Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2008 January 21; 14(3): 354-377
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Daniel C Baumgart, MD, PhD, *Series Editor*

Treatment of inflammatory bowel disease: A review of medical therapy

Patricia L Kozuch, Stephen B Hanauer

Patricia L Kozuch, Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, United States
Stephen B Hanauer, University of Chicago Hospitals, Department of Medicine, Section of Gastroenterology and Nutrition, Chicago, IL 60637, United States
Correspondence to: Stephen B Hanauer, MD, Department of Medicine and Clinical Pharmacology, Section of Gastroenterology and Nutrition, 5841 S. Maryland Ave., MC 4076 Chicago, IL 60637, United States. shanauer@uchicago.edu
Telephone: +1-773-7022182 Fax: +1-773-7022182
Received: May 16, 2007 Revised: July 4, 2007

Abstract

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract. While a cure remains elusive, both can be treated with medications that induce and maintain remission. With the recent advent of therapies that inhibit tumor necrosis factor (TNF) alpha the overlap in medical therapies for UC and CD has become greater. Although 5-ASA agents have been a mainstay in the treatment of both CD and UC, the data for their efficacy in patients with CD, particularly as maintenance therapy, are equivocal. Antibiotics may have a limited role in the treatment of colonic CD. Steroids continue to be the first choice to treat active disease not responsive to other more conservative therapy; non-systemic steroids such as oral and rectal budesonide for ileal and right-sided CD and distal UC respectively are also effective in mild-moderate disease. 6-mercaptopurine (6-MP) and its prodrug azathioprine are steroid-sparing immunomodulators effective in the maintenance of remission of both CD and UC, while methotrexate may be used in both induction and maintenance of CD. Infliximab and adalimumab are anti-TNF agents approved in the US and Europe for the treatment of Crohn's disease, and infliximab is also approved for the treatment of UC.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Medical therapy

Peer reviewer: Christian Maaser, MD, Department of Medicine B, University of Muenster, Albert Schweitzer Strasse 33, 48129 Muenster, Germany

Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: A review of medical therapy. *World J Gastroenterol* 2008; 14(3): 354-377 Available from: URL: http://www.wjgnet.com/1007-9327/14/354.asp DOI: http://dx.doi.org/10.3748/wjg.14.354

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the principle syndromes encompassed by the classification of inflammatory bowel disease (IBD). While CD can affect any part of the gastrointestinal tract, it most commonly occurs in the distal ileum and colon, whereas UC by definition affects only the colon. The etiology appears multifactorial: an underlying immune dysregulation coupled with an intolerance to gut flora seems fundamental to the pathogenesis that, in some cases, are associated with genetic mutations or are initiated by environmental factors. Apart from a total proctocolectomy for UC, there is no cure for IBD. Medications, however, aid in the induction and maintenance of remission, and target various points along the disordered immune pathway implicated in IBD.

CROHN'S DISEASE

Aminosalicylates

While there is solid data supporting 5-aminosalicylic acid (5-ASA, mesalazine or mesalamine) in the induction and maintenance of remission for UC, their efficacy in the treatment of CD is not as clear. Interpretation of the data is often confounded by the use of different formulations, doses, and varied applications to different disease scenarios (disease location, concomitant medications, and prior therapies). 5-ASA agents are likely to have multiple anti-inflammatory effects, including inhibition of cyclooxygenase, lipoxygenase, B-cells, and several key inflammatory cytokines. Most recently, 5-ASA has been shown to activate selective peroxisome proliferators-activated receptor ligand-γ (PPAR-γ), a nuclear receptor that controls cell proliferation and apoptosis[1]. Originally designed as treatment for rheumatoid arthritis (RA), sulfasalazine was discovered to also benefit patients with IBD[2]. An azo-bond links sulfapyridine to 5-ASA and is cleaved by bacterial azo-reductase in the colon, thus allowing delivery of the active 5-ASA moiety to

the large intestine. Limitations of sulfasalazine include allergic reactions and side effects, largely attributed to the sulfapyridine moiety, as well as its lack of efficacy in isolated small bowel disease that is proximal to the colonic release of 5-ASA. Two newer non-sulfa-containing 5-ASA agents, balsalazide and olsalazine were developed to treat colonic inflammation; further, mesalamine formulated to release in a pH (Asacol®, Claversal®, Mesasal®, and Salofalk®) or time-dependent manner (Pentasa®) can treat either small or large bowel CD[2].

Active disease

The National Cooperative Crohn's Disease Study (NCCDS) and European Cooperative Crohn's Disease Study (ECCDS) were large multicenter randomized controlled trials published in 1979 and 1984 that evaluated the comparative efficacy of sulfasalazine, prednisone and azathioprine in the treatment of both active and quiescent CD. While the NCCDS found sulfasalazine 6 g/d superior to placebo overall in treating active disease, when stratified by disease location only those with colonic and ileocolonic (but not isolated small bowel) disease obtained benefit[3]. In contrast, the ECCDS did not demonstrate efficacy for sulfasalazine 3 g/d alone, but only in combination with 6-methylprednisolone[4].

Subsequently, newer mesalamine agents have been evaluated in clinical trials for CD. In the largest of these studies (n = 310), patients with active ileal or ileocolonic CD were randomized to receive Pentasa®, 1, 2 or 4 g/d or placebo. The 4 g/d group experienced a greater decrease in CDAI than the placebo group (72 *vs* 21 points, $P < 0.01$), an effect more pronounced in isolated ileal disease, and remission was achieved in 43% *vs* 18% respectively[5]. Subsequently, two similarly designed trials described in a meta-analysis failed to replicate these findings although there was an overall statistical benefit for the 4 g dose of mesalamine that was of questionable clinical significance[6,7]. Several other trials also have demonstrated benefit for mesalamine in CD, but the quality of the trials was less robust[8,9]. When compared to other agents in controlled trials approximately 40%-55% of patients treated with mesalamine 4 g/d achieve remissions but the efficacy was less than budesonide (9 mg/d) for the induction of remission at both 8 wk (45% *vs* 65%, $P = 0.001$) and 16 wk (36% *vs* 62%, $P < 0.001$)[10] and comparable to ciprofloxacin 1 g/d[11].

Maintenance after medical remission

Sulfasalazine at reduced doses compared to the induction phase provided no benefit compared to placebo in the maintenance phase of the NCCDS and ECCDS, nor in a smaller study[3,4,12]. Gisbert *et al* have reviewed nine randomized placebo-controlled studies of mesalamine as a maintenance agent, four of which showed a significantly decreased risk of relapse compared to placebo, although there was great heterogeneity in formulation, dosage, duration of treatment, and disease location[13]. Further, a Cochrane review of seven randomized placebo-controlled trials concluded that treatment with 5-ASA agents for at least six months did not confer an advantage over placebo in patients with medically-induced remission[14]. When initiated within three months of a medically-induced remission, mesalamine (2 g bid), in contrast to placebo, prevented more relapses over a two year period[15]. In the context of a steroid-induced remission, short-term weaning from steroids may be slightly facilitated with mesalamine 4 g/d, but there was no benefit at one year in relapse rate between patients maintained on mesalamine compared with placebo[16].

Post-operative maintenance

The natural history of CD after ileocolonic resection is variable, and may be influenced by such factors as pattern, extent, and duration of disease pre-operatively as well as smoking history. Endoscopic recurrence rates range from 28%-93% at one year[17], while clinical relapse rates have been reported at 20% and 34% at one and three years respectively[18]. Approximately 30% of patients require re-operation within 10 years[17], highlighting the relevance of identifying an effective post-operative maintenance strategy. Except for one study that showed a benefit at one (but not three) years, sulfasalazine has not been statistically superior to placebo in preventing post-operative relapse[17]. Data for mesalamine has been equivocal in the setting of post-operative maintenance trials. While a meta-analyses of 15 randomized controlled studies (n = 2097) of mesalamine as a maintenance medication in CD found a 13% pooled risk reduction for those patients with surgically-induced remissions[19], the largest (n = 318) and most rigorously conducted trial to date in which patients began mesalamine therapy (4 g/d) within ten days of surgery did not show benefit over placebo. While a post-hoc analysis did suggest efficacy for patients with isolated small bowel disease (21% *vs* 39% relapse rate, $P < 0.02$)[20], if this trial had been included in the meta-analysis, the overall findings of benefit compared to placebo would no longer have been significant[21]. Most recently, mesalamine at 3 g/d was inferior to mercaptopurine at 50 mg/d at preventing post-operative recurrence[22].

In summary, for the treatment of mild to moderate active CD, 5-ASA agents, while less efficacious than budesonide for ileal and or right colonic disease, may be a reasonable choice as first-line therapy: sulfasalazine should be reserved for patients with predominantly colonic disease, while time or pH-dependent release mesalamine are appropriate for patients with small bowel disease. The role of 5-ASA as a maintenance medication is equivocal at best, but is clearly of no benefit in patients with a steroid-induced remission and in the setting of post-operative maintenance, at least 3 g/d would need to be initiated immediately after surgery to provide any benefit for patients with small bowel disease.

ANTIBIOTICS

Active disease

Metronidazole, ciprofloxacin, combination anti-mycobacterials, and most recently ornidazole and rifaximin have been evaluated in the treatment of active CD. The few randomized controlled trials to study the efficacy of metronidazole and/or ciprofloxacin have been mostly small and provided negative results[7] despite subgroup

analyses suggesting a trend towards significant benefit in patients with colonic disease[23-25]. One small study (n = 47) showed ciprofloxacin 1 g/d for six months decreased CDAI scores significantly more than placebo ($P < 0.001$)[26] and while an eight month cross-over study between sulfasalazine 3 g/d and metronidazole 800 mg/d showed no treatment differences in the initial four months, 15 patients who switched from sulfasalazine to metronidazole had significant decreases in the CDAI compared to none of the group who crossed-over from metronidazole to sulfasalazine[27]. As previously described, 16-wk remission rates were similar for ciprofloxacin and mesalamine in a small, randomized trial[11] while another trial reported no differences in remission rates between the combination of ciprofloxacin and metronidazole *versus* methylprednisolone, despite a trend favoring steroids[28]. In contrast, a combination of ciprofloxacin and metronidazole provided no additional benefit over budesonide, alone, aside from a post-hoc analysis for patients with colonic disease[25]. A recent study that compared rifaximin 800 mg bid, 800 mg/placebo and placebo bid failed to show a significant difference between the three groups in clinical response or remission, despite a trend toward benefit with the higher dose[29].

Perianal disease and post-operative maintenance

Although antibiotic therapy is frequently used in the treatment of perianal fistulae, there are no randomized controlled trials to support this practice. Data from several small open-label trials conducted in the early 1980s reported the efficacy of metronidazole in healing perianal fistulae[30-32]. In the post-operative setting a three month course of metronidazole (20 mg/kg per day) decreased the severity of endoscopic lesions at one year (but not at two years) and delayed onset of clinical recurrence[33]. Most recently, ornidazole (1 g/d), started within 10 d of resection and continued for one year, showed significant benefit over placebo in both clinical and endoscopic recurrence rates[34]. The main limitation of long-term metronidazole and ornidazole is peripheral neuropathy.

In summary, while antibiotics are used frequently to treat perianal disease, their role in the treatment of active luminal disease and a safe and effective dose schedule in the post-operative setting, remain to be established.

SYSTEMIC STEROIDS

Mechanism of action

By binding to intracytoplasmic glucocorticoid receptors found in most cell types, glucocorticosteroids activate glucocorticoid-responsive elements (GREs), resulting in a broad spectrum of effects on the immune system including inhibition of the recruitment and proliferation of lymphocytes, monocytes and macrophages, migration of neutrophils to sites of inflammation, and decreased production of soluble inflammatory mediators including cytokines, leukotrienes, and prostaglandins[35].

Natural history

The natural history of 171 CD patients diagnosed between 1970 and 1993 has been studied in the Olmsted County, Minnesota population[36]. Of this cohort, only 43% ever required steroids before 1997 and of these, 58% were in complete remission after one month while 26% were in partial remission and 16% had no response. Of those who responded, the one-year outcomes were concerning as only 32% of patients had a prolonged response to corticosteroids, 28% became steroid-dependent and 38% had undergone surgery. These are data that are similar to the reported Danish, Copenhagen County experience[37]. Both exemplify the likelihood of developing steroid refractory or dependent disease with an accelerated course toward surgery. Hence, the requisite for steroids may be considered the "tipping point"[38] of CD that heralds a more complex subsequent course[39], including the need for surgery or the addition of an immunomodulatory agent.

Efficacy

Glucocorticosteroids are effective inductive agents for CD. The first definitive data came from the NCCDS, in which 60% of patients treated with prednisone (0.25-0.75 mg/kg per day) were in remission at 17 wk compared to 30% of placebo-treated patients[3]. Even more impressive were the results from the ECCDS in which 80% of patients treated with methylprednisolone (48 mg) achieved remission at 18 wk compared to less than 40% of placebo patients[4]. More recent randomized controlled studies have compared prednisolone (40 mg) or 6-methylprednisolone (48 mg) to budesonide (9 mg) in the treatment of active CD ileocolitis, with similar rates found for the induction of remission at 66% and 73% for the two systemic steroids[40,41].

Although in one retrospective review, 60% patients treated with alternate-day prednisone treatment (mean dose of 25 mg q.o.d.) maintained "favorable responses" for an average of 6.6 years[42], the overwhelming evidence does not support the use of corticosteroids for maintenance of remission. Neither the NCCDS nor ECCDS studies showed benefit of corticosteroids over placebo in maintaining remissions[3,4]. Conventional corticosteroids are not effective at preventing post-operative relapse[43] and a recent Cochrane review of three randomized double-blind placebo controlled studies showed no benefit of corticosteroid therapy in preventing relapses in patients with quiescent CD over 24 mo[44].

NON-SYSTEMIC STEROIDS

Budesonide, in delayed or controlled-release formulations that deliver the potent glucocorticoid to the ileum and/or right colon, has low systemic side effects owing to a high (80%-90%) first-pass metabolism[45]. Two randomized controlled studies demonstrated superiority of budesonide in the induction of remission in patients with ileal or ileo-right colonic disease[46]. In the first trial, 258 patients received 15, 9, or 3 mg of budesonide, daily, or placebo, with 43%, 51%, 33% and 20% of patients respectively achieving clinical remission in 8 wk ($P < 0.001$, $P = 0.009$ for the higher doses compared to placebo respectively)[47]. In the second study (n = 200), 9 mg/d, 4.5 mg BID twice daily budesonide or placebo yielded remission rates of 48%, 53%, and 33% respectively after 8 wk of treatment.

Although differences between the groups were not significant, when data from the two treatment groups were pooled, the budesonide group had a significantly greater decrease in CDAI than the placebo group ($P < 0.05$)[48]. One study comparing daily 18 mg, 9 mg, and 6 mg of budesonide found a dose-dependent effect, with 66%, 55% and 36% achieving remission. While for most patients, 9 mg/d is a sufficient dose, high disease activity (CDAI $\geqslant$ 300) or disease distal to the transverse colon responded better to the highest budesonide dose[49] and as discussed above, budesonide 9 mg/d has also been shown to be a more effective treatment than mesalamine for the induction of remission in mild-moderate active ileal and right-sided colonic CD[10]. When compared to prednisone, budesonide 9 mg/d there were no significant differences found in clinical remission rates[40,41,50,51] although a meta-analysis revealed the pooled rate difference of response of budesonide *vs* conventional corticosteroids to be - 8.5%, $P = 0.02$[52]. Budesonide was associated with fewer steroid side effects overall in three studies[40,41,50] and reduced incidence of moon facies and adrenal impairment in the other[51].

While extended treatment with budesonide has been shown to prolong the time to relapse compared to placebo, the difference was not sustained at one year with 3 mg[53] or 6 mg[54-56]. Similarly, another study found no difference in relapse rate at any time point over a one year period between patients treated with either 3 mg or 6 mg budesonide and placebo[57]. Neither budesonide 3 nor 6 mg/d was shown to be more effective than placebo in preventing post-operative clinical[58] or endoscopic recurrence[58,59]. Both a Cochrane review and meta-analysis confirmed that budesonide is ineffective at maintaining CD remissions[52,60]. However, in a trial that allowed flexible dosing of budesonide or prednisone over two years to maintain clinical quiescence and examined bone mineral density (BMD) in relation to efficacy and side effects in CD patients, only 37% of budesonide-treated patients withdrew from the study because of failure to improve or worsening disease. However, the average dose of budesonide required to maintain remissions was higher than (6.8 mg/d) doses used in the placebo-controlled trials. Nevertheless, among patients who were steroid-naïve prior to entering the study, smaller reductions in BMD were seen in the budesonide group compared to the prednisolone group (mean, -1.04% *vs* -3.84%; $P = 0.0084$)[61].

