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Diagnosis and natural history of preclinical and early inflammatory bowel disease

Iago Rodríguez-Lago[a], Yamile Zabana[b,c], Manuel Barreiro-de Acosta[d]

Hospital de Galdakao and Biocruces Bizkaia Health Research Institute, Galdakao; Hospital Universitari Mútua Terrassa, Terrassa; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd); Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain

Abstract

Inflammatory bowel disease is a chronic and progressive disorder of the gastrointestinal tract. A relevant proportion of patients develop complicated lesions, defined as strictures, fistulas and/or abscesses already at diagnosis, and this proportion increases over time. The preclinical phase defines the period of time from the appearance of the first immune disturbances until the development of overt disease, and it may be present months to years before the diagnosis. Multiple biomarkers (e.g., C-reactive protein, interleukin-6, fecal calprotectin) and cellular mechanisms (e.g., complement cascade, lysosomes, innate immunity, and glycosaminoglycan metabolism) are already altered during this period. Research in this area allows the description of the initial immune disturbances that may identify potential targets and lead to the development of new drug therapies. During this period, different interventions in high-risk individuals, including drugs or environmental factors, will open the possibility of innovative strategies focused on the reduction of complications, or even prevention trials for inflammatory bowel disease. Here, we review the most relevant findings regarding the characteristics, prevalence and biomarkers associated with preclinical disease, along with their possible use in our future clinical practice.

Keywords Crohn's disease, early stage, preclinical, ulcerative colitis

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[a]Gastroenterology Department, Hospital de Galdakao and Biocruces Bizkaia Health Research Institute, Galdakao (Iago Rodríguez-Lago); [b]Gastroenterology Department, Hospital Universitari Mútua Terrassa, Terrassa (Yamile Zabana); [c]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd) (Yamile Zabana); [d]Gastroenterology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela (Manuel Barreiro-de Acosta), Spain

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Correspondence to: Iago Rodríguez-Lago, MD PhD, Gastroenterology Department, Hospital de Galdakao and Biocruces Bizkaia Health Research Institute, Barrio Labeaga 48960 Galdakao, Spain, e-mail: iago.r.lago@gmail.com

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Introduction

Inflammatory bowel disease (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing and remitting disorder of the gastrointestinal tract. A remarkable increase in the incidence and prevalence of both diseases has been observed worldwide [1]. The increasing number of cases also affects some areas previously considered to have a low incidence, such as India, China or Latin America [2,3]. Multiple aspects may influence this observation, but it is expected to be driven mostly by a western lifestyle, urbanization and industrialization. However, the exact reasons for this trend have not yet been completely elucidated. One of the most relevant implications of this escalation in IBD cases worldwide is the impact that it may have on healthcare systems across all continents. This is due to the greater use of health resources secondary to long-term medical treatments and the rate of disease-related complications requiring surgical interventions. Strategies directed towards an early identification of these patients have been developed [4], but in a substantial proportion of patients there is still a significant delay until the establishment of a definite diagnosis of IBD [5,6]. This is a very relevant aspect, as this delay has been associated with a greater probability of a complicated disease course, poorer treatment outcomes, reduced quality of life and more frequent

disease-related surgery [7,8]. Therefore, there is an urgent need for strategies that can help us identify IBD patients earlier, as this might impact on the natural history of the disease. Here, we review the current literature about the early phases of the disease, including its preclinical period and the strategies that may influence the disease course and could potentially prevent it in the future.

Natural history of the disease

The diagnosis of IBD can be difficult because of its unspecific clinical manifestations and the absence of noninvasive diagnostic methods. As an example, iron deficiency anemia can be the only manifestation of the disease, and this might be more pronounced in CD cases limited to the small bowel, where the diagnosis can be challenging [9,10]. Thus, the establishment of the final diagnosis of IBD can be delayed for months, as has been described in European reports [5,6,8,11,12,13], or up to 1-2 years in some Asian cohorts [14,15], with even longer intervals, especially in CD [16,17]. We should differentiate between 2 different intervals: in the first place, there is a period between the onset of symptoms and the physician consultation, followed by the time period required for the clinical suspicion and the critical evaluation of all the results obtained from laboratory, endoscopic or radiological examinations [18]. But, most importantly, the relevance of this observation depends on the increased risk of developing complications or requiring surgery as the time from the first symptoms of the disease to the final diagnosis elapses, which has been described across diverse geographical areas [7,15]. Expert consensus has identified key aspects that may prompt an early evaluation in selected subjects with gastrointestinal symptoms in order to reduce this period of time [4]. Unfortunately, these strategies have not been universally implemented in clinical practice.

