J R Coll Physicians Edinb 2005; **35**:50–54

Recognition and management of inflammatory bowel disease

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ABSTRACT Inflammatory bowel disease comprising of ulcerative colitis and Crohn's disease can no longer be considered to be diseases confined to the West. Genetic susceptibility, mucosal immune dysregulation and intestinal bacterial flora contribute to the pathogenesis, but the exact causes remain uncertain. The identification of Nod2 gene mutations associated with Crohn's disease points to defects in innate immune system that alter interaction with microbial agents. Early recognition is important to prevent morbidity and complications. This poses special challenge in countries where the incidence is lower than that in the West and infective diseases involving the intestinal tract is common. Management requires a multidisciplinary medical-surgical team effort and is focussed on disease modifying therapy rather than simply management of acute relapses. Corticosteroid therapy, though valuable, is not disease modifying and is associated with considerable side effects and morbidity. Specific targeted therapy using monoclonal antibodies has been a most important advance in recent years, but the cost of such therapy continues to be prohibitive.

KEYWORDS 5-aminosalicylic acid, azathioprine, Crohn's disease, infliximab, methotrexate, ulcerative colitis

LIST OF ABBREVIATIONS 5-Aminosalicylates (ASA), Anti-tumour necrosis factor (TNF), Antibodies to infliximab (ATI), *Clostridium difficile* (*C. difficile*), Crohn's disease (CD), gastrointestinal (GI), inflammatory bowel disease (IBD), ulcerative colitis (UC)

DECLARATION OF INTERESTS Professor S Ghosh has lectured in educational conferences organised by Schering Plough, Celltech and Shire Pharmaceuticals and received honorariums. He has also served on advisory panels organised by Schering Plough, Centocor, Celltech, Pfizer and Procter and Gamble.

Published online ***November 2004***

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SUMMARY

Inflammatory bowel disease consists of UC and CD. Ulcerative colitis is characterised by continuous diffuse mucosal inflammation of the colon. Crohn's disease, in contrast, is characterised by patchy transmural inflammation of any part of the GI tract. In 5% of patients the disease is designated indeterminate colitis as features of both UC and CD are present. The incidence of UC is stable at approximately 10–20 per 100,000 per year, with a prevalence of 100–200 per 100,000. The incidence of CD is around 5–10 per 100,000 per year, with a prevalence of 50–100 per 100,000. The epidemiological trends are variable for CD, even in the West. Geographical prevalence of IBD has a North–South as well as an East–West gradient, though the incidence of the disease appears to be increasing in the Far East and South Asia. Recognition of the disease is therefore important worldwide. The disease occurs most commonly in the 20–40-year age group.

Inflammatory bowel disease occurs in genetically susceptible individuals in response to unknown environmental triggers. Gut bacterial flora interact with the innate and adaptive immune system of the intestine to perpetuate the inflammation. Significant advances in genetics have led to the identification of gene mutations on chromosome 16 associated with small intestinal CD in Caucasian but not Oriental populations, and further mutations on chromosomes 5 and 10 have recently been associated with CD. Involvement of other genes is strongly suggested. The key molecules and cells involved in the chronic inflammatory process in IBD are targets for development of specific novel therapy. The next decade is likely to be dominated by the development of biological therapies, and such novel therapies as well as conventional therapies are discussed in the overview. Well-recognised environmental influences include smoking, which decreases the risk of UC but increases the risk and worsens the clinical course of CD. Appendicectomy for an inflamed appendix is also protective against the development of UC.