Budesonide at doses below 6 mg/d has been demonstrated to be safe for long-term (one year) use. Results from a pooled analysis of five one-year controlled trials using budesonide 6 mg/d showed that while the overall number of adverse events were not different between the budesonide and placebo groups, patients treated with budesonide had more endocrine and "resistance mechanism" disorders (infection) ($P = 0.0042$ and $P = 0.042$, respectively). The higher incidence of endocrine problems was primarily driven by acne and moon facies, while viral infections accounted for the difference in infection rate. Serious adverse events were reported as rare[62].

In summary, while budesonide is an effective and safe medication for the induction of remission in patients with mild-moderate ileal and proximal colonic disease, optimal dosing schedules to maintain remissions have yet to be established. While budesonide > 6 mg/d or an adjustable dose may maintain remission, a randomized controlled trial is needed to confirm the results of the open-label studies.

IMMUNOMODULATORS

Azathioprine (AZA)/6-Mercaptopurine (6-MP)

6-MP and its prodrug AZA are purine analogs that are converted into 6-thioguanine nucleotides (6-TG); the therapeutically active metabolites interfere with nucleic acid synthesis, exhibit anti-proliferative effects on activated lymphocytes and, most recently, have been shown to induce apoptosis[63,64]. These agents have been studied for the treatment of CD since the late 1960s, with multiple uncontrolled trials showing favorable results. A meta-analysis of AZA and 6-MP for the induction of remission included eight randomized placebo controlled trials ($n = 425$) while another for maintenance of remission included five trials ($n = 319$); three trials with induction and maintenance arms were included in both analyses[65,66]. For active disease, the overall response rate was 54% for patients receiving treatment compared to 33% for those on placebo, yielding a pooled odds ratio (OR) of 2.36 and the number needed to treat (NNT) for one patient to respond was 5; for quiescent disease, overall remission was seen in 67% of patients on treatment compared to 52% of those on placebo, for an OR of 2.16 and NNT of 7. In active disease, those receiving AZA or 6-MP for $\geqslant$ 17 wk resulted in an increased pooled OR of 2.51 and decreased NNT to 4. No dose effect was seen for active disease, but in the maintenance analysis, the OR increased from 1.2 for those taking 1 mg/kg per day to 4.13 at 2.5 mg/kg per day. Fistula healing in the induction studies (defined as complete closure or decreased drainage) was not reported consistently and numbers were small, but a response rate of 55% for treatment compared to 29% for placebo was seen, with an OR of 4.58. One study that was not included because number of fistulae rather than number of patients with fistulae were reported also showed favorable results: 9/29 fistulae (31%) in patients treated with 6-MP compared to 1/17 (6%) in patients taking placebo closed completely[67]. Steroid sparing effects were seen in both the induction and maintenance meta-analyses, with an OR of 3.86 and 5.22 respectively. Patients under treatment for both active and quiescent disease were also more likely to suffer an adverse event leading to withdrawal from studies, with an OR of 3.01 and 4.36 respectively; these events were typically nausea, allergic reactions including fever and rash, pancreatitis and leukopenia. From these studies, it can be concluded that AZA and 6-MP are effective in both the induction and maintenance of remission for CD, although given that maximal clinical benefit may not be evident for three to four months, use of this medication in active disease is best initially coupled with another induction regimen such as steroids, and further, dosing should be optimized for long-term care.

Candy & Wright conducted what is probably the most cited study included in these meta-analyses and elucidates both of these points. Sixty three patients with

active CD were administered a three month taper of prednisolone while randomized to receive either AZA (2.5 mg/kg) or placebo. Although there was no difference in the number of patients achieving remission at wk 12, 42% of the AZA group compared to 7% of the placebo group were in remission at 15 mo ($P = 0.001$)[68]. Further, several studies have evaluated the maintenance benefits of AZA in "withdrawal" trials. In a 12 mo open trial in which 29 patients in remission on AZA for more than two years (median 37 mo) were randomized to continued AZA or withdrawal of AZA, 11/13 (85%) of patients who continued treatment remained in clinical remission compared to 7/15 (47%) of patients who had not continued AZA ($P = 0.043$). This difference was amplified when a subgroup analysis of patients treated with AZA > 1.6 mg/kg per day was performed: 89% of those continued on AZA remained in remission compared to 33% of those withdrawn from AZA ($P = 0.017$)[69]. A larger, longer randomized, controlled trial enrolled patients who had been maintained in remission on AZA for ⩾ 42 mo. Forty patients were randomized to continue the same dose of AZA and 43 to receive placebo for 18 mo. At the end of the study, three patients in the AZA group compared to nine in the placebo group had relapsed: the hypothesis that placebo was inferior to AZA was not rejected ($P = 0.195$). The authors concluded that for patients maintained in remission on AZA, medication should be continued beyond 3.5 years[70].

There is also expanding evidence that AZA is effective as a post-operative maintenance therapy. In an open-label study, 142 patients who had undergone limited bowel resection and/or stricturoplasty were randomized to receive either mesalamine 3 g/d or AZA 2 mg/kg per day within 2 wk of surgery for 24 mo. While risk of clinical (28% *vs* 17% respectively, $P = 0.2$) or surgical (10% *vs* 6% respectively, $P = 0.5$) relapse was equivalent between the two groups, AZA was more effective in preventing clinical relapse among those patients who had undergone more than one surgery for CD (36% *vs* 13%, $P = 0.03$). In this study, adverse events occurred more frequently in AZA-treated patients and caused more frequent study withdrawal (22% *vs* 8%, $P = 0.04$)[71]. In a double-blind, double-dummy multi-center trial, 131 patients who had undergone ileocolonic resection were randomized to daily 6-MP 50 mg, mesalamine 3 g or placebo and were assessed clinically, endoscopically and radiologically at regular intervals over 24 mo. 6-MP was superior at preventing clinical relapse (77%) *vs* mesalamine (58%) or placebo (50%) ($P = 0.045$ for 6-MP *vs* placebo) and endoscopic recurrence (63%, 63%, 43% respectively, $P = 0.03$ 6-MP *vs* placebo) over two years[22].

Thus, treatment with AZA or 6-MP is usually of an "indefinite" duration for patients who have responded. A recent, large European retrospective review of patients treated long-term with AZA demonstrated that in patients with CD, risk of relapse was not greater in patients who discontinued therapy after three to four years, although treatment beyond this time frame improved clinical activity and decreased steroid requirements. The authors conclude that for asymptomatic, steroid-free patients, it may be reasonable to consider discontinuing medication after three to four years of treatment[72].

While thus far treatment with 6-MP or AZA has often been reserved for patients who have required steroids on more than one occasion, there may be benefit to starting these medications earlier in the disease course. A pediatric study randomized children with CD diagnosed within the previous 8 wk to receive 6-MP or placebo for 18 mo, each given with concomitant prednisone. Similar to the Candy study the short-term remission rates were not different between the groups, although patients in the placebo group relapsed significantly more than the 6-MP group (47% *vs* 9%, $P = 0.007$) and required more steroids and for a longer duration[73].

Increased risk of lymphoma with 6-MP and AZA has been debated, with discrepant findings among large series. A recent meta-analysis of six studies ($n = 3891$) showed a four-fold increased risk of lymphoma in IBD patients treated with 6-MP or AZA as compared to the general population: this translated to needing to treat over 4300 patients aged 20-29 and 355 patients aged 70-79 to cause one additional case of lymphoma per year. It is unknown whether this risk relates directly to the medication or to the severity of the disease[74]. Increased risk of hematologic malignancies has also been associated with prolonged leucopenia in IBD patients on 6-MP[75], and EBV-positive lymphomas have also been found more frequently in patients exposed to 6-MP or AZA[76]. The risk of infection with these medication ranges between 0.3%-7.4%[77] and include herpes viruses, human papilloma virus and upper respiratory infections. Physicians prescribing 6-MP and AZA should understand how thiopurine methyltransferase (TPMT) activity affects metabolism of these drugs and should monitor for potential leukopenia and/or hepatotoxicity on a quarterly basis. Measurement of the active metabolite 6-TG may be useful in guiding dosage of these medications.

Methotrexate (MTX)

Methotrexate is a folate analog and reversible competitive inhibitor of dihydrofolate reductase (DHFR). Methotrexate interferes with DNA synthesis and also has multiple anti-inflammatory effects including decreased pro-inflammatory cytokine production and lymphocyte apoptosis[78]. Two exploratory, open-label trials in medically-refractory CD patients with oral[79] or intramuscular (IM)[80] MTX led to the large, multicenter study by Feagan *et al*, in which 141 steroid-refractory patients with active CD were randomized to MTX 25 mg or placebo, intramuscularly over 16 wk. Prednisone was stabilized at 20 mg/d and subsequently tapered over 10 wk. After four months, 39.4% in the MTX group compared to 19.1% in the placebo group had achieved remission (CDAI ⩽ 150 and discontinuation of steroids)[81]. Patients taking MTX suffered significantly more adverse events than the placebo group (16/94) leading to study withdrawal in 17% compared to 2%, although the majority of these side effects were either nausea or asymptomatic liver test abnormalities[81]. Two smaller randomized controlled trials in patients with chronic active disease that compared oral

MTX (12.5 and 15-22.5 mg/wk) did not demonstrate differences in remission rates[82] or flares[83]. More than likely, these unfavorable results are attributable to low, oral dosing with smaller sample sizes as compared to the larger trial. Indeed the bioavailability of oral MTX has been shown to have great variability, averaging 73% that of subcutaneously administered medication[84]. Retrospective data have also reported comparable remission rates to those of Feagan[85-87]. When compared to AZA (2 mg/kg per day) or 6-MP (1.5 mg/kg per day), MTX (25 mg IM changed to po after 3 mo or 15 po/wk) yielded equal rates of remission[88,89], and oral MTX (15 mg/wk) resulted in higher remission rates than 5-ASA 3 g/d (80% *vs* 14%, $P < 0.01$)[89].

MTX also maintains remission in CD. Seventy-six patients who achieved remission with MTX 25 mg IM were randomized to MTX 15 mg IM/wk or placebo. At wk 40, 65% of the MTX group were still in remission as compared to 39% of those in the placebo group and fewer patients required prednisone (28% *vs* 58%, $P = 0.01$). There were no serious adverse events and only one withdrawal from the study secondary to nausea[90]. Several retrospective studies have shown comparable rates patients maintained in remission with MTX[85-87,91].

Mycophenolate mofetil

Mycophenolate mofetil is an ester prodrug of mycophenolic acid which not only inhibits synthesis of guanosine nucleotides and thereby indirectly interferes with T- and B-cell activity, but also inhibits growth of intestinal smooth muscle and synthesis of fibronectin and thus, theoretically could decrease stricture formation. A randomized controlled trial comparing mycophenolate mofetil to AZA in 70 steroid-dependent CD patients with moderately active disease showed equivalent response rates but those with highly active disease seemed to benefit more from mycophenolate mofetil than AZA[92]. Smaller non-randomized studies or series have yielded a combined response rate of 52% overall and 69% in patients with perianal disease[93].

Tacrolimus

Tacrolimus is a macrolide antibiotic used primarily to prevent allograft rejection in the transplant setting. Similar to cyclosporine, it binds to calcineurin and suppresses transcription of activated T-cells leading to decreased pro-inflammatory cytokines such as IL-2, TNFα and INFγ as well as inducing T-cell apoptosis, modifying expression of IL-10 and TGFβ, and may have local effects on the intestine. In a recent review that pooled data from 22 studies with a combined total of 286 patients who had been treated with tacrolimus, promising results in fistulizing disease, unresponsive CD and UC as well as extra-intestinal manifestations were reported[94].

BIOLOGIC AGENTS

Infliximab

Infliximab (Remicade® Centocor, Malvern PA) is a chimeric (75% mouse/25% human) anti-TNFα monoclonal antibody; TNFα mediates multiple pro-inflammatory processes central to the pathogenesis of IBD. The first study that defined efficacy of infliximab in the treatment of active CD randomized patients with moderate-severe, medically-refractory, disease to receive a single infusion of placebo or 5, 10 or 20 mg/kg of infliximab. Seventeen percent, 81%, 50% and 64% of patients respectively had a response (CDAI decrease ⩾ 70 points) at wk 4 ($P < 0.001$ for all infliximab patients *vs* placebo). Overall, 33% of all infliximab patients compared to 4% of placebo achieved remission at wk 4 ($P = 0.005$). While significantly more infliximab patients maintained a response at 12 wk, 37% had relapsed, suggesting that a single dose was insufficient[95]. Those patients who had an initial response to the single infusion were subsequently randomized to receive continued dosing with 10 mg/kg every 8 wk or placebo. After 44 wk, 53% of the infliximab group were in remission compared to 20% of the placebo group ($P = 0.013$)[96].

The ACCENT I study expanded on the potential maintenance benefits of infliximab after an initial response. In the trial, 573 patients received a 5 mg/kg intravenous (Ⅳ) infusion of infliximab at wk 0, after which they were assessed for clinical response by CDAI (decrease in score ⩾ 70 and a 25% reduction in total score). Three hundred and thirty five patients (58%) met this criterion and were randomized to one of three treatment groups: placebo at wk 2 and 6 and then every 8 wk (group Ⅰ), infliximab 5 mg/kg on the same schedule (group Ⅱ) or 5 mg/kg at wk 2 and 6 followed by 10 mg/kg every 8 wk (group Ⅲ). Treatment was continued for 46 wk. At wk 14 or later, patients in all groups who initially had response and then worsened were allowed to cross over to active episodic retreatment (infliximab 5, 10 or 15 mg respectively for groups Ⅰ, Ⅱ, and Ⅲ given on an "as needed" basis). At wk 30, 21% of patients in group Ⅰ, 39% in group Ⅱ ($P = 0.003$) and 45% in group Ⅲ ($P = 0.0002$) respectively were in remission, while median time to loss of response was reported as 19, 38 ($P = 0.002$) and more than 54 wk ($P = 0.0002$) respectively. Significantly more patients in groups Ⅱ and Ⅲ combined (29%) compared with group Ⅰ (9%) had discontinued steroids at wk 54, and fewer hospitalizations and surgeries related to CD occurred in the maintenance therapy groups. There were no differences in serious adverse events between the three groups[97]. A recently published endoscopic sub-analysis of the ACCENT Ⅰ trial showed that scheduled maintenance therapy compared to episodic treatment resulted in greater improvement in mucosal ulceration and higher rates of mucosal healing although the correlation between clinical and endoscopic responses was weak[98].

Infliximab is also effective in the treatment of fistulizing CD. In an initial induction trial, 94 patients with actively draining perianal or abdominal fistulas were randomized to receive three infusions at 0, 2, and 6 wk of placebo, 5 or 10 mg/kg infliximab. Twenty six percent, 68% and 56% of patients respectively achieved reduction in drainage from greater than 50% of fistulas ($P = 0.002$ and $P = 0.02$). Only 13% on placebo compared to 55% and 38% of patients on infliximab had closure of all fistulas ($P = 0.001$ and $P = 0.04$)[99]. In the ACCENT Ⅱ study, 306 patients with one or more draining abdominal or perianal fistulas (⩾ three months duration) received an induction regimen of three infliximab infusions (5 mg/kg).

One hundred ninety-five patients with a response at wk 10 and 14 as well as 87 with no response were randomized to placebo or infliximab (5 mg/kg) every 8 wk to wk 54. Time to loss of response was significantly longer for patients in the infliximab group than placebo (> 40 *vs* 14 wk, $P < 0.001$). Furthermore, at wk 54, 36% in the infliximab group compared to 19% in the placebo group had no draining fistulas ($P = 0.009$)[100]. Relapse of perianal disease after cessation of infliximab may occur earlier than in patients with luminal disease[101].

Antibodies to infliximab are known as both ATIs or HACAs (human anti-chimeric antibodies), and have been associated with lower serum drug concentration levels[97,102] and in turn, with decreased efficacy with episodic treatment[102,103]. In the ACCENT I population, however, equal numbers of antibody-positive and negative patients maintained clinical responses[97]. Additionally, although ATIs are also associated with an increased risk of transfusion reactions[102,103], most ATI positive patients will not have a reaction after re-treatment with infliximab and therefore ATI should not be routinely tested in the absence of loss of response or an infusion reaction[104]. Risk of antibody formation may be decreased by the three-dose induction followed by maintenance therapy[97,103], concomitant use of steroids and/or immunomodulators[97,99,102,103], and pretreatment with hydrocortisone[103]. Sex, location of disease, and smoking status does not appear to correlate with development of ATI[102].

