UNC
SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE
Division of Gastroenterology
and Hepatology

UNC Inflammatory Bowel Disease Drug Protocol

PROGRAF (tacrolimus): Prograf is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. It is currently FDA approved for the prevention of organ transplant rejection. Its mechanism of action is via inhibition of t-lymphocyte activation. Clinical trials have demonstrated the efficacy in the treatment of fistulizing and luminal Crohn's disease. There is some suggestion that Prograf may be effective in the treatment of moderate to severe ulcerative colitis in patients who are steroid resistant. The ideal length of treatment is usually not more than 6 months secondary to potential nephrotoxicity however it has been used more chronically with careful monitoring.

Current indications for Prograf at UNC:

1. Medically refractory fistulizing and luminal Crohn's disease not responsive to first line immunomodulator therapy.
2. Ulcerative colitis that is steroid resistant (as rescue therapy vs. cyclosporine when consideration is being made for surgical intervention)
3. Pyoderma gangranosum

Treatment Regimen

Baseline evaluation

- Cholesterol Serum
- CBC with differential
- Liver function tests
- Serum glucose, potassium, magnesium, BUN, creatinine
- Vital signs (caution should be used in patients who are hypertensive)

Treatment Protocol

Prograf is available in 5mg, 1mg and 0.5mg capsules (Astellas Pharm). There is no generic equivalent

After baseline lab work is obtained, patients are started on 5mg BID. If there is any suggestion of impaired renal function, dose adjustment or alternative therapy should be considered.

Patient should be advised to take the Prograf twice daily at approximately the same time each day, Pharmacy distributed education materials emphasize exactly 12 hour spacing between doses, but this is necessary only in transplant anti-rejection protocols.

Patients can take Prograf with or without food, but they should be advised to take it the same way every time as this can affect the measured blood levels.

Monitoring of serum chemistries to include at minimum potassium, glucose, magnesium and creatinine are drawn weekly. CBC should be drawn at least monthly following the initiation of therapy. Trough tacrolimus levels are drawn weekly. Patients should be advised to hold their morning dose of Prograf and have blood work drawn at or around the time their morning dose of Prograf is due. Following the lab draw, the morning dose of Prograf can be taken as usual.

Prograf dose adjustments are made based on the following "algorithm". Target tacrolimus whole blood concentration is between 10 and 20ng/ml. For levels <5ng/ml, consider a 35% dose increase; for levels 5-9ng.ml increase dose by 20%. For tacrolimus levels >30ng/ml decrease dose by 35%, for levels 21-30 consider a 20% dose decrease. Individualized dosing adjustments are made for hyperkalemia, hyperglycemia and elevated creatinine levels.

Subjective dose adjustments can be made for side effects that include, but are not limited to infection, hypertension, headaches, tremor, paresthesias, insomnia, diarrhea, nausea, vomiting, alopecia, impotence. A lower whole blood tacrolimus concentration is acceptable if desired effect is achieved at lower dose.

Consideration must be made to the cost of this medication. It is generally considered a premium co-payment for those persons with insurance. Should a combination of doses be needed to provide the daily dose (i.e. patient requires 6mg BID: one 5mg and one 1mg capsule) each of these dose strengths is considered a separate prescription and patients will have double out of pocket expense for the prescription.

Prograf is considered a category "C" in pregnancy. Birth defects, neonatal hyperkalemia and renal dysfunction in the neonate have been associated with the use of Prograf in pregnancy. Risk vs. benefit must be discussed: it is likely that the use of Prograf in patients with IBD (vs. its use as an antirejection medication in solid organ transplantation) may not be justified during pregnancy. Prograf is excreted in human milk and should not be used while nursing.

References

1. Fukuda A, Nakase H, Seno H, Nabeshima M, Sawada M, Chiba T. Refractory enterovesical and duodenocolic fistulas in Crohn's disease successfully managed with tacrolimus. J Gastroenterol. 2005 Apr;40(4):433-5.

2. Gonzalez-Lama Y, Abreu L, Vera MI, Pastrana M, Tabernero S, Revilla J, Duran JG, Escartin P. Long-term oral tacrolimus therapy in refractory to infliximab fistulizing Crohn's disease: a pilot study. Inflamm Bowel Dis. 2005 Jan;11(1):8-15.

3. Gonzalez Lama Y, Abreu LE, Vera MI, de la Revilla J, Fernandez-Puga N, Escartin P. Long-term oral tacrolimus in refractory to infliximab fistulizing Crohn's disease: comments from Spanish experience. Gastroenterology. 2004 Mar;126(3):942-3; author reply 943.

4. Sandborn WJ, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, FeaganBG, Mayer L, Johnson T, Galanko J, Martin C, Sandler RS. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: A randomized, placebo-controlled trial. Gastroenterology. 2003 Aug;125(2):380-8.

5. Loftus CG, Egan LJ, Sandborn WJ. Cyclosporine, tacrolimus, and mycophenolate mofetil in the treatment of inflammatory bowel disease. Gastroenterol Clin North Am. 2004 Jun;33(2):141-69.

6. Hogenauer C, Wenzl HH, Hinterleitner TA, Petritsch W. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. Aliment Pharmacol Ther. 2003 Aug 15;18(4):415-23.

7. Baumgart DC, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. Aliment Pharmacol Ther. 2003 May 15;17(10):1273-81.

8. Fellermann K, Tanko Z, Herrlinger KR, Witthoeft T, Homann N, Bruening A, Ludwig D, Stange EF. Response of refractory colitis to intravenous or oral tacrolimus (FK506). Inflamm Bowel Dis. 2002 Sep;8(5):317-24.

9. Bousvaros A, Kirschner BS, Werlin SL, Parker-Hartigan L, Daum F, Freeman KB, Balint JP, Day AS, Griffiths AM, Zurakowski D, Ferry GD, Leichtner AM. Oral tacrolimus treatment of severe colitis in children. J Pediatr. 2000 Dec;137(6):794-9.

10. 6: Matsuhashi N, Nakajima A, Watanabe K, Komeno Y, Suzuki A, Ohnishi S, Omata M, Kondo K, Usui Y, Iwadare JI, Watanabe T, Nagawa H, Muto T. Tacrolimus in corticosteroid-resistant ulcerative colitis. J Gastroenterol. 2000;35(8):635-40.

11. Fellermann K, Ludwig D, Stahl M, David-Walek T, Stange EF. Steroid-unresponsive acute attacks of inflammatory bowel disease:

immunomodulation by tacrolimus (FK506). Am J Gastroenterol. 1998 Oct;93(10):1860-6.

12. Sandborn WJ. Tremaine WJ. Wolf DC. Targan SR. Sninsky CA. Sutherland LR. Hanauer SB. McDonald JW. Feagan BG. Fedorak RN. Isaacs KL. Pike MG. Mays DC. Lipsky JJ. Gordon S. Kleoudis CS. Murdock RH Jr.(1999) Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. Gastroenterology. 117(3):527-35

13. Ierardi, E et al 2001 Long Term Tacrolimus: A promising Therapeutic approach for Crohn's disease: Transplantation Proceedings 33: 2107-2109.

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Prograf (Tacrolimus) Monitoring Sheet

Patient Name _____ **Unit #** _____

Date							
Drug Dose							
Hgb/Hct							
WBC/Plts							
Cholesterol (baseline)							
AST/ALT							
Alk Phos/GGT							
BUN/Creatinine							
Prograf Level							