Therapy of ulcerative colitis: state of the art

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Purpose of review

Advances in conventional therapy, novel targets and therapeutic goals are the highlights of treatment for ulcerative colitis in the last year. There have also been disappointments. This review summarizes the highs and lows, with an emphasis on strategy as opposed to seeking the newest treatment option.

Recent findings

In conventional therapy, once daily therapy for 5-aminosalicylic acid is generally sufficient. Furthermore, a new 5-aminosalicylic acid (mesalamine MMX) has been released that effectively induces and maintains remission. There have been reappraisals of immunomodulators and further evaluation of (yes, now conventional!) infliximab for ulcerative colitis. Opportunistic infections, long-term outcomes and the burden of disease are being characterized. New therapeutic targets included an antibody against T cells (anti-CD3), but trials on visilizumab for acute severe colitis have been suspended. T-cell costimulation, phosphatidylcholine to promote barrier function, new anti-tumour necrosis factor agents, B-cell (anti-CD20) depletion and complementary therapies represent new therapeutic horizons. International agreement is needed on activity indices, definitions of remission, therapeutic goals (including mucosal healing) and outcomes that matter to patients, so that trials can be compared.

Summary

Advances will take time to alter mainstream practice, but 2007–2008 is the year of organized strategies, with European, American and British guidelines on ulcerative colitis published or in press. These should be the platform for better outcomes for patients.

Keywords

clinical trials, review, treatment, ulcerative colitis

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Introduction

As medical options increase, decisions about the sequence and timing of therapy and surgery in particular become more difficult. Consequently a therapeutic strategy is necessary, keeping an eye on the direction of travel to avoid going round in circles from one incompletely effective therapy to another. Patients live with a considerable symptom burden despite medical treatment (66% describe interference with work and 73% with leisure activities [1]) in the hope that a cure for ulcerative colitis will emerge. This article reviews the exciting advances (and reverses) in conventional as well as novel therapy that occurred in the past year, highlights new therapeutic goals, and adds a note of caution about complications from therapy.

What's new in conventional therapy?

The main advances in conventional therapy have been once-daily mesalamine therapy, the new MMX delivery system, reappraisal of high-dose mesalamine and immunomodulators for ulcerative colitis, and increasing recognition of the burden of disease from the risks of medical therapy to those of surgery.

Once-daily mesalamine

Once-daily oral formulations of 5-aminosalicylic acid (5-ASA) are likely to be preferred if they offer comparable efficacy and improved adherence. This premise appears correct. An investigator-blinded study of 362 patients [2] randomized to receive Pentasa (Shire, Wayne, Pennsylvania, USA) 2 g once or 1 g twice daily showed a 12% better remission rate at 1 year (73.8 versus 63.6%) in the single daily dose group. Questionnaires confirmed significantly greater compliance ($P < 0.05$) and acceptability ($P < 0.001$) in the once-daily group. The study has yet to be reported in full, but given comparable efficacy between once-daily and divided dosing regimes for the treatment of active ulcerative colitis with mesalamine MMX (Mezavant/Lialda, Shire) and Salofalk (Falk, Freibur, Germany) [3••,4,5,6•,7] the effect is likely to be generic rather than compound specific.

New delivery system

MMX technology has a pH-sensitive film which delays the release of 5-ASA until the tablet reaches the terminal ileum. Intestinal fluids are thought to interact with hydrophilic excipients causing the tablet to form a viscous gel, which slows diffusion of 5-ASA into the colonic lumen. It is supposed that other lipophilic excipients reduce the rate of dissolution and extend the process of delivery of 5-ASA. It is clear that it works, for both inducing and maintaining remission [3••,4,5,6•]. A study in 346 patients with active, mild-to-moderate ulcerative colitis [3••] achieved clinical and endoscopic remission in 40.5% given MMX 2.4 g/day once daily and 41.2% given 4.8 g/day once daily compared with 22.1% on placebo ($P = 0.01$ and 0.007, respectively) and 32.6% given Asacol (Procter & Gamble, Cincinnati, Ohio, USA) (ns). A total of 451 responders from this and another placebo-controlled study [4] were enrolled in a maintenance trial [6•]. At 12 months, 64.4% in the once-daily and 68.5% of patients in the twice-daily group were in clinical and endoscopic remission ($P = 0.351$). Of those in well defined remission at trial entry, 88.9 and 93.2%, respectively, maintained clinical remission. This therapy will prove popular, but if single dosing is all that is necessary for any mesalamine (above), there will be less temptation to switch horses.

