Re-defining outcomes and re-evaluating remission in inflammatory bowel disease: Assessing key evidence

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Introduction

The term inflammatory bowel disease (IBD) encompasses two conditions: Crohn's disease (CD) and ulcerative colitis (UC) (Abreu and Sparrow 2006). The term UC dates from 1888 (Baron 2000) and Burrill Crohn described the eponymous condition in 1932 (Crohn et al 1932).

Since the mid 1950s when it was first reported that oral cortisone induced clinical remission in UC (Truelove and Witts 1955), corticosteroids have since become a mainstay of IBD management. Yet approximately 16% of patients do not respond to these agents (Faubion et al 2001) and the side effects and serious adverse reactions associated with their use are well known (Yang and Lichtenstein 2002).

By 1980, researchers had isolated 5-aminosalicylate (5-ASA) as the moiety responsible for the activity of sulfasalazine in IBD (Azad Khan et al 1977; van Hees et al 1980). The immunosuppressant thiopurines are also widely used, despite the fact that they can take up to a median of 3 months to reach optimum efficacy (Lémann et al 2006).

It is in part because of the limitations associated with corticosteroids and immunosuppressant drugs that 50%–80% of people with CD ultimately require surgical interventions to treat the condition (National Institute for Health and Clinical Excellence [NICE] 2002); almost 10% of UC patients require colectomy in the year of diagnosis (Faubion et al 2001). Furthermore, mucosal inflammation seems to persist even during symptomatic remission induced by non-biological agents. This sub-clinical mucosal inflammation appears to be associated with the risk of clinical relapse (Arnott et al 2001, 2002).

In contrast, some biological agents that target tumor necrosis factor alpha (TNF-α) appear to heal the gastrointestinal mucosa in patients with IBD, as demonstrated in studies involving the anti-TNF-α agent infliximab. This healing is associated with improved signs and symptoms, long-term maintenance of remission, and a reduction in the risk of complications, surgery and hospitalization in CD and UC (Rutgeerts et al 2002, 2007). Although further studies are needed to determine whether mucosal healing is a feature of the other biological agents, it is plausible to pose the hypothesis that mucosal healing, as it appears to correlate with quiescent IBD, could offer a clinically useful marker indicating a favorable long-term prognosis.

Against this background, a group consisting of Professor Laurence J Egan, Chair of Clinical Pharmacology at the National University of Ireland, Dr Simon M Everett, Consultant Gastroenterologist at the University of Leeds, UK and Professor

Paul Rutgeerts, Professor of Medicine, Division of Gastroenterology, at the University of Leuven in Belgium, came together to examine whether the treatment goals and management of IBD should change to reflect the evolving evidence base. This supplement is based on these discussions, which primarily focused on evidence for CD. As more studies have been carried out on the use of infliximab in IBD than the other biological agents, some discussions focused on data from the infliximab evidence base to illustrate their points.

The authors hope that the supplement will stimulate debate and discussion about whether the outcome measures and pharmacological management of IBD should now be revised.

Inflammatory bowel disease: natural history

The incidence of CD appears to have risen 5-fold in Northern Europe since the 1950s. It affects 50 people per 100,000 of the UK population, thus, in total, around 36,000 people in the UK live with CD (Arnott et al 2002).

The incidence of UC is 6–15 per 100,000 a year, while the prevalence is around 12 times higher (Eaden and Mayberry 2002). Assuming a prevalence of 120 per 100,000, an estimated 72,000 people suffer from this condition in the UK.

In CD, dysregulated gastrointestinal mucosal immunity (possibly triggered by gut flora in a genetically predisposed person) results in inflammation that can arise anywhere along the gastrointestinal tract and is patchy, transmural, and sometimes granulomatous (Abreu and Sparrow 2006). Common symptoms of CD include abdominal pain, diarrhea and weight loss (NICE 2002). In UC, the dysregulated mucosal immunity produces inflammation that is more superficial than in CD and extends proximally from the rectum, with symptoms including bloody diarrhea, urgency, and rectal bleeding (Abreu and Sparrow 2006; Rutgeerts et al 2005).

The impact of IBD on sufferers and society is high, as not only does presentation often occur at a young age and has the potential to cause lifelong ill health, but there is also a slight increase in mortality rate for both UC and CD (Carter et al 2004).

Outcomes in CD

The clinical course of IBD varies between patients from a quiescent course, with remission lasting several years between relapses, to almost constantly active disease (Munkholm et al 1995). Complications are common: around one third of CD patients develop fistulae, and more than 15% of patients develop extra-intestinal manifestations, such as articular, ocular, hepatic, and skin disorders (NICE 2002). Other complications that can occur include obstruction and perforation of the gastrointestinal tract and perianal disease (characterized by fissures, fistulae, and abscesses) in patients suffering from colonic and ileocolonic CD.

Ultimately, 50%–80% of CD patients will require surgery, usually for strictures causing obstructive symptoms, fistulae, and failure to respond to medical therapy and complications (NICE 2002). An important retrospective study of 2002 patients with CD (Cosnes et al 2002) showed that the disease profile changes over time. The study demonstrated that, whereas more than 80% of patients have inflammatory disease at diagnosis, over a 20-year period up to 70% will develop penetrating disease and 18% stricturing disease, with only 12% remaining with a predominantly inflammatory disease (Figure 1).

Outcomes in UC and the impact of conventional therapies

Although there is an extensive evidence base supporting the use of conventional therapies for UC, as indicated below, they are not universally effective (Rutgeerts et al 2007). Outcomes among patients with UC remain relatively poor. A recent analysis suggested that 67% of patients with UC experience at least one relapse over a 10-year follow up (Höie et al 2007a).

The BSG Guidelines highlight evidence by Truelove and Witts which showed that oral prednisolone (starting at 40 mg daily) induced remission in 77% of 118 patients with mild to moderate disease within 2 weeks, compared with 48% treated with 8 g daily sulphasalazine (Truelove and Witts 1955). The Guidelines advise that a combination of oral and rectal steroids is better than either preparation alone (Carter et al 2004). A more recent meta-analysis compared the second generation steroid beclomethasone dipropionate (3 mg once daily, as enema/foam) with 5-ASA (1.4 g once daily) in mild-to-moderate distal UC (Manguso and Balzano 2007). The data demonstrated an improvement, or remission, in 65.3% of patients receiving beclomethasone dipropionate and in 69.9% of those in the 5-ASA patient group (Manguso and Balzano 2007).

A randomized study involving 87 patients with mildly to moderately active UC assessed the use of oral 4.8 g 5-ASA daily, coated with a pH-sensitive polymer, and found complete responses in 24% and partial responses in 50% of patients. This compares with complete responses in 5% and incomplete responses in 13% of patients in the placebo arm of the study (Schroeder et al 1987).

