**UNC MEDICAL CENTER GUIDELINE**

**Calcineurin Inhibitors in Severe Colitis**

**Introduction and Overview**

Calcineurin inhibitors (cyclosporine, tacrolimus) may be used as an alternative or as an adjunct to antimetabolite therapy for severe or refractory inflammatory bowel disease. Specifically, patients with severe steroid- refractory colitis, fistulous Crohn’s disease, and refractory proctosigmoiditis may benefit from calcineurin inhibitor therapy. It may also be helpful for corticosteroid-sparing in patients with Crohn’s disease or used as a bridge to surgery. Calcineurin inhibitors act by inhibiting production of interleukin-2 by activated T-lymphocytes. They also down-regulate the synthesis of other inflammatory cytokines.

A multicenter, cohort study, which included 740 patients with steroid-refractory acute ulcerative colitis, compared intravenous cyclosporine and infliximab regarding clinical efficacy and adverse events. The results of this study showed no significant differences in clinical efficacy and colectomy rates, but a lower incidence of adverse reactions.1 This was consistent with the CONSTRUCT study, an open-label, randomized trial, which found no significant differences between cyclosporine and infliximab in colectomy rates, adverse reactions, or mortality in the treatment of ulcerative colitis.2 Oral tacrolimus has been used as an alternative to intravenous cyclosporine for moderate to severe ulcerative colitis. A short-term placebo-controlled, double-blind study enrolled 62 patients with steroid-refractory moderate to severe active ulcerative colitis. Evaluation of Disease Activity Index (DAI) and mucosal healing demonstrated significant clinical improvement and mucosal healing with minimal side effects.3

**Common Adverse Effects**

The most common side effects in patients treated with cyclosporine for inflammatory bowel diseases are: hypertension, paresthesia, tremors, infections, and abnormalities in magnesium, potassium, liver function labs, and serum creatinine. Low magnesium, hypocholesterolemia, diarrhea, and renal insufficiency are specific risks for drug toxicity. Tacrolimus shares many of these side effects but also includes hyperglycemia with prolonged use. In addition, multiple drug interactions may occur with both cyclosporine and tacrolimus requiring close blood concentration monitoring and adverse effect monitoring.

**Cyclosporine**

Cyclosporine whole blood concentrations should be maintained in an effective, non-toxic range. A double blind, randomized, controlled clinical trial in patients with severe ulcerative colitis showed that a lower dosage regimen of 2 mg/kg/24 hours was as effective as a regimen of 4 mg/kg/24 hours.4 The side effect profile of the lower dose regimen had a lower incidence of hypertension. Serum concentration goals for this regimen are 150-250 ng/mL. In a comparative randomized, parallel, open label trial with infliximab, doses were adjusted to maintain concentrations in a range of 150-250 ng/ml which is consistent with the 2003 dosing trial.5 Thus, keeping steady-state concentrations between 150-250 ng/mL may be warranted to serve as a guideline to minimize toxicity.

**Tacrolimus**

Tacrolimus dosing in the majority of studies utilized an initial regimen of 0.05mg/kg orally twice daily with an induction trough range of 10-15 ng/mL for first 14 days, followed by a maintenance trough range of 5-10 ng/mL.3,6,7,8 The following dosing and monitoring guidelines seek to optimize cyclosporine and tacrolimus therapy, and to reduce risks of adverse side effects for cyclosporine.

**BASELINE LABORATORY MEASUREMENTS**

* Serum chemistries: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium and phosphorus
* Liver function tests
* Cholesterol
* Uric acid

**Cyclosporine**

**INITIATION OF THERAPY**

**Intravenous therapy should be initiated at 2 mg/kg/day** (rounded to the nearest 5 mg). It is best ordered as a continuous infusion as 0.083 mg/kg/hr (equals 2 mg/kg/day). When entering in Epic, choose 250 mg in 250 mL normal saline and change the frequency to continuous. Because the colonic concentrations of cyclosporine are significantly higher in patients receiving IV regimens compared to patients receiving oral regimens, a short course (5-7 days) of intravenous therapy may be preferred for the treatment of an acute flare.

Oral therapy, if desired, should be initiated at 5.5 mg/kg in two divided doses. Cyclosporine microemulsion (Neoral®) has better bioavailability than the original oral cyclosporine (Sandimmune®) and thus is preferred for oral administration.

**CONVERTING FROM INTRAVENOUS TO ORAL THERAPY**

When converting from IV to PO, the oral dose should be switched to 5.5 mg/kg/day or double the IV dosing if conversion > 5.5 mg/kg/day.2,9 This should be given in 2 divided doses per day. Oral cyclosporine is available in 25 mg and 100 mg capsules, so doses should be rounded to the nearest 25 mg.

**BLOOD CONCENTRATION MONITORING AND DOSAGE ADJUSTMENT**

Cyclosporine whole blood concentrations are measured by liquid chromatography-tandem mass spectrometry by our lab. Samples should be drawn in lavender tubes. Samples must be received by the lab by 12 noon to be run the same day.

