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Drug advances in inflammatory bowel disease

R Alexander Speight and John C Mansfield

ABSTRACT – The pathogenesis of inflammatory bowel disease (IBD) remains incompletely understood, but is thought to be a consequence of immune dysregulation, impaired mucosal integrity, enteric bacterial dysbiosis and genetic susceptibility factors. Recent drug advances in the treatment of IBD have clarified the role of existing medication, including 5-amino-salicylic acids (5-ASAs) and has seen a burgeoning use of treatment with biologicals. With recent advances in our understanding of these debilitating diseases, it is hoped that novel therapeutic targets can be identified.

KEY WORDS: Crohn's disease, ulcerative colitis, 5-amino-salicylic acid, anti-TNFα, deep remission

Background

The inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease (CD), are chronic, relapsing inflammatory conditions that have seen several therapeutic advances over the past 15 years. In UC, inflammation is limited to the superficial mucosal layers of the colon, classically affecting the rectum and spreading proximally to a variable extent. Conversely, CD is a deeper, transmural inflammatory condition that can occur in patches throughout the gastrointestinal tract. Chronic inflammation can lead to complications such as neoplasia, strictures, abscesses or fistula. The aetiopathology of IBD remains incompletely understood, but is thought to be a consequence of immune dysregulation, impaired mucosal integrity, enteric bacterial dysbiosis and genetic susceptibility factors (Fig 1). Advances in our understanding of IBD has lead to a better appreciation of the role of existing treatments and is fertile ground for research into novel therapeutic targets.

Aims of treatment in IBD are to induce and maintain remission, to improve quality of life and to prevent the development of complications and the need for surgery. Traditionally, the pharmaceutical armamentarium has included corticosteroids, 5-aminosalicylic acids (5-ASAs) and immunomodulators, such as azathioprine, 6-mercaptopurine (6-MP) and methotrexate. Over the past 15 years, biological therapy, in the form of antibodies to tumour necrosis factor α (anti-TNFα) has revolutionised the treatment of CD.

R Alexander Speight, specialist registrar in gastroenterology;
John C Mansfield, consultant gastroenterology

Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

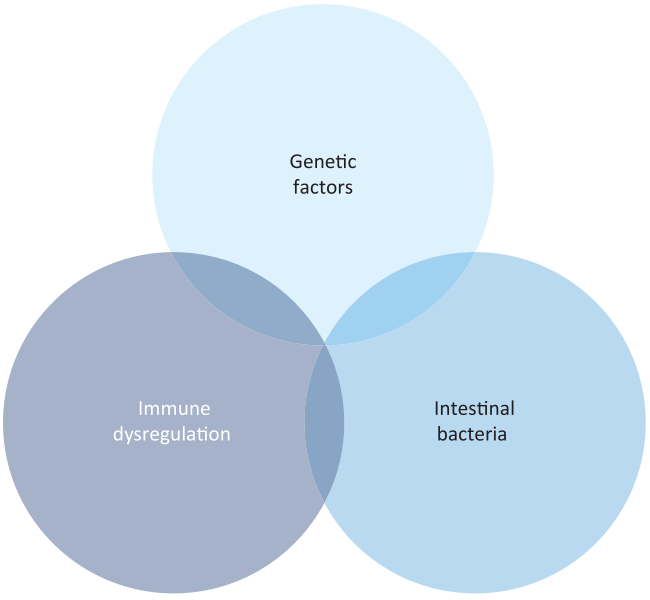

Fig 1. Factors involved in inflammatory bowel disease pathogenesis.

In this review, we focus on recent advances in the treatment of IBD, including the understanding that 5-ASAs have little or no role in the management of CD, the importance of 5-ASAs in the management of UC and the burgeoning use of biologicals.

