REVIEW ARTICLE

Drug Safety 2000 Nov; 23 (5): 429-448
0114-5916/00/0011-0429/$20.00/0

Comparative Tolerability of Treatments for Inflammatory Bowel Disease

Robert B. Stein[1] and *Stephen B. Hanauer*[2]

1 Department of Medicine, Division of Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

2 Pritzker School of Medicine University of Chicago, Clinical IBD Research Center, University of Chicago Hospitals and Clinics, Chicago, Illinois, USA

Contents

Abstract

Despite limited understanding of therapeutic aetiopathogenesis of ulcerative colitis and Crohn's disease, there is a strong evidence base for the efficacy of pharmacological and biological therapies. It is equally important to recognise toxicity of the medical armamentarium for inflammatory bowel disease (IBD).

Sulfasalazine consists of sulfapyridine linked to 5-aminosalicylic acid (5-ASA) via an azo bond. Common adverse effects related to sulfapyridine 'intolerance' include headache, nausea, anorexia, and malaise. Other allergic or toxic adverse effects include fever, rash, haemolytic anaemia, hepatitis, pancreatitis, paradoxical worsening of colitis, and reversible sperm abnormalities.

The newer 5-ASA agents were developed to deliver the active ingredient of sulfasalazine while minimising adverse effects. Adverse effects are infrequent but may include nausea, dyspepsia and headache. Olsalazine may cause a secretory diarrhoea. Uncommon hypersensitivity reactions, including worsening of colitis, pancreatitis, pericarditis and nephritis, have also been reported.

Corticosteroids are commonly prescribed for treatment of moderate to severe IBD. Despite short term efficacy, corticosteroids have numerous adverse effects that preclude their long term use. Adverse effects include acne, fluid retention, fat redistribution, hypertension, hyperglycaemia, psycho-neurological disturbances, cataracts, adrenal suppression, growth failure in children, and osteonecrosis. Newer corticosteroid preparations offer potential for targeted therapy and less corticosteroid-related adverse effects.

Azathioprine and mercaptopurine are associated with pancreatitis in 3 to 15% of patients that resolves upon drug cessation. Bone marrow suppression is dose related and may be delayed.

The adverse effects of methotrexate include nausea, leucopenia and, rarely, hypersensitivity pneumonia or hepatic fibrosis. Common adverse effects of cyclosporin include nephrotoxicity, hypertension, headache, gingival hyperplasia, hyperkalaemia, paresthesias, and tremors. These adverse effects usually abate with dose reduction or cessation of therapy. Seizures and opportunistic infections have also been reported.

Antibacterials are commonly employed as primary therapy for Crohn's disease. Common adverse effects of metronidazole include nausea and a metallic taste. Peripheral neuropathy can occur with prolonged administration. Ciprofloxacin and other antibacterials may be beneficial in those intolerant to metronidazole.

Newer immunosuppressive agents previously reserved for transplant recipients are under investigation for IBD. Tacrolimus has an adverse effect profile similar to cyclosporin, and may cause renal insufficiency. Mycophenolate mofetil, a purine synthesis inhibitor, has primarily gastrointestinal adverse effects.

Biological agents targeting specific sites in the immunoinflammatory cascade are now available to treat IBD. Infliximab, a chimeric antibody targeting tumour necrosis factor-α has been well tolerated in clinical trials and early postmarketing experience. Additional trials are needed to assess long term adverse effects.

1. Aminosalicylates

1.1 Sulfasalazine and 5-Aminosalicylic Acid

1.1.1 Clinical Pharmacology

Sulfasalazine consists of sulfapyridine linked to 5-aminosalicylic acid (mesalamine, mesalazine, 5-ASA) via an azo bond. Sulfasalazine remains mostly intact in the upper gastrointestinal tract, and is poorly absorbed.[1] A small, absorbed component undergoes significant enterohepatic circulation and is excreted, intact, in bile.[2] More than 75% of ingested

sulfasalazine reaches the colon where it is cleaved by bacterial azo-reductases into sulfapyridine and 5-ASA.[3] Sulfapyridine is almost completely absorbed in the colon and then acetylated in the liver. Acetylator status is genetically determined, leading to higher serum concentrations of free sulfapyridine in slow versus fast acetylators.[1,4] Sulfapyridine is primarily excreted in the urine as acetylated, hydroxylated or glucuronidated derivatives.[1,4]

In contrast to sulfapyridine, 5-ASA is poorly absorbed from the colon.[2] Instead, colonic 5-ASA is acetylated by lumenal bacteria or within the colonic epithelium whereupon it is re-excreted into the colonic lumen as *N*-acetyl-5-ASA. The majority of lumenal *N*-acetyl-5-ASA is excreted in the faeces.[5] Approximately 25% of the 5-ASA component is absorbed and transported to the liver, where it undergoes nongenetically determined acetylation, then urinary excretion.[6]

Recognition that 5-ASA contributes to the anti-inflammatory properties of sulfasalazine[7] has led to the development of alternative, nonsulfa-containing, oral and topical 5-ASA delivery systems.[8] Oral 5-ASA agents formulated to prevent proximal intestinal absorption of 5-ASA include 5-ASA dimers, compounds with alternative azo-bonded carriers, pH-dependent tablets, and time-dependent release preparations. In addition, topical 5-ASA preparations in the form of suppositories or foam and enemas remain important for the treatment of proctitis and left-sided colitis, respectively.[8]

Olsalazine is a 5-ASA dimer designed to deliver 5-ASA molecules to the colon. Although there is minimal absorption of this compound, olsalazine stimulates small intestinal bicarbonate secretion inducing diarrhoea in approximately 15% of patients.[9] Balsalazide is another azo prodrug, linking 5-ASA to the carrier 40-aminobenzoyl-β-alanine. Balsalazide is also minimally absorbed in the colon, but does not cause intestinal secretion or diarrhoea.[10]

Other mesalazine preparations have sustained release or pH-dependent release properties. Pentasa® is composed of ethylcellulose microgranules designed to release mesalazine in a time and pH-dependent distribution, resulting in equal proportions of 5-ASA delivery to the small intestine and colon.[11] Alternatively, acrylic-based resin coatings of mesalazine capsules allow for pH-dependent release-profiles.[8] Asacol® is coated with Eudragit-S, and is designed to dissolve at pH 7.[12] Other formulations (Claversal®, Salofalk®, Mesasal®) are coated with Eudragit-L to release mesalazine at a slightly lower pH.[13] Depending upon individual transit times and luminal pH, these coated compounds re-

Table I. Adverse effects of drugs commonly used in inflammatory bowel disease

Agent	Route of administration	Adverse effects
Sulfasalazine	PO	Nausea, headache, rash, fever, hypersensitivity reactions, folate malabsorption, sperm abnormalities, dyspepsia, fatigue
5-ASA	PO, topical	Nausea, dyspepsia, headache, rare hypersensitivity reactions[a]
Corticosteroids	IV, PO, topical	Acne, bodyweight gain, fat redistribution, mood changes, myopathy, hyperglycaemia, cataracts[b], osteoporosis, osteonecrosis[b], growth failure in children[b], insomnia, hypokalaemia, hypertriglyceridaemia
Azathioprine/6-MP	PO	Nausea, fever, rash, pancreatitis (3-15%), bone marrow suppression[c]
Methotrexate	PO, IM, SC	Nausea, vomiting, diarrhoea, leucopenia, hepatic fibrosis, pneumonitis, stomatitis, bone marrow suppression
Cyclosporine	IV, PO	Hypertension, headache, electrolyte abnormalities, tremor, paraesthesia, ↑ LFTs, gingival hyperplasia, nephrotoxicity, seizure (rare), opportunistic infections (rare), hypertrichosis
Metronidazole	PO	Nausea, metallic taste, disulfiram-like reaction with alcohol, peripheral neuropathy

a 5-ASA usually well tolerated. 80% of patients intolerant to sulfasalazine are able to tolerate 5-ASA.

b Subcapsular cataracts, osteonecrosis and growth failure in children are usually associated with prolonged exposure to corticosteroids.

c Bone marrow suppression with azathioprine or 6-MP may be delayed.

IM = intramuscularly; **IV** = intravenously; **PO** = Orally; **SC** = subcutaneously; ↑ **LFTs** = increased liver function tests; **5-ASA** = 5-aminosalicylic acid; **6-MP** = 6-mercaptopurine.

lease mesalazine into the distal ileum and proximal colon, with the Eudragit-L compounds undergoing more proximal release.[14]

Azad-Khan[7] was the first to demonstrate that topically applied (intrarectal) 5-ASA is effective in the treatment of distal colitis. Today, topical administration of mesalazine, as suppositories and enemas stabilised with antioxidants, has become a mainstay for the management of distal colitis. Mesalazine suppositories reach up to 20cm from the anal verge and are used to treat proctitis[15] whereas mesalazine enemas can spread retrograde to the splenic flexure to treat left-sided ulcerative colitis.[16]

1.1.2 Mechanism of Action

The precise mechanisms of action of sulfasalazine and the newer 5-ASA derivatives remain unclear. It has been suggested that the parent compound may have additional anti-inflammatory and antibacterial properties not shared by mesalazine,[17] including inhibition of nuclear factor kappa beta (NFκβ).[18] However, most lines of investigation have focused on aminosalicylate modulation of arachadonic acid metabolism. In contrast to inhibition of the cyclo-oxygenase enzyme by other salicylates, 5-ASA has inhibitory properties on both cyclo-oxygenase and lipoxygenase pathways.[13,19-22] 5-ASA also inhibits platelet activation factor.[3,20]

Inflammatory cell functions and natural killer cell activity are also inhibited by aminosalicylates,[20] and plasma cell antibody production is inhibited by sulfasalazine and 5-ASA.[17] In addition, 5-ASA decreases interleukin (IL)-1 production from macrophages, and inhibits tumour necrosis factor (TNF) activity[20] whereas both sulfasalazine and 5-ASA are free oxygen radical scavengers, further contributing to their anti-inflammatory properties.[3,23]

1.1.3 Adverse Effects

The tolerability profile of sulfasalazine therapy is related to a patient's genetically determined acetylator status (slow *vs* fast).[24,25] Between 10 and 45% of patients report dose-related adverse effects, including nausea, dyspepsia, headache and fatigue (table I).[24,26] Most of these adverse effects can be reduced or eliminated by gradual dose-escalation, administration with meals or dose reduction.[8]

Hypersensitivity reactions are less common and are not dose or acetylator status dependent.[24] Skin eruptions are usually maculopapular, and most often occur within the first days of treatment.[24] More serious cutaneous reactions to sulfasalazine include toxic epidermal necrolysis[27] and the Stevens Johnson syndrome.[24] Other allergic reactions, including fever, arthralgias, and rheumatological disorders (such as sulfasalazine-induced lupus[28] and Raynaud's phenomenon[29]), have been described and are primarily attributed to the sulfa moiety.

