

Medical management of Crohn's disease

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Crohn's disease is a chronic, relapsing and remitting inflammatory condition of the gastrointestinal tract. Treatment has changed radically over the past decade with the introduction of biological therapy and increased use of immunomodulators. Awareness of the therapeutic potential and associated adverse events is necessary both for offering benefit and for protecting patients from undue risks from these treatments.

How common is Crohn's disease?

The median population incidence of the disease is 6.7 (range 1.6 to 14.6) cases per 100 000 annually and prevalence is 140 (10-199) cases per 100 000 in the West.¹ About 690 000 people in Europe, including about 90 000 people in the United Kingdom, have the disease, with estimated healthcare costs of €3.04bn (£2.4bn; \$4.8bn) and £300m a year respectively.²

How does Crohn's disease present?

The disease presents at any age, although usually at age 16-30 years; it has a disproportionate effect on economically active individuals. Common presenting symptoms include diarrhoea, abdominal pain, weight loss, and fatigue. The disease is characterised by transmural intestinal inflammation, with occasional extraintestinal features such as arthropathy or dermatopathy. It is classified in terms of the intestinal site affected; stenotic or penetrating (fistulising) complications; and degree of active inflammation.

As the differential diagnosis is wide (table 1) and the incidence is relatively low (most general practitioners in the UK will see a new case of Crohn's disease every seven years), diagnosis is often appreciably delayed. This may become clinically relevant if the management of early disease is shown to alter long term outcomes. The diagnosis is established through the history, endoscopy, histopathology, and appropriate radiology—explained in authoritative guidelines.³

When to refer to a specialist

Prompt referral from primary care is indicated for any patient with abdominal pain and diarrhoea associated with weight loss, iron deficiency, or raised inflammatory markers, especially if diarrhoea is nocturnal (box 1). Patients with an established diagnosis of Crohn's disease who have an appreciable change in

METHODS BOX

We used the PubMed database and Cochrane Library to identify studies and articles relevant to this article. We also searched the published abstracts of the proceedings of several societies, including those from the European Crohn's and Colitis Organisation, the British Society of Gastroenterology, and the American Gastroenterology Association. The senior authors have a detailed knowledge of current research and advances in the field as well as being the authors of European and UK guidelines.

symptoms also need prompt referral. In these cases alternative diagnoses to active Crohn's disease should be considered, including infection, bacterial overgrowth, bile salt malabsorption, dysmotility, or gallstones. Evidence of active disease (such as a raised C reactive protein) should be sought before steroids are started, although tests are fallible.

Complex decisions on the timing of treatment with immunomodulators or biological therapy mean that management of inflammatory bowel disease is becoming a specialty in its own right. The UK IBD Audit (which sought to improve the quality and safety of care for patients with inflammatory bowel disease in hospitals) to which 75% of hospitals submitted data, found appreciable variation in provision of services.⁴ Patients with poor prognostic factors at diagnosis, those who cannot achieve steroid-free remission, and those who relapse in spite of immunomodulators should be considered for subspecialty referral from secondary care. A working party from the national patient group and specialist medical, nursing, and allied organisations is defining minimum standards of care for inflammatory bowel disease in the UK.

What are the treatment objectives?

Recent European and American guidelines are based on systematic reviews and expert consensus.^{3,4} They recommend that treatment is conceptualised in terms of induction and maintenance of remission. Patterns of disease vary, so a therapeutic strategy should be tailored to the individual, rather than dictated by crises. The goals of treatment are to achieve sustained remission with the least toxic therapy and to avoid complications; 75% of patients remain in work 10 years

TIPS FOR NON-SPECIALISTS

- Suspect an opportunistic infection if a patient presents with new symptoms within two months of having received biological therapies
- Remember that the timing of treatment with the potential to modify the pattern of Crohn's disease may be identifiable at diagnosis from simple, clinical features (age, stricturing, or perianal disease); seek advice sooner rather than later

after diagnosis, so these goals are realistic, although the burden of disease is high in severely affected individuals.

