REVIEW ARTICLE

Drug Safety 2002; 25 (8): 561-582
0114-5916/02/0008-0561/$25.00/0

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Comparative Tolerability of Therapies for Ulcerative Colitis

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Contents

Abstract

This article reviews the clinical pharmacology, adverse events, and comparative tolerability of the drugs commonly available for treating ulcerative colitis.

Synthetic glucocorticoids are the most commonly used conventional corticosteroids in the treatment of ulcerative colitis. Corticosteroids can be expected to impact on every organ system and most metabolic activities of the body. Suppression of the hypothalamic-pituitary-adrenal axis is common, but reversible, with conventional corticosteroids, but not with newer topically-acting corticosteroids. A serious complication of corticosteroids in children is growth retardation.

The frequent adverse effects associated with the use of corticosteroids have prompted the development of a new group of rectal agents with equivalent efficacy and a more benign adverse event profile such as prednisolone metasulfobenzoate, fluticasone propionate, tixocortol pivalate, beclomethasone dipropionate and budesonide.

The incidence of adverse effects related to the use of sulfasalazine (5-aminosalicylic acid plus sulfapyridine) is high and is dose related. The most frequently reported adverse effect is intolerance, not allergy, and relates to the sulfapyridine moiety correlating with the acetylator phenotype.

Tolerance to 5-aminosalicylic acid by 80 to 90% of those patients allergic to, or intolerant of, sulfasalazine has given further evidence suggesting that the sulfa moiety is responsible for much of the toxicity of sulfasalazine. However, 10 to 20% of patients who are sulfasalazine intolerant have similar reactions to 5-aminosalicylic acid formulations, indicating that the 5-aminosalicylic acid moiety is responsible for adverse events in some patients taking sulfasalazine.

Adverse effects resulting from treatment with azathioprine and mercaptopurine can be divided into two categories: allergic-type reactions that appear to be dose-independent and nonallergic-type reactions that are probably dose- and metabolism-dependent. It is well established now that genotype and thiopurine methyltransferase activity have an important impact on the rate of adverse effects during azathioprine or mercaptopurine therapy.

Adverse effects resulting from high dose cyclosporin therapy for inflammatory bowel disease include: renal insufficiency, hypertension, opportunistic infections, seizures, paresthesias, tremor, headache, gingival hyperplasia, hypertrichosis, and anaphylaxis with intravenous cyclosporin. In contrast, the incidence of adverse events was relatively low when low-dose oral cyclosporin was used.

The incidence of adverse events associated with any of the medications used in the treatment of ulcerative colitis is difficult to assess and it is therefore hard to make a comparative evaluation. The broadening of the drug regimen available to the clinician has advanced our knowledge about the disease, and further development of more effective, less toxic agents can be anticipated in the future.

Ulcerative colitis is an inflammatory disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. However, more than half of patients present with disease extending from the rectum to the splenic flexure.

While its aetiology is unclear, the pathogenesis of ulcerative colitis is better understood, and several drugs, interacting with various points along the immune and inflammatory cascades, are cur-

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rently available for its treatment. Corticosteroids, sulfasalazine and its derivatives the 5-aminosalicylic acids and immunosuppressants are the mainstay of medical treatment of ulcerative colitis. Effective in inducing remission, some of them are largely used to prevent disease recurrence. Other drugs may also have a potential role in this context (anti-tumour necrosis factor, nicotine, heparin, etc.), but their effectiveness needs to be established in controlled clinical trials or in confirmatory studies. Moreover, though effective, many of them can cause potential complications which may themselves lead to further morbidity. However, these drug complications can in some cases be avoided by careful patient selection, and in view of the wide spectrum of extent and severity of disease, a stepwise approach in care has commonly been advocated.

In order to limit toxicity and optimise the therapeutic effects of the current pharmaceutical treatments, a thorough understanding of the indications and complications of drug therapy is essential.

This article focuses on the clinical pharmacology, adverse events, and comparative tolerability of the drugs commonly used in the treatment of ulcerative colitis, highlighting the practical implications and educational messages.

1. Principles Governing the Use of Pharmacological Treatment

To reduce toxicity and maximise the therapeutic benefit of the different drugs available for the treatment of ulcerative colitis, thus improving their benefit-risk ratio, several important criteria should be considered when choosing the most appropriate therapeutic approach: (i) aims of the treatment; (ii) extent and the localisation of disease; (iii) disease activity; (iv) clinical pattern; and (v) proven efficacy of the current therapies.

1.1 Aims of Therapy

The clinical status of a patient with active ulcerative colitis reflects many different factors: the primary disease process of gut inflammation (confined to the mucosa in ulcerative colitis); metabolic consequences (e.g. protein-losing enteropathy and hypoalbuminaemia, anaemia, hypokalaemia, hypocalcaemia and hypomagnesaemia) and; structural abnormalities such as strictures and perforations. The treatment of the patient involves, and usually as a priority, control of these consequences of inflammation by transfusion, replacement of losses, minerals, vitamins and so on.

For a disease such as ulcerative colitis, which is characterised by recurrent attacks of symptoms with complete or partial remission of clinical manifestations, the primary aims of medical treatment must be the induction of remission of inflammatory activity and the prevention of recurrences. Moreover, considering the frequent development of extraintestinal complications, often severely affecting the patient's quality of life, another important objective of the medical therapy is to control the impact of these complications on the patient's life.

1.2 Extent and Anatomic Distribution of Ulcerative Colitis

Establishing the extent and localisation of ulcerative colitis is an important diagnostic and clinical step in the evaluation of patients with ulcerative colitis, because of its therapeutic implications and relative tolerability. Colonoscopy and radiology (barium enema) are the primary diagnostic tools used to define the extent and anatomic distribution of the disease.

In ulcerative colitis, the extent of colonic involvement during the first attack has been found to be reasonably uniform in several large series of patients. Approximately 30% of ulcerative colitis patients have disease which is limited to the rectum, in about 40% the disease extends above the rectum but not beyond the hepatic flexure (so-called sub-total colitis), and the remaining 30% develop total colitis.[1] However, in some population-based surveys, more than half of the patients present with disease extending from the rectum to the splenic flexure. In this context, while ulcerative colitis may be classified into proctitis, proctosigmoiditis, or left-sided colitis, the term 'distal

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colitis' is a working classification which implies that the inflammation is amenable to topical treatment, by means of intrarectal drug administration. Thus, potential toxicity may be reduced by giving pharmacological therapy this way.

1.3 Grading of Disease Activity

Disease activity indices are prediction rules used to measure the activity of disease objectively in order not only to judge response in clinical trials, but also and especially to choose which drug to administer and its optimal dose regimen. However, the use of these indices in clinical practice is limited, since they are intended to make the clinical global assessment objective, a prerogative most clinicians do not agree with.

In ulcerative colitis, the activity of the disease is usually assessed primarily on the basis of clinical features. The Truelove and Witts classification[2] in mild, moderate or severe disease, based on the some clinical parameters and laboratory findings (number of bowel movements, fever, presence of tachycardia, anaemia, sedimentation rate) is the most widely used clinical activity index in gastroenterological practice. However, although clinically useful, these criteria do not allow sufficient discrimination for the purpose of clinical studies. Expansion of the clinical profile by Powell-Tuck et al.[3] has improved clinical trials but lacks correlation with sigmoidoscopic appearance. Sutherland et al.[4] have proposed a useful disease activity index for ulcerative colitis including a grading of clinical and endoscopic signs (table I). However, other clinical, endoscopical, and histological indices are available for grading disease activity in ulcerative colitis.

