Implementing changes in clinical practice to improve the management of Crohn’s disease

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**KEYWORDS**
Corticosteroids
Crohn’s disease
Immunomodulators
Optimized monitoring
Treatment optimization

**Abstract**
The introduction of anti-tumour necrosis factor therapies has provided highly effective treatments for Crohn’s disease, making it possible to significantly improve the prognosis of patients. However, neither conventional non-biological therapies nor anti-tumour necrosis factor therapies are routinely used to optimum effect. There are several reasons for this, including a lack of specific evidence to guide common clinical questions and a lack of clearly defined treatment targets. This paper suggests some simple changes to the management of Crohn’s disease that have the potential to significantly improve patient outcomes. A new treatment target, ‘deep remission’, which includes mucosal healing as well as clinical remission, may be the first step in defining the successful treatment of Crohn’s disease; early clinical studies have demonstrated that this is a readily achievable target. Initiating appropriate treatment early can increase clinical remission rates, improve steroid sparing, induce mucosal healing and prevent structural bowel damage, whereby reducing the need for hospitalization and surgery. There are also clear indications that modifying treatment based on regular objective assessments of disease activity to provide tight disease control can improve patient outcomes in a similar way to that observed in rheumatoid arthritis. These simple changes to management strategy appear to allow the full potential of available treatments to be realized. Clinical studies to further define optimized treatment strategies for Crohn’s disease are underway and will provide future direction.

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1. Introduction
Crohn’s disease (CD) is characterized by inflammation that may affect any part of the gastrointestinal tract. Chronic uncontrolled inflammation can lead to the development of complications such as stenoses and fistulas, resulting in irreversible structural bowel damage which is not amenable to medical therapy. Such damage is often associated with the need for surgical removal of segments of bowel. Even during periods of clinical remission subclinical inflammation may persist, largely unrecognized, increasing the risk of complications. This disconnect between symptoms and the presence of inflammation needs to be recognized by treating physicians, and periodic re-evaluation of disease activity should be conducted routinely. It is hoped that by completely controlling inflammation in a timely manner using appropriate therapy it will be possible to improve prognoses by minimizing complications and bowel damage and thereby changing the course of the disease.\textsuperscript{1} Such a 'treat-to-target' approach, in which treatment is modified according to regular objective measurement, has proved successful in other chronic diseases with parallels to CD

**Abbreviations:** Anti-TNF, anti-tumour necrosis factor; CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index of Severity; CRP, C-reactive protein; DBE, double balloon enteroscopy; HBI, Harvey–Bradshaw index; IL, interleukin; MRI, magnetic resonance imaging; SES-CD, Simple Endoscopic Score for Crohn’s Disease; TNF, tumour necrosis factor.

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CD were first published over 30 years ago,\textsuperscript{11,12} and their efficacy in CD has been confirmed in Cochrane systematic reviews of controlled studies.\textsuperscript{13,14} However, once remission has been achieved the goal is to maintain steroid-free remission. Despite inducing remission in most patients, a prolonged response to corticosteroids is observed in less than half of all patients.\textsuperscript{15} More importantly, corticosteroids are associated with substantial toxicity and should not be continued long term.\textsuperscript{14,16,17} Furthermore, it has been shown that corticosteroids induce mucosal healing in only 29\% of patients achieving clinical remission.\textsuperscript{12}

To induce remission in active CD, most studies of systemic corticosteroids have used doses of 40–60 mg or 1 mg/kg prednisolone (or equivalent) for 1–3 weeks, followed by different tapering regimens. Prolongation of treatment at full dose in those with ongoing symptoms does not improve remission rates\textsuperscript{18} and, as the risk of side effects increases with cumulative doses of corticosteroids, continued treatment beyond 1–3 weeks does not appear to be justified. Thus, corticosteroids alone are inadequate for achieving the proposed treatment goal of deep remission and should normally be supplemented with, and ultimately replaced by, immunomodulators early in the treatment course.

2.2. Which immunomodulator regimen should be used and when?

It is important to optimize an immunomodulator regimen soon after diagnosis to achieve mucosal healing and prevent disease progression. Therefore target dosing should be achieved quickly; this can be aided by obtaining a patient’s thiopurine methyltransferase genotype and phenotype, as well as measuring thiopurine metabolite concentrations. In addition, immunomodulators decrease the need for steroid exposure and are able to achieve long-term corticosteroid-free remission in a proportion of patients.

