

THERAPY UPDATE

Cyclosporin for refractory ulcerative colitis

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Approximately 15% of patients with ulcerative colitis will have a severe attack requiring hospitalisation for intravenous steroids at some stage in their illness.¹ Sixty per cent of patients treated with corticosteroids will be symptom free by the end of five days, 15% will have significant improvement, and 25% will not improve. Those who fail to improve may be treated with intravenous cyclosporin or undergo colectomy.

EFFICACY OF INTRAVENOUS CYCLOSPORIN IN SEVERE ULCERATIVE COLITIS

There have been four controlled studies of intravenous cyclosporin in patients with severe ulcerative colitis. Of 20 patients reported by Lichtiger *et al*, nine were randomised to receive placebo and 11 to receive cyclosporin 4 mg/kg/day as a continuous infusion for 14 days.² Nine of 11 cyclosporin treated patients (82%) responded compared with none of the placebo treated patients. Those who responded were continued on oral cyclosporin 8 mg/kg/day. At six months, 5/11 cyclosporin treated patients (45%) maintained a clinical response.

In the second study, 30 patients were randomised to monotherapy with a continuous infusion of either cyclosporin 4 mg/kg/day or methylprednisolone 40 mg/day.³ After eight days, 9/14 patients (64%) who received cyclosporin responded compared with 8/15 (53%) who received methylprednisolone. Patients who responded received the same medication orally in combination with azathioprine. At 12 months, 7/9 patients (78%) initially controlled with cyclosporin maintained remission compared with 3/8 (37%) treated with methylprednisolone.

In the third study, 30 patients were randomised to monotherapy with intravenous cyclosporin 4 mg/kg/day or intravenous cyclosporin in combination with continued prednisolone 1 mg/kg/day.⁴ After seven days, 10/15 patients (67%) in the cyclosporin monotherapy group compared with 14/15 (93%) in the combination therapy group had complete remission.

A Belgian study in which 70 patients with severe ulcerative colitis were randomised to receive either 2 or 4 mg/kg/day of intravenous cyclosporin was recently reported in preliminary form.⁵ After eight days, 29/35 patients (83%) in the 2 mg/kg group and 28/34 (82%) in the 4 mg/kg group had responded to treatment. One patient in the 4 mg/kg group had an anaphylactic reaction after the first infusion and was withdrawn from the study.

CYCLOSPORIN USE AS A BRIDGE TO AZATHIOPRINE/6-MERCAPTOPYRINE

Cyclosporin is an effective "rescue therapy" which may serve as a rapidly acting "bridge" to maintenance therapy with the slowly acting agents azathioprine or 6-mercaptopurine in patients with severe ulcerative colitis. Patients initially receive 2-4 mg/kg/day of cyclosporin by continuous infusion. A monoclonal radioimmunoassay is used to obtain cyclosporin levels on alternate days with target whole blood levels of 150-250 ng/ml (2 mg/kg/day dose) or 300-350 ng/ml (4 mg/kg/day dose). If the patient responds, they are discharged on standard oral cyclosporin

8 mg/kg/day. Microemulsion cyclosporin (Neoral) has a greater oral bioavailability than standard oral cyclosporin, and lower oral doses may be effective.⁶ Azathioprine 2-2.5 mg/kg/day or 6-mercaptopurine 1-1.5 mg/kg/day is also initiated prior to discharge. Over one month after discharge, corticosteroids are tapered from 40-60 mg/day to 20 mg/day, and continued at this dose for 2-3 months. Prophylaxis against *Pneumocystis carinii* pneumonia during this period of triple immunosuppressive therapy is recommended. After 3-4 months, cyclosporin can be discontinued and beginning one week later, corticosteroids are tapered from 20 mg/day to 0 mg/day over 4-8 weeks.⁷ If the patient relapses at any point during the drug taper, they should be referred for colectomy.

TOXICITY ASSOCIATED WITH INTRAVENOUS CYCLOSPORIN

Of 111 patients with inflammatory bowel disease treated with intravenous cyclosporin 4 mg/kg/day, the most common toxic effects were paresthesias (51%), hypertension (43%), and hypomagnesaemia (42%).⁸ Major toxicities reported were renal insufficiency (23%), infections (20%), seizures (3%), death (2%), and anaphylaxis (1%). Low dose intravenous cyclosporin (2 mg/kg/day) may be associated with lower rates of toxicity.⁵ Both hypocholesterolaemia (serum cholesterol less than 120 mg/dl) and hypomagnesaemia (serum magnesium less than 1.5 mg/dl) significantly increase the risk of seizures in patients treated with intravenous cyclosporin.⁹

Summary

- Intravenous cyclosporin (with or without continued intravenous corticosteroids) is effective in 50-80% of patients with severe ulcerative colitis.
- An initial dose of 2 mg/kg/day intravenous cyclosporin appears to be as effective as 4 mg/kg/day and is thus preferred from the standpoint of safety.
- Long term response rates following short term treatment with intravenous cyclosporin in controlled trials ranged from 45% (without azathioprine maintenance) to 78% (with azathioprine).
- There is a small risk of opportunistic infection and death (1-2%) during combined cyclosporin, corticosteroid, and azathioprine therapy, but lower doses of cyclosporin may improve the safety profile.
- Toxicity may be reduced at a dose of 2 mg/kg/day intravenous cyclosporin.

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