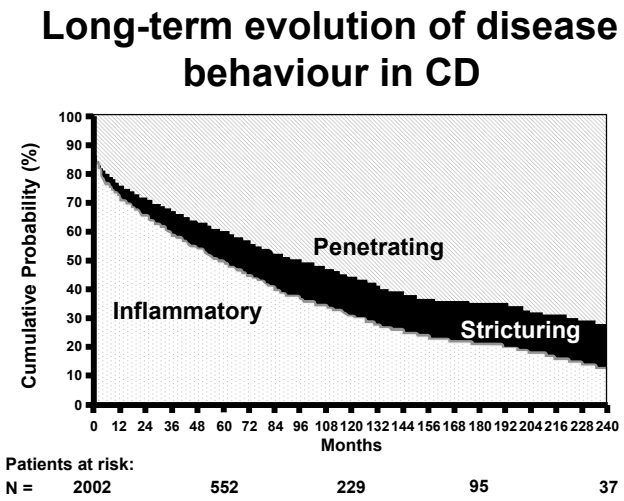

Figure 1 Long-term outcomes in Crohn's disease patients. Reprinted with permission from Cosnes J, Cattan S, Blain A, et al. 2002. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*, 8:244–50. Copyright © 2002 John Wiley and Sons.

More recently, the Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA (ASCEND) II trial assessed delayed-release oral mesalamine in 386 patients with mild-to-moderate active UC (Hanauer et al 2005). After 6 weeks, 72% of patients with moderate UC receiving 4.8 g mesalamine daily, and 59% of patients receiving 2.4 g mesalamine daily, showed either complete remission or a clinical response.

Nevertheless, approximately 9% of patients with distal colitis, 19% with substantial colitis, and 35% with total colitis undergo colectomy within 5 years of diagnosis, usually following failed medical therapy (Langholz et al 1992; Rutgeerts et al 2005). A recent paper suggests a lower rate of surgical intervention, with 8.7% of European UC patients undergoing colectomy in a 10-year period. However, colectomy rates varied from 10.4% in Northern Europe to 3.9% in the Southern centers (Höie et al 2007b).

Impact on quality of life and employment

Studies show that IBD can often profoundly undermine a patient's ability to perform the normal activities of daily living and to remain employed. Binder et al followed 185 patients with CD for a median of 5.5 years and found that, while 45% of these patients were asymptomatic each year, 30% experienced low-level symptoms and the remaining 25% endured a moderate to high symptom burden (Binder et al 1985). On average, work capacity declined by 25% in patients with CD compared with controls. Indeed, 15%–20% of patients with CD received disability allowances compared with 4.4% in the general population (Binder et al 1985).

Results from the cohort A Crohn's disease Clinical study Evaluating infliximab in a New long-term Treatment regimen (ACCENT) I, which enrolled patients with, on average, more severe disease than the Binder study, reinforce the impact of IBD on functional capacity. Patients with CD showed a significantly reduced quality of life (QoL), with 39% being unemployed and 25% receiving disability compensation (Feagan et al 2005). The high risk of surgical intervention for fistulating and stricturing complications is one important factor driving this disability; it also contributes to the direct and indirect economic burden imposed by IBD as discussed below (Feagan et al 2005).

Studies indicate that immunosuppressive drugs may not influence patients' likelihood of undergoing intestinal surgery. Cosnes et al found that in patients with CD, the cumulative risk of intestinal resection after 5 years (between 1978 and 2002) remained unchanged at approximately 35%, while prescription rates for immunosuppressants increased over the same time (Cosnes et al 2005).

Furthermore, symptoms recur in many patients after surgery for IBD. In a study investigating the predictability of the post-operative course of CD, endoscopic lesions were found in the neoterminal ileum in 73% of CD patients a year after surgery, with 20% of these patients showing symptoms (Rutgeerts et al 1990). Three years after surgery, the endoscopic recurrence rate was 85%, and the symptomatic recurrence rate was 34%. The severity of the early post-operative lesions on ileoscopy emerged as the most accurate predictor of disease course (Rutgeerts et al 1990).

The high incidence of surgery in IBD patients and the relatively high risk of post-operative recurrence reflect the progressive nature of CD and UC. It is possible that these conditions progress because the current treatments may leave a persistent 'smouldering' inflammation, even when patients are in remission. The recognition that this persistent, low-grade inflammation is clinically important challenges the traditional concept of remission, defined largely by symptomatic wellness in IBD.

Challenging the concept of remission

Over the years, several scoring systems to allow clinicians to assess IBD activity have been proposed. The most widely used systems are the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI) (NICE 2002).

The CDAI is the most widely used in CD (NICE 2002), and was developed by the National Cooperative Crohn's Disease Study (NCCDS) group to evaluate steroids in this condition. The group identified 8 variables that together form an index of disease activity: diarrhea, abdominal pain, general well-being, mass, extra-intestinal manifestations, hematocrit, weight, and anti-diarrheal drugs (Best et al 1976).

The CDAI cut-off values are somewhat arbitrary. Based on the range at which patients appeared well while taking steroids, a CDAI score of <150 was set as the value that indicated remission. Extremely severe CD can be associated with a CDAI score >450 (Best et al 1976). In the UK, NICE defines severe active CD as scores of at least 300 on the CDAI or at least 8–9 on the HBI system (NICE 2002).

Despite its widespread use, the CDAI has several limitations as an outcomes measure. As the scoring system is based on a physician's assessment, it is subjective and symptom-based, and does not take account of the underlying severity of mucosal damage and inflammation. Indeed, Cellier et al found that clinical activity seems to be virtually independent of the severity of the mucosal lesions and biological activity (Cellier et al 1994). In the same study, biological variables, such as markers of inflammation, accounted for 22% of the variations in the clinical index, and for 44% of those in the endoscopic index (Cellier et al 1994). In addition, because the CDAI is diary-based and evaluates the patient from a global perspective, it may fail to attach an appropriate emphasis on serious, local complications, such as fistulae, strictures and ileostomy. Furthermore, it is adult-derived and so may not be appropriate for children (Best et al 1976; Acciuffi et al 1996).

Corticosteroid-induced remission

Corticosteroids produce complete clinical remission in 48%–92% of patients with CD (Lémann et al 2006). Yet a significant proportion of patients with IBD fail to respond to these agents.

