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 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.
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[10].

**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[11]. In contrast, the ECCDS did not demonstrate efficacy for sulfasalazine 3 g/d alone, but only in combination with 6-methylprednisolone[12].

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[13]. 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 mesalazine that was of questionable clinical significance[14,15]. Several other trials also have demonstrated benefit for mesalamine in CD, but the quality of the trials was less robust[16]. 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 (30% vs 62%, P < 0.001)[17] and comparable to ciprofloxacin 1 g/d[18].

**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[19,20,21]. 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[22]. 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[23]. 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[24]. 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[25].

**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[26], while clinical relapse rates have been reported at 20% and 34% at one and three years respectively[27]. Approximately 30% of patients require reoperation within 10 years[28], 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[29]. 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[30], 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)[31], if this trial had been included in the meta-analysis, the overall findings of benefit compared to placebo would no longer have been significant[32]. Most recently, mesalamine at 3 g/d was inferior to mercaptopurine at 50 mg/d at preventing post-operative recurrence[33].

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-mycobacterial, 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[34] despite subgroup
analyses suggesting a trend towards significant benefit in patients with colonic disease\(^{[21-23]}\). 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\(^{[1]}\) while another trial reported no differences in remission rates between the combination of ciprofloxacin and metronidazole \(\text{versus}\) 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\(^{[29]}\). 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\(^{[30]}\).

**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.

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**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\(^{[40]}\).

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\(^{[41,42]}\).

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\(^{[43]}\), 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\(^{[44]}\). Conventional corticosteroids are not effective at preventing post-operative relapse\(^{[45]}\) 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\(^{[46]}\). Two randomized controlled studies demonstrated superiority of budesonide in the induction of remission in patients with ileal or ileo-right colonic disease\(^{[47]}\). 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 \( (P < 0.05) \). 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 \( \geq 300 \)) or disease distal to the transverse colon responded better to the highest budesonide dose\(^9\) 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\(^8\). When compared to prednisone, budesonide 9 mg/d there were no significant differences found in clinical remission rates\(^{10,41,40,51}\) although a meta-analysis revealed the pooled rate difference of response of budesonide vs conventional corticosteroids to be - 8.5%, \( P = 0.02 \). 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\(^{41}\).

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\(^{48} \) or endoscopic recurrence\(^{58,59}\). Both a Cochrane review and meta-analysis confirmed that budesonide is ineffective at maintaining CD remissions\(^{43,60}\). 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-naive prior to entering the study, smaller reductions in BMD were seen in the budesonide group compared to the prednisolone group (mean, \(-1.04\%) \); -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 \( \geq 17 \) 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)\[88\]. 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)\[89\]. 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\[90\].

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 relapse (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)\[91\]. 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\[92\].

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\[93\].

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\[94\]. Increased risk of hematologic malignancies has also been associated with prolonged leucopenia in IBD patients on 6-MP\[95\], and EBV-positive lymphomas have also been found more frequently in patients exposed to 6-MP or AZA\[96\]. The risk of infection with these medication ranges between 0.3%-7.4%\[97\] 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 synthesis and lymphocyte apoptosis\[98\]. Two exploratory, open-label trials in medically-refractory CD patients with oral\[99\] or intramuscular (IM)\[100\] 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)\[101\]. 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\[102\]. 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\textsuperscript{82} or flares\textsuperscript{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\textsuperscript{84}. Retrospective data have also reported comparable remission rates to those of Feagan\textsuperscript{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\textsuperscript{88,89}, and oral MTX (15 mg/wk) resulted in higher remission rates than 5-ASA 3 g/d (80% vs 58%, \(P < 0.01\))\textsuperscript{90}. 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\textsuperscript{91}. Several retrospective studies have shown comparable rates patients maintained in remission with MTX\textsuperscript{82,85-87,91}.

**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\textsuperscript{92}. Smaller non-randomized studies or series have yielded a combined response rate of 52% overall and 69% in patients with perianal disease\textsuperscript{93}.

**Tacrolimus**

Tacrolimus is a macroline 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, TNF\(_\alpha\) and INF\(_\gamma\) as well as inducing T-cell apoptosis, modifying expression of IL-10 and TGF\(_\beta\), 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\textsuperscript{94}.

**BIOLOGIC AGENTS**

**Infliximab**

Infliximab (Remicade\textsuperscript{8} Centocor, Malvern PA) is a chimeric (75% mouse/25% human) anti-TNF\(_\alpha\) monoclonal antibody; TNF\(_\alpha\) 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 \(\geq 70\) 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\textsuperscript{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 (\(P = 0.013\))\textsuperscript{96}.