Table I. Ulcerative colitis disease activity index[4]

Stool frequency
0 = normal
1 = 1 to 2 stools daily > normal
2 = 3 to 4 stools daily > normal
3 = >4 stools daily > normal
Rectal bleeding
0 = None
1 = Streaks of blood
2 = Obvious blood
3 = Mostly blood
Mucosal appearance
0 = Normal
1 = Mild friability
2 = Moderate friability
3 = Exudation, spontaneous bleeding
Physician's rating of disease activity
1 = Normal
2 = Mild
3 = Moderate
4 = Severe
Maximum score = 13

1.4 Clinical Pattern of Inflammatory Bowel Disease

In 1963, Edwards and Truelove[5] characterised the course of ulcerative colitis. Despite the use of more modern medical therapies, the distribution of the clinical pattern shown is still accurate. After the first episode, most patients (approximately two thirds) subsequently experience recurrent attacks. A small minority, from 7 to 15%, never achieve satisfactory remission and continue with symptoms to a greater or lesser degree (corticosteroid-resistant patients), while others have corticosteroid-dependent disease.

These different forms of disease must be considered when choosing the best pharmacological treatment for ulcerative colitis patients using drugs having several mechanisms of action, toxicity profiles, and routes of administration.

1.5 Proven Efficacy of the Current Therapies

Based on the data available,[6] patients with mild to moderate distal ulcerative colitis may be treated with either oral 5-aminosalicylic acid, topical 5-aminosalicylic acid, or topical corticosteroids. Patients refractory to all of the above agents may require treatment with oral prednisone in doses up to 40 to 60 mg/day. For maintenance of remission, 5-aminosalicylic acid suppositories or enemas are effective, as well as oral 5-aminosalicylic acid or sulfasalazine, whereas topical cor-

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ticosteroids have not proven effective for maintaining remission in distal ulcerative colitis.

Patients with mild to moderate extensive ulcerative colitis should begin therapy with oral sulfasalazine or 5-aminosalicylic acid. Oral corticosteroids are generally useful for patients who are refractory to oral 5-aminosalicylic acid with or without topical therapy. Mercaptopurine or azathioprine are effective for patients who do not respond to oral prednisone but are not so acutely ill as to require intravenous therapy. In these patients, when the acute attack is controlled, a maintenance regimen is usually required. Sulfasalazine or 5-aminosalicylic acid are effective in reducing relapses. As a rule, patients should not be treated long term with corticosteroids. Azathioprine or mercaptopurine may be useful as corticosteroid-sparing agents for corticosteroid-dependent and corticosteroid-resistant patients, and for maintenance of remission not adequately sustained by 5-aminosalicylic acid.

Patients with severe ulcerative colitis refractory to maximal oral treatment with prednisone, oral salicylates, and topical medications, or patients who present with toxicity, should be treated for 7 to 10 days with intravenous corticosteroids. Failure to demonstrate significant improvement within 7 to 10 days is an indication for either colectomy or treatment with intravenous cyclosporin in specialised centres.

2. Drug Classes

2.1 Corticosteroids

2.1.1 Traditional Systemic and Topical Corticosteroids

After the first demonstration that corticosteroids have a beneficial effect on the course of ulcerative colitis in the late 1940s, subsequent uncontrolled and controlled studies with corticotropin (adrenocorticotrophic hormone; ACTH), cortisone, and hydrocortisone in the early 1950s and 1960s supported the previous clinical observations that these substances were extremely useful and relatively safe in the treatment of this inflammatory condition.

Synthetic glucocorticoids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and corticotropin are the most commonly used traditional corticosteroids in the treatment of ulcerative colitis.

2.1.2 Pharmacokinetics

Corticosteroids are in general rapidly and fairly completely absorbed from the gastrointestinal tract. When given orally, approximately 80% of prednisolone, 70% of methylprednisolone, and 50% of hydrocortisone is absorbed.[7] Prednisolone is the most commonly used oral corticosteroid in the treatment of ulcerative colitis. Peak plasma concentrations occur in 30 minutes to 2 hours. Albumin has a greater capacity for prednisolone binding than does transcortin, and hypoalbuminemia can result in higher free drug concentrations, increasing the potential for toxicity.[7,8] Methylprednisolone is conjugated and hydroxylated in the liver, which is responsible for about 70% of corticosteroid metabolism; the small remainder is excreted in the urine as either prednisone or prednisolone.[9] Parenteral formulations most commonly used are prednisolone, methylprednisolone, and hydrocortisone. The pharmacokinetic activity of these agents is similar to that of prednisolone, as described above. An alternative to these synthetic corticosteroids is corticotropin, which may be administered intramuscularly or intravenously. Corticotropin is absorbed rapidly from muscle and, with a plasma half-life of 15 minutes, is cleared rapidly from the circulation. Hydrocortisone remains the most frequently used topical corticosteroid preparation. Although hydrocortisone enemas have been reported to have little systemic absorption and therefore to have little risk of systemic adverse effects,[10] it has been demonstrated that the bioavailability of a retention enema of at least 8 hours' duration is almost similar to that of an equivalent oral dose, with 50% to 90% available to the systemic circulation.[11] Prolonged topical administration of hydrocortisone is associated with a significant risk of adrenal suppression and exogenous hyperadrenalism.

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2.1.3 Adverse Effects

Corticosteroids can be expected to impact on every organ system and most metabolic activities of the body.[12-19] The adverse effects of corticosteroids can be classified into short-term and long-term table II. Most of the adverse reactions are dependent on dose and duration of therapy, and are readily reversible with discontinuation of therapy.

Short-term therapy is usually well tolerated, and adverse effects include metabolic effects sodium and fluid retention, hypokalaemic alkalosis, hyperglycaemia, hyperlipidaemia, alterations of fat distribution (Cushingoid appearance), steatosis of the liver], hypertension, mood changes (including psychosis, depression and agitation), weakness in all extremities with associated wasting.[14,15]

Long-term adverse effects include skin changes (striae, purpura, ecchymosis, acne, thinning, hirsutism), glaucoma, cataracts, central obesity, musculoskeletal complications (osteonecrosis, osteopenia and osteoporosis). Suppression of the hypothalamic-pituitary-adrenal axis is common but reversible with conventional corticosteroids, but not common with newer topically acting corticosteroids (see section 2.2). Evaluation of the hypothalamic-pituitary-adrenal (HPA) axis with the ACTH stimulation test should be considered in patients receiving long-term corticosteroid therapy, in patients experiencing signs of adrenal insufficiency, or who have recently been on corticosteroids at times of increased stress.[12,16,17]

The potential for gastric mucosal injury is controversial. When combined with a nonsteroidal anti-inflammatory agent the risk of peptic ulcer disease is increased. However, corticosteroids by themselves probably do not increase the risk of peptic ulcer disease. Pancreatitis has also been reported to be associated with corticosteroid use. A serious complication of corticosteroids in children is increased retardation of growth. Glucocorticoids cause inhibition of linear growth and epiphyseal closure, particularly with long-term, high dosage therapy. However, accelerated bone growth occurs upon drug withdrawal, and growth failure can be minimised by alternate-day corticosteroid treatment.[12,18,19]

Table II. Adverse effects of corticosteroid therapy[12]

Short-/long-term	Long-term
Bodyweight gain	Skin changes
Fluid retention	Osteoporosis
Psychiatric disturbance	Cataracts
Hyperglycaemia	Growth retardation
Hypokalaemia	
Aseptic necrosis	
Myopathy	
Immune suppression	
Hypertension	

In a review[20] of many diseases which require corticosteroid therapy, the risk of infectious complications in patients receiving corticosteroids was 12.7% compared with 8.0% in controls. The risk was most marked in patients with neurological disorders as compared with patients with hepatic, intestinal and renal disorders. The risk of infection is low if the dosage of prednisone is less than 10mg daily or a cumulative dose of less than 700mg.