It is well known that around 80% of patients with a new diagnosis of CD have a non-penetrating non-stricturing behavior [19]. Nonetheless, data from a recent European cohort (Epi-IBD) showed that up to one third of patients already present established bowel damage, including strictures, fistulas and/or abscesses, at first presentation [20]. This proportion increases to 39% during the first 5 years after the diagnosis. This observation illustrates the progressive and disabling course of this disease, despite the application of medical treatment according to current clinical practice. Furthermore, 9% of patients in this cohort already had perianal lesions (fistula or abscess) at diagnosis—considered as a marker of a more aggressive disease—and this increased to 14% during follow up. In tertiary referral centers, the prevalence of bowel damage at diagnosis can be up to 39%, and these advanced lesions have been associated with a worse prognosis in terms of disease-related surgery and hospitalization in real-world studies [21]. Due to the significant impact of the progression of the disease, the assessment of structural damage is currently considered as one of the main outcomes in the long-term management of IBD. Its evaluation should be considered in the therapeutic strategy of the disease in each patient—or at least in CD through the Lémann index [22] —together with quality of life and disability [23,24].

The concept of progressive disease has been underestimated in UC, although there are some important findings that reflect the chronic course of this disorder [25,26]. Firstly, regarding disease extension, most patients with UC present with lesions limited to the rectum (20%) or the left side of the colon (41%), and around half of these patients (52%) will demonstrate a proximal disease extension during the first 5 years after the diagnosis [27]. In a recent systematic review and meta-analysis, the estimated overall risk of proximal disease extension was 23%, being 18% and 31% after 5 and 10 years, respectively [28]. Importantly, the extent at diagnosis has also been associated with a greater need for immunomodulators or biologics, which highlights the need for tight monitoring that should be individualized from the early phases [29]. Secondly, even though UC has been traditionally considered an inflammatory disorder limited to the intestinal mucosa, an increased fibrosis and thickening of the *muscularis mucosae* is also observed in the long term [30]. This may explain the presence of an altered intestinal motility and the prevalence of functional disorders in around one third of UC patients [31,32,33]. Quality of life can be impaired in long-standing disease as a consequence of anorectal dysfunction (urgency, tenesmus and incontinence), which can profoundly impact daily activities. Although they are more frequent during active disease, patients with quiescent or mild endoscopically active UC may have these severe and limiting symptoms. Thirdly, advanced lesions may also be present in UC, as colonic strictures have been reported in 1.5-11% of patients [25]. These stricturing lesions are associated with long-standing disease and are considered to be the result of chronic changes in the bowel wall [34]. The progressive course of UC has also been evaluated in terms of cancer risk [35], which may be due to long-term uncontrolled inflammation [36].

Taken together, these data reflect the long-term course of both CD and UC and the urgent need for strategies towards early identification of patients. The early and even preclinical phases of IBD are promising areas of research, with encouraging data about the possible prediction or early diagnosis of this disabling condition.

Evidence of preclinical disease in immune-mediated inflammatory diseases

The term immune-mediated inflammatory diseases comprises a spectrum of disorders considered to arise in genetically susceptible individuals in whom environmental factors may trigger an immune response directed towards specific antigens. The humoral response precedes the onset of the clinical manifestations and it usually parallels the activity of the disease. The first symptoms of the disease arise once the tissue damage is already present, but it is expected that the triggers of this abnormal reaction might be present months to years before the initial symptoms develop [37,38]. The antibody response to some of these antigens and the immune

processes during the early phases of the preclinical period have been well described in systemic lupus erythematosus (SLE) [39]. In SLE there is an immune response that has been extensively detailed, with specific autoantibodies such as anti-nuclear antibodies (ANA), anti-DNA, anti-Smith (Sm) and anti-phospholipid antibodies. In fact, they are considered an essential diagnostic criterion [40]. However, there is so far no consensus regarding the best definition of preclinical SLE, because it can range from genetically susceptible subjects to symptomatic patients who do not fulfil the current diagnostic criteria for the disease [38]. Importantly, data from the Department of Defense Serum Repository showed that the first immunological changes appeared months to years before the final diagnosis of SLE, and it is possible to detect this preceding humoral response in 63-88% of patients later diagnosed with SLE [38,41,42]. Notably, the landmark study by Arbuckle *et al* showed that titers of these antibodies increased progressively during the preclinical period. During this period, some antibodies—ANA, anti-Ro, anti-La and anti-phospholipid—tend to appear earlier than others—anti-Sm and anti-RNP—showing the dynamic immune response over time. The antigenic response is accompanied by a humoral response in which some cytokines, such as IP-10, interferon-α and MCP-1 or C1q, are also dysregulated [42,43].

