Review on Dose, Destination and Delivery aspects of Methotrexate

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Abstract-Methotrexate drug belongs to the group of medicines i.e., Antineoplastics (cancer medicines). It leads inblockage of enzyme that is needed by cells to live. It is also used to treat certain types of cancer (such as acute lymphoblastic leukemia, non-Hodgkin's lymphoma) or to control severe psoriasis or rheumatoid arthritis that has not responded to other treatments. It may also be used to control juvenile rheumatoid arthritis. It is also used to reduce the activity of the immune system for people who are suffering from such problems. The immune system normally protects the body from infections by cause's inflammation to fight against them. There are several sign and symptoms of inflammation i.e., redness, swelling, heat and pain. MTX is now prescribed atleast 500,000 patients with RA worldwide, making it far the most commonly used disease modifyingantirheumatic drug. It has been used to treat millions of patients with malignant and autoimmune diseases. Methotrexate has been used clinically in the treatment of malignancy, psoriasis, rheumatoid arthritis, and other autoimmune and inflammatory disorders. Methotrexate has also been used with misoprostol for voluntary abortion and in the treatment of ectopic pregnancy.

Keywords: Inflammation, Methotrexate, immune system, Mechanism, dose, adverse effects.

INTRODUCTION

Methotrexate (MTX) is a chemotherapy agent and immune-system suppressant which also commonly known as amethopterin. Methotrexate was developed for the purpose like chemotherapy either alone or with combination of other agents. It is effective for the treatment of a number of cancers, including solid tumors of breast, head, neck or lung, acute lymphocytic leukemia, osteosarcoma, choriocarcinoma. Methotrexate was made in 1947 by team of researchers under the supervision of Sidney Farber. Methotrexate (MTX) is now one of the most popular drugs for the treatment of rheumatoid arthritis also. The low dose quantity for weekly i.e.(10 to 25 mg/wk.) It is used for either monotherapy purposes or combination with other drugs which has a superior efficacy profile as determined in placebo-controlled trials and comparable efficacy to other drugs including anti-TNF therapy.

The history of MTX dates back to 1948 with the initial report by Sidney Farber and the successful use of aminopterin or anti-folate for the treatment of childhood leukemia. The one of the effects observed with aminopterin was the interference of proliferation of connective tissue. Methotrexate has been widely used for the treatment of rheumatoid arthritis (RA). The mechanisms of action of methotrexate are complex. Developed as a folic acid analogue, methotrexate inhibits purine and pyrimidine synthesis, which accounts for its efficacy in the therapy of cancer as well as for some of its toxicities. Recently, many studies have focused on the adenosine-mediated anti-inflammatory effects of methotrexate. Certainaspects of methotrexate toxicities are also attributed to adenosine release. A better understanding of the mechanisms of action and toxicities of methotrexate will direct clinicians in their treatment approach and toxicity monitoring. Toward that objective, the latest developments in the pharmacokinetics, mechanism of action, pharmacogenetics, and toxicity of methotrexate are herein discussed. Low-dose methotrexate was first demonstrated to be a potent and effective therapy for rheumatoid arthritis (RA) in 1985.1 Because of its efficacy, acceptable safety profile, and low cost, methotrexate soon became a mainstay in the treatment of RA. More recently, new

agents, including biological agents, have been compared to methotrexate for their efficacy during development.

Fig 1: Methotrexate tablet

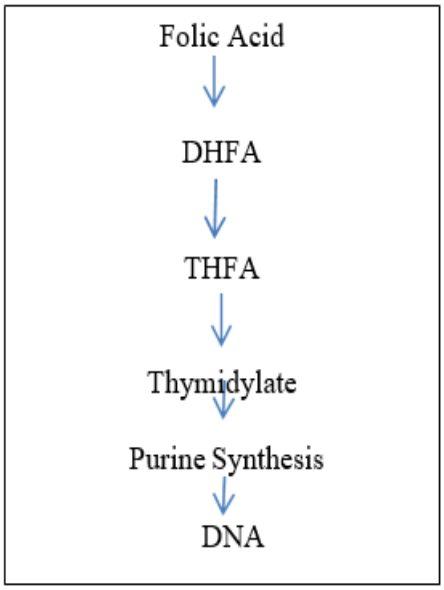
When begun earlier in the disease course, methotrexate is nearly as effective as biological response modifiers for the treatment of rheumatoid arthritis, although long-term follow-up suggests better prevention of bone destruction with biological agents. Methotrexate is now commonly administered in combination with either biological agents or other small molecule ant rheumatic drugs. Combination therapies have been reported to have greater efficacy than any single agent alone without greater toxicity.