Fever, hepatomegaly and lymphadenopathy may accompany sulfasalazine-induced hepatic toxicity, although transaminase level elevations and hyperbilirubinaemia alone are more common.[24] Rarely, granulomatous liver disease has been observed.[8] Tachycardia related to sulfasalazine has also been described,[24] as have pancreatitis[30] and pleuritis.[31]

Haematological toxicities of sulfasalazine include agranulocytosis, leucopenia, thrombocytopenia, red cell aplasia, and methaemoglobinaemia.[24,32,33] Haemolytic anaemia has also been observed related to both dose and acetylator phenotype.[25] Sulfasalazine impairs folate absorption,[34] which may contribute to the development of megaloblastic anaemia.[35] Male infertility may also result from sulfasalazine therapy. Up to 80% of men develop changes in sperm morphology, motility, and reduction in sperm count.[8] These effects are transient in most men, with return of normal sperm counts and motility within a few months of discontinuation or substitution with a nonsulfa containing aminosalicylate.[36]

The primary advantage of the newer 5-ASA agents over sulfasalazine is their improved adverse effect profile.[37,38] Approximately 80% of patients intolerant or allergic to sulfasalazine are able to tolerate mesalazine preparations.[37] In general, dose-related adverse effects from mesalazine are mild and include nausea, dizziness, dyspepsia, and headache (table I).[38] Less common hypersensitivity reactions, including hepatitis,[39] pulmonitis,[40] pericarditis or myocarditis,[41] and pancreatitis,[42] have been reported.

Although animal studies have raised the potential for 5-ASA induced nephrotoxicity, renal dys-

function in humans as a result of 5-ASA appears to be quite rare.[38,43,44] Another rare complication of mesalazine is paradoxical worsening of colitis[8,38] that requires discontinuation of the drug. This is in contrast to the known potential of olsalazine to induce a secretory diarrhoea[45] that can be controlled with gradual dose titration or administration with food.

Considerable data have accumulated on the use of sulfasalazine and the newer 5-ASA agents during pregnancy and lactation. Sulfasalazine does not increase the risk of fetal abnormalities, prematurity, or low birth weight.[46] However, because of the risk of sulfasalazine induced folate deficiency, maternal folate supplementation is recommended.[46] Approximately 50% of maternal serum sulfapyridine concentrations are reached in breast milk, however abnormalities have not been identified in nursing infants.[47] Although there are less data regarding the use of the newer 5-ASA agents in pregnancy, they appear to be well tolerated during pregnancy and nursing.[46,48,49]

2. Corticosteroids

2.1 Clinical Pharmacology

The high systemic bioavailability of corticosteroids after oral or parenteral administration[8,50] enables hydrocortisone, corticotropin (adrenocorticotrophic hormone) and the synthetic analogues of cortisol including prednisone, prednisolone, and methylprednisolone to be pivotal in the management of moderate to severe inflammatory bowel disease (IBD). Approximately 90% of cortisol is bound to plasma proteins, while the synthetic corticosteroid preparations undergo less protein binding.[50] Most cortisol binds to corticosteroid-binding protein (transcortin), while the remainder binds to albumin or enters the circulation as free cortisol.[50] Hypoalbuminaemia or high corticosteroid dosages may lead to increased free cortisol levels, resulting in enhanced toxicity.[51]

The plasma half-lives of these compounds vary, with the biological half-lives ranging from 18 to 54 hours.[13,50] Cortisol is metabolised in the liver to its biologically active moiety hydrocortisone, whereas prednisone is converted to its active metabolite prednisolone via hepatic reduction and conjugation.[50] Oral contraceptives increase transcortin levels resulting in diminished plasma clearance,[52] whereas enzyme inducing agents such as phenobarbital (phenobarbitone) and rifampicin (rifampin) increase corticosteroid clearance.[50]

Topical corticosteroids in the form of enemas and foams are also commonly employed in the management of distal colitis.[53] Agents such as hydrocortisone enemas may demonstrate significant systemic absorption and bioavailability. Depending upon the degree of inflammation and time of mucosal contact, more than half of the dose may be absorbed, resulting in adverse effects including adrenal insufficiency with prolonged administration.[8,54,55] Distal absorption into the rectal veins may lead to enhanced drainage to the portal circulation, with resultant hepatic metabolism and decreased free plasma corticosteroid concentrations. Alternatively, more proximal absorption into the vena cava results in decreased hepatic breakdown, resulting in higher systemic concentrations.[8]

2.2 Mechanism of Action

Corticosteroids dissociate from their protein carriers and enter target cells displaying cortisol receptors.[56] The corticosteroids then bind to cytoplasmic protein receptors, and move to the nucleus; resulting in transcription and translation of proteins vital to their response.[50]

Corticosteroids inhibit the inflammatory response in a variety of ways. They enhance capillary integrity, which diminishes fluid efflux and resultant oedema in inflamed tissues.[50] Corticosteroids inhibit margination, leading to increased plasma levels of neutrophils and diminished recruitment of neutrophils to inflamed tissues.[57] Macrophage phagocytosis is also inhibited, and lysosomal membranes are stabilised; further preventing enzyme release and subsequent tissue damage.[50] Glucocorticoids inhibit arachadonic acid release and the formation of cyclo-oxygenase and lipoxygenase products.[58] Corticosteroids also suppress the production of nu-

clear factors resulting in diminished IL-1 and IL-2 activation and TNF production, and depress T-helper cell function.[8,20,56,57]

2.3 Adverse Effects

The adverse effects of corticosteroids are well recognised and, primarily, are related to dosage and the duration of therapy.[13,59] Bodyweight gain, acne, insomnia, and mood swings are common (see table I). Higher dosages can lead to severe psychiatric disturbances, including psychosis.[60]

Metabolic effects are common and often include hypokalaemia. Corticosteroids may unmask latent diabetes mellitus or worsen glycaemic control in patients with pre-existing diabetes mellitus. Hypercholesterolaemia and hypertriglyceridaemia and accelerated atherogenesis are additional potential complications of long term corticosteroid therapy.[61] Sodium retention is a property of many corticosteroid preparations which may lead to hypertension and lower extremity oedema in some patients.[62] Prolonged administration may result in hepatic steatosis.[8] Ocular complications include subcapsular cataracts and glaucoma.[50,63]

Redistribution of fat, a 'buffalo hump,' abdominal striae, easy bruisability, and ecchymoses are common manifestations of corticosteroid treatment, and may be a result of altered fibroblast function.[64] Corticosteroids may also cause a myopathy notable for proximal muscle weakness and wasting.[65] A 'pseudoarthritis' may occur in some patients upon corticosteroid withdrawal, and must be discerned from the arthralgias associated with active intestinal inflammation. Most respond to paracetamol (acetaminophen) and reassurance, although re-institution of corticosteroids with a slow taper may be required to control symptoms in others.[8] Dyspepsia and nausea may occur during corticosteroid therapy, whereas peptic ulcer disease is likely not associated.[66] Additionally, pancreatitis is a rare complication of corticosteroid therapy.[67,68]

Growth retardation is an important complication of corticosteroid therapy in the paediatric population.[69] Glucocorticoids cause inhibition of linear growth and epiphyseal closure, particularly with long term, high dosage therapy. Fortunately, accelerated bone growth occurs upon drug withdrawal, and growth failure may be minimised with alternate-day therapy.[70]

Osteoporosis is one of the most important adverse effects of corticosteroid therapy, and may occur in up to 50% of patients requiring corticosteroid therapy.[71-73] The pathogenesis of glucocorticoid-induced osteoporosis is multifactorial, and is related to the dose and duration of therapy. Bone loss occurs secondary to increased osteoclast activity, decreased intestinal calcium resorption, increased calcium excretion, reduced osteoblast activity, suppression of gonadal hormone production, and secondary hyperparathyroidism. Furthermore, patients with IBD (particularly Crohn's disease) have higher circulating levels of proinflammatory cytokines (e.g. IL-6, IL-1, TNFα), resulting in increased osteoclast activation.[73] Patients with IBD should have baseline bone mineral density measurements with a dual energy x-ray absorptiometry scan of the hip and spine. Calcium supplementation, along with vitamin D and hormone replacement therapy when appropriate, should be given to patients receiving corticosteroids. Furthermore, bisphosphonate therapy should be considered in those with established osteoporosis.[72] Osteonecrosis (aseptic necrosis) of the hip, femur or humerus is much less common than osteoporosis, and typically occurs in patients receiving long term, high dosage corticosteroid therapy.[13,74,75]

Although corticosteroids inhibit the inflammatory response and cell mediated immunity, the risk of infection is likely to be minimal unless patients have been receiving long term, high dosage corticosteroids.[76] In a review of over 70 controlled trials, twice as many patients receiving corticosteroids developed infectious complications compared with those not receiving corticosteroid therapy. The patients at greatest risk of infection were those receiving >40 mg/day of prednisone, whereas those receiving <10 mg/day had no increased risk.[77]

Long term corticosteroid therapy results in adrenal suppression, although risk is difficult to predict.[77-79] Some degree of suppression of the adre-

nal axis should be presumed to persist for up to 1 year after corticosteroid cessation in patients treated on a long term basis.[13] Alternate-day therapy or administration in the morning may help prevent adrenal suppression, as corticosteroids are tapered.[80] Evaluation of the hypothalamic-pituitary axis with a cosyntropin stimulation test should be considered in patients receiving long term corticosteroid therapy, in patients experiencing signs of adrenal insufficiency, or in patients receiving corticosteroids or who have recently been on corticosteroids at times of increased stress (e.g. surgery).[80]

Extensive experience with corticosteroid therapy in pregnant women with IBD suggests that these agents are generally well tolerated, with no increase in the risk of fetal complications.[81,82] Corticosteroids are excreted in breast milk, however the risk to nursing infants appears to be minimal.[8]

2.4 Alternative Corticosteroid Preparations

A new generation of corticosteroids with enhanced receptor affinity and increased potency are becoming available for the management of IBD. Additionally, the ability of these agents to target to specific sites along the digestive tract and their rapid hepatic inactivation enhances the clinical benefits while minimising systemic adverse effects. Budesonide is the most notable of these novel agents, and exhibits almost 200 times the affinity for the corticosteroid receptor compared with hydrocortisone, while demonstrating only 10 to 15% systemic bioavailability.[83,84] Budesonide has been formulated in topical and oral controlled ileal release preparations. Clinical trials in patients with ulcerative colitis and Crohn's disease have demonstrated efficacy comparable with prednisolone, with fewer adverse effects, such as acne, hirsutism and moon face, as well as minimal suppression of the hypothalamic-adrenal-pituitary axis.[85,86] The long term effects of budesonide on bone metabolism are currently unknown.