Faubion et al found that after 30 days of treatment with corticosteroids, 58% of patients with CD were in complete remission, 26% were in partial remission, but 16% showed no response (Figure 2). Similar results were seen in patients with UC (Faubion et al 2001). After 1 year, 32% of patients with CD showed a prolonged response; they were not being

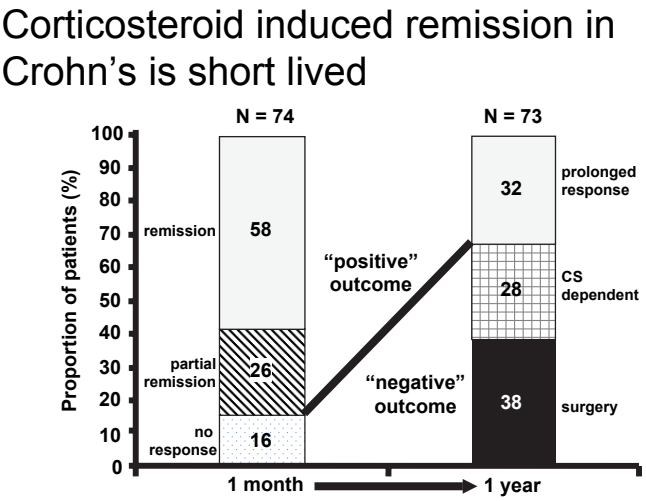

Figure 2 Steroids tend to produce short-term remission in Crohn's disease.

treated with corticosteroids and had not undergone surgery. However, 28% of patients in the study showed corticosteroid dependence and 38% needed surgery within 12 months; the remainder were lost to follow-up. Treatment outcomes were also suboptimal in those with UC: 49% maintained remission without surgery or prolonged treatment with corticosteroids, yet 22% of patients with UC were steroid-dependent, and 29% needed surgery within a year (Faubion et al 2001). These results suggest that the underlying inflammation continued unabated.

A growing evidence-base confirms that corticosteroid-induced remission is short-lived and associated with a lack of endoscopic improvement, as well as a high risk of serious adverse events, in many patients (Rutgeerts et al 2007; Yang et al 2002).

Modigliani et al studied 142 patients from the French Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID) study. They assessed the cohort with active colonic or ileocolonic CD and found that there was no correlation between clinical severity and the nature, surface, or severity of endoscopic lesions. While prednisolone (1 mg/kg daily) induced clinical remission in 92% of patients, only 29% of this group also showed endoscopic remission (Modigliani et al 1990).

Further studies of the GETAID group suggest that short-term steroids do not usually induce endoscopic healing and that, when endoscopic healing occurs, the benefits are temporary. In a study of 147 patients from the GETAID it was found that endoscopic activity after oral prednisolone (1 mg/kg daily) produced clinical remission in 93% of patients with CD (Landi et al 1992). At 18 months, however, although 22% of patients remained in remission without steroid usage, 71% of those in clinical remission still showed active endoscopic lesions.

Sub-clinical inflammation: the pathologic foundation of IBD

The first evidence of ongoing inflammation in patients with IBD during clinical remission emerged in a 1986 study by Saverymuttu. The study used fecal 111In granulocyte excretion to quantify gut inflammatory activity in patients with CD. In this study, 89% of patients with a CDAI of less than150 showed fecal 111In granulocyte excretion above the upper limit found in the irritable bowel syndrome. In some cases, 111In granulocyte excretion was 40% above the upper limit (Saverymuttu 1986).

Other studies also suggest that, because mucosal inflammation persists even during asymptomatic periods, the clinical remission induced by steroids is not an adequate endpoint for IBD. Indeed, sub-clinical mucosal inflammation may be followed by clinical relapse despite treatment (Arnott et al 2002; Rutgeerts et al 2007).

Furthermore, numerous studies have illustrated the close association between the over-production of several inflammatory cytokines and the trafficking of leukocytes into the bowel and the risk of relapse in patients with IBD (Nakamura et al 2006; Abreu and Sparrow 2006).

Calprotectin as a marker of clinical remission

The calcium-binding protein calprotectin accounts for up to 60% of the protein content in the cytosol of neutrophils. As calprotectin is stable against metabolic degradation, levels in feces offer a clinically useful marker specific for mucosal neutrophil levels (Arnott et al 2002).

In patients with active CD, there is a significant increase in the migration of neutrophils from the circulation to the diseased intestine (Saverymuttu et al 1983a, b). However, CD patients show elevated levels of calprotectin even during clinical remission. In one study, normal subjects showed median levels of around 2 mg/L, compared with 91 mg/L in those with CD. Patients with active CD showed a median fecal calprotectin concentration of 165 mg/L, compared with a median of 87 mg/L in patients with quiescent disease (Tibble et al 2000a). These concentrations suggest a continued presence of neutrophils in the mucosa of people with quiescent CD.

Follow-up studies by Tibble et al support the use of calprotectin as a marker for relapse in people with IBD (Tibble et al 2000b). The median calprotectin levels in patients who relapsed was found to be 122 mg/L for patients with CD and 123 mg/L for patients with UC. This compares with 41.5 mg/L for patients with CD who did not relapse and 29.0 mg/L for patients with UC who did not relapse. Contrastingly, healthy people show calprotectin levels of $<$10 mg/L. The sensitivity and specificity of a calprotectin threshold of 50 mg/L for predicting relapse were 90% for CD and 83% for UC. Preliminary data also suggest that calprotectin seems to normalize with complete mucosal healing on endoscopic and histological evaluation in IBD patients. If further studies confirm these findings, measuring calprotectin may offer an alternative to colonoscopies (Røseth 2003).

Fecal calprotectin may be an even stronger predictor of clinical relapse in UC than in CD (Costa et al 2005); findings that support the conclusion that fecal calprotectin

represents a promising non-invasive tool for monitoring and optimizing therapy.

Whole-gut lavage studies

Whole-gut lavage studies offer further evidence of the ongoing mucosal inflammation in patients in remission induced by non-biological therapy: almost two-thirds of patients with CD showed elevated levels of interleukin (IL)-1β and IL-8 when in remission. Abnormal immunoglobulin (Ig) G and raised concentrations of the enzyme granulocyte elastase were also present (Arnott et al 2001). Furthermore, patients with raised levels of IL-1β and IL-8 were more likely to relapse over the course of 1 year. IL-β emerged as an independent variable predicting relapse on multiple regression analysis: the mean absolute values were 37.4 pg/mL in patients who relapsed and 13 pg/mL in those who remained in remission (Arnott et al 2001).

The presence of these cytokines in the gastrointestinal tracts of patients with IBD corresponds with the subclinical mucosal inflammation that appears to be associated with a high risk of relapse (Arnott et al 2001, 2002).

Interleukins and C-reactive protein

Studies also show that levels of numerous cytokines, including IL-1, IL-6, IL-8, IL-12 and TNF-α, increase in patients with IBD compared to healthy controls (Mitsuyama et al 2006). For instance, serum levels of IL-6 >20 pg/mL were associated with a 17-fold increase in risk of relapse over a year compared with lower concentrations (Louis et al 1997). Levels of soluble IL-2 receptor also appear to have a positive correlation with relapse risk and disease activity (Louis et al 1997).