The lack of efficacy of 5-aminosalicylic acids in Crohn's disease

5-aminosalicylic acids (5-ASAs), such as mesalazine, have long been a staple in the management of IBD and, therefore, would seem to have no place in an article regarding drug advances. However, although several randomised controlled trials (RCTs) have demonstrated the efficacy of 5-ASAs in inducing and maintaining remission for patients with mild to moderate UC,[1] evidence for their use in CD is somewhat lacking. 5-ASAs exert their therapeutic effect topically, possibly by binding to the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ within colonocytes.[2] Therefore, it is intuitively difficult to imagine that 5-ASAs would be effective in treating the deep inflammation that is the hallmark of CD. This point is made eloquently by Bergman and Parkes in a systematic review of the evidence for 5-ASAs in IBD.[2] The authors describe six RCTs that failed to demonstrate a significant improvement in remission rates for patients with CD over placebo. Despite the lack of an evidence base for their use, as late as 2003, it was estimated that 75% of gastroenterologists were still using a 5-ASA as the first-line treatment for patients with mild to moderate CD.[3]

Controversy over the optimum dose of 5-aminosalicylic acids in ulcerative colitis

The optimum dose of systemic 5-ASA in the treatment of active UC is unknown. There is no doubt that 5-ASAs benefit patients with mild to moderately active UC, with a Cochrane database meta-analysis demonstrating a significant improvement over placebo for all dose ranges (<2 g, 2–2.9 g, >3 g). Even low doses of 5-ASA are effective, but the onset of action is thought to be unacceptably slow. The Cochrane database concluded that 5-ASA at a dose of 2 g or greater was superior to placebo in achieving clinical improvement.[1] Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA' trials (ASCEND I and II)[4,5] attempted to demonstrate a dose–response effect, with patients randomised to receive either 2.4 g or 4.8 g of mesalazine. ASCEND I found no significant difference in the endpoint of overall clinical improvement at week 6, whereas ASCEND II found a modest benefit for the higher dose of mesalazine in overall improvement at week 6. However, when the more pertinent endpoint of clinical remission was analysed, there was no significant difference between the higher and lower doses of mesalazine. This finding was replicated in trials assessing the efficacy of a modified-release mesalazine at both 4.8 g and 2.4 g[6,7] and in a further ASCEND III trial.[8] In none of the trials was the higher dose of 5-ASA found to be associated with any increase in risk, although there was a cost implication. Therefore, there is no evidence that high doses of 5-ASA are superior in achieving remission compared with moderate doses.

A greater role for topical 5-aminosalicylic acids in treating ulcerative colitis

The efficacy of 5-ASAs depends on the successful delivery of the drug to the superficial mucosa. It has been shown that topical treatment increases the concentration of 5-ASA within the mucosa by a factor of 100 compared with systemic treatment.[9] Traditionally, gastroenterologists have used topical treatment to manage limited proctitis or rectosigmoiditis. However, Marteau *et al* recently demonstrated that a combination of systemic and topical treatment increased the rate of remission even for patients with extensive disease, progressing more proximally than the sigmoid colon.[10] In a double-blind RCT, patients with extensive, mild to moderately active UC received systemic 5-ASA and were randomised to receive a mesalazine enema or placebo in addition. At 8 weeks, 64% of patients were in remission in the intervention arm compared with only 43% in the placebo group ($p<0.03$).

The role of anti-TNFα drugs in Crohn's disease

The introduction of monoclonal anti-TNFα drugs revolutionised the management of severe CD. Although the precise mechanism of action is unknown, it is thought that anti-TNFα drugs cause apoptosis of inflammatory cells carrying membrane-bound TNFα, an important cytokine in the pathogenesis of CD.