Beclomethasone has been used in left-sided ulcerative colitis in a topical formulation.[87] This agent has remarkably high potency and enhanced first pass metabolism, resulting in minimal systemic absorption.[88] Tixocortol is an esterified cortisol compound under study in patients with ulcerative colitis,[89] and also demonstrates enhanced hepatic and systemic metabolism.[90] Finally, oral fluticasone propionate is a fluorinated corticosteroid preparation that, despite having almost no systemic bioavailability,[84] has demonstrated no significant clinical benefit in IBD.[91,92]

3. Immunomodulators

3.1 Azathioprine and Mercaptopurine

3.1.1 Clinical Pharmacology

The thiopurine analogues, azathioprine and mercaptopurine are important immunomodulatory agents for IBD. After oral administration, most azathioprine is converted to mercaptopurine within red blood cells, then further metabolised into methylnitroimidazole and thiopurine components.[8,93] Methylnitroimidazole is subsequently metabolised into multiple, potentially immunomodulating endproducts.[94] Mercaptopurine is converted to its active metabolite thioinosinic acid by hypoxanthine guanine phosphoribosyl transferase (HGPRT).[57] Within red blood cells, thioinosinic acid is then inactivated via enzymatic methylation by thiopurine methyltransferase (TPMT). One in 300 individuals lacks this enzyme, resulting in increased susceptibility to adverse effects secondary to accumulation of thioguanine metabolites.[8,95] The smaller percentage (10 to 25%) of azathioprine not converted to mercaptopurine is oxidised in the liver to hydroxyazathioprine.[8]

The bioavailability of mercaptopurine is variable, and may be improved with evening administration of the drug.[96,97] Approximately half of the dosage of mercaptopurine (1 to 1.5 mg/kg/day) should be given compared with azathioprine (2 to 2.5 mg/kg/day), to account for the conversion factors, and limit potential adverse effects.[8,98] The use of xanthine oxidase inhibitors concomitantly with azathioprine or mercaptopurine may predispose patients to potential toxicity by delaying metabolism of the active agents.[8]

3.1.2 Mechanism of Action

Azathioprine and mercaptopurine have multiple effects on the immunoinflammatory cascades. The active end-product of azathioprine/mercaptopurine metabolism, thioinosinic acid, inhibits purine nucleotide biosynthesis, resulting in inhibition of cell proliferation.[57,95] Azathioprine also likely has immunomodulatory effects independent from mercaptopurine. In patients who are HGPRT deficient, lymphocyte activity is inhibited by azathioprine to a greater extent than mercaptopurine.[99] The reasons for this are unclear, but may be related to the alkylating effects of azathioprine on lymphocyte membranes.[95,100] Additionally, there are multiple metabolites of the methylnitroimidazole ring of azathioprine, perhaps accounting for some of its additional immunomodulatory effects.[93]

Mercaptopurine and azathioprine also have effects on cytotoxic T cell function and natural killer cell activity. The reduction of natural killer cells and cytotoxic T cell function is often delayed, and correlates with the 3 to 6 month delay in clinical response.[101,102] Additionally, azathioprine may inhibit prostaglandin synthesis, and decrease suppresser T cell function and cell mediated immunity.[8,57,95]

3.1.3 Adverse Effects

Although usually well tolerated, azathioprine and mercaptopurine are associated with various potential toxicities (see table I).[103] Pancreatitis may occur in 3 to 15% of patients,[104,105] and must be discriminated from nausea that often accompanies the initiation of therapy. Pancreatitis appears to be an allergic reaction and often occurs within 3 to 4 weeks of starting therapy. Following discontinuation of the drug, the pancreatitis resolves and does not lead to the development of chronic pancreatitis.[106] Other allergic reactions include fever and rash, and occur in up to 5% of patients.[105-107] Hepatitis has been reported,[108] as have hair loss and peripheral neuropathy.[8] In a study of paediatric patients with IBD, liver enzyme levels became elevated in 13% of patients receiving azathioprine or mercaptopurine[109] and most often resolved spontaneously or with dosage reduction.

Bone marrow suppression is an expected dose-related effect and may be delayed in onset.[110] The risk of leucopenia necessitates close monitoring of blood counts. Monitoring should continue to occur on a regular basis once a stable dose has been achieved; usually every 3 months (sooner if the dose is increased).[44] Low activity (11% of individuals) or deficiency (1 in 300 individuals) of TPMT has also been proposed to be a significant risk factor for severe bone marrow suppression, even when using these agents at standard doses.[111,112] At this point, routine monitoring of TPMT levels has not been advocated for all patients with IBD prior to initiation of azathioprine or mercaptopurine.[92,93] Recently, it has been observed that measuring TPMT genotype, as well as 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) concentrations may assist clinicians in determining the optimal therapeutic response of azathioprine and mercaptopurine, while minimising the potential for drug-induced toxicity (particularly hepatotoxicity).[113] In this trial, the frequency of therapeutic response was significantly higher in those patients with IBD with 6-TG levels >235 pmol/L per 8 x 10^8 erythrocytes, whereas 6-MMP levels >5700 pmol/L per 8 x 10^8 erythrocytes were associated with an increased frequency of hepatotoxicity. Additional data are necessary to validate these preliminary findings. Approximately 2% of patients receiving these agents will also develop thrombocytopenia, which is usually not severe.[107] Co-administration with other drugs, such as cortimoxazole (trimethoprim-sulfamethoxazole), may potentiate bone marrow suppression.[114] In a recent trial, a loading dose of intravenous azathioprine did not prove beneficial in corticosteroid-treated Crohn's disease and was associated with a higher risk of nausea and injection site reactions compared with the placebo group.[115]

Initial concern over the increased risk of neoplasia with prolonged administration of azathioprine and mercaptopurine has been allayed in recent years.[116] Lymphomas have been reported in patients with chronic inflammatory conditions such as IBD[117] and rheumatoid arthritis,[118] even in the absence of immunosuppressive therapies. Two cases

of brain lymphoma have been reported in patients with IBD treated with azathioprine/mercaptopurine,[106,119] and 1 case of a B cell lymphoma was reported in a 33-year-old patient with a 13-year history of Crohn's disease who had been receiving azathioprine for 5 years which was reversible upon cessation of azathioprine therapy.[120] A case of acute myeloblastic leukaemia has also been reported in a patient with Crohn's disease treated with mercaptopurine.[121] In contrast to these reports, Connell et al.[122], over a 20 year period, determined that patients with IBD treated with azathioprine or mercaptopurine had no increased risk of cancer. This has been further supported by Korelitz et al.[116] who recently reported on their 27-year experience following 591 patients with IBD receiving azathioprine/mercaptopurine.[116] In another study of 396 patients with IBD receiving mercaptopurine, Present et al.[106] also failed to identify a significantly increased incidence of neoplasm. Recent paediatric IBD literature also supports the notion of long term safety of azathioprine and mercaptopurine without significant increased risk for the development of cancer.[109]

The use of azathioprine and mercaptopurine in pregnancy remains controversial. There are data in animal studies, as well as case reports in humans suggesting a teratogenic effect of these agents.[123,124] However, large studies from the transplant literature suggest no increase in birth defects of children born to women taking azathioprine or mercaptopurine.[125] Studies in the IBD population also suggest no increased risk to the fetus when the mother has taken azathioprine; however, these studies were small.[126,127] A recent study assessed the outcome of pregnancies when fathers were taking mercaptopurine for treatment of their IBD.[128] Of 50 pregnancies conceived within 3 months of mercaptopurine therapy in the father, 2 spontaneous abortions and 2 congenital anomalies were reported compared with 3 spontaneous abortions and no congenital anomalies in a control group (no preconception use of mercaptopurine) and fathers not taking mercaptopurine for at least 3 months prior to conception. Larger studies are required to further examine the effects that azathioprine and mercaptopurine have during pregnancy in IBD.

3.2 Methotrexate

3.2.1 Clinical Pharmacology and Mechanism of Action

Methotrexate is a folic acid inhibitor with both anti-inflammatory and immunomodulatory effects. Methotrexate can be administered orally or by intramuscular or subcutaneous injections. Oral bioavailability is excellent at low doses, but decreases as the dose escalates; perhaps this may be related to intestinal receptor saturation.[129] Maximal absorption occurs after 1 to 2 hours. Higher dosage methotrexate may be better tolerated and better absorbed when administered parenterally.[130] Once absorbed, methotrexate is converted to methotrexate polyglutamate. Both methotrexate and methotrexate polyglutamate inhibit dihydrofolate reductase, and subsequently inhibit DNA synthesis. Additionally, methotrexate likely inhibits leukotriene B4 and IL-1 production, adding to its anti-inflammatory properties.[131]

Oral and parenteral methotrexate has been used in the treatment of corticosteroid-dependent and corticosteroid-resistant Crohn's disease. Success has been most clearly demonstrated with parenteral therapy with 25mg weekly intramuscular or subcutaneous injections.[132] There is no consensus on the use of methotrexate as a maintenance medication in Crohn's disease or in ulcerative colitis.

