary outcome was endoscopic recurrence at 18-months. Central endoscopic readers were blinded but not patients and clinicians. 177 patients were included. Endoscopic recurrence was significantly lower in the active group when compared to the standard 49% vs 67% ($p = 0{\cdot}03$) respectively. Secondary outcomes showed that mucosal was more likely to be maintained in active group, 22% vs 8% ($p = 0{\cdot}03$). Smoking increased the risk of endoscopic recurrence (odds ratio 2·4, 95% CI 1·2–4·8, $p = 0{\cdot}02$). Smoking or having two or more of the risk factors associated with recurrence doubles the risk of post-operative recurrence. In summary, treatment guided by recurrence risk, early colonoscopy and therapy escalation during recurrence was better than conventional therapy alone for reducing recurrence post-surgery. Drug therapy was best adjusted according to early recurrence and led to improved disease control. Low risk patients still required monitoring [76]. Mowat et al. also conducted a multi-centre trial investigating mercaptopurine verses placebo to prevent or delay post-operative recurrence. Mercaptopurine was only effective in preventing post-operative recurrence in smokers [77]. 5-aminosalicylates (5-ASA) do not provide sufficient treatment benefit in preventing post-operative recurrence [78].

In addition, a randomised controlled trial of infliximab verses placebo in 297 CD patients showed it was also effective in reducing post-operative recurrence. Primary end-points were clinical recurrence (CDAI >200 and a ≥70 increase from baseline, Rutgeerts score ≥ i2 or development of penetrating disease prior to 76 weeks). Secondary end-point was endoscopic recurrence (Rutgeerts score ≥ i2 or development of penetrating disease). Clinical recurrences were lower in the infliximab group compared to placebo but this was not statistically significant, 12.9% vs 20% respectively. The absolute risk reduction with infliximab was 7.1% (95% CI 1.3–15.5, $p = 0.097$). Endoscopic recurrence was lower with infliximab when compared to placebo, 30.6% vs 60% respectively. The absolute risk reduction with infliximab was 24.9% (95% CI 18.6–40.2, $P < 0.001$). Individuals who were previously treated with anti-TNF therapy or previous surgery were at greatest risk of recurrence [79].

Finally, a meta-analysis indicated that imidazole antibiotics reduced endoscopic recurrence relative risk 0.44; 95% CI 0.26–0.74 and clinical recurrence 0.23; 95% CI 0.09–0.57 when compared to placebo [80].

Biomarkers and clinical scores

Biomarkers

Non-invasive biomarkers such as FCP and CRP are effective as decision making tools but should not be treatment end-points because of the lack of evidence. Benefits of these biomarkers include being non-invasive and cost effective. The most robust data to predict clinical and endoscopic response is raised CRP at baseline (10.3 mg/L) and normalization [7,81]. The 'Stop infliximab in patients with CD' (STORI) study retrospectively analysed 115 CD patients in whom infliximab was withdrawn. They described the long-term outcome of patients in remission after the withdrawal of treatment. 20% of patients did not encounter complications or restart biologic therapy 7 years after withdrawal. Independent predictors of complications were shown to be upper-gastrointestinal disease, haemoglobin level and white blood cell count. Patients had a 40% risk of major complications when more than two of these factors were present following withdrawal [82]. Further studies have shown that a CRP >5 mg/L, haemoglobin level ≤145 g/L and a white cell count >6 × 109/L predicts relapse in CD when biological therapy is withdrawn [83,84]. In a sub-analysis CRP levels at baseline and 14 weeks were identified as predictors of response to infliximab. High baseline CRP was associated with maintained remission, however, there was no optimal cut-off for CRP which makes clinical translation into every day practice problematic [83]. Similarly, CRP >20 mg/L and haemoglobin level <120 g/L have been shown to be good predictors of relapse in azathioprine withdrawal [85].

