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

UNC Inflammatory Bowel Disease Drug Protocol

Methotrexate: *Methotrexate* is a mild immunosuppressant that also exhibits anti-inflammatory activity. *Methotrexate* is commonly used for the treatment of certain cancers including but not limited to leukemia, Hodgkin's disease and head and neck cancers. In these illnesses, *methotrexate* is used in very large doses so that it interferes with the reproduction of the cancer cells. *Methotrexate* is used in smaller doses for the treatment of rheumatoid arthritis, Crohn's disease and psoriasis. Clinical trials have demonstrated efficacy of Methotrexate in induction and maintenance of remission in Crohn's disease.

Current Indications for Methotrexate at UNC (February 2005)

- Medically refractory Crohn's disease
- Patients who have had pancreatitis or poor tolerance to azathioprine or 6 mercaptopurine and require immunomodulator therapy
- Patients who have active Crohn's disease as well as active inflammatory arthritis

Treatment Regimen

Pre-methotrexate evaluation

1. CBC with differential
2. BUN/ Creatinine
3. AST, ALT, Alkaline Phosphatase, GGT, T. Bilirubin, Albumin
4. Urinalysis
5. Hepatitis A, B and C serologies
6. Assess HIV risk and appropriate testing as indicatate.
7. Chest X-ray

Treatment Protocol

1. Methotrexate is available in 25 mg/ml vials or in 2.5 mg tablets. In small bowel Crohn's disease the parenteral form is commonly used.

2. Drug administration is **one time** per week. More frequent dosing may lead to toxicity.
3. Initial parenteral dosing is 25 mg per week (1ml) x 16 weeks, then dosage reduction to 15 mg/week (0.6 ml) if tolerated. (per Feagan et al *N Engl J Med*. 1995;332:292-297)
4. Initial oral dosing may be as high as 37.5 mg per week due to absorption considerations. Oral dosing more likely to be used in colonic disease or if parenteral form is not available. There have been shortages of the parenteral form in recent years.
5. For parenteral dosing the patient is taught self injection techniques in the clinic. Subcutaneous rather than IM injections are used with less morbiditiy seen.
6. Patients may experience nausea with dosing – we recommend giving at night and with Promethazine if nausea is a significant issue.
7. Patients should receive 1 mg/day or a single 7 mg/week dose of folate while they are receiving methotrexate due to interference with folate metabolism. Folate should not be taken on the same day as the methotrexate. Low dose folate does not interfere with the efficacy of the methotrexate. (Morgan et al Ann Intern Med 1994; 121:844-41)
8. Contraindications for Methotrexate therapy: creatinine clearance of less than 50 ml/ minute, pregnancy or contemplating pregnancy, breast feeding, active liver disease, alchoholism, active pulmonary disease. (Pregnancy and lactation are considered absolute contraindications – the others are relative.
9. Monitoring: Labs at baseline as noted above then at 2 weeks – CBC, LFTs, Albumin, BUN/Creatinine and if stable and on stable dose then every 8-12 weeks. Annual chest x-ray is recommended (Monitoring sheet attached)
10. Liver biopsy is indicated when patient has a persistent AST elevation. American College of Rheumatology states that liver biopsy can be avoided if the patient has AST and albumin within the normal range. (Arthritis Rheum 1996;39:723)

References:

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4. Mahadevan U, Marion JF, Present DH. Fistula response to methotrexate in Crohn's disease: a case series. Aliment Pharmacol Ther. 2003 Nov 15;18(10):1003-8.

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7. Fraser AG, Morton D, McGovern D, Travis S, Jewell DP. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. Aliment Pharmacol Ther. 2002 Apr;16(4):693-7.

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9. placebo-controlled trial. Hepatogastroenterology. 1999 May-Jun;46(27):1724-9.

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11. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med. 1995 Feb 2;332(5):292-7.

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Patient Safety Sheet: Methotrexate

Do not start taking Methotrexate

- If you are allergic to the drug
- If you are pregnant or trying to get pregnant
- If you have active liver disease

You should not start taking Methotrexate:

- If you have any type of active infection. An infection can be in one part of your body, such as an open sore, or it can be an illness such as the flu.

Tell your doctor:

- If you have a fever or feel like you have the flu
- If you develop worse diarrhea
- If you have a nagging cough
- If you feel short of breath
- If you have any unusual bruising or bleeding

If these or any other signs of infection appear after you take Methotrexate tell your doctor right away. Also speak with your doctor:

- before you receive any vaccines
- if you are pregnant, become pregnant or plan to become pregnant

The most common side effects of Methotrexate are:

- injection site reactions if you are taking it by injection
- loss of appetite
- nausea and vomiting
- diarrhea
- mouth sores

Less common but serious side effects include:

- Liver disease
- Lung problems
- Kidney disease
- Decreased bone marrow activity

(These are the side effects that are being monitored by blood work)

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Methotrexate Monitoring Sheet

Date Medical Record Number

Patient name Diagnosis

Physician

Laboratory Tests Performed

	Baseline	2 weeks	Every 8-12 weeks				
Hgb/Hct							
WBC/Plts							
Creatinine							
AST/Albumin							
	Baseline	Annually					
Chest X-ray							

More frequent laboratory monitoring may be needed to assess increasing values.

Liver biopsy assessment: Liver biopsy is indicated only when the patient has persistent AST elevation. The American College of Rheumatology states that liver biopsy can be avoided if the patient has AST and albumin values within normal range (Arthritis Rheum 1996;39:723). The dermatology literature recommends a liver biopsy after 1.5-g cumulative dose (J Am Acad Dermatol 1998;38:478-5).

Laboratory interpretation (J Am Acad Dermatol 1998;38:478-5) **Hb/leukocyte/platelets:** Assess Hb for anemia; MCV > 100 μm^3/cell (100 fL) may indicate folate deficiency, discontinue therapy if leukocyte count < 3,500/mm^3 (continuing beyond one week), platelet count < 100,000/mm^3, restart therapy after three weeks at 50 to 75 percent of original dose. **SCr:** Do not use in patients with an estimated CrCl < 50 mL per minute. **AST/albumin**: If elevated, obtain AST one week after last dose. If elevation persistent, withhold methotrexate for one to two weeks and repeat AST. AST should return to normal within one to two weeks. Persistent AST elevation for two to three months warrants liver biopsy.

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Methotrexate Monitoring Sheet

Patient Name _____ **Unit #** _____

Date							
Hgb/Hct							
WBC/Plts							
Creatinine							
AST/Albumin							
Chest X-ray							

Date							
Hgb/Hct							
WBC/Plts							
Creatinine							
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