Rheumatoid arthritis (RA), one of the most frequent immune-mediated inflammatory diseases worldwide, presents similar findings as those already reported regarding the preclinical period [44]. Rheumatoid factor can be detected in high-risk patients—defined by genetic susceptibility—and the presence of an increased seroreactivity is associated with an increased risk of developing the disease [45,46]. Other antibodies, such as those directed to citrullinated peptides, changes in epitope spreading or in some cytokines can also precede the onset of the disease [47,48]. Notably, during the preclinical period of RA this humoral immune response is not associated with radiological or histological signs of synovial damage [49], suggesting that preventive strategies focused on high-risk patients during this stage may interfere with the onset of overt disease [50]. Multiple trials have explored the possibility of primary or secondary prevention in RA, SLE and type 1 diabetes mellitus with encouraging results (Table 1).

Table 1 Preventive strategies in immune-mediated inflammatory diseases

Disease	Primary prevention	Secondary prevention
Rheumatoid arthritis	Educational intervention	Methotrexate Abatacept Methylprednisolone Dexamethasone Rituximab Hydroxychloroquine Atorvastatin
Type 1 diabetes mellitus	Nutritional intervention Omega-3 Oral insulin Rituximab Etanercept IL-1beta Abatacept Polyclonal Treg Antithymocyte globulin and G-CSF	Oral insulin Intranasal insulin Nicotinamide Abatacept Teplizumab Rituximab GAD-Alum
Systemic lupus erythematosus	Hydroxychloroquine	-

GAD, glutamic acid decarboxylase; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; reg, regulatory

Preclinical IBD

Both CD and UC, like the previously described immune-mediated diseases, are expected to arise in response to different triggering factors [51]. The main events in the pathophysiology of the disease have not yet been clearly elucidated, nor their sequence and relevance in each individual patient. As explained above, they are expected to be present years before the onset of the first symptoms. This fact may allow us to find a window period where the first dysregulated cytokines or immunological markers may be detected in an asymptomatic population. It is possible that some environmental factors, such as diet, tobacco smoking, air pollution, infections or drugs, play an important role as triggers for disease initiation and progression. Interestingly, the presence of a pre-symptomatic period in IBD is suggested by the increased costs associated with healthcare use in the years previous to the diagnosis in CD and UC patients, but a possible bias due to a diagnostic delay should be considered in this type of analysis [52]. Thus, an uncontrolled inflammatory process arising in the gut, which may also be associated with extraintestinal manifestations and non-specific symptoms (e.g., asthenia, weight loss), may precede the final diagnosis of an underlying disorder like IBD. Fortunately, we have the opportunity to detect subclinical endoscopic lesions in certain high-risk or asymptomatic individuals [53,54]. Moreover, the possibility of tissue sampling during endoscopic procedures may prompt the identification of the initial histologic abnormalities, even in the absence of macroscopic endoscopic lesions.

The immunological disturbances during the initial phases of IBD pathogenesis have also been described through the analysis of blood samples included in serum repositories from patients later diagnosed with CD or UC [55,56,57]. The first report on this field by Israeli *et al* described a case-control study of 32 patients with CD and 8 with UC from the Israeli Defense Force tested for ASCA and pANCA antibodies a mean of 59 months before the diagnosis [55]. Interestingly, 31% and 25% of CD and UC patients were positive for ASCA or ANCA, respectively, and these markers were detected at a mean of 38 months before the final diagnosis. Nevertheless, as the majority of these cases had their first serum sample positive, the latent period of this observation may have been underestimated. Some years after this finding, van Schaik *et al* were able to conduct another case-control

study where they analyzed blood samples obtained during the European Prospective Investigation into Cancer and Nutrition study [57]. They analyzed the presence of ASCA IgG, ASCA IgA, perinuclear anti-neutrophil cytoplasmic antibody (pANCA), antibodies against *Escherichia coli* outer membrane porin C (OmpC) and flagellin CBir1 in 77 patients with CD and 167 with UC, where they found that the combination of these serological markers was able to predict the future development of IBD in a low-risk population. In contrast to previous observations in SLE, there was not a specific sequence in the appearance of individual antibodies related to time to diagnosis.