A better understanding of the underlying pathophysiology of CD has resulted in more frequent use of immunomodulators, such as azathioprine, mercaptopurine and methotrexate. However, the increase in immunomodulator usage in CD was not accompanied by a decrease in the percentage of patients developing complications or requiring surgical resection.\textsuperscript{19} The lack of association between thiopurine use and a decreased need for surgery in one survey has been attributed to immunomodulation not being introduced soon enough after diagnosis, rather than an inability of the drugs to modify CD natural history. Indeed, Cosnes et al. reported that only 9\% of patients treated with azathioprine had received it for long enough for an effect to have been observed before undergoing surgery.\textsuperscript{19} A more recent population-based cohort showed marked changes in the rates of surgery that are associated temporally with increased and earlier thiopurine use.\textsuperscript{20} Furthermore, early initiation of immunomodulator treatment in children has been shown to lessen the need for prednisone and improve maintenance of remission compared with controls.\textsuperscript{21} However, similar evidence is lacking for adults.\textsuperscript{22}

Evidence to guide the choice of immunomodulator is also limited. In the only randomized study directly comparing 6-mercaptopurine and methotrexate in steroid-dependent patients, both drugs were effective at steroid-sparing and achieving and maintaining remission.\textsuperscript{23} Remission rates

2.1. When should we introduce corticosteroids and for how long?

High quality studies showing that corticosteroids were effective at inducing clinical remission in patients with
at 30 weeks were significantly (p < 0.01) higher with 6-mercaptopurine (93.7%) than with methotrexate (80%). There is a need to continue immunomodulator maintenance treatment as long as it is efficacious and well tolerated. It has been demonstrated that withdrawal of azathioprine from patients in clinical remission after 3.5 years tripled the relapse rate compared with continued azathioprine treatment (21% versus 8%). Similarly, a high relapse rate was observed when azathioprine was discontinued in patients in clinical remission who had been receiving azathioprine for a median of 68.4 months. Fortunately, however, patients generally respond well to re-treatment with azathioprine if they relapse, with the proportion of patients achieving remission and receiving <10 mg prednisone over 12 months among patients receiving a second course of azathioprine being similar to that among those receiving their first course. However, the potential benefit of early initiation of immunomodulators must be weighed against the possibility of an increased risk of side effects, such as infections and malignancies.

### Table 1  Questions answered in the IBD Ahead programme

<table>
<thead>
<tr>
<th>Questions/answers</th>
<th>% Agreement at international meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When should we introduce corticosteroids, and for how long?</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids are best used for moderately to severely active CD of any location. Their use in isolated perianal CD is not supported.</td>
<td>100%</td>
</tr>
<tr>
<td>Budesonide is preferred to systemic corticosteroids for mildly to moderately active ileocaecal disease and right colonic disease, but is not universally available. In countries where budesonide is not available, early introduction of immunomodulators (and/or anti-TNF therapy) for their corticosteroid-sparing properties is appropriate.</td>
<td>100%</td>
</tr>
<tr>
<td>The duration of initial treatment with systemic corticosteroids at full dose depends on the response of the patient. There is no clear evidence that continuing the full dose (40–60 mg prednisone or equivalent) beyond weeks 1–3 influences remission rates. Patients who do not respond within 2–4 weeks had best be further investigated and other therapeutic options considered.</td>
<td>100%</td>
</tr>
<tr>
<td><strong>What is the best dosing strategy for the use of corticosteroids?</strong></td>
<td></td>
</tr>
<tr>
<td>The optimal initial dose of oral systemic corticosteroids in Crohn’s disease ranges from 40–60 mg/day to 1 mg/kg/day. For intravenous hydrocortisone, the optimal starting dose is 300–400 mg/day.</td>
<td>94%</td>
</tr>
<tr>
<td>The optimal starting dose of budesonide is 9 mg/day.</td>
<td>94%</td>
</tr>
<tr>
<td>Tapering of corticosteroids is generally initiated within a week of starting therapy, and after no more than 3–4 weeks. There are no trials assessing different tapering regimens, and ‘standard’ regimens differ amongst centres. A reasonable approach is to reduce the dose by 5 mg/week, tapering to zero over 8 weeks (from an initial dose of 40 mg/day). Treatment should not exceed 12 weeks except in exceptional circumstances. Early introduction of immunomodulators or anti-TNF therapy is appropriate.</td>
<td>94%</td>
</tr>
<tr>
<td>No data are available to allow evaluation of any benefit of intentional dose escalation of corticosteroids.</td>
<td>94%</td>
</tr>
<tr>
<td>Systemic corticosteroids and budesonide are ineffective as maintenance therapy. It is strongly recommended to taper all corticosteroids to zero and switch appropriate patients to immunomodulator (or anti-TNF) therapy.</td>
<td>94%</td>
</tr>
<tr>
<td>Corticosteroids have been shown to increase the risk of serious, opportunistic infections and mortality, both independently or in combination with immunomodulators and anti-TNF agents.</td>
<td>94%</td>
</tr>
<tr>
<td>The best way to prevent corticosteroid-induced side effects is to avoid prolonged or repetitive use and to switch appropriate patients to immunomodulator therapy and/or anti-TNF therapy. Surgery is an appropriate option for some patients demonstrating corticosteroid dependency and could be considered.</td>
<td>94%</td>
</tr>
<tr>
<td>To prevent corticosteroid-induced loss of bone mineral density, calcium and vitamin D supplements should be provided. Clinicians treating with corticosteroids should familiarize themselves with local guidelines in managing corticosteroid-induced metabolic bone disease.</td>
<td>94%</td>
</tr>
<tr>
<td>Not all corticosteroid-induced side effects occur dose- or time-dependently</td>
<td>94%</td>
</tr>
<tr>
<td><strong>How early should immunomodulators be introduced and which regimen should be used?</strong></td>
<td></td>
</tr>
<tr>
<td>Initiation of immunomodulators (± anti-TNF therapy) early in the disease course (often within a week or two of diagnosis) should be considered for patients with severe disease, paediatric patients and for patients at high risk of progression to disabling disease.</td>
<td>89%</td>
</tr>
<tr>
<td>It is generally appropriate to start thiopurines or methotrexate in immunomodulator-naïve patients who have a relapse, are corticosteroid-dependent, or who need repeated courses of corticosteroids. This may include patients who need two or more courses of corticosteroids within 12 months; who relapse as the corticosteroid dose is tapered below 15 mg; or who relapse within 3 months of stopping corticosteroids. These limits are arbitrary, but serve as guidance for clinical practice. The aim is to withdraw corticosteroids completely.</td>
<td>89%</td>
</tr>
<tr>
<td>Thiopurines are currently indicated for postoperative prophylaxis immediately after surgical resection of ileocolonic disease. This is true in patients with high risk of recurrence; in the other patients thiopurines should be introduced if there is evidence of recurrence at 6–12 months.</td>
<td>89%</td>
</tr>
</tbody>
</table>
3. Early treatment