In Europe, infliximab and adalimumab are both licensed for the treatment and maintenance of moderate to severe CD that is refractory to conventional treatment or for the treatment of patients who are intolerant of conventional treatment. Infliximab is a chimeric mouse–human monoclonal antibody, whereas adalimumab is a fully humanised monoclonal antibody and, as such, might demonstrate less immunogenicity. Immunogenicity can lead to the development of antibiological antibodies, which inactivate the drug, leading to a loss of clinical response. It has been shown that using regular maintenance infusions leads to less antibody development compared with episodic treatment (30% vs 10%).[11]

Good data exist demonstrating the efficacy of anti-TNFα drugs for inducing and sustaining remission for patients with moderate to severely active disease,[12,13] with approximately 60% of patients showing overall clinical improvement. Long-term data have shown infliximab to be beneficial, in initial responders, over a median follow-up period of 4.6 years.[14]

The concept of deep remission in Crohn's disease

The natural history of CD can be viewed in two ways. One hypothesis suggests that patients with CD are a heterogeneous group with different phenotypes with fibrostenosing disease, penetrating disease or simple chronic inflammation.[15] However, more recent research suggests that the disease is progressive, with chronic inflammation leading to cumulative intestinal damage. In this model, surgical resection becomes the most extreme form of bowel injury.[16] Therefore, a window of opportunity exists in which the aim of treatment would be to intervene with immunosuppression early to prevent cumulative inflammatory damage, thus reducing complications and the need for surgery (Fig 2).

During periods of clinical remission, subclinical inflammation can persist, contributing to cumulative bowel injury. It is proposed that, by treating this subclinical inflammation, it might be possible to prevent cumulative inflammatory damage, altering the natural history of the disease.[17] Therefore, the aim of treatment in CD becomes not only clinical remission, but also mucosal healing, known as 'deep remission'. Mucosal healing has been compared by some experts to joint damage in rheumatoid arthritis, in which the aggressive treatment of subclinical joint inflammation has proved to be successful in reducing long-term complications.

Current studies are attempting to model cumulative damage to better understand the therapeutic aim of deep remission.[17] However, to date, there is no convincing evidence that mucosal healing and deep remission can alter the long-term, natural history of CD. Achievement of deep remission could simply be a marker of patients with less aggressive and, therefore, easier to treat, disease.

Evidence for the use of early immunosuppression in Crohn's disease

The concept that patients, particularly those with severe or high-risk disease, should receive prompt treatment, has gained more credence with evidence that early intervention can improve outcomes. Ramadas *et al* recently published a cohort of 341 patients

