Methotrexate Contraindications and Risk Factors for Serious Adverse Events in Inflammatory Disorders

Recommendations for Use
February 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

When to Avoid and Not Require Methotrexate Before Biologics

A trial of methotrexate should generally be avoided and should not be required before biologics in the presence of any of the following conditions[1]:

Contraindications

- Persistently abnormal liver function or enzyme tests and, if available, other markers of hepatic damage such as procollagen type III n-terminal peptide (PIIINP) levels
- Liver disease, including active or recurrent hepatitis and hepatic fibrosis or cirrhosis on liver biopsy (biologics may also not be advisable in this situation)
- Active infectious disease, including active untreated tuberculosis or advanced HIV infection; excludes acute infections for which methotrexate may be temporarily withheld
- Untreated immunodeficiency (does not apply to treatment with other immunosuppressives such as biologic agents)
- Blood dyscrasias or cytopenias (contraindication for methotrexate; requires caution and risk-benefit evaluation for biologics)
- Conception in men or women; patients planning conception or patients of childbearing potential and not using adequate contraceptive method (conception should be avoided during methotrexate therapy and for at least 3 months after stopping therapy in males or at least one ovulatory cycle in females)
- Pregnant or nursing women
- Pneumonitis or significant pulmonary disease that may interfere with diagnosis or monitoring for methotrexate-induced lung disease / pulmonary fibrosis
- Recent vaccination, especially with live vaccine (also refer to live vaccine and BCG vaccination restrictions for biologics)
- Third-compartment spacing, such as persistent pleural effusion and ascites
- Malignant lymphoma (biologic therapy is also not advisable in this situation)
- Hypersensitivity

Relative Risk Factors (Methotrexate May Be Used, But Not Required)

- Renal insufficiency (CrCl < 50 ml/min). (No CrCl cutoff is recommended in U.S. product information online for methotrexate / RHEUMATREX, OTREXUP, RASUVO but other sources recommend modifying dosage in renal impairment[2,3,4] or avoiding use at CrCL < 50 or < 10 ml/min.[2,3])

- Lifetime cumulative dose of methotrexate is 3 grams or greater. Consider alternative systemic therapies at these cumulative doses, given the limitations of existing data to support or refute lifetime dose of methotrexate as a risk factor.
- Significant lifetime alcohol consumption (e.g., past or current use of >1–2 drinks per day). Methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy. The exact amount of alcohol that confers risk is unknown and differs among persons.
- Chronic hepatitis C without evidence of significant liver disease (contraindicated in patients with HCV and cirrhosis).
- Family history of inheritable liver disease
- Obesity (body mass index greater than 30)
- Diabetes mellitus
- History of significant exposure to hepatotoxic drugs (e.g., azathioprine, retinoids, sulfasalazine) or chemicals
- Steatohepatitis
- Untreated hyperlipidemia
- Lack of folate supplementation (i.e., folic acid 1 or 5 mg daily or folinic acid 5 mg every 12 h for 3 doses then once every week, with the first dose given 12 hours after the methotrexate dose)

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REFERENCES

1 Kalb, et al. Methotrexate and Psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60:824–37.

2 Methotrexate Product Monograph, Pfizer Canada, last updated October 14th, 2015.

3 Methotrexate. In: MedScape, WebMD LLC, 2016.

4 Bressolle F, Bologna C, Kinowski JM, Sany J, Combe B. Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. Ann Rheum Dis 1998;57:110–113.