Fig 2: Methotrexate Injection

Methotrexate is generally administered once weekly to RA patients, with doses ranging from 7.5 to 25 mg/week.3. It is well absorbed when given orally or intramuscularly. Intramuscular administration may help reduce side effects, especially nausea, which is commonly associated with oral ingestion. At the doses typically used for the treatment of RA, the bioavailability of oral methotrexate varies considerably between individuals, but generally itis approximately 70%. Oral absorption of methotrexate is not reduced by concomitant food intake. When taken orally, the uptake of methotrexate by the gastrointestinal tract is primarily mediated by transporter, reduced folate carrier.

Mechanism of Action

The mechanisms of action of methotrexate are complex. Developed as a folic acid analogue, methotrexate inhibits purine and pyrimidine synthesis, which accounts for its efficacy in the therapy of cancer as well as for some of its toxicities.

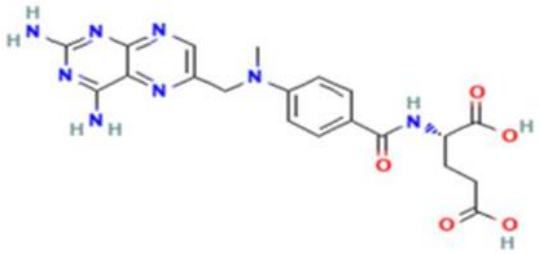


Toxicity:

Patients taking methotrexate are more likely to discontinue therapies because of the adverse effects of medication rather than lack of efficacy. However, compared with other DMARDs (disease modifying ant rheumatic drugs), including biological agents, methotrexate has a relatively good safety profile. The adverse effects of low-dose methotrexate are usually mild, self-limited, or preventable, but may be more severe in some patients. Toxicities from folate antagonism, including anemia, neutropenia, and stomatitis, and oral ulcers, can be prevented or alleviated by folate supplementation.

Toxicities unrelated to suppression of folate metabolism include nodulosis, hepatic fibrosis, pulmonary fibrosis, lethargy, fatigue, and renal insufficiency. Since adenosine, acting on adenosine receptors, plays an important role in anti-inflammatory effects of methotrexate, many studies have investigated the role of the adenosine pathway in toxicities.

Structure feature of Methotrexate



IUPAC NAME:
(2S)-2-[(4-{[(2,4-Diaminopteridin-6-yl)methyl](methyl)amino}benzoyl)amino]pentanedioic acid Molecular formula: $C_{20}H_{22}N_8O_5$
Molecular Weight: 454.4 g/mol

Terminal Half Life: 3-10 hr.

Metabolism: The high dose of MTX is metabolized by hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes.

Excretion: the kidney is a result of both glomerular filtration and tubular secretion.

Dose: For oral dosage form (tablets):

For acute lymphoblastic leukemia (ALL):
Adults and children
Dose is based on body size and must be determined by your doctor. At first, 20 milligrams (mg) per meter squared(m(2)) of body size once a week. Your doctor may adjust your dose as needed and tolerated.

For mycosis fungicides:
Adults
Used alone: 25 to 75 milligrams (mg) once a week.
Used with other medicines: Dose is based on body size and must be determined by your doctor. The dose is usually 10mg per meter squared (m(2)) of body size 2 times a week.
Children—
Use and dose must be determined by your doctor.

For non-Hodgkin lymphoma:
Adults—2.5 milligrams (mg) 2 to 4 times a week. Your doctor may adjust your dose as needed and tolerated.However, the dose is usually not more than 10 mg per week.
Children—Use and dose must be determined by your doctor.

For polyarticular juvenile arthritis (pJIA):
Children—Dose is based on body size and must be determined by your doctor. At first, 10 milligrams (mg) per metersquared (m2) once a week. Your doctor may adjust your dose as needed and tolerated.

For psoriasis:
Adults—At first, 10 to 25 milligrams (mg) once a week. Your doctor may adjust your dose as needed and tolerated.However, the dose is usually not more than 30 mg per week.
Children—Use and dose must be determined by your doctor.

For rheumatoid arthritis:
Adults—At first, 7.5 milligrams (mg) once a week. Your doctor may adjust your dose as needed and tolerated.
Children—Use and dose must be determined by your doctor.For oral dosage form (Jylamvo® solution)

For acute lymphoblastic leukemia (ALL):
Adults—Dose is based on body size and must be determined by your doctor. At first, 20 milligrams (mg) per metersquared (m(2)) of body size once a week. Your doctor may adjust your dose as needed and tolerated.
Children—Use and dose must be determined by your doctor.

