

Medical management of inflammatory bowel disease

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Introduction

Patients who have recently been diagnosed as suffering from inflammatory bowel disease face two disturbing realities: firstly the true cause of the disease has not yet been defined and secondly the long term prognosis is unpredictable. The physician fighting the disease is often faced with a bewildering variety of drugs and preparations assembled in different regimens. Some of these regimens are still awaiting rigorous comparison by well conducted prospective trials in comparable cohorts of patients. This undesirable situation has resulted partly from the rapidity with which the main protagonists of the inflammatory response were characterised in recent years as a result of rapid expansion in the fields of immunology and cellular molecular biology. The exciting potential for targeting different steps in the inflammatory cascade with new drugs, many of which await clinical appraisal, suggests that medical treatment of inflammatory bowel disease is still in its infancy. This article therefore attempts to put in perspective the therapeutic regimens that have established themselves so far in this field, and to provide practical guidelines for their use in commonly encountered scenarios.

Inflammatory bowel disease: from cause to cure

In both ulcerative colitis (UC) and Crohn's disease (CD) unknown antigens appear to activate immune cells to release a number of cytokines and inflammatory mediators which then activate neighbouring macrophages and neutrophils in an uncontrolled fashion. These pro-inflammatory cytokines include the interleukins IL1, IL6 and IL8, granulocyte-monocyte colony stimulating factor (GM-CSF) and tumour necrosis factor alpha (TNF alpha). The eicosanoid inflammatory mediators include leukotrienes (e.g. LTB₄), prostaglandins (e.g. PG E₂), platelet activating factor and thromboxane. Further entry of macrophages and neutrophils into the area is encouraged by adhesion molecules elaborated by the inflamed vascular endothelium and by strong chemo attraction induced by LTB₄. Phagocytic leukocytes show enhanced inducible nitric oxide synthetase (iNOS) activity which results in enhanced liberation of nitric oxide (NO). NO is a vasodilator which maintains colonic mucosal integrity through its beneficial effects on the mesenteric circulation. However, excess NO may promote diarrhoea by stimulating the enteric nervous system to release

vasoactive intestinal peptide (VIP)¹ and by combining with free radicals such as peroxide which have been shown to stimulate intestinal secretion². Changes in mucosal blood flow and epithelial cell permeability are among the mechanisms causing diarrhoea. Each newly discovered inflammatory mediator has become a target for the design of new anti inflammatory agents which hold our hopes for the discovery of a drug which can maintain life long remission in this chronic disease.

Over the last two decades, we have witnessed the introduction of a number of new preparations for the treatment of inflammatory bowel disease. Many of these drugs have been evaluated in typical clinical scenarios and their efficacy in terms of induction and maintenance of remission has been compared by meta analysis of a large number of trials. This article will review the therapeutic options available to treat adults suffering from IBD, with particular reference to areas where consensus exists on specific regimens.

Both UC and CD are often chronic diseases which vary in the extent of the disease and its response to treatment. Continuity of follow up, ideally in the same sub-speciality clinic, over a number of years must be combined with careful serial endoscopic or radiological documentation of disease activity, the extent of bowel involvement, and its response to each therapeutic regimen. Since UC is a mucosal disease with a diffuse pattern, serial endoscopy is a useful guide to treatment. In contrast CD is best followed up by using a clinical non-endoscopic index such as the Crohn's disease activity index (CDAI)³.

Fighting IBD: Know your weapons

UC can be treated with amino salicylates and glucocorticosteroids used singly or in combination, via topical and / or systemic routes.

By inhibiting cyclooxygenase, thromboxane synthetase and platelet activating factor synthetase aminosalicylates such as 5 - amino salicylic acid (5-ASA) reduce inflammatory-mediating eicosanoids generated from arachidonic acid. LTB₄ and NO are now established as inflammatory mediators in inflammatory bowel disease (IBD) and it is hoped that inhibitors of enzymes synthesising these chemicals may emerge as alternative anti inflammatories in the future. 5-ASA is available for topical use as retention enemas or suppositories or as an oral preparation. Orally administered 5-amino salicylic acid (5-ASA) is rapidly absorbed from the jejunum. Therefore oral formulations