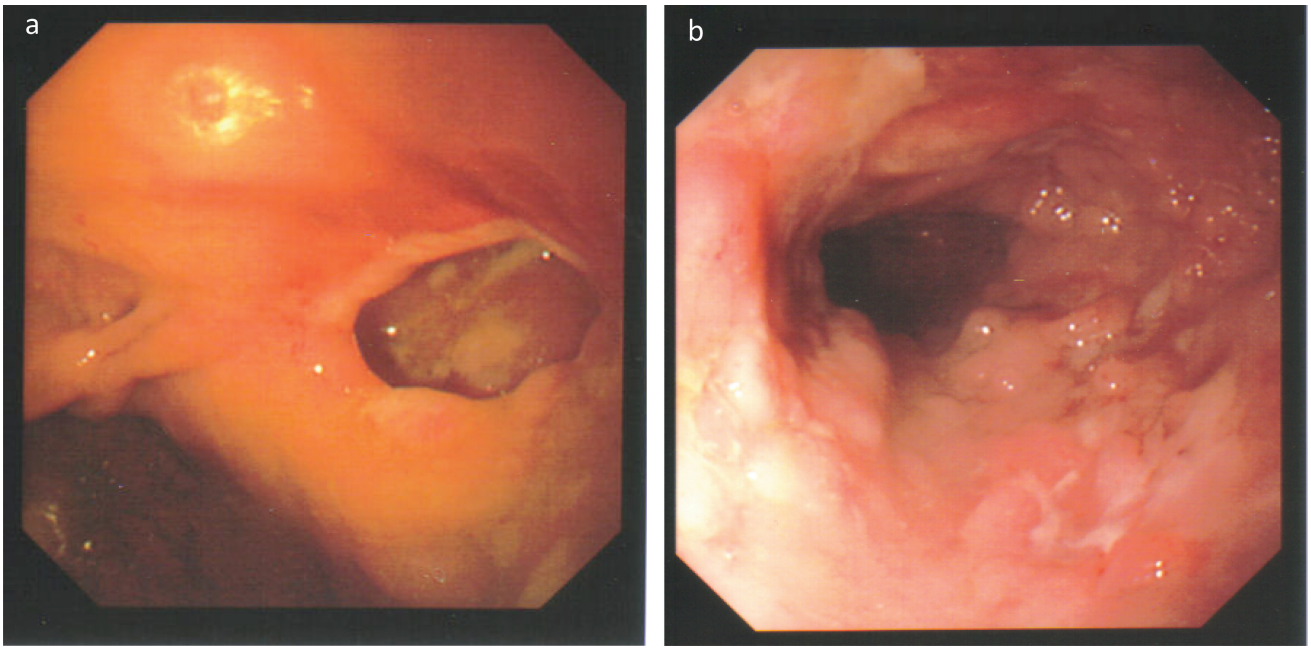

Fig 2. Examples of active Crohn's disease. Active CD at an ileocolic anastomosis (a) and in the colon (b) in a patient with extensive CD who had previously undergone surgical ileocaecal resection. CD = Crohn's disease.

found to have CD over a 17-year period in Cardiff.[18] Over the study period, the rate of surgical resection fell significantly, whereas the overall and early use of thiopurines (azathioprine and 6-mercaptopurine) increased. Analysis found an independent association between the early use of thiopurines and reduced surgical resection rates.

Evidence for the use of early, more potent immunosuppression also comes from an open-label RCT that compared a conventional, step-up treatment strategy with an early combined immunosuppression (anti-TNFα and thiopurine) top-down treatment strategy.[19] The patients in the top-down treatment group achieved remission sooner and fewer required steroid treatment 1 year after diagnosis. At week 52, 61.5% of patients in the early combined immunosuppression group were in remission, compared with only 42.2% in the conventional treatment group. Rates of mucosal healing were also higher in the top-down group. However, this benefit was not sustained, with rates of steroid use being equivalent between the two groups by the end of the second year of follow-up.

Further support for potent, combined immunosuppression in patients with moderate to severe CD, was demonstrated by results of a 2010 study published by the Study of Immunomodulator Naive Patients in CD (SONIC) Group.[20] The study tested the efficacy of infliximab and azathioprine in combination against monotherapy with either drug. In a double-blind RCT, patients received either infliximab with placebo, azathioprine with placebo or a combination of infliximab and azathioprine. The combination of both treatments was found to be significantly more effective than monotherapy, with 56.8% of patients maintained in a steroid-free remission in the combination group compared with 44.4% in the infliximab group and 30% in the azathioprine group (at 6 months follow-up). The rate of serious infections was similar between all three groups, at approximately 4%, during the initial 6 months of treatment.

The role of anti-TNFα treatment in ulcerative colitis

The efficacy of biologicals in the treatment of UC is less impressive than their effect in CD. Active UC Trials (ACT I and ACT II) were large, multicentre RCTs that compared infliximab with placebo in the treatment of moderate to severe active UC.[21] The headline endpoint for both trials was a moderate clinical improvement, rather than the harder endpoint of clinical remission. There was a modest, but significant benefit in clinical improvement over placebo. However, only 25–35% of patients in the infliximab arm were in clinical remission at all stages of follow-up, with only approximately one-quarter of patients remaining off corticosteroids after 1 year of treatment with infliximab.

In the UK, infliximab has a license for the treatment of acute, severe UC in patients who are refractory to, or intolerant of, intravenous corticosteroid treatment and a conventional drug that affects the immune response. Currently, the conventional drug used for patients in this scenario would be ciclosporin. A French group of investigators (Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif [GETAID]) recently published a trial that compared ciclosporin with infliximab in patients with severe UC refractory to intravenous steroids.[22] A similar trial (the comparison of infliximab and ciclosporin in steroid resistant UC: a trial [CONSTRUCT]) is currently being conducted in the UK. The GETAID group found no significant difference between ciclosporin and infliximab, with just under half the patients benefiting in both groups (40% and 46% respectively).