In their analysis of biopsies from patients with CD, Schreiber et al found that stimulated levels of cytokines, including TNF-α, were higher in patients with active disease than in healthy controls. Levels taken from patients in remission were higher than those in controls, but lower than those taken from patients with active disease (Schreiber et al 1999).

Serum concentrations of C-reactive protein (CRP) also appear to be associated with persistent gastrointestinal inflammation. In general, serum levels of CRP correlate with the clinical score in IBD. However, Boirivant et al found that one-third of patients with clinically active CD have normal CRP levels, while one third of patients in clinical remission have raised CRP levels. In CD patients who achieved or remained in remission, the likelihood of clinical relapse after 2 years of entry was higher in those with persistently raised CRP than those who showed normal CRP levels (Boirivant et al 1988).

The central role of TNF-α in IBD

While a complex network of mediators controls IBD, studies show that TNF-α is central to, and critical in, driving the cycle of inflammation that underlies the disease (Rutgeerts et al 2004). TNF-α modulates immune and inflammatory responses to infections, cancer and autoimmune conditions; most cell types express TNF-α receptors.

Binding of TNF-α to cell surface receptors will trigger apoptosis or, alternatively, activate the transcription factor NF-kappa B. This, in turn, increases the production of many pro-inflammatory factors, including IL-1, IL-8, cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS). COX-2 increases production of pro-inflammatory prostaglandins and iNOS induces increased production of nitric oxide. NF-kappa B also stimulates the production of more TNF-α, producing an amplification loop that creates symptoms as well as increases the risk of relapse and complications (Figure 3) (Ivashkiv 2003).

In patients with CD, TNF-α production is elevated in mucosal biopsies, gastrointestinal lumen, stools and serum. CD patients also show an increase in the number of TNF-α producing cells in the mucosa (ten Hove et al 2002). UC patients show increased TNF-α concentrations in blood, colonic tissue, and stools (Rutgeerts et al 2005). The median serum concentrations of TNF-α is 640-fold higher in patients with CD than in healthy controls and 380-fold higher in those with UC patients than in healthy controls. Median levels have also been found to be 1.7-fold higher in patients with active, compared with the inactive form of, UC (Komatsu et al 2001).

It appears, therefore, that excess TNF-α production, usually from activated monocytes and macrophages, may contribute to the pathogenesis of several conditions (Siegel et al 1995), in rheumatoid arthritis, psoriasis, and psoriatic arthritis, as well as IBD. In IBD, the main cells involved are monocytes and macrophages in the gastrointestinal mucosa. Indeed, T cells in the *lamina propria* (the connective tissue beneath the epithelium) may be the main target for infliximab (Di Sabatino et al 2004) and other anti-TNF-α treatments.

TNF-α concentrations and outcomes in IBD

Concentrations of TNF-α appear to be closely related to outcomes in patients with IBD. Schreiber et al followed 137

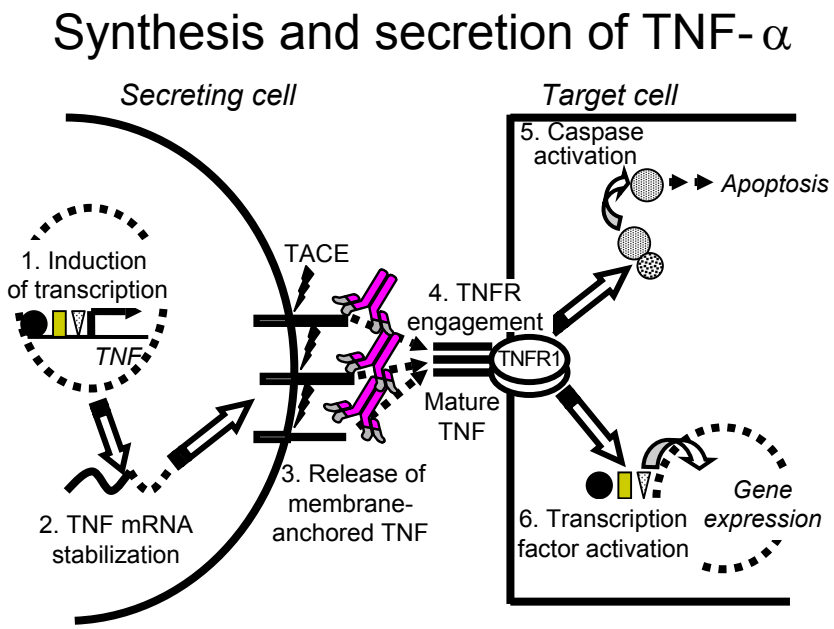

Figure 3 The synthesis and secretion of TNF-α.

patients with CD who were in steroid-induced remission for a follow-up period of one year. Increased secretion of TNF-α and IL1-β, after short-term culture of human *lamina propria* mononuclear cells, were strong predictors of the risk of acute relapse over the year. In contrast, the site and extent of CD, baseline demographics, and serum acute-phase proteins showed little predictive value in the study (Schreiber et al 1999).

Similarly, Yamamoto et al enrolled 36 patients who remained in remission after resection for terminal ileal or ileo-cecal CD. Levels of IL-1β, IL-6, and TNF-α in the ileal mucosa were significantly higher in the 16 patients who relapsed after a year compared with those in remission. Cytokine levels in the rectal mucosa, conventional blood markers, and plasma cytokine levels did not correlate with relapse (Yamamoto et al 2004).

Beyond remission: mucosal healing and bowel preservation

Current immunological evidence challenges the concept of steroid-induced remission, quantified in the CDAI and other clinical scoring systems, and offers the prospect of improving long-term outcomes in IBD. In a study examining the effect of treatment with azathioprine on inflammatory lesions in the neoterminal ileum of 15 CD patients who experienced a severe recurrence post-operatively, for example, azathioprine was found to induce and maintain clinical remission in all 15 patients for at least 6 months after the withdrawal of corticosteroids (D'Haens et al 1997). Six patients showed complete macroscopic healing of the neoterminal ileum; 5 showed superficial erosions; 3 showed partial healing; and lesions remained unchanged in 1 patient (D'Haens et al 1997).

Nevertheless, the most compelling evidence comes from studies suggesting that the molecular, cellular and tissue effects of anti-TNF-α agents result in clinical improvement in patients with IBD.

Anti-TNF-α agents: pharmacodynamics and pharmacokinetics

There are currently several anti-TNF-α agents available for a range of indications, and several more are in development.