What are the treatment options?

Management is both medical and surgical, together with appropriate nutritional, specialist nursing and other support. Table 2 summarises the medical options.

Mesalazine

Since 2006 important findings have emerged about the value of mesalazine. For mild or moderately active Crohn's disease, mesalazine seems little better than placebo.⁴ For maintenance, mesalazine seems to reduce the risk of relapse after surgery but not after medically induced remission. The odds ratio for mesalazine as maintenance therapy was 1.00 (95% confidence interval 0.80 to 1.24) in one meta-analysis,⁵ although the exact delivery system may make a difference. No maintenance therapy is an option for mild disease; those who smoke should be helped to stop.

Corticosteroids

Corticosteroids effectively induce remission but do not prevent relapse. The guidelines of the European Crohn's and Colitis Organisation advise that long term treatment with corticosteroids is inappropriate and should always be questioned, given their propensity for side effects.³ Corticosteroids with low systemic

Box 1 Investigation of suspected inflammatory bowel disease in primary care

Full blood count
C reactive protein
Urea and electrolytes
Liver function tests
Stool culture and microscopy

bioavailability, such as budesonide, are preferred for mild or moderately active Crohn's disease.³ They are superior to both placebo (odds ratio 2.9, 1.67 to 4.87) and mesalazine 4 g a day (2.8, 1.50 to 5.20).

Antibiotics

Antibiotics are appropriate for septic complications and perianal disease in particular. Treatment of Crohn's disease with broad spectrum, anti-mycobacterial antibiotics, however, failed to show benefit.⁶

Biological therapy and immunomodulators

Biological therapy uses genetically engineered proteins (such as monoclonal antibodies), which target mediators such as cytokines that are involved in biological processes. In Crohn's disease, the cytokine tumour necrosis factor α (TNF α) mediates inflammation, and the therapeutic antibodies infliximab and adalimumab (which are licensed for the disease) block its action. Biological therapies are administered parenterally and typically persist in the body for many weeks with long lasting effects. Immunomodulators modify immune function in a generic and less specific way. The distinction may be semantic because both suppress the immune system with the potential to modify the disease course at the expense of opportunistic infections or other complications. Immunomodulators such as azathioprine, mercaptopurine, or methotrexate help to maintain remission and are increasingly considered sooner rather than later, particularly for those likely to have aggressive disease.

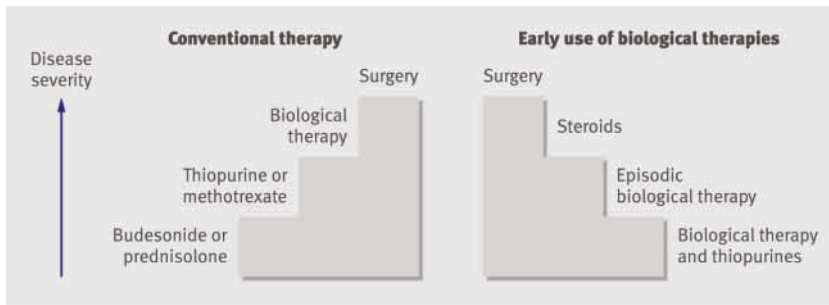
A meta-analysis estimates that azathioprine is twice as likely as placebo to maintain remission (odds ratio 2.16; 95% confidence interval 1.35 to 3.47).⁷ A dose-response effect was found, with 2.5 mg/kg a day being most effective (4.13; 1.59 to 10.71). A randomised withdrawal study for patients in remission taking azathioprine showed a relapse rate of 21% after 18 months (versus 8% for continued therapy) and

Box 2 Relative or absolute contraindications to anti-TNF α therapy: the STOIC acronym