Approximately 30% of patients have no response to infliximab and not all responders have a complete response. As reviewed by Rutgeerts and colleagues, positive predictors of response include elevated CRP, non-stricturing and pure colonic disease subtypes, and concomitant use of immunomodulators[105]. AZA or 6-MP are the immunomodulators most commonly paired with infliximab for CD and it is not clear if the higher response rates seen in combination therapy compared to infliximab alone represents an effect of decreased antibody formation alone or combined efficacy *via* other mechanisms. In contrast to IBD, infliximab has been used concomitantly with MTX in rheumatoid arthritis and a small pilot CD study showed that MTX dosed concomitantly with infliximab may increase remission rates, speed time to remission and decrease steroid use as compared to infliximab monotherapy[106]. Smoking has been found to be a negative predictor of response in two studies[107,108], but surprisingly not in one of the larger studies to examine factors influencing response to infliximab[109].

There has been considerable debate as to whether duration of infliximab treatment must necessarily be life-long or "indefinite," or whether episodic treatment may be a viable alternative. While the clinical and endoscopic benefits of maintenance therapy are demonstrated by ACCENT I and Ⅱ, it has been proposed that the traditional three-dose infliximab induction regimen 0, 2, and 6 wk could serve as a bridge to AZA, but this strategy appeared effective for only six to twelve months[110]. Thus, currently infliximab continues to be recommended for an indefinite period. Another emerging debate is how to position infliximab in the Crohn's treatment algorithm since current regulatory approvals have reserved indications for infliximab for patients who are steroid-refractory or dependent despite immunomodulator therapy. Some argue that this pyramid should be turned upside-down to position infliximab closer to the top, as it has been demonstrated that in steroid-free patients, initial treatment with infliximab and AZA compared with steroids and later addition of AZA leads to significantly more patients in remission and off steroids at 26 wk (60% *vs* 41%, $P = 0.03$) and mucosal healing[111]. If treating early in the disease course with infliximab proved to be disease-modulating, then the "top-down" approach could prove to be the better option to treat those patients on the brink of needing steroids. Arguments against this strategy include the economic costs and the possible safety risks[112].

The safety of infliximab also remains a significant concern with potential serious adverse events including infusion reactions, opportunistic infections including tuberculosis, non-Hodgkin's lymphoma (NHL) and other malignancies, as well as death. A true risk has been difficult to calculate, since most clinical trials did not have continuous placebo arms but instead, were cross-over designs or employed episodic treatment regimens such that most patients were exposed to infliximab at some point[113]. Serious infections were reported in 4% of patients overall in ACCENT I [97] and infliximab-related infections were seen in 8% of a large Mayo ($n = 500$) cohort study of infliximab-treated patients, half of which were serious[114]. As of February 2005, 709 cases of reactivated TB had been reported with infliximab, including 62 deaths[105]. The risk of lymphoma and other malignancies has been difficult to elucidate. The ACCENT I and the Mayo cohort study reported extra-colonic malignancy rates of 1% and 1.5% respectively, but a causal link to infliximab is unclear. CD patients overall likely have a slightly higher risk of NHL[115,116] and squamous cell cancer[116,117].

The TREAT registry has enrolled over 6000 patients from community and academic practices who have been classified in two groups: those who had received infliximab and those who had been treated only with other therapies. The infliximab and non-infliximab patients had similar risks of death, lymphoma and other malignancies; risk of serious infection was slightly higher in the infliximab-treated patients but Cox proportional hazard analysis later found that this risk was independently associated with steroid and narcotic use[118]. In contrast, a recently published decision analytic model projected a slightly increased rate of lymphoma and death in those treated with infliximab compared to those treated with standard therapy, although more quality-adjusted life years were demonstrated in the infliximab group[119]. Twelve cases of hepatosplenic T-cell lymphoma, a rare and incurable type of lymphoma, have been reported in a largely pediatric population (ages 12-31) on combination infliximab and 6-MP or AZA therapy; this association has led to a heightened concern for using these medications concomitantly especially in children, and studies are ongoing to better understand efficacy and safety issues with regard to combination *vs* single agent therapy.

Adalimumab

Adalimumab (D2E7, Humira®; Abbott Laboratories,

Chicago, IL) is a subcutaneously administered recombinant human IgG_1 monoclonal antibody that binds with high specificity and affinity to human TNFα and consists of human-derived heavy and light chain variable regions and human IgG_1 constant region. Adalimumab is now approved in the US and Europe for the treatment of CD. Two open-label trials treated patients with adalimumab who had previous exposure to infliximab. In the first, 24 patients who had lost responsiveness or developed intolerance to infliximab were treated with an initial dose of adalimumab 80 mg and then 40 mg every other week for 12 wk. Although 79% required dose escalation to 40 mg weekly, clinical remission and response at wk 12 was seen in 29% and 59% respectively[120]. In the second trial, 15 patients with attenuated response to infliximab were treated for six months with the same schedule of adalimumab as in the first study. Of the 13 patients who completed the trial, 54% had a complete response, 31% had a partial response, and 73% were able to discontinue steroids[121]. Most recently, the CLASSIC- I trial randomized 299 moderate to severe CD patients naïve to anti-TNF therapy to one of three dose combinations administered at wk 0 and 2 (160/80 mg, 80/40 mg, or 40/20 mg) or placebo. At wk 4, 36% (P = 0.001), 24% (P = 0.06), and 18% (P = 0.36) in the adalimumab groups, respectively, were in clinical remission compared to 12% in the placebo group[122]. Fifty-five patients who were in remission at wk 4 of CLASSIC I were randomized to receive continued adalimumab 40 mg every other week, weekly or placebo for up to one year as part of the CLASSIC Ⅱ trial in which 74%, 83% and 44% of patients, respectively, maintained remission at wk 56[123]. Similar to the ACCENT I study with infliximab, immunomodulator therapy again did not alter these results[124]. Finally, the CHARM trial (n = 854) examined adalimumab induction and maintenance efficacy in patients with moderately to severely active CD. An 80 mg dose at week zero and 40 mg dose at wk 2 were administered to all patients, with 499 (58%) achieving clinical response and then randomized to placebo, adalimumab 40 mg every other week, or 40 mg weekly through wk 56. Significantly higher rates of remission were seen in the adalimumab groups compared to placebo at both wk 26 (40% and 47% *vs* 17%, $P < 0.001$) and wk 56 (36% and 41% *vs* 12%, $P < 0.001$). The adalimumab groups also had significantly more steroid discontinuation and complete fistula closure. Safety data was comparable to other TNF therapy[125].

Certolizumab

Certolizumab pegol or CDP870 (UCB; Smyrna, GA) is a monoclonal humanized anti-TNFα antibody Fab' fragment linked chemically to polyethylene glycol (PEG). In contrast to infliximab and adalimumab the antibody fragment does not induce apoptosis[126]. Certolizumab has been evaluated in both induction and maintenance trials for CD[126,127]. In 92 patients with moderate to severe CD randomized to a single intravenous dose of 1.25, 5, 10 or 20 mg/kg of CDP870 or placebo, the primary endpoints of clinical response or remission after four weeks were not different between treatment groups and placebo, but the remission rate at wk 2 was 47% in the 10 mg/kg group compared to 16% in the placebo group (P = 0.041)[127]. The PRECISE 1 study compared subcutaneous certolizumab (100, 200 or 400 mg) to placebo administered at wk 0, 4, and 8 in 292 patients with moderate-severe CD. While all doses of certolizumab produced significant clinical benefit over placebo at wk 2, 400 mg had the strongest effect at all time points, most markedly at wk 10 (52.8% *vs* 30.1%, P = 0.006); however, no statistical significance in clinical response was seen at wk 12, the primary endpoint. When re-analyzed according to stratification by C-reactive protein level (> 10 mg/L), the 400 mg group had a significantly better response at wk 12 (53.1% *vs* 17.9%, P = 0.005) that was attributed to a lower placebo response rate than those patients with a CRP < 10[126]. In the PRECISE 2 trial, patients who responded to a 400 mg induction dose at wk 0 and 2 (428/668, 64%) were randomized to receive 400 mg certolizumab or placebo every 4 wk for 26 wk. Significantly more patients in the certolizumab arm achieved clinical response (62.8% *vs* 36.2%, $P < 0.001$) and remission (47.9% *vs* 28.6%, $P < 0.001$) at wk 26[128]. Safety and tolerability were similar to other anti-TNF agents, although patients treated with certolizumab had lower rates of autoantibody formation.

Fontalizumab

Interferon γ is cytokine with wide-ranging proinflammatory activity implicated in both animal models of colitis and found to have mucosal elevations in CD. Fontalizumab (Protein Design Labs Inc, Fremont, CA, USA) is a humanized form of mouse antihuman interferon γ antibody recently studied in CD. A controlled trial randomized 133 patients with moderate-severe CD to receive one or two doses of fontalizumab 4 mg/kg, 10 mg/kg, or placebo (28 d apart). Although no differences in response were demonstrated with single dose therapy, in those receiving two doses, response rate at d 56 was found to be 69% and 67% for the fontalizumab groups compared to 32% in the placebo groups (P = 0.02 and 0.03 respectively). This difference was more robust in patients with elevated CRP. Adverse rates were similar across treatment and placebo groups, and all serious adverse events except one were related to CD exacerbations[129].

SELECTIVE ADHESION MOLECULE INHIBITORS

Leukocyte emigration from the vascular space to inflamed tissue is a complicated process involving multiple leukocyte-endothelial interactions including tethering, rolling, firm adhesion, spreading, and migration. Leukocyte adhesion to activated endothelium is mediated primarily by the α_4 and β_2 integrins. The α_4 integrin is expressed on all types of white blood cells and can pair with either the β_1 or β_7 subunit. Endothelial ligands recognized by α_4 integrin include vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MadCAM-1); the former is induced at sites of inflammation, whereas the latter is expressed constitutively on the endothelium within Peyer's patches and other gut-associated lymphoid tissues[130].

Natalizumab

Natalizumab is a recombinant humanized antibody derived from a murine monoclonal antibody (AN100226m) (95% human and 5% mouse-derived) and targets human α_4 integrin. Antibodies to α_4 integrin have shown efficacy in animal models of multiple sclerosis and colitis[131,132]. The preliminary data supporting the use of natalizumab as an induction agent was equivocal as two trials of natalizumab in CD showed a trend toward clinical benefit with either one or two doses of 3 or 6 mg/kg compared to placebo, but primary endpoints did not reach significance[133,134]. Similarly, ENACT-1 did not demonstrate significant differences in clinical response or remission at 10 wk between CD patients (n = 905) treated with an intravenous infusion (300 mg) of natalizumab and placebo at wk 0, 4, and 8[135]. In contrast, the ENCORE study enrolled only patients with an elevated CRP (n = 509) and showed significantly higher rates of clinical response and remission at all time points in those treated with three doses of 300 mg natalizumab (0, 4 and 8 wk) compared to placebo[136].

More consistent outcomes have been shown in maintenance trials for natalizumab. In ENACT-2, initial responders to natalizumab (n = 339) received natalizumab (300 mg) or placebo every 4 wk through wk 56. Significantly more patients in the treatment group compared to placebo had a sustained response (61% *vs* 28%, $P < 0.001$) and remission (44% *vs* 26%, $P = 0.003$) through wk 36[135] and concomitant use of immunomodulators did not affect efficacy[137]. An open-label extension study of ENCORE showed that 84% of patients who were in remission after one year remained in remission for two years after continued monthly treatment with natalizumab[138].

In early 2005, three cases of progressive multifocal leukoencephalopathy (PML) were reported in patients treated with natalizumab, two of them fatal. Two patients had multiple sclerosis and one had CD. Natalizumab trials were subsequently suspended by the U.S. Food and Drug Administration (FDA) and the drug was removed from the market. A safety trial that included 90% of all CD, multiple sclerosis and rheumatoid arthritis participants from all previous natalizumab clinical trials failed to find any additional cases of PML, and the overall risk of PML was estimated at 0.1%[139]. In June 2006, the FDA approved resumption of natalizumab marketing targeting a restricted distribution program for selected MS patients.

MLN02

MLN02 is a humanized monoclonal antibody which specifically recognizes the α_4B_7 heterodimer but does not cross-react with the individual component monomers[140]. The major ligand for α_4B_7 is MadCAM1, and therefore this antibody should be gut-specific in theory. Although clinical and endoscopic efficacy has been demonstrated in patients with UC, patients with mild to moderate CD (n = 185) who received two doses of either 0.5 or 2.0 mg/kg at 0 and 29 d did not achieve the primary endpoint of clinical response at two months. On the other hand, clinical remission was seen in 36.9% of the 2.0 mg/kg group compared with 20.7% of the placebo group ($P < 0.05$)[141].

OTHER BIOLOGIC AGENTS

Visilizumab

Visilizumab (Nuvion™, Protein Design Labs) is a humanized IgG_2 monoclonal antibody (HuM291) to the CD3ε chain of the T-cell receptor expressed on activated T-cells. Designed to capitalize on the potent immunosuppressive effect of OKT3 (a mouse monoclonal antibody used primarily in the transplant setting), it minimizes the anti-mouse antibody response and also the adverse effects of the cytokine release syndrome. While trials in UC have demonstrated safety and efficacy, only one small open-label trial in medically-refractory (including infliximab) CD patients (n = 14) given two doses of visilizumab10 μg/kg on d 0 and 1, 58% and 33% experienced clinical response and remission respectively on d 89, with the mean prednisone dose dropping from 19 mg/d at baseline to 4 mg/d[142].

Anti IL-6 receptor antibody

IL-6 is another cytokine that plays a central role in the inflammatory process of CD. A monoclonal antibody to IL-6 receptor (IL-6R) has been shown to decrease expression of adhesion molecules and multiple pro-inflammatory cytokines in animal models of colitis. A randomized pilot study of humanized anti IL-6R (MRA) in 36 patients with active CD found that those given a biweekly infusion of MRA had an 80% clinical response rate compared to 31% of placebo patients ($P = 0.019$), although endoscopic and histologic examination showed no differences[143].

Anti IL-12 antibody

Interleukin-12 is an important cytokine in the Th1-mediated inflammatory response. A monoclonal antibody targeting IL-12 has been evaluated in a randomized trial in which uninterrupted weekly dosing at 3 mg/kg for seven weeks yielded higher response rates than placebo (75% *vs* 25%, $P = 0.03$), but a statistically significant difference was lost at 18 wk (69% *vs* 25%, $P = 0.08$). The more robust clinical response in the anti-IL-12 group was paralleled by decreases in colonic mononuclear cell secretion of IL-12, INF-γ, and TNFα[144].

Thalidomide

Because of its anti-TNFα and anti-IL-12 properties, thalidomide has been studied in two small open-label trials in mixed IBD populations, with the majority of patients in each achieving either clinical response or remission[145,146]; use of this medication is severely restricted because of its well-known teratogenicity and it is further limited by side effects of sedation and mood disturbances.

IMMUNE STIMULATION

Although immune dysregulation is believed to be a part of the pathogenesis of IBD, an alternative hypothesis proposes that an altered innate immune response is inherent to the etiology of CD. Based upon positive results in other disorders of neutrophil function, granulocyte-

macrophage colony-stimulating factor (GM-CSF), a myeloid growth factor that stimulates the growth and function of phagocytic cells, has been studied in CD. One hundred and twenty-four patients were randomized to receive sargramostim (GM-CSF) 6 mcg/kg per day subcutaneously or placebo for 8 wk: while the primary endpoint of a clinical response (defined by a decrease in CDAI of $\geqslant$ 70 points) was not met, significantly more patients in the sargramostim group reached the secondary endpoints of a decrease in CDAI of $\geqslant$ 100 points (48% *vs* 26%, $P = 0.01$) and remission at d 57 (40% *vs* 19%, $P = 0.01$). The sargramostim group suffered from significantly more injection site reactions and experienced more bone pain[147].

PROBIOTICS AND HELMINTHS

The theory of dysbiosis maintains that a decrease in protective or "good" bacteria and a concomitant increase in harmful or "bad" bacteria contribute to the pathogenesis of IBD. As a result, probiotics have been studied as both induction and maintenance treatment in CD. Open label and small randomized controlled trials using various preparations of probiotics have shown inconsistent results as summarized by Rioux and Fedorak[148]. Large randomized placebo controlled trials are needed in order to determine true efficacy. Similarly, observations that IBD is uncommon in developing countries where helminthic colonization is prevalent and that helminths downregulate Th1 immune responsiveness have led to trials utilizing non-pathogenic helminthes in an attempt to treat UC and CD. An open-label trial of *Trichuris suis* (porcine whipworm) has been studied as a therapy for CD in which 29 patients with active CD ingested 2500 live *Trichuris suis* ova every 3 wk for 24 wk: as defined by CDAI scores, 79% responded and 72% remitted[149]. While results from this study are intriguing, a controlled trial again is essential before deeming worm therapy beneficial.