The PREDICTS cohort (Proteomics Evaluation and Discovery in an IBD cohort of Tri-service Subjects) is one of the most promising initiatives in this field [58]. This nested case-control study was designed to identify up to 1000 IBD cases each of UC and CD from the Defense Medical Surveillance System and to link them with serum samples available at the Department of Defense Serum Repository [59]. This project allows the assessment of the initial immune processes present during the preclinical period through the availability of sequential serum samples from each individual. Data from this cohort have demonstrated that patients with CD can show multiple antimicrobial antibodies years before the diagnosis, including ASCA, anti-Fla2, anti-FlaX, anti-CBir1 and anti-OmpC [56]. Interestingly, ASCA IgA was the most prevalent among these, but 65% of the first serum samples—obtained a median of 6 years (interquartile range 5.6-8.1) before the diagnosis—were already positive for at least one antibody. Moreover, this study demonstrated that the presence of this seroreactivity and its titers were associated with a complicated behavior in patients with CD [56]. Both studies by Choung [56] and Israeli [55] found similar results regarding the progressive immunoreactivity of these antimicrobial antibodies as the time of the diagnosis approaches, which may be compared to other immune-mediated inflammatory diseases discussed above. Recently, it has been found that these observations in the humoral response are accompanied by changes in multiple relevant mechanisms, such as the complement cascade, lysosomes, innate immunity and glycosaminoglycan metabolism, years before the IBD diagnosis [60]. Interestingly, the identification of a specific protein panel was able to predict the future development of CD with 76% accuracy at 5 years prior to the diagnosis and 88% in the year before it. Preliminary data from this cohort has shown that antimicrobial antibodies with innate immune activation and dysregulated complement pathways are specifically altered in complicated CD, and they are also present years before the diagnosis [61]. Future analyses from the PREDICTS cohort are expected to show relevant data in this field. In a second initiative, the GEM project (http://www.gemproject.ca), an international consortium recruiting first-degree relatives and multiplex families considered at higher risk of developing CD. The prospective evaluation and analysis of biological samples of these subjects is already showing interesting results regarding the early findings in an at-risk population; some of its findings are discussed below.

First-degree relatives

A family history of CD is the strongest risk factor associated with an increased risk of developing the disease [62]. Screening for IBD in the general population is not a cost-effective strategy, thus strategies focused on high-risk subgroups might be better in a population with a genetic background and medium to high risk of developing the disease. Certain cohorts with a higher risk of IBD (e.g., Ashkenazi Jews [63] or Roma/Gypsy ethnicity [64]) may also be a target group, as multiple siblings within the same family can develop the disease, so tight monitoring of non-affected individuals could be a strategy for detecting early signs of the disease [65]. Nevertheless, the balance between the genetic and environmental factors underlying the risk of IBD in these populations should be well described and further evaluated. Some mutations, such as those located in the *NOD2/CARD15* gene, have been also considered as potential screening tools for IBD, but their application is limited by their low sensitivity, even in high-risk populations [66]. CD is considered a model of complex traits [67], with more than 240 loci associated with IBD so far [68], so genetic risk assessment in most populations is still not an option [69]. Another important aspect that may contribute to the familial aggregation is the gut microbiota, as dysbiosis has also been observed in first-degree relatives [70]. Interestingly, Torres *et al* have demonstrated that pregnant women with IBD and their offspring have lower bacterial diversity, and this is maintained during the first months of life [71]. Gut microbiome composition and diversity could be used as a biomarker and a preventive or therapeutic strategy in the future, with some promising interventions such as fecal microbiota transplantation.

