

Endpoints for Clinical Trials Evaluating Disease Modification and Structural Damage in Adults with Crohn's Disease

Geert R. D'Haens, MD,* Richard Fedorak, MD,[†] Marc Lémann, MD,[‡] Brian G. Feagan, MD,[§] Michael A. Kamm, MD,[¶] Jacques Cosnes, MD,^{||} Paul J. Rutgeerts, MD,** Philippe Marteau, MD,^{††} Simon Travis, MD,^{‡‡} Jürgen Schölmerich, MD,^{§§} Steven Hanauer, MD,^{¶¶} William J. Sandborn, MD^{|||} and the IOIBD Membership

Abstract: The management of Crohn's disease is rapidly changing. The advent of potent immunomodulatory and biologic therapies has led to more demanding endpoints for clinical trials than only clinical response and remission. Complete withdrawal of corticosteroids, healing of endoscopically visible lesions, and prevention of structural damage are only a few new endpoints that are finding their way into the clinical trials of today and those that are being developed for the future. Given the importance of selecting the most appropriate and relevant endpoints, the International Organization for Inflammatory Bowel Diseases (IOIBD) decided to develop guidelines that could be used by individual researchers, the pharmaceutical industry, and the regulatory bodies. The current document is to be read as a "position paper," which is the result of several years of discussion and consensus finding that was finally approved by the entire membership of the group. The proposed instruments will need further validation and standardization to demonstrate that they are reliable in stable disease and responsive to change, and to determine the cutoff points for response and remission.

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Key Words: endpoints, clinical trials, disease modification, structural damage, Crohn's disease

Crohn's disease (CD) is a chronic, systemic disorder in which immune mediated inflammation of the gastrointestinal tract manifests as mucosal ulceration and transmural inflammation,^{1,2} which are diagnosed using colonoscopy,

mucosal biopsy, and radiological tests (small bowel x-ray, computed tomography [CT] enterography, and magnetic resonance imaging [MRI] enterography). In the early phase of CD, the disease pathology is predominantly inflammatory and can relapse and remit, resulting in intermittent symptoms of diarrhea and abdominal pain.³ In the late phase of CD the disease pathology includes complications such as stricture, perforation, and fistula formation that often need surgical treatment.⁴ Following surgical resection, recurrence of CD is virtually inevitable.⁵ Thus, the natural history of CD over the longer term can be characterized as chronic, progressive, and destructive, eventually leading to irreversible structural damage to the bowel. CD is often a disabling and painful condition, which can lead to substantial loss of intestinal function due to structural damage to the bowel and surgical resection. Examples of loss of intestinal function include bile salt diarrhea, steatorrhea, vitamin and mineral deficiencies, anemia, short bowel syndrome with dehydration and malnutrition, stoma, and loss of continence.

Various treatments for CD are available including glucocorticosteroids, immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate), and biologic agents (infliximab, adalimumab, certolizumab, natalizumab) that also have immunomodulatory properties.^{6,7} Steroids are inductive agents that mainly suppress the symptoms and immunosuppressives are maintenance agents that prevent symptom recurrence. Biologics are both inductive and maintenance agents. Disease-modifying anti-CD drugs (DMACDs) are drugs that would reverse the disease process and prevent long-term structural damage and surgical resection, thereby preventing loss of intestinal function. Immunosuppressives and biologics have the potential for DMACD activity, but few clinical trials have been performed that have disease modification and prevention of structural damage as endpoints. The available medications are primarily directed against inflammatory processes. As patients progress from inflammation with no luminal narrowing to inflammatory luminal narrowing that may be reversible to fibrosis with stricture that is not reversible, a challenge will be to identify patients for DMACD therapy who do not yet have irreversible changes, as no medications have been shown to reverse fibrosis.