ULCERATIVE COLITIS

Aminosalicylates

Aminosalicylates (5-ASA) remain the first-line therapy for both induction and maintenance of mild-moderate UC. The efficacy of sulfasalazine specifically has been well-established, but dose-dependent intolerance to the sulfa moiety limits its use in up to one-third of patients[150]. Therefore, non-sulfa-containing 5-ASA agents have been studied as well. Recent Cochrane reviews analyzed the effectiveness of these newer 5-ASA medications both in comparison to placebo and sulfasalazine for the induction and maintenance of remission in UC. Twenty one randomized controlled trials ($n = 2124$) of 5-ASA were included in the induction meta-analysis, nine comparing 5-ASA to placebo and 12 to sulfasalazine[151]; results were reported in terms of failure rates. 5-ASA provided benefit over placebo in the induction of remission, with a pooled OR of 0.53 overall and 0.36 when only the Asacol trials were included. While 5-ASA was better than placebo across all dosage ranges, there was a trend toward a dose-effect. 5-ASA was also more likely to elicit a global or clinical response than placebo, with a pooled OR of 0.40 and higher doses yielding better results, $P = 0.002$. 5-ASA was also superior to placebo at inducing endoscopic remission, but only at doses $\geqslant$ 3 g/d. No significant differences were found between 5-ASA and sulfasalazine in induction of remission or response, although a trend towards 5-ASA superiority was observed. Significantly more patients taking sulfasalazine withdrew from studies secondary to adverse events, with an OR of 0.34; it should be noted that tolerance to sulfasalazine was an inclusion criteria for most of the studies, which may have made this effect less robust.

Sixteen trials ($n = 2479$) were included in the 5-ASA maintenance of remission meta-analysis, five comparing 5-ASA to placebo and 11 to sulfasalazine[152]. 5-ASA was more effective than placebo in maintaining endoscopic or clinical remission, with an OR of 0.47; a dose effect was not observed. Sulfasalazine was superior to 5-ASA in the maintenance of remission in trials of six month duration, with an OR of 1.29, but the statistical significance was lost when only studies with endpoints at 12 mo were included. In subgroup analyses by specific 5-ASA preparation, only olsalazine was found inferior to sulfasalazine, likely secondary to the greater number of adverse events (the most common being diarrhea) and subsequent withdrawals in patients receiving this medication. The authors stated that conclusions could not be reached with regard to other 5-ASA preparations. Save for olsalazine, there were no differences in adverse events between 5-ASA when compared to placebo or sulfasalazine. If sulfasalazine truly has superiority over 5-ASA in maintenance of remission (beyond olsalazine), the authors conjecture that unknown pharmacologic effects of the sulfapyridine moiety previously thought to function only as a carrier of 5-ASA to the colon, could contribute to this finding.

5-ASA formulations

There is no definitive data to suggest that one 5-ASA preparation is superior to another. In one study, balsalazide 6.75 g/d (Colazal®, Salix Pharmaceuticals, Morrisville, NC, USA) was found to induce remission in a greater number of patients with active moderate-severe UC than equivalent doses of Asacol 2.4 g/d (62% *vs* 37% at 12 wk, $P = 0.02$). Further, the median time to complete symptom relief was significantly shorter in the balsalazide than mesalamine group (10 *vs* 25 d, $P = 0.004$)[153]. Two subsequent studies comparing these same medications at the same doses did not demonstrate differences in primary endpoints of rectal bleeding and at least one other sign or symptom at wk 8[154] or symptomatic remission at wk 8[155]. Secondary endpoints showing balsalazide to have a faster time to onset[154,155] or better effect in new onset left-sided disease[155] cannot be considered more than preliminary given that primary endpoints were not met[156]. Further, no differences between balsalazide and sulfasalazine or Salofalk® (a delayed-release pH dependent mesalamine formulation) have been found[156]. Additionally, as will become evident below, a suboptimal dose of Asacol® was used in these studies[157]. As well, non-traditional clinical assessments were employed[158], and the Asacol® was not equivalent to that used in the US and in pivotal trials, as demonstrated by *in vitro* dissolution experiments[159].

Pharmacokinetic data in healthy patients demonstrates no differences in systemic absorption of 5-ASA between Asacol and balsalazide at equimolar doses[160]. Therefore, choice of 5-ASA agent should be based upon tolerability, ability to titrate dose to effect and cost.

Dose-effect

The recent ASCEND trial showed a dose-effect based on severity of disease. An overall response rate of 72% at wk 6 was found in patients with moderate activity (n = 268) treated with mesalamine 4.8 g/d (investigational 800 mg tablet, Procter and Gamble Pharmaceuticals, Mason, OH) compared to 59% in those receiving Asacol® 2.4 g/d (P = 0.036). No difference in response rate in patients with mild disease was demonstrated with the two different doses[161]. Patient compliance in taking 5-ASA may be enhanced by a higher dose tablet, SPD476 (1.2 g/tablet) which uses both a gastro-resistant polymer film to delay release of active drug until it reaches the terminal ileum and Multi Matrix System (MMX) which helps deliver 5-ASA evenly throughout the colon. MMX 2.4 g/d and 4.8 g/d are superior to placebo in the induction of remission in mild-moderate UC[162].

Topical mesalamine

Rectal mesalamine induces remission more effectively than placebo or topical steroids in distal UC[163,164], although both medications taken concomitantly are superior to mesalamine alone[164]. Topical mesalamine is superior to placebo and at least as effective as oral mesalamine in the maintenance of remission for distal UC[163,164].

STEROIDS

For patients without sufficient response to 5-ASA agents or those with moderate-severe disease, glucocorticosteroids have remained the foundation for inducing remission in UC since the early 1950s when Truelove and Witts reported significant benefit for cortisone over placebo[165]. For mild to moderate UC, a dose effect for prednisone 20-60 mg/d has been reported, but doses greater than 60 mg/d confer no additional benefit[166]; further, there does not appear to be a difference between once daily and divided dosing[167]. For those with severe colitis or not responding to oral regimens, parenteral steroids are administered. While mineralocorticoid and anti-inflammatory potencies vary, no data suggests one preparation is superior to another; methylprednisolone 40-60 mg/d or an equivalent dose of hydrocortisone is the most commonly used. Adrenocorticotropic hormone (ACTH) promotes endogenous corticosteroid production and may have benefit in steroid-naïve patients, but is no longer commonly utilized due to the potential for adrenal hemorrhage[35]. Pulse-dose steroids in the form of dexamethasone 100 mg/d have shown efficacy in a small open-label trial[168], but a controlled trial has not yet been conducted and a recent systematic review suggests the absence of a dose-response above the equivalent of 40 mg of prednisone[169]. Dividing intravenous bolus dosing is equally effective to a continuous infusion[170].

Predictors of decreased response rate to steroids and increased risk for colectomy include greater severity and extent of colitis[171,172], and most recently persistence of stool frequency > 8/d or CRP > 45 mg/L beyond three days of treatment[173]. Higher levels of glucocorticoid receptor beta (GRβ) have also been associated with glucocorticoid resistance in several studies[174-176]. Of those patients who will respond to IV steroids, the majority do so within five days[177], but most practitioners will continue treatment for 7-10 d[35].

NON-SYSTEMIC STEROIDS

With the multitude of adverse effects of systemic steroids, non-systemic steroids have generated great interest in UC given their high-first pass metabolism and minimal toxicity. Because most of budesonide is released in the distal ileum and proximal colon, making it an effective medication for the treatment of CD in this location, its role in UC is likely very limited, although one study showed equal efficacy to prednisolone in those with left-sided or extensive colitis[178]. An oral formulation of beclomethasone dipropionate (BDP) coated with Eudragit L preventing gastric dissolution and releasing at pH 6.0 for delivery in the terminal ileum and throughout the colon was evaluated in a single-blind randomized trial enrolling 177 patients with mild-moderate UC[179]. Patients who received BDP 5 mg/d for 4 wk had equivalent reductions in mean disease activity index or DAI (assessment of clinical and endoscopic response) and clinical remission rates as those receiving 5-ASA 2.4 g/d, although a significantly greater improvement in DAI was seen in those with extensive disease in the BDP group. BDP was also found to have an additive effect when given in conjunction with 5-ASA[180].

Non-systemic steroid enemas are beneficial in the treatment of active distal UC. Budesonide enemas have significantly higher remission rates than placebo, between 19%-51% with daily 2 mg/100 cc dosing[181,182]; higher doses do not appear to be of greater benefit but may result in more adrenal impairment[182]. While 2 mg twice weekly was not any more effective than placebo in the maintenance of remission[182], it is possible that the optimal dosage for preventing relapses has not been defined. When compared to topical mesalazine (1 g/100 mL per day), budesonide enemas were equally effective in improving histologic and endoscopic scores but clinical remission rates were higher in the mesalazine group[183]. Budesonide enemas are equally or more beneficial than traditional steroid enemas in clinical, endoscopic and histologic measures and induce less adrenal suppression[184-186]. Budesonide foam and enemas resulted in similar clinical remission rates in a large double-blind, double-dummy trial[187]. Similarly, BDP enemas have shown equal efficacy to 5-ASA[188] and prednisolone enemas[189], but are not associated with adrenal axis suppression[189]. The combination of 5-ASA and BDP was superior to either alone[188].

IMMUNOMODULATORS

AZA and 6-MP

The first reported use of AZA in the treatment of UC was in the 1960s, but results from initial controlled trials

in the mid-1970s did not show clinical or endoscopic benefits over placebo[190,191]. However, it became apparent that treatment with AZA consistently permitted significant steroid reduction compared to placebo[191,192]. Patients with UC in remission on AZA ⩾ six months relapsed at a higher rate over one year when withdrawn to placebo (59%) as compared to those who continued AZA (36%), $P = 0.039$; this effect was more pronounced with longer pre-trial remission rates[193]. Later retrospective studies also reported the steroid-sparing effect of AZA and 6-MP[194-197], higher relapse rates with cessation of 6-MP[194,195], and fewer colectomies in those patients maintained on AZA[196,197]. Length of treatment appears to correlate with efficacy: a large retrospective review of both CD ($n = 272$) and UC ($n = 346$) patients treated with AZA found a remission rate of 87% in those patients treated more than six months, compared to 59% overall. Other factors predictive of remission were the diagnosis of UC (*vs* CD), lower white blood cell (WBC) or neutrophil count, a higher mean corpuscular volume and older age. On continued AZA, 95%, 69%, 55% of patients at 1, 3 and 5 years respectively were maintained in remission compared to 63%, 44%, and 35% after discontinuation of AZA; risk of relapse was lower in those with WBC ⩽ 5.0×10^5 ($P = 0.03$)[198].

Compared to mesalazine at a dose of 3.2 g/d, significantly more steroid-dependent patients treated with AZA, 2 mg/kg, achieved both clinical and endoscopic remission as well as steroid discontinuation (53 *vs* 21%, $P = 0.006$)[199]. The addition of 5-ASA to AZA does not confer greater benefit than AZA alone in the maintenance of remission[200,201] or steroid-withdrawal[200].

METHOTREXATE (MTX)

While an initial small open-label study of MTX in IBD held promise for both CD and UC[80], randomized controlled trials have shown benefit in CD only[81,90]. Although several additional open-label or retrospective studies of MTX in UC showed favorable effect[91,202,203], two randomized controlled trials showed no differences in the induction or maintenance[89,204] of remission between patients given oral MTX 12.5[204] or 15 mg[89] per week compared to placebo. It should be noted, however, that in the definitive study that established the efficacy of MTX in the induction of remission in CD, patients were given 25 mg IM; ideally, a second randomized controlled trial in UC utilizing a higher dose of MTX would be conducted.

CYCLOSPORINE

Cyclosporine (CSA) is a lipophilic peptide with multiple anti-inflammatory effects including downregulation of IL-2, thus inhibiting proliferation and activation of T-helper cells[205]. After the first promising open-label trial in 1990 in which 73% of 15 severe, steroid-refractory UC patients treated with Ⅳ CSA (4 mg/kg) improved over an average of 5.8 d and avoided colectomy[206], a double-blind controlled trial that randomized 20 patients with severe steroid-refractory UC to Ⅳ CSA (4 mg/kg) or placebo showed an 82% response rate in the CSA group at a mean of seven days compared to zero in the placebo group ($P < 0.001$). All five placebo group patients given CSA during the open-label phase responded to treatment and over two-thirds of all responders avoided colectomy at six months[207]. In non-randomized controlled trials, long-term remission rates have been less impressive ranging between 14%-40%[208-212]; "bridging" to AZA after induction with Ⅳ CSA and a short course of oral CSA improves maintenance rates, with 40%-90% of patients avoiding colectomy after 16-78 mo[213-215]. Similarly, in a retrospective review at the University of Chicago, 62% of all UC patients ($n = 42$) treated with CSA avoided colectomy over a mean follow-up of 23 mo. This rate improved to 72% among initial CSA responders and to 80% in initial responders who were later transitioned to 6-MP or AZA[216]. Skipping oral CSA and transitioning directly to (6-MP or AZA) after Ⅳ therapy does not seem to alter long-term outcome[217].

CSA is associated with significant morbidity, including opportunistic infections, neurologic and renal toxicity, hypertension, and rarely, death[218]. Several variations in therapy may decrease the risk of these adverse events without compromising efficacy: the use of low-dose CSA (2 mg/kg)[218-220], oral microemulsion CSA (Neoral®) with 60% bioavailability[221-223], and Ⅳ CSA without concomitant steroids[224]. Higher percentages of band forms on differential WBC count[225], tachycardia > 90 bpm, fever > 37.5℃, elevated CRP > 45 mg/L, and greater than one severe endoscopic lesion are negative predictors of response[226]. Ideally, administration of CSA should be limited to physicians trained or experienced in the use of potent immunosuppressants or transplantaion[227].

TACROLIMUS

UC patients with active refractory moderate-severe disease ($n = 63$) were randomized to tacrolimus dosed to maintain either a high (10-15 ng/mL) or low (5-10 ng/mL) trough or placebo for two weeks with an open-label extension segment. Sixty-eight percent of patients in the high-trough group achieved partial response as measured by the UCDAI (number of bowel movements, bleeding and physician's global assessment) compared to 10% in the placebo group ($P < 0.001$). While 38% in the low-trough group achieved a partial response, this did not meet statistical significance; however, significant differences were found on multiple components of the UCDAI between the low-trough group and placebo. When placebo patients crossed-over to the open-label extension, 58% achieved response ($P = 0.012$). While no differences in overall adverse events were found, patients in the high-trough group experienced more medication-related adverse events than the placebo group[228]. A recent review of tacrolimus in IBD patients also found overall favorable results in the treatment of refractory UC[94].

MYCOPHENOLATE MOFETIL

Few trials have examined the efficacy of mycophenolate mofetil (MMF) in UC. In a six month open-label uncontrolled study, 24 steroid-dependent chronic active IBD patients received MMF 2 g/d and were tapered to

5 mg of prednisone per day by the second three months. Among the 13 UC patients, six achieved remission by three months, but all relapsed during the second part of the study[229]. The results were equally disappointing in the CD population, with only one patient maintaining remission by the end of the study. A retrospective study of 39 largely steroid-dependent and AZA-refractory or intolerant IBD patients given a median dose of MMF 1.5 g/d reported more favorable results, with 40% of patients in remission off steroids after a mean duration of 19 mo of treatment[230]. An open-label study randomized 24 patients with active UC to receive either MMF (20 mg/kg) or AZA (2 mg/kg), each given with a tapering dose of prednisolone over one year. While the AZA group experienced significantly greater decreases in the clinical colitis activity index (CAI) than the MMF group at three and six months, these differences were no longer significant at nine and twelve months. Further, although at almost all time points, more AZA-treated patients were in remission and using fewer steroids than the MMF group, none of these differences were statistically significant[231].