The evaluation of high-risk populations has focused on identifying early signs of subclinical intestinal inflammation, with most studies focusing on intestinal permeability, antimicrobial antibodies and fecal calprotectin. Overall, 10-30% of first-degree relatives have a greater intestinal permeability as compared to healthy controls [72,73,74], but genetic [75] or environmental factors like age or smoking [74] may have influenced these observations. The prospective evaluation of first-degree relatives included in the GEM project led to the observation that an abnormal intestinal permeability may precede the onset of CD in asymptomatic subjects [76]. This abnormal intestinal permeability does not differ according to the presence of small bowel lesions in first-degree relatives, suggesting that the variable observations of the integrity of intestinal epithelium by this test is not associated with the inflammatory lesions in the gut [77]. Besides the initial hypothesis of a potential relationship with subclinical IBD in this high-risk population, there is no evidence that this observation is associated with mucosal lesions and the presence of early IBD. Environmental triggers may predispose to a higher antigenic exposure in susceptible individuals, leading to a dysregulated immune response. Future research should aim to identify the main drivers of this process and its relationship during the different stages of the disease. The scarce prospective data and the absence of

correlation with endoscopic findings in most studies limit our conclusions in the evaluation of the potential application of noninvasive biomarkers as surrogate indicators of subclinical IBD in these individuals.

Incidental IBD

The improvement of endoscopic techniques and the increased access to healthcare assistance have led to a growing number of endoscopic examinations being performed each year worldwide. Although this achievement has an inherent benefit in the diagnosis of multiple gastrointestinal diseases, some of these examinations may demonstrate incidental findings that will be not directly related to the indication for a specific procedure. This would be of special relevance in those individuals undergoing a colorectal cancer screening test (Table 2) [53,54,78,79,80,81,82,83]. Park *et al* observed that, after the performance of 71,000 screening colonoscopies, 17 patients were finally diagnosed with UC, leading to a 0.024% incidental diagnosis of UC in the Korean population [54]. During the follow up of this cohort, no patient required steroids, immunomodulators or biologics. In a similar setting, a study performed within a community-based colorectal cancer screening program in the Basque Country (Spain) found that, among a population of 2.2 million people, 0.35% of patients were diagnosed with IBD after the performance of 31,005 endoscopic examinations during a 5-year period [53]. The most common diagnosis was UC in these case series and that might, in turn, explain the elderly-onset cases of the disease [84]. The time between the onset of endoscopic lesions and the first symptoms is still not known, but in this case series 23% of patients had a negative fecal occult blood test in the previous 2 years, suggesting that the endoscopic lesions may have appeared during that interval, although intermittent inflammatory abnormalities cannot yet be excluded. The data from this cohort are in line with data from the United Kingdom, with a 0.37% of new IBD diagnosis in the British Bowel Cancer Screening Programme [81,83,85]. Prevalence rates in the different cohorts range between 6 and 355/10^5 inhabitants [86], thus reflecting the high heterogeneity in the underlying risk of IBD within each population and the different procedures performed during the screening. Factors such as the difficult interpretation of unspecific endoscopic and histological findings in asymptomatic subjects may have influenced these rates [82].

Subjects included in screening programs are usually above 50 years of age, so they may not represent the whole undiagnosed IBD population [87]. While some authors have reported a second peak of UC in the elderly population, this finding is not consistently observed across all cohorts [84]. Many important questions still remain unexplored, as the prevalence of similar findings across different age groups or the triggers that lead to the development of symptomatic disease in patients with subclinical endoscopic activity. As in patients with established disease who are in clinical remission, we could expect an increase in fecal calprotectin months before the start of symptoms [88]. Recent data suggests that this can be observed during the preclinical period in those first-degree relatives with a higher risk of developing CD [89,90]. The elevation of this biomarker will serve as a link to previous studies, where 21% and 24% of first-degree relatives showed abnormal endoscopic findings on ileocolonoscopy or capsule endoscopy, respectively [77,91].

A more profound description of the characteristics of the early histological and innate or adaptive immune alterations may prompt the identification of the first pathophysiological mechanisms involved with the pathogenesis of the disease. Additionally, the application of tools and biomarkers that can aid in the identification of patients with a higher risk of a complicated disease course could detect the subjects who will benefit most from early and more aggressive medical therapy that could reduce the progression of structural damage [92]. But many questions still remain open. Will preventive strategies be available for these subclinical findings in otherwise healthy subjects? When would be the best moment to apply these strategies during the disease course? Multiple approaches may be considered in this scenario, where the balance between risks and benefits must be finely balanced. The modification of some environmental factors, such as diet, show promising results, as the Mediterranean diet has been recently associated with a lower risk of CD [93]. Modification of the gut microbiome is an alternative strategy, but most of the evidence comes from early intervention with medical therapy.

