Cyclosporine in ulcerative colitis : state of the art

W. J. Sandborn

Inflammatory Bowel Disease Clinic, Division of Gastroenterology and Hepatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A.

Abstract

Forty percent of patients with severe ulcerative colitis will fail to respond to intravenous corticosteroids. Cyclosporine and other calcineurin inhibitors offer an alternative to colectomy for these patients. Intravenous cyclosporine will induce remission within 14 days in 50-80% of patients who fail intravenous corticosteroids. The long-term response rates for responding patients are 40-60%. Subsequent maintenance therapy with azathioprine or 6-mercaptopurine is recommended at the present time, although the uncontrolled studies underlying this observation have yielded variable results. Toxicity occurs frequently in patients treated with high dose cyclosporine, and there is a small risk of opportunistic infection and death. Pilot studies have suggested that the microemulsion cyclosporine formulation Neoral and tacrolimus may also be of benefit in this patient population. Additional studies to determine the dose response of intravenous cyclosporine, to determine the role of azathioprine for maintenance, and to determine the efficacy of Neoral and tacrolimus are needed. (Acta gastroenterol. belg., **2001**, 64, **201-204**).

Introduction

Approximately 10 percent of all patients with ulcerative colitis will develop a severe flare up at some point in their disease course, with 1-2% progressing on to toxic, fulminant colitis or megacolon (1). The standard therapy for patients with severe or toxic ulcerative colitis, as defined by Truelove and Jewell, consists of intravenous fluids, electrolyte supplements, bowel rest, transfusion if indicated, intravenous antibiotics, intravenous corticosteroids, and rectal corticosteroids (2). Sixty percent of patients treated with this regimen will be symptom free by the end of five days, 15% will have significant improvement, and 25% will not improve. Until the 1990s, patients who failed to respond to intravenous corticosteroids underwent colectomy. In 1990, Lichtiger and Present reported that intravenous cyclosporine at a dose of 4 mg/kg/day might be effective in patients with severe, steroid refractory ulcerative colitis (3). This article reviews the use of cyclosporine and other calcineurin inhibitors in patients with severe ulcerative colitis.

Calcineurin inhibitors

Calcineurin inhibitors with proven or possible efficacy for severe ulcerative colitis include cyclosporine (Sandimmune), cyclosporine microemulsion formulation (Neoral), and tacrolimus (FK506, Prograf). Another calcineurin inhibitor recently approved for use in the transplant setting is sirolimus (rapamycin, Rapamune). To date, the use of sirolimus in patients with severe ulcerative colitis has not been reported.

Clinical pharmacology of cyclosporine (Sandimmune)

The standard formulation of cyclosporine (Sandimmune) has relatively low oral bioavailability, averaging 20% (4). Cyclosporine is absorbed from the small bowel, and diseases that disrupt the mucosal integrity of the small bowel alter the absorption of cyclosporine. Cyclosporine is also dependent on bile for absorption. Low-dose cyclosporine is defined as an oral dose of ≤ 5 mg/kg/day, and high-dose cyclosporine is defined as an oral dose > 5 mg/kg/day (5). Trough concentrations of cyclosporine should be measured in whole blood by HPLC or monoclonal RIA. In transplantation, the therapeutic window for whole blood cyclosporine is 150-300 ng/ml. In individual studies of cyclosporine for the treatment of ulcerative colitis or Crohn's disease, there has been little correlation between blood levels of cyclosporine and clinical response (6-8). However, individual studies are usually designed to achieve a target blood concentration or a relatively narrow target range of blood cyclosporine concentrations. If the blood levels achieved in various clinical trials are compared, stratifying for the outcome of the trial (efficacy or no efficacy), then a strong trend towards greater efficacy with higher blood concentrations (approximately 400 ng/ml whole blood cyclosporine concentration as measured by HPLC or RIA) is apparent (4).