BIOLOGIC AGENTS

Infliximab

While several small studies of infliximab collectively showed equivocal efficacy in UC, the ACT (Active Ulcerative Colitis Trials) 1 and 2 provided definitive evidence supporting its efficacy in this population[232]. ACT 1 patients were refractory or intolerant to steroids and/or AZA/6-MP, while ACT 2 also included those refractory or intolerant to 5-ASA agents as well. In each trial, 364 patients received either placebo or infliximab 5 or 10 mg/kg at wk 0, 2, and 6 and then every 8 wk through wk 46 and 22 with follow-up data collected to wk 54 and 30 respectively. In ACT 1 and 2, infliximab at either dose was significantly more beneficial than placebo at all time points in achieving clinical response and remission, mucosal healing, and discontinued use of steroids. Overall, approximately two-thirds in the infliximab group achieved clinical response and one-third achieved long-term remission, while 22% discontinued steroids. Rates of adverse events were similar between groups, although one case each of tuberculosis and histoplasmosis (the latter resulting in death) as well as three neurologic complications occurred in the infliximab group. ATIs were found in 6% and conferred a mildly higher risk of infusion reaction. Concomitant immunomodulator therapy was associated with a lower rate of antibody formation, but no conclusions can be reached given the small numbers with ATI overall. Five mg/kg is the recommended starting dose given that there were no significant differences found between the two doses.

While the ACT studies have established infliximab as effective treatment for UC in the outpatient setting, the role of infliximab in the treatment of hospitalized patients is uncertain. Forty-five moderate-severe or fulminant UC patients refractory to Ⅳ steroids at 5 and 3 d respectively were treated with a single dose of infliximab 5 mg/kg or placebo. Overall, infliximab patients avoided colectomy within the first three months more often than placebo patients (67% *vs* 29%, $P = 0.017$); however, in a subgroup analysis of those with fulminant colitis compared to placebo, this difference was no longer significant (69% *vs* 47%, $P = 0.276$)[233]. In an open-label trial of infliximab in 12 hospitalized steroid-refractory UC patients, nine underwent colectomy within three months[234]. Two recent studies showed favorable response profiles to infliximab in patients with acute severe UC[235,236], and it has been hypothesized that this subset of patients may be different than those with established disease.

SELECTIVE ADHESION MOLECULE INHIBITORS

Natalizumab (Tysabri®, Elan and Biogen Inc, USA)

Only one open-label trial of natalizumab has been conducted in UC, in which 10 patients with active disease were given a single dose of 3 mg/kg: while significant clinical and quality of life improvement were seen at one month, only two patients entered remission and by 8 wk, 80% of patients required rescue medication[237]. Given the association of PML with this medication in CD and MS patients, the status of future trials is unknown.

MLN02

Compared to those who received placebo, mild-moderate UC patients ($n = 181$) who received two doses of MLN02 0.5 or 2.0 mg/kg over one month experienced higher rates of clinical remission (33% and 32% *vs* 14%, $P = 0.03$), clinical response (66% and 53% *vs* 33%, $P = 0.002$), endoscopic remission (28% and 12% *vs* 8%, $P = 0.007$) and endoscopic improvement (48% and 35% *vs*16%, $P = 0.001$)[140]. Antibodies to MLN02 were found in 44% of patients; of those with titers ⩾ 1:125, 24% had loss of saturation to $\alpha_4\beta_7$ binding sites with the clinical remission rate in this group close to that of placebo. There were no differences in adverse events. MLN02 appears promising, but more research will need to assess long-term response and optimal dosing.

Alicaforsen

Alicaforsen (ISIS 2302, Isis Pharmaceuticals, Inc. Carlsbad, CA) is a 20-base phosphorothioate oligodeoxynucleotide antisense molecule that down-regulates messenger RNA for intracellular adhesion molecule I (ICAM-1), a transmembrane glycoprotein that is up-regulated by pro-inflammatory mediators. ICAM-1 is involved in leukocyte activation and migration and elevated levels in serum and mucosa have been found in animal models and patients with IBD[238]. Parenteral alicaforsen was not effective in CD[239], but enema formulations appear beneficial in UC and pouchitis in small studies. In one trial ($n = 40$), mild-moderate active distal UC patients who received daily alicaforsen enemas at 0.1, 0.5, 2, or 4 mg/mL for one month experienced an overall dose-dependent improvement in disease activity index (DAI) ($P = 0.003$). At three months, DAI in the 4 mg/mL group dropped by 72% compared with 11.5% in the placebo group ($P = 0.016$), and no one in the alicaforsen group needed additional therapy at six months compared to 50% of placebo patients[240]. No serious adverse events were reported.

ANTI-INTERLEUKIN-2 (IL-2)

IL-2 is a cytokine produced by activated T-cells that binds to the high affinity receptor IL-2R in the presence of the α-chain CD25 and thereby perpetuates T-cell proliferation and activation[241]. Further, high levels of IL-2 have been associated with steroid-resistance[242]. Two anti-IL2 antibodies have been evaluated in UC.

Daclizumab (Zenapax, Roche, Basel, Switzerland), is a recombinant humanized monoclonal antibody (IgG_1) to IL-2R. Although a small, open-label pilot study initially held promise for this antibody[243], a recently published randomized controlled trial (n = 159) found no difference in response or remission rates between two doses of daclizumab and placebo given every other week for 8 wk[244]. Basiliximab, a chimeric monoclonal antibody to the IL-2R (CD25) α-chain, induced remission in the majority of 10 steroid-resistant UC patients given a single dose in an open-label trial[241]. Additionally, *in vitro* testing performed in healthy volunteers and quiescent UC patients as part of this study showed that basiliximab reverses steroid-resistance, and thus anti-IL-2 treatment might have particular potential in steroid-resistant patients.

VISILIZUMAB (NUVION)

Visilizumab, an anti-CD3 monoclonal antibody is undergoing evaluation in severe UC. In an open-label phase I trial, 79% and 54% of steroid-refractory UC patients treated with 10 mcg/kg per day (n = 24) for two consecutive days experienced response and remission respectively at d 30, and 100% of those treated with 15 mcg/kg per day (n = 8) achieved both response and remission[245]. Sixty-three percent of patients receiving the higher dose remained in remission at one year. Almost two-thirds of patients experienced symptoms of cytokine release syndrome 1-3 h post-infusion, including nausea, chills, fever, headache and arthralgias. Decreased T-cell levels persisted for a mean of three weeks post-infusion. Because elevations in EBV titers were reported in patients with graft versus host disease who received visilizumab[246], this UC study excluded EBV+ patients, but a large open-label trial including EBV+ patients is ongoing.

INTERFERONS

Interferon-alpha (IFNα)

IFNα has a range of anti-viral, anti-tumor and anti-inflammatory activity, including induction of IL-1 receptor antagonist and soluble TNF receptor p55, and downregulation of Th-2 cytokines[247]. With the recognition that IFNα does not induce colitis flares in those being treated for chronic hepatitis who have co-morbid UC[248,249] IFNs have been studied as treatment for UC.

In a small (n = 28) open-label trial of IFNα2a given subcutaneously for 6-12 mo in UC patients, 93% achieved and maintained clinical and endoscopic remission for two years[250], while another small study showed only short-lived benefit of IFNα2a over prednisolone enemas in treating distal UC[251]. In the only randomized placebo controlled trial, UC patients refractory to 5-ASA agents, steroids or AZA (n = 60) received either weekly pegylated INFα2b 0.5 or 1 mg/kg or placebo: no difference in clinical or endoscopic response was demonstrated, and a high attrition rate was seen in all groups, mostly secondary to lack of efficacy[247]. Thus, while INFα does not appear to exacerbate UC when treating chronic hepatitis, it is not effective as a primary treatment for UC.

Interferon B

Interferon β (INF-β) also has anti-inflammatory properties including the upregulation of IL-10 and IL-1 receptor antagonist and downregulation of TNF and IL-2. INF-β has had varied results in the treatment of UC. In an open-label pilot study, 88% of 25 steroid-refractory UC patients treated with either Ⅳ human natural IFN-β or subcutaneous recombinant IFN-β for a mean of 52 wk achieved remission lasting over a year[252]. While one small randomized trial showed endoscopic benefit in patients treated with IFNβ1 compared to placebo[253], a larger controlled trial failed to show any advantage recombinant IFNβ1a over placebo in clinical response or remission, endoscopic index, or steroid reduction[254].

GROWTH FACTORS

Growth factors may restore the protective and reparative foundation of the colon, and therefore represent a possible therapeutic option for UC. Growth factors that have been identified as potentially beneficial in treating UC include transforming growth factor β (TGF-β), epidermal growth factor (EGF), keratinocyte growth factor-1 and 2 (KGF-1 or 2, also known as fibroblast growth factor 7 or 10). Repifermin is a truncated, purified KGF-2 expressed in *Escheria coli*, and induces the proliferation of intestinal and colonic mucosa and reduces intestinal ulcers and inflammation in animal models[255]. Intravenously administered repifermin (1-50 μg/kg) for five consecutive days did not yield different rates of clinical response or remission at wk 4 compared to placebo in patients with active UC[255]. Among other reasons, the authors suggested that under-dosing and/or under-powering could have accounted for the negative findings. EGF is a mitogenic peptide produced by salivary and duodenal Brunner's glands: topical application is beneficial in wound healing and systemic EGF is useful in treating neonatal necrotizing enterocolitis[256]. An 83% remission rate was demonstrated in patients with mild to moderate left-sided UC (n = 24) randomized to daily EGF enemas for 2 wk compared to 8% in the placebo group ($P < 0.001$); disease activity, endoscopic and histologic scores remained significantly better in the EGF group through 12 wk[256]. Rebamipide is an amino acid analog of 2-(1H)-quinolinone used to treat gastric ulcers in Japan. It aids mucosal healing by stimulating local prostaglandin synthesis and epithelial cell regeneration *via* upregulation of EGF and its receptor, neutrophil suppression, and decreased production of inflammatory cytokines stimulated by NSAIDs and/or *H pylori*[257]. A small open-label trial in which twice daily Rebamipide enemas were given to patients with UC proctitis for one month demonstrated significant clinical, endoscopic and histopathologic improvement[258]. Larger

controlled trials are needed to evaluate this class of therapy in UC.

CURCUMIN

Derived from tumeric, curcumin appears to inhibit NFκB and possesses anti-inflammatory, anti-microbial and tumor-suppressing characteristics; it has been shown to prevent and treat colitis in animal models. Fewer patients with quiescent UC (n = 82) randomized to 5-ASA plus curcumin compared to 5-ASA plus placebo relapsed over six months (2 *vs* 8, $P = 0.04$)[259].

NICOTINE

While CD is exacerbated and more difficult to treat in active smokers, UC by contrast is a disease of non-smokers. Older patients diagnosed with UC are commonly ex-smokers[260]. One study showed that while the risk of developing UC was not statistically different between those who never smoked and active smokers, ex-smokers were at greater risk to develop UC, suggesting that cessation of smoking increases risk[261]. It is speculated that nicotine alters systemic and/or gut immune function in a protective way; the exact mechanism remains unknown[262]. A Cochrane review found that transdermal nicotine (15-25 mg/d for 4-6 wk) induces remission more readily than placebo although benefit was not greater than mesalamine or corticosteroids. More patients experienced side effects (nausea and light-headedness) with nicotine compared to the other medications[263]. In contrast, transdermal nicotine is no more effective than placebo in the maintenance of remission[264], and nicotine enemas are no more effective than placebo in achieving remission in patients with distal UC[265].

APHERESIS

Selective apheresis of leukocytes, including the targeted removal of monocytes, granulocytes, and lymphocytes is a growing area of research in the treatment of UC. Review of leukocyte apheresis studies shows efficacy in inducing remission across various UC populations in small, open trials[266], but the inherent process of apheresis makes controlled studies difficult to conduct. Two larger trials have demonstrated that leukocyte apheresis (n = 76) and granulocyte/monocyte apheresis (Adacolumn®) (n = 69) are equally or more effective than steroids in the induction of remission[267,268], with fewer adverse events[267] and greater steroid-sparing effects[268]. In the only sham-controlled trial to date, 19 patients with moderate to severe UC treated with five weekly sessions of either leukocyte apheresis (followed by every other week for 4 wk) or sham apheresis demonstrated that the leukocyte apheresis group had significantly greater clinical improvement (80%) than the sham group (33%)[269]. Maintenance of remission after apheresis has been equivocal: in one study of 71 patients with active UC treated with leukocyte apheresis, only 27% of those with an initial response (n = 53) maintained remission for more than six months; rapid response to treatment was the only factor correlated with long-term response in multivariate analysis[270]. In another study, however, 26 of 33 patients maintained remission at one year after 11 weekly sessions of granulocyte/monocyte apheresis[271]. Apheresis may be effective in other settings as well, including a small group of patients with toxic megacolon[272], acute pouchitis[273] and a patient with pyoderma gangrenosum[274].

PROBIOTICS

While there is suggestion that probiotics may benefit patients with active UC, data are limited. Open-label studies with VSL #3[275] and *Saccharomyces boulardii*[276] have shown promise, while a small randomized controlled trial of bifidobacterium fermented milk (100 cc/d for 12 wk) in 20 patients demonstrated significant clinical, endoscopic and histologic improvement over placebo[277]. *Bifidobacterium longum* combined with Synergy, a prebiotic (inulin oligofructose growth substrate) showed a trend toward endoscopic improvement over placebo and significantly decreased inflammatory cytokines such as TNFα and IL-1 in the treated group[278]. No difference in relapse rates were seen among 327 patients with quiescent UC given *Escherichia coli* Nissl 1917 compared to mesalamine over 12 mo[279]. Among 187 patients with inactive UC given either *Lactobacillus* GG, mesalamine or a combination of the two treatments, no differences in relapse rates at six or twelve months were seen across the three groups, although treatment with lactobacillus GG alone or together with mesalamine prolonged relapse-free time[280]. A review by Rioux and Fedorak, showed that VSL #3 has also been beneficial in the maintenance of remission for pouchitis[148].

TRICHURIS SUIS

Although the mechanism is unclear, helminthic colonization has been theorized to be protective against the development of IBD based both on epidemiologic and animal model data. In a randomized controlled trial of 54 patients with active UC, those who received *Trichuris suis* ova every 2 wk for 12 wk had a greater response rate (43%) compared to those who received placebo (16.7%), $P = 0.04$[281]. While intriguing, this study has been questioned regarding whether the statistically significant decrease in activity index of the treated group represents a clinically significant difference[282].

CONCLUSION

The treatment of IBD is a burgeoning field: in particular, the introduction of infliximab, an anti-TNFα medication, almost a decade ago, has been the most significant addition to the spectrum of therapeutic options in IBD, which for many years was primarily limited to 5-ASAs, antibiotics, steroids and immunomodulators. Medications may be used either to induce or maintain remission. Choice of therapy depends largely on the severity of disease, and may also be influenced by such factors as disease location, side effects and adverse events, as well as cost. While there is much debate presently regarding "top-down" compared to the traditional "step-up" treatment a reversal of the

"therapeutic pyramid" awaits more data regarding short- and long-term efficacy, safety, and pharmacoeconomic data. Aminosalicylates remain the standard induction and maintenance therapies for UC but have a more equivocal role in CD. Despite a paucity of evidence, antibiotics are also commonly used in CD, especially with colonic and perianal disease. Budesonide is effective as a first-line agent for ileal and/or right colonic CD although maintenance benefits remain to be proven. Conventional steroids induce remission for both CD and UC but are reserved for patients with moderate-severe disease or for those who have failed more first-line therapy. Immunomodulators such as 6-MP and azathioprine, as well as methotrexate, are effective steroid-sparing and maintenance therapies. Cyclosporine or tacrolimus can be effective for severe or refractory UC. Anti-TNF agents have been effective for patients with moderate-severe UC and CD, independent of concomitant medications. Potential side effects, costs and immunogenicity remain issues relating to current and future biologic agents. Novel therapies continue to be explored as the immunopathophysiologic underpinnings of IBD continue to be elucidated and an ultimate etiopathogenesis remains undetermined.

