THERAPEUTIC ADVANCES in
Gastroenterology

Review

Can we change the natural course of inflammatory bowel disease?

Ther Adv Gastroenterol

2023, Vol. 16: 1–19

DOI: 10.1177/17562848231163118

Catherine Le Berre, Silvio Danese and Laurent Peyrin-Biroulet

***Abstract*:** Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are lifelong diseases characterized by chronic inflammation of the gastrointestinal tract leading to its progressive and irreversible destruction. Whether early initiation of IBD-specific therapy impacts the long-term course of the disease remains unclear and has to be further explored in prospective disease-modification trials. Historically, surgery and hospitalization rates have been the surrogate markers to measure disease progression in IBD, providing an overview of the effectiveness of medical therapies. However, neither surgery nor hospitalization necessarily reflects a fail in therapeutic medical management, and many confounding factors make them biased outcomes. The Selecting Endpoints for Disease-Modification Trials consensus has defined the disease-modification endpoints required for these trials, including the impact of the disease on patient's life (health-related quality of life, disability, and fecal incontinence), the mid-term disease complications (bowel damage in CD, IBD-related surgery and hospitalizations, disease extension in UC, extra-intestinal manifestations, permanent stoma, short bowel syndrome), and the development of dysplasia/cancer and mortality in the long term. Most available data in the literature regarding the impact of current therapies on disease progression focused on anti-tumor necrosis factor agents and are based on retrospective or post-hoc studies. Thus, prospective disease-modification trials are pressingly required to explore the effectiveness of early intensified treatment in patients with severe disease or at risk for disease progression.

Keywords: complications, Crohn's disease, disease modification, disease progression, inflammatory bowel disease, treat-to-target, ulcerative colitis

Received: 18 November 2022; revised manuscript accepted: 1 February 2023.

Video Abstract Please click on the image to play the video (also available as supplemental material).

Correspondence to:
Catherine Le Berre
Hépato-Gastro-Entérologie et Assistance Nutritionnelle, Inserm CIC 1413, Inserm UMR 1235, Institut des Maladies de l'Appareil Digestif (IMAD), Nantes Université, CHU Nantes, 1 place Alexis Ricordeau, Nantes F-44000, France.
catherine@leberre.org

Silvio Danese
Department of Gastroenterology and Digestive Endoscopy, IRCCS San Raffaele Hospital and Vita-Salute San Raffaele University, Milan, Italy

Laurent Peyrin-Biroulet
Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic inflammation of the gastrointestinal tract. The highest prevalence rates for both diseases have been reported in Europe and North America.[1] Although the incidence of IBD in those continents is stabilizing, there remains a high disease burden with a prevalence greater than 0.3%. In newly industrialized countries in Africa, Asia, and South America, rates of IBD have continued to rise since 1990.[1]

Both CD and UC are characterized by a lifelong progression of relapsing-remitting symptoms that can be severely debilitating. Chronic inflammation in CD is transmural and can occur throughout the entire gastrointestinal tract but commonly affects the small bowel. CD has an inexorable tendency to progress to bowel damage, and is now recognized as a disabling, progressive, and destructive disease.[2] About one-fifth of patients experience penetrating or stricturing complications within the first 90 days of diagnosis, increasing to half of patients 20 years after diagnosis.[2] About 50% of patients require surgery within 10 years of diagnosis due to those complications, and postoperative recurrence is frequent.[3] By contrast, UC causes more superficial lesions which are limited to the colon. Its progressive nature is less clear and probably underestimated, even though evidence is accumulating that UC and CD can lead to similar outcomes and should be treated and monitored in the same intensive way.

The main goal of managing IBD is to achieve deep and sustained remission, encompassing clinical and endoscopic remission.[4,5] In the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II guidelines updated recently, the normalization of biomarkers including C-reactive protein (CRP) and fecal calprotectin (FC) has been added as a new therapeutic objective to reach rapidly,[6] reflecting the more and more stringent goals and timelines imposed for the treatment of both CD and UC patients. Moreover, the absence of disability and normalization of quality of life have also been added as therapeutic goals in themselves, reflecting the value that gastroenterologists should provide their patients today in the restoration of a 'normal life'.[6]

Increasing evidence suggests that early intervention with disease-modifying agents within a therapeutic window of opportunity is able to slow down the development of bowel damage in CD compared with a step-up treatment approach.[7,8] Nevertheless, this is exclusively based on retrospective or post-hoc studies, making it difficult to affirm that this strategy impacts the natural course of CD. Available data on the prevention of disease progression in UC are even more limited than in CD. Thus, whether the timing of initiating IBD-specific therapy impacts the long-term progressive course of CD and UC remains unknown and has to be further explored in prospective disease-modification trials (Figure 1).

How was disease progression historically measured in IBD?

Historically, surgery and hospitalization rates were the surrogate markers for quantifying disease progression in IBD, due to their objective nature and their ease of use retrospectively, allowing to perform systematic reviews based on population-based cohorts. For patients with CD, the main review dating back from 2010 reported an annual incidence of hospitalizations of about 20% and a surgery rate of 50% within 10 years after diagnosis.[3] Patients with perianal disease carry an even greater risk of abdominal surgery [hazard ratio (HR), 3.92; 95% confidence interval (CI), 1.86–8.67] and hospitalization (HR, 1.01; 95% CI, 1.00–1.01).[9] In UC, almost 50% of patients require hospitalization at some point during disease course, and the 5- and 10-year cumulative risk of colectomy is 10–15%.[10]

The same outcomes were also widely used to describe the disease course of pediatric-onset IBD. In a population-based cohort study identifying 113 children with UC, the cumulative rate of colectomy was 8% at 1 year, 15% at 3 years, and 20% at 5 years.[11] A review based on 26 population-based studies ranging from 40 to 2609 pediatric patients with UC estimated that one-half required hospitalizations and 20% required colectomy after a follow-up of 10 years.[12] More recently, a retrospective cohort study including 269 children with very early onset IBD (39% CD, 39% UC, and 22% IBD unclassified) reported a risk of bowel surgery in CD of 3%, 12%, and 15%, and a risk of colectomy in UC/IBD unclassified of 0%, 3%, and 14% by 1, 3, and 5 years,

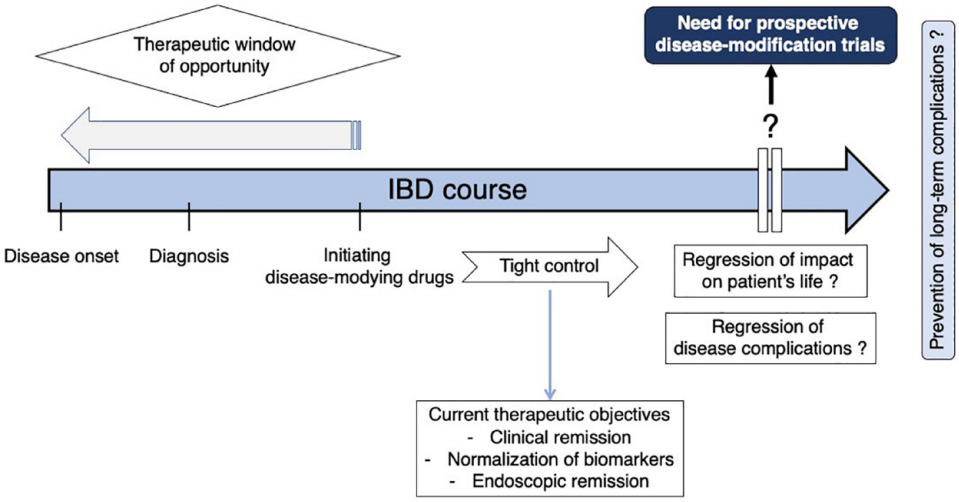

Figure 1. Schematic representation of the concept of 'therapeutic window of opportunity' in IBD.
IBD, inflammatory bowel disease.

respectively, without any difference by age of diagnosis.[13]

Surgery and hospitalization rates have also been used to describe the natural history of IBD in elderly patients. In a population-based study including 370 patients with elderly onset CD (63%, ⩾70 years; 37%, 60–69 years), the cumulative risk of surgery in patients ⩾70 years was 23.3%, 29.8%, and 34.2% at 1, 5, and 10 years, respectively, *versus* 17.6%, 27.4%, and 30.8% in patients aged 60–69 years, without any difference between both groups.[14] Regarding patients with UC, in a study including 1225 patients of whom 12.8% diagnosed after 60 years, colectomy rates have been reported to be similar between elderly-onset and non-elderly-onset groups, but more elderly-onset patients were hospitalized for UC exacerbation (50.6% *versus* 41.8%, $p=0.037$).[15] A case–control study including more than 2600 patients (62% UC, 38% CD) reported a significantly higher surgery rate among elderly-onset UC cases (8.3% *versus* 5.1%; $p<0.009$) but not among CD cases, and a higher rate of hospitalizations (66% *versus* 49%; $p<0.0001$) even if this difference was due to a higher rate of hospital admissions not related to IBD among elderly-onset patients.[16] Another study based on Hong Kong IBD registry, including a total of 2413 patients of whom 11.2% with elderly onset IBD, reported an increased number of overall hospitalizations [odds ratio (OR), 1.14; 95% CI, 1.09–1.20; $p<0.001$), infections-related hospitalizations (OR, 1.87; 95% CI, 1.47–2.38; $p<0.001$), and IBD-related hospitalizations (OR, 1.09; 95% CI, 1.04–1.15; $p=0.001$) compared with adult-onset IBD patients.[17]