use pH-dependent delivery systems that release the drug in higher concentrations in the distal small intestine and colon. These formulations, referred to as mesalazine (or mesalamine in the USA) employ a semipermeable membrane (Pentasa[®]) or a resin-coat (Asacol[®]) which delays release until intestinal pH has risen above 6.0. In addition pro-drugs are available such as olsalazine (two molecules of 5-ASA linked by an azo-bond), balsalazide (5-ASA linked to a peptide), and salazopyrine (5-ASA linked to sulfapyridine by an azo-bond). All three drugs release 5-ASA into the intestinal lumen after colonic bacteria digest the azo-bond. Less 5-ASA is released in the small intestine by pro-drugs than is the case with the mesalazine preparation. This minimises the risk of salicylate-induced renal damage, which includes an interstitial nephritis. Salazopyrine, originally introduced for the treatment of rheumatoid arthritis remains a popular anti inflammatory drug but carries added side effects such as hypersensitivity skin rashes, Heinz-body haemolytic anaemia and reversible male infertility, all of which are associated with the sulphonamide carrier.

Alternatively, Glucocorticosteroids (GCS) represent a different approach to the inflammatory problem. They bind to the ubiquitous cellular glucocorticoid receptor which, when activated, travels to the nucleus where it influences DNA translation to produce potent anti inflammatory effects, which unfortunately extend to many tissues outside the bowel wall. The danger of side effects such as osteoporosis, cataracts and adrenal suppression limit their long term use. GCS can be administered intravenously e.g. hydrocortisone, orally e.g. prednisolone or rectally as foams e.g. hydrocortisone acetate 125 mg (Colifoam[®]) or Prednisolone metasulphobenzoate 20 mg (Predfoam[®]), as enemas e.g. prednisolone 20 mg (Predsol Enema[®]), or as suppositories e.g. prednisolone 5 mg (Predsol suppository[®]). Radioisotopic studies have shown a variable mucosal coverage by topical preparations. While suppositories and foams often coat the rectal mucosa, typical 100 ml enemas vary in their distribution, some coating only the lower sigmoid colon while others reach the splenic flexure. Positioning of the patient, bowel contents and motility may affect this distribution. Foams occupy a lower volume and are more likely to be retained than liquid enemas. In order to maximise compliance to enemas, the patient's motivation must be encouraged and any initial problems with self administration must be dealt with by close supervision. Since GCS are highly absorbed from inflamed bowel, systemic side effects (including adrenal suppression) can be minimised by administering budesonide 2mg in 100 ml (Enterocort Enema[®]), a potent steroid which after being highly absorbed is largely cleared from the circulation by first pass hepatic metabolism to metabolites of low GCS potency.

Patients who show an unsatisfactory response to intravenous steroids may require treatment with cyclosporin (Sandimmun[®]) 4 mg/kg iv as monotherapy⁴ or combined with iv GCS which has a higher incidence of cumulative toxicity. Cyclosporin is a fungal metabolite which suppresses cytotoxic T lymphocytes with relative preservation of T suppressor cells and bone marrow, but with marked dose-related nephrotoxic potential. The intravenous preparation includes a hydrophobic vehicle which has been associated with anaphylaxis and with convulsions. The oral route may present problems with erratic absorption. Hypertension, hypomagnesaemia, hypertrichosis and a

microangiopathic haemolytic anaemia can complicate the treatment. Absorption after oral dosing is less erratic if tacrolimus is used instead of cyclosporin but the scope of this drug is limited by more frequent neurotoxic and nephrotoxic side effects. Oral azathioprine (Imuran[®]) (1-3 mg/kg) is a purine antagonist anti metabolite with immunosuppressive effects which are more potent in CD than in UC. It can be used as a sole agent or in combination with GCS as a steroid sparing drug (see below). Its commonest side effect is bone marrow suppression, predominantly thrombocytopenia or lymphopenia which is usually dose related and more likely to occur if angiotensin converting enzyme inhibitors are co-administered. Hepatotoxicity is usually reversible although life-threatening veno-occlusive liver disease may occur. Pancreatitis may also complicate use of azathioprine. Blood picture, serum amylase and liver function tests should therefore be regularly monitored. As with all immunosuppressive therapy there is an increased risk of opportunistic infection and of neoplastic complications such as lymphoma, but many of these complications have been reported in renal transplant recipients receiving high doses of these drugs.