REFERENCES

1 **Desreumaux P**, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid - new evidence. *Aliment Pharmacol Ther* 2006; **24** Suppl 1: 2-9
2 **Harrell LE**, Hanauer SB. Mesalamine derivatives in the treatment of Crohn's disease. *Gastroenterol Clin North Am* 2004; **33**: 303-317, ix-x
3 **Summers RW**, Switz DM, Sessions JT Jr, Becktel JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847-869
4 **Malchow H**, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984; **86**: 249-266
5 **Singleton JW**, Hanauer SB, Gitnick GL, Peppercorn MA, Robinson MG, Wruble LD, Krawitt EL. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993; **104**: 1293-1301
6 **Hanauer SB**, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2**: 379-388
7 **Sandborn WJ**, Feagan BG. Review article: mild to moderate Crohn's disease--defining the basis for a new treatment algorithm. *Aliment Pharmacol Ther* 2003; **18**: 263-277
8 **Prantera C**, Cottone M, Pallone F, Annese V, Franze A, Cerutti R, Bianchi Porro G. Mesalamine in the treatment of mild to moderate active Crohn's ileitis: results of a randomized, multicenter trial. *Gastroenterology* 1999; **116**: 521-526
9 **Tremaine WJ**, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994; **19**: 278-282
10 **Thomsen OO**, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, Vatn M, Persson T, Pettersson E. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998; **339**: 370-374
11 **Colombel JF**, Lemann M, Cassagnou M, Bouhnik Y, Duclos B, Dupas JL, Notteghem B, Mary JY. A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Am J Gastroenterol* 1999; **94**: 674-678
12 **Lennard-Jones JE**. Sulphasalazine in asymptomatic Crohn's disease. A multicentre trial. *Gut* 1977; **18**: 69-72
13 **Gisbert JP**, Gomollon F, Mate J, Pajares JM. Role of 5-aminosalicylic acid (5-ASA) in treatment of inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2002; **47**: 471-488
14 **Akobeng AK**, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005: CD003715
15 **Gendre JP**, Mary JY, Florent C, Modigliani R, Colombel JF, Soule JC, Galmiche JP, Lerebours E, Descos L, Viteau JM. Maintenance treatment of Crohn's disease using orally administered mesalazine (Pentasa). A controlled multicenter study. The Study Groups on the Treatment of Inflammatory Digestive Disorders. *Ann Gastroenterol Hepatol* (Paris) 1993; **29**: 251-256
16 **Modigliani R**, Colombel JF, Dupas JL, Dapoigny M, Costil V, Veyrac M, Duclos B, Soule JC, Gendre JP, Galmiche JP, Danne O, Cadiot G, Lamouliatte H, Belaiche J, Mary JY. Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1996; **110**: 688-693
17 **Achkar JP**, Hanauer SB. Medical therapy to reduce postoperative Crohn's disease recurrence. *Am J Gastroenterol* 2000; **95**: 1139-1146
18 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963
19 **Camma C**, Giunta M, Rosselli M, Cottone M. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology* 1997; **113**: 1465-1473
20 **Lochs H**, Mayer M, Fleig WE, Mortensen PB, Bauer P, Genser D, Petritsch W, Raithel M, Hoffmann R, Gross V, Plauth M, Staun M, Nesje LB. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000; **118**: 264-273
21 **Sutherland LR**. Mesalamine for the prevention of postoperative recurrence: is nearly there the same as being there? *Gastroenterology* 2000; **118**: 436-438
22 **Hanauer SB**, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127**: 723-729
23 **Sutherland L**, Singleton J, Sessions J, Hanauer S, Krawitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; **32**: 1071-1075
24 **Blichfeldt P**, Blomhoff JP, Myhre E, Gjone E. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand J Gastroenterol* 1978; **13**: 123-127
25 **Steinhart AH**, Feagan BG, Wong CJ, Vandervoort M, Mikolainis S, Croitoru K, Seidman E, Leddin DJ, Bitton A, Drouin E, Cohen A, Greenberg GR. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 2002; **123**: 33-40
26 **Arnold GL**, Beaves MR, Pryjdun VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 10-15
27 **Ursing B**. Treatment of Crohn disease with metronidazole. A Swedish multicentre study. *Lakartidningen* 1982; **79**: 543-545
28 **Prantera C**, Zannoni F, Scribano ML, Berto E, Andreoli A, Kohn A, Luzi C. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91**: 328-332
29 **Prantera C**, Lochs H, Campieri M, Scribano ML, Sturniolo GC, Castiglione F, Cottone M. Antibiotic treatment of Crohn's disease: results of a multicentre, double blind, randomized,

placebo-controlled trial with rifaximin. *Aliment Pharmacol Ther* 2006; **23**: 1117-1125
30 **Bernstein LH**, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**: 357-365
31 **Brandt LJ**, Bernstein LH, Boley SJ, Frank MS. Metronidazole therapy for perineal Crohn's disease: a follow-up study. *Gastroenterology* 1982; **83**: 383-387
32 **Jakobovits J**, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. *Am J Gastroenterol* 1984; **79**: 533-540
33 **Rutgeerts P**, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108**: 1617-1621
34 **Rutgeerts P**, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, Aerden I, De Hertogh G, Geboes K, Hiele M, D'Hoore A, Penninckx F. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2005; **128**: 856-861
35 **Katz JA**. Treatment of inflammatory bowel disease with corticosteroids. *Gastroenterol Clin North Am* 2004; **33**: 171-189, vii
36 **Faubion WA Jr**, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; **121**: 255-260
37 **Munkholm P**, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994; **35**: 360-362
38 **Hanauer SB**. The 'tipping point' applied. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 59
39 **Beaugerie L**, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006; **130**: 650-656
40 **Rutgeerts P**, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, Danielsson A, Goebell H, Thomsen OO, Lorenz-Meyer H. A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 1994; **331**: 842-845
41 **Gross V**, Andus T, Caesar I, Bischoff SC, Lochs H, Tromm A, Schulz HJ, Bar U, Weber A, Gierend M, Ewe K, Scholmerich J. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1996; **8**: 905-909
42 **Bello C**, Goldstein F, Thornton JJ. Alternate-day prednisone treatment and treatment maintenance in Crohn's disease. *Am J Gastroenterol* 1991; **86**: 460-466
43 **Bergman L**, Krause U. Postoperative treatment with corticosteroids and salazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. *Scand J Gastroenterol* 1976; **11**: 651-656
44 **Steinhart AH**, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2003: CD000301
45 **Kane SV**, Schoenfeld P, Sandborn WJ, Tremaine W, Hofer T, Feagan BG. The effectiveness of budesonide therapy for Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 1509-1517
46 **Otley A**, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2005: CD000296
47 **Greenberg GR**, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994; **331**: 836-841
48 **Tremaine WJ**, Hanauer SB, Katz S, Winston BD, Levine JG, Persson T, Persson A. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002; **97**: 1748-1754
49 **Herfarth H**, Gross V, Andus T, Caesar I, Vogelsang H, Adler G, Malchow H, Petri A, Gierend M, Scholmerich J. Analysis of the therapeutic efficacy of different doses of budesonide in patients with active Crohn's ileocolitis depending on disease activity and localization. *Int J Colorectal Dis* 2004; **19**: 147-152
50 **Bar-Meir S**, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, Reshef R, Odes S, Moshkovitz M, Bruck R, Eliakim R, Maoz E, Mittmann U. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology* 1998; **115**: 835-840
51 **Campieri M**, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997; **41**: 209-214
52 **Papi C**, Luchetti R, Gili L, Montanti S, Koch M, Capurso L. Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000; **14**: 1419-1428
53 **Gross V**, Andus T, Ecker KW, Raedler A, Loeschke K, Plauth M, Rasenack J, Weber A, Gierend M, Ewe K, Scholmerich J. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. *Gut* 1998; **42**: 493-496
54 **Hanauer S**, Sandborn WJ, Persson A, Persson T. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005; **21**: 363-371
55 **Sandborn WJ**, Lofberg R, Feagan BG, Hanauer SB, Campieri M, Greenberg GR. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. *Am J Gastroenterol* 2005; **100**: 1780-1787
56 **Greenberg GR**, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996; **110**: 45-51
57 **Ferguson A**, Campieri M, Doe W, Persson T, Nygard G. Oral budesonide as maintenance therapy in Crohn's disease--results of a 12-month study. Global Budesonide Study Group. *Aliment Pharmacol Ther* 1998; **12**: 175-183
58 **Ewe K**, Bottger T, Buhr HJ, Ecker KW, Otto HF. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1999; **11**: 277-282
59 **Hellers G,** Cortot A, Jewell D, Leijonmarck CE, Lofberg R, Malchow H, Nilsson LG, Pallone F, Pena S, Persson T, Prantera C, Rutgeerts P. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology* 1999; **116**: 294-300
60 **Simms L**, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2001: CD002913
61 **Schoon EJ**, Bollani S, Mills PR, Israeli E, Felsenberg D, Ljunghall S, Persson T, Hapten-White L, Graffner H, Bianchi Porro G, Vatn M, Stockbrugger RW. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin Gastroenterol Hepatol* 2005; **3**: 113-121
62 **Lichtenstein G**, Hapten-White L, Sandborn WJ. Long-term safety analysis of budesonide in Crohn's disease: a pooled analysis of five 1-year studies. *Gastroenterology* 2006; **130**: A484
63 **Schroll S**, Sarlette A, Ahrens K, Manns MP, Goke M. Effects of azathioprine and its metabolites on repair mechanisms of the intestinal epithelium in vitro. *Regul Pept* 2005; **131**: 1-11
64 **Tiede I**, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, Lehr HA, Wirtz S, Becker C, Atreya R, Mudter J, Hildner K, Bartsch B, Holtmann M, Blumberg R, Walczak H, Iven H, Galle PR, Ahmadian MR, Neurath MF. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest* 2003; **111**: 1133-1145
65 **Sandborn W**, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2000: CD000545

66 **Pearson DC**, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000: CD000067

67 **Present DH**, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987

68 **Candy S**, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995; **37**: 674-678

69 **Vilien M**, Dahlerup JF, Munck LK, Norregaard P, Gronbaek K, Fallingborg J. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Aliment Pharmacol Ther* 2004; **19**: 1147-1152

70 **Lemann M**, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812-1818

71 **Ardizzone S**, Maconi G, Sampietro GM, Russo A, Radice E, Colombo E, Imbesi V, Molteni M, Danelli PG, Taschieri AM, Bianchi Porro G. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004; **127**: 730-740

72 **Holtmann MH**, Krummenauer F, Claas C, Kremeyer K, Lorenz D, Rainer O, Vogel I, Bocker U, Bohm S, Buning C, Duchmann R, Gerken G, Herfarth H, Lugering N, Kruis W, Reinshagen M, Schmidt J, Stallmach A, Stein J, Sturm A, Galle PR, Hommes DW, D'Haens G, Rutgeerts P, Neurath MF. Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51**: 1516-1524

73 **Markowitz J**, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**: 895-902

74 **Kandiel A**, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54**: 1121-1125

75 **Disanti W**, Rajapakse RO, Korelitz BI, Panagopoulos G, Bratcher J. Incidence of neoplasms in patients who develop sustained leukopenia during or after treatment with 6-mercaptopurine for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1025-1029

76 **Dayharsh GA**, Loftus EV Jr, Sandborn WJ, Tremaine WJ, Zinsmeister AR, Witzig TE, Macon WR, Burgart LJ. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002; **122**: 72-77

77 **Siegel CA**, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. *Aliment Pharmacol Ther* 2005; **22**: 1-16

78 **Pierik M**, Rutgeerts P, Vlietinck R, Vermeire S. Pharmacogenetics in inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 3657-3667

79 **Baron TH**, Truss CD, Elson CO. Low-dose oral methotrexate in refractory inflammatory bowel disease. *Dig Dis Sci* 1993; **38**: 1851-1856

80 **Kozarek RA**, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989; **110**: 353-356

81 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297

82 **Oren R**, Moshkowitz M, Odes S, Becker S, Keter D, Pomeranz I, Shirin C, Reisfeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Villa Y, Arber N, Gilat T. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92**: 2203-2209

83 **Arora S**, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH, Podolsky D. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46**: 1724-1729

84 **Kurnik D**, Loebstein R, Fishbein E, Almog S, Halkin H, Bar-Meir S, Chowers Y. Bioavailability of oral vs. subcutaneous low-dose methotrexate in patients with Crohn's disease. *Aliment Pharmacol Ther* 2003; **18**: 57-63

85 **Chong RY**, Hanauer SB, Cohen RD. Efficacy of parenteral methotrexate in refractory Crohn's disease. *Aliment Pharmacol Ther* 2001; **15**: 35-44

86 **Hayee BH**, Harris AW. Methotrexate for Crohn's disease: experience in a district general hospital. *Eur J Gastroenterol Hepatol* 2005; **17**: 893-898

87 **Lemann M**, Chamiot-Prieur C, Mesnard B, Halphen M, Messing B, Rambaud JC, Gendre JP, Colombel JF, Modigliani R. Methotrexate for the treatment of refractory Crohn's disease. *Aliment Pharmacol Ther* 1996; **10**: 309-314

88 **Ardizzone S**, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; **35**: 619-627

89 **Mate-Jimenez J**, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000; **12**: 1227-1233

90 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632

91 **Fraser AG**, Morton D, McGovern D, Travis S, Jewell DP. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002; **16**: 693-697

92 **Neurath MF**, Wanitschke R, Peters M, Krummenauer F, Meyer zum Buschenfelde KH, Schlaak JF. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; **44**: 625-628

93 **Loftus CG**, Egan LJ, Sandborn WJ. Cyclosporine, tacrolimus, and mycophenolate mofetil in the treatment of inflammatory bowel disease. *Gastroenterol Clin North Am* 2004; **33**: 141-169, vii

94 **Gonzalez-Lama Y**, Gisbert JP, Mate J. The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; **51**: 1833-1840

95 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035

96 **Rutgeerts P**, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117**: 761-769

97 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549

98 **Rutgeerts P**, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63**: 433-442; quiz 464

99 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T,

DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405

100 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885

101 **Domenech E**, Hinojosa J, Nos P, Garcia-Planella E, Cabre E, Bernal I, Gassull MA. Clinical evolution of luminal and perianal Crohn's disease after inducing remission with infliximab: how long should patients be treated? *Aliment Pharmacol Ther* 2005; **22**: 1107-1113

102 **Baert F**, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**: 601-608

103 **Farrell RJ**, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003; **124**: 917-924

104 **Sandborn WJ**, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. *Am J Gastroenterol* 2002; **97**: 2962-2972

105 **Rutgeerts P**, Van Assche G, Vermeire S. Review article: Infliximab therapy for inflammatory bowel disease--seven years on. *Aliment Pharmacol Ther* 2006; **23**: 451-463

106 **Schroder O**, Blumenstein I, Stein J. Combining infliximab with methotrexate for the induction and maintenance of remission in refractory Crohn's disease: a controlled pilot study. *Eur J Gastroenterol Hepatol* 2006; **18**: 11-16

107 **Arnott ID**, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther* 2003; **17**: 1451-1457

108 **Parsi MA**, Achkar JP, Richardson S, Katz J, Hammel JP, Lashner BA, Brzezinski A. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology* 2002; **123**: 707-713

109 **Vermeire S**, Louis E, Carbonez A, Van Assche G, Noman M, Belaiche J, De Vos M, Van Gossum A, Pescatore P, Fiasse R, Pelckmans P, Reynaert H, D'Haens G, Rutgeerts P. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol* 2002; **97**: 2357-2363

110 **Lemann M**, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadiot G, Picon L, Bourreille A, Sobahni I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130**: 1054-1061

111 **Hommes D**, Baert F, van Assche G, Caenepeel, Vergauwe P, Tuynman H, de Vos M, van Deventer S, Stitt L, Rutgeerts P, Feagan B, D'haens G. The ideal management of Crohn' s disease: top down versus step up strategies, a randomized controlled trial. *Gastroenterology* 2006; **130**: A108

112 **Caprilli R**, Angelucci E, Cocco A. Early or late guided missile in the treatment of Crohn's disease? *Dig Liver Dis* 2005; **37**: 973-979

113 **Loftus EV**. Infliximab: lifetime use for maintenance is appropriate in Crohn's Disease. CON: "lifetime use" is an awfully long time. *Am J Gastroenterol* 2005; **100**: 1435-1438

114 **Colombel JF**, Loftus EV Jr, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, Zinsmeister AR, Sandborn WJ. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004; **126**: 19-31

115 **Askling J**, Brandt L, Lapidus A, Karlen P, Bjorkholm M, Lofberg R, Ekbom A. Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut* 2005; **54**: 617-622

116 **Greenstein AJ**, Gennuso R, Sachar DB, Heimann T, Smith H, Janowitz HD, Aufses AH Jr. Extraintestinal cancers in inflammatory bowel disease. *Cancer* 1985; **56**: 2914-2921

117 **Ekbom A**, Helmick C, Zack M, Adami HO. Extracolonic malignancies in inflammatory bowel disease. *Cancer* 1991; **67**: 2015-2019

118 **Lichtenstein GR**, Cohen RD, Feagan BG, Sandborn WJ, Salzberg BA, Chen DM, Pritchard ML, Broussard DL, Diamond RH. Safety of infliximab and other Crohn's disease therapies: TREAT registry data with nearly 15,000 patient-years of follow-up. *Gastroenterology* 2006; **130**: A71

119 **Siegel CA**, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1017-1024; quiz 976

120 **Sandborn WJ**, Hanauer S, Loftus EV Jr, Tremaine WJ, Kane S, Cohen R, Hanson K, Johnson T, Schmitt D, Jeche R. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004; **99**: 1984-1989