Cyclosporine blood samples should not be drawn through existing intravenous lines because of possible contamination. Therefore, the samples should only be drawn via a peripheral venipuncture. Since the time to steady state concentrations averages 2 to 3 days, timed whole blood cyclosporine concentrations should be drawn 48 to 72 hours after initiation of therapy or a change in dose.

**Trough goals for cyclosporine in the treatment of colitis are 150-250 ng/ml**. Reported concentrations, which are above or below the desired range, may be adjusted as follows:

1. Below 150 ng/mL: Increase dose by 20-30% and recheck concentration in 48 to 72 hours.
2. 250-350 ng/mL: Decrease dose by 20-30% and recheck concentration in 48 to 72 hours.
3. Above 350 ng/mL: Hold dose for 6 to 12 hours and decrease dose by 30-40%.
4. Recheck concentration in 48 to 72 hours.
5. If serum creatinine increases by 30%, decrease dose by 30% even if timed level is at goal
(150-250 ng/mL).
6. If increasing disease activity is seen, may increase dose by 30% even if timed level is at goal (150-250 ng/mL).

**ROUTINE MONITORING**

Serum creatinine, potassium, magnesium, and uric acid should be measured every other day initially, then weekly. Magnesium supplementation is suggested for levels < 1.5 mcg/mL to reduce risk of neurological side effects.

Liver function tests should be checked weekly at first, then every other week.

Trough cyclosporine concentrations should be measured every two to three days until stable dosing is established. Further trough monitoring should then be done weekly for 2 weeks, then every other week thereafter.

**DRUG INTERACTIONS**

Several medications are known to interact with cyclosporine. When any new medication is added to the patient’s regimen after initiation of cyclosporine therapy, the potential for drug interactions should be evaluated.

**Tacrolimus**

**INITIATION OF THERAPY**

**Oral dosing should be initiated at 0.05 mg/kg BID with immediate-release forms of tacrolimus**. Oral tacrolimus is available in 0.5 mg, 1 mg, and 5mg capsules. The oral solution is available in the hospital as it is compounded, but it may not easily available for outpatient use.

**BLOOD CONCENTRATION MONITORING AND DOSAGE ADJUSTMENT**

Similar to cyclosporine, the time to steady state concentrations averages 2-3 days. Timed or trough concentrations should be drawn 36-72 hours after initiation of therapy or change in dose.
**Trough goals for tacrolimus in the treatment of colitis are 10-15 ng/ml during the induction period and 5-10 ng/ml during the maintenance period.** Trough concentrations which are above or below the desired range may be adjusted as follows:

Induction period (first 14 days):

1. Below 10 ng/mL: Increase dose by 20-30% and recheck concentration in 36-72 hours
2. 16-18 ng/mL: Decrease dose by 20-30% and recheck concentration in 36-72 hours
3. > 18 ng/mL: Hold dose for 12 hours, decrease dose by 30%, recheck concentration daily.
4. If serum creatinine increases by 30% or neurological side effects, consider decrease in dose even if concentration is in therapeutic range.

Maintenance period:

1. Below 5 ng/mL: Increase dose by 20-30% and recheck concentration in 36-72 hours
2. 11-15 ng/mL: Decrease dose by 20-30% and recheck concentration in 36-72 hours
3. > 15 ng/mL: Hold dose for 12 hours, decrease dose by 30%, recheck concentration daily.
4. If serum creatinine increases by 30% or neurological side effects, consider decrease in dose even if the concentration is in therapeutic range.

**ADDITIONAL INFORMATION**

For assistance with this guideline, consult your clinical service pharmacist or contact the clinical pharmacist on call (pager 347-1464).

**REFERENCES**

1. Ordas I, et al. Long-Term Efficacy and Safety of Cyclosporine in a Cohort of Steroid-Refractory Acute Severe Ulcerative Colitis Patients from the ENIEDA Registry (1989-2013): A Nationwide Multicenter Study. AmJ Gastroenterol 2017; 112:1709-1718.
2. Williams, JG et al. Inliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomized trial. Lancet Gastroenterol Hepatol. 2016 Sep; 1(1): 15-24.
3. Ogata H, et al. Double-Blind, Placebo-Controlled Trial of Oral Tacrolimus (FK06) in the Management of Hospitalized Patients with Steroid-Refractory Ulcerative Colitis. Inflamm Bowel Dis 2012: 18:803-808.
4. Van Assche G, et al; Randomized, Double-Blind Comparison of 4mg/kg vs 2mg/kg Intravenous Cyclosporine in Severe Ulcerative Colitis. Gastroenterology 2003; 125:1025-1031
5. Laharie D, et al; Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory in intravenous sterolids: a parallel, open-label randomized controlled trial. Lancet 2012; 380: 1909-15.
6. Kawakami, K, et al. Effects of oral tacrolimus as a rapid induction therapy in ulcerative colitis. World J Gastroenterol. 2015 Feb 14; 21(6): 1880-1886.
7. Miyoshi J, et al. Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients. Journal of Crohn’s and Colitis (2013) 7: 609-614.
8. Yamamoto S, et al: Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. Aliment Pharmacol Ther 2008 (28): 589-597.
9. Lamb CA, Kennedy NA, Raine T, et al: British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1–s106