Attacking ulcerative colitis: decide your strategy

Modern medical management should not be based on open studies or isolated comparisons but on guidelines derived from meta analysis of reports by expert committees. Extensive reference is therefore made below to the practice guidelines published by the Practice Parameters Committee of the American College of Gastroenterology for the treatment of UC^{5,6}.

Colonoscopy is desirable to classify UC into distal (involvement only distal to splenic flexure) or extensive (involvement extending proximal to splenic flexure) colitis. Clinically the disease is classified as mild (less than four stools per day, with or without blood, no systemic toxicity, normal ESR), moderate (more than four stools per day, minimal signs of toxicity), severe (more than six stools per day, toxicity such as fever, tachycardia, anaemia, raised ESR)

Mild to moderate distal disease

This category of patients may be treated with oral or topical treatment depending on patient preference. Oral treatment often takes longer to induce a remission than topical treatment but is frequently the patient's first choice. Combined oral and topical therapy is often recommended to achieve fast remission. Oral therapy consists of salazopyrine 4 - 6 g per day, mesalazine 2 to 4 g per day or olsalazine 1.5 to 3 g per day, all in divided doses. The response is dose-related and many treatment failures are due to insufficient dosing. Regular full blood counts and tests of renal function are required. Caution should be exercised if there is mild renal impairment. Topical treatment includes mesalazine suppositories 500 mg bd for proctitis or mesalazine enemas 2 - 4 g daily, while mesalazine 1 g enemas (available in Malta as Pentasa enemas[®]) are effective in maintaining remission⁷. Budesonide (2g/100 ml) enemas are also recommended as an alternative topical treatment, while hydrocortisone 10% foam was not found effective in maintaining remission. In general 5-ASA preparations are superior to topical steroids in maintaining remission

Mild to moderate extensive disease

Here the disease is partly beyond the reach of enemas and its extent necessitates doses of oral 5-ASA preparations towards the upper limit of the dose ranges listed above. However, as the dose is titrated upwards side effects may occur. In addition a proportion of patients will not respond to maximum doses of 5-ASA. Such patients should be started on oral prednisolone 20 - 60 mg per day tapering the dose downwards once clinical response is achieved. There are no official guidelines on tapering doses but dose reduction should proceed more gradually by 2.5 - 5 mg per week once lower doses are achieved. The tapering may take into account the steroid dose at which breakthrough of rectal bleeding or diarrhoea occurred during a previous exacerbation. Alternatively, a repeat colonoscopy may be performed while on low dose steroids (5 - 10 mg daily) to look for residual active disease before further tapering. Even if the mucosa appears normal, it is important to note that active cryptitis on biopsies is predictive of a recurrence if the steroid dose is lowered further. Distal residual disease may be healed by the addition of topical therapy while proximal incomplete healing may require the addition of azathioprine before steroid doses can be tapered or withdrawn. The therapeutic benefit of a given dose of azathioprine is not usually evident before three weeks and may not be complete before several months. Besides its steroid-sparing effect, azathioprine is also useful in maintaining remission although many patients achieve satisfactory prolongation of remission time if they tolerate and comply with sufficiently high doses of oral mesalazine. Long term mesalazine is generally recommended in order to maintain remission. However, a study of patients who had been in remission for two years and who were randomised to long term mesalazine versus placebo did not show significant differences in relapse rates over several years between the two treatment arms⁸.

Severe colitis

Patients with clinically severe colitis and those with extensive colitis not responding to medical treatment should be admitted to hospital and treated with hydrocortisone 100 mg qds iv. Blood transfusion, intravenous fluids, antibiotics and total parenteral nutrition may also be required. Typically, 40% of patients with severe colitis will need surgery and it is important to identify these patients early. Approximately one third of these patients will have had one or more of these symptoms in the first 24 hours: more than 9 bowel actions per day, pulse above 100/min and maximum temperature above 38°C. By day 3, more than 8 stools per day, and a C-Reactive protein > 45 mg/l carry an 85% chance of surgery⁹. Persistent colonic tenderness, early colonic dilatation or more than 3 distended small bowel loops are also ominous signs. The addition of intravenous cyclosporine 4 mg / kg /day reduces the need for urgent surgery, but many of these patients require surgery within the next six months under less dangerous conditions.