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From the *Imelda GI Clinical Research Ctr, Bonheiden, Belgium, [†]University of Alberta, Canada, [‡]Hôpital St Louis, Paris, France, [§]Robarts Clinical Trials Centre, London, Ontario, Canada, [¶]St Vincent's Hospital, University of Melbourne, Australia, ^{||}Hôpital St Antoine, Paris, France, ^{**}University of Leuven, Belgium, ^{††}Lariboisière Hospital, Paris, France, ^{‡‡}Radcliffe Infirmary, Oxford, UK, ^{§§}University of Regensburg, Regensburg, Germany, ^{¶¶}University of Chicago Hospitals, Chicago, USA, ^{|||}Mayo Clinics, Rochester, USA.

Reprints: Geert R. D'Haens, MD, Imelda GI Clinical Research Center, Imeldalaan 9, 2820 Bonheiden, Belgium (e-mail: geert.dhaens@imelda.be)

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MATERIALS AND METHODS

The goal of this review is to propose potential endpoints for clinical trials that evaluate disease modification and structural damage in patients with CD. Several versions of the article were discussed at the International Organization of Inflammatory Bowel Disease (IOIBD) meetings in 2006, 2007, and 2008, leading to consensus and approval of these recommendations by the whole membership.

RESULTS

Natural History of CD

The natural history of CD has been described in both population-based and referral center cohort studies, although evolutions in therapy, practice guidelines, and environmental conditions likely have a substantial influence on the natural history of the disease. One population-based incidence cohort study reported on the year-by-year clinical activity of the disease over a 25-year period. After year 1, over a 5-year period of follow-up, $\approx 25\%$ of patients had continuously active disease, 53% had relapses and remissions, and 22% was continuously in remission.³ Subgroups of patients can be defined based on disease location,⁸ disease behavior,⁹ or a combination of age at diagnosis, disease location, and disease behavior.^{10,11} Disease *location* has been studied longitudinally and only limited changes were observed.¹² In contrast, the *behavior* of CD in the majority of patients changed from purely inflammatory to fibrostenotic (stricturing) and/or fistulizing (internal fistulas and abscesses) disease, suggesting that these latter disease phenotypes were merely complications of chronic inflammation.^{12–14} These complications developed more frequently in patients with ileal or ileocolonic disease than in patients with colonic disease only, and usually required surgical resection.^{13,14}

Following surgical resection, a majority of patients will have postoperative recurrence of CD. Endoscopic postoperative recurrence of CD occurs in 50%–75% of patients at 3 months and in 50%–90% at 12 months after surgery.^{5,15–17} The severity and extent of endoscopic lesions are predictive of the subsequent clinical disease course.⁵ Patients with no lesions or only a few aphthous ulcers in the neoterminal ileum have a low risk for early symptomatic clinical recurrence, whereas more than half of patients with diffuse ileitis or ulcerative ileitis will have symptomatic recurrence within 1–3 years. Clinical postoperative recurrence of CD is observed in 10%–20% of patients per year,^{18,19} and can occur as early as 3 months after surgery.¹⁵ Many patients will require additional surgical resections and reoperation rates at 10 years have varied from 16%–65%.^{4,20,21}

Factors That May Predict the Natural History of CD

Given that complications of CD often arise after years of disease, it has been difficult to demonstrate that