Important molecular and mechanistic differences exist between the anti-TNF-α agents. Adalimumab and infliximab, for example, induce apoptosis and down-regulate production of IL-10 and IL-12 in cultured monocytes; this is not seen in etanercept (Shen et al 2005). Appreciating such differences in the molecular pharmacology and pharmacokinetics of anti-TNF-α biopharmaceuticals may allow clinicians to individualize treatment and tailor it to the patient.

Infliximab, the prototype and most widely-studied anti-TNF-α agent in IBD, has a high affinity and specificity for recombinant and natural human TNF-α. Infliximab is a mouse-human chimeric IgG1 monoclonal antibody (MAB), with human constant regions and murine antigen binding regions (Knight et al 1993).

Adalimumab has been introduced more recently and is a fully human IgG1 MAB. Certolizumab pegol (CDP870), which is currently in late phase clinical development, is a pegylated Fab fragment of humanized anti-TNF MAB (Nakamura et al 2006). There is currently relatively little data available on this agent, but the addition of polyethylene glycol to the protein backbone aims to enhance the pharmacokinetic profile. The structural variations between these agents translate into pharmacokinetic differences, as illustrated in Table 1 (Maser et al 2006; De Ruiter and Riley 2003; Schering-Plough 2007).

Infliximab shows a high and rapid maximum serum concentration (C_{max}) (Table 1). Importantly, when serum levels were analyzed, 82% of patients with detectable trough levels of infliximab levels remained in remission compared with 6% of those in whom serum infliximab was undetectable. Detectable trough serum infliximab was also associated with lower levels of CRP than those with undetectable levels (2.0 vs 11.8 μg/L, respectively) and a higher rate of endoscopic improvement (88% vs 33%, respectively) (Maser et al 2006).

Infliximab binds to the monomer and trimer forms of soluble TNF-α, forming stable complexes. Infliximab also binds avidly to, and forms stable complexes with, the transmembrane form of TNF-α. In contrast, etanercept binds to the trimer form, resulting in relatively unstable complexes, which lead to dissociated TNF-α. Furthermore, more molecules of infliximab bind to the transmembrane form more avidly than etanercept. Such differences may help explain the differential efficacy of the anti-TNF-α biopharmaceuticals in CD and psoriasis (Scallon et al 2002). For example, the dose of etanercept that is effective in rheumatoid arthritis (25 mg subcutaneously twice weekly) appears to be ineffective in moderate to severe CD (Nakamura et al 2006).

Infliximab inhibits mitogenesis and the IL-6 secretion by human fibroblasts and the stimulation of human umbilical vein endothelial cells (measured by the expression of the adhesion molecules E-selectin and ICAM-1, as well as procoagulant activity) produced by TNF-α (Siegel et al 1995). Infliximab also reduces the number of cells producing TNF-α as well as the chemokines RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted; also called CCCL5) and MIP-1 α (Macrophage Inflammatory Protein) in the *lamina propria* (ten Hove et al 2002). Chemokines attract other cells to the site of inflammation. Ljung et al reported that infliximab reduces rectal nitric oxide levels, parallel with the decreases in iNOS, TNF-α, IL-1β, and interferon gamma (Ljung et al 2007).

Apoptosis and TNF-α

When TNF-α binds to a target cell, it can either stimulate the production of inflammatory mediators or induce apoptosis. Apoptosis plays an important role in regulating the gastrointestinal immune response through its down-regulation of the gastrointestinal T cells (ten Hove et al 2002).

The inflammatory cells in the *lamina propria* of CD patients appear to be relatively resistant to apoptosis, which propagates and perpetuates the inflammatory response. A growing body of evidence suggests that the ability of anti-TNF-α agents to induce apoptosis of T lymphocytes and other inflammatory cells in the *lamina propria* may contribute to their efficacy in CD.

Adalimumab and infliximab both induce apoptosis in cultured monocytes (Shen et al 2005), while infliximab induces apoptosis of activated, but not resting, T lymphocytes. Furthermore, in CD patients, infliximab causes a rapid and specific increase in the number of apoptotic T lymphocytes in the gut mucosa, without affecting peripheral blood mononuclear cells (ten Hove et al 2002). Studies also show that infliximab induces sustained apoptosis of *lamina propria* T cells, which persists 4 weeks after the last infusion in patients with CD. Indeed in the study, *lamina propria* T cells were more susceptible to infliximab-induced apoptosis than T lymphocytes isolated from peripheral blood (Di Sabatino et al 2004). In contrast, certolizumab pegol does not appear to induce

Table 1 Comparative pharmacokinetics for infliximab, adalimumab and certolizumab

	Time to C_{max}	Serum C_{max}	Route	Trough serum concentration
Infliximab	2 hours (infusion time)	118 μg/mL 5 mg/kg	IV	0–11.7 μg/mL after 8 weeks
Adalimumab	131 hours	4.7 μg/mL 40 mg	SC	5–9 mg/mL after 2 weeks
Certolizumab pegol	Unknown	Unknown	SC	Unknown

apoptosis, so further research is needed to help characterize the role of apoptosis in determining therapeutic outcomes with anti-TNF-α agents in IBD (Blick and Curran 2007).

Until such studies are carried out, optimizing anti-TNF-α therapy means considering the molecular pharmacological effects that underlie the cellular, tissue and clinical outcomes. Therefore, clinicians could consider choosing an agent with a high affinity for TNF-α. Prescribers could also consider the pharmacokinetic profile: higher trough levels of infliximab are associated with better clinical outcomes, while maintenance dosing reduces the risk of immunogenicity, as discussed below.

Efficacy of biological agents in IBD

Biological agents appear to be relatively effective in CD and UC (Akobeng and Zachos 2003; Lawson et al 2006). The following discussion focuses on the most widely studied agent, infliximab.

A number of studies show that infliximab is effective and well tolerated in its UC and CD indications, and appears to promote mucosal healing (Sands et al 2004; Rutgeerts et al 2002; Rutgeerts et al 2004). As TNF-α over-expression is associated with increased relapse in patients with IBD, continuous therapy suppresses disease activity and may increase the chances of patients remaining in remission. Indeed, in one study in which patients received a single dose of infliximab, 7% of those who showed a response after 2 weeks still showed endoscopic healing 54 weeks after treatment (Rutgeerts et al 2002).

The ACCENT I study confirmed the safety and efficacy of infliximab as scheduled maintenance treatment in patients with non-fistulizing CD (Rutgeerts et al 2004), and the ACCENT II in those with fistulizing CD (Sands et al 2004).

Rutgeerts et al randomized 573 patients with luminal CD to the placebo arm, which received infusions at weeks 2 and 6, and then every 8 weeks until week 46 (episodic), or to one of the infliximab patient groups, which received 5 mg/kg at weeks 2 and 6, followed by either 5 mg/kg (5 mg/kg scheduled) every 8 weeks or 10 mg/kg (10 mg/kg scheduled) every 8 weeks. Results showed that the scheduled infliximab groups, particularly the 10 mg/kg group, had better CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) responses than the episodic group. Both scheduled groups had fewer hospitalizations, higher rates of mucosal healing, and fewer patients developed antibodies than those in the episodic group, with no increase in side effects (Rutgeerts et al 2004).