A transverse colon with a diameter greater than 5 or 6 cm with absent haustration on an abdominal radiograph associated with tachycardia and fever in a patient established on intravenous treatment (toxic megacolon) requires emergency colectomy. When colonic dilation

occurs at presentation, full intravenous treatment, correction of hypokalaemia and avoidance of opiates and anticholinergics may allow sufficient improvement after 24 hours to avoid emergency colectomy. Medical management of severe colitis must also include vigilance for two complications that require emergency surgery, namely accelerated colonic bleeding and colonic perforation without preceding toxic dilation.

Cancer surveillance: getting them soon enough

When compared to non-colitics, colitis-associated cancer occurs at an earlier age, is often multiple and frequently lacks the polyp-cancer sequence. Onset of colitis in childhood and a long period of continuous disease increase the risk of cancer in a time-dependent fashion (typically 7% risk at 20 years and 16% risk at 30 years)¹⁰. This has prompted many clinicians to recommend prophylactic colectomy in the past.

Whereas many of these patients with a long duration of active disease extending beyond the rectosigmoid area underwent prophylactic colectomy in the past, most clinicians will now only consider this operation if persistent dysplasia is demonstrated in one or more multiple biopsies (taken at 10 cm intervals) during surveillance colonoscopies. Surveillance should start after 10 years of disease activity and should be repeated every 1 -3 years if no dysplasia is found. A finding of low grade dysplasia should be confirmed by repeating colonoscopy after a few weeks and then at six -monthly intervals until it disappears or high grade dysplasia is found, whereupon prophylactic colectomy is recommended. A 19% incidence of cancer was found in colons resected from UC patients shortly after their colonoscopy showed low grade dysplasia, while the five-year predictive value of low grade dysplasia for cancer or for high grade dysplasia is as high as 54%. Colectomy should therefore be considered in all patients with persistent low grade dysplasia.

The future in UC: feeding the colonocyte?

Colonic mucosal cells derive 80% of their energy requirement from luminal short chain fatty acids (SCFA), mostly butyrate, produced by anaerobic bacterial fermentation of undigested dietary carbohydrates, mainly fibre polysaccharides¹¹. Absence of luminal SCFA is thought to be the cause of "diversion colitis" in segments of colon which have been surgically isolated from the faecal stream. Reduced beta oxidation of butyrate by the colonic epithelial cells, with consequent energy deficiency, may promote mucosal cell death in UC. Several trials of SCFA enemas in UC have yielded disappointing results. Initial studies have shown that dietary fibre administered as *Plantago Ovata* seeds may be as effective as mesalazine in preventing relapse in ulcerative colitis¹². By maintaining an acid pH in the colonic lumen, fermented fibre promotes the predominance of acidogenic bacteria over putrefactive bacteria. The latter digest protein to produce ammonia and sulphur-containing compounds which, by acting as reducing agents¹³, may impair colonocyte nutrition. Regimens that include dietary fibre which, while resisting enteric enzyme digestion are highly fermentable to butyrate in the colon, are likely to be scrutinised in the next few years for their ability to maintain remission in UC.

Attacking Crohn's disease: be prepared to intensify treatment

The presence of many subtypes of CD (colonic, ileocolonic, fistulating, stenotic) and the poor correlation of endoscopic appearance with disease activity for which there is no scientifically based index have prevented the definition of clear therapeutic endpoints. In comparison with UC many drug regimens used in CD have not been rigorously compared.

Mild disease

These patients are able to eat without developing signs of transmural inflammation such as fever, abdominal mass or tenderness. Sulphasalazine 3-6g/day was shown to induce remission in mild colonic and ileo-colonic disease by the National Cooperative Crohn's Disease (placebo-controlled) Study (NCCDS)¹⁴ and other studies, but only in some studies in ileal Crohn's. This may be due to insufficient splitting of azo-bonds in the ileum where the bacterial load is usually low. The pH-dependent release preparation mesalazine (Pentasa®) induced remission in both ileal and colonic disease at a dose of 4g/day in a dose dependent fashion¹⁵ and maintained remission at a dose of 3g/day as long as treatment was started within 3 months of remission. The efficacy of mesalazine in preventing inflammation in the neo-terminal ileum after resection of the terminal ileum and ileocaecal valve has not been adequately studied.

