Early Crohn disease: a proposed definition for use in disease-modification trials

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INTRODUCTION
Crohn disease is a chronic condition characterised by intestinal inflammation and progressive bowel damage associated with impaired functioning.

In rheumatoid arthritis, which shares some common aetiological pathways and treatments with Crohn disease, treatment goals no longer include symptom control alone, but also alteration of the biological processes underlying synovial inflammation and progressive structural destruction, thereby preventing structural joint damage and functional decline.1 Analogous disease-modifying treatment goals for Crohn disease are currently being conceptualised and may include prevention of structural bowel damage (stricture, fistula, abscess) and impaired gastrointestinal physiology (ie, maintaining normal gastrointestinal physiology).2,3

In order to achieve disease modification, an effective intervention must occur at the right time, that is, before the development of bowel damage and impaired functioning. While it has been said in this context ‘the earlier, the better’, there is no formal definition of early Crohn disease.4 This article will review the rationale for defining early Crohn disease and the rationale for specifically targeting early Crohn disease from both immunopathological and clinical points of view, using rheumatoid arthritis (another chronic, progressive, destructive disease), as an example. We will then propose a definition of early Crohn disease and briefly discuss its potential application in future clinical trials.

RATIONALE FOR DEFINING EARLY CROHN DISEASE (SEE BOX 1)
Studies from referral centres have demonstrated that the clinical features of Crohn disease change over time with a decreasing frequency of inflammatory (non-stricturing non-penetrating) disease behaviour and an increasing frequency of strictureing and/or penetrating disease behaviour (disease progression).5 6 Population-based studies have demonstrated that more than 50% of adult patients with Crohn disease develop strictureing or penetrating intestinal complications within 20 years of diagnosis7 and similarly these complications occur in more than 50% of children after a median follow-up of 84 months.8 The development of these complications is associated with a need for surgical resection. Recent population-based studies reported that the cumulative risk for first intestinal resection in adults with Crohn disease was 64% at years 30 from diagnosis9 and in children 34% at 5 years from diagnosis.8 These data suggest that Crohn disease, similar to rheumatoid arthritis,10 is a chronic progressive destructive disease and that effective intervention before the onset of bowel damage (stricture, fistula, abscess) may be required to optimise patient outcomes.

The concepts of a ‘therapeutic window of opportunity’ for early intervention in rheumatoid arthritis and in Crohn disease, aimed at preventing the development of disease complications such as joint or bowel damage, are shown in figures 1, 2.11 The identification of patients with early Crohn disease in clinical practice and for enrolment in clinical trials remains a challenge, as no formal definition exists. In clinical practice, early Crohn disease is usually considered as a newly diagnosed case. This definition may be inadequate to alter the clinical course of Crohn disease, since approximately 20% of adult patients already have evidence of a strictureing or penetrating intestinal complication at diagnosis or within 90 days of diagnosis,7 and disease complications are present in 29% of children at diagnosis.8

Current concepts of Crohn disease pathogenesis suggest a complex interplay between the host susceptibility genes,12 the host intestinal microbiological flora and the environment, resulting in an increased immunological response towards microbiological and self antigens,13 followed by the development of subclinical intestinal inflammation that can be considered as the earliest form of Crohn disease (figure 2). In one serum bank study, the presence of anti-Saccharomyces cerevisiae antibody (ASCA) in asymptomatic Israeli military recruits was associated with a subsequent diagnosis of Crohn disease after a median delay of 38 months.13 Increased immune reactivity to the intestinal microbiological flora has also been associated with an increased risk of intestinal complications in patients with Crohn disease.14

Overall, the preclinical stages of Crohn disease remain unexplored, and the question ‘when does Crohn disease start?’ remains unanswered. Currently, it is not possible to identify individuals at risk of developing Crohn disease, and current molecular tools, such as genetic markers (nucleotide-binding oligomerisation domain containing (NOD2), interleukin (IL)-23 receptor, etc), do not allow the identification of subclinical intestinal inflammation with accuracy. Thus, at present, the only way to define early Crohn disease is to use clinical, biological, endoscopic and radiological criteria (figure 2).

RATIONALE FOR EARLY INTERVENTION IN CROHN DISEASE: LESSONS FROM RHEUMATOID ARTHRITIS (SEE BOX 2)
Immunopathological evidence
Rheumatoid arthritis is a systemic autoimmune disorder primarily affecting the synovium of peripheral joints.15 Patients with early rheumatoid arthritis have significantly elevated synovial concentrations of IL-2, IL-4, IL-13 and IL-17 as compared with those with established rheumatoid arthritis.16 Later in the disease course of rheumatoid arthritis, increased production of interferon-gamma (IFN-γ) in synovial fluid has been reported17–21. These data indicate a transient T-helper 2 (Th2) disease phenotype in the early phase of rheumatoid arthritis, with a shift towards a Th1 disease phenotype in the late phase of disease.