Although the rate of surgery within 5 years of a CD diagnosis has reduced significantly over the last 50 years, the reduction is not as great as the increase in the prescription of immunomodulators and biological therapies. The clinical features of CD change over time, with a decreasing frequency of purely inflammatory disease and an increasing frequency of stricturing and/or penetrating disease leading to the need for surgery. Accordingly, in order to change the course of the disease, disease-modifying treatments must be prescribed early in the course of CD, before complications occur. There is thus a small ‘therapeutic window of opportunity’ for early intervention in CD during which treatment can prevent the development of bowel damage (Fig. 1). Such a strategy has proven highly successful in the treatment of rheumatoid arthritis, a chronic progressive disorder with obvious parallels to CD.

There is now increasing clinical evidence to support the hypothesis that early treatment improves outcome in CD. A sub-analysis of the CHARM (Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) study showed that disease duration had a significant effect on the likelihood of achieving remission. Remission rates were higher in patients receiving adalimumab within 2 years of being diagnosed with CD than those in patients diagnosed >5 years ago (51% vs 35% at Week 54). Similarly, in the Step Up, Top Down Study, despite similar exposure to thiopurines by the end of the study, mucosal healing rates were higher with early anti-TNF therapy than with conventional step-up therapy. The importance of this was highlighted in patients from an endoscopic cohort of this study in whom complete mucosal healing at 2 years was predictive of steroid-free remission at 3 and 4 years. More recent studies have also demonstrated that early treatment with anti-TNF therapy is associated with sustained steroid-free remission and complete mucosal healing. In the EXTEND (EXTend the safety and Efficacy of adalimumab through eNDoscopic healing) study, mucosal healing at 12 weeks was significantly greater among patients with early disease (44% vs 21% for disease duration of <2 years and ≥5 years, respectively). Thus, the data available to date suggest that introducing biological therapy early increases the chances of attaining deep remission and improves patient outcomes; additional studies are underway that will further our understanding.

Figure 1 Early treatment is needed to change the disease course in RA. (Adapted from Kirwan 1999 with permission from the author and Journal of Rheumatology.) There is increasing evidence that this strategy of early intervention can prevent the development of bowel damage and improve outcome in CD.

Figure 2 Targeting early CD to optimize outcome.