The impact of therapies on hospitalization and surgery rates

Both of these markers have been widely used to assess the effect of medical treatments on IBD disease course. Early use of thiopurines in CD within the first 12–18 months of diagnosis has been shown to reduce the risk of intestinal surgery at 5 years (HR, 0.47; 95% CI, 0.27–0.79; $p=0.005$)[18] and at 10 years (HR, 0.40; 95% CI, 0.18–0.83; $p<0.023$).[19] The same was true in UC patients treated by thiopurines with a reduced risk of colectomy at 10 years (HR, 0.39; 95% CI, 0.21–0.73; $p<0.01$), but also a reduced risk of hospital admission within 10 years (HR, 0.36; 95% CI, 0.23–0.56; $p<0.01$).[20]

Regarding biologic agents, early introduction of anti-tumor necrosis factor (TNF) therapy within 2 years of diagnosis has been shown to reduce or at least slow down bowel damage in patients with CD,[7,21,22] encompassing stricturing and penetrating complications as well as intestinal resections.[2] Another retrospective cohort study, based on 190 CD patients who were primary responders to anti-TNF therapy, of whom 27.9% were initiated within 2 years of diagnosis, confirmed that much more patients in the late initiation group required

surgery (HR, 5.92; 95% CI, 1.83–19.16; $p < 0.01$), and in Kaplan–Meier analysis, early initiation of anti-TNF therapy prolonged time to first surgery ($p = 0.001$).[23] In a Spanish cohort, among 272 patients who received anti-TNF agents, the OR for surgery was 1.008 (95% CI, 1.005–1.010) for each month of delay in starting anti-TNF therapy, confirming that time between diagnosis and anti-TNF initiation is associated with the risk of surgery in CD.[24] More recently, a Korean nationwide population-based study based on 1207 patients, of whom 50% were early initiators of anti-TNF (<1 year after diagnosis), confirmed that late anti-TNF initiation was associated with increased risk of surgery (HR, 1.64; 95% CI, 1.05–2.55).[25] By contrast, a register-based observational cohort Swedish study based on 1856 CD patients showed no difference in bowel resection rates between patients on sustained anti-TNF treatment beyond 12 months and those who discontinue anti-TNF treatment earlier; however, the mean disease duration before initiation of anti-TNF therapy was 7.6 years in this study.[26] Another retrospective study from Hungary showed that hospitalization rates decreased significantly in 152 CD patients after the introduction of anti-TNF therapy and was associated with time to therapy (OR, 0.60; 95% CI, 0.48–0.75; $p < 0.001$ within 3 years of diagnosis).[27] These data have been confirmed at the experimental level in a peptidoglycan–polysaccharide-injected rat model of CD in which anti-TNF is known to prevent inflammation and fibrosis,[28] with the existence of a stepwise loss of responsiveness when anti-TNF is begun on Day 7 and Day 14 compared with Day 1, consistent with the clinical observation that improved outcomes occur when anti-TNF therapy is initiated early in the course of CD.[29] In pediatric CD, several studies demonstrated that early surgery is difficult to prevent among patients with significant and progressing disease at presentation, but early use of biologics can delay later disease progression thus reducing the risk of further surgeries.[30–32] A very recent study based on the EPIMAD registry including a total of 1007 pediatric patients diagnosed with CD and followed up for a median duration of 8.8 years showed a decreased risk of both intestinal resections and stricturing complications between the pre-anti-TNF era and the anti-TNF era.[33] The benefit of anti-TNF therapy on perineal surgery and diverting stoma reversal seems more limited.[34,35]

Data regarding UC are less frequent and more conflicting. A retrospective study comparing two cohorts of UC patients who underwent colectomy during the years 2005–2007 and 2014–2016 showed an increased use of biological therapy during the time preceding colectomy (2.3% *versus* 18.8%, $p < 0.001$) and a significantly decreased rate of surgery (8.6 *versus* 5.1/1.000 patient-years, $p < 0.001$) but no changes in the indications for colectomy.[36] This is consistent with a nationwide cohort study from Norway that included 8257 IBD patients (2829 CD and 5428 UC) showing the large regional differences that exist during the first 3 years after diagnosis and in which the region with the lowest anti-TNF use had the highest surgery rates for both UC and CD.[37] However, the timing of anti-TNF initiation seems less important than in CD, as reflected by two retrospective studies in which earlier treatment within 2–3 years of diagnosis prevents neither hospitalization nor colectomy.[38,39] Furthermore, a population-based interrupted time-series study from Canada recently showed that marketplace introduction of infliximab has not yielded anticipated reductions in the population rates of IBD-related hospitalizations or intestinal resections, despite robust market penetration especially among patients with CD.[40]

Data are more scarce regarding non-anti-TNF biologics. A systematic review of randomized controlled trials (RCTs) published between 1980 and 2016 in both CD and UC showed that anti-TNF biologics are efficacious in reducing the odds of hospitalization by half and surgery by 33–77%, while vedolizumab was not associated with a similar improvement probably due to paucity of RCTs; there were no data regarding ustekinumab.[41] In a recent cohort study including 1753 CD patients between 2000 and 2017, the increased and earlier use of biologic therapy corresponded with a decreasing requirement for surgery over time, but data were extremely limited for vedolizumab (2.8%) and even more for ustekinumab (0.2%).[42] In a real-world cohort of 321 UC patients starting vedolizumab between 2014 and 2016, overall cumulative rates of colectomy over 12 months were 13%, with lower rates observed in patients naive to anti-TNF (2%) than those who had been exposed to anti-TNF (19%).[43] Partially based on the same consortium and since its approval, vedolizumab has been proved to be associated with lower rates of UC-related

hospitalization (22.4% *versus* 9.6%, $p < 0.001$) and surgery (17.2% *versus* 9.4%, $p = 0.008$), which was not observed for CD.[44] In CD, a post-hoc analysis of the GEMINI phase III showed that the risk of surgery was lower in patients with a high probability of response *versus* those with a low/intermediate probability of response to vedolizumab (HR, 0.50; 95% CI, 0.29–0.85), especially when initiated within 2 years of diagnosis.[45] Data on ustekinumab are lacking. In a retrospective multicentre cohort study of 122 CD patients treated by ustekinumab for a median of 26.6 months, more than 50% of patients continued treatment without any surgery,[46] but the benefit of this treatment on surgical rates needs to be further explored.

Regarding small molecule drugs, data are also limited. Two small retrospective multicenter observational studies, one from Germany, the other from France, reported real-world effectiveness of tofacitinib in patients with UC especially after multiple biologic failures. Both studies each included 38 patients, with a survival without colectomy of 81.6% after a median follow-up of 4 months in Germany,[47] 77% at Week 24 and 70% at Week 48 in France.[48] In a larger cohort coming from the United States, including 260 patients with UC followed-up for a median of 6 months, 13.5% had colectomy of whom 97% for refractory disease.[49]

Overall, surgery and hospitalization rates are relatively good markers for disease progression in IBD, providing an overview of the effectiveness of medical therapies. However, they may be biased because neither surgery nor hospitalization necessarily reflects a fail in therapeutic medical management. In that respect, the LIR!C trial demonstrated that laparoscopic resection in patients with limited non-stricturing non-penetrating ileocaecal CD is a reasonable and cost-effective alternative to anti-TNF therapy, with similar quality-of-life outcomes, including in the long term.[50–52] Moreover, surgery habits may depend on countries and national reimbursement policies regarding medical therapies. Hospitalization rate is even more biased because its definition varies widely between studies, some considering all hospitalizations together, others focusing on IBD-related hospitalizations, that can also be related either to adverse events of therapies or to an IBD flare. Thus, there was until now a lack of consensus on which specific outcomes to consider for disease-modification trials.

The Selecting Endpoints for Disease-Modification Trials consensus better defines the concept of disease progression in IBD

We recently published a systematic literature review based on real-world evidence for defining disease progression in IBD, that was performed prior to the Selecting Endpoints for Disease-Modification Trials (SPIRIT) consensus led by the International Organization for the Study of Inflammatory Bowel Diseases on the outcomes to consider for future disease-modification trials in IBD.[53]

Based on this systematic literature review of retrospective studies, Tables 1 and 2 summarize the

Table 1. Main results on the natural history of adult CD in observational, real-world, case–control, cohort, and registry studies.