For mycosis fungoides:
Adults—
Used alone: 25 to 75 milligrams (mg) once a week.
Used with other medicines: Dose is based on body size and must be determined by your doctor. The dose is usually 10mg per meter squared (m(2)) of body size 2 times a week.
Children—Use and dose must be determined by your doctor.

For non-Hodgkin lymphoma:
Adults—2.5 milligrams (mg) 2 to 4 times a week. Your doctor may adjust your dose as needed and tolerated.However, the dose is usually not more than 10 mg per week.

Children—Use and dose must be determined by your doctor.

For psoriasis:
Adults—At first, 10 to 25 milligrams (mg) once a week. Your doctor may adjust your dose as needed and tolerated.However, the dose is usually not more than 30 mg per week.
Children—Use and dose must be determined by your doctor.

For rheumatoid arthritis:
Adults—At first, 7.5 milligrams (mg) once a week. Your doctor may adjust your dose as needed and tolerated.

Children—Use and dose must be determined by your doctor.For oral dosage form (Xatmep™ solution):

For acute lymphoblastic leukemia (ALL):
Children—Dose is based on body size and must be determined by your doctor. At first, 20 milligrams (mg) per metersquared (m(2)) of body size once a week. Your doctor may adjust your dose as needed.+

For polyarticular juvenile idiopathic arthritis (pJIA):
Children—Dose is based on body size and must be determined by your doctor. At first, 10 milligrams (mg) per metersquared (m(2)) of body size once per week. Your doctor may adjust your dose as needed.

How does methotrexate actually work?
Methotrexate is a type of disease-modifying anti-rheumatic drug (DMARD). It's used to reduce activity of the immune system for people who have certain conditions. The immune system normally protects the body from infections by causing inflammation to fight them. Inflammation can cause swelling, heat, redness and pain. It inhibits the synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins by binding to dihydrofolate reductase. Currently, methotrexate is among the most commonly used drugs for the treatment of rheumatoid arthritis (RA).

Fig 3: Methotrexate market scale

What is the patient advice for methotrexate?
It is important that you do not miss your blood test. You must not take methotrexate unless you are having regular blood tests every 4 to 12 weeks. They tell your doctor how well methotrexate is working. Methotrexate reduces theproduction of blood cells and this can make you more vulnerable to infections. Patients and their careers should be advised to avoid exposure to UV light (including intense sunlight, sunlamps, and sunbeds)—see Important safety information. Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.

Clinical manifestation of methotrexate?
Even a low dose of methotrexate is not free from side effects. The most common adverse effects are gastrointestinal manifestations such as nausea, vomiting, mucosal ulcers, and loss of appetite. These are noted in most of the patients and are easily managed.

What is the clinical significance of methotrexate?
Methotrexate is in a class of medications called antimetabolites. Methotrexate treats cancer by slowing the growth of cancer cells. Methotrexate treats psoriasis by slowing the growth of skin cells to stop scales from forming.
Methotrexate may treat rheumatoid arthritis by decreasing the activity of the immune system

How do you dissolve methotrexate?
Methotrexate (MTX) (hydrate) is supplied as a crystalline solid. A stock solution may be made by dissolving the MTX(hydrate) in the solvent of choice, which should be purged with an inert gas. MTX (hydrate) is soluble in organic solvents such as DMSO and dimethyl formamide.

Medical Uses

Methotrexate is a medication that treats inflammatory arthritis, psoriasis and other inflammatory conditions. It decreases inflammation in your body. This can reduce pain and prevent long-term damage to your joints and skin. It can also slow down the growth of cancer cells to treat cancer

Side Effects:

- Loss of appetite. Eat when you would usually expect to be hungry. ...
- Feeling or being sick. Eat simple meals and do not eat rich or spicy food. ...
- Stomach pain or indigestion. Try to rest and relax.
- Diarrhea
- Feeling tired or drowsy.
- Hair loss

Table: Possible mechanisms of resistance to MTX in patients with rheumatoid arthritis

Sr.No	Metabolic Event	Effect	Inciting events
1	DHFR gene duplication	Increased DHFR	MTX Treatment
2	Increased translation of DHFR mRNA	Increased DHFR	MTX binding to DHFR
3	Increased DHFR gene expression	Increased DHFR	Cellular stress, hypoxia, UV radiation, environmental carcinogen
4	Genetic variation in MTX Metabolism	Altered intracellular MTX conc	MTX exposure