specific environmental factors and/or therapeutic interventions alter the natural history of the disease. Older series have suggested a negative impact of smoking on the disease course, in particular on the occurrence of postoperative recurrence in female patients.²² In a retrospective study by Beaugerie et al,²³ several clinical factors were associated with a more severe disease course. These included young age, need for corticosteroid therapy, and perianal disease at diagnosis. Based on a scoring system that incorporated these items, 85% of the patients were classified with disabling disease. A potential explanation for this observation is that these patients were treated at a tertiary care center. Nevertheless, these associations have been independently confirmed by Loly et al²⁴ in Liège, who then defined a more restrictive category of “severe disease.” Severe CD was defined as the development of complex perianal disease, any colonic resection, 2 or more small bowel resections, or the construction of a stoma within 5 years of diagnosis. The prevalence was 37% and stricturing behavior or loss of weight >5 kg at diagnosis were independently associated with the time to development of severe disease. Munkholm et al⁴ reported an increased mortality in patients with extensive (>100 cm) small bowel disease. Franchimont et al²⁵ demonstrated an increased risk of corticoid dependency in cigarette smokers with colonic, nonfibrostenotic disease and a young age at diagnosis. Lichtenstein et al²⁶ observed a higher incidence of obstruction due to stenosis in patients with ileal disease, a severe disease course and treatment with corticosteroids. Taken together, these studies suggest that certainly young age and presence of perianal disease are associated with a poor prognosis. However, the cutoff for age (40 years) should be questioned, since the majority of patients with CD are diagnosed before the age of 40 and the selection of this cutoff point was probably influenced by the Vienna Classification.¹⁰

In addition, a number of genetic parameters (HLA DRB1 0103), serologic markers, immune response measurements or combinations of these biologic factors (e.g., Card8 + anti-Omp C associated with internal perforating disease) may be relevant markers associated with worse prognosis.²⁷ The time to onset of a clinically relevant stricture has been associated with the number of CARD15 variants.²⁸ Patients with CARD15 mutations were also more likely to require surgical resection.^{29–31} Ferrante et al³² demonstrated a higher frequency of debilitating disease if a higher number of serological markers were abnormal (gASCA, AMCA, ALCA, ACCA, Omp C).

Proposed Definitions of Disease Modification in CD

Disease modification of CD is defined as reversal of mucosal and transmural inflammation, thereby preventing

structural damage (strictures, fistulas, abscesses) and surgical resection, with the goal of preventing loss of intestinal function.

In the early phase of CD, the disease pathology is predominantly inflammatory with mucosal ulceration and transmural inflammation without major tissue destruction in the deeper layers. Complications of irreversible stricture formation, fistulas, or abscesses are characteristic of the late phase of the disease. The symptoms resulting from inflammation are diarrhea and abdominal pain, and can relapse and remit.³ A minority of patients present with the late phase of CD in which complications are already present at diagnosis. In most instances these patients require surgical resection. It is logical to believe that sufficient control of inflammation in the earliest phase of CD will reduce the number of relapses (sustained remission) and thereby prevent complications and surgical resection, although it is possible that structural damage might be self-propagating in some patients despite sufficient control of inflammation. Some patients in symptomatic remission will experience silent disease progression that manifests suddenly as complications of stricture, fistula, or abscess and leads to surgical resection. Continued myofibroblast proliferation after initiation by inflammation might explain this phenomenon. In this event, inhibition of fibrogenesis might be an important therapeutic target in CD that has received relatively little attention. Alternatively, these patients with disease progression despite symptomatic remission might have evidence of active inflammation if they were evaluated with ileocolonoscopy and biopsy and/or CT or MRI enterography.

An epidemiological study reported that mucosal healing after 1 year of medical treatment was predictive of reduced subsequent disease activity and the need for anti-inflammatory therapies. Moreover, treatment without corticosteroids was predictive for mucosal healing.³³ Mucosal healing has recently been introduced as a treatment goal for CD. An endoscopic substudy of a maintenance trial of the biologic agent infliximab reported that patients with mucosal healing had a lower likelihood of needing surgeries and hospitalizations.³⁴

Potential Endpoints for Disease Modification Studies

Sustained Clinical Remission

The majority of clinical trials analyze the proportion of patients with clinical response or clinical remission at a prespecified timepoint and, less frequently, time-to-relapse. Recently, a number of studies have defined co-primary endpoints with assessment of response or remission at 2 timepoints, e.g., weeks 6 and 26, weeks 26 and 56, or weeks 30 and 52.^{35–37} A very rigorous extension of this

analysis is sustained response and remission over 48 weeks.³⁸ It is our opinion that clinical remission should include the absence of corticosteroid maintenance therapy, as was recently done in a GETAID trial by Lémann et al³⁹ and in the SONIC trial.⁴⁰ A potential weakness of this approach is the relatively poor definition of response and remission with both the CD activity index and the Harvey-Bradshaw score (HBI), the 2 indices that are most commonly used in clinical trials for CD and the variability in the use of these instruments.