Variable	Results	References
Disease location	• Overall progression rates: 6.5–24.4% over follow-up periods of 63–100.8 months • Cumulative risk of progression in disease location: 17% at 1 year, 23% at 5 years, and 25% at 7 years	54–57
Disease behavior	• Cumulative risk of progression in disease behavior: 3% at 1 year, 14% at 5 years, and 16% at 7 years • (8–13% from B1 to B2, 4–13% from B1 to B3, 10% from B2 to B3) • Cumulative risk of stricturing disease: 7.2% at 1 year, 12.4% at 5 years, 15.2% at 10 years, 21.6% at 20 years, and 21.6% at 30 years. • Cumulative risk of penetrating disease: 15.7% at 1 year, 24.1% at 5 years, 27.5% at 10 years, 37.1% at 20 years, and 41.7% at 30 years.	54–58
Perianal disease	• Cumulative risk of developing perianal disease: 9% at 1 year, 24% at 30 years.	57,59
EIMs	• Overall rate of developing all EIMs considered together: 24% over a median follow-up time of 14 years.	60

(Continued)

Table 1. (Continued)

Variable	Results	References
Disease activity and relapse	• Clinical remission (HBI < 5): 33% at 1 year, 77% at 5 years. • Mild activity (HBI = 5–7): 29% at 1 year, 12% at 5 years • Moderate (HBI = 8–16): 33% at 1 year, 9% at 5 years • Severe activity (HBI ⩾ 16): 5% at 1 year, 3% at 5 years	56
Hospitalization	• Risk for CD-related hospitalization after the introduction of anti-TNF: 41.2/100 patient-years • Cumulative risk of any CD-related hospitalization: 32% at 1 year, 52% at 5 years, and 62% at 10 years	27,61
Surgery	• Cumulative rate of intestinal surgery: 7–9% at diagnosis, 19–29% at 1 year, up to 50% at the end of follow-up in one study with a median follow-up time of 7.6 years	18,62,63
Postoperative recurrence	• Cumulative rate of postoperative recurrence, including surgical and non-surgical recurrence: 53 per 100 patient-years at 1 year, 33 per 100 patient-years at 12 years	63
Medication usage	• Use of steroids: 30.3–47%. • Median time to first use of anti-TNF: 2.1 years.	63–65

Source: Adapted from Le Berre *et al.*[53]
5-ASA, 5-aminosalicylates; CD, Crohn's disease; EIMs, extra-intestinal manifestations; HBI, Harvey Bradshaw index; TNF, tumor necrosis factor.

Table 2. Main results on the natural history of adult UC in observational, real-world, case–control, cohort, and registry studies.

Variable	Results	References
Disease location	• Overall progression rates: 21%–28.7% over follow-up periods of 63–108 months. (34.5% from E1 to E2 or E3, 15–60.8% from E1 or E2 to E3). • Overall regression rates: 0–27% over follow-up periods of 63–108 months.	55,66–70
EIMs	• Overall rate of developing all EIMs considered together: 8.9–66% over median follow-up periods of 8.3–13.5 years	67,70–73
Disease activity and relapse	• Clinical remission (SCCAI ⩽ 2): 27% at 1 year, 71% at 5 years • Mild activity (SCCAI = 3–5): 32% at 1 year, 18% at 5 years • Moderate (SCCAI = 6–11): 36% at 1 year, 10% at 5 years • Severe activity (SCCAI ⩾ 12): 5% at 1 year, 1% at 5 years	66
Hospitalization	• Risk for UC-related hospitalization after the introduction of anti-TNF: 54.3/100 patient-years • Cumulative risk of first hospitalization: 29.4% at 5 years, 38.7% at 10 years, 49.2% at 20 years, and 52.3% at 30 years	27,74
Surgery	• Cumulative risk of colectomy: 11.7% at 5 years, 17.2% at 10 years, and 20.8% at 15 years	73
Medication usage	• Cumulative probability of being treated by oral 5-ASA: 79.8% at 1 year, 85.3% at 7 years • Cumulative rate of receiving steroids: 57% during a median follow-up of 6.8 years	55,63

Source: Adapted from Le Berre *et al.*[53]
5-ASA, 5-aminosalicylates; EIMs, extra-intestinal manifestations; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumor necrosis factor; UC, ulcerative colitis.

main results on the natural history of CD and UC patients, respectively. However, this systematic literature review highlighted major gaps, including high heterogeneity regarding the definition of progression outcomes, study design, number of patients, patient characteristics, and follow-up period. Moreover, many articles included in this systematic literature review reported outcomes only at one time, making it difficult to assess progression trends and patterns over time. There was

limited information identified on response rate, use of biologics other than anti-TNF agents or Jak inhibitors, FC level, comorbidities, cancer, and postoperative complications during follow-up. Information on lines of treatment was not reported, as was the case for safety data and definition of treatment failure. Thus, the SPIRIT consensus is largely based on expert opinion.

Figure 2 summarizes the process leading to this consensus. The consensus meeting took place on 22 October 2019 during the United European Gastroenterology Week (UEGW) Congress in Barcelona, during which predefined proposed statements were discussed in a plenary session and voted on anonymously. The group of 39 experts agreed on 12 outcome measures accounting for the ultimate therapeutic goals to reach in IBD, the evaluative instrument and the time point that should be used to assess each of these outcome measures (Table 3). These recommendations aim at preventing disease impact on patient's life (health-related quality of life, disability, and fecal incontinence), mid-term [bowel damage in CD, IBD-related surgery and hospitalizations, disease extension in UC, extra-intestinal manifestations (EIMs), permanent stoma, short bowel syndrome], and long-term complications (dysplasia or cancer, mortality).[53] Fatigue, anxiety/depression, and work productivity were excluded from the SPIRIT consensus, considering that these endpoints cannot confidently be impacted with disease-modifying therapeutic agents given other factors that can influence them, and because most of the experts considered that these aspects are already evaluated by the more global IBD Disability Index.

The impact of therapies on SPIRIT outcomes

Many studies have already proved the impact of currently available therapies on patient's quality of life (Table 4). Thiopurine immunomodulators alone or with other treatments have been shown to induce a long-lasting improvement in health-related quality of life of IBD patients.[75] Anti-TNF agents have demonstrated rapid improvement in quality of life, as early as Day 4,[76,77] which is maintained in the long term in both UC and CD,[78,79] including in patients with perineal fistulas.[80] Ustekinumab has also been associated with long-term clinical improvement in health-related quality of life in both types of IBD,[81–83] as well as vedolizumab, whether in post-hoc analysis of RCTs or real-word studies.[84–86] In a post-hoc analysis of the OCTAVE data, health-related quality of life was also significantly improved using tofacitinib, in a rapid manner with a sustained effect at 1 year.[87] In the absence of specific tool dedicated to disability in IBD until recently, disability has been much less explored than quality of life, and the same was true for fecal incontinence. A French prospective study including 130 CD patients in a tertiary referral center showed that high disability scores as assessed by the IBD Disability Index were significantly associated with anti-TNF exposure, but the responsiveness to change under treatment was not explored.[88] Infliximab in combination with surgical repair has been shown to be efficient in incontinent patients with CD involving both a sphincter defect and severe or refractory fistulas, but the number of patients treated was extremely limited, highlighting the need for further studies to demonstrate the impact of anti-TNF agents on fecal incontinence.[89]

Regarding mid-term complications, the presence of EIMs and the impact of therapies on it is the one that has been the most explored, with good response rates under anti-TNF for almost all EIMs.[90,91] Using ustekinumab, dermatologic manifestations (psoriasis, pyoderma gangrenosum, erythema nodosum) and peripheral arthralgia and psoriatic arthritis are significantly improved,[92] while no efficacy was found in axial spondyloarthritis.[93,94] Promising results for aphthous stomatitis and uveitis have also been reported using ustekinumab but data are limited.[92] Vedolizumab therapy is commonly associated with improvement in peripheric articular symptoms,[95,96] as well as erythema nodosum,[97] probably as a consequence of the concomitant control of gut inflammation, but has no effect on axial spondyloarthritis[96] and pyoderma gangrenosum[98] that are independent of disease activity. Jak inhibitors, especially tofacitinib, demonstrated clinical efficacy in active ankylosing spondylitis,[99] and may have a therapeutic effect on dermatologic manifestations (erythema nodosum, pyoderma gangrenosum)[100,101] as well as uveitis.[102,103]

Since the landmark publication on the Lémann index to quantify bowel damage in CD,[104] few publications focused on its responsiveness to change under medical therapy. However, the Lémann index is more suitable for clinical trials than for clinical practice because segmentation of