3.2.2 Adverse Effects

The most common adverse effects of methotrexate include nausea, abdominal pain, diarrhoea, and stomatitis (see table I).[133-135] Headache, dizziness, and fatigue may also occur. Supplementation with 1 mg/day of folic acid may help to alleviate these adverse effects without diminishing efficacy.[136,137]

Bone marrow suppression is less common with methotrexate than with azathioprine or mercaptopurine, particularly when using low doses.[137] However, use of methotrexate requires monitoring of the blood count on a regular basis.[138] Further, folate deficiency or concomitant use of other marrow toxic

drugs (e.g. cotrimoxazole) may potentiate bone marrow suppression. The development of leucopenia or significant thrombocytopenia with methotrexate therapy requires discontinuation of the drug until white cell counts improve, and then re-initiation of the drug at a lower dose.[129]

Hypersensitivity pneumonitis has also been reported with methotrexate therapy.[139] Although rare, this can be a serious complication and may occur even while on low dose therapy. This condition must be differentiated from atypical or community acquired pneumonias, as the treatment of hypersensitivity pneumonitis requires drug discontinuation and high dosage corticosteroids. Lymphomas have also been reported during methotrexate therapy. In 1 report, 2 cases of reversible lymphomas associated with Epstein-Barr virus occurred during methotrexate therapy for rheumatoid arthritis and dermatomyositis.[140] To date, no cases of lymphomas have been reported in patients with IBD treated with methotrexate.

An important concern regarding prolonged administration of methotrexate is risk of hepatotoxicity.[141,142] The reported incidence of serious liver toxicity has varied according to the indication for use in rheumatoid arthritis and psoriasis.[142,143] Factors which may predispose patients to liver toxicity from methotrexate include alcohol use, abnormal baseline liver enzyme levels, concomitant diabetes mellitus, obesity, or a cumulative dose of >1.5g of methotrexate.[129] Transaminase level elevation are common in patients with rheumatoid arthritis receiving methotrexate therapy.[135] Although studies are limited in the IBD population, a small trial suggested a low risk of hepatotoxity in those treated with methotrexate.[144] It is recommended that liver enzymes be monitored routinely during long term methotrexate therapy. There is a poor correlation between elevation of serum transaminase levels and fibrosis/cirrhosis, and more trials are necessary before formal recommendations can be made regarding the utility of liver biopsy in patients with IBD receiving methotrexate.

Women planning conception should not use methotrexate, as it is a known abortifacient.[145]

3.3 Cyclosporin

3.3.1 Clinical Pharmacology and Mechanism of Action

Cyclosporin is a lipophilic polypeptide produced by the soil fungus *Tolypocladium inflatum gams*. The drug alters the immune response by acting as a potent inhibitor of cellular immunity. Cyclosporin primarily blocks the production of IL-2 from T-helper cells.[146] Additionally, cyclosporin inhibits other cytokines, including IL-3, IL-4, interferon-γ and TNFα.[147]

At the cellular level, cyclosporin binds to the protein cyclophilin. This complex serves as an inhibitor of the enzyme calcineurin, which in turn inhibits the activation of the nuclear factor for activated T cells.[129] This effectively down regulates the transcription of messenger RNA encoding IL-2.[148] Cyclosporin may also inhibit the function of other enzymes within T cells related to the immune response, and indirectly inhibit the production of B cell activating factors.[129] Granulocyte, monocyte and macrophage functions are not affected by cyclosporin.[129,147]

Compared with the purine analogues and methotrexate, cyclosporin has a rapid onset of action.[147] This has made cyclosporin a particularly attractive agent for use in severe, corticosteroid-refractory IBD. Cyclosporin may be administered orally or intravenously. Absorption from gelatin capsules or liquid is variable depending upon a variety of factors including small bowel length, motility, and mucosal integrity.[149] Additionally, these preparations are dependent on bile for adequate absorption.[147] A new microemulsion formulation of cyclosporin (Neoral®) has significantly enhanced bioavailability compared with the older gelatin preparation (i.e. Sandimmune®). Further, the microemulsion formulation follows dose-dependent pharmacokinetics, is less dependent upon bowel length and integrity, and is not dependent on bile for absorption.[150] Preliminary trials using this new microemulsion formulation in Crohn's disease and ulcerative colitis suggest it may be as effective as intravenous cyclosporin.[151]

Once absorbed, cyclosporin is primarily metabolised by the liver and excreted in the bile. Grapefruit juice and certain drugs that inhibit cytochrome

P450 increase cyclosporin concentrations, including calcium antagonists, erythromycin, antifungal agents and methylprednisolone.[152] Alternatively, rifampicin, phenobarbital and phenytoin decrease cyclosporin concentrations.

Cyclosporin has been most extensively evaluated as an intravenous infusion for severe IBD. The usual starting dosage of 4 mg/kg/day as a continuous infusion may be lower in elderly patients or those with renal insufficiency. It is recommended that cyclosporin concentrations be followed while patients are receiving therapy, although the optimal method of measuring trough concentrations remains in question. Additionally, there does not appear to be good data showing correlation between blood concentrations of cyclosporin and clinical response. In general, high performance liquid chromatography assays should be used to measure cyclosporin concentrations, with the goal of achieving trough concentrations of the drug of 200 to 400 μg/L.[149,152] Patients who respond to an infusion of the drug are then changed to oral cyclosporin, usually at a dosage of 8 mg/kg/day (a lower dosage if prescribed as a microemulsion formulation). The goal is to then wean patients off of cyclosporin over several months, while other medications, such as azathioprine or mercaptopurine in combination with aminosaicylates, are continued long term.

3.3.2 Adverse Effects

Cyclosporin has multiple potential adverse effects, including potent immunosuppression. Monitoring for both benefits and toxicity are essential. The most common adverse effects include hypertension, hypertrichosis, gingival hyperplasia, tremors, paresthesias, headaches, and electrolyte abnormalities (see table I).[149,153,154] Renal insufficiency is also common and results from both afferent arteriolar vasoconstriction as well as tubular atrophy and interstitial fibrosis.[149] Creatinine clearance is reduced in most patients, but usually returns to normal after drug cessation.[155] Dose reduction or discontinuation of therapy is indicated if there is evidence of nephrotoxicity during treatment. There are data suggesting that up to 20% of patients treated with cyclosporin may have irreversible histological evidence of nephrotoxicity.[149,156]

Seizures have been reported during therapy with cyclosporin, and there appears to be a greater risk to patients with hypocholesterolaemia (<120 mg/dl) and/or hypomagnesaemia.[143]

Cyclosporin may also induce elevated liver enzyme levels in up to 20% of patients who have undergone renal transplantation.[157] Cholestasis or mild transaminase level elevations may occur, and reports in the IBD literature have demonstrated a 5 to 19% incidence of increased liver enzyme levels during cyclosporin treatment.[153,154] No severe liver toxicity has been reported, and liver tests usually return to normal upon dose reduction or drug withdrawal.

Opportunistic infections, including *Pneumocystis carinii* pneumonia have been reported during cyclosporin treatment, and have been the cause of 1 death in a patient with Crohn's disease treated with concomitant corticosteroids and azathioprine.[153] This has led to the recommendation for prophylaxis in those receiving cyclosporin in combination with other immunomodulatory agents.[153] There has also been 1 reported case of fatal invasive aspergillosis in a patient with Crohn's disease receiving concomitant corticosteroids.[158] Two other deaths have been reported in patients with IBD receiving cyclosporin; 1 secondary to septic shock and the other from a massive upper gastrointestinal haemorrhage.[154] Other reported complications during cyclosporin therapy in patients with IBD include herpes esophagitis, bacterial lung abscess, and carotid artery mycotic aneurysm.[149,153]

Another area of concern has been the potential for the development of malignancies related to cyclosporin. Results in the rheumatological literature suggest an increased relative risk of the development of malignancies, including lymphoma, in patients with rheumatoid arthritis who have received cyclosporin.[159] These data have not been duplicated in the IBD literature, and to date no malignancies have been reported during cyclosporin treatment of IBD.

The use of cyclosporin in pregnancy remains controversial. In a large trial involving over 150 pregnant renal transplant recipients, there was a 16% miscarriage rate in those receiving cyclosporin. Further, 21% of babies born to these women had complications, with a high incidence of prematurity and low birth weight.[160] Limited data suggests safety of cyclosporin in pregnant patients with IBD,[161] but its use should be reserved for those with severe, refractory disease.

4. Investigational Immunomodulators

4.1 Tacrolimus

4.1.1 Clinical Pharmacology and Mechanism of Action

Tacrolimus is a macrolide antibacterial with potent immunosuppressive properties that has become the drug of choice for prevention of solid organ rejection.[162] It can be administered orally or parentally and has a similar mode of action to cyclosporin. Specifically, tacrolimus inhibits IL-2 production by T-helper cells, but is approximately 50 to 100 times more potent than cyclosporin. IL-3 and IL-4 transcription are also inhibited, as is the release of other proinflammatory cytokines.[163] Additionally, tacrolimus suppresses nitrous oxide production, which contributes to its anti-inflammatory effects,[164] and a rapid onset of action makes tacrolimus an attractive agent for use in corticosteroid-refractory IBD. In contrast to cyclosporin (Sandimmune®), the oral bioavailability of tacrolimus is not affected by bile flow.[148,165,166] Some advocate initial intravenous administration to assure steady state drug concentrations, although this has not been studied in a controlled setting in patients with IBD.[167]

In ulcerative colitis and Crohn's disease, tacrolimus has been administered intravenously at dosages of 0.01 to 0.02 mg/kg/day and orally at dosages of 0.01 to 0.029 mg/kg/day.[167,168] Whole blood concentrations in the range of 10 to 20 μg/L have been recommended; however, there are no data correlating blood concentrations of the drug to clinical efficacy in patients with IBD.

4.1.2. Adverse Effects

Most of the adverse effects of tacrolimus are similar to those reported for cyclosporin, including nausea, headache, hirsutism, gingival hyperplasia and hypertension. Neurotoxicity, including tremors, insomnia and paresthesias, may also occur.[167,168] Nephrotoxicity with tacrolimus therapy is similar to that observed with cyclosporin.[167] In 1 study in patients with Crohn's disease with refractory fistulas, the most common adverse effect of tacrolimus was increased creatinine levels. Further trials are needed to evaluate the risk-benefits of tacrolimus in IBD, such as the development of opportunistic infections, renal toxicity and possible development of lymphoproliferative disorders.