121 **Papadakis KA**, Shaye OA, Vasiliauskas EA, Ippoliti A, Dubinsky MC, Birt J, Paavola J, Lee SK, Price J, Targan SR, Abreu MT. Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. *Am J Gastroenterol* 2005; **100**: 75-79

122 **Hanauer SB**, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323-333; quiz 591

123 **Rutgeerts PJ**, Mellili LE, Li J, Pollack PF. Adalimumab maintains improvement in inflammatory bowel disease questionnaire (IBDQ) scores over 1 year following the initial attainment of remisssion in patients with moderately severely active Crohn's disease: results of the CLASSIC II study. *Gastroenterology* 2006; **130**: A479

124 **Panaccione R**, Hanauer SB, Fedorak R, Rutgeerts P, Sandborn WJ, Pollack P. Concomitant immunosuppressive and adalimumab therapy in patients with Crohn's disease: 1-year results of the CLASSIC II study. *Gastroenterology* 2006 **130**: A479

125 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65

126 **Schreiber S**, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OO, Innes A. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005; **129**: 807-818

127 **Winter TA**, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. *Aliment Pharmacol Ther* 2004; **20**: 1337-1346

128 **Sandborn WJ**, CJ, Panes J, Scholmerich J, McColm JA, Schreiber S. Higher remission and maintenance of response rates with subcutaneous monthly certolizumab pegol in patients with recent-onset Crohn's disease: data from PRECiSE 2. *Am J Gastroenterol* 2006; **101**: S454-S455

129 **Hommes DW**, Mikhajlova TL, Stoinov S, Stimac D, Vucelic B, Lonovics J, Zakuciova M, D'Haens G, Van Assche G, Ba S, Lee S, Pearce T. Fontolizumab, a humanised anti-interferon gamma antibody, demonstrates safety and clinical activity in patients with moderate to severe Crohn's disease. *Gut* 2006; **55**: 1131-1137

130 **Sandborn WJ**, Yednock TA. Novel approaches to treating inflammatory bowel disease: targeting alpha-4 integrin. *Am J Gastroenterol* 2003; **98**: 2372-2382

131 **Kent SJ**, Karlik SJ, Cannon C, Hines DK, Yednock TA, Fritz LC, Horner HC. A monoclonal antibody to alpha 4 integrin suppresses and reverses active experimental allergic encephalomyelitis. *J Neuroimmunol* 1995; **58**: 1-10

132 **Hesterberg PE**, Winsor-Hines D, Briskin MJ, Soler-Ferran D, Merrill C, Mackay CR, Newman W, Ringler DJ. Rapid resolution

of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin alpha 4 beta 7. *Gastroenterology* 1996; **111**: 1373-1380

133 **Ghosh S**, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, Vyhnalek P, Zadorova Z, Palmer T, Donoghue S. Natalizumab for active Crohn's disease. *N Engl J Med* 2003; **348**: 24-32

134 **Gordon FH**, Lai CW, Hamilton MI, Allison MC, Srivastava ED, Fouweather MG, Donoghue S, Greenlees C, Subhani J, Amlot PL, Pounder RE. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. *Gastroenterology* 2001; **121**: 268-274

135 **Sandborn WJ**, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 1912-1925

136 **Targan SR**, Feagan B, Fedorak R, Lashner B, Panacionne R, Present D, Raedler A, Rutgeerts P, Tulassay Z, Volfova M, Wolf DC, Sandborn W. Natalizumab induces sustained response and remission in patients with active Crohn's disease: results from the ENCORE trial. *Gastroenterology* 2006; **130**: A108

137 **Sandborn W**, Colombel JF, Enns R, Feagan B, Hanauer S, Lawrance I, Panaccione R, Rutgeerts P, Schreiber S, Targan S, van Deventer S. Maintenance therapy with natalizumab does not require use of concomitant immunosuppressants for sustained efficacy in patients with active Crohn's disease: results from the ENACT-2 study. *Gastroenterology* 2006; **130**: A482

138 **Panaccione R**, Colombel JF, Enns R, Feagan B, Hanauer S, Lawrance I, Rutgeerts P, Sandborn S, Schreiber S, Targan S, van Deventer S. Natalizumab maintains remission in patients with moderately to severely active Crohn's disease for up to 2 years: results from an open-label extension study. *Gastroenterology* 2006; **130**: A111

139 **Sandborn W**, Targan S. A safety evaluation for progressive multifocal leukoencephalopathy (PML) in greater than 3,500 patients with Crohn's disease (CD), multiple sclerosis (MS), and rheumatoid arthritis (RA) previously treated with natalizumab in clinical trials. *Gastroenterology* 2006; **130**: A72

140 **Feagan BG**, Greenberg GR, Wild G, Fedorak RN, Pare P, McDonald JW, Dube R, Cohen A, Steinhart AH, Landau S, Aguzzi RA, Fox IH, Vandervoort MK. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med* 2005; **352**: 2499-2507

141 **Lindenboom K**, Brazier G. Millennium pharmaceuticals announces phase II data for MLN02 in Crohn's disease. Cambridge, MA: Millennium Pharmaceuticals, 2002

142 **Hommes D**, Targan S, Baumgart DC, Dignass AU, Mayer L, Lowder JN. A Phase I Study: Visilizumab therapy in Crohn's disease (CD) patients refractory to infliximab treatment. *Gastroenterology* 2006; **130**: A111

143 **Ito H**, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, Matsumoto T, Yamamura T, Azuma J, Nishimoto N, Yoshizaki K, Shimoyama T, Kishimoto T. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126**: 989-996; discussion 947

144 **Mannon PJ**, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, Dolin B, Goodman N, Groden C, Hornung RL, Quezado M, Yang Z, Neurath MF, Salfeld J, Veldman GM, Schwertschlag U, Strober W. Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med* 2004; **351**: 2069-2079

145 **Bariol C**, Meagher AP, Vickers CR, Byrnes DJ, Edwards PD, Hing M, Wettstein AR, Field A. Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17**: 135-139

146 **Bauditz J**, Wedel S, Lochs H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50**: 196-200

147 **Korzenik JR**, Dieckgraefe BK, Valentine JF, Hausman DF, Gilbert MJ. Sargramostim for active Crohn's disease. *N Engl J Med* 2005; **352**: 2193-2201

148 **Rioux KP**, Fedorak RN. Probiotics in the treatment of inflammatory bowel disease. *J Clin Gastroenterol* 2006; **40**: 260-363

149 **Summers RW**, Elliott DE, Urban JF Jr, Thompson R, Weinstock JV. Trichuris suis therapy in Crohn's disease. *Gut* 2005; **54**: 87-90

150 **Nielsen OH**. Sulfasalazine intolerance. A retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. *Scand J Gastroenterol* 1982; **17**: 389-393

151 **Sutherland L**, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006: CD000543

152 **Sutherland L**, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006: CD000544

153 **Green JR**, Lobo AJ, Holdsworth CD, Leicester RJ, Gibson JA, Kerr GD, Hodgson HJ, Parkins KJ, Taylor MD. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. The Abacus Investigator Group. *Gastroenterology* 1998; **114**: 15-22

154 **Levine DS**, Riff DS, Pruitt R, Wruble L, Koval G, Sales D, Bell JK, Johnson LK. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 1398-1407

155 **Pruitt R**, Hanson J, Safdi M, Wruble L, Hardi R, Johanson J, Koval G, Riff D, Winston B, Cross A, Doty P, Johnson LK. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 3078-3086

156 **Sandborn WJ**. Rational selection of oral 5-aminosalicylate formulations and prodrugs for the treatment of ulcerative colitis. *Am J Gastroenterol* 2002; **97**: 2939-2941

157 **Hanauer SB**. Balsalazide led to greater remission rates and tolerance than mesalamine in acute ulcerative colitis. *Gut* 1999; **44**: 455

158 **Gross V**. Efficacy of different mesalamine-releasing drugs. *Gastroenterology* 1998; **115**: 1306-1307

159 **Hanauer SB**. Treatment of ulcerative colitis with balsalazide: response to Drs Johnson, Green, and Pruitt. *Am J Gastroenterol* 2003; **98**: 697-698

160 **Sandborn WJ**, Hanauer SB, Buch A. Comparative pharmacokinetics of equimolar doses of 5-aminosalicylate administered as oral mesalamine (Asacol) and balsalazide: a randomized, single-dose, crossover study in healthy volunteers. *Aliment Pharmacol Ther* 2004; **19**: 1089-1098

161 **Hanauer SB**, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, Regalli G, Yeh C, Smith-Hall N, Ajayi F. 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* 2005; **100**: 2478-2485

162 **Lichtenstein GR**, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, Lees K, Joseph RE, Sandborn WJ. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007; **5**: 95-102

163 **Cohen RD**, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000; **95**: 1263-1276

164 **Marshall JK**, Irvine EJ. Putting rectal 5-aminosalicylic acid in its place: the role in distal ulcerative colitis. *Am J Gastroenterol* 2000; **95**: 1628-1636

165 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048

166 **Baron JH**, Connell AM, Kanaghinis TG, Lennard-Jones JE, Jones AF. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *Br Med J* 1962; **2**: 441-443

167 **Powell-Tuck J**, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978; **13**: 833-837

168 **Sood A**, Midha V, Sood N, Awasthi G. A prospective, open-

label trial assessing dexamethasone pulse therapy in moderate to severe ulcerative colitis. *J Clin Gastroenterol* 2002; **35**: 328-331
169 **Turner D**, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; **5**: 103-110
170 **Bossa F**, Fiorella S, Caruso N, Accadia L, Napolitano G, Valvano MR, Andriulli A, Annese V. Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: a randomized, double-blind trial. *Am J Gastroenterol* 2007; **102**: 601-608
171 **Kjeldsen J**. Treatment of ulcerative colitis with high doses of oral prednisolone. The rate of remission, the need for surgery, and the effect of prolonging the treatment. *Scand J Gastroenterol* 1993; **28**: 821-826
172 **Jarnerot G**, Rolny P, Sandberg-Gertzen H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterology* 1985; **89**: 1005-1013
173 **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910
174 **Honda M**, Orii F, Ayabe T, Imai S, Ashida T, Obara T, Kohgo Y. Expression of glucocorticoid receptor beta in lymphocytes of patients with glucocorticoid-resistant ulcerative colitis. *Gastroenterology* 2000; **118**: 859-866
175 **Zhang H**, Ouyang Q, Wen ZH, Fiocchi C, Liu WP, Chen DY, Li FY. Significance of glucocorticoid receptor expression in colonic mucosal cells of patients with ulcerative colitis. *World J Gastroenterol* 2005; **11**: 1775-1778
176 **Webster JC**, Oakley RH, Jewell CM, Cidlowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci USA* 2001; **98**: 6865-6870
177 **Truelove SC**, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974; **1**: 1067-1070
178 **Lofberg R**, Danielsson A, Suhr O, Nilsson A, Schioler R, Nyberg A, Hultcrantz R, Kollberg B, Gillberg R, Willen R, Persson T, Salde L. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996; **110**: 1713-1718
179 **Campieri M**, Adamo S, Valpiani D, D'Arienzo A, D'Albasio G, Pitzalis M, Cesari P, Casetti T, Castiglione GN, Rizzello F, Manguso F, Varoli G, Gionchetti P. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; **17**: 1471-1480
180 **Rizzello F**, Gionchetti P, D'Arienzo A, Manguso F, Di Matteo G, Annese V, Valpiani D, Casetti T, Adamo S, Prada A, Castiglione GN, Varoli G, Campieri M. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002; **16**: 1109-1116
181 **Hanauer SB**, Robinson M, Pruitt R, Lazenby AJ, Persson T, Nilsson LG, Walton-Bowen K, Haskell LP, Levine JG. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. *Gastroenterology* 1998; **115**: 525-532
182 **Lindgren S**, Lofberg R, Bergholm L, Hellblom M, Carling L, Ung KA, Schioler R, Unge P, Wallin C, Strom M, Persson T, Suhr OB. Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. *Scand J Gastroenterol* 2002; **37**: 705-710
183 **Lemann M**, Galian A, Rutgeerts P, Van Heuverzwijn R, Cortot A, Viteau JM, Elewaut A, Belaiche J, Froguel E, Modigliani R. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1995; **9**: 557-562
184 **Budesonide enema in distal ulcerative colitis**. A randomized dose-response trial with prednisolone enema as positive control. The Danish Budesonide Study Group. *Scand J Gastroenterol* 1991; **26**: 1225-1230
185 **Danielsson A**, Hellers G, Lyrenas E, Lofberg R, Nilsson A, Olsson O, Olsson SA, Persson T, Salde L, Naesdal J. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Scand J Gastroenterol* 1987; **22**: 987-992
186 **Lofberg R**, Ostergaard Thomsen O, Langholz E, Schioler R, Danielsson A, Suhr O, Graffner H, Pahlman L, Matzen P, Moller-Petersen JF. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1994; **8**: 623-629
187 **Gross V**, Bar-Meir S, Lavy A, Mickisch O, Tulassay Z, Pronai L, Kupcinskas L, Kiudelis G, Pokrotnieks J, Kovacs A, Faszczyk M, Razbadauskas A, Margus B, Stolte M, Muller R, Greinwald R. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; **23**: 303-312
188 **Mulder CJ**, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol* 1996; **8**: 549-553
189 **Campieri M**, Cottone M, Miglio F, Manenti F, Astegiano M, D'Arienzo A, Manguso F, D'Albasio G, Bonanomi A, Galeazzi R, Orlando A, Castiglione GN, Gionchetti P. Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. *Aliment Pharmacol Ther* 1998; **12**: 361-366
190 **Jewell DP**, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974; **4**: 627-630
191 **Rosenberg JL**, Wall AJ, Levin B, Binder HJ, Kirsner JB. A controlled trial of azathioprine in the management of chronic ulcerative colitis. *Gastroenterology* 1975; **69**: 96-99
192 **Kirk AP**, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J* (Clin Res Ed) 1982; **284**: 1291-1292
193 **Hawthorne AB**, Logan RF, Hawkey CJ, Foster PN, Axon AT, Swarbri ck ET, Scott BB, Lennard-Jones JE. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992; **305**: 20-22
194 **Adler DJ**, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85**: 717-722
195 **George J**, Present DH, Pou R, Bodian C, Rubin PH. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91**: 1711-1714
196 **Ardizzone S**, Molteni P, Imbesi V, Bollani S, Bianchi Porro G. Azathioprine in steroid-resistant and steroid-dependent ulcerative colitis. *J Clin Gastroenterol* 1997; **25**: 330-333
197 **Lobo AJ**, Foster PN, Burke DA, Johnston D, Axon AT. The role of azathioprine in the management of ulcerative colitis. *Dis Colon Rectum* 1990; **33**: 374-377
198 **Fraser AG**, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50**: 485-489
199 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53
200 **Mantzaris GJ**, Sfakianakis M, Archavlis E, Petraki K, Christidou A, Karagiannidis A, Triadaphyllou G. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 1122-1128
201 **Campbell S**, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. *Eur J Gastroenterol Hepatol* 2001; **13**: 1297-1301
202 **Cummings JR**, Herrlinger KR, Travis SP, Gorard DA, McIntyre AS, Jewell DP. Oral methotrexate in ulcerative colitis. *Aliment Pharmacol Ther* 2005; **21**: 385-389
203 **Paoluzi OA**, Pica R, Marcheggiano A, Crispino P, Iacopini F,

Iannoni C, Rivera M, Paoluzi P. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002; **16**: 1751-1759

204 **Oren R, Arber N**, Odes S, Moshkowitz M, Keter D, Pomeranz I, Ron Y, Reisfeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Bardan E, Villa Y, Gilat T. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110**: 1416-1421

205 **Jani N**, Regueiro MD. Medical therapy for ulcerative colitis. *Gastroenterol Clin North Am* 2002; **31**: 147-166

206 **Lichtiger S**, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet* 1990; **336**: 16-19

207 **Lichtiger S**, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845

208 **Kornbluth A**, Lichtiger S, Present D, et al Long-term results of oral cyclosporine in patients with severe ulcerative colitis: a double-blind randomized, multi-center trial. *Gastroenterology* 1994; **106**: A714

209 **Poritz LS**, Rowe WA, Swenson BR, Hollenbeak CS, Koltun WA. Intravenous cyclosporine for the treatment of severe steroid refractory ulcerative colitis: what is the cost? *Dis Colon Rectum* 2005; **48**: 1685-1690

210 **McCormack G**, McCormick PA, Hyland JM, O'Donoghue DP. Cyclosporin therapy in severe ulcerative colitis: is it worth the effort? *Dis Colon Rectum* 2002; **45**: 1200-1205