How quickly its works

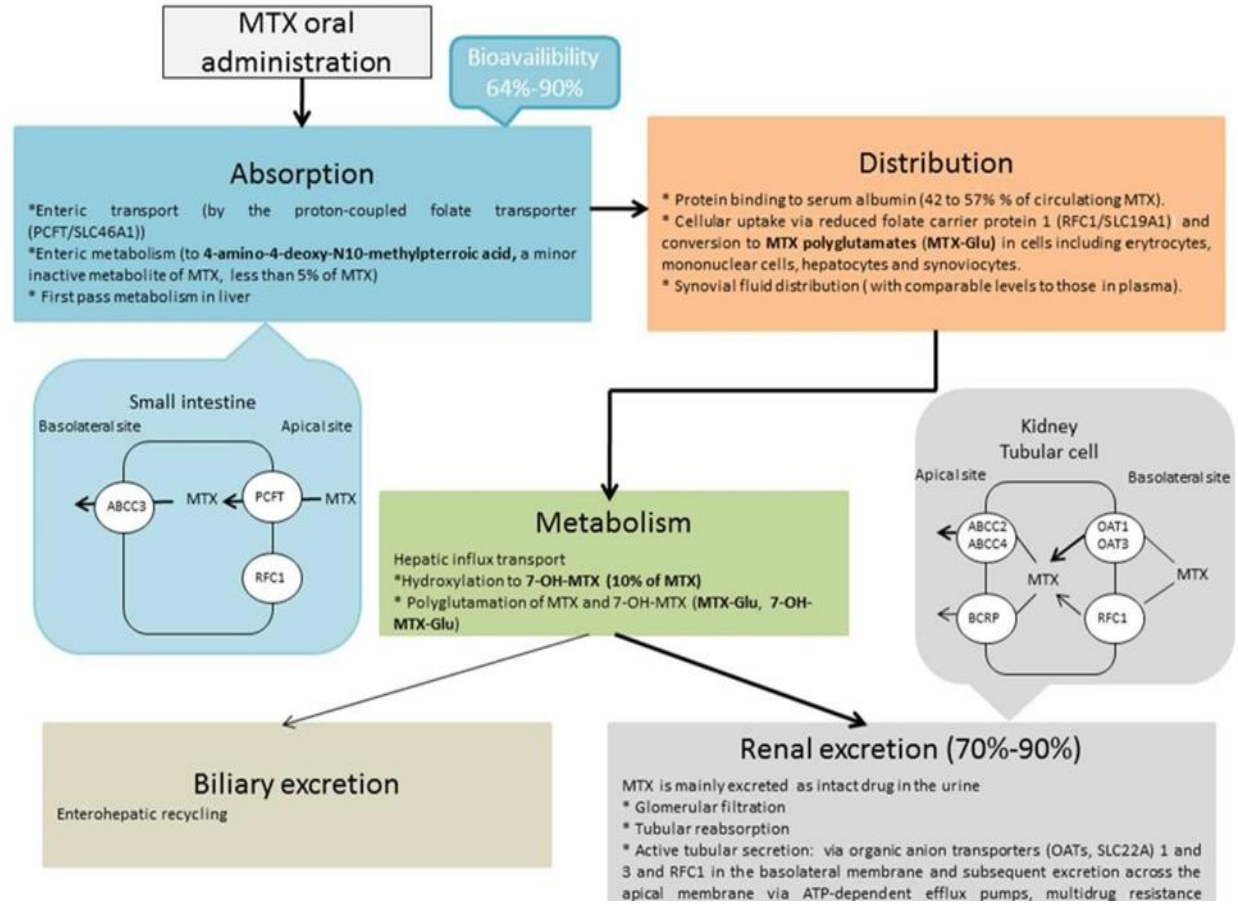


Fig 4: Pharmacokinetic action of Methotrexate

Expected future Aspects of Methotrexate injection

Fig 5: Future goals of MTX injection

Adverse effects:

- Black, tarry stools.
- Bleeding gums.
- Blood in the urine or stools.
- Bloody vomit.
- Diarrhea.
- Increased heartbeat.
- Itching, rash, reddening of the skin

Degradation on Methotrexate when exposure to U.V.

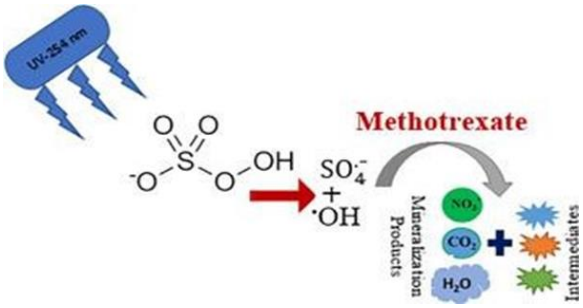


Fig 6: MTX degradation during expose to U.V.

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