4.2 Mycophenolate Mofetil

4.2.1 Clinical Pharmacology and Mechanism of Action

Mycophenolate mofetil was first derived from the mould *Penicillium brevicompactum* in the 1940s.[169] Mycophenolate mofetil is an ester prodrug of mycophenolic acid that has high oral bioavailability.[170] Upon oral administration, mycophenolate is rapidly hydrolysed to mycophenolic acid; the active agent. Mycophenolic acid is an inhibitor of inosine monophosphate dehydrogenase and guanine nucleotide synthesis, resulting in reduced lymphocyte proliferation.[171] Mycophenolate mofetil additionally inhibits the humoral immune response.[172] It has been used for many years in the transplant population, and is an effective agent for the prevention of allograft rejection.[173] There is preliminary evidence that mycophenolate mofetil may be of benefit for patients with chronically active IBD who are intolerant to azathioprine or mercaptopurine.[174,175]

4.2.2 Adverse Effects

Although experience with patients with IBD is limited, the majority of adverse events reported with mycophenolate mofetil therapy, aside from immunosuppression, have been of a gastrointestinal nature. Nausea, vomiting, abdominal pain and diarrhoea have all been reported, but generally have not led to drug discontinuation of treatment.[174,176]

Mycophenolate usually does not induce bone marrow suppression, but rarely has been reported to cause neutropenia and has been associated with opportunistic infections.[173,177,178]

5. Antibacterials

5.1 Metronidazole

5.1.1 Clinical Pharmacology and Mechanism of Action

Metronidazole has been the most extensively studied antibacterial in IBD. After oral administration it is rapidly absorbed and distributed throughout most tissues of the body. Metronidazole is metabolised by the liver and excreted in the urine.[8] Although the mechanisms of action are unclear, both antimicrobial as well as anti-inflammatory effects have been described. Metronidazole reduces anaerobic bacterial levels and appears to inhibit cell-mediated immune function.[8] Metronidazole has demonstrated benefit in active intestinal and perianal Crohn's disease, as well as for prevention of postoperative recurrence, at dosages of 10 and 20 mg/kg/day, respectively.[179,180]

5.1.2 Adverse Effects

The most common adverse effects of metronidazole include nausea, a metallic taste, coating of the tongue and peripheral neuropathy manifest as distal paraesthesia (see table I).[181,182] The neuropathy is unpredictable in occurrence, often is subclinical and may persist despite discontinuation of therapy.[183] When taken with alcohol, a disulfiram-like reaction has been described with high dosages of metronidazole.[8] The tolerability of long term metronidazole therapy administered throughout pregnancy is unknown. However, 1 large retrospective study of over 1300 women found no increase in the incidence of birth defects associated with short term (10 days) fetal exposure.[184]

5.2 Ciprofloxacin

Ciprofloxacin is a flouroquinolone antibacterial effective against aerobic gram-negative bacteria. It has been used in both ulcerative colitis and active perianal and fistulising Crohn's disease.[185-187] At dosages of 1.0 to 1.5 g/day ciprofloxacin has been well tolerated. In developing animals skeletal abnormalities have been reported, although there are no data on the risks of ciprofloxacin treatment in children or in pregnant women.[8] No serious adverse effects have been reported in the IBD literature.

6. Novel Biological Agents

Increased understanding of the immunoinflammatory cascade has led to the development of a number of new 'biological' agents targeting specific cytokines and inflammatory mediators believed to be important to the pathogenesis of IBD. A humanised formulation of an anti-TNF monoclonal antibody (CDP571) is also under investigation.[188,189]

The most notable of these agents is a chimeric monoclonal antibody to TNFα, infliximab. Infliximab binds to circulating TNF and also induces lysis or apoptosis of cells bearing TNF on their surface. Infliximab has been successful in treating both refractory Crohn's disease[190] and fistulising disease[191] at dosages of 5 mg/kg. This agent has a rapid onset of action and a half-life of approximately 9 days, with no accumulation of infliximab following repeated administration.[189] In clinical trials, infliximab has been well tolerated, with the most common adverse effects being headache, nausea, upper respiratory tract infection and fatigue.[189] Infusion reactions, including anaphylactoid responses, chest pain and dyspnea, may be related to autoantibody production or the rate of infusion of the protein, but rarely necessitate cessation of the infusion. Autoantibodies have been associated with low-priming doses and include human antichimeric antibodies and antidouble stranded DNA associated with a 'lupus-like' syndrome.[189] Delayed-hypersensitivity reactions have also been described after long delays (greater than 6 months) between infusions. Finally, there is concern regarding the potential development of malignancies with the use of infliximab. To date, 6 lymphomas have been reported in 6 patients treated with infliximab: rheumatoid arthritis (n = 3), Crohn's disease (n = 2) and HIV (n = 1).[192] Of the 2 patients with Crohn's disease; 1 developed a B cell lymphoma 8 months after a single infusion of in-

fliximab, and the other developed Hodgkin's lymphoma only a few weeks after an infliximab infusion. Further studies are under way to investigate the long term risks of anti-TNFα therapy.

Thalidomide has received attention in recent years as an anti-inflammatory agent in IBD, as it inhibits TNFα production by monocytes and other cells.[193,194] In 2 recent open label trials, thalidomide has shown benefit in the treatment of corticosteroid-dependent Crohn's disease and Crohn's disease fistulae.[193,194] Adverse effects associated with thalidomide therapy were common, however, as almost all patients experienced sedation and several other patients developed skin rash, constipation, peripheral neuropathy or oedema.

Intercellular adhesion molecule 1 (ICAM-1), a glycoprotein expressed on endothelial cells and leucocytes, facilitates leucocyte migration and activation.[188,195] A small placebo-controlled study has been performed using an antisense oligonucleotide to ICAM-1 (ISIS 2302) to treat corticosteroid-refractory Crohn's disease. The antisense oligonucleotide was administered by intravenous infusion at doses of 0.5, 1, or 2 mg/kg. It has a half-life of 30 to 80 minutes and is cleared via distribution in tissues and subsequent nucleotide degradation.[195] Overall, ISIS 2302 appears to be well tolerated although nausea, vomiting, facial flushing, and a transient rise in activated partial thromboplastin time have been reported.[195] Further data are required to assess the short and long term tolerability of this treatment.

In contrast to the proinflammatory cytokines noted above, evidence suggests that other cytokines play a vital role in 'down regulation' of the inflammatory response.[188] Early trials have been underway to evaluate both IL-10 and IL-11 as both have demonstrated anti-inflammatory properties in animal models.[188] Human recombinant IL-11 (rhIL-11, thromobopoietin) has demonstrated preliminary benefit in active Crohn's disease after weekly intravenous injections of 5, 16 or 40 μg/kg for a total of 3 weeks.[196] The study medication was tolerated well, with the only significant adverse event being mild irritation at the injection site.[196] IL-10 decreases IL-2 production by T cells and inhibits monocyte secretion of a variety of other proinflammatory cytokines.[188,197] In 2 recent Crohn's disease trials, human recombinant IL-10 was administered at variable dosages between 1 to 25 μg/kg by daily subcutaneous or intravenous administration.[197,198] Mild to moderate adverse effects were common including neutropenia, abdominal pain, arthralgia, nausea, fatigue, and headache.[197,198] At the highest doses some patients developed reversible neutropenia, anaemia, and thrombocytopenia.[198] No renal impairment or hepatotoxicity was identified in any treated patients. Further trials of rhIL-11 and rhIL-10 are essential to determine their long term efficacy and tolerability.

There continues to be ongoing evaluation of novel therapies for IBD that will continue until the ultimate causes and cures have been identified. Current trials involving heparin have demonstrated efficacy for the treatment of active ulcerative colitis,[199] although further studies are required to determine the ultimate risk of haemorrhage.

Short chain fatty acids are a substantial energy source for colonic epithelium and have been investigated for the treatment of ulcerative colitis. Butyrate enemas have modest benefits in ulcerative colitis and have been well tolerated.[200] Similarly, omega-3 fatty acids, in the form of fish oils for oral administration, have been used to treat IBD under the auspices that these agents will divert arachadonic acid to form less inflammatory leukotrienes (e.g. LTB5).[201] However, the large doses of fish oils required may lead to fishy breath and subsequent patient noncompliance.[98]

The relationship between smoking and IBD has been well established in recent years. Smoking has opposing effects in ulcerative colitis and Crohn's disease; whereby it prevents or ameliorates disease activity in ulcerative colitis but has a negative impact in Crohn's disease.[202] These observations led to the investigation of nicotine preparations for the treatment of ulcerative colitis. Nicotine gum was the first nicotine preparation tested in patients with IBD. Although a benefit was observed, adverse effects were common, including headache, taste in-

tolerance and nausea.[203] The introduction of transdermal nicotine led to controlled trials in patients with ulcerative colitis using dosages of 15 to 24 mg/day.[204,205] Despite the apparent benefit, adverse effects were common, including local skin irritation, nausea, headache, lightheadedness and insomnia. In addition, there is an addiction potential. Further studies are in progress to evaluate a new topical nicotine formulation in patients with ulcerative colitis.

7. Conclusions

Despite progress in our understanding of the pathogenesis of these chronic inflammatory conditions, the aetiology of Crohn's disease and ulcerative colitis remain unknown. The agents used in the management of IBD impact at various points along the immune and inflammatory cascades. While effective, most current therapies are associated with significant adverse effects. Novel corticosteroids, newer immunomodulators and advances in the field of recombinant genetic engineering are expanding the armamentarium of agents available to treat patients with IBD. As we gain more experience using these medications, it will be essential to monitor patient tolerability and the long term adverse effects of therapy.