Table 2 Incidental diagnosis of inflammatory bowel disease (IBD) across different colorectal cancer screening programs

Author	Country	No. screening procedures	No. of IBD	% IBD	Ulcerative colitis	Crohn's disease
Yang [78]	China	241 colonoscopies	6	2.5%	6	0
Mayberry [81]	United Kingdom	481 fecal occult blood tests	8	1.7%	6	2
Sakata [82]	Japan	2829 colonoscopies	14	0.5%	12	2
Park [54]	South Korea	71,000 colonoscopies	19	0.024%	19	0
Howarth [83]	United Kingdom	1,778 fecal occult blood tests	53	2.4%	52	1
Rodríguez-Lago [53]	Spain	31,005 colonoscopies	110	0.35%	87	26
Katičić [79]	Croatia	8541 colonoscopies	320	3.7%	-	-
Logan [80]	United Kingdom	17,192 colonoscopies	~366	2,1%	302	64

Early CD

The interest in the early phases of CD and the availability of medical therapy that can potentially modify the natural history of the disease led to the establishment of a definition of early CD by an expert consensus panel in 2010 (Table 3) [94]. This definition was updated in 2012 and was termed the "Paris definition" of early CD [95]. Unfortunately, despite this important step forward in the development of new strategies for the treatment of CD [96], this definition has still not been consistently applied in many recent studies [97]. Moreover, in contrast to the increasing data on preclinical and early CD, the most important observational studies and ongoing cohorts—PREDICTS and GEM—have not been designed or have failed to demonstrate robust data in UC. This is expected to be secondary to a lower frequency of systemic immunological abnormalities during the pathogenesis of UC; therefore, tissue studies will be better to explore the initial phases of this disorder.

The definition of early CD is a landmark for the disease-modifying strategies. Nevertheless, it is interesting to consider whether patients with preclinical disease will fulfil all the criteria included in the Paris definition [95]. As it includes subjects with ≤18 months since diagnosis, incidental patients may be considered to have early disease. However, the expert panel declares that they did not include the onset of symptoms to avoid a possible recall bias and the influence of the delay in the diagnosis, which may not apply in preclinical or incidental cases. This is an evolving field of research, and current evidence may prompt new definitions and concepts.

Evidence concerning the benefits from early treatment with immunomodulators or biologics is still limited, and no clinical trial has formally evaluated the efficacy of these drugs in the preclinical phase. The early treatment intervention should be carefully balanced with the potential risks of infection and cancer in each individual, but there are no validated tools for stratifying patients according to their benefit–risk assessment [89]. In the pediatric population, early treatment with mercaptopurine has been associated with better clinical outcomes [98]. Additionally, early anti-tumor necrosis factor (TNF) therapy can reduce the progression from an inflammatory to a stricturing or penetrating behavior, as well as the need for surgery [99,100]. In adult cohorts, retrospective observational studies have shown that early treatment with immunomodulators can improve the rates of clinical remission, corticosteroid-free remission rates [101], risk of surgical intervention and the development of complications, defined as intestinal stenosis or fistulas [102]. In 2013, a randomized, placebo-controlled Spanish clinical trial was carried out with the aim of evaluating the efficacy of the onset of azathioprine within the first 8 weeks after the diagnosis of CD [103]. In this study, where the main objective was to evaluate steroid-free remission after 76 weeks, no statistically significant difference was observed between the treatment group and the control group (44% vs. 36%). Despite this negative result, a *post-hoc* analysis revealed that the early treatment group had a lower risk of moderate-to-severe flares (12% vs. 30%). A similar clinical trial conducted in France, where patients considered at high risk for a "disabling" disease—age <40 years, perianal disease, steroids in the first 3 months after diagnosis—were treated with azathioprine in the first 6 months after the diagnosis [104]. As with the Spanish trial, the latter study did not find differences in the proportions of patients achieving corticoid-free remission and biological anti-TNF treatment (67% vs. 56%), but early treatment with azathioprine reduced the risk of perianal surgery (96% vs. 82% at 36 months). This observation is consistent with data from 2 additional cohorts where the use of immunomodulators was associated with a reduction in the number of perianal and abdominal interventions [105,106]. Overall, the findings summarized here suggest that immunomodulators may be able to reduce bowel damage, as well as the need for perianal surgery. As most of the evidence comes from observational studies, clinical trials focusing on these outcomes are eagerly awaited.