However, the identification of patients with early CD in clinical practice remains a challenge since no formal definition exists. An international consensus was established to develop a formal definition of early CD. The agreed definition was a disease duration <18 months in the absence of the use of disease-modifying agents (immunomodulators, biological therapy). General acceptance of such a definition will help widespread use of an optimized treatment strategy, such as that illustrated in Fig. 2, to improve outcomes in CD.

4. Monitoring disease activity in CD

If ongoing inflammation is associated with poor outcome then it is logical that, in order to alter the disease course in CD, it is necessary not only to induce, but also to maintain, deep remission. A lack of symptoms does not necessarily indicate a lack of inflammation and it is, therefore, important to conduct regular monitoring using objective measures to drive treatment decisions and to ensure that this goal is achieved. Such tight disease control has been highly successful in improving patient outcomes in diabetes and rheumatoid arthritis. This is discussed in more detail in the preceding paper of this supplement.

Monitoring is essential at all stages of CD management; at presentation to obtain a quick diagnosis and determine disease location and severity; in symptomatic patients to determine the stage of disease and optimize treatment; in asymptomatic patients to ensure that inflammation is controlled and mucosal healing is achieved; and in postoperative patients to detect early disease recurrence or complications.

The IBD Ahead 2011 programme addressed key areas of uncertainty in order to help optimize monitoring in CD, providing recommendations regarding which monitoring tools should be used and how often [data on file].

4.1. Symptom assessment

Several assessment tools are available for evaluating IBD symptoms, including the CD activity index (CDAI) and Harvey-Bradshaw index (HBI), but these are often not used routinely in clinical practice. Routine baseline symptom assessment using standard tools would provide values against which treatment effects can be gauged. Measurements are best repeated at 2–4 weeks after initiating corticosteroids,
3–6 months after initiating immunosuppressive therapy, or 8–12 weeks after initiating biological therapy to establish therapeutic response, and then reassessed every 3–6 months as part of a comprehensive approach to assess remission and ensure ongoing response to treatment.

4.2. Endoscopy and imaging

Endoscopy is required for all patients at baseline to confirm the diagnosis and establish disease location, extent and severity. Since mucosal healing is a key treatment goal, gold standard assessment of ongoing disease activity and therapeutic response requires endoscopic evaluation. However, due to the invasive nature of endoscopy, repeat assessments are not recommended unless they are needed to aid therapeutic decisions, e.g. in patients with persistent or recurrent symptoms despite therapy.

Since the introduction of The Simple Endoscopic Score for Crohn’s Disease (SES-CD), it is relatively easy to record endoscopic findings and quantify changes in the extent of tissue damage. The SES-CD has a strong correlation with the Crohn’s Disease Endoscopic Index of Severity (CDEIS), good reproducibility and is an easy-to-use endoscopic scoring system for CD. The SES-CD can correlate with CDAI, HBI and serum CRP level, although precise correlation is neither necessary nor desirable, since it would make one of the assessments redundant.

Endoscopy is best supported by imaging, such as magnetic resonance imaging (MRI) enterography or ultrasonography (computed tomography scanning is being used less frequently because of the associated radiation risks), to ensure that the disease is completely assessed and to rule out the presence of complications such as fibrostenosing or penetrating disease. MRI variables have been validated for the diagnosis of active CD and severe CD and a quantitative index of activity (that correlates with CDEIS) was developed to facilitate objective assessment interpretation of MRI results. This means that accurate assessments can be made using MRI rather than repeating invasive, unpleasant endoscopic procedures.

4.3. Laboratory markers

Laboratory investigations can provide an indication of disease activity and the level of inflammation to facilitate treatment decisions. A range of serum and faecal biomarkers of inflammation have been investigated, with C-reactive protein (CRP) and faecal calprotectin currently being used most commonly. Regular monitoring of faecal calprotectin can provide advanced warning of an impending clinical relapse allowing pre-emptive treatment adjustments to be made, and quantification of mucosal TNF-alpha can identify those patients most likely to achieve long-term remission with anti-TNF therapy.

4.4. Role of endoscopy in daily clinical practice: example from Japan

Endoscopy is key to the monitoring of CD. It allows assessment of the extent and severity of disease, aids treatment decisions and can detect signs of progression. One study, conducted at Keio University Hospital, evaluated the use of endoscopy over 5 years in 166 patients receiving anti-TNF therapy [Hibi et al., unpublished data]. It showed that, despite endoscopy being the best means by which to assess the therapeutic effect of anti-TNF therapy, only 26.7% of patients underwent endoscopy within 1 year after starting anti-TNF treatment. The main reasons for a follow-up endoscopy not having been performed included reluctance of patients to consent to endoscopy, disappearance of symptoms, and normalisation of CRP levels. Of the patients who did undergo endoscopy, 40.92% displayed mucosal healing within 1 year after starting anti-TNF treatment. CRP levels have been shown to correlate with the degree of healing observed by endoscopy. However, in our study it was noted that not all patients with ongoing disease activity had elevated CRP levels, illustrating the value of endoscopic monitoring. The invasive nature of endoscopy limits its use as a routine monitoring tool. Therefore it is important to develop an objective and easy-to-use index to facilitate assessment of the therapeutic effect of anti-TNFs in daily clinical practice.