The long-term safety of anti-TNFα treatment

Given their action as potent immunosuppressants and also the role of TNFα in tumorigenesis, the long-term safety of anti-TNFα drugs has been carefully studied. Information has been gathered from clinical trials, cohort studies, post-marketing surveillance and also disease registries. The evidence regarding safety data is complicated by the fact that chronic inflammatory conditions confer an increased risk of neoplasia and sepsis inherent to the disease itself. In addition, patients treated with alternative immunosuppressants, such as steroids or thiopurines, are also at an increased risk of sepsis or of developing cancer. Beaugerie *et al* recently demonstrated that there is an approximate fivefold increased risk of developing a lymphoproliferative disorder in patients with IBD treated with thiopurines vs thiopurine-naive patients.[23]

However, when all confounding factors are taken into consideration, the adverse effects of long-term anti-TNFα are becoming clearer. Sepsis is by far the most serious adverse event reported, with an approximate doubling of the risk of serious infections.[24] In CD, the most common sources of sepsis are gastrointestinal tract abscesses, gastroenteritis and pneumonia.[25] Anti-TNFα treatment is usually stopped during an episode of severe sepsis, but evidence would suggest that it is safe to restart the treatment once the infectious episode has resolved.[26]

Reactivation of latent tuberculosis (TB) has been a well-recognised adverse event since the early days of anti-TNFα treatment. Guidelines recommend testing for latent TB before starting treatment, either via chest radiograph or serological testing. Since the introduction of pre-treatment testing, the incidence of active TB in patients taking anti-TNFα has dropped from 1.5/100 person years to 0.2/100 person years.[25]

TNFα is thought to inhibit tumorigenesis and, therefore, the association of anti-TNFα with the development of neoplasia has been of great concern. Data from several clinical trials and large cohort studies have failed to support this concern, with no overall increase in the risk of solid organ tumours or lymphomas. However, there is an increased risk of non-melanoma skin cancers and, thus, regular skin surveillance is advised.[26] Recently, a few case reports have emerged of patients developing hepatosplenic T cell lymphoma (HSTCL) in association with combined treatment with anti-TNFα and a thiopurine. This rare, usually fatal lymphoma classically affects young male patients. In total, 36 cases of HSTCL had been identified by 2011, most of which were associated with long-term thiopurine therapy and anti-TNFα therapy. No reported cases exist of HSTCL associated with anti-TNFα treatment alone.[27]

Other adverse events related to anti-TNFα include the development of demyelinating neurological conditions, a drug-induced lupus syndrome, the development of psoriasis and the exacerbation of severe congestive heart failure.[28]

Summary

The most significant recent advance in drug therapy in the management of IBD has been in the use of anti-TNFα, particularly for patients with severe CD. Over the past 10 years, an understanding of the most effective use of anti-TNFα drugs has developed, including continuous treatment, early use in severe disease and combination with other immunosuppressants. There are now clear safety data with evidence that sepsis is the main adverse event. Controversies remain, including determining when it is reasonable to withdraw treatment safely, the long-term effects of achieving deep remission and treatment options for patients who fail to respond, or lose response, to anti-TNFα drugs.

There has also been a development in understanding of the use of 5-ASAs, particularly the importance of topical therapy in UC and their lack of efficacy in CD.

Advances in understanding of the pathogenesis of IBD have resulted in the development of multiple new therapies that might represent an alternative to current treatments. These new therapies include biologicals targeted at other inflammatory cytokines and anti-integrins that inhibit the migration of leucocytes into the mucosa.[29] There is a clear need for safer, more efficacious treatments in IBD, but these remain in development.

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Address for correspondence: Dr JC Mansfield, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP. Email: John.mansfield@nuth.nhs.uk