References

1. Schroder H, Campbell DES. Absorption, metabolism and excretion of salicylazosulfapyridine in man. Clin Pharm Ther 1972; 13: 359-1
2. Peppercorn MA. Sulfasalazine. Pharmacology, clinical use, toxicity and new drug development. Ann Int Med 1984; 101: 377-86
3. Greenfield SM, Punchard NA, Teare JP, et al. Review article: The mode of action of the aminosalicylates in inflammatory bowel disease. Aliment Pharmacol Ther 1993; 7: 369-83
4. Das KM, Eastwood MA. Acetylation polymorphism of sulfapyridine in patients with ulcerative colitis and Crohn's disease. Clin Pharm Ther 1975; 18: 514-20
5. Ireland A, Priddle JD, Jewell DP. Acetylation of 5-aminosalicylic acid by isolated human colonic epithelial cells. Clin Science 1990; 78: 105-11
6. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites, and other prodrugs of 5-aminosalicylic acid. Clin Pharmacokinetics 1985; 10: 285-302
7. Azad-Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977; II: 892-5
8. Hanauer SB, Meyers S, Sachar DB. The pharmacology of anti-inflammatory drugs in inflammatory bowel disease. In: Kirsner JB, Shorter RG, editors. Inflammatory bowel disease. 4th ed. Baltimore (ML): Williams & Wilkins, 1995: 643-63
9. Sandberg-Gertzen H, Ryde M, Janerot G. Absorption, metabolism and excretion of a single 1gm dose of azodisal sodium in subjects with ileostomy. Scand J Gastroenterol 1983; 18: 107-111
10. McIntyre PB, Rodrigues CA, Leonard-Jones JE, et al. Balsalazide in the maintenance treatment of patients with ulcerative colitis, a double-blind comparison with sulphasalazine. Aliment Pharmacol Ther 1988; 2: 237-43
11. Rasmussen SN, Bondesen S, Hvidberg, et al. 5-Aminosalicylic acid in a slow-release preparation: Bioavailability, plasma level, and excretion in humans. Gastroenterology 1982; 83: 1062-70
12. Dew MJ, Ebden P, Kidwai NS, et al. Comparison of the absorption and metabolism of sulfasalazine and acrylic-coated 5-aminosalicylic acid in normal subjects and patients with ulcerative colitis. Br J Clin Pharmacol 1984; 17: 474-6
13. Hanauer SB, Stathopoulos G. Risk-benefit assessment of drugs used in treatment of inflammatory bowel disease. Drug Saf 1991; 6: 192-219
14. Laursen SL, Stokholm M, Bukhave K, et al. Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. Gut 1990; 31: 1271-6
15. Sutherland LR. Topical treatment of ulcerative colitis. Med Clin North Am 1990; 74: 119-31
16. Campieri M, Corbelli C, Gionchetti P, et al. Spread and distribution of 5-ASA colonic foam and 5-ASA enema in patients with ulcerative colitis. Dig Dis Sci 1992; 37: 1890-7
17. Gaginella TS, Walsh RE. Sulfasalazine: multiplicity of action. Dig Dis Sci 1992; 37: 801-12
18. Wahl C, Liptay S, Adler G, et al. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. J Clin Invest 1998; 101: 1163-74
19. Lauritsen K, Laursen S, Bukhave K, et al. Inflammatory intermediaries in inflammatory bowel disease. Int J Colorectal Dis 1989; 4: 75-90
20. Zimmerman MJ, Jewell DP. Cytokines and mechanisms of action of glucocorticoids and aminosalicylates in the treatment of ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther 1996; 10: 93-8
21. Bjarnason I, Hayllar J, MacPherson A, et al. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 1993; 104: 1832-47
22. Rask-Madsen J, Burkhave K, Laursen LS, et al. 5-Lipoxygenase inhibitors for the treatment of inflammatory bowel disease. Agents Actions 1992; 37: 36-46
23. Grisham MB. Oxidants and free radicals in inflammatory bowel disease. Lancet 1994; 344: 859-61
24. Taffet SL, Das KM. Sulfasalazine: Adverse effects and desensitization. Dig Dis Sci 1983; 28: 833-42
25. Das KM, Eastwood MA, McManus JP, et al. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Engl J Med: 1973; 289: 491-5
26. 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: 389-93
27. Strom J. Toxic epidermal necrolysis (Lyell's syndrome)- a report on four cases with three deaths. Scand J Infect Dis 1969; 1: 209-16

28. Griffiths MB, Kane MA. Sulphasalazine-induced lupus syndrome in ulcerative colitis. BMJ 1977; 2: 188-9
29. Reid J, Holt S, Housley E, et al. Raynaud's phenomenon induced by sulphasalazine. Postgrad Med J 1980; 56: 106-7
30. Block MB, Genant HKI, Kirsner JB. Pancreatitis as an adverse reaction to salicylazosulfapyridine [letter]. N Engl J Med 1970; 282: 380
31. Hamadeh MA, Atkinson J, Smith LJ. Sulfasalazine-induced pulmonary disease [letter]. Chest 1992; 101: 1033
32. Jamshidi K, Arlander T, Garcia MC, et al. Azulfidine agranulocytosis with bone marrow megakaryocytosis, histiocytosis, plasmacytosis. Minn Med 1972; 55: 545-8
33. Davies G, Palek J. Selective erythroid and megakaryocytic aplasia after sulfasalazine administration [letter]. Arch Intern Med 1980; 140: 1122
34. Franklin JL, Rosenberg IH. Impaired folic acid absorption in inflammatory bowel disease: effects of salicylazosulfapyridine (azulfidine). Gastroenterology 1973; 64: 517-25
35. Schneider RE, Beeley L. Megaloblastic anemia associated with sulphasalazine treatment BMJ 1977; 1: 1638-9
36. Riley SA, Lecarpentier J, Mani V, et al. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. Gut 1987; 28: 1008-12
37. Gaiffer MH, O'Brien CJ, Holdsworth CD. Clinical tolerance to three 5-aminosalicylic acid releasing preparations in patients with inflammatory bowel disease intolerant or allergic to sulphasalazine. Aliment Pharm Ther 1992; 6: 51-9
38. Walker AM, Szneke P, Bianchi LA, et al. 5-Aminosalicylates, sulfasalazine, steroid use, and complications in patients with ulcerative colitis. Am J Gastroenterol 1997; 92: 816-20
39. Hautekeete ML, Bourgeois N, Potvin P, et al. Hypersensitivity with hepatotoxicity to mesalazine after hypersensitivity to sulfasalazine. Gastroenterology 1992; 103: 1925-7
40. Reinoso MA, Schroeder KW, Pisani RJ. Lung disease associated with orally administered mesalamine for ulcerative colitis. Chest 1992; 101: 1469-70
41. Kristensen KS, Hoegholm A, Bohr L, et al. Fatal myocarditis associated with mesalazine [letter]. Lancet 1990; I: 605
42. Abdullah AM, Scott RB, Martin SR. Acute pancreatitis secondary to 5-aminosalicylic acid in a child with ulcerative colitis. J Pediatr Gastroenterol Nutr 1993; 17: 441-4
43. Calvino JR, Romero J, Pintos E, et al. Mesalazine-associated tubulo-interstitial nephritis in inflammatory bowel disease. Clin Nephrol 1998; 49: 265-7
44. Elton E, Hanauer SB. Review article: the medical management of Crohn's disease. Aliment Pharmacol Ther 1996; 10: 1-22
45. Raimundo AH, Patil DH, Frost PG, et al. Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. Gut 1991; 32: 270-4
46. Korelitz BI. Inflammatory bowel disease and pregnancy. Gastro Clin North Am 1998; 27: 213-24
47. Jarnerot G, Into-Malberg MB. Sulphasalazine treatment during breast feeding. Scand J Gastroenterol 1979; 14: 869-71
48. Diav-Citrin O, Park Y, Veerasuntharam G, et al. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. Gastroenterology 1998; 114: 23-8
49. Miller LG, Hopkinson JM, Motil KJ, et al. Disposition of olsalazine and metabolites in breast milk. J Clin Pharmacol 1993; 33: 703-6
50. Swartz SL, Dluhy RG. Corticosteroids: Clinical pharmacology and therapeutic use. Drugs 1978; 16: 238-55
51. Lewis GP, Jusko WJ, Burke CW, et al. Prednisone side effects and serum protein levels. Lancet 1971; II: 778-80
52. Boekenoogen SJ, Szefler SJ, Jusko WJ. Prednisolone disposition and protein binding in oral contraceptive users. J Clin Endocrinol Met 1983; 56: 702-9
53. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997; 40: 775-81
54. Petitjean O. Pharmacokinetics and absolute rectal bioavailability of hydrocortisone acetate in distal colitis. Alim Pharm Ther 1992; 6: 351-7
55. Farmer RG, Schumacher OP. Treatment of ulcerative colitis with hydrocortisone enemas: relationship of hydrocortisone absorption, adrenal suppression and clinical response. Dis Colon Rectum 1970; 13: 355-61
56. Brattsand R, Linden M. Cytokine modulation by glucocorticoids: mechanisms and actions in cellular studies. Aliment Pharmacol Ther 1996; 10: 81-92
57. Hawthorne AB, Hawkey CJ. Immunosuppressive drugs in inflammatory disease: a review of their mechanisms of efficacy and place in therapy. Drugs 1989; 38: 267-88
58. Flower FJ, Blackwell CJ. Anti-inflammatory steroids induce biosynthesis of a phospholipase A2 inhibitor which prevents prostaglandin generation. Nature 1979; 278: 456-9
59. Lindmark B. Short and long-term steroid side effects: the importance for patients with inflammatory bowel disease. Res Clin Forums 1993; 15: 35
60. Hall RCW, Popkin MK, Stichney SK, et al. Presentation of steroid psychosis. J Ner Ment Disorder 1979; 167: 229-35
61. Nashel DJ. Is atherosclerosis a complication of long-term corticosteroid treatment? Am J Med 1986; 80: 925-9
62. Bar-Meir S, Chowers Y, Lavy A, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. Gastroenterology 1998; 115: 835-40
63. Tripathi RC, Kirshner BS, Kipp M, et al. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. Gastroenterology 1992; 102: 1957-61
64. Dujorne CA, Azarnoff DL. Clinical complications of corticosteroid therapy. Med Clin No Amer 1973; 57: 1331-42
65. Mandel S. Steroid myopathy: insidious cause of muscle weakness. Postgrad Med 1982; 72: 207-15
66. Conn HO, Blitzer BL. Non-association of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294: 473-9
67. Nelp WB. Acute pancreatitis associated with steroid therapy. Arch Int Med 1961; 108: 702-10
68. Seyrig JA, Jian R, Modigliani R, et al. Idiopathic pancreatitis associated with inflammatory bowel disease. Dig Dis Sci 1989; 30: 1121-6
69. Issenman RM. Bone mineral metabolism in pediatric inflammatory bowel disease. Inflammatory Bowel Dis 1999; 5: 192-9
70. Sadeghi-Nejad A, Senior B. The treatment of ulcerative colitis in children with alternate-day corticosteroids. Pediatrics 1968; 43: 840-4
71. Olbricht T, Benker G. Glucocorticoid-induced osteoporosis: pathogenesis, prevention and treatment, with special regard to the rheumatic diseases. J Intern Med 1993; 234: 237-44
72. Valentine JF, Sninsky CA. Prevention and treatment of osteoporosis in patients with inflammatory bowel disease. Am J Gastroenterol 1999; 94: 877-83
73. Compston JE. Review article: osteoporosis, corticosteroids and inflammatory bowel disease. Aliment Pharmacol Ther 1995; 9 (3): 237-50
74. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis. Rheum Dis Clin No Amer 1994; 20: 629-50

