Regular Review

Drug management of ulcerative colitis

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Ulcerative colitis is a common disease affecting about 1 in 1000 of the population in the United Kingdom.¹ Recent therapeutic advances have improved our management of this condition, even though the aetiology remains unknown.

Effective treatment of ulcerative colitis depends on making a precise diagnosis and determining the extent and severity of the disease. Crohn's disease, enteric infections, irradiation, and ischaemic colitis should all be excluded. This review covers drug treatment but other factors such as nutrition, psychological factors, risk of cancer in those with longstanding disease, and surgical options all form part of the management.

Pharmacology

CORTICOSTEROIDS

The efficacy of corticosteroids in acute colitis is proved, but they should not be used for maintaining remission.^{2,4} They remain the standard by which other drugs are judged. Steroids modify almost every part of the inflammatory response, including cell mediated immunity and the production of inflammatory mediators such as prostaglandins,⁵ leukotrienes,^{5,6} platelet activating factor,⁷ and cytokines. Their biological effects last longer than their plasma half life.

The main side effects of short term treatment with oral corticosteroids are weight gain, changes in mood, acne, and less commonly hypertension or hyperglycaemia; but these problems can be minimised by reducing the dose quickly as an acute episode is brought under control. No patient should take steroids long term because of bone necrosis and osteoporosis and growth retardation in children.

Prednisolone or hydrocortisone in equivalent doses are equally effective at controlling symptoms; preparations such as corticotrophin offer no advantage and are no longer used. Prednisolone is the preferred treatment because it has a lower mineralocorticoid effect at the equipotent anti-inflammatory dose. The optimum initial dose of oral prednisolone is 40 to 60 mg per day⁸ in a single morning dose.⁹ Intravenous preparations of prednisolone are no longer available, but methylprednisolone 20 mg three times a day can be given; this is slightly higher than the equivalent dose of prednisolone (4 mg methylprednisolone equals 5 mg prednisolone).¹⁰

Steroids are also available as enemas, rectal foam, and suppositories. These act through a local effect on the mucosa. When considering enema preparations, prednisolone metasulphobenzoate is absorbed slightly less than prednisolone sodium phosphate,¹¹ although neither is absorbed to a great extent. The available preparations of prednisolone metasulphobenzoate foam and hydrocortisone foam have roughly equivalent

Practice points

- Corticosteroids work in acute colitis but should not be used to maintain remission
- 5-Aminosalicylic acid compounds prevent relapses and are effective in mild and moderate episodes of colitis
- Azathioprine is valuable in patients with severe disease

potency, but some patients find the disposable prednisolone foam applicator easier to use.

A recent approach to treatment is to use steroids that are poorly absorbed from the gastrointestinal tract and act on the mucosa or are absorbed but rapidly destroyed on first pass through the mucosa or liver. For example, budesonide, a new steroid that is not yet commercially available, is metabolised during its first pass through the liver, thereby reducing its serum half life and causing less adrenal suppression.¹² These steroids offer the prospect of similar therapeutic efficacy with decreased systemic side effects. Although they have been tried mainly in local preparations, oral preparations may also have a role.

5-AMINOSALICYLIC ACID COMPOUNDS

5-Aminosalicylic acid acts locally on the colonic mucosa. Because it is readily absorbed from the small bowel it must be linked to another compound or coated in resin to ensure it is released in the large bowel. This compound also acts at many points in the inflammatory process and has effects on neutrophil function, superoxide production, prostaglandin synthesis,¹³ cytokine production, permeability, and chemotaxis.¹⁴

When taken orally drugs containing 5-aminosalicylic acid are effective in controlling only mild to moderate episodes.¹⁵ Their great advantage, however, is in preventing relapse; these drugs can reduce the incidence of relapse from about 70% to about 20% in one year.¹⁶ The greater the dose the greater the prevention of recurrence, and this efficacy is maintained even after several years of treatment. When used in suppository¹⁷ or enema¹⁸ preparations for distal disease these compounds are equally effective as local steroids.

The longest established drug is sulphasalazine, which contains 5-aminosalicylic acid linked to sulphapyridine by an azo bond that is split by bacteria in the terminal ileum and colon. Sulphasalazine may cause headaches and nausea, but these are often dose related and can sometimes be overcome by using an enteric

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coated form. It should not be used in patients with an allergy to sulphur. Other side effects include skin rashes and reversible male infertility due to oligospermia.¹⁹ Many published reports exist supporting sulphasalazine's efficacy and it has the longest safety record; it is therefore still regarded by many as a first choice of treatment, although about 15% of patients do not tolerate it.²⁰

Other 5-aminosalicylate drugs do not contain a sulphur component, are equally effective as sulphasalazine,²¹ and are often better tolerated. Mesalazine is 5-aminosalicylic acid coated with the resin Eudragit-S, which dissolves at pH 7, the pH found in the terminal ileum and colon. It has few side effects, although there have been a few reports of nephrotoxicity²²; this may be related to the release and absorption of large amounts of unacetylated 5-aminosalicylic acid in the terminal ileum.