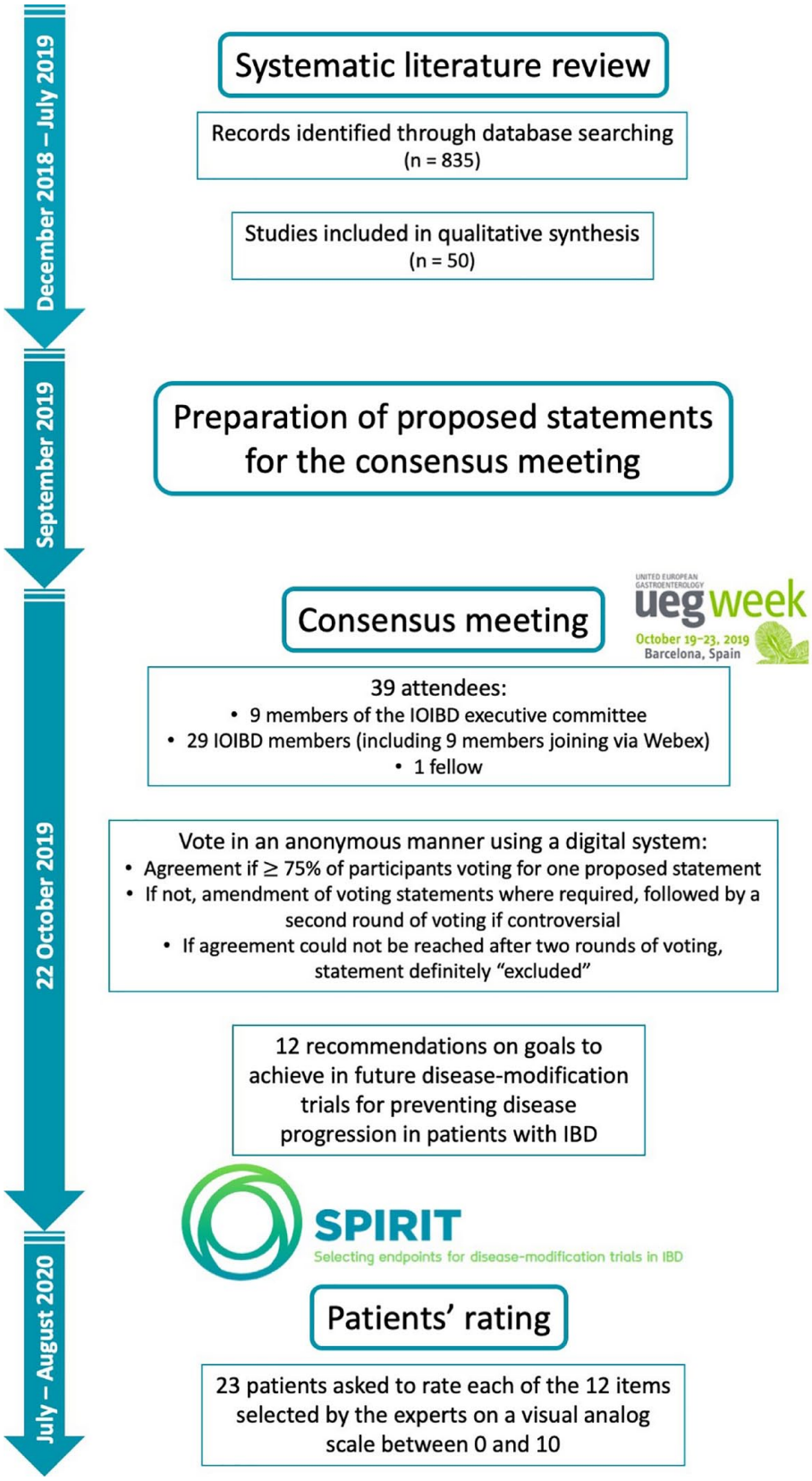

Figure 2. Summary of the process leading to the SPIRIT consensus.
IBD, inflammatory bowel disease; IOIBD, International Organization for the Study of Inflammatory Bowel Diseases; SPIRIT, Selecting Endpoints for Disease-Modification Trials.

Table 3. Disease-modification outcomes defined in the SPIRIT consensus.

Outcome measures	Measuring tool	Target values	Time point
Impact on patient's life			
Health-related quality of life	Combination of IBDQ 36 + SF-36	IBDQ-36 ⩾ 209 + SF-36 ⩾ 50	6–12 months
Disability	IBD disability index	<20	6–12 months
Fecal incontinence	Jorge and Wexner (Cleveland score)	<5	6–12 months
Disease complications			
Bowel damage in CD	Lémann index	<4.8?[1]	12–24 months
IBD-related surgery	UC: any colectomy CD: • any CD-related surgery • any endoscopic balloon dilation • any perianal surgery	Not applicable	24–36 months
IBD-related hospitalizations (excluding hospitalization at diagnosis)	Number of hospitalizations + cumulative length of hospital stay	Not defined	12–24 months
Disease extension in UC	Macroscopic proximal disease extension (excluding patients with pancolitis)	Not applicable	2–5 years
EIMs	All considered together		12–36 months
Permanent stoma	Not applicable	Not applicable	Not voted
Short bowel syndrome	Not applicable	Not applicable	Not voted
Long-term complications			
Dysplasia or cancer	All considered together	Not applicable	5 years
Mortality	Both IBD-related and non-IBD-related mortality	Not applicable	5 years

CD, Crohn's disease; EIMs, extra-intestinal manifestations; IBD, inflammatory bowel disease; IBDQ-36, Inflammatory bowel disease questionnaire (36 questions); SF-36, Short Form Health Survey 36; SPIRIT, Selecting Endpoints for Disease-Modification Trials; UC, ulcerative colitis.
[1]Several other cutoff values have been suggested to define damage and the minimally important difference over time. Further prospective studies are needed to clarify the cutoff to define bowel damage and to confirm the index's responsiveness to change.
? undetermined.

Table 4. Positive or negative impact of currently available therapies on SPIRIT disease progression outcomes.

Outcome measures	Immunosuppressants	Anti-TNF	Ustekinumab	Vedolizumab	Tofacitinib
Impact on patient's life					
Health-related quality of life	+	+++	+	+	+
Disability	?	+	?	?	?
Fecal incontinence	?	+	?	?	?
Disease complications					
Bowel damage in CD	–	++	?	?	NA

(Continued)

Table 4. (Continued)

Outcome measures	Immunosuppressants	Anti-TNF	Ustekinumab	Vedolizumab	Tofacitinib
IBD-related surgery	++	+++	+	+	+
IBD-related hospitalizations (excluding hospitalization at diagnosis)	++	+++	+	+	+
Disease extension in UC	?	?	?	?	?
EIMs	–	+++	++	+/–	++
Permanent stoma	?	–?	?	?	?
Short bowel syndrome	?	?	?	?	?
Long-term complications					
Dysplasia or cancer	++	++	?	–?	?
Mortality	?	+?	?	?	?

CD, Crohn's disease; EIMs, extra-intestinal manifestations; IBD, inflammatory bowel disease; NA, not applicable; SPIRIT, Selecting Endpoints for Disease-Modification Trials; TNF, tumor necrosis factor; UC, ulcerative colitis.
? undetermined.

the small bowel is difficult in routine and its calculation is time-consuming. Real-word studies should focus on the impact of disease-modifying therapeutic agents on stricturing and penetrating complications as well as surgery or endoscopic therapy instead of the Lémann index in itself. Anti-TNF therapy, especially when initiated early after diagnosis, has demonstrated its ability to reverse or at least stabilize bowel damage in patients with CD,[7,22,88,105] while azathioprine does not halt its progression.[106] Data regarding the impact of other biologics on bowel damage progression are lacking.

The same is true regarding the impact of therapies on the probability of disease extension in UC and the rate of short bowel syndrome in CD. A recent retrospective study, based on a nationwide cohort of 18,815 incident patients from Sweden, showed that the cumulative incidence of stoma formation within 5 years of CD diagnosis has not decreased from 2003 to 2019 despite increasing use of anti-TNF (3.5%), with less than half of the patients (44%) having their stoma reversed so that 0.8% of the incident patients had a permanent stoma within 5 years of diagnosis.[107] However, again, prospective data are lacking.

Finally, regarding long-term complications, few retrospective studies focused on the impact of therapies on the development of dysplasia or cancer and mortality. It is now well established that chronically active disease is the only modifiable risk factor for colorectal cancer,[108] apart from disease duration and extent, concomitant primary sclerosing cholangitis, and family history of colorectal cancer that are invariable. Thus, it is likely that any medication that successfully controls inflammation and maintains endoscopic remission would reduce the risk of colorectal cancer, as has been observed with long-term thiopurine use.[109] Based on a very large database from the United States, it has been shown that patients with IBD who are treated with anti-TNF therapy are less likely to develop colorectal cancer, although prospective studies are further needed to evaluate whether it provides a chemoprotective effect by inflammation control and mucosal healing.[110] This has been also demonstrated in a French nationwide cohort of more than 30,000 patients with UC, especially in patients with long-standing colitis (disease duration $\geq$10 years).[111] Similarly, a nationwide nested case–control study from the Netherland showed that the risk of IBD-related colorectal cancer is decreased using immunosuppressive therapy (OR, 0.3; 95% CI, 0.16–0.56, $p < 0.001$) or anti-TNF (OR, 0.09; 95% CI: 0.01–0.68, $p < 0.02$).[112] Again, data regarding the impact of non-anti-TNF biologics and small molecules are almost

non-existent. This is especially lacking for vedolizumab for which there is the hypothesis that, by reducing the migration of activated leukocytes to the gastrointestinal tract, it may also reduce immunosurveillance, increasing the colorectal malignancy risk in the long term. Recently, a case of a 76-year-old man with a history of melanoma and steroid-dependent left-sided colitis refractory to mesalamine and thiopurines was published, with a diagnosis of a multifocal colorectal adenocarcinoma shortly after clinical and endoscopic remission 1 year after starting vedolizumab, highlighting the call for caution using this gut-selective anti-α4β7-integrin antibody, although more studies are necessary to address this issue.[113]

Very few studies specifically analyzed the impact of biologics on the risk of mortality in patients with IBD. A retrospective cohort study conducted in the United States from 2001 to 2013 compared the mortality risk with prolonged corticosteroid use *versus* anti-TNF drugs in IBD, showing that compared with prolonged steroid exposure, anti-TNF agents are associated with reduced mortality in patients with CD that may be explained by lower rates of major adverse cardiovascular events and hip fracture.[114] Similar results have been published in patients treated with anti-TNF agents for all autoimmune diseases considered together,[115] but the impact of other therapies has not been explored and prospective data are lacking.