2.2 Newer Topical Corticosteroids

The frequent adverse effects associated with the use of corticosteroids have prompted the development of a new group of rectal and oral agents that may provide certain advantages over currently available corticosteroids by achieving equivalent or superior efficacy with a lower incidence and more benign adverse event profile. The absence of toxicity, and in particular the lack of suppression of the HPA axis by these newer topical agents is related to their low systemic bioavailability which can be achieved in three ways: (i) extensive first-pass metabolism in the blood by erythrocytes and in the liver; (ii) lack of rectal absorption; or (iii) both mechanisms. All these account for the low frequency of systemic effects of these agents. Moreover, these new drugs should have a high intrinsic glucocorticoid activity, high topical potency, and good metabolic stability in the bowel. Prednisolone metasulfobenzoate, tixocortol pivalate, fluticasone propionate, beclomethasone dipropionate and budesonide are all considered to fulfil

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these requirements but only the latter two are approved for the therapy of distal ulcerative colitis.[21-24]

2.2.1 Pharmacokinetics

Rectal and oral prednisolone metasulfobenzoate is a drug with lower absorption compared with prednisolone-21-phosphate. Prednisolone metasulfobenzoate has been shown to give higher rectal tissue levels than rapidly absorbed systemic corticosteroids in patients with ulcerative colitis. Beclomethasone 17, 21-dipropionate has little systemic glucocorticoid activity with oral or rectal administration despite having marked anti-inflammatory activity (500 times the anti-inflammatory potency compared with dexamethasone) on the skin and the efficacy of the enema form is similar to that of prednisolone. Budesonide, a nonhalogenated glucocorticoid, also undergoes rapid liver biotransformation, affording low systemic availability (approximately 15%) with oral or rectal administration. Budesonide is metabolised by cytochrome P450 (CYP) 3A enzymes in the human liver. Tixocortol pivalate exhibits topical anti-inflammatory activity similar to cortisol but does not induce a measurable systemic glucocorticoid effect when given orally or rectally.[21-24]

2.2.2 Adverse Effects

Although infrequent, the drug-related adverse effects include nausea, abdominal distension, fatigue, and perianal irritation. The long-term effects on bone metabolism are currently unknown.[21-24]

3. Aminosalicylates

3.1 Sulfasalazine

Sulfasalazine was developed by Nanna Svartz, of the Karolinska Institute, from an attempt in 1942 to combine the known anti-inflammatory properties of salicylates with the recently discovered antimicrobial qualities of sulfa drugs.[25] The sulfasalazine molecule consists of sulfapyridine attached by an azo bond to 5-aminosalicylic acid.[26] Svartz tested the new compound in rheumatoid arthritis and in ulcerative colitis, which was then thought to be possibly of an infectious origin. Her uncontrolled series of patients with active ulcerative colitis treated with sulfasalazine suggested great benefit from the drug. Since then, sulfasalazine has become a mainstay of medical therapy for inflammatory bowel disease.

3.1.1 Pharmacokinetics

After oral administration the unchanged drug is absorbed to only a limited extent, and about 90% of the original dose reaches the colon. The initial metabolism of sulfasalazine takes place in the distal small bowel and colon through the activity of a wide range of colonic bacteria. These bacteria have the ability to split the azo-bond as they possess an intracellular enzyme called azo-reductase which reduces and thus breaks the azo-bond.[27] Sulfasalazine is generally ineffective in the treatment of isolated ileitis, presumably because this relatively germ-free area lacks bacterial azoreductase.[28,29] Concurrent use of antibiotics affecting colonic flora can decrease sulfasalazine metabolism, as can shortened colonic transit time (e.g. diarrhoea, colectomy).[30]

The cleavage of the azo-bond then releases the two major metabolites 5-aminosalicylic acid and sulfapyridine. The hepatic metabolism of sulfasalazine consists of an N-acetylation and ring hydroxylation and a final conjugation with glucuronic acid.[26,31] Patients who are slow acetylators may be expected to show a higher than average serum concentration of sulfapyridine for a longer period of time after administration of sulfasalazine, when compared with patients who fall into the fast acetylator category. Sulfapyridine seems to be responsible for most of the adverse effects associated with sulfasalazine, although adverse reactions with 5-aminosalicylic acid therapy are increasingly being recognised. Therefore, if a patient does experience adverse effects he/she is more likely to be a slow acetylator than a fast acetylator. The acetylation of sulfapyridine and therefore its levels in serum depend on the genetic acetylator status of the patients: for the same dose, slow acetylators have higher serum levels and are more likely to reach toxic levels and have adverse effects than are fast acetylators. Acetylator genetic status is easily determined from a single serum measurement of

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free and acetylated sulfapyridine.[32] Acetylation of 5-aminosalicylic acid takes place in colonic epithelium, liver, and kidney and does not depend on acetylator status.[26,31,33] The combination of slow acetylator and slow hydroxylator status can result in sulfasalazine levels as much as twice normal.[26,34]

If given separately, 5-aminosalicylic acid and sulfasalazine are absorbed proximally, metabolised, and excreted in the urine, never reaching the distal small intestine or colon. It is the azo-bond, therefore, that allows for transport of sulfasalazine to the distal small intestine and colon without significant absorption.

Table III. Adverse effects of sulfasalazine and aminosalicylates

Adverse effects unique to sulfasalazine
Neurotoxicity
Male infertility
Haematological: haemolysis, folate malabsorption, Heinz body anaemia, methaemoglobinaemia, sulfhaemoglobinaemia, thrombocytopenia, atypical lymphocytosis with eosinophilia, neutropenia and agranulocytosis
Intolerant: headache, malaise, nausea, anorexia, vomiting, epigastric pain and dyspepsia
Adverse effects common to all aminosalicylates
General: fever, rash
Allergic reactions: skin eruptions, pancreatitis, pulmonitis, hepatotoxicity, drug-induced connective tissue disease
Gastrointestinal: exacerbation of colitis, watery diarrhoea
Other: pericarditis, nephritis

3.1.2 Adverse Effects

The incidence of adverse effects related to sulfasalazine use is high and is dose related, like its therapeutic effects. Up to 45% of patients report adverse effects with sulfasalazine.[35] The adverse effect profile of sulfasalazine include many which are unique to the compound and others which are common to all aminosalicylates (table III).

By far the vast majority of these effects are intolerance, not allergy, and relate to the sulfapyridine moiety correlating with the acetylator phenotype.[36] They include nausea, vomiting, dyspepsia, anorexia, and headache. Symptoms are usually noted soon after initiation of therapy and generally occur in patients who are taking more than 4g daily.

More severe reactions are uncommon and include generalised allergic response, various skin eruptions (urticaria, maculopapular lesions, epidermal necrolysis), pancreatitis (reversible, as with other drugs with a sulfa moiety, but also fatal in patients presenting with jaundice and abdominal pain), pulmonitis (but also tracheolaryngitis, bronchospasm, bronchiolitis obliterans with fibrosing alveolitis, reversible interstitial fibrosis, and syndrome of pulmonary infiltrates with eosinophilia), hepatotoxicity (transaminitis, cholestasis, and granulomatous hepatitis), drug-induced connective tissue disease (arthralgias, arthritis, and Raynaud's disease).[36,37]

Haematological adverse effects are uniformly related to the sulfapyridine moiety.[38-40] Also the finding of abnormal sperm counts, motility, and morphology that may contribute to reversible male infertility associated with sulfasalazine, have been attributed to sulfapyridine and inhibition of folate absorption from the diet. Sulfasalazine inhibits folate absorption by way of competitive inhibition of folate conjugase, which is normally essential for folate absorption at the jejunal brush border.[41,42] Sulfasalazine may cause diarrhoea, thought to be secondary to inhibition of the absorption of water from the small intestine by the 5-aminosalicylic acid moiety.[43] Exacerbation of ulcerative colitis secondary to sulfasalazine administration has also been reported, with worsening of symptoms recurring when sulfasalazine was readministered after cessation and initial improvement.[44-46]

