

Pharmacovigilance in Methotrexate Therapy: A Review

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ABSTRACT

Methotrexate (MTX) is a potent antimetabolite and folate antagonist extensively used for the treatment of various malignancies and autoimmune disorders, including rheumatoid arthritis and psoriasis. Despite its broad therapeutic utility, MTX possesses a narrow therapeutic index, rendering patients susceptible to severe toxicities such as hepatotoxicity, pulmonary fibrosis, myelosuppression, nephrotoxicity, and neurotoxicity. The implementation of robust pharmacovigilance practices is therefore essential to enhance patient safety and optimize therapeutic outcomes. Pharmacovigilance, as defined by the World Health Organization (WHO), encompasses the science and activities dedicated to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug-related issues. Through post-marketing surveillance and adverse event reporting systems like WHO Vigibase, FAERS, and EudraVigilance, critical safety signals have been identified, leading to refined monitoring protocols and regulatory updates. Effective pharmacovigilance in MTX therapy relies on continuous patient monitoring, laboratory investigations, education on potential toxicities, and the prevention of drug-drug interactions. Strengthening global pharmacovigilance networks and promoting awareness among healthcare professionals are pivotal steps toward mitigating MTX-related risks while maintaining its therapeutic efficacy.

Keywords: Methotrexate, Pharmacovigilance, Adverse drug reactions, Toxicity, Post-marketing surveillance, WHO Vigibase, FAERS, EudraVigilance

INTRODUCTION

Methotrexate (MTX), a structural analogue of folic acid, is one of the oldest and most widely used antimetabolites in medicine. Originally introduced in the 1940s as a chemotherapeutic agent, it later became a cornerstone in the management of autoimmune diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Its mechanism of action involves inhibition of dihydrofolate reductase, leading to impaired DNA synthesis and suppression of rapidly dividing cells [1-5]. Although highly effective, MTX therapy is associated with a narrow therapeutic index and multiple dose-dependent and idiosyncratic toxicities, including hepatotoxicity, pulmonary toxicity, myelosuppression, nephrotoxicity, and mucositis [6]. These adverse drug reactions (ADRs) significantly impact treatment adherence, morbidity and mortality. Pharmacovigilance, as defined by the World Health Organization (WHO), refers to the “science and activities relating to the detection, assessment,

understanding, and prevention of adverse effects or any other drug-related problem” [7]. In the context of MTX, pharmacovigilance is particularly crucial because of its widespread use across oncology and rheumatology, its complex pharmacokinetics, and the potential for life-threatening ADRs. Post-marketing surveillance has been instrumental in detecting rare but serious toxicities such as MTX-induced pneumonitis, thereby influencing clinical guidelines and regulatory recommendations [8]. Therefore, a comprehensive review of pharmacovigilance in MTX therapy is essential to highlight the spectrum of ADRs, monitoring strategies, and regulatory frameworks designed to optimize patient safety while maintaining therapeutic efficacy.

Pharmacology of Methotrexate:

MECHANISM OF ACTION

Methotrexate (MTX) is a folic acid analogue that competitively inhibits dihydrofolate reductase

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(DHFR), blocking the conversion of dihydrofolate to tetrahydrofolate. This inhibition disrupts DNA, RNA, and protein synthesis, particularly in rapidly dividing cells [9]. At low doses, MTX also increases extracellular adenosine, contributing to its anti-inflammatory effects in autoimmune diseases [10].

Pharmacokinetics

Absorption: Oral MTX shows variable bioavailability (25–100%), reduced at higher doses (>15 mg/week) [11].

Distribution: Widely distributed; accumulates in liver, kidney, and synovial tissues; crosses into third-space fluids (pleural, peritoneal).

Metabolism: Partially metabolized in the liver to 7-hydroxymethotrexate; undergoes polyglutamine intracellularly, prolonging activity.

Excretion: Primarily renal via glomerular filtration and active tubular secretion; impaired renal function markedly increases toxicity risk [12].

Routes of Administration

Oral (commonly used in low-dose regimens for rheumatoid arthritis and psoriasis).

Parenteral (subcutaneous, intramuscular, intravenous, and intrathecal). High-dose regimens in oncology require leucovorin rescue to mitigate toxicity.

Clinical Uses

Oncology: Acute lymphoblastic leukemia, non-Hodgkin's lymphoma, osteosarcoma and choriocarcinoma.

Autoimmune disorders: Rheumatoid arthritis, psoriasis, Crohn's disease and juvenile idiopathic arthritis.

Adverse Drug Reactions of Methotrexate:

Methotrexate (MTX), despite its wide therapeutic applications, is associated with multiple dose-dependent and idiosyncratic adverse drug reactions (ADRs). These ADRs may involve various organ systems and can range from mild to life-threatening.

