

Lecture

Maintenance treatment in Inflammatory Bowel Disease (IBD)

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SUMMARY

Ulcerative colitis and Crohn's disease are complex disorders reflected by wide variation in clinical practice.

Lifelong maintenance treatment is recommended for all patients with ulcerative colitis, especially those with left-sided or extensive disease and those with distal disease, who relapse more than once a year. Oral mesalazine 2g/day should be considered as first-line therapy. Steroids are not effective at maintaining remission. Azathioprine 1,5-2,5 mg/kg/day or mercaptopurine 0,75-1,5 mg/kg/day should be reserved for patients who frequently relapse, despite adequate doses of aminosalicylates. Patients who have failed to respond to immunomodulators benefit from repeated maintenance therapy with infliximab, ideally on an every 8 week basis.

The efficacy of drug therapy in the maintenance treatment of Crohn's disease depends on whether remission was achieved with medical or surgical therapy, on the risk of relapse and on the site of disease. Mesalazine seems to be ineffective at doses < 2 g/day. It is clearly ineffective for those who have needed steroids to induce remission. Azathioprine should be reserved as second line therapy. Steroid dependent patients and patients with steroid refractory disease should be considered for treatment with immunomodulators. Infliximab is effective at a dose of 5 mg/kg every 8 weeks in patients who have responded to the initial infusion. It is best used with immunomodulators. Moreover, it is the best evidenced-based therapy for the fistulating disease at the present time.

Ulcerative colitis and Crohn's disease, collectively termed

inflammatory bowel disease, are complex disorders reflected by wide variation in clinical practice.

Drugs used in the treatment of IBD

The principal drugs in the treatment of IBD are: aminosalicylates, corticosteroids, thiopurines, methotrexate, ciclosporin and finally infliximab and the new biological agents under investigation.

Aminosalicylates:¹ are available as oral tablets, sachets or suspension, liquid or foam enemas, or suppositories. They act on epithelial cells and moderate the release of lipid mediators, cytokines and reactive oxygen species.

Oral forms: pH dependent release (Asacol, Salofalc), time-controlled release (Pentasa), release of 5-ASA after splitting by bacterial enzymes in the large intestine (sulphasalazine (Salazopyrin), olsalazine (Dipendum).

Corticosteroids: oral prednisolone, prednisone, budesonide, foam or liquid enemas. Budesonide (Entocort, Budenofalk), a poorly absorbed corticosteroid, has extensive first-pass metabolism, thus limiting systemic side effects. It is released in the terminal ileum and right colon.

Thiopurines: they are immunomodulators and they induce T- cell apoptosis. Azathioprine is metabolized to mercaptopurine and subsequently to 6-thioguanine.

Methotrexate: oral, subcutaneous or intramuscular injection. Methotrexate metabolites have cytotoxic effects. They also inhibit cytokine and eicosanoid synthesis.

Ciclosporin: oral or intravenous, prevents clonal expansion of T-cell subsets.

Infliximab (Remicade): an anti-TNF monoclonal antibody with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells.

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Maintenance treatment of ulcerative colitis

Lifelong maintenance treatment is recommended for all patients, especially those with left-sided or extensive disease and those with distal disease who relapse more than once a year.² Discontinuation of medication is reasonable for those with distal disease, who have been in remission for two years. However, maintenance therapy with all 5-ASA drugs may reduce the risk of colorectal cancer by up to 75%.³

Oral mesalazine 2g/daily should be considered as first-line therapy. Sulphasalazine 2-4 g daily comparing to the newer 5-ASA drugs has a higher incidence of side effects, however, selected patients may benefit (patients with a reactive arthropathy). Topical mesalazine 1g daily is best for patients with distal disease with/without oral mesalazine, but patients are less likely to be compliant.

All aminosaliclates have been associated with nephrotoxicity, which could be idiosyncratic or dose-related. Patients with preexisting renal disease are at higher risk. Aminosaliclates should be stopped if renal function deteriorates.

Steroids are not effective at maintaining remission.⁴ Budesonide 6 mg/d prolongs the time to relapse in patients with medically induced remissions but does not meet the conventional criteria for maintenance of remission at 1 year.

Azathioprine 1,5-2,5 mg/kg/day or mercaptopurine 0,75-1,5mg/kg/day should be reserved for patients who frequently relapse, despite adequate doses of aminosaliclates.^{5,6} They are also indicated in the group of patients intolerant to aminosaliclates. They are effective at maintaining remission in ulcerative colitis. Aminosaliclates could be administered with azathioprine, but there is limited evidence that this is necessary. Patients presented with gastrointestinal intolerance to azathioprine could be tried on mercaptopurine before being considered for other treatment.

Patients who have failed to respond to immunomodulators benefit from repeated maintenance therapy with infliximab,⁷⁻¹⁰ ideally on an every 8 week basis. Given the immunogenicity of infliximab it is recommended that patients are started on immunomodulators before or at least simultaneously with infliximab treatment.¹¹ Thus, corticosteroid dependent patients can often be weaned from steroids.

Cyclosporin has serious shortcomings and is not con-

sidered an acceptable maintenance therapy in ulcerative colitis.