Immunopathological studies in both animals and humans have also demonstrated that cytokine profiles change during the clinical course of Crohn disease.22–24

In experimental murine models of colitis and ileitis, early disease is characterised by Th1 immune responses with upregulation of IL-12 and IFN-γ, whereas a Th2 phenotype (IL-4 and IL-13) is observed when disease enters the chronic phase.25–26

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Gut: first published as 10.1136/gut.2009.187120 on 22 February 2010. Downloaded from http://gut.bmj.com/ on September 9, 2023 by guest. Protected by copyright.
Whether data from animal models of spontaneous colitis or ileitis could be extrapolated to human Crohn disease has only recently been investigated. Kugathasan et al demonstrated that mucosal T cells derived from colonoscopic biopsies from children with early Crohn disease that were conditioned with IL-12 mounted a Th1 response characterised by elevated concentrations of IFN-γ, a phenotype that was not observed in mucosal T cells from patients with late disease. In addition, the colonic mRNA concentrations of IL-12 and IL-12Rβ2 chain were higher in early than late Crohn disease. In another human study, early-endoscopic recurrence of Crohn disease 3 months after ileal resection was associated with a significant increase in IL-4 mRNA concentration and a concomitant decrease in IFN-γ mRNA concentration. In contrast, a significant increase in IFN-γ concentration was observed in chronic ileal lesions, together with a marked decrease in IL-4 concentration.

Disease-specific changes also occur in the expression of adhesion molecules and their ligands, such as the chemokine receptor 9 (CCR9), a highly specific receptor expressed by T cells migrating selectively to the digestive tract.

The results from these immunopathological studies suggest some potential targets for therapeutic intervention in patients with early Crohn disease, including tumour necrosis factor-alpha (TNF-α) inhibition with infliximab, adalimumab or certolizumab pegol, and chemokine receptor CCR9 inhibition with CCX282-B.

**Evidence from clinical trials**

The first randomised controlled trials in patients with early rheumatoid arthritis were conducted more than 30 years ago. Clinical response, progression of disability and erosive damage are now all routinely assessed in early rheumatoid arthritis trials. Results from recent large trials have demonstrated that combination therapy with TNF-α antagonists and methotrexate prevents disability and radiographic damage in early rheumatoid arthritis. The BeSt (Dutch acronym for Behandel-Strategieën, ‘treatment strategies’) study enrolled 508 patients with early rheumatoid arthritis and compared four different treatment strategies: (1) sequential monotherapy; (2) step-up combination therapy; (3) initial combination therapy with prednisone and methotrexate; and (4) initial combination therapy with infliximab and methotrexate. After 4 years of treatment, joint damage progression remained significantly lower after initial combination therapy compared with initial monotherapy.

Safety is an important concern when treating patients with disease-modifying drugs. A potential caveat regarding early use of highly effective combination therapy treatment strategies is the possibility of overtreatment, as some patients will have a mild disease course. All the studies in rheumatoid arthritis showed a tendency for more adverse events with combination therapy independently from disease duration, but the differences between studies are small. Interestingly, a pooled analysis of clinical trials with TNF antagonists in patients with early rheumatoid arthritis suggested that many adverse effects occur at a lower frequency among patients with early disease. Patients with early rheumatoid arthritis in general are younger, use concomitant medications less frequently and have less comorbidity than individuals with longstanding rheumatoid arthritis. Whether early intervention with highly effective therapy that is disease-modifying may reduce the risk of adverse events is unknown.

Few studies have been performed in patients with early Crohn disease. Two trials have evaluated the use of early surgical intervention. This idea has limited appeal because it permanently alters the gastrointestinal physiology and function. Both observational and placebo-controlled trials have suggested that azathioprine and 6-mercaptopurine may be more effective when administered to children and adolescents early in the course of their disease. A small controlled trial demonstrated that 6-mercaptopurine significantly reduced the need for prednisone and was more effective than placebo for maintenance of clinical remission. In a population-based study from northern France, the use of immunosuppressive therapy in paediatric patients was associated with a decreased risk for surgery. Moreover, azathioprine was introduced earlier in the course of disease in patients not undergoing surgery than in patients requiring surgery. In adults, experience from a referral centre suggested that despite increasing use of azathioprine in Crohn disease over time, it did appear not to change surgical rates. However, these results should be interpreted with caution because less than 10% of patients followed during this period received azathioprine before surgery, the study was not designed to investigate the impact of azathioprine on surgery rates, and many of the patients likely received azathioprine later in the disease course.

