**RISK FACTORS FOR HEMATOLOGIC TOXICITY FROM METHOTREXATE**

- Renal insufficiency
- Advanced age
- Lack of folate supplementation
- Methotrexate dosing errors
- Drug interactions
- Hypoalbuminemia
- Greater than moderate alcohol intake

**RISK FACTORS FOR HEPATOTOXICITY FROM METHOTREXATE**

- History of or current greater than moderate alcohol consumption (methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy. The exact amount of alcohol that leads to risk is unknown and differs from person to person.)
- Persistent abnormal liver chemistry studies
- History of liver disease including chronic hepatitis B or C
- Family history of inheritable liver disease
- Diabetes mellitus
- Obesity
- History of significant exposure to hepatotoxic drugs or chemicals
- Hyperlipidemia
MONITORING FOR HEPATOTOXICITY IN PATIENTS WITH NO RISK FACTORS FOR HEPATOTOXICITY\textsuperscript{1,2}

- No baseline liver biopsy
- Monitor liver function tests monthly for the first 6 months and then every 1-3 months thereafter
  - For elevations < two fold upper limit of normal — repeat in 2-4 weeks
  - For elevations > two fold but < three fold upper limit of normal — closely monitor, repeat in 2-4 weeks, and decrease dose as needed
  - For persistent elevations in 5/9 AST levels over a 12-month period or if there is a decline in the serum albumin below the normal range with normal nutritional status, in a patient with well-controlled disease, a liver biopsy should be performed
- Consider liver biopsy after 3.5 - 4.0 g total cumulative dosage
  or
- Consider switching to another agent or discontinuing therapy after 3.5 - 4.0 g total cumulative
dosage
  or
- Consider continuing to follow according to above guidelines without biopsy

MONITORING FOR HEPATOTOXICITY IN PATIENTS WITH RISK FACTORS FOR HEPATOTOXICITY\textsuperscript{1,2}

- Consider the use of a different systemic agent
- Consider delayed baseline liver biopsy (after 2-6 months of therapy to establish medications efficacy and tolerability)
- Repeat liver biopsies after approximately 1 - 1.5 gm of methotrexate
# Medications that may increase Methotrexate Toxicity

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<th>Nonsteroidal Anti-Inflammatory Drugs</th>
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<td>Thiazide-diuretics</td>
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Abnormalities in renal function may require a marked reduction in the dose as 85% of methotrexate is renally excreted

Abnormalities in liver function – LFT’s should be followed and all elevations require careful monitoring

Hepatitis, active or recurrent

Greater than moderate alcohol consumption – While there is little data to support specific limits on alcohol consumption, some physicians require patients to completely refrain from alcohol while others allow daily alcohol intake. A history of alcoholism is particularly worrisome if there is baseline liver damage

Concomitant use of hepatotoxic drugs – more frequent monitoring of liver function tests should be considered

Active infectious disease, particularly chronic infections that are likely to be worsened by immunosuppressive effects of methotrexate such as active untreated tuberculosis or acquired immunodeficiency syndrome. Methotrexate should be withheld during acute infections

Current use of other immunosuppressive agents

Conception should be avoided during methotrexate treatment and afterwards for at least three months in the male and three ovulatory cycles in women

Recent vaccination with a live vaccine

Obesity (body mass index greater than 30)