Hospitalization

Patients with CD may be hospitalized for severe flares or complications of CD. Hospitalization endpoints for clinical trials can include measurement of the rate of hospitalization and the time to hospitalization.^{34,41,42} However, different countries and different practices vary widely in their criteria and eligibility for hospitalization, and hospitalization is often a negotiated event between a physician and a patient. It is unknown how reproducible or responsive this endpoint is. In theory, variance might make it difficult to achieve statistical significance, although, as discussed above, it has been possible to achieve statistical significance in several clinical trials.^{34,41,42}

Mucosal Healing

In spite of circumstantial evidence it is still unclear whether mucosal healing prevents the development of complications.^{33,34,43,44} Mucosal healing does not necessarily equal absence of active inflammation, but it is likely a useful surrogate endpoint to evaluate antiinflammatory activity of medications. It can presently be evaluated using standard endoscopy or capsule endoscopy but a clear definition of mucosal healing is still lacking. The interobserver reproducibility to diagnose specific lesions is a limit in the evaluation and the endoscopic disease activity scores therefore consider only the lesions with the best interindividual agreement (various ulcers, stenosis, and surface-extension of each lesion). The French GETAID group developed the CDEIS score⁴⁵ and defined cutoff values for endoscopic response and remission.⁴⁶ The SES-CD score is a validated simplification of this score, but the cutoff value for endoscopic remission has not been defined.⁴⁷ An endoscopic substudy of a maintenance trial of the biologic agent infliximab used the absence of ulcers as an endpoint.^{34,44} A recent observational study reported that patients with absence of endoscopic lesions after 2 years of early combined immunosuppressive therapy or conventional management had a clinically superior outcome with fewer relapses, less use of corticosteroids, and less anti-TNF (tumor necrosis factor) treatment during the 2 years thereafter than patients with persistent endoscopic lesions.⁴⁸ Overall, most data suggest that mucosal ulcers are associated with symptoms

and complications, but further investigation appears necessary.

Furthermore, effective treatment should not only focus on healing mucosal lesions, but rather on the entire thickness of the intestinal wall. Several techniques have been used for the assessment of bowel wall changes including MRI, CT-enteroclysis, and ultrasound. None of these tools have been validated as of today and none have been used longitudinally in clinical trials, with the exception of an MRI score that was developed for the follow-up of patients with fistulizing CD treated with infliximab.⁴⁹

Prevention of Complications

Complications include strictures and bowel perforation (fistula and/or abscess). There are 2 potential approaches that can be taken to demonstrate prevention of complications: 1) reduction in the number of defined complications that a patient develops during a defined period of time; and 2) time until 1 or more complications occur. In a controlled trial comparing early combined immunosuppression with conventional management, significantly less fistulizing complications developed in the first group.⁴⁴

There are several challenges with the use of this endpoint. Usually, the event rate over a limited period of time (for instance 1–2 years) is relatively low. Thus, it may be difficult to distinguish random variation from disease progression and damage. Furthermore, consensus definitions on the different types of complications and the methods to measure them are lacking. As a consequence, these approaches to the assessment of disease modification have not yet been used in controlled trials so far.