Subgroup analyses from placebo-controlled trials with TNF antagonists have also suggested that patients with early Crohn disease may experience greater efficacy than patients with established disease. One small randomised trial suggested that combination therapy with azathioprine and anti-TNF therapy may be more effective in patients with early Crohn disease. However, no definite conclusions can be drawn from this study, as efficacy results at 2 years were negative, and the authors used an empirical definition of early Crohn disease.

Collectively, these observations suggest that the development of a formal definition of early Crohn disease is needed to facilitate the development of new therapeutic strategies.

**PROPOSAL FOR A DEFINITION OF EARLY CROHN DISEASE FOR USE IN CLINICAL TRIALS (SEE BOX 3)**

**Example of rheumatoid arthritis**

Early rheumatoid arthritis is defined by the American College of Rheumatology...
(formerly, the American Rheumatism Association) 1987 revised criteria as a disease duration of ≥2 years, age ≥18 years, and active disease with ≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either an erythrocyte sedimentation rate ≥28 mm/h or a global health score of ≥20 mm on a 0–100 mm visual analogue scale, where 0 is the best and 100 is the worst (table 1). This definition has been widely used in recent disease modification trials in rheumatoid arthritis such as the BeSt study, even though significant variations in the definition of disease duration exist. The time frame of early rheumatoid arthritis ranged up to 5 years in some studies. At this time, ‘early rheumatoid arthritis’ is defined as ≤6–24 months of symptoms. The median duration of symptoms at the time of enrolment in most early rheumatoid arthritis cohorts was 5–8 months. Very early rheumatoid arthritis has been defined with a maximum duration of symptoms of 12 weeks. Currently, the American College of Rheumatology and the European League Against Rheumatism are in the process of defining new criteria for rheumatoid arthritis that will allow earlier diagnosis and treatment of patients in both clinical practice and clinical trials.

**Defining early Crohn disease**
In the study by D’Haens et al., early Crohn disease was defined by the investigators as ‘a diagnosis within 4 years in patients who had not previously received corticosteroids, antimetabolites or biological agents’. This empirical definition did not take into account bowel damage or impaired gastrointestinal functioning. A definition that is more analogous to the American College of Rheumatology definition of early rheumatoid arthritis may better define an early disease population. Only patients with evidence of clinical and biological disease activity will be considered as having early active Crohn disease. The Crohn Disease Activity Index (CDAI) is a validated instrument which is used to measure disease activity in clinical trials. The cut-off value of 220 points is generally chosen to distinguish moderate to severely active Crohn disease. In a Scandinavian population-based study, the mean and median C-reactive protein (CRP) concentration at diagnosis were 51 and 33 mg/l (range 0–266 mg/l). A total of 25% of patients (44/176) had a CRP level below 10 mg/l at diagnosis. In order to limit the risk of including patients with symptoms related to functional disorders, a cut-off value of 10 mg/l seems reasonable. Because some patients may have
active Crohn disease with normal CRP concentrations despite abnormal small-bowel radiographic imaging. A significant endoscopic or radiological evidence (CT or MRI bowel enhancement) of disease activity can be included in the definition as an alternative to the CRP concentration cut-off value. Patients with large coalescent and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colorectum will be considered as having endoscopic evidence of active inflammation. When available, active disease may be detected by using faecal markers, such as faecal calprotectin or lactoferrin.

We propose that both paediatric and adult patients with Crohn disease can be included in the definition of early Crohn disease. First, about 10% of Crohn disease is diagnosed in childhood. Second, Crohn disease results in paediatric-specific complications such as growth failure and delayed puberty. Third, in a population-based study from France, disease complications were already present in 29% of children at diagnosis, and disease progression led to a cumulative incidence of disease complication of 59% during a median follow-up of 7 years with a cumulative incidence of surgery of 34% at 5 years from diagnosis. Overall, the consequences of Crohn disease can severely impair physical and social functioning (disability) in paediatric patients.