To reduce dyspepsia, sulfasalazine therapy should be initiated slowly and given with meals. One regimen begins with 500mg on the first day, and increasing by 500mg each day until the desired therapeutic dose per day is reached. Minor allergic manifestations such as fever or rash can be overcome by discontinuation of the drug or by a process of gradual desensitisation-readministering one-eighth of a tablet daily, then doubling the dose every 3 days until the desired therapeutic dosage is achieved. Patients who have experienced severe

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hypersensitivity reactions such as anaphylaxis or agranulocytosis should not be re-challenged with sulfasalazine.[36]

Finally, because the sulfapyridine moiety binds albumin, sulfasalazine may have a potential for displacing protein-bound medications such as oral hypoglycaemics and warfarin, although this has not been studied in depth.[47]

3.2 5-Aminosalicylic Acid

The demonstration by Azad Khan et al.[48] in 1977 that 5-aminosalicylic acid is the active therapeutic moiety of sulfasalazine and acts topically on colonic mucosa, led to the development of new oral 5-aminosalicylic acid formulations which do not contain the sulfa component (table IV). In some of these sulfapyridine has simply been replaced by another carrier and linked to the 5-aminosalicylic acid molecule by a nitrogen bridge: (i) another 5-aminosalicylic acid in olsalazine; and (ii) 4-aminobenzoylglicine and 4-amino-benzoyl-β-alanine, linked respectively in ipsalazine and balsalazine. As in the case of sulfasalazine, however, 5-aminosalicylic acid is released into the colon by these formulations only after bacterial splitting of the nitrogen bond. To obviate the need for bacterial splitting, other formulations have been developed in which 5-aminosalicylic acid is not linked to another carrier. In these gastrointestinal formulations, 5-aminosalicylic acid is coated either with a semipermeable ethyl cellulose membrane (Pentasa®)[1] releasing the drug throughout the intestine in a time-and-pH-dependent manner, or, as in the case of mesalazine, with a pH-sensitive acrylic resin (Eudragit S® in Asacol®, EudragitL® in Salofalk® or Claversal®), which retards release of the active molecule, especially in the colon, at a pH greater than 6. Moreover, the fact that 5-aminosalicylic acid is only partially absorbed on rectal administration, has promoted the development of several topical formulations of 5-aminosalicylic acid, now available as enemas, foam and suppositories.

Table IV. Oral and topical formulations of 5-aminosalicylic acid

Formulation	Target
Azo-bond formulations	
Olsalazine	Colon
Ipsalazine	Colon
Balsalazine	Colon
Mesalazine formulations	
Salofalk®	Ileum, colon
Claversal®	Ileum, colon
Asacol®	Distal ileum, colon
Pentasa®	Small bowel, colon

3.2.1 Pharmacokinetics

As previously outlined, the azo bond of sulfasalazine is cleaved by bacteria of the distal small intestine and colon, freeing 5-aminosalicylic acid and sulfapyridine, and 5-aminosalicylic acid is subsequently poorly absorbed. 5-Aminosalicylic acid is only partially absorbed on rectal administration.[49,50]

Although 5-aminosalicylic acid is poorly absorbed in the distal small bowel and colon after it is cleaved from sulfasalazine by bacterial azoreductase, sulfapyridine is quickly absorbed and has been implicated in much of the systemic toxicity associated with sulfasalazine therapy. To avoid sulfapyridine-related toxicity, alternative mechanisms have been developed for delivery of 5-aminosalicylic acid, which is only partially absorbed on rectal administration, such as 5-aminosalicylic acid enemas, foams, gel, and suppositories. Oral delayed-release systems and carrier molecules have also been used to mimic the distal delivery of 5-aminosalicylic acid that occurs with sulfasalazine.

3.2.2 Adverse Effects

Tolerance of 5-aminosalicylic acid by 80 to 90% of those patients allergic to, or intolerant of, sulfasalazine has given further credence to evidence suggesting that the sulfa moiety is responsible for much of the toxicity of sulfasalazine. However, 10 to 20% of patients who are sulfasalazine intolerant have similar reactions to other 5-aminosalicylic acid formulations, indicating that the 5-aminosalicylic acid moiety is responsible for

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adverse events in some patients taking sulfasalazine. Caution should therefore be used in administering 5-aminosalicylic acid to patients who have had severe reactions to sulfasalazine.[37] Both topical and oral forms have been associated with pneumonitis, pericarditis, myocarditis, a Kawasaki-like syndrome, pancreatitis, and paradoxical exacerbation of colitis.[51-56] Serious but less well substantiated effects include possible hearing impairment and nephrotoxicity.[57,58] Cross-reactivity in those allergic to aspirin (acetylsalicylic acid) may also be seen. As a potentiator of ileal chloride secretion, olsalazine has been implicated in causing often intolerable watery diarrhoea, particularly in patients already with extensive colitis.[59] The most common complication associated with topical preparations is anal irritation, which in some cases may be secondary to the sulphite preservative included in the preparation.

4. Immunomodulators

Before 1990, immune modifier therapy in patients with inflammatory bowel disease (IBD) was limited to a few centres, and its use in this setting was a subject of great controversy. Over the last 10 years, the knowledge base has grown significantly with regard to immunomodulatory treatment of IBD, resulting in a degree of consensus as well as new areas of debate. There are four immune modifying agents for which adequate data from controlled clinical trials exist to draw some conclusions about treatment of IBD: azathioprine, mercaptopurine, cyclosporin, and methotrexate. As far as ulcerative colitis is concerned, only azathioprine/mercaptopurine and cyclosporin have an effective therapeutic role.

4.1 Azathioprine/Mercaptopurine

Since their first use in the 1960s, azathioprine and mercaptopurine are the most common immunosuppressive agents used in the treatment of ulcerative colitis. Several open and controlled clinical trials have suggested their efficacy in patients suffering from corticosteroid-dependent and corticosteroid-resistant ulcerative colitis.[60-65]

4.1.1 Pharmacokinetics

Azathioprine is a pro-drug that is quickly converted to mercaptopurine via a nonenzymatic nucleophilic attack by sulfhydryl-containing compounds, such as glutathione present in erythrocytes and other tissues.[66] Three enzyme systems then compete to metabolise mercaptopurine: xanthine oxidase and thiopurine methyltransferase (TPMT), which break down mercaptopurine to inactive metabolites, and hypoxanthine phosphoribosyl transferase, followed by several other enzymes [hypoxanthine phosphoribosyl transferase (HPRT), inosine monophosphate dehydrogenase and guanosine monophosphate synthetase] that convert mercaptopurine to inactive metabolites, and 6-thioguanine nucleotides (6-TGNs).[67] Mercaptopurine can also be converted to 6-methylthionosine 5′-monophosphate by competing pathways acetylised by both TPMT and HPRT (figure 1). The active 6-TGNs then act as purine antagonists to inhibit synthesis of protein, RNA, and DNA, thereby inhibiting cell growth. An apparent genetic polymorphism has been observed in the TPMT activity.[68,69] This enzymatic activity is virtually absent in 0.3% of the population heterozygously low in 11%, and normal in 89%.[70] This genetic variation has potential implication on individual response to therapy and development of toxicity (see section 4.1.2).