The burning need for disease-modification trials

Current 'treat-to-target' strategies aim at avoiding long-term bowel damage and subsequent complications using appropriate therapy in high-risk patients, then closely monitoring and adjusting treatment according to predefined therapeutic objectives.[116] In the last two decades, these therapeutic targets have progressively shifted from clinical outcomes to 'deep remission', combining clinical and endoscopic remission in the STRIDE consensus published in 2015.[117] The STRIDE-II updated recently those therapeutic objectives that become more and more tough, with the addition of normalization of serum and fecal markers as short-term targets, and of transmural and histological healing in CD and UC, respectively, that might be considered as adjunctive measures of the remission depth.[6]

Nevertheless, despite the fact that these therapeutic targets become more and more stringent, whether the timing of initiating disease-modifying therapy impacts the long-term progressive course of IBD remains uncertain. As demonstrated above, most available data in the literature regarding the impact of current therapies on disease progression focused on anti-TNF agents and are based on retrospective studies. Thus, prospective disease-modification trials are pressingly required to settle whether a top-down approach should be favored in routine practice.

The value of early treatment in neurology and rheumatology has been much more explored and multiple prospective clinical trials have confirmed the ability to modify the natural history of the disease in those fields. In multiple sclerosis, the first publication about this concept of early disease and the subsequent 'therapeutic window of opportunity' dates back from the 1990s.[118,119] Since then, multiple disease-modification trials have demonstrated the long-term benefits of early treatment both on clinical and socioeconomic levels, some studies with a follow-up period of up to 11 years.[120–126] In rheumatology, this concept has now been extensively explored in rheumatoid arthritis since 2010,[127–129] with disease-modification outcomes to use clearly defined by the OMERACT consensus,[130–132] allowing the achievement of numerous disease-modification trials demonstrating the effectiveness of early therapy to reduce or at least stabilize the risk of undesirable sequelae for up to 20 years.[133–138]

In gastroenterology, the REACT trial was the forerunner of disease-modification trials in the field of IBD. This open-label cluster RCT included 41 gastroenterology practices that could provide data on up to 60 CD patients, and randomly assigned them to either early combined immunosuppression or conventional management. Although early combined immunosuppression was not more effective than conventional management for achieving corticosteroid-free clinical remission at 12 months, the risk of surgery, hospital admission, or serious disease-related complications (abscess, fistula, stricture, EIM, or serious drug complication) was lower at 24 months (HR, 0.73; 95% CI, 0.62–0.86; $p = 0.0003$).[139] However, the primary endpoint was clinical remission; disease-modification outcomes were only secondary endpoints.

The REACT2 trial (NCT01698307), of which results have been very recently presented at UEGW 2022, is the first IBD disease-modification trial. This prospective cluster-randomized study compared an enhanced-care algorithm with early use of a combination therapy using an immunosuppressant and an anti-TNF agent (adalimumab) submitted to treatment intensification targeting absence of ulcers (>5 mm), *versus* a step-care algorithm with treatment escalation targeting clinical remission. The primary endpoint was the risk of first CD-related complications at 2 years including CD-related surgeries, non-surgical CD events (disease flare, bowel obstruction, fistula, abscess), CD-related hospitalizations, and complications related to treatments. At baseline, 15 practices ($n=569$ patients) were assigned to the step-care approach and 14 practices ($n=525$ patients) were assigned to the enhanced-care approach. The primary outcome was analyzable at 24 months in 13 practices ($n=397$) in the step-care algorithm and in 14 practices ($n=415$ patients) in the enhanced-care algorithm. At 2 years, there was no difference between both arms, neither considering all CD-related complications together [40.9% *versus* 43.1% in the enhanced-care and the step-care arms, respectively; adjusted risk difference −1.5% (95% CI, −10.2% to 7.2%; $p=0.73$); risk ratio 0.95 (95% CI, 0.79–1.15; $p=0.59$)], nor splitting them between surgery, non-surgical events, hospitalizations, and medication-related events. However, when considering only patients with active disease defined on a level of CRP above 5 mg/L, the rate of CD-related complications was lower in the enhanced-care arm (44.1%) than in the step-care arm (58.7%) [adjusted risk difference −15.1% (95% CI, −27.8% to −2.4%); risk ratio 0.75 (95% CI, 0.60–0.95)]. This risk difference was even higher in favor of the enhanced-care algorithm when considering patients with active disease based on CRP > 5 mg/L and the presence of ulcers at baseline [−21.6% (95% CI, −34.3% to −8.9%)]. Treating to a target of ulcer healing may thus be more effective than symptom-based management in patients with evidence of active inflammation, but this needs to be confirmed.

As has been done in neurology and rheumatology, further prospective disease-modification trials using the SPIRIT outcomes with much longer follow-up periods are now required to address the burning issue of knowing if an early aggressive treatment may decrease the impact of IBD on patient's life and the risk of mid-term complications, and potentially avoid neoplastic complications and mortality in the long term.

Conclusion

Therapeutic goals in IBD have radically changed for the last decade, both in the short and in the long terms. Until recently, therapeutic strategies targeted the control of IBD-related symptoms and were based on a step-wise approach depending on clinical response. Such strategies did not significantly change the natural course of any type of IBD,[3,140] probably due to the poor correlation that exists between symptoms and endoscopic disease activity. Yet, several studies demonstrated that early mucosal healing is associated with favorable long-term outcomes.[141,142] Thus, short-term objectives in both CD and UC have moved from exclusively controlling symptoms to achieving deep remission encompassing clinical, biologic, and endoscopic remission, with even transmural and histological healing as adjunctive measures reflecting the remission depth.[6]

With these short-term goals becoming more and more stringent, in line with the 'treat-to-target' paradigm based on regular assessment of disease activity and subsequent therapeutic adjustment,[116] the supposed final goal is to avoid long-term intestinal damage and subsequent complications. However, whether the timing of disease-modifying therapies impacts the natural course of CD and UC is unclear. Disease-modification trials are eagerly awaited to explore whether early patient-tailored and optimized treatment decrease the impact of IBD on patients' lives, disease complications, and the risk of cancer and mortality.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Catherine Le Berre: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Silvio Danese: Conceptualization; Writing – review & editing.

Laurent Peyrin-Biroulet: Conceptualization; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
CLB has served as a consultant for Abbvie, Janssen and Gilead, and reports receiving payment for lectures from AbbVie, Celltrion, Ferring, Fresenius Kabi, Galapagos, Janssen, MSD, Pfizer and Takeda. SD has served as a speaker, consultant and advisory board member for Schering-Plough, AbbVie, MSD, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & Johnson, Nikkiso Europe GMBH, Theravance. LPB has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance.

Availability of data and materials
Available on demand.

ORCID iD

Catherine Le Berre https://orcid.org/0000-0002-1124-2019

Supplemental material

Supplemental material for this article is available online.

Writing assistance

No writing assistance was provided for this manuscript.

References

1. Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; 390: 2769–2778.
2. Pariente B, Mary J-Y, Danese S, *et al.* Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology* 2015; 148: 52–63.e3.
3. Peyrin-Biroulet L, Loftus EV, Colombel J-F, *et al.* The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; 105: 289–297.
4. Harbord M, Eliakim R, Bettenworth D, *et al.* Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017; 11: 769–784.
5. Torres J, Bonovas S, Doherty G, *et al.* ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020; 14: 4–22.
6. Turner D, Ricciuto A, Lewis A, *et al.* 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.
7. Fiorino G, Bonifacio C, Allocca M, *et al.* Bowel damage as assessed by the Lémann index is reversible on anti-TNF therapy for Crohn's disease. *J Crohns Colitis* 2015; 9: 633–639.
8. Safroneeva E, Vavricka SR, Fournier N, *et al.* Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther* 2015; 42: 977–989.
9. Zhao M, Lo BZS, Vester-Andersen MK, *et al.* A 10-year follow-up study of the natural history of perianal Crohn's disease in a Danish population-based inception cohort. *Inflamm Bowel Dis* 2019; 25: 1227–1236.
10. Fumery M, Singh S, Dulai PS, *et al.* Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol* 2018; 16: 343–356.e3.
11. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, *et al.* The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009; 104: 2080–2088.
12. Fumery M, Duricova D, Gower-Rousseau C, *et al.* Review article: the natural history of paediatric-onset ulcerative colitis in

population-based studies. *Aliment Pharmacol Ther* 2016; 43: 346–355.