Mesalazine is also available in a slow release, resin coated formulation that is released throughout the small bowel. The slow release formulation may need to be given in higher doses than other formulations because only 60% of a given dose is available as free 5-aminosalicylate in the colon.²³

Olsalazine consists of two molecules of 5-aminosalicylic acid joined by an azo bond which is split by colonic bacteria. Because of its structure the effective dose of aminosalicylate delivered to the colon is higher than with other similar drugs.²³ It is associated with a higher incidence of diarrhoea,²⁴ possibly because of reduced small intestinal absorption of water, sodium, and chloride; increased secretion of bicarbonate; and increased fluid delivery to the colon.²⁵ Diarrhoea may be reduced if olsalazine is taken with meals and may resolve with time.

Balsalazide consists of a 5-aminosalicylic acid molecule bound to an inert carrier by an azo bond. It is better tolerated than sulphasalazine and equally effective but it is not yet commercially available.

Sulphasalazine 1 g twice a day is recommended for prevention of relapse. Although a dose of 1 g three times a day is slightly more effective,¹⁶ the side effects are more common and compliance is poorer. Olsalazine achieves high colonic concentrations and can be given in a dose of 0.5-1 g twice a day. Mesalazine

FIG 2—Acute active colitis extending distally from splenic flexure. An unprepared "instant" barium enema can be used to define proximal extent of active disease when patient presents for the first time if plain radiography does not provide this information. This patient was successfully managed with steroid retention enemas

should be given at a dose of 800 mg (two tablets) two to three times per day and slow release mesalazine at 500 mg (two tablets) three times per day. The cost of maintenance treatment varies with these drugs. The currently listed prices for one month's maintenance treatment are sulphasalazine 2 g/day, £8; mesalazine 1.6 g/day, £34; slow release mesalazine 1.5 g/day, £29; and olsalazine 1 g/day, £29.²⁶

STRONGER IMMUNOSUPPRESSANTS

The most widely used drug is azathioprine, which is metabolised to 6-mercaptopurine. As shown by a study published in this week's journal (p 20)²⁷ this drug is valuable in patients who have frequent relapses despite taking an aminosalicylate,²⁷ as well as in patients with chronic active disease which flares up when steroids are reduced.^{28, 29} A recent placebo controlled, withdrawal study of patients who were well established on azathioprine showed its effectiveness in maintaining remission.²⁷

Little information is available about the mode of action of azathioprine in inflammatory bowel disease. The drug has an effect on lymphoid cell populations,^{30, 31} and some of these changes are slow to occur, paralleling the long duration of treatment required to produce a clinical effect.

Azathioprine should be given at a dose of 2 mg/kg/day and several months of treatment are required for the drug to have its maximum effect. About 6% of patients cannot tolerate the drug because of nausea, a flu-like syndrome, drug fever, or pancreatitis.³² To avoid leucopenia a blood count should be done every two weeks initially and thereafter monthly.³³ Falls in the white cell count reverse on stopping the drug. A significant increase in malignancy has been reported in patients with renal transplants taking this drug. However, in ulcerative colitis the dose used, the use of associated immunosuppressive drugs, and the changes in the immune system are different from those in transplant recipients and malignancy does not seem to be increased.³⁴

Azathioprine can be started on its own, as a course of

FIG 1—Flow chart of drug management of ulcerative colitis

steroids is being reduced after an acute attack, or as steroids are slowly withdrawn in a patient who has been taking them long term. Methotrexate may also be effective in patients who require strong immunosuppression,³⁵ but there are insufficient data to appraise its effectiveness.

Treatment

Figure 1 shows an algorithm which provides a guide to the management of ulcerative colitis.

PROCTITIS

When inflammation is confined to the lower 10 cm of the rectum prednisolone or mesalazine suppositories are usually effective within a few days. Occasionally patients do not respond to either of these drugs, and acetarsol (an arsenic derivative) suppositories are then often helpful and can be used in the short term without apparent side effects.³⁶ Severe episodes may require a short course of oral prednisolone.

RECTOSIGMOID OR LEFT COLONIC INFLAMMATION

Enemas used each night are usually effective.³⁷ Enemas containing 20 mg of prednisolone extend as proximally as the descending colon or splenic flexure. If the whole 100 ml cannot be retained a smaller volume should be used initially or prednisolone foam used. For more severe episodes prednisolone foam can be added during the day, after patients have finished opening their bowels.