The ACCENT I trial 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 \(\geq 70\) 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\textsuperscript{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 healing and higher rates of mucosal healing although the correlation between clinical and endoscopic responses was weak\textsuperscript{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 \(P = 0.04\))\textsuperscript{99}. In the ACCENT II study, 306 patients with one or more draining abdominal or perianal fistulas (\(\geq 3\) months duration) received an induction regimen of three infliximab infusions (5 mg/kg).

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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). Relapse of perianal disease after cessation of infliximab may occur earlier than in patients with luminal disease.

Antibodies to infliximab are known as both ATIs or HACAs (human anti-chimeric antibodies), and have been associated with lower serum drug concentration levels and in turn, with decreased efficacy with episodic treatment. In the ACCENT I population, however, equal numbers of antibody-positive and negative patients maintained clinical responses. Additionally, although ATIs are also associated with an increased risk of transfusion reactions, 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. Risk of antibody formation may be decreased by the three-dose induction followed by maintenance therapy, concomitant use of steroids and/or immunomodulators, pretreatment with hydrocortisone, and smoking status does not appear to correlate with development of ATI.

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. 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. Smoking has been found to be a negative predictor of response in two studies, but surprisingly not in one of the larger studies to examine factors influencing response to infliximab.

There has been considerable debate as to whether duration of infliximab treatment must necessarily be lifelong 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. 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. 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.

The safety of infliximab also remains a significant concern with potential serious adverse events 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. Serious infections were reported in 4% of patients overall in ACCENT I 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. As of February 2005, 709 cases of reactivated TB had been reported with infliximab, including 62 deaths. 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 and squamous cell cancer.

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. 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. 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<sup>®</sup>; Abbott Laboratories,......
Chicago, IL) is a subcutaneously administered recombinant human IgG 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 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 naive 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 α4 and β2 integrins. The α4 integrin is expressed on all types of white blood cells and can pair with either the β1 or β2 subunit. Endothelial ligands recognized by α4 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 α₄ integrin. Antibodies to α₄ integrin have shown efficacy in animal models of multiple sclerosis and colitis. 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. 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. 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.

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 and concomitant use of immunomodulators did not affect efficacy. 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.

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% in 2006. 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 α₄β₇ heterodimer but does not cross-react with the individual component monomers. The major ligand for α₄β₇ 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).

OTHER BIOLOGIC AGENTS

Visilizumab

Visilizumab (Nuvion™, Protein Design Labs) is a humanized IgG₂ 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.

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.

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.

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, 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-
macrophid 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 ≥ 70 points) was not met, significantly more patients in the sargramostim group reached the secondary endpoints of a decrease in CDAI of ≥ 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 helminths in an attempt to treat UC and CD. An open-label trial of *Trichurus suis* (porcine whipworm) has been studied as a therapy for CD in which 29 patients with active CD ingested 2500 live *Trichurus 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 sulfapyridine 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 ≥ 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] 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].

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Pharmacokinetic data in healthy patients demonstrates no differences in systemic absorption of 5-ASA between Asacol and balsalazide at equimolar doses\(^{180}\). 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\(^{18}\) 2.4 g/d (\(P = 0.036\)). No difference in response rate in patients with mild disease was demonstrated with the two different doses\(^{180}\). 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-naive patients, but is no longer commonly utilized due to the potential for adrenal hemorrhage\(^ {135}\). 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 (GR\(\beta\)) 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\(^ {39}\).

**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\(^ {182}\). 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\cite{190,191}. However, it became apparent that treatment with AZA consistently permitted significant steroid reduction compared to placebo\cite{191,192}. Patients with UC in remission on AZA \( \geq \) 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\cite{193}. Later retrospective studies also reported the steroid-sparing effect of AZA and 6-MP\cite{194-197}, higher relapse rates with cessation of 6-MP\cite{194,195}, and fewer colectomies in those patients maintained on AZA\cite{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 \( \leq 5.0 \times 10^9 \) (\( P = 0.03 \))\cite{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\%, \( P = 0.006 \))\cite{199}. The addition of 5-ASA to AZA does not confer greater benefit than AZA alone in the maintenance of remission\cite{200,201} or steroid-withdrawal\cite{202}.

**METHOTREXATE (MTX)**

While an initial small open-label study of MTX in IBD held promise for both CD and UC\cite{203}, randomized controlled trials have shown benefit in CD only\cite{204,205}. Although several additional open-label or retrospective studies of MTX in UC showed favorable effects\cite{205,206,207}, two randomized controlled trials showed no differences in the induction or maintenance\cite{208,209} of remission between patients given oral MTX 12.5\cite{209} or 15 \( mg/\)kg\cite{201} 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\cite{210}. 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\cite{211}, 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\cite{212}. In non-randomized controlled trials, long-term remission rates have been less impressive ranging between 14\%-40\%\cite{213-215}; “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\cite{216-218}. 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\cite{219}. Skipping oral CSA and transitioning directly to (6-MP or AZA) after IV therapy does not seem to alter long-term outcome\cite{220}.