The half-lives of azathioprine and mercaptopurine in plasma are very short, ranging from 1 to 2 hours. In contrast, the half-life of the thioguanine nucleotides in erythrocytes is prolonged (3 to 13 days), and the time required to reach the steady state may help explain the clinical observation that prolonged treatment (3 to 4 months) with azathioprine and mercaptopurine for IBD is required before there is a therapeutic response. Both azathioprine and mercaptopurine have poor oral bioavailability: 50 and 16%, respectively. It is important to note that azathioprine is 55% mercaptopurine by molecular weight and that 88% of azathioprine is converted to mercaptopurine. Thus, a conversion factor of 2.07 should be used to convert a dose of mercaptopurine to azathioprine.[60,61]

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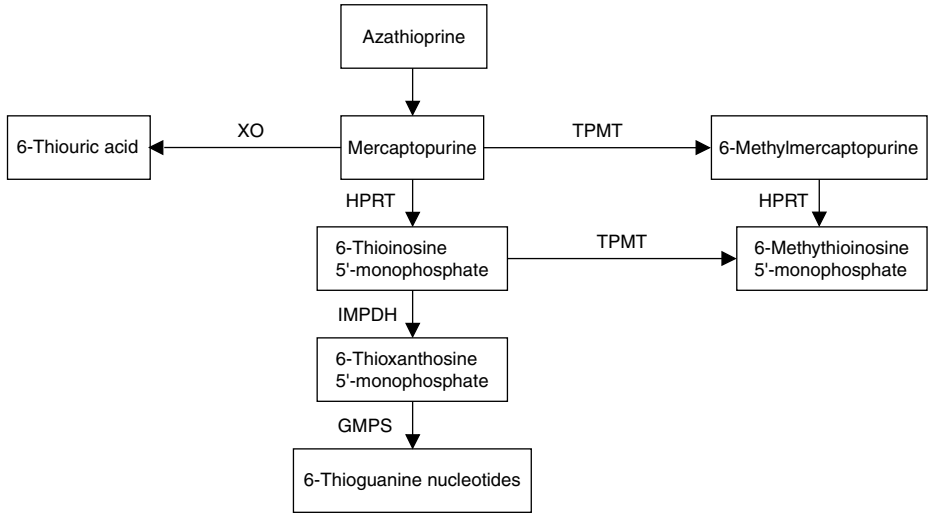

Fig. 1. Metabolism of azathioprine and mercaptopurine. **GMPS** = guanosine monophosphate synthetase; **HPRT** = hypoxanthine phosphoribosyl transferase; **IMPDH** = inosine monophosphate dehydrogenase; **TPMT** = thiopurine methyltransferase; **XO** = xanthine oxidase.

4.1.2 Adverse Effects

Adverse effects resulting from treatment with azathioprine and mercaptopurine can be divided into two categories: allergic-type reactions that appear to be dose-independent, and nonallergic-type reactions that are probably dose- and metabolism-dependent (table V). One large study in 1985, by Present at al,[71] reported the following frequency of adverse effects during treatment of IBD with mercaptopurine: overall risk of an adverse effect (15%); pancreatitis (3%); bone marrow depression (2%); infection (7%); hepatitis (0.3%); and miscellaneous allergic reactions (2%).

The major concern on the short-term adverse effects of azathioprine/mercaptopurine is bone marrow suppression.[61,62,71] This effect is dose-related and is managed with dose reduction or withdrawal of the drug. Leucopenia is the most common presentation of this haematological effect. Routine monitoring of blood count is recommended. The utility of monitoring the level of erythrocyte 6-TGNs to reduce this dose-dependent toxicity in patients with ulcerative colitis has not been adequately evaluated, and is currently being investigated.

The greatest fear against use of azathioprine/mercaptopurine is probably the long-term potential for developing neoplasia, particularly lymphoma. These agents have been associated with an increased risk of non-Hodgkin's lymphoma in patients with rheumatoid arthritis and patients undergoing solid organ transplantation.[72,73] A study by Greenstein et al.[74] addressing the risk of extra-intestinal malignancy among patients with IBD reported an association between IBD and lymphoma. Among the 1961 patients with a 10-year mean du-

Table V. Adverse effects of the purine analogues azathioprine and mercaptopurine

Allergic-type reactions	Nonallergic-type reactions
Pancreatitis	Leucopenia
Fever	Thrombocytopenia
Rash	Infection
Arthralgias	Hepatitis
Malaise	Malignancy
Nausea	
Diarrhoea	
Abdominal pain	

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ration of disease seen at a tertiary centre, 54 extra-intestinal malignancies were diagnosed. Although there was no overall increased incidence of extra-intestinal malignancies, two groups of malignancy were associated with increased risk, reticuloendothelial cancers and squamous cell cancer of the perianal and vaginal region. When the ulcerative colitis and Crohn's disease patients were pooled together, the calculated standardised incidence ratios for non-Hodgkin's lymphoma and Hodgkin's disease were 6.12 and 3.41, respectively. The incidence of leukaemia in ulcerative colitis patients was significantly increased to 8.7 times the expected incidence. Two recent studies study also identified an increased risk of non-Hodgkin's lymphoma and Hodgkin's disease among ulcerative colitis patients.[75,76] In contrast to these reports, Connell et al.,[77] over a 20 year period, determined that patients with IBD treated with azathioprine/mercaptopurine had no increased risk of cancer. This has been further supported by Korelitz et al.[78]

Combining studies of nearly 1000 patients, the overall incidence of adverse events reported was 15%, and 10% of patients experienced significant adverse events requiring withdrawal from the studies.[63]

Because the parent drugs and their metabolites are excreted in the urine, all dose-related toxicities may be potentiated by renal failure. Inhibitors of xanthine oxidase, such as allopurinol, may interfere with the oxidation of either azathioprine or mercaptopurine and thereby increase plasma levels and potentiate further toxicity. One potential drug interaction that is of particular importance in the treatment of ulcerative colitis is the drug interaction between azathioprine/mercaptopurine and 5-aminosalicylic acid. *In vitro* studies have shown that compounds containing 5-aminosalicylic acid noncompetitively inhibit recombinant human TPMT activity.[79,80] In this context, one case report has been published in which a patient with refractory Crohn's disease treated with both mercaptopurine and olsalazine developed two episodes of bone marrow suppression.[79] The first episode required reduction of mercaptopurine and the second led to withdrawal of both mercaptopurine and olsalazine. Whether this potential mechanism for interaction of these agents with 5-aminosalicylic acid compounds translates to a clinically significant drug-drug interaction has yet to be clarified.

4.2 Cyclosporin

Cyclosporin has revolutionised the field of transplantation and has a recognised mode of action, selectively inhibiting T-cell function by interfering with the transcription of interleukin-2 and its receptor.[81] Because of the toxicity of the compound and profound level of immune suppression, cyclosporin was first tested in an uncontrolled manner in the treatment of patients with IBD, providing encouraging results, especially in the treatment of chronically active Crohn's disease. However, the results of controlled studies, have limited its use to only some clinical situations including its use in ulcerative colitis.

4.2.1 Pharmacokinetics

The absorption and pharmacokinetics of cyclosporin are not completely understood. Maximum absorption of cyclosporin after an oral liquid dose occurs at 4 hours, and bioavailability is variable, ranging from 12 to 35.[82] The bioavailability of oral gelatine cyclosporin capsules is equivalent to the oral liquid cyclosporin solution. Cyclosporin is also dependent on the presence of bile, and biliary diversion results in drug malabsorption. The absorption of cyclosporin from the new microemulsion formulation is not dependent on the presence of bile. In comparison to standard preparations, the bioavailability of this cyclosporin form is increased significantly (145 to 239% increase).[83] Once absorbed, cyclosporin is metabolised in the liver by the CYP system, and excreted primarily in the bile.[82]

4.2.2 Adverse Effects

Adverse effects resulting from high dose cyclosporin therapy for IBD include: renal insufficiency (6%); hypertension (11%); opportunistic infections (3%); seizures (1%); paresthesias (26%); tremor (7%); headache (5%); gingival hyperplasia (2%); hypertrichosis (13%); and anaphylaxis with

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intravenous cyclosporin (0.3%).[60-81,83,84] In contrast, the incidence of adverse events was relatively low when low dose oral cyclosporin was used. The biggest issue that prevents the long-term (and perhaps short-term) use of cyclosporin at doses >5 mg/kg/day for IBD is the potential for permanent renal damage. All patients undergoing long-term cyclosporin treatment for autoimmune diseases, including patients with IBD will have a 20% reduction in the glomerular filtration rate.[60-81,83,84] The other two areas for concern for patients with IBD treated with high dose cyclosporin are infection and malignancy. A small number of severe opportunistic infections have been reported in patients with IBD treated with cyclosporin and corticosteroids, including *Pneumocystis carinii* pneumonia, a carotid artery mycotic aneurysm, herpetic oesophagitis, and invasive aspergillosis.[60,84] Cyclosporin treatment of other autoimmune diseases has been found to cause a slight increase in the incidence of malignant lymphoma to approximately 0.3%, although to date, lymphoma has not been reported in patients with IBD treated with cyclosporin.