Efficacy of intravenous cyclosporine for the treatment of severe ulcerative colitis

To date, three controlled studies of intravenous cyclosporine have been performed in patients with severe ulcerative colitis. The first study, led by Lichtiger and colleagues, reported on 20 patients with severely active ulcerative colitis who had failed at least seven days of intravenous corticosteroids (8). Nine patients were randomized to placebo and 11 patients were randomized to treatment with cyclosporine administered at a dose of 4 mg/kg/day as a continuous infusion for

Corresponding author : Sandborn W. J., Gastroenterology & Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, U.S.A.

14 days. The dose of cyclosporine was adjusted by an unblinded clinician to maintain adequate blood levels, the whole blood cyclosporine levels achieved during the study ranged from 339-653 ng/ml. For patients who improved, the mean time to clinical response was seven days. Four patients experienced paresthesias, 2 patients developed hypertension, and one patient had a seizure. After 14 days of therapy, 9 of 11 cyclosporine treated patients (82%) responded compared with 0 of 9 (0%) placebo treated patients. Responding patients were converted to oral cyclosporine 8 mg/kg/day. At 6 months, 5 of 11 patients treated with cyclosporine (45%) maintained a clinical response (9).

In the second study, 20 patients with severely active ulcerative colitis were randomized at the time of hospitalization to monotherapy with a continuous intravenous infusion of either cyclosporine 4 mg/kg/day or methylprednisolone 40 mg/day (10). Patients who had received oral corticosteroids as an outpatient for < 2 weeks were eligible (oral corticosteroids were discontinued at study entry), whereas patients who had received oral corticosteroids for ≥ 2 weeks were excluded. Over the following week, 7 of 10 patients (70%) receiving cyclosporine responded compared to 6 of 10 patients (60%) treated with methylprednisolone. Of the non-responding patients, 1 of 3 cyclosporine treated patients and 1 of 3 methylprednisolone treated patients subsequently responded to open therapy with a combination of cyclosporine and methylprednisolone. Two of 10 patients treated with methylprednisolone and 1 of 10 patients treated with cyclosporine underwent colectomy. No serious toxicity was observed.

In the third study, 30 patients with severely active ulcerative colitis who had failed one week of intravenous steroids were randomly assigned to monotherapy with intravenous cyclosporine 4 mg/kg/day (steroids were discontinued) or intravenous cyclosporine 4 mg/kg/day in combination with continued prednisone at a dose of 1 mg/kg/day (11). Over the subsequent seven days, 10 of 15 patients in the cyclosporine monotherapy group experienced complete remission, 3 of 15 had partial improvement, and 2 of 15 underwent urgent colectomy. In the cyclosporine/prednisone combination therapy group, 14 of 15 patients had complete remission and 1 of 15 underwent urgent colectomy. Toxicities observed included paresthesias, hypertension, and nephrotoxicity.

Given the relatively high relapse rate observed at 6 months in the Lichtiger study (9), investigators began to explore the use of azathioprine and 6-mercaptopurine as long-term maintenance agents for patients in whom cyclosporine had been effectively used as a rescue agent. Three uncontrolled studies have suggested that patients have a lower relapse rate if they receive maintenance therapy with azathioprine or 6-mercaptopurine (12-14), and alternatively two uncontrolled studies have suggested little benefit (15,16). A randomized controlled trial is planned to address this issue. In the mean time, a strategy of azathioprine maintenance in patients who have had successful cyclosporine rescue seems reasonable (17).

It is important to try and put the overall use of cyclosporine rescue into context. A recent study from Oxford University reported on the outcome of 216 consecutive patients with severe ulcerative colitis seen at a referral center that required hospitalization and treatment with intravenous steroids over a 6-year period (18). One hundred thirty two of 216 patients (61%) achieved remission, 34 of 216 patients (16%) underwent colectomy, and 50 of 216 patients (23%) were treated with intravenous cyclosporine. Of those 50 patients who were treated with cyclosporine, 28 (56%) responded. Eight of the 28 responders relapsed when they were converted to oral cyclosporine. Thus, only 20 of 50 (40%) of cyclosporine treated patients avoided colectomy in the long-term, with a mean follow-up of 19 months. It was not stated whether azathioprine or 6-mercaptopurine was used as a maintenance agent. Taking these results in total, cyclosporine was only required and of long term clinical benefit in 20 of 216 patients (9%) with severe ulcerative colitis.