CSA is associated with significant morbidity, including opportunistic infections, neurologic and renal toxicity, hypertension, and rarely, death\cite{221}. Several variations in therapy may decrease the risk of these adverse events without compromising efficacy: the use of low-dose CSA (2 \( mg/\)kg\cite{222,223}), oral microemulsion CSA (Neoral\cite{224} with 60\% bioavailability\cite{225,226}, and IV CSA without concomitant steroids\cite{224}. Higher percentages of band forms on differential WBC count\cite{227}, tachycardia > 90 bpm, fever > 37.5\(^\circ\)C, elevated CRP > 45 mg/L, and greater than one severe endoscopic lesion are negative predictors of response\cite{228}. Ideally, administration of CSA should be limited to physicians trained or experienced in the use of potent immunosuppressants or transplantation\cite{229}.

**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\cite{230}. A recent review of tacrolimus in IBD patients also found overall favorable results in the treatment of refractory UC\cite{231}.

**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

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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\textsuperscript{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\textsuperscript{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\textsuperscript{231}.

**BIOLOGIC AGENTS**

**Infliximab**

While several small studies of infliximab collectively showed equivocal efficacy in UC, the ACT (Active Ulcerative Colitis Trials) I and 2 provided definitive evidence supporting its efficacy in this population\textsuperscript{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 5 mg/kg is the recommended starting dose given that any of those with fulminant colitis compared to placebo, this difference was no longer significant (69% vs 47%, \( P = 0.276 \))\textsuperscript{233}. In an open-label trial of infliximab in 12 hospitalized steroid-refractory UC patients, nine underwent colectomy within three months\textsuperscript{234}. Two recent studies showed favorable response profiles to infliximab in patients with acute severe UC\textsuperscript{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\textsuperscript{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%, \( P = 0.001 \))\textsuperscript{140}. Antibodies to MLN02 were found in 44% of patients; of those with titers \( \geq 1:125 \), 24% had loss of saturation to \( \alpha, \beta \)-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\textsuperscript{238}. Parenteral alicaforsen was not effective in CD\textsuperscript{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\textsuperscript{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\cite{1}. Further, high levels of IL-2 have been associated with steroid-resistance\cite{2}. Two anti-IL2 antibodies have been evaluated in UC.

Daclizumab (Zenapax, Roche, Basel, Switzerland), is a recombinant humanized monoclonal antibody (IgG1) to IL-2R. Although a small, open-label pilot study initially held promise for this antibody\cite{3}, 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\cite{4}. 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\cite{5}. 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\cite{6}. 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\cite{7}, this UC study excluded EBV+ patients, but a large open-label trial including EBV+ patients is ongoing.

INTERFERONS

Interferon-alpha (IFN-α)

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\cite{8}. With the recognition that IFNα does not induce colitis flares in those being treated for chronic hepatitis who have co-morbid UC\cite{9,10}, 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\cite{11}, while another small study showed only short-lived benefit of IFNα2a over prednisolone enemas in treating distal UC\cite{12}. In the only randomized placebo controlled trial, UC patients refractory to 5-ASA agents, steroids or AZA (n = 60) received either weekly pegylated IFNα2b 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\cite{13}. Thus, while IFNα does not appear to exacerbate UC when treating chronic hepatitis, it is not effective as a primary treatment for UC.

Interferon β

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\cite{14}. While one small randomized trial showed endoscopic benefit in patients treated with IFNβ1 compared to placebo\cite{15}, a larger controlled trial failed to show any advantage recombinant IFNβ1a over placebo in clinical response or remission, endoscopic index, or steroid reduction\cite{16}.

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\cite{17}. 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\cite{18}. 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\cite{19}. 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\cite{20}. Rebamipide is an amino acid analog of 2-[(1H)-quinoxaline 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 Helicobacter pylori\cite{21}. 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\cite{22}. Larger
controlled trials are needed to evaluate this class of therapy in UC.

CURCUMIN

Derived from turmeric, curcumin appears to inhibit NFkB 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)\(^{208}\).

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\(^ {209}\). 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\(^ {204}\). It is speculated that nicotine alters systemic and/or gut immune function in a protective way; the exact mechanism remains unknown\(^ {202}\). 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\(^ {204}\).

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\(^ {260}\), 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\(^ {8}\)) (n = 69) are equally or more effective than steroids in the induction of remission\(^ {267,268}\), with fewer adverse events\(^ {277}\) and greater steroid-sparing effects\(^ {204}\). In the only sham-controlled trial to date, 19 patients with moderate to severe UC treated with five weekly sessions of each type of 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%)\(^ {208}\). 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\(^ {277}\) 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\(^ {241}\). 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.

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