Hepatotoxicity

Long-term MTX therapy is linked with hepatic fibrosis and cirrhosis, especially in patients with risk factors such as obesity, diabetes, alcohol use, or concomitant hepatotoxic drugs. Monitoring of liver enzymes (ALT, AST) and periodic imaging or biopsy in high-risk patients is recommended [13,14].

Pulmonary Toxicity

MTX-induced pneumonitis is an idiosyncratic, potentially fatal reaction, occurring in up to 1–7% of patients. Symptoms include nonproductive cough, dyspnea, fever and hypoxemia. Discontinuation of MTX and corticosteroid therapy are standard management strategies [15, 16].

Hematologic Toxicity

Myelosuppression (leukopenia, anemia, thrombocytopenia, or pancytopenia) is dose related and more common in renal impairment or when combined with drugs like; trimethoprim-sulfamethoxazole. Folic acid supplementation helps reduce risk [17,18].

Renal Toxicity

High-dose MTX can precipitate in renal tubules, leading to acute kidney injury. Hydration, urine alkalization and leucovorin rescue are essential preventive strategies. [19]

Gastrointestinal Toxicity

Common side effects include nausea, vomiting, anorexia, stomatitis, and mucositis. Severe mucositis can limit therapy in oncology settings [20,21].

Neurotoxicity

Occurs mainly with intrathecal or high-dose intravenous MTX. Manifestations: headaches, seizures, cognitive dysfunction, leukoencephalopathy.

Dermatologic Reactions

Rash, alopecia, photosensitivity, and rare cases of toxic epidermal necrolysis or Stevens–Johnson syndrome [22].



Pharmacovigilance and Signal Detection in Methotrexate Therapy:

1. Importance of Pharmacovigilance in MTX

Methotrexate (MTX) has a narrow therapeutic index and is associated with serious, sometimes fatal, adverse drug reactions (ADRs). Pharmacovigilance is therefore crucial to detect, assess, and prevent ADRs that may not have been fully recognized during premarketing clinical trials [23].

2. Global Pharmacovigilance Systems

WHO Vigibase: The world's largest international drug safety database, containing over 30 million reports of suspected ADRs, including thousands related to MTX [24]. FDA Adverse Event Reporting System (FAERS): Collects post-marketing reports in the U.S., enabling detection of signals such as MTX-associated pneumonitis and hepatotoxicity [25]. EudraVigilance (EMA): The European system for managing and analyzing ADR reports. MTX-related cases of pulmonary fibrosis and pancytopenia have led to stricter monitoring recommendations [26].

3. Signal Detection Methods

Spontaneous reporting systems (SRS): Primary source of early warnings for rare or severe ADRs. Disproportionality analysis: Statistical methods such as Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Bayesian approaches help identify unexpected associations between MTX and ADRs [27]. Case control and cohort studies: Used to confirm signals detected in pharmacovigilance databases, e.g., risk of pulmonary fibrosis in long-term MTX users.

4. Examples of Signal Detection in MTX

Pulmonary toxicity: Cumulative pharmacovigilance reports identified MTX-induced pneumonitis as a serious risk, leading to guideline updates [28;29].

Hepatotoxicity: Long-term data analysis demonstrated increased risk of fibrosis and cirrhosis, prompting stricter liver function monitoring [30].

Drug interactions: Pharmacovigilance data flagged enhanced toxicity with NSAIDs and trimethoprim-

sulfamethoxazole, leading to warnings in drug labels [31].

5. Regulatory Impact

Signal detection from pharmacovigilance systems has directly influenced: Updates to Summary of Product Characteristics (SmPCs). Issuance of black box warnings. Implementation of Risk Evaluation and Mitigation Strategies (REMS) for MTX in certain indications.

Monitoring and Risk Minimization in Methotrexate Therapy

Methotrexate (MTX) requires vigilant monitoring and proactive risk minimization strategies due to its potential for life-threatening adverse drug reactions (ADRs). The approach differs depending on whether MTX is used in low-dose regimens (e.g., rheumatology, dermatology) or high-dose regimens (oncology).

1. Laboratory Monitoring

Baseline tests (before initiation):

Complete blood count (CBC) with differential

Liver function tests (ALT, AST, albumin)

Renal function tests (serum creatinine, eGFR)

Chest X-ray or pulmonary assessment (for baseline lung status) [32;33].

