

CYCLOSPORINE is an effective drug in acute exacerbations of corticosteroid resistant ulcerative colitis, but its efficacy to maintain disease remission is not clear. Cyclosporine may not be as effective in Crohn's disease. However, being a rapidly acting immunosuppressant, cyclosporine may be a valuable therapeutic option in the short-term to treat corticosteroid resistant Crohn's disease and ulcerative colitis.

Key words: cyclosporine, Crohn's disease, ulcerative colitis

Cyclosporine and inflammatory bowel disease: buying time

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Introduction

The efficacy of immunosuppressive drugs like azathioprine and 6-mercaptopurine to treat the chronic inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD) is now generally accepted. However, a major drawback to the use of these immunosuppressants is the 2–3 month delay in onset of their clinical action, thereby limiting their role in severe acutely active disease.

The success of the rapidly acting immunosuppressive drug cyclosporine in solid organ transplantation and chronic inflammatory diseases such as psoriasis and rheumatoid arthritis paved the way to determine the efficacy of cyclosporine in IBD. The following review will focus on clinical response in controlled trials, pharmacology, side effects and toxicity of cyclosporine treatment in CD and UC.

Cyclosporine in Crohn's Disease

Numerous open studies have suggested that cyclosporine may be effective in active CD which has not responded to conventional treatment including corticosteroids, aminosalicylates and antibiotics.¹ However, only four controlled trials of cyclosporine for the treatment of CD have been published.^{2–6} In three of these studies a total number of 633 patients was treated with low-dose oral cyclosporine (5 mg/kg/day and whole blood concentrations ranging from 100–250 ng/ml) or placebo.^{4–6} These studies failed to demonstrate any significant beneficial

effect of chronic low-dose oral cyclosporine for chronically active CD or for remission maintenance. Given alone as initial treatment, cyclosporine was less effective than conventional treatment.⁷

Only one controlled study using high-dose oral cyclosporine (5–7.5 mg/kg/day) for CD has been published.^{2,3} At 3 months 59% of the patients treated with cyclosporine had improved compared with 32% in the placebo group.² The whole blood concentrations were higher in the responders (471 ng/ml) than in the nonresponders (309 ng/ml). However, the beneficial effect did not persist after cyclosporine was stopped.³ Two studies have suggested efficacy of cyclosporine for fistulizing CD.^{8,9} At present, it seems reasonable to limit the use of cyclosporine to patients with severely active CD who failed to respond to corticosteroids and aminosalicylates, and preferably in a clinical research setting.

Cyclosporine in Ulcerative Colitis

Several open studies have reported a beneficial effect of cyclosporine in the treatment of UC.^{10,11} Only one small controlled trial showed that cyclosporine, given in an intravenous dosage of 4 mg/kg/day comparable with an oral dosage of 12–16 mg/kg/day, will induce a remission in 83% of patients with severe ulcerative colitis compared with 0% of the placebo-treated patients.¹² It is important to realize that only 45% of these patients avoided colectomy during 6 months of follow-up.¹³ One controlled trial of low-dose cyclosporine enemas for left-sided UC had negative results.¹⁴

The general experience of these studies in UC is that 50–70% of the patients will require surgery during the following 12 months after starting cyclosporine therapy. However, using cyclosporine treatment some patients, especially those with a first attack, will not lose their colon. In others, colectomy can be performed when the patient is in a better physical condition and the ileo-anal pouch anastomosis done as a one-stage procedure without the need of a stoma. Recently, an excellent paper has been published describing in detail guidelines how to use and monitor cyclosporine treatment in UC patients.¹⁵

Pharmacology

Cyclosporine is a lipophilic peptide which inhibits Thelper cell interleukin-2 (IL-2) mRNA transcription and production, and also the release of other lymphokines such as interferon-gamma, IL-3, IL-4, IL-5, and tumour necrosis factor-alpha, resulting in altered T cell and B cell function.^{16,17} At present, it is not known whether these effects on cellular and humoral immunity account for any therapeutic effect in IBD. Alternatively, neutralization of the neutrophil chemotactic properties of extracellular cyclophillin by cyclosporine has been proposed as the primary mode of action in IBD.¹⁸ This hypothesis could explain the better responsiveness to cyclosporine in UC compared with CD, because in UC neutrophil influx may play a bigger role than in CD. Although the effectiveness of cyclosporine in treating IBD could be dose related, there is also evidence that low-dose cyclosporine may even worsen tissue inflammation and injury by changing specific lymphocyte subpopulations.¹⁸ In mice, it has been shown that low-dose cyclosporine causes a switch from a Thelper 1 to a Thelper 2 response thereby augmenting the inflammatory response.¹⁹