Sands et al studied 306 patients with fistulizing CD who all received 5 mg/kg infliximab at baseline and at weeks 2 and 6. The 195 patients who had a response at weeks 10 and 14, as well as 87 patients who had not responded, then received placebo or 5 mg/kg infliximab every 8 weeks until week 54 (Sands et al 2004).

The time to loss of response was >40 weeks in patients who received infliximab maintenance therapy compared with 14 weeks for placebo. At week 54, 19% of the placebo group showed no draining fistulas, compared with 36% of those who received infliximab maintenance treatment (Sands et al 2004).

Long-term safety of biological agents in IBD

The biological agents available appear to be relatively well tolerated during long-term treatment, as demonstrated by a number of studies with infliximab (Rutgeerts et al 2005; Lawson et al 2006).

A Cochrane systematic review by Lawson et al concluded that short-term adverse events related to infliximab were usually mild, and included headache, pruritis, arthralgia, and upper respiratory or urinary infections (Lawson et al 2006). Severe adverse events were relatively rare. A review of 500 patients' medical records, all of who received a median of three infliximab infusions and had a median follow-up of 17 months, found that 6.0% experienced a serious adverse event related to infliximab, while 8.2% of patients developed an infection attributed to infliximab (Colombel et al 2004).

It is important to note that anti-TNF-α monoclonal antibodies may reactivate latent tuberculosis by disrupting the granuloma that compartmentalizes *Mycobacterium tuberculosis*. Screening for, and treating, latent tuberculosis prevents reactivation in most patients taking anti-TNF-α monoclonal antibodies (Keane 2005).

The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry was established to study the long-term safety of infliximab in 5807 patients with CD. Infusion reactions occurred after 5.4% of the infusions; severe reactions were uncommon, occurring after just 0.16% of infusions (Lichtenstein et al 2006). Early infusion reactions can be managed with hydrocortisone and cetirizine prophylaxis. Methylprednisolone given 2 days before, until 5 days after, the infusion can help manage most delayed reactions.

Mortality and incidence of neoplasms were similar for infliximab patients and non-infliximab patients with the incidence per 100 patient-years for all types of cancer being 0.53 and 0.49, respectively. Data relating to lymphomas

alone showed an incidence of 0.10 for infliximab patients and 0.06 for non-infliximab patients. The incidence of serious infections was 1.27 per 100 patient-years within 3 months of an infliximab infusion. This compared with 0.85 in patients who received infliximab more than 3 months previously (relative risk = 1.51). However, logistic regression showed that infliximab was not an independent predictor of the risk of serious infections. In contrast, prednisolone was independently associated with serious infection (Lichtenstein et al 2006).

The authors comment that the risk of serious infection and mortality among patients who received infliximab was similar to that among patients who received 6-mercaptopurine, azathioprine and methotrexate. While the study did not find evidence of an increased risk of malignancy associated with infliximab, longer follow-up is necessary to confirm this (Lichtenstein et al 2006).

Immunological reactions

Biological agents are foreign proteins so immunological reactions could compromise efficacy or tolerability. In the active UC trial (ACT) 1, 6.1% of patients tested positive for antibodies in the 54 weeks after the first infusion of infliximab. Furthermore, 15.7% showed undetectable levels of infliximab in their serum. The remaining patients were negative for antibodies but showed detectable serum infliximab concentrations. A clinical response at week 54 occurred in 21.4% of those with positive antibody tests; this compared with 8.3% of patients with negative tests and 57.5% of patients with inconclusive tests (Rutgeerts et al 2005).

In ACT 2, 6.4% of the patients tested positive for antibodies and 18.1% showed undetectable serum infliximab levels. Again, the remaining patients tested negative for antibodies, but showed detectable serum infliximab concentrations. A clinical response at week 30 occurred in 57.9% of those with positive tests for antibodies. This compared with 57.0% in the undetectable, and 77.2% in the antibody-negative, patient groups (Rutgeerts et al 2005).

Maintenance treatment appears to reduce immunogenicity. For example, in the ACCENT I study, which assessed maintenance infliximab in 573 CD patients with a score of at least 220 on the CDAI, antibodies to infliximab were detected by week 72 in 30% of patients receiving placebo after an initial infliximab infusion. This compared with 10% of patients receiving 5 mg/kg of infliximab through the study period, and 7% in those taking 10 mg/kg of infliximab throughout. Patients receiving concurrent immunomodulators were less likely to develop antibodies (10%) than those receiving infliximab alone (18%) (Hanauer et al 2004).

Antibodies were associated with a 12% increase in the number of infusion reactions. However, antibodies were not associated with an increased risk of serious infusion reactions or serum sickness-like reactions. Overall, 64% of antibody-positive and 62% antibody-negative patients achieved clinical response by week 54. Similarly, 41% of antibody-positive and 39% of antibody negative patients were in clinical remission by week 54. In addition, 86% of patients responded to re-treatment, and 63% were in clinical response at week 54. However, 31% of antibody-positive patients in the placebo arm attained clinical remission compared with 37% and 54% of those who were antibody negative or inconclusive, respectively (Hanauer et al 2004).

Cost-effectiveness

In addition to being clinically efficacious and well tolerated, biological agents may be cost-effective, largely because the improved mucosal healing translates into a reduced need for hospitalization and surgery, as demonstrated by studies of infliximab. In ACCENT 1, for example, patients with CD in whom the mucosal lesions were healed at week 10 or week 54, or both, had a lower incidence of hospitalization or surgery compared with those patients who showed no evidence of mucosal healing. No patients with mucosal healing at both week 10 and week 54 required hospitalization or surgery. Of the patients who showed evidence of healing at one of the two visits, 25% required hospitalization. However, none of these patients required surgery. In contrast, in patients with CD who showed no mucosal healing, the hospitalization rate was 46% and 8% required surgery (Rutgeerts et al 2006).

Nevertheless, few studies have formally assessed the pharmacoeconomics of anti-TNF-α therapy in either UC or CD from the perspective of the UK's National Health Service (NHS). (The audience for the symposium was predominately from the UK.) One study, a retrospective audit carried out at 7 UK centers, seems to have quantified infliximab's impact on health care resource utilization from the perspective of the NHS (Jewell et al 2005). The authors reviewed notes from 205 patients with moderate or severe CD during the 6 months before and 6 months after an initial infusion of infliximab. More than 60% of the patients had the licensed indication of chronic active CD. Over 70% of patients and clinicians rated the response to treatment as good to excellent. The number of patients taking steroids declined by 45% and steroid dosage was reduced in a further 34% (Jewell et al 2005).