211 **Hyde GM**, Thillainayagam AV, Jewell DP. Intravenous cyclosporin as rescue therapy in severe ulcerative colitis: time for a reappraisal? *Eur J Gastroenterol Hepatol* 1998; **10**: 411-413

212 **Carbonnel F**, Boruchowicz A, Duclos B, Soule JC, Lerebours E, Lemann M, Belaiche J, Colombel JF, Cosnes J, Gendre JP. Intravenous cyclosporine in attacks of ulcerative colitis: short-term and long-term responses. *Dig Dis Sci* 1996; **41**: 2471-2476

213 **Message L**, Bourreille A, Laharie D, Quinton A, Galmiche JP, Lamouliatte H, Alamdari A, Zerbib F. Efficacy of intravenous cyclosporin in moderately severe ulcerative colitis refractory to steroids. *Gastroenterol Clin Biol* 2005; **29**: 231-235

214 **Fernandez-Banares F**, Bertran X, Esteve-Comas M, Cabre E, Menacho M, Humbert P, Planas R, Gassull MA. Azathioprine is useful in maintaining long-term remission induced by intravenous cyclosporine in steroid-refractory severe ulcerative colitis. *Am J Gastroenterol* 1996; **91**: 2498-2499

215 **Campbell S**, Ghosh S. Combination immunomodulatory therapy with cyclosporine and azathioprine in corticosteroid-resistant severe ulcerative colitis: the Edinburgh experience of outcome. *Dig Liver Dis* 2003; **35**: 546-551

216 **Cohen RD**, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999; **94**: 1587-1592

217 **Domenech E**, Garcia-Planella E, Bernal I, Rosinach M, Cabre E, Fluvia L, Boix J, Gassull MA. Azathioprine without oral ciclosporin in the long-term maintenance of remission induced by intravenous ciclosporin in severe, steroid-refractory ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 2061-2065

218 **Rayner CK**, McCormack G, Emmanuel AV, Kamm MA. Long-term results of low-dose intravenous ciclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2003; **18**: 303-308

219 **Actis GC**, Ottobrelli A, Pera A, Barletti C, Ponti V, Pinna-Pintor M, Verme G. Continuously infused cyclosporine at low dose is sufficient to avoid emergency colectomy in acute attacks of ulcerative colitis without the need for high-dose steroids. *J Clin Gastroenterol* 1993; **17**: 10-13

220 **Van Assche G**, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003; **125**: 1025-1031

221 **Actis GC**, Aimo G, Priolo G, Moscato D, Rizzetto M, Pagni R. Efficacy and efficiency of oral microemulsion cyclosporin versus intravenous and soft gelatin capsule cyclosporin in the treatment of severe steroid-refractory ulcerative colitis: an open-label retrospective trial. *Inflamm Bowel Dis* 1998; **4**: 276-279

222 **Actis GC**, Lagget M, Rizzetto M, Fadda M, Palmo A, Pinna-Pintor M, Morino F. Long-term efficacy of oral microemulsion cyclosporin for refractory ulcerative colitis. *Minerva Med* 2004; **95**: 65-70

223 **de Saussure P**, Soravia C, Morel P, Hadengue A. Low-dose oral microemulsion ciclosporin for severe, refractory ulcerative colitis. *Aliment Pharmacol Ther* 2005; **22**: 203-208

224 **D'Haens G**, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001; **120**: 1323-1329

225 **Rowe FA**, Walker JH, Karp LC, Vasiliauskas EA, Plevy SE, Targan SR. Factors predictive of response to cyclosporin treatment for severe, steroid-resistant ulcerative colitis. *Am J Gastroenterol* 2000; **95**: 2000-2008

226 **Cacheux W**, Lemann M, Marteau P, Seksik P, Nion-Larmurier I, Afchain P, Allez M, Daniel F, Beaugerie L, Gendre JP, Cosnes J. Predictive factors of response to cyclosporine (CsA) in severe steroid-refractory ulcerative colitis (SSRUC). *Gastroenterology* 2006; **130**: A143

227 **Kornbluth A**, Present DH, Lichtiger S, Hanauer S. Cyclosporin for severe ulcerative colitis: a user's guide. *Am J Gastroenterol* 1997; **92**: 1424-1428

228 **Ogata H**, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55**: 1255-1262

229 **Fellermann K**, Steffen M, Stein J, Raedler A, Hamling J, Ludwig D, Loeschke K, Stange EF. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14**: 171-176

230 **Ford AC**, Towler RJ, Moayyedi P, Chalmers DM, Axon AT. Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **17**: 1365-1369

231 **Orth T**, Peters M, Schlaak JF, Krummenauer F, Wanitschke R, Mayet WJ, Galle PR, Neurath MF. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. *Am J Gastroenterol* 2000; **95**: 1201-1207

232 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476

233 **Jarnerot G**, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Danielsson A, Verbaan H, Hellstrom PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128**: 1805-1811

234 **Regueiro M**, Curtis J, Plevy S. Infliximab for hospitalized ulcerative colitis patients failing intravenous corticosteroids. *Gastroenterology* 2006; **130**: A655

235 **Lees C**, Shand AG, Penman ID, Arnott ID, Satsang J. Infliximab is effective as rescue therapy for acute severe ulcerative colitis: the initial Edinburgh experience. *Gastroenterology* 2006; **130**: A656

236 **Walsh A**, Cooley R, Templeton D, Florin T, Radford-Smith G. Acute severe ulcerative colitis: a study of predictors of outcome and efficacy for cyclosporin and infliximab. *Gastroenterology* 2006; **130**: A84

237 **Gordon FH**, Hamilton MI, Donoghue S, Greenlees C, Palmer T, Rowley-Jones D, Dhillon AP, Amlot PL, Pounder RE. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. *Aliment Pharmacol Ther* 2002; **16**: 699-705

238 **van Assche G**, Rutgeerts P. Antiadhesion molecule therapy

in inflammatory bowel disease. *Inflamm Bowel Dis* 2002; **8**: 291-300

239 **Yacyshyn BR**, Chey WY, Goff J, Salzberg B, Baerg R, Buchman AL, Tami J, Yu R, Gibiansky E, Shanahan WR. Double blind, placebo controlled trial of the remission inducing and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, alicaforsen (ISIS 2302), in active steroid dependent Crohn's disease. *Gut* 2002; **51**: 30-36

240 **van Deventer SJ**, Tami JA, Wedel MK. A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis. *Gut* 2004; **53**: 1646-1651

241 **Creed TJ**, Norman MR, Probert CS, Harvey RF, Shaw IS, Smithson J, Anderson J, Moorghen M, Gupta J, Shepherd NA, Dayan CM, Hearing SD. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther* 2003; **18**: 65-75

242 **Walker KB**, Potter JM, House AK. Interleukin 2 synthesis in the presence of steroids: a model of steroid resistance. *Clin Exp Immunol* 1987; **68**: 162-167

243 **Van Assche G**, Dalle I, Noman M, Aerden I, Swijsen C, Asnong K, Maes B, Ceuppens J, Geboes K, Rutgeerts P. A pilot study on the use of the humanized anti-interleukin-2 receptor antibody daclizumab in active ulcerative colitis. *Am J Gastroenterol* 2003; **98**: 369-376

244 **Van Assche G**, Sandborn WJ, Feagan BG, Salzberg BA, Silvers D, Monroe PS, Pandak WM, Anderson FH, Valentine JF, Wild GE, Geenen DJ, Sprague R, Targan SR, Rutgeerts P, Vexler V, Young D, Shames RS. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut* 2006; **55**: 1568-1574

245 **Plevy S**, Regueiro M, et al. A humanized ant-CD3 monoclonal antibody, visilizumab, for treatment of severe steroid-refractory ulcerative colitis: results of a phase I study. *Gastroenterology* 2004; **126**: A75

246 **Carpenter PA**, Appelbaum FR, Corey L, Deeg HJ, Doney K, Gooley T, Krueger J, Martin P, Pavlovic S, Sanders J, Slattery J, Levitt D, Storb R, Woolfrey A, Anasetti C. A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. *Blood* 2002; **99**: 2712-2719

247 **Tilg H**, Vogelsang H, Ludwiczek O, Lochs H, Kaser A, Colombel JF, Ulmer H, Rutgeerts P, Kruger S, Cortot A, D'Haens G, Harrer M, Gasche C, Wrba F, Kuhn I, Reinisch W. A randomised placebo controlled trial of pegylated interferon alpha in active ulcerative colitis. *Gut* 2003; **52**: 1728-1733

248 **Cottone M**, Magliocco A, Trallori G, Brignola C, Vandelli C, Ardizzone S, Meucci G, Zannoni F, Di Maio G, Astegiano M. Clinical course of inflammatory bowel disease during treatment with interferon for associated chronic active hepatitis. *Ital J Gastroenterol* 1995; **27**: 3-4

249 **Bargiggia S**, Thorburn D, Anderloni A, Ardizzone S, Giorgi A, Bianchi Porro G, Parente F. Is interferon-alpha therapy safe and effective for patients with chronic hepatitis C and inflammatory bowel disease? A case-control study. *Aliment Pharmacol Ther* 2005; **22**: 209-215

250 **Sumer N**, Palabiyikoglu M. Induction of remission by interferon-alpha in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995; **7**: 597-602

251 **Madsen SM**, Schlichting P, Davidsen B, Nielsen OH, Federspiel B, Riis P, Munkholm P. An open-labeled, randomized study comparing systemic interferon-alpha-2A and prednisolone enemas in the treatment of left-sided ulcerative colitis. *Am J Gastroenterol* 2001; **96**: 1807-1815

252 **Musch E**, Andus T, Malek M. Induction and maintenance of clinical remission by interferon-beta in patients with steroid-refractory active ulcerative colitis-an open long-term pilot trial. *Aliment Pharmacol Ther* 2002; **16**: 1233-1239

253 **Nikolaus S**, Rutgeerts P, Fedorak R, Steinhart AH, Wild GE, Theuer D, Mohrle J, Schreiber S. Interferon beta-1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study. *Gut* 2003; **52**: 1286-1290

254 **Musch E**, Andus T, Kruis W, Raedler A, Spehlmann M, Schreiber S, Krakamp B, Malek M, Malchow H, Zavada F, Engelberg Feurle G. Interferon-beta-1a for the treatment of steroid-refractory ulcerative colitis: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2005; **3**: 581-586

255 **Sandborn WJ**, Sands BE, Wolf DC, Valentine JF, Safdi M, Katz S, Isaacs KL, Wruble LD, Katz J, Present DH, Loftus EV Jr, Graeme-Cook F, Odenheimer DJ, Hanauer SB. Repifermin (keratinocyte growth factor-2) for the treatment of active ulcerative colitis: a randomized, double-blind, placebo-controlled, dose-escalation trial. *Aliment Pharmacol Ther* 2003; **17**: 1355-1364

256 **Sinha A**, Nightingale J, West KP, Berlanga-Acosta J, Playford RJ. Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003; **349**: 350-357

257 **Arakawa T**, Kobayashi K, Yoshikawa T, Tarnawski A. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. *Dig Dis Sci* 1998; **43**: 5S-13S

258 **Makiyama K**, Takeshima F, Hamamoto T. Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005; **50**: 2323-2329

259 **Hanai H**, Iida T, Takeuchi K, Yamada M, Iwaoka, Y, Andoh A, Tujikawa T, Fujiyama Y, Watanbe F, Maruyama Y, Mitsuyama K, Sata M, Kanke K, Hiraishi H, Hirayama K, Arai H, Yoshii S, Uchijima M, Nagata T, Koide Y. Curcumin, a promising drug for long-term maintenance therapy in patients with ulcerative colitis: results from a multicenter, randomized double-blind placebo-controlled clinical trial. *Gastroenterology* 2006; **130**: A84

260 **Regueiro M**, Kip KE, Cheung O, Hegazi RA, Plevy S. Cigarette smoking and age at diagnosis of inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 42-47

261 **Abraham N**, Selby W, Lazarus R, Solomon M. Is smoking an indirect risk factor for the development of ulcerative colitis? An age- and sex-matched case-control study. *J Gastroenterol Hepatol* 2003; **18**: 139-146

262 **Birrenbach T**, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis* 2004; **10**: 848-859

263 **McGrath J**, McDonald JW, Macdonald JK. Transdermal nicotine for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2004: CD004722

264 **Thomas GA**, Rhodes J, Mani V, Williams GT, Newcombe RG, Russell MA, Feyerabend C. Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995; **332**: 988-992

265 **Ingram JR**, Thomas GA, Rhodes J, Green JT, Hawkes ND, Swift JL, Srivastava ED, Evans BK, Williams GT, Newcombe RG, Courtney E, Pillai S. A randomized trial of nicotine enemas for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2005; **3**: 1107-1114

266 **Katz S**. Update in medical therapy of ulcerative colitis: newer concepts and therapies. *J Clin Gastroenterol* 2005; **39**: 557-569

267 **Sawada K**, Muto T, Shimoyama T, Satomi M, Sawada T, Nagawa H, Hiwatashi N, Asakura H, Hibi T. Multicenter randomized controlled trial for the treatment of ulcerative colitis with a leukocytapheresis column. *Curr Pharm Des* 2003; **9**: 307-321

268 **Hanai H**, Watanabe F, Yamada M, Sato Y, Takeuchi K, Iida T, Tozawa K, Tanaka T, Maruyama Y, Matsushita I, Iwaoka Y, Kikuch K, Saniabadi AR. Adsorptive granulocyte and monocyte apheresis versus prednisolone in patients with corticosteroid-dependent moderately severe ulcerative colitis. *Digestion* 2004; **70**: 36-44

269 **Sawada K**, Kusugami K, Suzuki Y, Bamba T, Munakata A, Hibi T, Shimoyama T. Leukocytapheresis in ulcerative colitis: results of a multicenter double-blind prospective case-control study with sham apheresis as placebo treatment. *Am J Gastroenterol* 2005; **100**: 1362-1369

270 **Takemoto K**, Kato J, Kuriyama M, Nawa T, Kurome M, Okada

H, Sakaguchi K, Shiratori Y. Predictive factors of efficacy of leukocytapheresis for steroid-resistant ulcerative colitis patients. *Dig Liver Dis* 2007; **39**: 422-429

271 **Hanai H**, Watanabe F, Takeuchi K, Iida T, Yamada M, Iwaoka Y, Saniabadi A, Matsushita I, Sato Y, Tozawa K, Arai H, Furuta T, Sugimoto K, Bjarnason I. Leukocyte adsorptive apheresis for the treatment of active ulcerative colitis: a prospective, uncontrolled, pilot study. *Clin Gastroenterol Hepatol* 2003; **1**: 28-35

272 **Sawada K**, Egashira A, Ohnishi K, Fukunaga K, Kusaka T, Shimoyama T. Leukocytapheresis (LCAP) for management of fulminant ulcerative colitis with toxic megacolon. *Dig Dis Sci* 2005; **50**: 767-773

273 **Sakuraba A**, Sato T, Iwakami Y, Takada Y, Inoue N, Takaishi M, Ogata H, Iwao, Hibi T. An open-labeled trial of granulocyte and monocyte adsorption apheresis for pouchitis. *Gastroenterology* 2006; **130**: A661

274 **Fujimoto E**, Fujimoto N, Kuroda K, Tajima S. Leukocytapheresis treatment for pyoderma gangrenosum. *Br J Dermatol* 2004; **151**: 1090-1092

275 **Bibiloni R**, Fedorak RN, Tannock GW, Madsen KL, Gionchetti P, Campieri M, De Simone C, Sartor RB. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol* 2005; **100**: 1539-1546

276 **Guslandi M**, Giollo P, Testoni PA. A pilot trial of Saccharomyces boulardii in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003; **15**: 697-698

277 **Kato K**, Mizuno S, Umesaki Y, Ishii Y, Sugitani M, Imaoka A, Otsuka M, Hasunuma O, Kurihara R, Iwasaki A, Arakawa Y. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther* 2004; **20**: 1133-1141

278 **Furrie E**, Macfarlane S, Kennedy A, Cummings JH, Walsh SV, O'neil DA, Macfarlane GT. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005; **54**: 242-249

279 **Kruis W**, Fric P, Pokrotnieks J, Lukas M, Fixa B, Kascak M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004; **53**: 1617-1623

280 **Zocco MA**, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23**: 1567-1574

281 **Summers RW**, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005; **128**: 825-832

282 **Mayer L**. A novel approach to the treatment of ulcerative colitis: is it kosher? *Gastroenterology* 2005; **128**: 1117-1119

S- Editor Liu Y **L- Editor** Roberts SE **E-Editor** Li JL