The distribution and elimination kinetics of cyclosporine in patients with CD do not differ from those in other patient groups or controls, whereas the extent and rate of oral bioavailability may be decreased.^{20,21} The absorption of cyclosporine can be described by zero-order kinetics in patients with CD, implying that the gut transit time is important for the amount of cyclosporine absorbed.²⁰ In one study, 10% of patients with CD showed cyclosporine malabsorption based on blood levels.⁴ In addition, absorption of cyclosporine is significantly affected by bile salts. Recently, a new formulation of cyclosporine—Neoral—has been developed, which consists of a micro-emulsion of cyclosporine employing a surfactant, a lipophilic solvent, a hydrophilic solvent, and a cosolvent.²² This new formulation ensures rapid release of cyclosporine within the gastrointestinal tract and a more uniform presentation to the absorptive surface of the upper small bowel. This results in consistent

dispersion of the drug in the gastrointestinal tract without the need for additional emulsifiers like bile salts. Studies have demonstrated that in patients with CD who have problems absorbing cyclosporine, conversion to Neoral results in correction of cyclosporine malabsorption.²² At present, however, it remains unclear whether initial therapy with intravenous cyclosporine is superior to oral administration.

Side Effects and Toxicity

Being a powerful immunosuppressant, cyclosporine also has potential side effects including: renal insufficiency (6%), hypertension (11%), infectious complications (3%), severe neurological disorders including epilepsy (1%), paresthesias (26–70%), tremor (7%), headache (5%), hypertrichosis (13%), gingival hyperplasia (2%), and anaphylaxis (0.3%)^{23–26} (Table 1).

Cyclosporine is metabolized in the liver and both cyclosporine and its metabolites are excreted in bile and little cyclosporine appears in the urine. Renal impairment does not alter the elimination of cyclosporine. Any drug that inhibits the cytochrome P-450 system will increase cyclosporine levels (ketoconazole, fluconazole, cimetidine, erythromycin, diltiazem, verapamil), whereas drugs that induce the P-450 system will decrease cyclosporine levels (rifampicin, phenobarbital, phenytoin, carbamazepine).

Nephropathy due to long-term cyclosporine treatment is an important issue. The direct effect of cyclosporine is a vasoconstriction of preglomerular arterioles with a secondary decrease in glomerular filtration rate and an increased proximal tubular fractional reabsorption rate. This may result in increased tubular transit time and tubular atrophy and

Table 1. Side effects of cyclosporine

Side effects which tend to occur during chronic administration

- hypertrichosis
- gingival hyperplasia
- hypomagnesaemia
- gout
- diabetes mellitus

Side effects requiring dose reduction

- hypertension
- paresthesias
- tremor
- headache
- increase in serum creatinine > 30%

Side effects requiring stopping cyclosporine administration

- jaundice
 - infectious complications (especially *Pneumocystis carinii* and fungal infections)
 - lymphoma
 - anaphylaxis
 - severe neurological disorders including epilepsy
-

interstitial fibrosis.²⁰ It has been suggested that one-fifth of patients with autoimmune diseases treated with cyclosporine have histological evidence of nephropathy.²⁷

A few case reports dealing with severe and sometimes fatal opportunistic infections have been reported.^{23–26} Importantly, these infections occurred during high-dose cyclosporine treatment in combination with corticosteroids.

Conclusions

Cyclosporine is an effective therapeutic option in acute exacerbations of UC not responding to corticosteroids. When given orally, its long-term efficacy is questionable. Low-dose oral cyclosporine is not effective in either quiescent or active CD. Cyclosporine can be used as rescue therapy to 'buy time': most patients who benefit on the short-term from cyclosporine, will require further treatment for their IBD in the form of follow-up surgery or other remission maintaining drugs like azathioprine or 6-mercaptopurine. The introduction of a new formulation of cyclosporine has improved the absorption kinetics of the drug and the consistency of plasma levels after oral dosage. Cyclosporine side effects, especially nephrotoxicity, are common necessitating adequate monitoring.

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