High-dose 5-aminosalicylic acid

The benefit of mesalamine 4.8 over 2.4 g/day is limited to symptom improvement rather than remission in mild or moderately active colitis, as confirmed in the large ASCEND I trial [8] and a systematic review [9]. Combining topical 5-ASA with oral therapy is more likely to improve response, so efforts continue to improve tolerability of 5-ASA enemas by reducing the volume [10].

Immunomodulators

Thiopurines (azathioprine/mercaptopurine) struggle to achieve the same credibility in ulcerative colitis as they have in Crohn's disease, because of poorly designed early trials. A Cochrane review [11] reported an odds ratio for failure to maintain remission with azathioprine of 0.41 [95% confidence interval (CI) 0.24–0.70] compared with placebo. Methotrexate for ulcerative colitis fared worse in a similar analysis, although inadequate dosing and the need for further studies was recognized [12]. A controlled trial of methotrexate for ulcerative colitis ('METEOR') has started in Europe, and most specialists use azathioprine or methotrexate for ulcerative colitis as they do in Crohn's disease. Dosing of thiopurines may be suboptimal in many patients [13], but for some patients not responding to azathioprine, there may be preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. This can be inhibited by allopurinol deliberately to shunt metabolism of 6-mercaptopurine toward 6-thioguanine and improve clinical response [14]. It should be emphasized that this should only be attempted when metabolite measurements are available, because there is a risk of profound myelotoxicity when azathioprine and allopurinol are combined. A practical option for patients who cannot tolerate thiopurines is to try mycophenolate mofetil. In a case series of 70 patients, 24% achieved steroid-free remission for almost 3 years [15].

Anti-tumour necrosis factor therapy for ulcerative colitis

The rapid transition of infliximab from experimental to conventional therapy for ulcerative colitis is notable, but the modest steroid-free remission rate (21% at 6 months in the combined active ulcerative colitis trials ACT 1 and ACT 2) should be remembered. Nevertheless, subsequent analysis showed an associated reduction in colectomy (hazard ratio 0.57, 95% CI 0.37–0.89) [16], but whether this benefit is maintained remains unclear. Outside of clinical trial settings, outpatient case series have reported colectomy rates of up to 50% after a median follow up of 13 months [17], but lower rates in less refractory patients. Older patients and those who are perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positive may respond less well [18]. A single series of 10 patients with ulcerative colitis who had lost response to infliximab were given adalimumab (160/80) in a 4-week open-label trial. Four patients improved, six did not respond, and of these, two went onto colectomy [19]. Phase III studies of adalimumab for ulcerative colitis are in progress. Infliximab for acute severe colitis is best considered separately, as is the question of whether to continue immunomodulators.

Acute severe colitis

Hospitalized patients with severe colitis are a very different population compared with outpatients. Intravenous corticosteroids remain the mainstay for acute severe colitis, but in a systematic review of 32 trials of steroid therapy for acute severe colitis involving 1991 patients from 1974 to 2006, it is clear that the response has not changed for 30 years ($R^2 = 0.07$, $P = 0.8$) [20]. The overall response was 67% (95% CI 65–69%), while 29% (95% CI 28–31%) came to colectomy and mortality was 1% (95% CI 0.7–1.6%). The question is not only how to improve the outcome, but how to do this safely. The choice for rescue therapy in 2008 is between infliximab and calcineurin inhibitors (cyclosporine A or tacrolimus). Controlled trials are needed, because case series report 20–75% coming to colectomy after infliximab for intravenous-steroid resistant ulcerative colitis [17,18,21,22]. Safety is a key factor, especially if surgery becomes necessary. While it is generally accepted that elective surgery in the presence of infliximab is safe, the same may not apply to emergency colectomy for acute severe colitis. In a Scottish survey [22], 13/39 patients came to colectomy after infliximab treatment for acute severe colitis. One patient initially responded to infliximab, but died of septic shock from bronchopneumonia 3 weeks after treatment, and another had fungal septicaemia. There has also been a worrying report of 20 patients receiving cyclosporine A before infliximab, or vice versa [23], in which one patient died from *Escherichia coli* septicaemia, and others had opportunistic infections. Combination therapy in an attempt to avoid colectomy cannot be recommended. The message should be to use objective indices that predict outcome at an early stage (on the third day of intravenous steroid treatment). A new index for children with acute severe colitis has been developed and validated [24]. The outcome and predictive factors in children (C-reactive protein and stool frequency) are similar to those in adults [25•].