With this in mind, a procedure for investigating the small bowel was developed in Japan in 2001 that is associated with minimal discomfort and a very low complication rate. Double balloon enteroscopy (DBE) allows complete examination of the small bowel, which is important for determining the extent of mucosal healing. Furthermore, it is also possible for biopsies to be taken or therapeutic interventions (such as balloon dilatation of strictures) to be made during DBE. This added functionality means that DBE may offer an alternative to surgery for some patients. DBE has successfully been used to dilate strictures that would otherwise have prevented access with an endoscope. A prospective, open-label study is currently underway in Japan to evaluate the efficacy and safety of endoscopic balloon dilatation for small bowel strictures in patients with CD. DBE also provides a useful tool for post-operative surveillance for asymptomatic lesion recurrence. It has shown that recurrence rates are particularly high (94%) after surgery for anastomoses [Hibi et al., unpublished data].

5. Summary and conclusions

It is increasingly apparent that there is a disconnect between a patient’s symptoms and the presence or absence of inflammation in CD. Treatment goals are evolving and the concept of deep remission is an attractive potential target currently being explored. Deep remission can be achieved and sustained in CD by using optimized therapy early and by monitoring disease activity using objective parameters. A number of simple changes to the management of CD have the potential to significantly improve patient outcomes (Box 1). This includes initiating appropriate treatment early, optimizing dosing, aiming for elimination of steroids and treating to achieve mucosal healing and prevent structural bowel damage. Such a strategy allows the natural history of the disease to be changed, reducing the need for hospitalization and surgery. There are also clear indications that modifying treatment based on regular objective assessments of disease activity to provide tight disease control can improve patient outcome. Several studies are currently underway (Table 2) that will elucidate the clinical benefits of optimized monitoring and its impact on the timing of therapeutic decision-making to achieve optimal disease control.
Box 1. Steps towards optimizing the treatment of CD

**DO**
- Identify patients with poor prognosis
- Make steroid-free remission a goal
- Intervene early with drugs that induce mucosal healing
- Optimize dosing of immunosuppressants early
- Treat beyond symptoms
  - Biomarkers
  - Mucosal healing
- Reassess patients at appropriate time points
  - Prednisone 2–4 weeks
  - Azathioprine 10–12 weeks

**DON’T**
- Use prolonged or repetitive courses of corticosteroids
- Underestimate corticosteroid toxicity
- Prolong the use of azathioprine at standard doses if full remission is not achieved

Table 2  Ongoing studies evaluating the effects on patient outcome of treating-to-target through optimized monitoring of CD activity

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ADACAL (calprotectin and hsCRP as markers of a new Diagnostic-therapeutic strategy that assesses mucosal Activity to individualize treatment, and improve the prognosis of patients with Crohn’s disease treated with immunosuppressants)</td>
<td>Multinational clinical study to assess the effect of individualised treatment according to a new calprotectin/hs-CRP-based diagnostic-therapeutic strategy on the mid-term outcome treatment in CD patients.</td>
</tr>
<tr>
<td>CALM (tight Control of disease Activity using CDAI, CRP and calprotectin Monitoring) Clinical trial identifier NCT01235689</td>
<td>An open-label, phase III, multicentre, efficacy and safety study to evaluate two treatment algorithms in subjects with moderate to severe CD who are naive to anti-TNF and immunomodulator therapy.</td>
</tr>
<tr>
<td>POCER (Post Operative Crohn’s Endoscopic Recurrence)</td>
<td>A randomized, controlled study that combines early endoscopic assessment of the anastomosis with optimized step-up treatment including adalimumab, for prevention of early severe disease recurrence.</td>
</tr>
<tr>
<td>REACT (Randomized Evaluation of an Algorithm for CD Treatment) Clinical trial identifier NCT01030809</td>
<td>A cluster randomization study of 40 sites (20 algorithm/20 Standard of Care) in Canada and Belgium with each site enrolling 60 patients with CD.</td>
</tr>
</tbody>
</table>

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