Sepsis
Tuberculosis
Optic neuritis (demyelination)
Infusion reaction
Cancer

Table 1 | Differential diagnosis of Crohn's disease

Infectious v non-infectious	Comment
Infectious	
<i>Yersinia</i> spp	Serological diagnosis
<i>Mycobacterium tuberculosis</i>	Travel history and ethnic background important
Atypical mycobacteria	
Non-infectious (inflammatory)	
Diverticulitis	
Ulcerative colitis	Often bloody diarrhoea
Microscopic colitis	Watery diarrhoea, often associated with NSAIDs and other drugs
Behçet's syndrome	Ethnic background important (Middle Eastern)
Radiation enteritis	Can present at any time after radiotherapy
Sarcoidosis	
Coeliac disease	
Ulcerative jejunoileitis	
Non-infectious (toxic)	
Postoperative diversion colitis	
Bile acid loss	
Overuse of non-steroidal anti-inflammatory and other drugs	Detailed drug history, including over the counter medications, is necessary
Excessive use or misuse of laxatives	Associated with eating disorders
Non-infectious (malignant)	
Colorectal cancer	
Small-bowel cancer and lymphoma	
Non-infectious (other)	
Irritable bowel syndrome	
Ischaemic colitis	Associated with other cardiovascular risk factors
Chronic pancreatitis and malabsorption	



Step-up versus top-down therapy. A recent study has challenged our approach to the management of newly diagnosed patients with the disease by examining early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease¹² in the hope of changing the long term course of the disease. It is too early to say if this objective has been achieved

53% after three years, suggesting benefit from continuing therapy.³

When should biological therapies be used?

Infliximab, introduced a decade ago, heralded a major advance in treatment, with response rates up to 80%.^{3,4} Steroid-free remission rates, however, were much lower (24% and 9% at 54 weeks in groups treated with 5 mg/kg every eight weeks and with placebo respectively).⁸ Data on adalimumab are similar.⁹ Indications for anti-TNF α therapy include induction of response, remission, and maintenance for patients with moderate or severely active Crohn's disease despite (or because of or intolerance of) therapy with corticosteroids and/or immunomodulators.³ Patients with fistulas or extraintestinal manifestations may derive particular benefit.

Guidelines for anti-TNF α therapy from the National Institute for Health and Clinical Excellence (NICE) have not kept pace with advances in clinical practice. For example, maintenance therapy with infliximab has been associated with reduced admission to hospital over 12 months, from 25% to 10%, especially when mucosal healing is achieved¹⁰ yet maintenance therapy is not currently sanctioned by NICE. This matters to individuals with refractory disease because treatment options are few and surgery is common.³

European consensus guidelines advise that for individual patients, decisions on biological therapy

need to be based on disease activity, response to previous therapy, disease complications, and external factors such as the proximity of major life events. Large randomised controlled trials have shown few differences in efficacy between infliximab, adalimumab, and a third anti-TNF α drug, certolizumab pegol,⁴ although there have been no head to head studies, so the choice depends on availability, evaluation of the risks of immunogenicity, adverse events, ease of administration, and costs.

Are we using biological therapies at the correct time in the disease course?

The hope is that early treatment with immunomodulators or biological therapy might alter the pattern of hospital admission, surgery, and associated morbidity. A well conducted trial in a paediatric cohort with newly diagnosed Crohn's disease and remission induced by steroids showed an 18 month relapse rate of 9% among those taking mercaptopurine and 47% among controls (P=0.007).¹¹ In adults with a new diagnosis, initial treatment with infliximab and azathioprine ("top-down" therapy), compared with steroids and then azathioprine before infliximab ("step-up" therapy), showed a difference in remission without steroids or surgery at six months (60% v 36%, 95% confidence for absolute difference 7% to 40%, P=0.006) and at one year (figure).¹²

These are preliminary data for a disease that lasts for decades, but the concept is attractive. Furthermore, selecting patients with a poor prognosis both makes sense and is clinically possible. Two independent cohorts have shown that patients who, at diagnosis, have perianal disease, need steroids, are young (age <40 years), or have a high inflammatory burden (such as weight loss >5 kg) are two to five times more likely to need major resection.^{13,14} Such patients should be identified at diagnosis and considered for primary prophylaxis with thiopurines. In the future, genetic, immunological, and biochemical markers may more accurately predict disease course, as well as side effects or therapeutic response.