FCP better reflects inflammation at the mucosal level and is associated with endoscopic and clinical scoring indices. A change in FCP correlates with endoscopy scores and a high FCP is associated with a significant higher one-year risk of relapse in CD. However, in the Gisbert et al. study the sensitivity was low at 28% and specificity 93% [7,86–88]. FCP is also a useful marker in predicting relapses post intestinal surgery [76]. Sipponen et al. showed that there was a drop from 1173 μg/g to 130 μg/g with anti-TNF therapy, with good correlation shown between FCP and endoscopy severity scores (Spearman's rank-order correlation = 0.561) but no correlation with histological scores [87]. A review of six studies looking at both CD and UC found that higher FCP measured in asymptomatic individuals on a minimum of two occasions were associated with increased rate relapses by 3 months. Normal values were also associated with lower rates of relapses [89]. Wright et al. investigated whether FCP could substitute endoscopy assessment of the mucosa and found that a FCP >100 μg/g was indicative of endoscopic recurrence with a sensitivity, specificity and negative predictive value of 89%, 58% and 91% respectively. FCP had a higher accuracy of predicting recurrence than CRP and CDAI [90]. However, its sensitivity maybe affected by disease location but data is limited. A systemic review of the diagnostic accuracy of FCP by disease location described the median sensitivity and specificity values for small bowel as 75% (range 42.9%–100%) and 75% (range 50%–100%) respectively. For the large bowel, the sensitivity and specificity median values were 94% (range 8.9%–100%) and 71% (range 28.6%–100%) respectively [91]. Ultimately, more data is required before FCP can be recommended as a treatment target [6].

Limited evidence to date is insufficient to recommend these non-invasive biomarkers as therapeutic targets in CD and they are not yet a safe or effective surrogate for endoscopy, clinical and radiological assessments. Their role is to mainly act as an adjunct measure to highlight the need for further investigations in CD. Although used in clinical scoring indices, there is no evidence for other biomarkers like ESR, serum albumin and haemoglobin being effective as a therapeutic goal in CD [92].

Clinical scores

The Lémann score was developed to measure cumulative bowel damage and disease burden. It measures bowel damage at specific time points, progression over time, identifies high risk patients and compares effects of therapy on disease progression. This score combines information from clinical, endoscopic and imaging from all segments of the intestinal tract into a single score. This score was developed to guide therapy in CD [93]. Pariente et al. performed a multicentre prospective study assessing the Lémann score in assessing bowel damage. The overall correlation coefficients between predicted and investigator evaluations was 0.84. Patients with a disease duration of less than two years have less bowel damage than individuals with a longer duration of disease [94]. High scores at presentation, increased disease duration, clinical activity and a history of surgery were associated with bowel damage [95]. The Lémann score gradually increases within 10 years in a minimum of two-thirds of CD patients. Patients with progression of this score are at higher risk of surgery, disease relapses and the use of health care services. Lémann score measurements over time could serve as a future marker of disease and prognosis,

therefore, acting as a useful therapeutic target [96]. Limitations of this score are due to its complex interpretation, requiring specialist training and its time-consuming nature.

Quality of life

Improved quality of life and prevention of disability are key targets in the management of CD. This is assessed by the IBD questionnaire (IBDQ). A low IBDQ score is associated with female sex, recurrent admissions for flare of disease, lower education level, surgery and disease recurrence [97]. A specific work related questionnaire has been validated for measuring work related disability in CD [98]. Disability refers to both the subjective and objective effects on a patient's life. The IBD disability index (IBD DI) which examines body structures and function, activity and the environment was developed in 2012 according to the standard WHO process. The aim of this index was to evaluate the long-term functional effects of CD in research settings and will form the basis of a new disease modification endpoint. Prior to this there were no other index to assess disability [99]. This index was recently validated on both UC and CD patients. The inter-observer and intra-observer reliability were 0.91 and 0.54 respectively. There was good correlation with IBDQ. Factors associated with higher scores were disease activity ($p < 0.0001$), female sex ($p < 0.001$) and duration of disease ($p = 0.02$) [100]. Farré et al. evaluated the correlation between the Lémann score and IBD DI in a large prospective cohort study. Disease duration, activity and anal lesion location were associated with bowel damage. Female sex, lesion location and disease activity were associated with IBD DI but correlation between the Lémann score and IBD DI were poor [101].

Disease burden, early treatment and impact of disease duration

In terms of disease burden, Fiorino et al. investigated the effect of anti-TNF treatment on bowel damage (disease activity and complications) using the Lémann score on 30 CD patients in a prospective single centre cohort study. Patients were followed up for 32.5 months. Therapy was associated with a significant reduction in Lémann score at 12 months ($p = 0.007$). CD patients whose scores progressed were more likely to undergo major abdominal surgery (hazard ratio 0.19, $p = 0.005$). Anti-TNF therapy was shown to reverse bowel damage, demonstrating that the Lémann score may be able predict major surgery in this cohort of patients. This provided some evidence that anti-TNF are potential disease modifying treatments that can hinder or reverse the structural bowel damage seen in CD. Anti-TNFs have been shown to maintain mucosal healing but whether bowel damage is reversible with this therapy is largely unknown. This is vitally important to determine how effective biologics are at reversing bowel damage in this transmural disease [102].