Follow-up monitoring:

CBC, LFTs, renal function: every 2–4 weeks for the first 3 months, every 8–12 weeks thereafter in stable patients. More frequent testing in high-risk patients (elderly, alcohol use, diabetes, renal impairment).[33]

2. Low-Dose MTX (Rheumatology/Dermatology)

Folic acid supplementation (1–5 mg/day, except on MTX day) reduces risk of mucositis, cytopenias and liver toxicity [34]. Patient education on avoiding alcohol and promptly reporting symptoms such as dyspnea, cough, jaundice or mouth ulcers. Avoid concomitant drugs that enhance toxicity (e.g., trimethoprim-sulfamethoxazole, NSAIDs in high doses) [35,36].

3. High-Dose MTX (Oncology)

Hydration & urine alkalization: IV fluids and sodium bicarbonate to maintain urine pH > 7.0 to prevent MTX crystallization in renal tubules.

Leucovorin (folinic acid) rescue: Administered within 24–36 hours of MTX infusion to reduce toxicity without impairing anticancer efficacy.

Therapeutic drug monitoring (TDM): Serial serum MTX levels guide leucovorin dosing and identify delayed clearance [37,38].

4. Pulmonary Monitoring

MTX-induced pneumonitis is unpredictable and not dose-dependent. Patients should be educated about early respiratory symptoms and advised to seek medical care immediately. Routine pulmonary function testing is not universally recommended but may be useful in high-risk patients [39].

Risk Minimization Strategies

Patient education: Clear instructions on once-weekly dosing (to avoid daily dosing errors).

Electronic alerts/packageaging: Use of weekly pill boxes or prescribing software reminders.

Regulatory measures: European Medicines Agency (EMA) recommends restricted pack sizes and clearer labeling to minimize dosing errors.

FDA includes black box warnings on MTX packaging for toxicity risks [40,41].

Role of Pharmacovigilance in Methotrexate Safety:

Methotrexate (MTX) is a high-alert medication due to its narrow therapeutic index, dose dependent and idiosyncratic toxicities, and risk of dosing errors. Pharmacovigilance (PV) plays a vital role in ensuring its safe use by focusing on prevention, early detection, causality assessment and regulatory interventions.

1. Prevention of Adverse Drug Reactions (ADRs)

Development of Risk Management Plans (RMPs) to identify and mitigate MTX-related risks [42]. Patient

and healthcare professional education to prevent medication errors (e.g., once weekly dosing errors that have caused fatalities). Labeling and packaging interventions: restricted pack sizes, blister packs, and warnings have been implemented in Europe to reduce accidental overdosing [42;43].

2. Detection of Safety Signals

PV databases (WHO Vigibase, FDA FAERS, EMA EudraVigilance) collect spontaneous ADR reports. Signals detected include pulmonary fibrosis, hepatotoxicity and severe myelosuppression. Case reports and cohort analyses have further highlighted life-threatening ADRs, prompting updates in monitoring guidelines [44,45].

3. Assessment of ADRs

Causality assessment tools such as the WHO-UMC system and Naranjo algorithm are applied to evaluate MTX-related ADRs.

Example: determining whether pneumonitis or hepatic fibrosis is directly linked to MTX or confounded by comorbidities [46,47].

4. Regulatory Actions

Black box warnings mandated by the FDA for risks such as hepatotoxicity, pulmonary toxicity, myelosuppression, and pregnancy contraindications. EULAR/ACR monitoring guidelines based on accumulated PV data [48, 49]. Post-marketing surveillance and safety updates leading to tighter monitoring intervals and laboratory testing recommendations [42, 49].

5. Global Collaboration

International PV networks (WHO Programme for International Drug Monitoring) share ADR data to strengthen detection of rare toxicities. Collaboration enables harmonized safety warnings and consistent patient protection worldwide [50-57].

CONCLUSION:

Methotrexate remains a cornerstone in the management of both malignancies and autoimmune disorders due to its effectiveness, affordability, and

broad therapeutic applications. However, its narrow therapeutic index, dose-dependent and idiosyncratic adverse drug reactions (ADRs), and potential for dosing errors make it a high-risk medication. The integration of pharmacovigilance systems is therefore essential to optimize patient safety. Routine laboratory monitoring, patient and physician education, and adherence to international guidelines (EULAR/ACR, FDA, EMA) significantly reduce the incidence of severe toxicities such as hepatotoxicity, pulmonary fibrosis and myelosuppression. Moreover, spontaneous reporting systems, global safety databases and post-marketing surveillance continue to detect rare or unexpected ADRs, ensuring continuous refinement of safety measures. The future of MTX safety lies in personalized medicine approaches, pharmacogenomics and stronger international collaboration in pharmacovigilance. By combining vigilant monitoring, signal detection, and proactive risk-minimization strategies, the therapeutic benefits of methotrexate can be maximized while minimizing harm, thereby ensuring its safe and effective long-term use.

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