Growing evidence exists for a role of the intestinal microflora in the pathogenesis of inflammatory bowel disease. Therefore treatment with probiotics, viable non-pathogenic microorganisms that confer health benefits to the host, has been proposed. According to recent studies probiotics show efficacy and safety in maintaining remission equivalent to mesalazine in patients with ulcerative colitis. Additionally they have been shown to prevent the development of pouchitis after pouch formation.

Ulcerative colitis is a premalignant condition in which prolonged medical treatment replaces surgery. Patients can keep their colon and, hence enjoy a better quality of life, than with an ileoanal pouch. As far as the detection of dysplasia and cancer is concerned, well organized surveillance programs will be more than necessary in the new era of treatment of ulcerative colitis.

Maintenance treatment of Crohn's disease

The general principles in the management of Crohn's disease are to consider the site (colonic, ileocolic, ileal, other sites) the pattern (inflammatory, structuring, fistulating) and the activity of the disease, before treatment decisions are made in conjunction with the patient. The severity of Crohn's disease is more difficult to assess than ulcerative colitis.

The efficacy of drug therapy depends on whether remission was achieved with medical or surgical therapy, on the risk of relapse and on the site of disease. Smoking cessation is a very important factor in maintaining remission.¹² Patients with Crohn's disease who smoke should be offered help to stop (counselling, nicotine patches).

Mesalazine seems to be ineffective at doses < 2g/day. It is clearly ineffective for those who have needed steroids to induce remission.¹³

Azathioprine 1,5-2,5 mg/kg/day or mercaptopurine 0,75-1,5mg/kg/day are effective.¹⁴⁻¹⁶ Because of their potential toxicity should be reserved as second line therapy.

Methotrexate is appropriate for the patients who are intolerant of azathioprine, or who have failed azathioprine / mercaptopurine therapy. Methotrexate 15-25 mg IM weekly is effective especially for patients whose active disease responded to IM methotrexate.¹⁷ Subcutaneous or oral treatment may be effective. Folic acid 5 mg /week may reduce side effects.

Immunomodulation with azathioprine, mercaptopurine or methotrexate is usually appropriate if patients relapse after discontinuation of steroids more than once per year.

Sulphasalazine is not recommended in the maintenance treatment of Crohn's disease.

Corticosteroids appear not effective. Long term treatment with steroids is undesirable.¹⁸ Patients who have a poor response to corticosteroids can be divided into steroid refractory and steroid dependent. Steroid – refractory disease can be defined as active disease in spite of an adequate dose and duration of corticosteroids (prednisolone >20 mg/d for > 2 weeks). Steroid dependent may define a patient who relapses when the steroid dose is reduced below 20 mg/day, or within 6 weeks of stopping steroids. These patients should be considered for treatment with immunomodulators. Immunomodulation should be tried if steroids cannot be withdrawn without deterioration of disease activity.

Azathioprine 1,5-2,5mg/day or mercaptopurine 0,75-1,25 mg/kg/day are the first choice agents for patients with steroid – dependent disease. Monitoring the patients to detect neutropenia is advisable. However, there is no evidence that this is effective because profound neutropenia and sepsis can develop rapidly.¹⁹ Some patients at risk of neutropenia can be identified by thiopurine methyltransferase activity measurement. However, this is not recommended, as according to large published series the use of azathioprine is safe without this assay. When the overall risks and benefits of prolonged maintenance therapy with azathioprine are balanced, it is likely that most clinicians will accept the small risk of a lymphoid malignancy or myelodysplasia and the small risk of opportunistic infections to prevent the ongoing morbidity and impact on quality of life related to the chronic symptomatic activity of Crohn's disease.

Methotrexate IM 25mg weekly for up to 16 weeks followed by 15 mg weekly is effective for chronic active disease. Oral therapy is equally effective for many patients.

Infliximab is effective at a dose of 5-10 mg/kg every 8 weeks in patients who have responded to the initial infusion. It is best used with immunomodulators. Infliximab should be reserved for patients with moderate to severe Crohn's disease who are refractory to treatment with steroids, mesalazine, azathioprine/mercaptopurine, and methotrexate. It should also be reserved for patients who do not tolerate the above treatments and for the patients where surgery is considered inappropriate.

Infliximab is effective not only for inducing but also for maintaining fistula closure.²⁰ It is the best evidenced-based therapy for the fistulating disease at the present. However, concomitant immunosuppression is required.

Antibiotics may be effective for fistula closure and cyclosporin as well, however, placebo-controlled trials need to be performed.

Postoperative maintenance treatment

Metronidazol 20mg /kg/day for three months is effective in patients with ileocolic resection. Metronidazole effectively delays recurrence for up to 18 months. In patients with ileal resection and ileocolonic anastomosis, metronidazole 20mg/kg/day for three months was effective for reducing the frequency of severe endoscopic recurrence.²¹ However, it failed to show efficacy for maintenance of clinical remission at 1 year. A major side effect of metronidazol is peripheral neuropathy.

Mesalazine >2 gr/day lowers postoperative recurrence in small bowel disease, but is ineffective after colonic resection. Azathioprine (1,5-2,5mg/kg/day) and mercaptopurine (0,75-1,25mg/kg/day) may be better than mesalazine in preventing postoperative recurrence.

Cessation of smoking significantly reduces postoperative relapse and patients should be strongly advised to stop and be offered help to achieve this.

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