Surgery

Surgery for ulcerative colitis is often neglected in medical reviews, although colectomy is an integral component of an overall therapeutic strategy. Unplanned readmissions occurred in 19% of 202 patients after colectomy for ulcerative colitis, although attempts to predict those at highest risk were unsuccessful [26]. In spite of this, patients with an ileal pouch anal anastomosis (IPAA) have a quality of life similar to patients with ulcerative colitis in remission or mild disease, although it depends on the measure used [27]. Complications of IPAA have been reviewed [28], but a common dilemma is the impact of pelvic surgery on fecundity and pregnancy on pouch function. A systematic review [29] reports an infertility rate of 12% before and 26% after IPAA among 945 patients in seven studies. No significant difference was seen in pouch function after vaginal delivery, but elective caesarean section for patients with a pouch tends to be favoured after discussion with the obstetrician and patient. The burden for ulcerative colitis is substantial, but has to be balanced against the risks of medical therapy.

Risks of medical therapy

Biological and immunomodulatory therapy represent major advances in the treatment of ulcerative colitis whose potential is still not realized. This is tempered by greater appreciation of the risks of medical therapy, and opportunistic infections or malignancy in particular. All gastroenterologists recall an occasional case of disseminated varicella, *Pneumocystis jiroveci* pneumonia or cytomegalovirus colitis in patients on immunomodulators, but these are rarely reported and there are fewer case–control studies, leading to negative publication bias. It is time to re-evaluate. The report of eight cases of hepatosplenic T-cell lymphoma in young patients treated concurrently with infliximab and thiopurines provides the impetus [30]. The Danish Crohn's and Colitis database [31] has the best population-based experience, and there were 75 episodes of serious sepsis in 651 patients treated with infliximab between 1999 and 2005. This included 38 abscesses, 18 cases of pneumonia (including two caused by aspergillus and one by actinomyces, who died), 12 fungal infections, two cases of tuberculosis, and one osteomyelitis, among others. Not all were directly related to infliximab (that is, within 3 months), but these were patients under medical therapy. The TREAT Registry [32] suggests a 77% increase in serious sepsis within 3 months of infliximab [relative risk (RR) 1.77, 95% CI 1.27–2.46, $P < 0.001$], although the risks from steroids – still medical therapy – remain higher. Almost all these patients had Crohn's rather than ulcerative colitis, but caution is required, especially when two or more immunosuppressive drugs are used. Combination biologic and immunomodulatory therapy has been questioned [33]. Since antibodies to infliximab occur early in the treatment, discontinuing the immunomodulator after 6 months has been studied in a randomized withdrawal trial [34]. There was no loss of response to infliximab for Crohn's disease over 2 years. Short-term combination (6 months) appears to offer a balance between risks and efficacy for those in whom infliximab is continued. If a patient is naïve to azathioprine when given infliximab, a reasonable option is to determine whether remission will be maintained by azathioprine alone.

Occasional dilemmas

Each year odd nuggets of information inform specialist clinical practice. Reports on the successful outcome after cyclosporine A for ulcerative colitis in pregnancy (two cases) [35], intentional treatment with infliximab during pregnancy [36], and the limited impact of liver transplant for primary sclerosing cholangitis on chronic pouchitis (possibly less if transplanted first) [37] are some examples.

New targets, novel therapies

Although conventional therapy accounts for the management of at least 90% of patients with ulcerative colitis, it is often new treatment that attracts attention, although 56% of 5636 European patients reported that their doctors never discussed new therapy [1]. Unfortunately 2007 has been a triumph of hope over expectation. Therapeutic targets other than tumour necrosis factor (TNF) are sorely needed, since conventional therapy, however well used, is reaching its limits.

Visilizumab

This anti-CD3 monoclonal antibody binding to activated T cells to induce apoptosis showed real promise as rescue therapy for intravenous steroid-resistant ulcerative colitis. The phase 1 dose-ranging study has been reported [38], but sadly the phase III study was suspended in 2007 when interim analysis showed no benefit.

Phosphodiesterase 4 inhibitor

Phosphodiesterase 4 is a key enzyme in cell homeostasis and inflammation, and its inhibition has been useful in rheumatoid arthritis and other diseases. A phase II study of tetomilast (OPC-6535) in 186 patients with active ulcerative colitis [39] showed potential benefit in those with more active disease, but did not reach significance for remission or overall response.