Surgical Resection

Multiple series have demonstrated that the majority of patients with CD will have some surgical intervention during their lifetime, and that the majority of those operated patients will require a second surgical intervention at some stage. These surgical interventions may be for luminal or fistulizing disease. Such surgical interventions serve as “hard” endpoint, although the indication and need for surgery will vary between centers and will contain a subjective element. Surgical resection endpoints for clinical trials can include measurement of the rate of surgical resection, extent of resection, and the time to surgical resection.^{34,41–43}

Composite Endpoints

The endpoint that would most closely reflect normal gastrointestinal tract health would be sustained remission without corticosteroids with mucosal (and transmural?) healing and the absence of complications and surgical resection. This endpoint has not been used routinely in clinical trials and has not been validated, but most of the components have been used reliably and have been vali-

dated individually. It may require clinical trials exceeding the present observation periods of 6 or 12 months.

Two recent clinical trials have introduced a composite endpoint as the primary endpoint. The SONIC trial⁴⁰ compared azathioprine monotherapy, infliximab monotherapy, and combination therapy with infliximab and azathioprine in patients with active CD who were naïve to both agents. The primary endpoint was a composite of clinical remission and a steroid-free state at week 26. A secondary endpoint was “mucosal healing” defined as the absence of ulcers. The COMITT trial (Feagan et al, submitted) compared infliximab monotherapy and combination therapy with infliximab and methotrexate in patients with active CD who were receiving induction therapy with steroids. The primary endpoint was a composite of clinical remission and a steroid-free state at week 14 and the absence of clinical relapse thereafter up to 52 weeks.

Bowel Damage (Structural Damage) Scores

The development of quantitative scores that can be used longitudinally, reflect the extent and severity of mucosal and transmural disease, the development of complications, and the amount of surgically resected bowel is currently ongoing. The general approach is combined colonoscopy and CT enterography or MRI enterography. One early version of a bowel damage score demonstrated good correlation with fecal fat and fecal weight.⁵⁰

Anal Sphincter Damage

The extent to which sphincter damage is permanent in patients with perineal fistulizing CD remains to be determined. Such an evaluation may require assessment of external skin damage, deep muscle damage to the internal and external sphincter muscles (either through the disease process or through surgical intervention), and assessment of sphincter function (such as manometric assessment). Such assessments require longitudinal evaluation and validation. A validated index for the assessment of perianal damage and fistulizing disease is needed.

DISCUSSION

Historically, the management of CD has focused on induction and maintenance of symptomatic response and remission. The natural history of CD under such a treatment strategy has been to progress from primarily inflammatory disease in the early phase to complications of stricture, fistula, and abscess that require surgery in the late phase. Ultimately, many patients experience a loss of intestinal function due to structural damage and surgical loss of bowel.

This observation prompted investigators to begin to use additional measures beyond the validated instruments that measure clinical disease activity (the CDAI and the HBI). One of these evolving endpoints that would appear

to be clinically meaningful is the “complete withdrawal of steroids,” given that many patients become steroid-dependent and steroid dependency is associated with significant toxicity. Another evolving endpoint that is also of interest is mucosal inflammation and ulceration and the subsequent disappearance of ulcers, which has been called “mucosal healing.” Preliminary data suggest that this endpoint is also clinically meaningful because it has been associated with a reduction in the rates of hospitalization and surgery. More studies are needed to further evaluate the concept of “transmural healing” (defined with CT or MRI enterography) and its relationship to mucosal healing (defined with ileocolonoscopy). The use of these modalities in patients who are clinically asymptomatic may give clues as to why some patients develop strictures despite the absence of symptoms.

Other evolving disease modification endpoints include the incidence and prevention of hospitalization, the prevention of intestinal complications (stricture, fistula, abscess), the prevention of surgery, and reduction in anal sphincter damage. Before these evolving endpoints can be used as the primary measure of efficacy in large clinical trials, further development and validation of consensus definitions and determination of definitions of clinically meaningful “change” and “remission” will need to be performed.

This article is intended to raise awareness of these issues and to stimulate stakeholders including clinicians, regulatory bodies, and industry to work together to standardize and harmonize new endpoints for clinical trials in patients with CD that are highly clinically meaningful and can positively impact the natural history of the disease.

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