There is currently insufficient long-term follow up data on disease burden in CD, but as seen in RA the use of early disease modification agents may lead to the halting of disease progression and an improvement in a patient's quality of life. This is demonstrated by the declining rate of surgical resection for CD, with elective surgery becoming more common than emergency surgery [103]. The advantages of early intervention include a greater rate of early disease control in terms of remission rates, adjusting the disease outcome in terms of hospital admission, surgery, bowel damage and surgery. The effectiveness of biologics is greater if used early and reduces the risk of undertreatment that can be associated with step up approaches. Downsides include overtreatment of individuals, lack of quality evidence and the fact that current monitoring and risk stratification is not currently adequate for this approach [104]. The 'Personalised medicine in CD' (PROFILE) phase IV study is currently underway predicting outcomes in CD using a molecular biomarker. This large prospective study of 400 patients with CD aims to potentially achieve personalised therapy in CD [105]. Further prospective trials are needed to confirm initial findings and to improve future management.

Table 1 summaries the key treatment targets in CD.

Conclusion

Potential treat to target management strategies have been cumulated by international expert consensus and are evolving over time. Both endoscopic and clinical remission are recognised and obtainable targets for CD. Multiple disease modification studies have been conducted to try to prevent long term complications of CD. Biological therapies have the potential to become disease modifying agents but more research is needed. Further studies are needed to confirm initial findings related to anti-TNF persistence over longer follow up periods and as to whether these features translate across to other biologic agents like vedolizumab and ustekinumab. Deep remission is the ultimate treatment target to halt the progression of disease and improve quality of life. Also, the development of IBD specific disability indices can provide a better understanding of the effect of CD on a patient's well-being. A combination of biomarkers aid disease management and an accurate assessment of disease activity with cross sectional imaging can improve treatment adjustment. Mucosal healing and the absence of luminal disease activity are the most important treatment targets to date. There is currently insufficient data to support the use of

Table 1
Summary of treatment targets in Crohn's disease.

	Treatment Target	Key References
Clinical	Resolution of abdominal pain and bowel habits Objective evidence of bowel inflammation resolution	Vermeire et al. (2010) [19]
Endoscopic	Objective endoscopic evidence demonstrating the absence of ulceration Objective evidence of bowel inflammation resolution	Froslie et al. (2007) [29] Baert et al. (2010) [38] Rutter et al. (2004) [43]
Histologic	Histological remission is not a target	Baars et al. (2010) [66]
Imaging	Inflammation resolution on cross sectional imaging when endoscopy is unable to evaluate this	Taylor et al. (2018) [63] Pariente et al. (2015) [94]
Biomarkers	CRP and FCP are not treatment targets Adjunctive measures of inflammation for monitoring	Reinisch et al. (2012) [83] Wright et al. (2015) [90]
Patient reported outcomes	Resolution of abdominal pain and the normalization of bowel movements Individual patients' goals should be assessed Outcome assessment every three months until resolution	Spiegel et al. (2014) [25] Gower-Rousseau et al. (2017) [100]
Composite end-points	Clinical/PRO remission assessed at 3 monthly intervals in active disease Endoscopic remission assessed at 6–9 months during active disease	Peyrin-Biroule et al. (2015) [6]

histological remission. Going forward, disease burden as measured through the Lémann score will become a strong therapeutic target as it takes into consideration both the patient's disease burden and clinical findings. Further long-term validation datasets in larger cohorts across a number of treatment spectrums are needed. Its use in reassessment over time may allow it be a future predictor of disease prognosis and the ultimate primary endpoint in clinical practice.

Practice points

- Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract associated with significant morbidity
- Patients often require lifelong therapy depending on the severity of disease
- A significant number of patients are primary non-responders or lose response to anti-TNF therapy

Research agenda

- Further studies are required to determine whether biological therapies have the potential to become disease modifying agents
- Development of molecular biomarkers to help achieve personalised therapy
- Further advancement of cross sectional imaging to aid clinical decision making

Conflicts of interest

J.R.W. has no conflicts of interest.

Disclosure statement

G.W.M. has received educational support from Abbvie, Janssen, NAPP, Takeda Pharmaceuticals, Merck Sharp & Dohme Ltd, Ferring and Dr Falk. He has received speaker honoraria from Merck Sharp & Dohme Ltd, Abbvie, Janssen, Ferring and Takeda Pharmaceuticals. He attended advisory boards for Abbvie, Takeda Pharmaceuticals, Janssen, Medtronic, Phebra Pharmaceuticals, Servertus Associates Ltd and Dr Falk.

V.J. has received has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, Celltrion; speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, Pfizer.

Acknowledgments

J.R.W. and G.W.M research is supported by the National Institute for Health Research (NIHR), through Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

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