OVERVIEW

Recognition of IBD

The cardinal symptom of UC is bloody diarrhoea. When symptoms have persisted for 2 weeks or more, an infection is unlikely unless the patient is immunocompromised, has picked up a parasitic infection such as amoebiasis, or has been exposed to antibiotics (pseudomembranous colitis due to *C. difficile*). Diagnosis is made on the basis of sigmoidoscopy or colonoscopy demonstrating confluent inflammation of the mucosa with loss of vascular pattern, friability, ulcerations, mucopus, and, in severe cases, overt bleeding. Typical histological findings on biopsy and negative stool microscopy and culture provide confirmatory evidence. Histological evidence is essential as the colonoscopic appearances in microscopic colitis are normal. The hallmark of UC is a diffuse mixed inflammatory cell infiltrate within the lamina propria and crypts with mucosal architectural distortion. The severity of UC is evaluated by the Truelove and Witts classification. It is particularly important to recognise severe UC, characterised by severe diarrhoea (six or more motions daily), obvious blood in the stool, fever (³37·5°C), resting tachycardia (>90 beats per minute), anaemia (haemoglobin >10 mg/l) and ESR above 30 mm/h, as hospital care is needed. The extent of UC is described, from the rectum, as distal (rectum and sigmoid), left-sided (to spleen flexure), extensive (to hepatic flexure), and total (or pancolitis) involving the whole colon.

Crohn's disease has many manifestations including abdominal pain, diarrhoea, perianal pain, mouth ulcers, vomiting, weight loss, pyrexia of unknown origin, and impairment of growth and development in children. Endoscopic or radiological investigations demonstrate classically focal asymmetric ulcerations involving the small and/or large intestine with histological demonstration of transmural chronic inflammation. Sarcoid-like non-caseating granulomas are detected in up to 60% of patients. The disease location, disease behaviour (inflammatory, fistulating, fibrostenosing), and age at diagnosis define 24 subgroups in the Vienna classification, illustrating the heterogeneity of the disease.

A number of diseases may mimic IBD and must be included in the differential diagnosis, as shown in Table 1.

Treatment of IBD

Management depends on whether the diagnosis is CD or UC, and is tailored to disease severity, extent, and presence of nutritional deficiencies. Crohn's disease is incurable, whereas UC can only be cured by a panproctocolectomy. The chronicity of both diseases poses special challenges in psychological support, education, employment, and avoidance and management of iatrogenic complications.

Pharmacological therapy

5-Aminosalicylates

All oral formulations deliver the drug to the colon (sulphasalazine, olsalazine, balsalazide), whereas only the pH (asacol, salofalk, ipocol) or time-controlled release (pentasa) preparations deliver the drug to the small intestine. Rectal preparations such as suppositories and foam or liquid enemas are used for distal colitis and are considered more effective than rectal corticosteroids. The main role of 5-ASA is maintenance of remission in UC, though these drugs also help in inducing remission. Their efficacy in CD is very doubtful. There is no convincing evidence of superiority of one 5-ASA preparation over another, either in terms of efficacy or in terms of safety.

Side-effects of 5-ASA occur in about 15% of patients and include headaches, nausea, diarrhoea, and rarely, renal impairment. Stevens–Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis are extremely rare. Regular monitoring of renal function is necessary as renal failure may become irreversible.

Corticosteroids

Corticosteroids are powerful anti-inflammatory agents often used as first-line therapy in moderate to severe relapses of UC and CD. Prednisolone 40 mg/day is the most common starting dose, and hydrocortisone and prednisolone can be used intravenously in severe cases. Budesonide is a synthetic oral steroid with limited bioavailability and extensive hepatic first-pass metabolism, thus limiting systemic toxicity. Corticosteroids can also be given rectally.

Ulcerative colitis tends to respond to corticosteroids more quickly than CD. In acute, severe UC about 30% fail to respond and require colectomy, about 30% make a partial response, and about 40% pass into remission. A

TABLE 1 Differential diagnosis: diseases that mimic IBD.

Ulcerative colitis

Radiation proctopathy: history of pelvic radiotherapy
Solitary rectal ulcer: rectal prolapse, manual evacuation
Pseudo-membranous colitis (*C. difficile*): history of antibiotic exposure
Sexually transmitted infections: history of anal sex
Amoebiasis: recent travel to endemic areas
Microscopic colitis: normal mucosa at colonoscopy

Crohn's disease

Yersinia infection: serodiagnosis, acute illness
Behçet's syndrome: thromboembolism, genital ulcers, uveitis
Appendicular abscess: acute illness, appearance at surgery
Non-steroidal anti-inflammatory enteropathy: history of NSAID intake
Intestinal tuberculosis: residence in poor or developing countries
Ischaemic colitis: cardiac or vascular disease, pro-thrombotic conditions

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year after responding to corticosteroids, about one-half have had a prolonged response, about one-third are corticosteroid-dependent, and about one-fifth are resistant to therapy.