How can biological therapies and immunomodulators be used safely?

Side effects

About 60% of patients with Crohn's disease in western Europe will be treated with immunomodulators and 30% with biological therapies.³ The balance between benefit and risk of any treatment should be discussed with individual patients. Major side effects of azathioprine include myelosuppression, hepatitis, and pancreatitis; minor, often transient effects, include nausea, vomiting, and flu-like symptoms. Despite these side effects, thiopurines are tolerated by 75% of patients. The value of measuring thiopurine methyltransferase genotype or activity remains unclear. Thirty one of 41 patients with inflammatory bowel disease who had myelosuppression induced by azathioprine did not carry a thiopurine methyltransferase mutation,¹⁵ and normal

Table 2 | Medical therapies used in Crohn's disease

Drug	Induction	Maintenance	Ileocaecal disease	Crohn's colitis	Fistulating disease
Budesonide	Yes	No	Yes	Possibly	No
Mesalazine	No	Possibly	No	No	No
Prednisolone	Yes	No	Yes	Yes	No
Immunomodulator	Yes	Yes	Yes	Yes	Yes
Biological therapy	Yes	Yes	Yes	Yes	Yes
Ciprofloxacin	No	No	No	No	Yes
Metronidazole	No	No	No	Yes	Yes
Primary nutritional therapy*	Yes	No	Yes	Possibly	Possibly

*Primarily for paediatric patients.

thiopurine methyltransferase genotype does not obviate the need for careful monitoring of the blood count.

Opportunistic infections and malignancy

The risk of opportunistic infections in inflammatory bowel disease is increasingly recognised.¹⁶ The risk of serious infection from anti-TNF α agents is 2.8-4% in large trials lasting 12-18 months.^{8,9,17,18} Comparison with patients who have disease of similar severity but are not having biological therapy is difficult in real life, but a post-marketing registry (TREAT) of 6273 patients with inflammatory bowel disease included 3334 who received infliximab.¹⁹ Infliximab had a hazard ratio for serious infection of 1.77 (95% confidence interval 1.27 to 2.46). On the other hand, prednisolone was associated with double the risk of serious infection and increased mortality.

The Danish Crohn's and Colitis Database includes 651 patients from everyday practice who had 3351 infusions of infliximab. Of these patients, 116 (18%) had severe adverse events (most were related to sepsis), including abscess, pneumonia, aspergillosis, and tuberculosis.²⁰ This rate seems high but may represent the real world outside carefully controlled clinical trials. Caution is needed. No increase was seen in the risk of malignancy in the Danish Crohn's and Colitis Database or the TREAT registry, although a meta-analysis of anti-TNF α therapy in rheumatoid arthritis reports a relative risk of 3.3 (1.2 to 9.1).²¹

Checks prior to starting anti-TNF α therapy

A useful acronym for remembering contraindications to anti-TNF α therapy is STOIC (box 2). The history identifies the principal risk factors, including symptoms of current sepsis, ethnicity (such as from the Indian sub-continent), exposure to tuberculosis, or previous malignancy, and in some countries identification is aided by a chest radiography and tuberculin skin testing.²² A high level of awareness for complications with early investigation and treatment are the keys to safe administration.

ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- Travis SP, Stange EF, for the European Crohn's and Colitis Organisation (ECCO). European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;55(suppl 1):i1-58.
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- Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369:1641-57.
- Mathew CG. New links to the pathogenesis of Crohn disease provided by genome-wide association scans. *Nat Rev Genet* 2008;9(1):9-14.