Patients with early Crohn disease should be naïve to drugs that are potentially disease-modifying. These drugs include azathioprine, 6-mercaptopurine, methotrexate, and biologicals, including corticosteroids, previously steroid-dependent with oral steroids or any treatment with intravenous steroids. Bowel damage, surgery, endoscopy procedures or impaired GI functioning will be necessary to demonstrate the presence of inflammation and the absence of complications in patients with early Crohn disease. While high-quality CT is available in almost all centres managing patients with Crohn disease, there is still a limited access to MRI. MRI is preferred when both techniques are available because of the risks of exposure to ionising radiation from serial CT examinations in patients with Crohn disease, especially those under the age of 35 years. Several studies now indicate that MRI is accurate for detecting disease activity and assessing disease severity in Crohn disease. In other cases, CT will be performed. In a Norwegian population-based study, at the time of diagnosis, 121 (61%) had non-stricturing non-penetrating disease, 55 (28%) had stricturing complications, and 24 (12%) had penetrating complications. In Olmsted County, Minnesota, USA, 19% of Crohn disease patients had already experienced penetrating or stricturing complications within the first 90 days of diagnosis, and fully half of all patients had experienced an intestinal complication 20 years after diagnosis. To be considered as early Crohn disease, patients should undergo gastrointestinal imaging, and no fistulas (including perianal fistulas), abscesses or strictures (defined as wall thickening and luminal narrowing with prestenotic dilatation—defined as a diameter greater than the normal diameter of the small bowel or colon) on CT or MRI is not allowed. No history of Crohn disease-related surgery (minor or major surgical procedures) is not allowed. No history of endoscopic balloon dilation of a stricture. Normal faecal continence, no previous or current use of oral or parenteral substitution (vitamins, minerals), no enteral or parenteral nutrition since diagnosis.

Table 1: Proposal for a definition of early Crohn disease and comparison with the definition of early rheumatoid arthritis by the American College of Rheumatology.

<table>
<thead>
<tr>
<th>Early rheumatoid arthritis</th>
<th>Criterion</th>
<th>Early Crohn disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease</td>
<td>Active disease</td>
<td>Crohn disease Activity Index (CDAI)–220</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate ≥28 mm/h or a global health score of ≥20 mm</td>
<td>C-reactive protein &gt;10 mg/l or significant endoscopic (large coalescent and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colorectum) or radiological evidence (CT or MRI bowel enhancement) of disease activity or positive faecal markers</td>
<td></td>
</tr>
<tr>
<td>Age ≥18 years</td>
<td>Age</td>
<td>No limit of age (both paediatric and adult patients can be included)</td>
</tr>
<tr>
<td>Immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate), biologicals, corticosteroids (previously steroid-dependent with oral steroids or any treatment with intravenous steroids)</td>
<td>No previous or current use</td>
<td></td>
</tr>
<tr>
<td>Bowel damage</td>
<td>Bowel damage</td>
<td>No fistula (including perianal fistulas), abscess, stricture (wall thickening and luminal narrowing with prestenotic dilatation—defined as a diameter greater than the normal diameter of the small bowel or colon) on CT or MRI</td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery</td>
<td>No history of Crohn disease-related surgery (minor or major surgical procedures)</td>
</tr>
<tr>
<td>Endoscopy procedures</td>
<td>Endoscopy procedures</td>
<td>No history of endoscopic balloon dilation of a stricture</td>
</tr>
<tr>
<td>Impaired GI functioning</td>
<td>Impaired GI functioning</td>
<td>Normal faecal continence, no previous or current use of oral or parenteral substitution (vitamins, minerals), no enteral or parenteral nutrition since diagnosis</td>
</tr>
<tr>
<td>Disease duration ≤2 years</td>
<td>Disease duration</td>
<td></td>
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</table>

The patient must fulfil all inclusion criteria without any exception. As a prerequisite, the previous diagnosis of Crohn disease has to be confirmed according to the criteria adopted by Lennard-Jones. When available, MRI is preferred.

*All 5-aminosalicylate formulations permitted (previous or current use).
†When available, MRI is preferred.
Crohn disease is shown in table 1.

...circumstance of very early Crohn disease (possibly very early rheumatoid arthritis).

...economic burden of the disease and attention should be given to developing a de...disease. However, in the future, consider—without including those with longstanding disease, particularly in clinical trials,...

...large randomised placebo-controlled trials, inclusion as early Crohn disease. Ideally, 1 year should be part of...2 years.43 44Ideally, 1 year should be part of the definition of early Crohn disease, when...< 2 years is more realistic and will allow the identification of a sufficient number of patients with early Crohn disease, particularly in clinical trials, without including those with longstanding disease. However, in the future, consideration should be given to developing a definition of very early Crohn disease (possibly ≤12 weeks, which is the definition used for very early rheumatoid arthritis).