Toxicity associated with intravenous cyclosporine

Toxicity associated with high-dose intravenous cyclosporine therapy in 111 patients with inflammatory bowel disease treated at the Mount Sinai Hospital in New York City was reported as follows : renal insufficiency 23% ; infections 20% ; seizures 3% ; deaths 2% ; anaphylaxis 1% ; paresthesias 51% ; hypertension 43% ; hypertrichosis 27% ; and gingival hyperplasia 4% (19). Severe infections included one case of pneumocystis pneumonia, three bacterial pneumonias, and 3 catheter related sepsis episodes. The two deaths were related to septic shock and massive duodenal hemorrhage.

Toxicity associated with high-dose intravenous cyclosporine therapy in 74 patients with inflammatory bowel disease treated at the University of Chicago was also recently reported (14,20). There were a total of 40 complications in 74 patients (54%). Eleven of 74 patients (15%) had major complications including two cases of pneumocystis pneumonia (one of which resulted in death), jejunitis, colon perforation, long abscess, grand mal seizure, mycotic aneurysm, and renal insufficiency in four patients. Minor complications occurred in 33 of 74 patients (45%) and included hypertension, headache, hyperkalemia, paresthesias, tremor, and abnormal liver enzymes.

One of the biggest concerns about the use of high-dose cyclosporine in patients with inflammatory bowel disease is the potential for nephrotoxicity (4). Virtually all patients undergoing chronic cyclosporine treatment for autoimmune diseases will have a 20% reduction in the glomerular filtration rate, which is often underestimated when serum creatinine is used to monitor renal function. This acute decrease in renal function results

from vasoconstriction of afferent arterioles in the kidney and initially was thought not to be associated with significant histopathologic changes. Subsequently, a renal biopsy study in 192 patients with autoimmune diseases without associated renal insufficiency treated with oral cyclosporine suggested that histologic evidence of nephrotoxicity is frequent (5). Twenty-one percent of patients had histologic evidence of cyclosporine-induced nephropathy including striped interstitial fibrosis and tubular atrophy (15%), moderate to severe arteriolar alterations (2%), or both striped interstitial fibrosis and arteriolar alterations (5%). Risk factors for developing histologic evidence of nephropathy included a greater initial cyclosporine dose, a greater maximum increase in serum creatinine, and greater age. The authors recommended that patients receiving cyclosporine for autoimmune diseases should not receive oral cyclosporine at doses > 5 mg/kg/day, and that the cyclosporine dose should be adjusted downward whenever the serum creatinine increased to levels > 30% above baseline (5). It should be pointed out that the intravenous dose of cyclosporine commonly used in patients with severe ulcerative colitis (4 mg/kg/day) is equivalent to 12-16 mg/kg/day of oral cyclosporine (assuming oral bioavailability of 20-25%).

Clinical pharmacology of microemulsion cyclosporine (Neoral)

Because of the unfavorable pharmacokinetic characteristics of standard oral cyclosporine outlined above, a new microemulsion formulation of cyclosporine (Neoral) was developed (4). This microemulsion contains polyethylene glycol, caster oil, medium chain triglycerides, and low molecular weight glycols. Suspension of cyclosporine in the microemulsion formulation results in a marked increase in oral bioavailability (145-239%) (21). In addition, the microemulsion formulation reduces both inter- and intra-individual variation in pharmacokinetics. There is improved absorption from the small bowel (even in the setting of mucosal disease) and this formulation is less dependent on the presence of bile for absorption. In the transplant setting, the microemulsion formulation of cyclosporine is therapeutically equivalent to the standard oral cyclosporine formulation (22).