Diabetes mellitus

Unreliable patient
Recommendations for methotrexate

- **Indication:** Severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy
- **Dosing:** Methotrexate is administered as a weekly single oral dose
  - Doses can be increased gradually until an optimal response is achieved.
  - Total dose should not ordinarily exceed 30mg per week. Doses should be reduced to the lowest possible amount of drug needed to achieve adequate control of psoriasis with concomitant topical therapy.
  - A test dose of 2.5 – 5 mg is recommended
- **Duration of Dosing:**
  - Treatment can be continued for as long as is necessary provided there are no meaningful signs of liver or bone marrow toxicity with adequate monitoring
  - Folic acid supplementation 1-5mg daily by mouth, except for the day of methotrexate dosing, reduces the frequency of side effects
- **Therapeutic Results:**
  - In the only placebo-controlled trial of methotrexate for psoriasis, 36% of patients treated with 7.5mg orally per week, increased as needed up to 25mg per week, reached PASI 75 after 16 weeks
- **Absolute Contraindications**
  - Pregnancy
  - Nursing mothers
  - Alcoholism
  - Alcoholic liver disease or other chronic liver disease
  - Immunodeficiency syndromes
  - Bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia
  - Hypersensitivity to methotrexate
- **Relative Contraindications**
  - Abnormalities in renal function
  - Abnormalities in liver function
  - Active infection
  - Obesity
  - Diabetes mellitus
- **Toxicity**
  - Elevated LFT’s
    - Minor elevations of LFTs are common. If elevation exceeds 2x normal, must check more frequently; if exceeds 3x normal, consider dose reduction; if exceeds 5x normal discontinue.
    - Anemia, aplastic anemia, leukopenia, thrombocytopenia
    - Interstitial pneumonitis
    - Ulcerative stomatitis
    - Nausea, vomiting, diarrhea
    - Malaise or fatigue
    - Chills and fever
    - Dizziness
    - Decreased resistance to infection
    - Gastrointestinal ulceration and bleeding
    - Photosensitivity (“radiation recall”)
    - Alopecia
- **Drug Interactions**
  - Hepatotoxic drugs such as barbiturates
  - Acitretin has been used successfully in combination with methotrexate despite the potential for hepatotoxicity from both medications
  - Drugs that interfere with renal secretion of methotrexate such as sulfamethoxazole, NSAID’s and penicillins
  - Folic acid antagonists such as trimethoprim
Recommendations for methotrexate (continued)

- **Liver Biopsy**
  - Low risk patients – at baseline, not necessary
  - First biopsy: 3.5-4g; subsequent biopsies to be considered after 1.5g
  - High risk patients including history of diabetes, obesity, abnormal LFT's, excessive EtOH ingestion, chronic liver disease, family hx of heritable liver disease
  - Consider baseline biopsy or at 6 months with subsequent biopsies after 1-1.5 grams

- **Baseline Monitoring**
  - History and Physical Examination
  - CBC and platelet count
  - BUN, creatinine and LFT's
  - Liver biopsy is only indicated in patients with a history of significant liver disease
  - Pregnancy test and test for HIV in selected patients
  - Consider PPD
  - Consider chest x-ray if patient has underlying pulmonary disease

- **Ongoing Monitoring**
  - CBC and platelet count at varying intervals (initially every 2-4 weeks for first few months and then every 1-3 months depending upon dosage adjustments, symptoms, and previous CBC results)
  - LFT's at monthly intervals, BUN, creatinine every 2-3 months depending on dosage adjustments, symptoms and previous blood results
  - Pregnancy test if indicated
  - Consider liver biopsy in high risk patients including history of diabetes, obesity, abnormal LFT's, excessive EtOH ingestion, chronic liver disease, family hx of heritable liver disease
  - For those without risk factors, consider liver biopsy in patients with cumulative doses of more than 3.5-4g methotrexate
  - For patients without risk factors, consider repeat liver biopsies after each subsequent 1.5g dosage, based on LFT's, risk factors such as diabetes and obesity, or in consultation with a hepatologist
  - The aminoterminal peptide of procollagen III is used in Europe (but is generally not available in the United States) as a test for hepatic fibrosis, reducing the need for frequent liver biopsies

- **Pregnancy:** Category X; Males and females considering conception should be off methotrexate for 3 months prior to attempting to conceive. Should pregnancy ensue prior to this time period, consider genetic counseling.

- **Nursing:** Mothers receiving methotrexate should not breast feed

- **Pediatric Use:** Methotrexate is approved for the treatment of juvenile rheumatoid arthritis. Low dose methotrexate has been used effectively and safely in children for a variety of dermatologic and rheumatologic disorders.

- **Psoriatic Arthritis:** Although there are only two small controlled trials evaluating methotrexate for psoriatic arthritis that are inadequately powered to assess clinical benefit, methotrexate is often used as the primary agent to treat psoriatic arthritis

**REFERENCES**


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