13. Kerur B, Benchimol EI, Fiedler K, *et al*. Natural history of very early onset inflammatory bowel disease in North America: a retrospective cohort study. *Inflamm Bowel Dis* 2021; 27: 295–302.
14. Fumery M, Pariente B, Sarter H, *et al*. Natural history of Crohn's disease in elderly patients diagnosed over the age of 70 years: a population-based study. *Inflamm Bowel Dis* 2016; 22: 1698–1707.
15. Shi HY, Chan FKL, Leung WK, *et al*. Natural history of elderly-onset ulcerative colitis: results from a territory-wide inflammatory bowel disease registry. *J Crohns Colitis* 2016; 10: 176–185.
16. Mañosa M, Calafat M, de Francisco R, *et al*. Phenotype and natural history of elderly onset inflammatory bowel disease: a multicentre, case-control study. *Aliment Pharmacol Ther* 2018; 47: 605–614.
17. Mak JWY, Lok Tung Ho C, Wong K, *et al*. Epidemiology and natural history of elderly-onset inflammatory bowel disease: results from a territory-wide Hong Kong IBD registry. *J Crohns Colitis* 2021; 15: 401–408.
18. Ramadas AV, Gunesh S, Thomas GAO, *et al*. Natural history of Crohn's disease in a population-based cohort from cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010; 59: 1200–1206.
19. Lakatos PL, Golovics PA, David G, *et al*. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from western hungary between 1977–2009. *Am J Gastroenterol* 2012; 107: 579–588.
20. Eriksson C, Rundquist S, Cao Y, *et al*. Impact of thiopurines on the natural history and surgical outcome of ulcerative colitis: a cohort study. *Gut* 2019; 68: 623–632.
21. Oh EH, Oh K, Han M, *et al*. Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. *PLoS One* 2017; 12: e0177479.
22. Panchal H, Wagner M, Chatterji M, *et al*. Earlier anti-tumor necrosis factor therapy of Crohn's disease correlates with slower progression of bowel damage. *Dig Dis Sci* 2019; 64: 3274–3283.
23. Ma C, Beilman CL, Huang VW, *et al*. Anti-TNF therapy within 2 years of Crohn's disease diagnosis improves patient outcomes: a retrospective cohort study. *Inflamm Bowel Dis* 2016; 22: 870–879.
24. González-Lama Y, Suárez C, González-Partida I, *et al*. Timing of thiopurine or anti-TNF initiation is associated with the risk of major abdominal surgery in Crohn's disease: a retrospective cohort study. *J Crohns Colitis* 2016; 10: 55–60.
25. Jung YS, Han M, Park S, *et al*. Impact of early anti-TNF use on clinical outcomes in Crohn's disease: a nationwide population-based study. *Korean J Intern Med* 2020; 35: 1104–1113.
26. Eberhardson M, Söderling JK, Neovius M, *et al*. Anti-TNF treatment in Crohn's disease and risk of bowel resection-a population based cohort study. *Aliment Pharmacol Ther* 2017; 46: 589–598.
27. Mandel MD, Balint A, Golovics PA, *et al*. Decreasing trends in hospitalizations during anti-TNF therapy are associated with time to anti-TNF therapy: results from two referral centres. *Dig Liver Dis* 2014; 46: 985–990.
28. Adler J, Rahal K, Swanson SD, *et al*. Anti-tumor necrosis factor α prevents bowel fibrosis assessed by messenger RNA, histology, and magnetization transfer MRI in rats with Crohn's disease. *Inflamm Bowel Dis* 2013; 19: 683–690.
29. Schmiedlin-Ren P, Reingold LJ, Broxson CS, *et al*. Anti-TNFα alters the natural history of experimental Crohn's disease in rats when begun early, but not late, in disease. *Am J Physiol Gastrointest Liver Physiol* 2016; 311: G688–G698.
30. Kerur B, Machan JT, Shapiro JM, *et al*. Biologics delay progression of Crohn's disease, but not early surgery, in children. *Clin Gastroenterol Hepatol* 2018; 16: 1467–1473.
31. Ashton JJ, Borca F, Mossotto E, *et al*. Increased prevalence of anti-TNF therapy in paediatric inflammatory bowel disease is associated with a decline in surgical resections during childhood. *Aliment Pharmacol Ther* 2019; 49: 398–407.
32. Woo MH, Cho YH, Sohn MJ, *et al*. Use of anti-TNF alpha blockers can reduce operation rate and lead to growth gain in pediatric Crohn's disease. *Pediatr Gastroenterol Hepatol Nutr* 2019; 22: 358–368.
33. Ley D, Leroyer A, Dupont C, *et al*. New therapeutic strategies have changed the natural history of pediatric Crohn's disease: a two-decade population-based study. *Clin Gastroenterol Hepatol* 2022; 20: 2588–2597.e1.
34. Wallenhorst T, Brochard C, Le Balch E, *et al*. Anal ulcerations in Crohn's disease: natural history in the era of biological therapy. *Dig Liver Dis* 2017; 49: 1191–1195.

35. Hain E, Maggiori L, Orville M, *et al.* Diverting stoma for refractory ano-perineal Crohn's disease: is it really useful in the anti-TNF era? A multivariate analysis in 74 consecutive patients. *J Crohns Colitis* 2019; 13: 572–577.
36. Kolehmainen S, Lepistö A and Färkkilä M. Impact of anti-TNF-alpha therapy on colectomy rate and indications for colectomy in ulcerative colitis: comparison of two patient cohorts from 2005 to 2007 and from 2014 to 2016. *Scand J Gastroenterol* 2019; 54: 707–711.
37. Lirhus SS, Høivik ML, Moum B, *et al.* Regional differences in anti-TNF-α therapy and surgery in the treatment of inflammatory bowel disease patients: a Norwegian nationwide cohort study. *Scand J Gastroenterol* 2018; 53: 952–957.
38. Ma C, Beilman CL, Huang VW, *et al.* Similar clinical and surgical outcomes achieved with early compared to late anti-TNF induction in mild-to-moderate ulcerative colitis: a retrospective cohort study. *Can J Gastroenterol Hepatol* 2016; 2016: 2079582.
39. Han M, Jung YS, Cheon JH, *et al.* Similar clinical outcomes of early and late anti-TNF initiation for ulcerative colitis: a nationwide population-based study. *Yonsei Med J* 2020; 61: 382–390.
40. Murthy SK, Begum J, Benchimol EI, *et al.* Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. *Gut* 2020; 69: 274–282.
41. Mao EJ, Hazlewood GS, Kaplan GG, *et al.* Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2017; 45: 3–13.
42. Jenkinson PW, Plevris N, Siakavellas S, *et al.* Temporal trends in surgical resection rates and biologic prescribing in Crohn's disease: a population-based cohort study. *J Crohns Colitis* 2020; 14: 1241–1247.
43. Narula N, Peerani F, Meserve J, *et al.* Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. *Am J Gastroenterol* 2018; 113: 1345.
44. Koliani-Pace JL, Singh S, Luo M, *et al.* Changes in vedolizumab utilization across US academic centers and community practice are associated with improved effectiveness and disease outcomes. *Inflamm Bowel Dis* 2019; 25: 1854–1861.
45. Dulai PS, Peyrin-Biroulet L, Demuth D, *et al.* Early intervention with vedolizumab on longer term surgery rates in Crohn's disease: post hoc analysis of the GEMINI phase 3 and long-term safety programs. *J Crohns Colitis* 2020; 15: 195–202.
46. Wils P, Bouhnik Y, Michetti P, *et al.* Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Aliment Pharmacol Ther* 2018; 47: 588–595.
47. Hoffmann P, Globig A-M, Thomann AK, *et al.* Tofacitinib in treatment-refractory moderate to severe ulcerative colitis: real-world experience from a retrospective multicenter observational study. *J Clin Med* 2020; 9: 2177.
48. Lair-Mehiri L, Stefanescu C, Vaysse T, *et al.* Real-world evidence of tofacitinib effectiveness and safety in patients with refractory ulcerative colitis. *Dig Liver Dis* 2020; 52: 268–273.
49. Deepak P, Alayo QA, Khatiwada A, *et al.* Safety of tofacitinib in a real-world cohort of patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2021; 19: 1592–1601.e3.
50. Ponsioen CY, de Groof EJ, Eshuis EJ, *et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017; 2: 785–792.
51. de Groof EJ, Stevens TW, Eshuis EJ, *et al.* Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C trial. *Gut* 2019; 68: 1774–1780.
52. Stevens TW, Haasnoot ML, D'Haens GR, *et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial. *Lancet Gastroenterol Hepatol* 2020; 5: 900–907.
53. Le Berre C, Peyrin-Biroulet L and SPIRIT-IOIBD study group. Selecting end points for disease-modification trials in inflammatory bowel disease: the SPIRIT consensus from the IOIBD. *Gastroenterology* 2021; 160: 1452–1460.e21.
54. Thia KT, Sandborn WJ, Harmsen WS, *et al.* Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010; 139: 1147–1155.
55. Vester-Andersen MK, Prosberg MV, Jess T, *et al.* Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of

immunomodulating therapy. *Am J Gastroenterol* 2014; 109: 705–714.