There have been many descriptions of effects of other drugs on the disposition of cyclosporin, but only a few of these interactions appear to be clinically relevant.[60,84] Accelerated clearance of cyclosporin has been demonstrated in patients receiving phenytoin, phenobarbital (phenobarbitone), cotrimoxazole (trimethoprim-sulfamethoxazole), and rifampicin (rifampin), presumably as a result of induction of hepatic CYP systems. Decreased clearance of cyclosporin has been associated with concurrent administration of aminoglycoside antibiotics, erythromycin, ketoconazole, or amphotericin B; this engenders a higher risk of toxicity from cyclosporin if its concentration in blood is not carefully monitored.

5. Effects of Medical Therapy for Ulcerative Colitis on Pregnancy

Commonly, the pregnant patient with ulcerative colitis is advised by her obstetrician to discontinue sulfasalazine, 5-aminosalicylic acid, corticosteroids and other drugs, for the safety of patient and fetus. As almost all patients with ulcerative colitis are taking medical therapy, this drug issue is a frequent and important problem.[85,86]

Sulfasalazine and corticosteroids have been used consistently throughout pregnancy without causing harm to the fetus or new-born baby. In one large series,[87] sulfasalazine and conventional corticosteroids did not alter the rate of spontaneous abortion, prematurity, or fetal weight. The incidence of fetal complications was lower than in the general population. Although a later report suggested that fetal complications may be higher in a medically treated group, this is more likely to be caused by disease activity and not the effects of drug therapy alone.

Few data are available concerning the safety of the several 5-aminosalicylic acid formulations during pregnancy and lactation, suggesting that oral and topical 5-aminosalicylic acid do not cause harm to mother and fetus.[88-93] However, a recent French national survey, showed one case of renal disease in a neonate, and three neonates with congenital malformations (congenital cataract, thumb malformation, cardiac malformation) related to 5-aminosalicylic acid exposure *in utero*.[94] A subsequent letter from the manufacturers reported the absence of nephrotoxicity in 60 women treated with Pentasa® during pregnancy.[95]

Azathioprine and mercaptopurine have been associated with teratogeny and chromosomal abnormalities, abortion, and low birth weight in different animal species. Furthermore, azathioprine crosses the placenta in humans. A preliminary retrospective study of azathioprine during the course of 16 pregnancies in 14 women with IBD by Alstead et al.,[96] from England, demonstrated no congenital abnormalities. Seven women continued the drug throughout pregnancy without complications. All the offspring were well during a follow-up period of 6 months to 16 years. Similar results were observed in another study with mercaptopurine.[97] Because of nephrotoxicity, hepatic toxicity, hypertension, and the long-term risk of neoplasm, cyclosporin cannot be used during pregnancy. However, limited data suggest that cyclosporin is safe in the

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treatment of pregnant patients with IBD,[98] but its use should be reserved for those with severe refractory ulcerative colitis.

6. Comparative Evaluation of the Safety of Drugs Currently Used in the Treatment of Ulcerative Colitis

Determination of adverse events associated with any medication is difficult. Well designed, randomised, placebo-controlled trials usually have the power to differentiate frequent adverse events, which occur by chance alone, from true medication-related events. Many reports of adverse events in therapeutic interventions in ulcerative colitis, however, are not drawn from placebo-controlled or randomised trials. Furthermore, considering that only a small proportion of the total population affected is enrolled in clinical trials, a selection bias may limit the evaluation of the tolerability of therapy. Finally, the short duration of most clinical trials will miss adverse events that may occur during the long-term therapy of ulcerative colitis. In the following section of this paper, the tolerability of the drugs most commonly used in the treatment of ulcerative colitis will be compared, by reviewing the most significant literature.

6.1 Traditional Systemic and Rectal Corticosteroids

It was first suggested in the late 1940s that corticosteroids have a beneficial effect on the course of ulcerative colitis.[7] Subsequent uncontrolled and controlled studies with corticotropin, cortisone, and hydrocortisone in the 1950s and 1960s, confirmed that these drugs are effective in inducing remission of disease activity,[2,7] but not in the maintaining remission.[99,100] In these and other historical studies, the serious adverse effects associated with prolonged corticosteroid use became increasingly apparent, especially, in comparison to their lack of effectiveness in the treatment of ulcerative colitis in remission.

Several dosages and different corticosteroids with various modalities of daily administration (single or fractioned daily doses), were compared.

In order to optimise the prednisone dose in the treatment of mild to moderate ulcerative colitis, Baron et al.[101] examined the efficacy of several doses of the drug. Both the 40 and 60mg doses were effective in achieving remission than the 20mg dose. As expected, there were more frequent adverse effects with the 60mg dose than with the lower doses. In two consecutive trials of out-patient treatment for mild cases of active ulcerative colitis, Lennard-Jones et al.[102] compared the efficacy of oral prednisone, sulfasalazine, and topical hydrocortisone in comparison with placebo. He found that prednisone gave significantly better results than placebo, and that sulfasalazine gave final results approaching those of prednisone. On the contrary, topical hydrocortisone gave disappointing results. However, the incidence of adverse events was higher in patients treated with sulfasalazine in comparison with those receiving therapy with prednisone, topical hydrocortisone and placebo. Powell-Tuck et al.[103] compared once-daily prednisolone doses with four-times-a-day doses of the same drug (same total daily dose) in mild to moderate disease of variable extent. There was no difference in clinical or sigmoidoscopic response or in adverse effects between the two regimens in the 2 week trial, although once-daily corticosteroid administration could cause less adrenal suppression than divided doses.

Rectal corticosteroid preparations have been the main treatment for attacks of mild to moderate distal ulcerative colitis since the 1950s, when Truelove et al.[104] performed a controlled trial of a rectal drip of hydrocortisone hemisuccinate 100 mg/day versus placebo for 1 week in ulcerative colitis of varying severity. Short-term therapy is not associated with clinical evidence of systemic effects or significant impairment of the response to ACTH stimulation. Occasionally systemic effects develop, such as fluid retention, mooning of the face or acne, but these usually occur only in patients receiving long-term treatment.[23,24] Although absorption of corticosteroids after topical administration is less than after oral administration, prolonged treatment with corticosteroid enemas may also produce adrenal suppression.[105] Several ga-

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lenic formulations of rectal corticosteroids have been developed: liquid enemas, foam enemas, and suppositories. A 100ml liquid enema often reaches the splenic flexure, foam enemas only occasionally reach as far as the descending colon, while corticosteroids released from suppositories remain in the rectum.[23,24] Thus, for disease affecting the rectum and sigmoid, a foam enema is preferred. For proctitis alone, suppository administration may be sufficient, while a liquid enema can be more effective for more extensive colitis, up to the splenic flexure. However, patients tend to dislike inserting medication through the anus and many, especially those with a poorly distensible rectum, have problems in retaining liquid enemas, particularly in the daytime. The foam enema is retained more easily, is more portable, and often preferred by patients.[106] In a study measuring the quality of life in ulcerative colitis, hydrocortisone foam enemas caused significantly less disturbance to work, outdoor and occupational activities and sexual relationships than prednisolone liquid enemas.[107]

