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:

**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)

Contact:  Francine Goodman, PharmD, BCPS, National Clinical Pharmacy Program Manager – Formulary, VA Pharmacy Benefits Management Services (10P4P)

REFERENCES

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