56. Burisch J, Kiudelis G, Kupcinskas L, *et al.* Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2019; 68: 423–433.

57. Lo B, Vester-Andersen MK, Vind I, *et al.* Changes in disease behaviour and location in patients with Crohn's disease after seven years of follow-up: a Danish population-based inception cohort. *J Crohns Colitis* 2018; 12: 265–272.

58. Zabana Y, Garcia-Planella E, Van Domselaar M, *et al.* Does active smoking really influence the course of Crohn's disease? A retrospective observational study. *J Crohns Colitis* 2013; 7: 280–285.

59. Park SH, Aniwan S, Scott Harmsen W, *et al.* Update on the natural course of fistulizing perianal Crohn's disease in a population-based cohort. *Inflamm Bowel Dis* 2019; 25: 1054–1060.

60. Henckaerts L, Van Steen K, Verstreken I, *et al.* Genetic risk profiling and prediction of disease course in Crohn's disease patients. *Clin Gastroenterol Hepatol* 2009; 7: 972–980.e2.

61. Ingle SB, Loftus EV and Harmsen WS. Hospitalization rates for Crohn's disease patients in Olmsted county, Minnesota, in the pre-biologic era. *Am J Gastroenterol* 2007; 102: S487.

62. Reenaers C, Pirard C, Vankemseke C, *et al.* Long-term evolution and predictive factors of mild inflammatory bowel disease. *Scand J Gastroenterol* 2016; 51: 712–719.

63. Romberg-Camps MJL, Dagnelie PC, Kester ADM, *et al.* Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. *Am J Gastroenterol* 2009; 104: 371–383.

64. van Deen WK, van Oijen MGH, Myers KD, *et al.* A nationwide 2010–2012 analysis of U.S. health care utilization in inflammatory bowel diseases. *Inflamm Bowel Dis* 2014; 20: 1747–1753.

65. Fiorino G, Morin M, Bonovas S, *et al.* Prevalence of bowel damage assessed by cross-sectional imaging in early Crohn's disease and its impact on disease outcome. *J Crohns Colitis* 2017; 11: 274–280.

66. Burisch J, Katsanos KH, Christodoulou DK, *et al.* Natural disease course of ulcerative colitis during the first five years of follow-up in a European population-based inception cohort-an Epi-IBD study. *J Crohns Colitis* 2019; 13: 198–208.

67. Manetti N, Bagnoli S, Rogai F, *et al.* Disease course and colectomy rate of ulcerative colitis: a follow-up cohort study of a referral center in Tuscany. *Inflamm Bowel Dis* 2016; 22: 1945–1953.

68. Eriksson C, Cao Y, Rundquist S, *et al.* Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Örebro, Sweden, 1963–2010. *Aliment Pharmacol Ther* 2017; 46: 748–757.

69. Huguet JM, Ferrer-Barceló L, Suárez P, *et al.* Endoscopic progression of ulcerative proctitis to proximal disease. Can we identify predictors of progression? *Scand J Gastroenterol* 2018; 53: 1286–1290.

70. Waterman M, Knight J, Dinani A, *et al.* Predictors of outcome in ulcerative colitis. *Inflamm Bowel Dis* 2015; 21: 2097–2105.

71. van der Heide F, Dijkstra A, Weersma RK, *et al.* Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2009; 15: 1199–1207.

72. van der Heide F, Wassenaar M, van der Linde K, *et al.* Effects of active and passive smoking on Crohn's disease and ulcerative colitis in a cohort from a regional hospital. *Eur J Gastroenterol Hepatol* 2011; 23: 255–261.

73. Sahami S, Konté K, Buskens CJ, *et al.* Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. *United European Gastroenterol J* 2017; 5: 554–562.

74. Samuel S, Ingle SB, Dhillon S, *et al.* Cumulative incidence and risk factors for hospitalization and surgery in a population-based cohort of ulcerative colitis. *Inflamm Bowel Dis* 2013; 19: 1858–1866.

75. Bastida G, Nos P, Aguas M, *et al.* The effects of thiopurine therapy on health-related quality of life in inflammatory bowel disease patients. *BMC Gastroenterol* 2010; 10: 26.

76. Feagan BG, Sandborn WJ, Wolf DC, *et al.* Randomised clinical trial: improvement in health outcomes with certolizumab pegol in patients with active Crohn's disease with prior loss of response to infliximab. *Aliment Pharmacol Ther* 2011; 33: 541–550.

77. Marín-Jiménez I, Acosta MB, Esteve M, *et al.* Rapidity of clinical response to adalimumab and improvement of quality of life in luminal Crohn's disease: RAPIDA study. *Gastroenterol Hepatol* 2022; 45: 165–176.

78. Sherman M, Tsynman DN, Kim A, *et al.* Sustained improvement in health-related quality of life measures in patients with inflammatory bowel disease receiving prolonged anti-tumor necrosis factor therapy. *J Dig Dis* 2014; 15: 174–179.

79. Hossain A, Lördal M, Olsson AE, *et al*. Sustained clinical benefit, improved quality of life, and reduced intestinal surgery from maintenance infliximab treatment in inflammatory bowel disease. *Scand J Gastroenterol* 2020; 55: 178–183.

80. Ng SC, Plamondon S, Gupta A, *et al*. Prospective assessment of the effect on quality of life of anti-tumour necrosis factor therapy for perineal Crohn's fistulas. *Aliment Pharmacol Ther* 2009; 30: 757–766.

81. Forss A, Clements M, Myrelid P, *et al*. Ustekinumab is associated with real-world long-term effectiveness and improved health-related quality of life in Crohn's disease. *Dig Dis Sci* 2023; 68: 65–76.

82. Thunberg J, Björkqvist O, Hedin CRH, *et al*. Ustekinumab treatment in ulcerative colitis: real-world data from the Swedish inflammatory bowel disease quality register. *United European Gastroenterol J* 2022; 10: 631–639.

83. Sands BE, Han C, Gasink C, *et al*. The effects of ustekinumab on health-related quality of life in patients with moderate to severe Crohn's disease. *J Crohns Colitis* 2018; 12: 883–895.

84. Feagan BG, Patel H, Colombel J-F, *et al*. Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. *Aliment Pharmacol Ther* 2017; 45: 264–275.

85. Vivio EE, Kanuri N, Gilbertsen JJ, *et al*. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis* 2016; 10: 402–409.

86. Eriksson C, Rundquist S, Lykiardopoulos V, *et al*. Real-world effectiveness of vedolizumab in inflammatory bowel disease: week 52 results from the Swedish prospective multicentre SVEAH study. *Ther Adv Gastroenterol* 2021; 14: 17562848211023386.

87. Panés J, Vermeire S, Lindsay JO, *et al*. Tofacitinib in patients with ulcerative colitis: health-related quality of life in phase 3 randomised controlled induction and maintenance studies. *J Crohns Colitis* 2018; 12: 145–156.

88. Lauriot Dit Prevost C, Azahaf M, Nachury M, *et al*. Bowel damage and disability in Crohn's disease: a prospective study in a tertiary referral centre of the Lémann index and inflammatory bowel disease disability index. *Aliment Pharmacol Ther* 2020; 51: 889–898.

89. Alvarez JA, Bermejo F, Algaba A, *et al*. Surgical repair and biological therapy for fecal incontinence in Crohn's disease involving both sphincter defects and complex fistulas. *J Crohns Colitis* 2011; 5: 598–607.

90. Vavricka SR, Gubler M, Gantenbein C, *et al*. Anti-TNF treatment for extraintestinal manifestations of inflammatory bowel disease in the swiss IBD cohort study. *Inflamm Bowel Dis* 2017; 23: 1174–1181.

91. Guillo L, D'Amico F, Serrero M, *et al*. Assessment of extraintestinal manifestations in inflammatory bowel diseases: a systematic review and a proposed guide for clinical trials. *United Eur Gastroenterol J* 2020; 8: 1013–1030.

92. Guillo L, D'Amico F, Danese S, *et al*. Ustekinumab for extra-intestinal manifestations of inflammatory bowel disease: a systematic literature review. *J Crohns Colitis* 2021; 15: 1236–1243.

93. Liefferinckx C, Verstockt B, Gils A, *et al*. Long-term clinical effectiveness of ustekinumab in patients with Crohn's disease who failed biologic therapies: a national cohort study. *J Crohns Colitis* 2019; 13: 1401–1409.

94. Deodhar A, Gensler LS, Sieper J, *et al*. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019; 71: 258–270.

95. Tadbiri S, Peyrin-Biroulet L, Serrero M, *et al*. Impact of vedolizumab therapy on extra-intestinal manifestations in patients with inflammatory bowel disease: a multicentre cohort study nested in the OBSERV-IBD cohort. *Aliment Pharmacol Ther* 2018; 47: 485–493.