6.2 Newer Topical Corticosteroids

The main advantage of topically acting over traditional corticosteroids, especially budesonide, is the lack of systemic effect as well as of adrenal gland suppression. This is particularly useful for patients suffering from refractory distal ulcerative colitis or frequently relapsing disease, who need long-term or high-dose therapy. Marshall and Irvine,[108] from Canada, performed a meta-analysis of all reported randomised controlled trials with old and new rectal corticosteroid versus alternative treatments (topical 5-aminosalicylic acid and 4-aminosalicylic acid or placebo), with the aim of critically examining the therapeutic efficacy, safety, and cost comparison of these agents in the treatment of active distal ulcerative colitis. Of the 83 trials retrieved, 33 met inclusion criteria. Rectal budesonide was clearly superior to placebo, and of comparable efficacy to conventional corticosteroids. In one out of two trials comparing rectal budesonide with rectal 5-aminosalicylic acid, 5-aminosalicylic acid exceeded budesonide in achieving symptomatic remission. Adverse effects of treatment were inconsistently reported in the accepted trials. Nine of the 33 trials made no reference whatsoever to adverse effects, whereas a further 11 trials reported no drug-related adverse effects in any treatment arm. Among the remaining 13 trials, seven patients discontinued therapy for drug related effects: four with 5-aminosalicylic acid, one taking conventional corticosteroids, one taking budesonide, and one taking 4-aminosalicylic acid. Other related adverse effects such as nausea, abdominal distension, fatigue, and perianal irritation were infrequent. Overall, 10 trials reported HPA axis function before and after treatment. Three of these compared rectal budesonide with conventional rectal corticosteroids, noting mean cortisol concentrations after 4 weeks of treatment.[109-111] Cortisol concentrations were consistently higher, indicating less suppression, in the budesonide group than in the group receiving conventional corticosteroids (figure 2). The weighted mean difference between pooled treatment arms was 119.1 mmol/L, confirming that this difference was statistically significant. Finally, the cost comparisons of rectal preparations showed 5-aminosalicylic acid to be less expensive than corticosteroids, with budesonide enemas marginally more

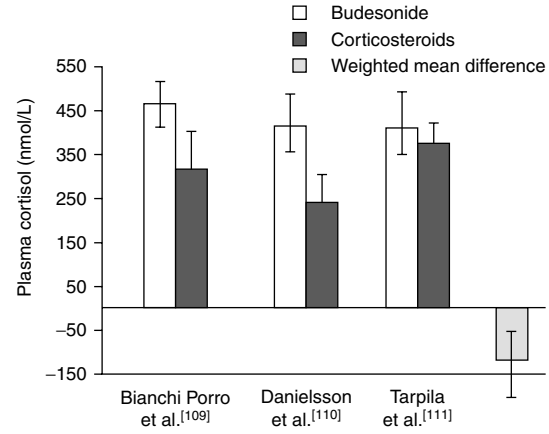

Fig. 2. Plasma cortisol concentrations and weighted mean difference after 4 weeks of treatment, when conventional corticosteroids are compared with rectal budesonide (from Marshall and Irvine[108] Gut 1997; 40: 775-781, with permission from the BMJ Publishing Group).

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expensive than hydrocortisone liquid enema, and hydrocortisone foam costs slightly less.

6.3 Aminosalicylates

6.3.1 Oral 5-Aminosalicylic Acid and Sulfasalazine

Two very recent meta-analyses compared the efficacy and safety of 5-aminosalicylic acid with that of sulfasalazine and placebo, in inducing and maintaining remission of ulcerative colitis. Three different outcome measures were used to evaluate the safety and clinical utility of 5-aminosalicylic acid relative to sulfasalazine and placebo: (i) the number of patients with adverse events; (ii) the number of patients withdrawing due to adverse events; and (iii) the total number of patients excluded or withdrawn before completion of the study. Since many studies only reported the total number of adverse events rather than the number of patients who experienced an event, the authors were often unable to include such data in the analysis.

In the first,[112] the efficacy, dose-responsiveness and safety of 5-aminosalicylic acid was compared to sulfasalazine or placebo for the induction of remission in active ulcerative colitis. In 5-aminosalicylic acid versus placebo studies, the total proportion of patients excluded or withdrawn from 5-aminosalicylic acid treatment was significantly lower than that of patients who were withdrawn or excluded from the placebo groups; pooled odd ratio (OR) 0.59 [95% confidence interval (CI) 0.45 to 0.77] (figure 3). However, when five olsalazine studies were pooled, 8.8% of patients receiving olsalazine and 3.3% receiving placebo were withdrawn due to adverse events; pooled OR 2.53 (95% CI 1.23 to 5.22). In 5-aminosalicylic acid versus sulfasalazine studies, there were significantly more withdrawals due to adverse events with sulfasalazine than 5-aminosalicylic acid. In particular, olsalazine caused a significantly higher proportion of withdrawals due to adverse events relative to placebo, but lower than the proportion caused by sulfasalazine. The most common adverse effect attributed to olsalazine was diarrhoea.

In the second meta-analysis,[113] the efficacy, dose-responsiveness and safety of 5-aminosalicylic acid was compared with sulfasalazine or placebo for maintaining remission in ulcerative colitis. 5-Aminosalicylic acid and sulfasalazine had similar adverse event profiles, with an OR of 1.16

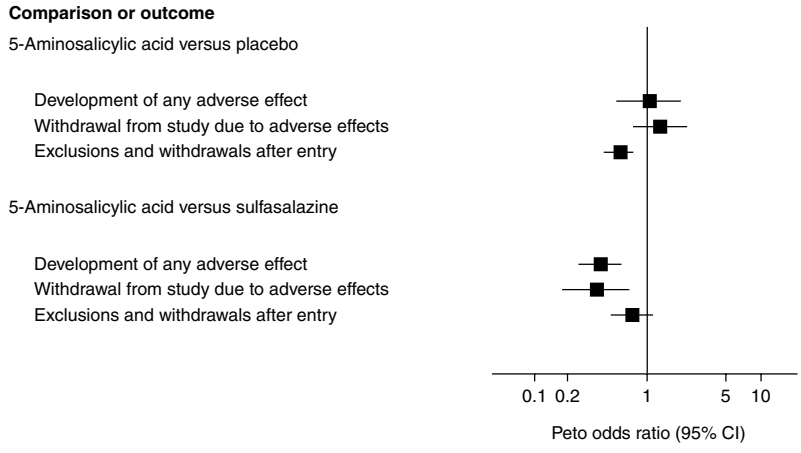

Fig. 3. Meta-analytic evaluation of safety 5-aminosalicylic acid for inducing remission of active ulcerative colitis: a comparison versus sulfasalazine and placebo. The total proportion of patients excluded or withdrawn from 5-aminosalicylic acid treatment was significantly lower than that of patients who were withdrawn or excluded from the placebo and sulfasalazine groups (reproduced from Sutherland et al.,[112] with permission). **CI** = confidence interval.