The audit confirmed that infliximab reduces the likelihood that CD patients will require surgery and hospitalization. The number of inpatient days reduced by 1093 in

the 6 months after infliximab compared with the 6 months prior to treatment with infliximab. There were also 7 fewer operations, 33 fewer examinations under anesthetic, and 99 fewer diagnostic procedures in the 6 months after treatment. Infliximab reduced the total direct costs of managing CD in this group of patients by an estimated £591,006. When the acquisition cost of infliximab is taken into account, the total net reduction in direct costs was £28,287. Although further studies are needed to confirm the findings, these results indicate that infliximab may be a potentially cost-effective treatment option in selected patients with CD (Jewell et al 2005).

This study was performed from the perspective of the NHS. Therefore, the study does not take into account the indirect costs (such as lost productivity and disability payments) associated with CD. Indeed, patients with CD may be up to 5 times more likely to receive disability allowances than the general population (Binder et al 1985). As a result, this study is likely to underestimate the total economic benefit that could be gained through improved management of CD, although further studies are also needed to confirm this.

Conclusions

IBD is a chronic, progressive condition, characterized by relapses and, unless managed effectively, unremitting intestinal inflammation may ensue. Mortality rates remain slightly higher than those of the general population and patients are likely to develop complications and require surgery. Corticosteroids and immunosuppressant drugs are the conventional mainstays of management, but there is a growing body of clinical and experimental evidence to suggest that the previous gold standard of steroid-induced clinical remission is an inadequate outcome measure in IBD. Mucosal inflammation seems to persist even during symptomatic remission induced by these agents. It appears that this sub-clinical mucosal inflammation ultimately induces clinical relapse (Arnott et al 2002).

Compelling evidence, through studies with infliximab, now suggests that anti-TNF-α therapy can induce complete and sustained mucosal healing, which is associated with lack of significant complications, alleviation of signs and symptoms, and better long-term course and natural history of IBD. Experience with the anti-TNF-α agent infliximab has led to the definition of "new" goals for IBD management: modification of its long-term course; complete and persistent healing of the bowel mucosa; avoiding complications, hospitalization and surgery; and improving the cost-effectiveness of treatment. While further studies are needed to determine whether mucosal healing is a feature of all anti-TNF-α agents, evidence provided by infliximab suggest that, through their proven ability to elicit improved and sustained mucosal healing, and potentially bowel preservation, anti-TNF-α agents may offer the opportunity to modify the long-term course of IBD in selected patients.

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References

Abreu MT, Sparrow MP. 2006. Translational research in inflammatory bowel disease. *Mt Sinai J Med*, 73:1067–73.

Acciuffi S, Ghosh S, Ferguson A. 1996. Strengths and limitations of the Crohn's disease activity index, revealed by an objective gut lavage test of gastrointestinal protein loss. *Aliment Pharmacol and Therap*, 10:321–6.

Akobeng AK, Zachos M. 2003. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*, CD003574.

Arnott ID, Drummond HE, Ghosh S. 2001. Gut mucosal secretion of interleukin 1beta and interleukin-8 predicts relapse in clinically inactive Crohn's disease. *Dig Dis Sci*, 46:402–9.

Arnott ID, Watts D, Ghosh S. 2002. Review article: is clinical remission the optimum therapeutic goal in the treatment of Crohn's disease? *Aliment Pharmacol Ther*, 16:857–67.

Azad Khan AK, Piris J, Truelove SC. 1977. An experiment to determine the active therapeutic moiety of sulphasalazine. *Lancet*, 2:892–5.

Baron JH. 2000. Inflammatory bowel disease up to 1932. *Mt Sinai J Med*, 67:174–89.

Best WR, Becktel JM, Singleton JW, et al. 1976. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*, 70:439–44.

Binder V, Hendriksen C, Kreiner S. 1985. Prognosis in Crohn's disease – based on results from a regional patient group from the county of Copenhagen. *Gut*, 26:146–50.

Blick S, Curran M. 2007. Certolizumab Pegol in Crohn's disease. *Biodrugs*, 21:195–201.

Boirivant M, Leoni M, Tariciotti D, et al. 1988. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. *J Clin Gastroenterol*, 10:401–5.

Carter J, Lobo AJ, Travis SPL. 2004. Guidelines for the management of inflammatory bowel disease in adults. *Gut*, 53(Suppl V):v1–16.

Cellier C, Sahmoud T, Froguel E, et al. 1994. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut*, 35:231–5.

Colombel JF, Loftus EV, Tremaine WJ, et al. 2004. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology*, 126:19–31.

Cosnes J, Cattan S, Blain A, et al. 2002. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*, 8:244–50.

Cosnes J, Nion-Larmurier I, Beaugerie L, et al. 2005. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut*, 54:237–41.

Costa F, Mumolo MG, Ceccarelli L, et al. 2005. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut*, 54:364–8.

Crohn BB, Ginzburg L, Oppenheimer GD. 1932. Regional ileitis: a pathologic and clinical entity. *JAMA*, 99:1323–9.

De Ruiter J, Riley TN. 2003. How can adalimumab (Humira) be used to treat rheumatoid arthritis? *US Pharmacist*. Accessed 09.08.07. URL: http://www.uspharmacist.com/index.asp?show=article&page=8_1083.htm.

D'Haens G, Geboes K, Ponette E, et al. 1997. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology*, 112:1475–81.

Di Sabatino A, Ciccocioppo R, Cinque B, et al. 2004. Defective mucosal T cell death is sustainably reverted by infliximab in a caspase dependent pathway in Crohn's disease. *Gut*, 53:70–7.

Eaden JA, Mayberry JF. 2002. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut*, 51(Suppl 5):V10–2.

Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. 2001. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*, 121:255–60.

Feagan BG, Yan S, Bala M, et al. 2003. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastro*, 98:2232–8.

Feagan BG, Bala M, Yan S, et al. 2005. Unemployment and disability in patients with moderately to severely active Crohn's disease. *J Clin Gastroenterol*, 39:390–5.

Hanauer SB, Wagner CL, Bala M, et al. 2004. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol*, 2:542–3.

Hanauer SB, Sandborn WJ, Kornbluth A, et al. 2005. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol*, 100:2478–85.

Höie O, Wolters FL, Riis L, et al. 2007a. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology*, 132:507–15.