75. Vakil N, Sparberg M. Steroid-related osteonecrosis in inflammatory bowel disease. Gastroenterology 1989; 96: 62-6
76. Summers RW, Switz DM, Jr Sessions JT, et al. National Cooperative Crohn's Disease Study (NCCDS): results of drug treatment. Gastroenterology 1979; 77: 847-69
77. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticoids. Rev Infect Dis 1989; 6: 954-63
78. Schlaghecke R, Kornely E, Santen RT, et al. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med 1992; 326: 226-30
79. Christy NP. Pituitary-adrenal function during corticosteroid therapy. Learning to live with uncertainty. N Engl J Med 1992; 326: 265-7
80. Cook DM. Safe use of glucocorticoids. Postgrad Med 1992; 91: 145-54
81. Mogadam DM, Dobbins WO III, Korelitz BI, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcomes. Gastroenterology 1981; 80: 72-6
82. Barocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. J Clin Gastroenterol 1984; 6: 211-6
83. Hamedani R, Feldman RD, et al. Review article: drug development in inflammatory bowel disease: budesonide-a model of targeted therapy. Aliment Pharmacol Ther 1997; 11 Suppl. 3: S98-S107
84. Stotland BR, Lichtenstein GR. Newer treatments for inflammatory bowel disease. Primary Care Clin No Am 1996; 23: 577-608
85. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose ranging study. Gastroenterology 1998; 115: 525-32
86. Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. Gut 1997; 41: 209-14
87. Kumana CR, Seaton T, Meghji M, et al. Beclomethasone dipropionate enamas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic-pituitary-adrenal suppression. Lancet 1982; I: 579-83
88. Brogden RN, Heel RC, Speight TM, et al. Beclomethasone dipropionate: A reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. Drugs 1984; 29: 99-126
89. Hanauer SB, Kirsner JB, Barrett WE. The treatment of left-sided ulcerative colitis with tixocortal pivalate [abstract]. Gastroenterology 1986; 90: A1449
90. Larochelle P, Du Sovich P, Bolte E, et al. Tixocortol pivalate, a corticosteroid with no systemic glucocorticoid effect after oral, intrarectal, and intranasal application. Clin Pharm Ther 1983; 3: 343-50
91. Hawthorne AB, Record CO, Holdsworth CD, et al. Double-blind trial of oral fluticasone-propionate versus prednisolone in the treatment of active ulcerative colitis. Gut 1993; 34: 125-8
92. Wright JP, Jaarnum S, Muckadell OS, et al. Oral fluticasone propionate compared with prednisolone in the treatment of active Crohn's disease: a randomized double-blind multicenter study. Eur J Gasto Hepatol 1993; 5: 499-503
93. Van Scoik KG, Johnson CA, Porter WR. The pharmacology and metabolism of the thiopurine drugs 6-mercaptopurine and azathioprine. Drug Metab Rev 1985; 16: 157-74
94. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease: azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. Am J Gastroenterol 1996; 91 (3): 423-33
95. Sandborn WJ. Azathioprine: state of the art in inflammatory bowel disease. Scand J Gastroenterol 1998; 225 Suppl.: S92-S99
96. Zimm S, Collins JM, Riccardi R, et al. Variable bioavailability of oral mercaptopurine: is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? N Engl J Med 1983; 308: 1005-9
97. Langevin AM, Koren GT, Soldin SJ, et al. Pharmacokinetic case for giving 6-mercaptopurine maintenance doses at night. Lancet 1987; II: 505-6
98. Hanauer SB. Drug therapy: inflammatory bowel disease. N Engl J Med 1996; 334: 841-8
99. Szawlowski PWS, Al-Safi SA, Dooley T, et al. Azathioprine suppresses the mixed lymphocyte reaction of patients with Lesch-Nyhan syndrome. Br J Clin Pharm 1985; 20: 489-91
100. Chalmers AH. Studies on the mechanism of formation of 5-mercapto-1-methyl-4-imidazole: a metabolite of the immunosuppressive drug azathioprine. Biochem Pharm 1974; 23: 1891-901
101. Leman B, Shanahan F, Targan S. Serial study of immunologic alterations in patients with IBD on long-term treatment with 6-MP [abstract]. Gastroenterology 1988; 94: A255
102. Present DH, Korelitz BI, Wishc JL, et al. Treatment of Crohn's disease with 6-mercaptopurine. N Engl J Med 1980; 302: 981-7
103. Marion JF. Toxicity of 6-mercaptopurine/azathioprine in patients with inflammatory bowel disease. Inflamm Bowel Dis 1998; 4: 117-8
104. Haber DJ, Meltzer SJ, Present DH, et al. Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. Gastroenterology 1986; 91: 982-6
105. Singleton JW, Law DH, Kelley ML, et al. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology 1979; 77: 870-82
106. Present DH, Meltzer SJ, Krumholz MP, et al. 6-mercaptopurine in the management of inflammatory bowel disease: short and long term toxicity. Ann Intern Med 1989; 111: 641-9
107. Baert F, Rutgeerts P. Immunomodulatory therapy in inflammatory bowel disease. Acta Clin Belgica 1997; 52: 251-7
108. Gross R, Scapa E. Hepatotoxicity of 6-mercaptopurine in Crohn's disease. Am J Gastroenterol 1992; 87: 1885-6
109. Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. Gastroenterology 1998; 115: 813-21
110. Connell WR, Kamm MA, Ritchie JK, et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut 1993; 34: 1081-5
111. Lennard L, van Loon J, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. Clin Pharmacol Ther 1989; 46: 149-54
112. Stolk JN, Boerbooms AMT, DeAbreu RA, et al. Reduced thiopurine methyltransferase activity and development of side effects of azathioprine treatment in patients with rheumatoid arthritis. Arthritis Rheum 1998; 41: 1858-66
113. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000; 118: 705-13

114. Bradley PP, Warden GD, Maxwell JG, et al. Neutropenia and thrombocytopenia in renal allograft recipients treated with trimethoprim-sulfamethoxazole. Ann Int Med 1980; 93: 560-2
115. Sandborn WJ, Tremaine WJ, Wolf DC, et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. Gastroenterology 1999; 117: 527-35
116. Korelitz BI, Mirsky FJ, Fleisher MR, et al. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. Am J Gastroenterol 1999; 94: 3248-53
117. Greenstein AJ, Mullin GE, Strauchen JA, et al. Lymphoma in inflammatory bowel disease. Cancer 1992; 69: 1119-23
118. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am J Med 1985; 78: 44-9
119. Leman M, Bonhomme P, Biton A, et al. Traitment de la maladie de Crohn's par l'azathioprine ou la 6-mercaptopurine: etude retrospective chez 126 malades. Gastroenterol Clin Biol 1990; 14: 548-54
120. Larvol L, Soule JC, LeTourneau A. Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease. N Engl J Med 1994: 331: 883-4
121. Present D, Heizer WD, Peterson JL. Acute myeloblastic leukemia following prolonged treatment of Crohn's disease with 6-mercaptopurine. Dig Dis Sci 1998; 43: 1791-3
122. Connell WR, Kamm MA, Dickson M, et al. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. Lancet 1994; 343: 1249-52
123. Merker HJ, Pospisil M, Mewes P. Cytotoxic effects of 6-mercaptopurine on the limb-bud blastemal cells of rat embryos. Teratology 1975; 11: 199-217
124. Williamson RA, Karp LE. Azathioprine teratogenicity: review of the literature and case report. Obstet Gynecol 1981; 58: 247-50
125. Hou S. Pregnancy in organ transplant recipients. Med Clin North Am 1989; 73: 667-83
126. Alstead EM, Ritchie RK, Lennard-Jones JE, et al. Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology 1990; 99: 443-6
127. Marteau P, Tennenbaum R, Elefant E, et al. Drug treatment of inflammatory bowel disease during pregnancy. Res Clin Forums 1998; 20 (1): 57-64
128. Rajapakse RO, Korelitz BI, Zlatanic J, et al. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. Am J Gastroenterol 2000; 3: 683-8
129. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease: azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. Am J Gastroenterol 1996; 91: 423-33
130. Jolivet J, Cowan KH, Curt GA, et al. The pharmacology and clinical use of methotrexate. N Engl J Med 1983; 309: 1094-104
131. Egan LJ, Snadborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. May Clin Proc 1996; 71: 69-80
132. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment Crohn's disease. N Engl J Med 1995; 332: 292-7
133. Baron TH, Truss CD, Elson CO. Low-dose oral methotrexate in refractory inflammatory bowel disease. Dig Dis Sci 1993; 38: 1851-6
134. Kozorek RA, Patterson DJ, Gelfand MD, et al. Methotrexate induces clinical and histological remission in patients with refractory inflammatory bowel disease. Ann Intern Med 1989; 110: 353-6
135. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986; 29: 822-31
136. Morgan SL, Baggott JE, Vaughn WH, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. Ann Intern Med 1994; 121: 833-41
137. Weinblatt ME. Methotrexate for chronic diseases in adults. N Engl J Med 1995; 332: 330-1
138. Al-Awadhi A, Dale P, McKendry RJ. Pancytopenia associated with low dose methotrexate therapy: a regional survey. J Rheum 1993; 20: 1121-5
139. Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: Potential risk factors. Four case reports and a review of the literature. J Rheumatol 1987; 14: 1164-71
140. Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993; 328: 1317-21
141. Alarcon GS, Goodman TA, Polisson RP. Methotrexate: adverse reactions and major toxicities. Rheumatic Dis Clin North Am 1994; 20: 513-28
142. Kremer JM, Alarcon GS, Lightfoot Jr RW, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. Arthritis Rheum 1994; 37: 316-28
143. Roenigk Jr HH, Auebach R, Maibach HI, et al. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol 1988; 19: 145-56
144. Te H, Schiano TD, Kuan SF, et al. Is long term methotrexate use hepatotoxic in IBD patients? [abstract]. Gastroenterology 1999; 116: A830
145. Goldenberg M, Bider D, Admon D, et al. Methotrexate therapy for tubal pregnancy. Hum Reprod 1993; 8: 660-6
146. Hess AD, Tutschka PJ, Santos GW. Effect of cyclosporin A on human lymphocyte response in vitro. J Immunol 1982; 128: 355-9
147. DiPavoda FE. Pharmacology of cyclosporine (sandimmune). Pharm reviews 1989; 41: 373-97
148. Flanagan WM, Corthesy B, Bram RJ, et al. Nuclear association of a T-cell transcription factor blocked by FK-506 and cyclosporin. Nature 1991; 352: 803-7
149. Sandborn WJ. A critical review of cyclosporine therapy in inflammatory bowel disease. Inflamm Bowel Dis 1995; 1: 48-63
150. Trull AK, Tan KKC, Uttridge J, et al. Cyclosporine absorption form microemulsion formulation in liver transplant recipient [letter]. Lancet 1993; 341: 433
151. Oppong K, Record CO. Neoral may be as effective as intravenous cyclosporine in the treatment of steroid-resistant ulcerative colitis. Am J Gastroenterol 1998; 93: 1188-9
152. Kornbluth A, Present DH, Lichteger S, et al. Cyclosporin for severe ulcerative colitis: a user's guide. Am J Gastroenterol 1997; 92: 1424-8
153. Stein R, Cohen R, Hanauer S. Complications during cyclosporine therapy for inflammatory bowel disease. Gastroenterology 1997; 112: A1096
154. Sternthal M, George J, Kornbluth A, et al. Toxicity associated with the use of cyclosporin in patients with inflammatory bowel disease [abstract]. Gastroenterology 1996; 110: A1019
155. Brynskov J, Thomsen H, Nielsen SL. Renographic monitoring of renal function in patients with Crohn's disease treated with