We usually prescribe steroid enemas initially as they are effective and reassure the patient that their disease can be relatively easily controlled. However, mesalazine enemas are equally effective and can be tried subsequently. Mesalazine enemas have the advantage of avoiding steroids, but some patients do not tolerate them because of abdominal cramps. Occasionally, they are effective in patients who have not responded to steroid enemas.³⁸

FIG 3—Active colitis affecting whole colon. Oral steroids, starting at 50 mg per day, successfully controlled this episode. The patient stopped taking steroids after six weeks

FIG 4—Patients with very severe episodes of colitis should be monitored with plain abdominal radiography. In this patient with acute severe left sided colitis there is marked isolated dilatation of the sigmoid colon, which at operation had a small perforation. The associated gas filled loops of bowel in the radiograph should also alert the clinician that this is a severe episode

Severe episodes of proctitis or distal colitis usually manifest as a high bowel frequency (six to eight times a day or more), rectal bleeding, severe inflammation on sigmoidoscopy, and more pronounced systemic symptoms. Patients with such episodes usually require oral steroids as enemas are not retained. The optimum dose is 30-60 mg prednisolone per day, which should be reduced quickly.³⁸ As the disease improves it may be possible to change to enemas. If a patient with left sided or distal disease fails to respond to oral steroids intravenous steroids should be given.

EXTENSIVE OR TOTAL COLITIS

Very mild episodes of extensive or total colitis may respond to a high dose of 5-aminosalicylate such as six or more tablets per day.¹⁵ However, a dose high enough to control an episode is often associated with unacceptable side effects. More severe episodes require oral prednisolone at a dose of 40-60 mg per day.

In very severe episodes, which are characterised by a high bowel frequency, fever, tachycardia, or other serious systemic symptoms, the patient should be admitted to hospital and treated with intravenous steroids. Antibiotics give no added benefit³⁹ unless infection is proved. Food restriction to provide bowel rest is of no benefit.⁴⁰

A recent report indicates that intravenous cyclosporin may be a valuable adjunct in the treatment of severe total colitis.⁴¹ Remission was induced in 11 out of 15 patients who did not respond to a 10 day course of intravenous steroids and who would otherwise have required a colectomy.

Figures 2-4 show radiographs of patients with different types of colitis.

General comments

The success of treatment of individual episodes is judged on the relief of symptoms, especially bowel frequency and bleeding, a sense of well being, and improvement in the sigmoidoscopic appearance. Regardless of the extent of disease 80% of acute

episodes improve substantially with treatment in two weeks. The dose of drugs should then be reduced over the subsequent three or four weeks, provided that the condition continues to improve. If symptoms worsen as the dose of drug is reduced it should then be temporarily increased until symptoms improve and then decreased more slowly.

When relapses occur frequently (more than once a year) an oral 5-aminosalicylate should be taken to maintain remission. This applies to patients with any extent of disease. If a patient still relapses frequently or has chronic active disease despite adequate doses of 5-aminosalicylate then azathioprine can be started.

For many patients the most distressing symptom and cause of greatest social inconvenience is faecal urgency. Urgency may occur in patients with disease of any extent and is more common in active disease, which must be assessed and treated. Antidiarrhoeal drugs should not be taken in the presence of acute inflammation.

Occasionally, however, urgency persists when there is low grade chronic active disease or the patient is in remission. Provided that severe inflammation has been excluded urgency can sometimes be relieved by the judicious use of a small morning dose of codeine (15 or 30 mg) or loperamide (2-4 mg). The risk of addiction is negligible.

CHILDREN

The same treatment principles apply to children with ulcerative colitis as to adults. Immunosuppressive therapy is not contraindicated but is more controversial because of the long projected duration of illness in children. This factor, together with impaired growth, occasionally lowers the threshold for surgery.

PREGNANCY AND LACTATION

The treatment of acute episodes is the same during pregnancy. Despite fears about taking oral steroids during the first trimester there is no evidence of teratogenic effects in pregnant women with colitis.⁴² An acute episode is probably more threatening to the pregnancy than any theoretical risk from the drugs used. Women taking aminosalicylates to maintain remission should continue taking the drug when trying to conceive or when pregnant, for the same reasons.

Women taking azathioprine should be advised to stop the drug if trying to conceive. However, there are no data showing teratogenic effects from this drug in patients treated for inflammatory bowel disease. In a recent study of 14 women who accidentally conceived 16 times while taking azathioprine for colitis, all had a successful pregnancy and delivered a normal child.⁴³ Sulphasalazine is excreted in breast milk but not in high concentrations, and it may be continued during lactation.⁴⁴

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