Early side-effects include acne, moon face, oedema, mood disturbances, and glucose intolerance. Side-effects on prolonged use, particularly at doses above 10 mg/day, include osteoporosis, osteonecrosis of femoral head, cataracts, glaucoma, and myopathy. Consequences of steroid withdrawal include adrenal insufficiency, myalgia, malaise, arthralgia, and raised intracranial pressure.

Immunosuppressive agents

Three groups of drugs are generally used: thiopurines such as azathiopurine and 6-mercaptopurine, are used in both CD and UC; methotrexate, is used generally in CD; and ciclosporin, is used in severe UC. They should be avoided in pregnancy or in those who plan to become pregnant.

- *Azathioprine* is metabolised to 6-mercaptopurine and subsequently to 6-thioguanine nucleotides. The main role for thiopurines is steroid sparing in both CD and UC. Steroid dependence or steroid resistance necessitates initiation of therapy with thiopurines. Optimum dose is important and the dose used is azathiopurine 2·0–2·5 mg/kg/day or 6-mercaptopurine 1·0–1·5 mg/kg/day. Onset of action is slow and peak efficacy may take up to 12 weeks to achieve. Approximately 45–60% of patients with UC or CD may be expected to remain in remission on thiopurines, and the relapse rate increases after discontinuation, irrespective of duration of previous therapy. Up to 20% of patients may be intolerant of thiopurines and side-effects include leucopenia, pancreatitis, hepatitis, flu-like symptoms, myalgia, and skin rash. Full blood count and liver function tests need to be monitored. Leucopenia is particularly important, and blood counts must be checked weekly for 4 weeks after treatment is started and at least every 3 months thereafter. Thiopurine methyltransferase is involved in azathiopurine metabolism, and it is deficient for genetic reasons in a few patients. These patients are very liable to develop leucopenia and it is important that this be detected.
- *Methotrexate* is considered in patients with CD intolerant of thiopurines who need immunosuppressive therapy. The standard starting dose is 25 mg/week orally, though occasionally 25 mg/week parenteral therapy may be more effective and even essential in those with extensive small intestinal involvement. Onset of action is slow. Approximately 50–60% of patients with CD maintained on methotrexate can be expected to remain in remission. Gastrointestinal side-effects are minimised by the concomitant use of folic acid. Hepatotoxicity and pneumonitis are the most serious side-effects. Full blood count and liver function tests require monitoring, but routine liver biopsy is unnecessary.
- *Ciclosporin* given intravenously or orally has a rapid onset of action in UC, and is used in hospital in the management of severe active disease after failure of intravenous corticosteroid therapy. These patients would normally be candidates for colectomy if ciclosporin were not used, but toxicity and long-term failure rate limits its use to patients unsuitable for surgery. A lower dose of 2 mg/kg may be safer and as effective as the standard dose of 4 mg/kg. Major complications include renal impairment, infection, and neurotoxicity. Minor side-effects include tremor, paraesthesia, malaise, headaches, liver function abnormalities, gingival hyperplasia, and hirsutism. Prophylaxis against Pneumocystis carinii pneumonia may be desirable in ill, severely immunosuppressed patients.

Other immunosuppressive therapies are rarely used in IBD. Thalidomide is used as an immunomodulatory agent in selected CD patients with persistent oral ulcerations, but neurotoxicity during long-term use may be a problem. Topical tacrolimus may also help refractory oral ulcerations.

Biological therapies

Biological therapies in IBD have evolved from increasing understanding of the immunopathological mechanisms of chronic inflammation and the consequent increasing identification of strategic therapeutic targets (Figure 1). These include monoclonal antibodies, anti-inflammatory cytokines, growth factors, nucleic acid, and gene therapies. Anti-tumour necrosis factor, the most studied of biological therapies, includes chimeric monoclonal (infliximab) antibodies, humanised monoclonal (CDP571 and CDP870) antibodies, fully human monoclonal