Höie O, Wolters F, Riis L, et al. 2007b. Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based Cohort. *Am J Gastroenterol*, Jun 7 [Epub ahead of print]:

Ivashkiv LB. The history, basic science and biology of TNF. Hospital for Special Surgery (web). Accessed 09.08.07. URL: http://www.hss.edu/professional-conditions_13504.asp?refName=Rheumatic+Diseases+–+Therapeutics&refUrl=professional-conditions_10197.asp

Jewell DP, Satsangi J, Lobo A, et al. 2005. Infliximab use in Crohn's disease: impact on healthcare resources in the UK. *Eur J Gastroenterol Hepatol*, 17:1047–52.

Keane J. 2005. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. *Rheumatology*, 44:714–20.

Knight DM, Trinh H, Le J, et al. 1993. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol Immunol*, 30:1443–53.

Komatsu M, Kobayashi D, Saito K, et al. 2001. Tumor necrosis factor-alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immuno-PCR. *Clin Chem*, 47:1297–301.

Landi B, Anh TN, Cortot A, et al. 1992. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology*, 102:1647–53.

Langholz E, Munkholm P, Davidsen M, et al. 1992. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology*, 103:1444–51.

Lawson MM, Thomas AG, Akobeng AK. 2006. Tumor necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*, CD005112.

Lémann M, Mary JY, Duclos B, et al. 2006. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology*, 130:1054–61.

Lichtenstein GR, Feagan BG, Cohen RD, et al. 2006. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol*, 4:621–30.

Ljung T, Axelsson LG, Herulf M, et al. 2007. Early changes in rectal nitric oxide and mucosal inflammatory mediators in Crohn's colitis in response to infliximab treatment. *Aliment Pharmacol Ther*, 25:925–32.

Louis E, Belaiche J, van Kemseke C, et al. 1997. A high serum concentration of interleukin-6 is predictive of relapse in quiescent Crohn's disease. *Eur J Gastroenterol Hepatol*, 9:939–44.

Manguso F, Balzano A. 2007. Meta-analysis: the efficacy of rectal beclomethasone dipropionate vs 5-aminosalicylic acid in mild to moderate distal ulcerative colitis. *Aliment Pharmacol Ther*, 26:21–9.

Maser EA, Villela R, Silverberg MS, et al. 2006. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*, 4:1248–54.

Mitsuyama K, Tomiyasu N, Takaki K, et al. 2006. Interleukin-10 in the pathophysiology of inflammatory bowel disease: increased serum concentrations during the recovery phase. *Mediators Inflamm*, 2006:1–7.

Modigliani R, Mary JY, Simon JF, et al. 1990. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. *Gastroenterology*, 98:811–8.

Munkholm P, Langholz E, Davidsen M, et al. 1995. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol*, 30:699–706.

Nakamura K, Honda K, Mizutani T, et al. 2006. Novel strategies for the treatment of inflammatory bowel disease: Selective inhibition of cytokines and adhesion molecules. *World J Gastroenterol*, 12:4628–35.

[NICE] National Institute for Health and Clinical Excellence. 2002. Guidance on the use of infliximab for Crohn's disease. Technology Appraisal Guidance No. 40. London, UK.

Røseth AG. 2003. Determination of faecal calprotectin, a novel marker of organic gastrointestinal disorders. *Dig Liver Dis*, 35:607–9.

Rutgeerts P, Geboes K, Vantrappen G, et al. 1990. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*, 99:956–63.

Rutgeerts P, Van Assche G, Van Deventer S, et al. 2002. Infliximab maintenance treatment strategy results in mucosal healing in patients with Crohn's disease. *Gastroenterology*, 122(Suppl):A–618.

Rutgeerts P, Feagan BG, Lichtenstein GR, et al. 2004. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*, 124:402–13.

Rutgeerts P, Sandborn WJ, Feagan BG, et al. 2005. Infliximab for induction and maintenance therapy for ulcerative Colitis. *N Engl J Med*, 353:2462–76.

Rutgeerts P, Diamond R, Bala M, et al. 2006. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc*, 63:433–42.

Rutgeerts P, Vermeire S, van Assche Gl. 2007. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut*, 56:453–5.

Sands BE, Anderson FH, Bernstein CN, et al. 2004. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*, 350:876–85.

Saverymuttu SH, Peters AM, Lavender JP, et al. 1983a. 111-Indium autologous leucocytes in inflammatory bowel disease. *Gut*, 24:293–9.

Saverymuttu SH, Peters AM, Lavender JP, et al. 1983b. Quantitative faecal Indium-111 labeled leucocyte excretion in assessment of disease activity in Crohn's disease. *Gastroenterology*, 85:1333–9.

Saverymuttu SH. 1986. Clinical remission in Crohn's disease – assessment using faecal 111In granulocyte excretion. *Digestion*, 33:74–9.

Scallon B, Cai A, Solowski N, et al. 2002. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther*, 301:418–26.

Schering-Plough. Summary of Product Characteristics: Remicade 100mg powder for concentrate for solution for infusion. 21 August 2007. Accessed 09.08.07. URL: http://emc.medicines.org.uk/.

Schreiber S, Nikolaus S, Hampe J, et al. 1999. Tumour necrosis factor alpha and interleukin 1beta in relapse of Crohn's disease. *Lancet*, 353:459–61.

Schreiber S, Sandborn WJ. 2006. CLASSIC-1 study the efficacy of adalimumab. *Gastroenterology*, 130:1929–30.

Schroeder KW, Tremaine WJ, Ilstrup DM. 1987. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*, 317:1625–9.

Shen C, Assche GV, Colpaert S, et al. 2005. Ceuppens JL Adalimumab induces apoptosis of human monocytes: a comparative study with infliximab and etanercept. *Aliment Pharmacol Ther*, 21:251–8.

Siegel SA, Shealy DJ, Nakada MT, et al. 1995. The mouse/human chimeric monoclonal antibody cA2 neutralizes TNF in vitro and protects transgenic mice from cachexia and TNF lethality in vivo. *Cytokine*, 7:15–25.

ten Hove T, van Montfrans C, Peppelenbosch MP, et al. 2002. Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut*, 50:206–11.

Tibble J, Teahon K, Thjodleifsson B, et al. 2000a. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut*, 47:506–13.

Tibble JA, Sigthorsson G, Bridger S, et al. 2000b. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology*, 119:15–22.

Truelove SC, Witts LJ. 1955. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J*, 2:1041–8.

van Hees PA, Bakker JH, van Tongeren JH. 1980. Effect of sulphapyridine, 5-aminosalicylic acid, and placebo in patients with idiopathic proctitis: a study to determine the active therapeutic moiety of sulphasalazine. *Gut*, 21:632–5.

Yamamoto T, Umegae S, Kitagawa T, et al. 2004. Mucosal cytokine production during remission after resection for Crohn's disease and its relationship to future relapse. *Aliment Pharmacol Ther*, 19:671–8.