Moderate disease

These patients have often failed to respond to 5 ASA and have signs of transmural inflammation or anaemia. Patients tolerating oral medication should receive 0.5 - 0.75 mg/kg prednisolone per day. This regimen induced remission in 47% and improvement in 60% of patients at 16 weeks in the NCCDS. Dose tapering should commence once clinical remission occurs and need not wait for endoscopic improvement which often lags behind transmural healing. Treatment with Enterocort® capsules (controlled release oral budesonide) 9 mg daily can be expected to induce remission in 52 - 60% of patients at 8 weeks and 62% of patients at 16 weeks¹⁶. 50 - 80% of the drug is absorbed in the ileum and right colon, the bioavailability remaining unaltered after feeding. The preparation has a high solubility, a high affinity for steroid receptors, a high hepatic first-pass metabolism and a high potency, 9 mg of oral Enterocort® being equivalent to 40 mg of oral prednisolone.

Patients who respond poorly or partially to steroids should also receive azathioprine starting at 0.5 - 1.5 mg/kg and increasing to 2 to 2.5 mg/kg. In addition to its steroid-sparing effect, azathioprine prolongs remission and has specific healing effects on patients with fistulous disease. When allergic reactions limit the use of purine antagonists, methotrexate 25 mg i.m. weekly for 12 weeks followed by 12.5 mg i.m. weekly may permit steroid tapering, but the potential for causing pulmonary or liver fibrosis and bone marrow suppression make methotrexate a less popular drug.

Antibiotics are advocated in CD complicated by chronic suppuration such as abscess, sinus or fistula and in patients where intestinal strictures may cause prolonged contact with high counts of abnormal bacterial

flora. The potential antigenic role of bacteria has been suggested by the protective effect of diverting the faecal stream (e.g. by the protective effects of loop ileostomy on the neo-terminal ileum after terminal ileal resection). Antibiotics include oral metronidazole 20 mg/kg/day, reducing to 10mg/kg/day during remission, ciprofloxacin 1 g/day and clarithromycin, the latter being chosen in some studies because of its activity against *Mycobacterium Paratuberculosis* which has been implicated in the aetiology of CD. Elemental diets may also be added to limit antigenic stimulation by protein and to help reverse malnutrition. Total parenteral nutrition, often combined with Octreotide 50 ug s.c. 8 hourly is useful when high output fistulae co-exist.

Severe disease

These patients are treated with intravenous steroids and all the supportive therapy listed under severe UC above. In addition, intestinal obstruction may require nasogastric suction and total parenteral nutrition until adhesive or fibrostenotic disease resolves. Abscesses may require surgical drainage.

Maintaining remission

Steroid doses below 8 mg per day are generally ineffective in maintaining a steroid induced remission but useful steroid sparing effects are to be expected by adding azathioprine 2.5 mg/kg/day. The early addition of oral mesalazine at doses above 3 grams per day is helpful in prolonging remission.

The future in CD: harnessing the immune response?

A number of research drugs have been shown to reduce activity in CD. For example, an alternative to the old methods of antigen reduction and immunomodulation is the exciting method of specific cytokine modulation. The most promising in early placebo-controlled trials are the TNF-alpha blocking agents. These include chimeric (75% human, 25% mouse) and humanised antibodies against TNF-alpha which have been administered as single or multiple iv infusions in treatment-resistant CD patients. The anti-inflammatory cytokine IL-10 which decreases macrophage secretion of pro inflammatory cytokines such as IL1 is still under trial. Going back to immunomodulation, we now have the possibility of targeting CD4 cells using anti-CD4 monoclonal antibodies which have been shown to reduce populations of circulating CD4 cells, as well as reduced antigen presentation. Another logistic approach is to interfere with leukocyte recruitment to the site of inflammation by blocking strong adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1). This has been achieved using an antisense nucleotide with clinical responses in steroid dependent CD patients.

Conclusion

The impressive array of inflammatory mechanisms unearthed by research into the pathogenesis of inflammatory bowel disease makes it difficult for scientists to know where best to intercept the inflammatory cascade. It is not yet clear whether certain inflammatory events occur in tandem or in quick

succession. It is hoped that the early triggers of inflammation will prove to be amenable to suppression by new agents so that drugs that prevent remission will be used less commonly than those which prevent relapse.

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