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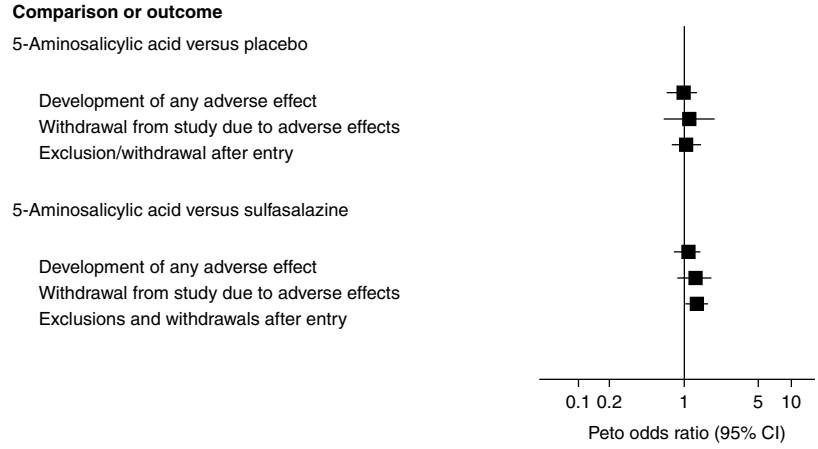

Fig. 4. Meta-analytic evaluation of safety 5-aminosalicylic acid for maintaining remission of ulcerative colitis: a comparison versus sulfasalazine and placebo. All the three treatment groups showed a similar adverse event profiles (reproduced from Sutherland et al.,[113] with permission). **CI** = confidence interval.

(95% CI 0.62 to 2.16) and 1.31 (95% CI 0.86 to 1.99), respectively, for any adverse effect (figure 4).

6.3.2 Rectal 5-Aminosalicylic Acid

Although minor adverse event rates are inconsistently reported in clinical trials, three published prospective comparisons of oral versus rectal 5-aminosalicylic acid have confirmed the reduced toxicity of rectal therapy.[114] Kam et al.[115] compared 5-aminosalicylic acid enemas with oral sulfasalazine and reported adverse events in 83% of sulfasalazine-treated patients versus 42% of those receiving enemas. Similarly, Safdi et al.,[116] reported adverse events in 41% of patients treated with oral 5-aminosalicylic acid versus 17% of those receiving 5-aminosalicylic acid enemas. Finally, Gionchetti et al.[117] reported minor adverse effects in none of the 29 patients receiving suppositories, but in 6 of 29 randomised to oral tablets.

Two published meta-analyses of rectal therapy for distal ulcerative colitis have also reported a low incidence of adverse events associated with rectal therapy after a systematic review of published trials.[108,118] Most of the trials pooled for these analyses reported no adverse effects in the rectal 5-aminosalicylic acid arm, and/or no significant difference from placebo.

Because rectally administered 5-aminosalicylic acid is poorly absorbed and there are infrequent adverse events attributable to drug therapy, those that are reported are more likely to reflect the discomfort and inconvenience of drug instillation. For example, a prospective comparison of 5-aminosalicylic acid foam and gel enemas found the most common complaints attributable to drug administration, and difficulty in retaining the 5-aminosalicylic acid. These complaints were all less common with the gel preparation.[119]

In an effort to increase the benefits of 5-aminosalicylic acid rectal therapy, improving either the delivery of a high amount of the drug to the distal diseased colonic tract, or quality of life and patient acceptance, several galenic formulations of rectal 5-aminosalicylic acid are available in clinical practice for patients with distal ulcerative colitis. Thus, some clinical trials of rectal therapy have assessed relative patient tolerance and preference as an important criterion for selection of the optimal delivery system.[120-123]

6.4 Azathioprine/Mercaptopurine

A comparative evaluation of tolerability of azathioprine/mercaptopurine for patients with ulcerative colitis is very difficult.

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In the first five controlled trials comparing azathioprine/mercaptopurine with placebo or sulfasalazine,[124-128] adverse events were inconsistently reported. However, when reported, the adverse effects due to azathioprine/mercaptopurine were few and not dangerous. Recently, we conducted an investigator-blind study comparing azathioprine, at the dose of 2 mg/kg/day, with oral 5-aminosalicylic acid 3.2 g/day, in the treatment of corticosteroid-dependent ulcerative colitis.[65] As shown in table VI, more patients treated with azathioprine had adverse effects (azathioprine *vs* 5-aminosalicylic acid, $p < 0.5$). However, some of these were transient or reversible, warranting only a reduction of the drug dose.

As mentioned before, the genotype and TPMT-activity have an important impact on the rate of adverse effects during azathioprine or mercaptopurine therapy.[129] Patients with low or intermediate TPMT enzyme activity shunt mercaptopurine away from the 6-methylmercaptopurine metabolite and towards the 6-TGNs. Excess concentration of 6-thioguanine nucleotides have been associated with leukopenia. Thus, a baseline determination of thiopurine methyltransferase activity (phenotype) or genotype could be clinically useful to 'customise' the drug dose with the goal of reducing the frequency of leucopenia. Patients with normal TPMT activity may receive standard doses of azathioprine (2 to 2.5 mg/kg/day) or mercaptopurine (1.0 to 1.5 mg/kg/day); patients with intermediate TPMP enzyme activity may have their dose of azathioprine or mercaptopurine reduced by 50%; finally, patients with low TPMP activity should not be treated with azathioprine or mercaptopurine, due to high mortality from leucopenia and sepsis.

In a very recent work[130] the measurement of 6-TGN levels was used in 82 adult patients with IBD receiving long-term (more than 3 months) antimetabolite therapy, was found helpful in optimising the dose of azathioprine to achieve an improved clinical response without inducing leucopenia.

Table VI. Frequency of adverse events in patients treated with azathioprine (AZA) and 5-aminosalicylic acid (5-ASA) for corticosteroid-dependent ulcerative colitis[65]

Adverse event	AZA (n = 27)	5-ASA (n = 25)	Measure
Leucopenia	4		Dose reduction
↑ ALT/AST	1		Dose reduction
Fever	2		
Epigastric pain	2		
Alopecia	1		
Dermatitis		1	
Total	**10/27***	**1/25**	

* $p < 0.05$.

6.5 Cyclosporin

As mentioned before, cyclosporin is indicated in the treatment of severe attacks of ulcerative colitis refractory to intravenous corticosteroid therapy. In this setting, the following comparisons were made: intravenous cyclosporin versus placebo; single-dose intravenous cyclosporin versus intravenous corticosteroid therapy;[131] and oral cyclosporin versus intravenous cyclosporin.[132] When compared with placebo,[133] significantly more patients treated with cyclosporin had adverse events, with paresthesias, hypertension, nausea and vomiting being the most frequent adverse effects. None of the patients had nephrotoxicity or hepatotoxicity, while one patient had a grand mal seizure after initiation of therapy. No statistically significant difference was found between cyclosporin 4 mg/kg/day and corticosteroid 40 mg/day for 8 days as single intravenous therapy with respect to frequency of adverse events, none of which were clinically significant. In particular, no patient had a seizure or a clinically significant decrease in renal function.[131] Similarly, no difference was found between oral and intravenously administered cyclosporin.[132] Finally, a comparison of the quality of life in patients with severe ulcerative colitis treated with intravenous cyclosporin or surgery was performed.[134] Patients with severe corticosteroid-refractory ulcerative colitis treated with cyclosporin scored as well as or better than their surgical counterparts.

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7. Conclusions

The most common drugs used in the treatment of ulcerative colitis (sulfasalazine, oral and topical 5-aminosalicylic acid, systemic and topical corticosteroid, and immunosuppressors), when used after accurate patient selection, are generally well tolerated. The choice of the drug formulation, its route of administration and optimal dosage depend on several factors such as an exact knowledge the specific goals of therapy, the extent of disease, and the grading of disease activity. Moreover, a thorough understanding of the indications and complications of drug therapy is essential. The search for an optimal benefit-risk ratio is always necessary to avoid additional morbidity and an excess of costs for the patient and the community. The broadening of the drug regimen available to the clinician has advanced with our knowledge of the disease, and further development of more effective, less toxic agents can be anticipated in the future.

Acknowledgements

The authors thank Mary Trotter for assistance in preparing the manuscript.

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