96. Macaluso FS, Orlando R, Fries W, *et al*. The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel diseases. *Dig Liver Dis* 2018; 50: 675–681.

97. Fleisher M, Marsal J, Lee SD, *et al*. Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. *Dig Dis Sci* 2018; 63: 825–833.

98. Phillips FM, Verstockt B, Sebastian S, *et al*. Inflammatory cutaneous lesions in inflammatory bowel disease treated with vedolizumab or ustekinumab: an ECCO CONFER multicentre case series. *J Crohns Colitis* 2020; 14: 1488–1493.

99. van der Heijde D, Deodhar A, Wei JC, *et al*. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2017; 76: 1340–1347.

100. Vavricka SR, Galván JA, Dawson H, *et al*. Expression patterns of TNFα, MAdCAM1, and STAT3 in intestinal and skin manifestations of inflammatory bowel disease. *J Crohns Colitis* 2018; 12: 347–354.

101. Kochar B, Herfarth N, Mamie C, *et al*. Tofacitinib for the treatment of pyoderma gangrenosum. *Clin Gastroenterol Hepatol* 2019; 17: 991–993.

102. Paley MA, Karacal H, Rao PK, *et al*. Tofacitinib for refractory uveitis and scleritis. *Am J Ophthalmol Case Rep* 2019; 13: 53–55.

103. Bing SJ, Lyu C, Xu B, *et al*. Tofacitinib inhibits the development of experimental autoimmune uveitis and reduces the proportions of Th1 but not of Th17 cells. *Mol Vis* 2020; 26: 641–651.

104. Pariente B, Cosnes J, Danese S, *et al*. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis* 2011; 17: 1415–1422.

105. Bodini G, Giannini EG, De Maria C, *et al*. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lémann index. *Dig Liver Dis* 2017; 49: 175–180.

106. Ribaldone DG, Caviglia GP, Pellicano R, *et al*. Adalimumab versus azathioprine to halt the progression of bowel damage in Crohn's disease: application of Lémann Index. *Scand J Gastroenterol* 2019; 54: 1339–1345.

107. Everhov ÅH, Kalman TD, Söderling J, *et al*. Probability of stoma in incident patients with Crohn's disease in Sweden 2003–2019: a population-based study. *Inflamm Bowel Dis* 2022; 28: 1160–1168.

108. Dulai PS, Sandborn WJ and Gupta S. Colorectal cancer and dysplasia in inflammatory bowel disease: a review of disease epidemiology, pathophysiology, and management. *Cancer Prev Res (Phila)* 2016; 9: 887–894.

109. Lu MJ, Qiu XY, Mao XQ, *et al*. Systematic review with meta-analysis: thiopurines decrease the risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2018; 47: 318–331.

110. Alkhayyat M, Abureesh M, Gill A, *et al*. Lower rates of colorectal cancer in patients with inflammatory bowel disease using anti-TNF therapy. *Inflamm Bowel Dis* 2021; 27: 1052–1060.

111. Charkaoui M, Hajage D, Tubach F, *et al*. Impact of anti-tumour necrosis factor agents on the risk of colorectal cancer in patients with ulcerative colitis: nationwide French cohort study. *J Crohns Colitis* 2022; 16: 893–899.

112. Baars JE, Looman CWN, Steyerberg EW, *et al*. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011; 106: 319–328.

113. Nascimento C, Oliveira H, Fidalgo C, *et al*. Aggressive colorectal cancer in an inflammatory bowel disease patient following treatment with vedolizumab: a case report. *GE Port J Gastroenterol* 2022; 29: 203–208.

114. Lewis JD, Scott FI, Brensinger CM, *et al*. Increased mortality rates with prolonged corticosteroid therapy when compared with antitumor necrosis factor-α-directed therapy for inflammatory bowel disease. *Am J Gastroenterol* 2018; 113: 405–417.

115. Herrinton LJ, Liu L, Chen L, *et al*. Association between anti-TNF-α therapy and all-cause mortality. *Pharmacoepidemiol Drug Saf* 2012; 21: 1311–1320.

116. Bouguen G, Levesque BG, Feagan BG, *et al*. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol* 2015; 13: 1042–1050.e2.

117. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al*. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015; 110: 1324–1338.

118. Comi G, Barkhof F, Durelli L, *et al*. Early treatment of multiple sclerosis with Rebif (recombinant human interferon beta): design of the study. *Mult Scler* 1995; 1 Suppl 1: S24–S27.

119. Comi G. Why treat early multiple sclerosis patients? *Curr Opin Neurol* 2000; 13: 235–240.

120. Goodin DS and Bates D. Treatment of early multiple sclerosis: the value of treatment initiation after a first clinical episode. *Mult Scler* 2009; 15: 1175–1182.

121. Kappos L, Freedman MS, Polman CH, *et al*. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol* 2009; 8: 987–997.

122. Kavaliunas A, Manouchehrinia A, Stawiarz L, *et al*. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler* 2017; 23: 1233–1240.

123. Landfeldt E, Castelo-Branco A, Svedbom A, *et al*. The long-term impact of early treatment of multiple sclerosis on the risk of disability pension. *J Neurol* 2018; 265: 701–707.

124. Kavaliunas A, Manouchehrinia A, Gyllensten H, *et al*. Importance of early treatment decisions on future income of multiple sclerosis patients. *Mult Scler J Exp Transl Clin* 2020; 6: 2055217320959116.

125. Hartung H-P, Graf J and Kremer D. Long-term follow-up of multiple sclerosis studies and outcomes from early treatment of clinically isolated syndrome in the BENEFIT 11 study. *J Neurol* 2020; 267: 308–316.

126. Iaffaldano P, Lucisano G, Butzkueven H, *et al*. Early treatment delays long-term disability accrual in RRMS: results from the BMSD network. *Mult Scler* 2021; 27: 1543–1555.

127. Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569–2581.

128. Ma MHY, Kingsley GH and Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. *Rheumatol Oxf Engl* 2010; 49: 91–98.

129. Resman-Targoff BH and Cicero MP. Aggressive treatment of early rheumatoid arthritis: recognizing the window of opportunity and treating to target goals. *Am J Manag Care* 2010; 16: S249–S258.

130. Kloppenburg M, Bøyesen P, Smeets W, *et al*. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. *J Rheumatol* 2014; 41: 810–818.

131. Kloppenburg M, Bøyesen P, Visser AW, *et al*. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015; 42: 2190–2197.

132. Rasch LA, Boers M, Hill CL, *et al*. Validating rheumatoid arthritis remission using the patients' perspective: results from a special interest group at OMERACT 2016. *J Rheumatol* 2017; 44: 1889–1893.

133. Kyburz D, Gabay C, Michel BA, *et al*. The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatol Oxf Engl* 2011; 50: 1106–1110.

134. Fiehn C, Belke-Voss E, Krause D, *et al*. Improved radiological outcome of rheumatoid arthritis: the importance of early treatment with methotrexate in the era of biological drugs. *Clin Rheumatol* 2013; 32: 1735–1742.

135. Levitsky A, Wick MC, Möttönen T, *et al*. Early treatment intensification induces favourable radiographic outcomes according to predicted versus observed radiographic progression in early rheumatoid arthritis: a subanalysis of the randomised FIN-RACo and NEO-RACo trials. *Clin Exp Rheumatol* 2016; 34: 1065–1071.

136. Varela-Rosario N, Arroyo-Ávila M, Fred-Jiménez RM, *et al*. Long-term outcomes in puerto ricans with rheumatoid arthritis (RA) receiving early treatment with disease-modifying anti-rheumatic drugs using the American college of rheumatology definition of early RA. *Open Rheumatol J* 2017; 11: 136–144.

137. Gwinnutt JM, Symmons DPM, MacGregor AJ, *et al*. Twenty-year outcome and association between early treatment and mortality and disability in an inception cohort of patients with rheumatoid arthritis: results from the Norfolk arthritis register. *Arthritis Rheumatol* 2017; 69: 1566–1575.

138. Hirata A, Suenaga Y, Miyamura T, *et al*. Effect of early treatment on physical function in daily management of rheumatoid arthritis: a 5-year longitudinal study of rheumatoid arthritis patients in the National Database of Rheumatic Diseases in Japan. *Int J Rheum Dis* 2018; 21: 828–835.

139. Khanna R, Bressler B, Levesque BG, *et al*. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet* 2015; 386: 1825–1834.

140. Magro F, Rodrigues A, Vieira AI, *et al*. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. *Inflamm Bowel Dis* 2012; 18: 573–583.

141. Colombel JF, Rutgeerts P, Reinisch W, *et al*. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; 141: 1194–1201.

142. Bossuyt P, Baert F, D'Heygere F, *et al*. Early mucosal healing predicts favorable outcomes in patients with moderate to severe ulcerative colitis treated with golimumab: data from the real-life BE-SMART cohort. *Inflamm Bowel Dis* 2019; 25: 156–162.