Table 3 Paris definition of early Crohn's disease

Less than 18 months since the diagnosis
No previous treatment with immunomodulator or biologics
No evidence of bowel damage defined as internal or perianal fistula or abscess
Mesalamine and steroids could have been prescribed in the past

Adapted from Peyrin-Biroulet *et al*, *Am J Gastroenterol* 2012 [95]

Multiple studies have explored the possible influence of biologics on early CD, but they have examined heterogeneous drugs, different types of patients, treatment strategies, and multiple definitions of early disease or outcomes: therefore, no robust conclusions can be drawn from the currently available evidence [97]. Most data can be obtained from a *post-hoc* analysis of clinical trials. A sub-analysis of the SONIC trial observed higher rates of clinical remission, deep remission (clinical remission and mucosal healing) and normalization of C-reactive protein levels in each treatment arm, but the effect size was increased in those receiving combination therapy [107]. Although this study applied the current Paris definition, the outcomes were evaluated after 26 weeks of randomization, so there is no information about the long-term influence of this strategy. Data from the pivotal trials of adalimumab also support its beneficial effect in patients with a short disease duration [108]. A pooled analysis of data from 10 clinical trials demonstrated that the initiation of adalimumab during the first year in moderate-to-severe CD leads to greater clinical remission rates [108]. This benefit was later confirmed in a prospective observational study from the Swiss IBD cohort, where monotherapy with immunomodulators or biologics during the first 2 years reduced the rate of stricturing lesions [106]. The CALM trial examined the efficacy of 2 different treatment algorithms in a cohort of patients with early disease (mean disease duration 1.0 year, standard deviation 2.3, range 0-13.2 years), with better results in terms of mucosal healing in the tight control and proactive treatment arm [109]. The extension study of this landmark study shows that the beneficial effect of early control of the disease improves the long-term progression rate in terms of new internal fistulas or abscesses, strictures, perianal fistulas or abscesses, hospitalization or surgery [110]. In a recent systematic review with meta-analysis, Ungaro *et al* found that early use of biologics

was associated with greater rates of clinical remission (odds ratio [OR] 2.10, 95% confidence interval [CI] 1.69-2.60), lower relapse rates (OR 0.31, 95%CI 0.14-0.68) and higher mucosal healing rates (OR 2.37, 95%CI 1.78-3.16) compared with late/conventional management [111].

The concept of bowel damage is of special interest in IBD, and the Lémann index is the main tool in the quantification of bowel damage that may help in the follow up of an individual patient or a comparison between subjects. It has been shown to accurately parallel disease progression in CD [22,112], but evidence about its utility with the different treatments is still limited. Biologics, and specifically anti-TNFs, have been shown to be effective in stopping, and even reducing, cumulative damage as measured by this index [113,114]. However, more data are still needed about its application with the remaining drugs currently used in clinical practice.

Early anti-integrin therapy has not been formally examined in clinical trials or prospective cohorts. Only one study from the VICTORY Consortium reported a possible benefit in early CD if not in UC [115], but a significant proportion of patients had already developed stricturing or penetrating complications, or required surgery [116]. Thus, there is no evidence about the possible benefits of anti-integrin or anti-interleukin therapies in patients with early CD as defined by the Paris definition.

Evidence towards a possible benefit of early treatment in UC is still controversial, as no clinical trial or *post-hoc* analysis has explored this field directly [117]. Important confounding factors, such as disease severity, may influence the heterogeneity of results from observational data, as those subjects receiving early treatment with immunomodulators or biologics are expected to have worse outcomes in the long term. Thus, current data do not support early treatment with these drugs in UC, but more research evaluating their efficacy is awaited, as they have the potential to influence clinical and surgical outcomes in these patients.

Concluding remarks

IBD is a chronic and progressive disease with disabling complications in the long term. Early intervention with medical therapies or environmental factors, or by influencing the gut microbiota, are promising targets for disease modification trials in IBD, and especially in CD. Studies evaluating the identification of high-risk subjects and the potential biomarkers that could detect subclinical disease are already ongoing. The findings concerning the preclinical phase of IBD should be followed by prevention trials, where reducing the incidence of the disease will be the ultimate goal.

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