For patients

- The National Association for Colitis and Crohn's Disease (www.nacc.org.uk)—Provides support for patients and their families and raises funds to support research and patient care locally and nationally

ONGOING RESEARCH

- Many new molecules and specific biological therapies are under trial as a consequence of research into the mechanisms of mucosal inflammation over the past three decades
- Major advances have been made in understanding the genetic susceptibility to Crohn's disease through genome wide association studies such as the Wellcome Trust Case Control Consortium. Work is now focused on translating these results into functional studies, to understand the pathophysiological mechanisms leading to the development of the disease²⁶
- Current research is focused on the interaction between bacteria and epithelial cells, particularly through defensins, Paneth cells, and functional gene expression, as well as the mediators of mucosal inflammation that are targets for new drug therapy. A primary defect in the innate immune system that affects interactions between commensal bacteria and the intestinal epithelium may have a causal role, with dysregulated T cell function leading to chronic mucosal inflammation
- A European and Canadian trial of autologous stem cell transplant in Crohn's disease (ASTIC) is also in progress; this treatment could potentially alter the course of the disease

Surgery

Historically, up to 80% of patients with Crohn's disease have surgery at some stage, so surgery must be recognised as part of a coherent therapeutic strategy. Rates of surgery may already be decreasing.²³ Laparoscopic resection is becoming the standard of care (particularly for ileocaecal resection) as time in hospital is 1.6 days shorter than with open surgery, although the operation takes longer and expertise may not be locally available.²⁴ European guidelines recommend that for contingency planning, surgical options should be discussed with the patient when anti-TNF α therapy is considered.

New approaches to treatment

The development of biological therapy continues,²⁵ although both natalizumab (which inhibits lymphocyte trafficking and is highly effective at maintaining response, although it is associated with three cases of fatal multifocal leucoencephalopathy in 24 000 patients treated) and certolizumab pegol (effective before or after infliximab) have recently been refused licences for Crohn's disease by European regulators. This status therefore limits the therapeutic options available in Europe (compared with the United States) for patients most seriously affected by the disease.

Alternative strategies include blockade by abatacept of the co-stimulatory signal required for T cell activation (abatacept is already approved for rheumatoid arthritis); studies in Crohn's disease are in progress. Other therapies include inhibitors of IL12 and IL23, currently in clinical trials. The chemokine receptor CCR9 mediates intestine specific migration of

SUMMARY POINTS

Biological therapies have radically changed the management of Crohn's disease but must be used judiciously with great awareness of possible adverse events

Treatment strategies for the disease are rapidly evolving, with immunomodulator and biological therapy being considered in patients who have indicators for developing early severe disease

Clinical indicators of a poor prognosis (at diagnosis) include perianal or stricturing disease, weight loss >5 kg, or the need for steroids

Treatment of active disease with mesalazine is little better than placebo; mesalazine is used mainly to reduce the risk of relapse after small intestinal resection

Access to specialist services, parallel medical and surgical clinics, nurse specialists, dietitians, pharmacists, and other allied professionals is as important as the medication

Publication of standards of care should drive improvement in the care and provision of resources for patients with Crohn's disease

leucocytes, and studies of an inhibitor in moderate to severely active disease have been encouraging. An agonist of the intestinal growth factor glucagon-like peptide 2 shows potential; leukocytapheresis is largely unexplored in Crohn's disease. The relatively benign side effects of leukocytapheresis make it appealing if efficacy can be shown. A European and Canadian trial of autologous stem cell transplant in Crohn's disease (ASTIC) is also in progress, which could potentially alter the course of the disease.

Conclusions

Treatment options for Crohn's disease are increasingly complex and evolving. The potential risks of both under-treatment and over-treatment with immunomodulators and anti-TNF α therapy should be recognised at an early stage. Anti-TNF α therapy has revolutionised the management of severe cases and should be available as maintenance therapy for selected patients. Many new treatments are being researched, but the logistics of care—requiring direct access to a specialist service, parallel medical and surgical clinics, and multidisciplinary teams—are as important as drug therapy for helping patients to manage their life with Crohn's disease.

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