... potentially disease-modifying in patients with Crohn disease. A Europe-wide population-based cohort showed that total and hospitalisation costs were much higher in the first year after diagnosis than in subsequent years.74 A Markov chain analysis of this Europe-wide population-based cohort revealed that surgery accounted for 68% of total healthcare costs in first year, rising to 90% after 6 years of follow-up.75 Clinical trials that identify therapies that change this clinical course are needed. Defining early Crohn disease is a prerequisite to undertaking such trials.

...Without stricturing or penetrating intestinal complications at diagnosis. No impairment of gastrointestinal function (normal faecal continence, no incontinence) is sufficient to exclude the patient from the definition of early Crohn disease). No requirement for oral or parenteral vitamin or mineral supplementation (ie, vitamin B12, folate, fat-soluble vitamins, etc), and no requirement for nutritional support (enteral nutrition supplementation or parenteral nutrition) since diagnosis. Iron supplementation for iron-deficiency anaemia due to gastrointestinal blood loss is acceptable for inclusion as early Crohn disease. As discussed above, future therapeutic goals for Crohn disease may include not only a reduction in bowel damage but also maintaining normal gastrointestinal physiology.7 Thus, in addition to absence of structural damage and surgical loss of bowel, patients with early Crohn disease should have a normal gastrointestinal function, which consists of normal faecal continence (history of only one episode of incontinence is sufficient to exclude the patient from the definition of early Crohn disease), no requirement for oral or parenteral vitamin or mineral supplementation (ie, vitamin B12, folate, fat-soluble vitamins, etc), and no requirement for nutritional support (enteral nutrition supplementation or parenteral nutrition) since diagnosis. Iron supplementation for iron-deficiency anaemia due to gastrointestinal blood loss is acceptable for inclusion as early Crohn disease.

...Crohn disease is a chronic progressive destructive disease. Approximately one-fifth of adult and paediatric patients already have evidence of a strictureing or penetrating intestinal complications at diagnosis. Effective intervention before the onset of bowel damage (stricture, fistula, abscess) is required to modify the clinical course of Crohn disease. Current molecular tools, such as genetic and serological markers, do not allow the identification of subclinical intestinal inflammation with accuracy. At present, the only way to define early Crohn disease is to use clinical, biological, endoscopic and radiological criteria.

...of overtreatment of patients with minimal or inactive disease on one hand and patients who already have irreversible complications on the other. Finally, such clinical studies will evaluate whether specific therapeutic regiments are cost-effective in the treatment of Crohn disease by improving quality of life, reducing hospitalisation, surgeries and other procedures (intestinal resection, stricturoplasty, diverting procedure, fistulotomy, fistulotomy, drainage of abscess, placement of seton(s)), and no history of any endoscopic balloon dilation of a Crohn disease stricture. For studies that have the primary aim of preventing bowel damage, as opposed to preventing both bowel damage AND maintaining normal gastrointestinal physiology (see below), it might be reasonable to consider including patients who have had a previous surgical resection and have recurrent inflammatory disease without strictures, fistulas or abscesses. However, such patients should not be designated as having early Crohn disease.

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...crohn disease. Similarly to rheumatoid arthritis,47 a disease duration <2 years is more realistic and will allow the identification of a sufficient number of patients with early Crohn disease, particularly in clinical trials, without including those with longstanding disease. However, in the future, consideration should be given to developing a definition of very early Crohn disease (possibly ≤12 weeks, which is the definition used for very early rheumatoid arthritis).

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interventions, and preventing both bowel damage (stricture, fistula, abscess) and impaired gastrointestinal physiology. 

Competing interests None.

Received 20 September 2008 Accepted 22 September 2009

Gut 2010;59:141—147. doi:10.1136/gut.2008.187120

REFERENCES


A 61-year-old man with abdominal pain for 6 months

CLINICAL PRESENTATION

This 61-year-old man presented complaining of a 6-month history of intermittent abdominal fullness and dull periumbilical pain. There were no obvious aggravating factors, no radiation and no vomiting. He noticed loose stool with increased frequency of defecation about three to four times per day unrelated to eating. There was no history of previous abdominal surgery. Physical examination revealed a soft abdomen with mild distention. The initial laboratory data, including amylase, lipase and haemogram, were within normal limits. Plain abdominal radiography revealed focal dilated bowel gas over left upper quadrant. Abdominal computed tomography (CT) (figure 1) was performed. Then he was referred to our hospital for further evaluation.

Figure 1 Two cross-sectional computed tomography (CT) images.

QUESTION

What is your diagnosis?

See page 185 for the answer.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Gut 2010;59:147. doi:10.1136/gut.2009.178616