UNC Inflammatory Bowel Disease Drug Protocol

GUIDELINES FOR CYCLOSPORIN IN SEVERE COLITIS

Cyclosporin may be used as an alternative or as an adjunct to anti-metabolite therapy for severe or refractory inflammatory bowel disease. Specifically, patients with fistulous Crohn's Disease, severe ulcerative colitis, and refractory proctosigmoiditis may benefit with cyclosporin therapy. It may also be helpful for corticosteroid sparing in patients with Crohn's Disease or used as a bridge to surgery. Cyclosporin acts by inhibiting production of Interleukin 2 by activated T-lymphocytes. It also down-regulates the synthesis of other inflammation cytokines.

Current Indications for Cyclosporin at UNC (February 2005)

1. Hospitalized ulcerative colitis patients failing IV steroid therapy for severe colitis
2. Pyoderma gangranosum

(In patients who are less acutely ill can consider oral tacrolimus)

The risks of cyclosporin administration are nephrotoxicity, hypertension, infectious complications, seizures, tremors, paresthesias, headache, gingival hyperplasia, hypertrichosis, and electrolyte abnormalities. The most common side-effects in patients treated for inflammatory bowel diseases are hypertension, paresthesias, tremors, and abnormalities in magnesium, potassium, and creatinine.

Also to be considered with cyclosporine: 1. maintaining whole blood concentrations in an appropriate, non-toxic range and 2. multiple drug interactions that may occur. A recent double-blind, randomized, controlled clinical trial(Gastroenterology. 2003 Oct; 125(4):1025-31) has shown that using a lower dosage regimen of 2mg/kg/24hr is equally effective to regimens of 4mg/kg/24hr. The lower dose regimen appears to have a lower incidence of hypertension. Serum concentration goals for this regimen are
150-250 ng/ml. Keeping steady-state concentrations between 150-250ng/ml may be warranted to serve as a guideline to minimize toxicity.

The following guideline seeks to optimize cyclosporin therapy, both IV and PO, and to reduce risks of adverse side-effects for cyclosporin.

1. Prior to treatment, a baseline electrolyte panel including Ca, Mg and Phos, LFT's, cholesterol, and uric acid should be obtained.

2. Intravenous treatment should be initiated at 2mg/kg/day by continuous infusion ordered in mg/hr (0.083 mg/kg/hr) rounded to the nearest 5mg dose.

3. Timed whole blood cyclosporin concentrations should be drawn 36-72 hours after initiation or a change in dosing as time to steady state is 2-3 days. Reported concentrations which are above or below the desired range may be adjusted as follows:

   A. 250-350: Decrease dose by 20-30% and recheck in 36-72 hrs
   B. 350+: Hold dose for 6-12 hours and decrease dose by 30-40%
      Recheck level in 36-72 hours.
   C. Below 150: Increase dose by 20-30% and recheck level in 36-72 hr.
   D. If serum creatinine increases by 30%, decrease dose by 30% even if timed level is normal
   E. If increasing disease activity is seen, may increase dose by 30% even if timed level is normal.

4. Oral dosing is much less predictable than intravenous dosing because of wide variability between and within patients despite being on stable dosing. Because of this large variability, initial dosing should be based on a mg/kg basis over serum concentrations.

5. When converting from IV to PO, it is recommended that the oral dose be double the IV dose using Neoral brand (less absorption problems) with a minimum dose of 3.5mg/kg/day. This should be given in 2 divided doses per day (i.e. 2mg/kg po bid). Trough concentrations should be checked
after 36-72 hours and adjusted as above. Oral cyclosporin is available in capsules of 25mg and 100mg strengths, so increments of 25mg/dose should be used.

6. If it is desired to initiate therapy using oral administration, a dose of 4mg/kg po bid is recommended, adjusting with steady-state concentrations.

7. Monitoring of cyclosporin includes, serum Cr, Mg, K, Uric acid QOD initially, then weekly. LFT's should be checked weekly, at first, then every two weeks. Trough concentrations should be checked weekly after stable dosing is established, then every two weeks. Cyclosporin whole blood concentrations are measured by FPIA(TDX) monoclonal whole blood assay. Samples should be drawn in purple top tubes.

8. When any new medication is added after initiation of cyclosporin therapy, drug interactions should be investigated. Consult with pharmacist or call Drug Information at 65134.

For further assistance, please page Sue Kent, Paul Dombrower, or the on-call clinical pharmacist at 347-1464

Updated 01/09/2004

2. Van Assche G, D'Haens G, Noman M et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025-1031