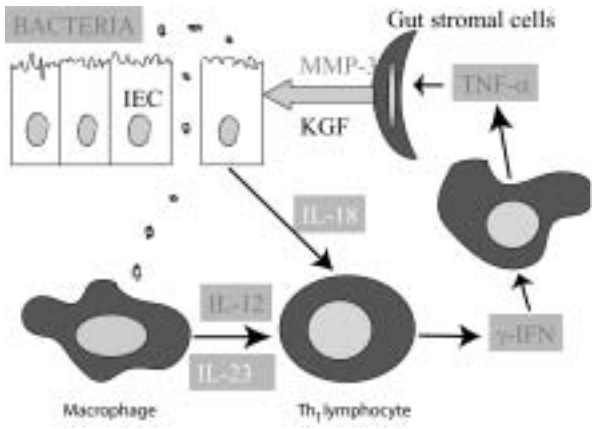

FIGURE 1 Schematic diagram showing key steps in the pathogenesis of CD; the important therapeutic targets are highlighted in red (MMP – matrix metalloproteins; KGF – keratinocyte growth factor; IEC – intestinal epithelial cell line)

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(adalimumab) antibodies, p75 fusion protein (etanercept), and p55 soluble receptor (onercept).

Infliximab is the only biological therapeutic agent widely available for clinical use currently. Its main use is in treating active CD not responding to, or intolerant of, conventional therapies. Infliximab is also steroid sparing. Concomitant immunosuppressive therapy reduces the immunogenic response and continuation of such treatment is desirable if tolerated. Patients who have failed to respond to corticosteroids and immunosuppressive therapy and who are poor surgical candidates, and patients with fistulising disease, are likely to require regular maintenance therapy with infliximab. The development of antibodies against infliximab is associated with an increased risk of infusion reactions and a reduced duration of response to treatment. Maintenance therapy every 8 weeks is less immunogenic and more effective than episodic therapy. Mucosal healing can be striking (Figure 2). In UC the role of infliximab remains uncertain.

Other biologicals

Other anti-TNF therapies that appear promising include humanised pegylated Fab1 fragment CDP870 and adalimumab. Etanercept is ineffective in CD, despite its efficacy in rheumatoid arthritis. A number of other monoclonal antibody therapies appear to be promising including a humanised monoclonal antibody against a4 integrin (natalizumab) and anti-IL12p40 antibody. Appropriate pharmaco-economic analysis of the efficacy and risk of these expensive therapies is required relevant to actual clinical use, and initial analysis of infliximab use in CD appears to show that it is cost-effective.

Serious opportunistic infections may occur after anti-TNF therapy. Tuberculosis, histoplasmosis, listeriosis, and aspergillosis with infliximab and etanercept have been reported in rheumatoid arthritis. Tuberculosis is most frequent and generally manifests itself within the first 6 months of therapy, representing re-activation of latent tuberculosis. A chest radiograph and tuberculin skin testing prior to starting infliximab is recommended. Four per cent of 500 CD patients treated with infliximab at the Mayo Clinic had serious infections attributable to infliximab, and 4 patients died.

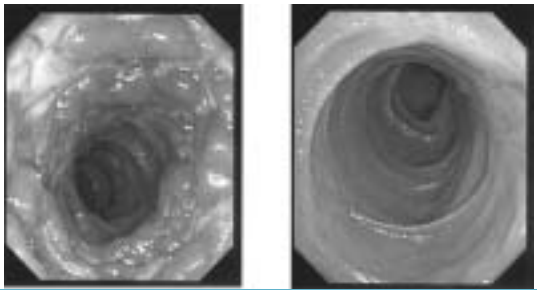

FIGURE 2 Healing of CD ulcerations 6 weeks after administration of infliximab. (a) Endoscopy before treatment. (b) Endoscopy 6 weeks after treatment.

Antibodies to infliximab have been reported in 28% of patients in an integrated safety data set including CD and UC. Infusion reactions occur in 17% of patients treated with infliximab, compared with 7% treated with placebo. However, these reactions can be prevented or treated in nearly all patients. Auto-antibody formation, such as antinuclear antibody (34%) and anti-double-stranded DNA (9%), rarely leads to drug-induced lupus. Currently, the safety data regarding the risk of malignancy appear reassuring despite at least 4 patients each with CD and rheumatoid arthritis developing non-Hodgkin's lymphoma. Chronic inflammatory diseases are associated with an increased baseline risk of malignant lymphoma. Infliximab may exacerbate demyelinating disorders, and rarely may be associated with a new demyelination disorder.