Pilot efficacy data of Neoral for the treatment of severe ulcerative colitis

A small non-randomized pilot study of Neoral and standard oral cyclosporine in patients with severely active ulcerative colitis has been conducted (23). Fifteen patients received Neoral 5 mg/kg/day for three months, with the dose adjusted to a target cyclosporine blood level of 200 ng/ml. Fifteen of 15 patients (100%) initially achieved remission, and 9 of 15 (60%) had prolonged remission (6 of these 9 patients received maintenance therapy with azathioprine). No major toxicity related to Neoral was observed in these 15 patients.

Clinical pharmacology of Tacrolimus

Tacrolimus has relatively low oral bioavailability, ranging from 21-27%, but there is relatively less interpatient variability than there is with oral cyclosporine (24-26). Tacrolimus has poor aqueous solubility and, because it is a macrolide antibiotic, can result in increased gastric motility, both of which can result in low oral bioavailability. Tacrolimus is not dependent on bile for absorption. Similarly, small bowel mucosal integrity is not important for absorption of tacrolimus. The recommended starting dose for oral tacrolimus in the transplantation setting is 0.15 mg/kg twice daily. Trough concentrations of tacrolimus should be measured in whole blood by enzyme immunoassay. In transplantation, the therapeutic window is 10-20 ng/ml.

Pilot efficacy data of Tacrolimus for the treatment of severe ulcerative colitis

There are several pilot or preliminary reports that in tacrolimus may be of benefit in patients with severely active ulcerative colitis. Bousvaros published a case report of a single child with severe ulcerative colitis who responded to oral tacrolimus (27). He later reported a pilot study in which 5 of 6 children with severe ulcerative colitis or Crohn's colitis responded to oral tacrolimus (28). Finally, Fellerman reported that 4 of 6 patients with severely active ulcerative colitis or Crohn's colitis responded to intravenous tacrolimus (29).

Clinical use of cyclosporine/Tacrolimus as a bridge to azathioprine/6-Mercaptopurine

Given the discussion above, it seems reasonable to consider the practical aspects of using cyclosporine or tacrolimus as a rescue therapy which would serve as a "bridge" to maintenance therapy with azathioprine or 6-mercaptopurine in patients with severely active ulcerative colitis (30,31). Patients treated with cyclosporine should initially receive a continuous intravenous infusion of cyclosporine at a dose of 4 mg/kg/day, adjusted to whole blood RIA concentrations of 250-350 ng/ml. Patients treated with tacrolimus should receive oral tacrolimus at a starting dose of 0.10-0.15 mg/kg twice daily, adjusted to a whole blood tacrolimus concentration of 10-20 ng/ml. If the patient responds, he or she should be discharged on oral cyclosporine or tacrolimus with the dose adjusted to maintain the target whole blood concentrations outlined above. During the hospitalization or at the time of discharge, azathioprine should be initiated at a dose of 2-2.5 mg/kg/day or 6-mercaptopurine at a dose of 1-1.5 mg/kg/day. Corticosteroids should be tapered from a discharge dose of 40-60 mg/day to 20 mg/day over one month and then

fixed at 20 mg per day for 2-3 months (resulting in overlap with continued oral cyclosporine or tacrolimus for 3-4 months). Prophylaxis against pneumocystis pneumonia during this period of triple drug immunosuppression is recommended. After 3-4 months, cyclosporine or tacrolimus can be discontinued (without tapering). Beginning one week later, corticosteroids can be tapered from 20 mg/day to 0 mg/day over 4-8 weeks. If the patient relapses at any point during the drug tapering process, he or she should be referred for colectomy.

Conclusions

In conclusion, intravenous cyclosporine (with or without continued intravenous corticosteroids) is effective in 50-80% of patients with severely active ulcerative colitis who fail treatment with oral or intravenous corticosteroids. The long-term response rates drop to 40-60%, even when azathioprine or 6-mercaptopurine is used as maintenance therapy. There is a small risk of opportunistic infection and death (1-2%) during combination therapy with azathioprine, cyclosporine, and corticosteroids. In the big picture, only 9% of patients with severely active ulcerative colitis both require intravenous cyclosporine and benefit from it over the long-term. Additional studies to determine the role of Neoral, tacrolimus, and possibly sirolimus should be undertaken.

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