low-dose cyclosporine: A controlled study. Br Med J 1990; 300: 1438-9
156. Feutren G and Mihatsch MJ. Thank you.] et al. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune disease. N Engl J Med 1992; 326: 1654-60
157. Lorber MI, Van Buren CT, Flechner SM, et al. Hepatobiliary complications of cyclosporine therapy following renal transplantation. Transplant Proc 1987; 19: 1808-10
158. Scalzini A, Barni C, Stellini R, et al. Fatal invasive aspergillosis during cyclosporine and steroids treatment for Crohn's disease [letter]. Dig Dis Sci 1995; 40: 528
159. Arellano F, Krupp P. Malignancies in rheumatoid arthritis patients treated with cyclosporin A. Br J Rheumatol 1993; 32: 72-5
160. Armenti VT, Ahlswede KM, Ahlswede BA, et al. National transplantation pregnancy registry: outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. Transplantation 1994; 57: 502-6
161. Marion JF, Rubin PH, Lichtiger S, et al. Cyclosporine is safe for severe colitis complicating pregnancy [abstract]. Am J Gastroenterol 1996; 91: A1975
162. European FK-506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK-506) and cyclosporin in prevention of liver allograft rejection. Lancet 1994; 344: 423-8
163. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK-506. Immunol Today 1992; 13: 136-42
164. Aiko S, Conner EM, Fuseler JA, et al. Effects of cyclosporine or FK-506 in chronic colitis. J Pharm Exp Ther 1997; 280: 1075-6
165. Morris RE. Mechanisms of action of new immunosuppressive drugs. Ther Drug Monit 1995; 17: 564-9
166. Peters DH, Fitton A, Plosker GL, et al. Tacrolimus: a review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. Drugs 1993; 46: 746-94
167. Fellerman K, Ludwig D, Stahl M, et al. Steroid-unresponsive acute attacks of inflammatory bowel disease. Immunomodulation by tacrolimus (FK-506). Am J Gastro 1998; 93: 1860-6
168. Sandborn WJ. Preliminary report on the use of oral tacrolimus (FK-506) in the treatment of complicated proximal small bowel and fistulizing Crohn's disease. Am J Gastroenterol 1997; 92: 876-9
169. Florey HW, Gilliver K, Jennings MA, et al. Mycophenolic acid: an antibiotic from Penicillium brevicompactum. Lancet 1946; I: 46
170. Johnson HD, Swan SK, Heim-Duthoy KL, et al. The pharmacokinetics of a single oral dose of mycophenolate mofetil in patients with varying degrees of renal function. Clin Pharm Ther 1998; 63: 512-8
171. Fulton B, Markham A. Mycophenolate mofetil, a review of its pharmacodynamic and pharmocokinetic properties and clinical efficacy in renal transplantation. Drugs 1996; 51: 278-98
172. Smith KG, Isbel N, Catton MG, et al. Suppression of the humoral immune response by mycophenolate mofetil. Nephrol Dial Transplant 1998; 13: 160-4
173. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. US Renal Transplant Mycophenolate Mofetil Study Group. Transplantation 1995; 60: 225-32
174. Florin THJ, Roberts RK, Watson MR. Treatment of steroid refractory inflammatory bowel disease (IBD) with mycophenolate mofetil (MMF). Aust NZ J Med 1998; 28: 344-5
175. Neurath MF, Wanitschke R, Krummenauer F, et al. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease [abstract]. Gastroenterology 1998: 113: A491
176. Horgan K. Initial experience with mycophenolate mofetil in the treatment of severe inflammatory bowel disease [abstract]. Gastroenterology 1997; 112: A999
177. Roth D, Colona J, Burke GW, et al. Primary immunosuppression with tacrolimus and mycophenolate mofetil for renal allograft recipients. Transplantation 1998; 65: 248-52
178. Paterson DL, Singh N, Panebianco A, et al. Infectious complications occurring in liver transplant recipients receiving mycophenolate mofetil. Transplantation 1998; 66: 593-8
179. Ursing B, Alm T, Barany F, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: The Cooperative Crohn's disease study in Sweden. Gastroenterology 1982; 83: 550-62
180. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995; 108: 1617-21
181. Feagan B. Antibiotics are not effective for Crohn's disease (time to remove coloured glasses). Inflamm Bowel Dis 1997; 3: 314-7
182. Peppercorn MA. Antibiotics are effective for Crohn's disease. Inflamm Bowel Dis 1997; 3: 317-20
183. Duffy LF, Daum F, Fisher SE, et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 1985; 88: 681-4
184. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. Obstet Gynecol 1993; 82: 348-52
185. Turunen UM, Farkkila MA, Hakala K, et al. Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study. Gastroenterology 1998; 115: 1072-8
186. Greenbloom SL, Steinhart AH, Greenberg GR. Combination ciprofloxacin and metronidazole for active Crohn's disease. Can J Gastroenterol 1998; 12: 53-6
187. Colombel JF, Lemann M, Cassagnou M, et al. 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: 674-8
188. Sands BE. Biologic therapy for inflammatory bowel disease. Inflamm Bowel Dis 1997; 3: 95-113
189. Sandborn WE, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: a review of agents, pharmacology, clinical results, and safety. Inflamm Bowel Dis 1999; 5: 119-33
190. Targan SR, Hanauer SB, van Derventer SJH, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. N Engl J Med 1997; 337: 1029-35
191. Present D, Mayer L, VanDerventer SJH, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 1398-405
192. Bickston SJ, Lichtenstein GR, Arseneaus KO, et al. The relationship between infliximab treatment and lymphoma in Crohn's disease. Gastroenterology 1999; 117: 433-7
193. Ehrenpreis ED, Kane SV, Cohen LB, et al. Thalidomide therapy for patients with refractory Crohn's disease. An open label trial. Gastroenterology 1999; 117: 1271-7
194. Vasiliauskas EA, Kam LA, Abreau-Martin MT, et al. An open-label pilot study of low-dose thalidomide in chronically-active, steroid-dependent Crohn's disease. Gastroenterology 1999; 117: 1278-87

195. Yacyshyn B, Woloschuk MB, Yacyshyn D, et al. Efficacy and safety of ISIS 2302 (ICAM antisense oligonucleotide) treatment of steroid dependent Crohn's disease [abstract]. Gastroenterology 1997; 112: A1123
196. Sands BE, Bank S, Sninsky CA, et al. Preliminary evaluation of safety and activity of recombinant human interleukin 11 in patients with active Crohn's disease. Gastroenterology 1999; 117: 58-64
197. van Derventer SJ, Elson CO, Fedorak RN, et al. Multiple doses of interleukin 10 in steroid refractory Crohn's disease [abstract]. Gastroenterology 1997; 113: A383
198. Schreiber S, Fedorak RN, Nielsen OH, et al. A safety and efficacy study of recombinant human interleukin-10 (rhIL-10) treatment in 329 patients with chronic active Crohn's disease [abstract]. Gastroenterology 1998; 114: A266
199. Evans RC, Wong VS, Morris AI, et al. Treatment of corticosteroid-resistant ulcerative colitis with heparin- a report of 16 cases. Aliment Pharmacol Ther 1997; 11: 1037-40
200. Kim YI. Short-chain fatty acids in ulcerative colitis. Nutr Rev 1998; 56; 17-24
201. Burke A, Lichtenstein GR, Rombeau JL. Nutrition and ulcerative colitis. Baillieres Clin Gastroenterol 1997; 11; 153-74
202. Thomas GAO, Rhodes J, Green JT. Inflammatory bowel disease and smoking-A review. Am J Gastroenterol 1998; 93: 144-9
203. Lashner BA, Hanauer SB, Silverstein MD. Testing nicotine gum for ulcerative colitis. Dig Dis Sci 1990; 35: 827-32
204. Pullan RD, Rhodes J, Ganesh S. Transdermal nicotine for active ulcerative colitis. N Engl J Med 1994; 330: 811-5
205. Sandborn WJ, Tremaine W, Offord K, et al. A randomised, double-blind, placebo-controlled trial of transdermal nicotine for mildly to moderately active ulcerative colitis. Ann Intern Med 1997; 126: 364-71

Correspondence and offprints: Professor *Stephen B. Hanauer*, University of Chicago Hospitals, Division of Gastroenterology, MC-9028, 5758 S. Maryland Avenue, Chicago, IL 60637, USA.
E-mail: shanauer@medicine.bsd.uchicago.edu