Contraindications to the use of infliximab include sepsis, tuberculosis, a history of optic neuritis, severe previous infusion reactions, and cancer.

Antibiotics and probiotics

The commensal bacterial flora is essential in perpetuating chronic inflammation. Metronidazole and ciprofloxacin are effective in perianal CD. Probiotics such as VSL #3, containing a cocktail of bacteria, may maintain remission in UC with efficacy equal to 5-ASA. Probiotics are also useful in pouchitis affecting ileal pouch anal anastomosis (IPAA) after panproctocolectomy for UC.

Nutritional therapy

Defined formula elemental or polymeric liquid diets are less effective than corticosteroids, but are popular for induction of remission in juvenile CD. Such therapies are anti-inflammatory in addition to promoting growth and development. In complex fistulating disease, total parenteral nutrition may be useful. In a small number of CD patients with short bowel syndrome after multiple resections, home parenteral nutrition may be necessary. In CD and UC nutritional support is important, and this includes preventing deficiencies, particularly of calcium, vitamin D, and iron, and rectifying nutritional deficiencies as they arise. In ileal CD or after ileocaecal resection, parenteral vitamin B12 replacement is necessary.

Surgical management

General indications for surgery are shown in Table 2. In UC, panproctocolectomy is curative, and IPAA is the procedure of choice. In patients with poor anal sphincter function, and in those at high surgical risk, an ileostomy is an acceptable alternative. In CD, surgery is not curative and hence should be conservative. In CD patients

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TABLE 2 General indications for surgery

Ulcerative colitis
Acute fulminant colitis
Severe acute colitis not responding to intensive medical therapy
Dysplasia complicating long-standing UC
Steroid-dependent patient despite immunosuppressive therapy
Recurrent frequent relapses with poor quality of life despite optimal medical therapy

Crohn's disease
Mechanical complications such as intestinal obstruction due to fibrotic strictures
Intra-abdominal or perianal abscesses
Complex fistulating disease
Fulminant or severe acute colonic CD not responding to intensive medical therapy

requiring colectomy, an ileostomy is necessary. Patients with long-standing UC and CD should have annual or 2-yearly surveillance colonoscopy with biopsies to detect dysplasia (see also JN Plevris. Screening and surveillance of upper and lower gastrointestinal cancer. *J R Coll Physicians Edinb* 2005; **35:**55–59).

Prevention of relapse

Usually, no cause for relapse in UC and CD can be found. However, avoidance of smoking in CD and of NSAIDs may help. Corticosteroids, salicylates, and azathiopurine/6-mercaptopurine can be continued in pregnancy. Patients travelling to areas where enteric infections are common may benefit from antibiotic prophylaxis (see PD Welsby. Traveller's Diarrhoea. *J R Coll Physicians Edinb* 2005; **35:**40–44)

HIGHLIGHTS

- Ulcerative colitis and CD can usually be distinguished from each other, but this is not possible in about 5% of cases, referred to as indeterminate colitis.
- Severe UC is recognised from diarrhoea (>6 movements per day), blood in the stool, fever, tachycardia, anaemia, and a raised ESR. It requires hospital management.
- Histological evidence for the diagnosis of UC is important as the colonoscopic appearances in microscopic colitis are normal.
- 5-Aminosalicylates are used mainly to maintain remission, and no one preparation is superior to another.
- Corticosteroids can be the first-line treatment in acute relapse, but prolonged treatment at high doses is associated with serious side-effects and requires corticosteroid-sparing agents.
- Immunosuppressive agents are useful in inducing remission, maintaining remission, and allowing reductions in corticosteroid dosage. Azathiopurine and 6-mercaptopurine can be used in UC and CD, methotrexate in CD and ciclosporin in acute relapses of UC.
- Infliximab is the only biological agent generally available at present. It is indicated for patients who have not responded to other treatments or who have fistulising disease.
- Panproctocolectomy and ileo-anal anastomosis is curative in UC, but surgery for CD should be as conservative as possible since cure is not possible.

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