Phosphatidylcholine

Insufficient phosphatidylcholine in colonic mucus fits with current concepts of a primary defect in barrier function. Significantly more patients given phosphatidylcholine 2 g/day were able to stop steroids compared with placebo [40].

Other agents

Interferon-β still seeks a role for treating ulcerative colitis [41], although a case report [42] describes the onset of the condition during treatment with interferon-β for multiple sclerosis. A similar disparity applies to rituximab, an anti-CD20-antibody that might inhibit B-cell-mediated destruction of epithelial cells. It is undergoing pilot studies in ulcerative colitis, but a case report describes disease exacerbation [43]. Abatacept prevents T-cell activation by inhibiting costimulation through CD28 and worked in two animal models of colitis [44]; it is undergoing clinical trials at present.

Treating the cause

The current paradigm of a dysregulated adaptive immune response in inflammatory bowel disease led to the development of anti-TNF therapy. The concept of disturbed T-cell immunity as a primary event may, however, simply be wrong. There may instead be a primary defect in barrier function and innate mucosal immunity, such as deficient bacterial killing [45]. This then leads to secondary adaptive immune responses after bacterial invasion. If this is true, new drugs will be needed that enhance mucosal barrier protection against luminal bacteria. These are more likely to be effective at preventing relapse than suppressing adaptive immunity.

Complementary and alternative medicines

Complementary and alternative medicines proliferate in an unregulated fashion. Fashion is the word, so conventional physicians need to be aware. Probiotics [46] and ω3 fish oil [47] did not stand up to Cochrane scrutiny. Leucocyte (and granulocyte or monocyte) apheresis is fiercely fashionable and multiple case series indicate that it is doing something [48]. Until the results of properly designed randomized controlled trials are made available, then that something is undefined. Ecabet sodium, bromelain and tormentil all had their advocates last year [49–51]. At least their names appeal.

Therapeutic goals

Clinical trials on ulcerative colitis in the past 12 months [2,3••,7,8,10,39–42] have all used different endpoints to define response and remission. This accounts for the enormous variation in placebo response. A metaanalysis [52•] found a median placebo remission rate of 12% (range 0–40%) and response 30% (range 0–67%). These figures make it difficult to compare studies and continues to justify placebo-controlled trials for mild–moderately active ulcerative colitis. A comprehensive review of the nine different clinical activity indices has been published [53••]. Some outcomes that matter to patients, such as hospitalization, time off work, surgery and mortality, are difficult to measure, but are only now being captured in large trials [16,54]. Other outcomes (steroid-free remission, speed of response, time to relapse) also matter to patients, are readily understood, easily measured and more informative than composite indices. Surrogate markers for determining improved outcomes, such as fewer hospital visits, or surgery, include mucosal healing [55]. This was associated with a low risk of future colectomy for ulcerative colitis ($P = 0.02$) in an incidence cohort in Norway [56].

Prognosis

An important question is whether newer approaches to care for ulcerative colitis have improved overall prognosis. Evidence is conflicting, but the measurable impact is disappointingly small. Using US National Hospital Discharge data (1990–2003), admission and colectomy rates for ulcerative colitis were unchanged, although length of stay decreased [57]. This is similar to findings over five decades in a population-based cohort, in which colectomy rates and mortality for ulcerative colitis remained unchanged, although the number of medications increased [58]. There remain appreciable differences in practice (such as the threshold for colectomy) in different countries [59]. An interpretation of epidemiological evidence of a high mortality after emergency compared with elective colectomy for ulcerative colitis (13.2 versus 3.7%) was that the threshold for emergency colectomy may be too high, since mortality returned to normal after 3 months [60]. The mortality after emergency colectomy in the first truly national audit of practice was 4.7% (http://ibdaudit.rcplondon.ac.uk/college/ceeu/ceeu_uk_ibd_audit_2006.pdf).

Conclusion

It seems appropriate to conclude with guidelines, because 2007–2008 has been the year of guidelines. Authoritative European guidelines on ulcerative colitis have been published [61–63]. There are novel guidelines on anaemia in inflammatory bowel disease [64••], surgery, and the management of acute severe colitis [65,66]. The limits of evidence-based medicine are such that guidelines appear most necessary when evidence is lacking. Nevertheless, guidelines provide a platform for therapeutic decisions and draw attention to areas of unmet need, to be addressed by research into basic science.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 547–548).

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