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# Seminars in Arthritis and Rheumatism

Roy D. Altman, MD - Norman L. Gottlieb, MD - David S. Howell, MD  
*Editors*

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# Seminars in Arthritis and Rheumatism

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## Methotrexate in Rheumatoid Arthritis: An Update With Focus on Mechanisms Involved in Toxicity

Annelies E. van Ede, Roland F.J.M. Laan, Henk J. Blom,  
Ronney A. De Abreu, and Leo B.A. van de Putte

**Objectives:** To provide an update of the current knowledge of the mechanism of action of low-dose methotrexate (MTX) in the treatment of patients with rheumatoid arthritis (RA), with an emphasis on the mechanisms involved in toxicity. We also considered strategies currently used to prevent or decrease toxicity of MTX.

**Methods:** We reviewed the literature dealing with the subjects of MTX treatment of RA, the mechanisms of action of low-dose MTX regarding efficacy and toxicity, and strategies used to prevent or decrease MTX toxicity.

**Results:** MTX is a fast working and effective second-line antirheumatic agent (SLA). Its use is limited mainly because of side effects. The mechanisms of action regarding efficacy and toxicity are probably determined by different metabolic pathways. Recent data indicate that the antiinflammatory effect of MTX is mediated by adenosine. However, MTX side effects can only partly be explained by folate antagonism and may also depend on its action on other related metabolic pathways. The latter include the homocysteine-methionine-polyamine pathway and purine metabolism. Variants in these metabolic routes (ie, the C677T mutation in the methylene-tetrahydrofolate reductase [MTHFR] gene), may predispose to the development of side effects. Currently the most promising strategy to decrease or prevent toxicity of MTX is concomitant prescription of folic acid or folinic acid. Other strategies are currently under investigation.

**Conclusions:** MTX benefits a majority of RA patients. Approximately 30% of patients, however, abandon treatment because of drug-related side effects. Folic acid or folinic acid likely reduces MTX toxicity. More data, however, are needed to evaluate a potential detrimental effect on the antirheumatic efficacy of MTX.

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**INDEX WORDS:** Methotrexate; rheumatoid arthritis; mechanism of action; toxicity.

**M**ETHOTREXATE (MTX, amethopterin) is a folic acid antagonist that was introduced into the treatment of childhood leukaemia in 1947. In 1951 Gubner et al reported a favorable effect in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis (RA) (1). Low-dose MTX has been commonly used in the treatment of psoriasis since the 1960s and was approved for this purpose by the Food and Drug Administration in 1971. However, its use in the treatment of RA only began during the 1980s and it was not approved by the Food and Drug Administration for this indication until 1988 (2-5).

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Currently, MTX is prescribed by rheumatologists all over the world. MTX has proved to be a very effective, fast-working, second-line antirheumatic agent (SLA) with the best efficacy-toxicity ratio (6-8). Nevertheless, the main reason for discontinuation of MTX is not inefficacy but toxicity (9-12). Because of its clear-cut and long-lasting efficacy, much effort is currently being made to develop strategies to decrease or prevent its toxicity. In approximately 30% of RA patients, toxicity leads to discontinuation of MTX therapy. Therefore, diminishing of toxicity may result in better treatment of this group of RA patients (9-22).

MTX acts as a folate antagonist, but this does not directly explain the full spectrum of side effects. However, MTX exerts its action also on other related metabolic pathways. Recently, a gene mutation was discovered in one of these metabolic routes that may predispose to the development of side effects (23-25). Other promising research focuses on the homocysteine-methionine-polyamine pathway and on purine metabolism.

To better understand the possible mechanisms operative in both efficacy and toxicity of MTX in the treatment of RA patients, we describe folate metabolism and folate dependent metabolic pathways in which MTX is involved. Subsequently, we then discuss how these may relate to efficacy and side effects. Finally, we discuss strategies to prevent or decrease toxicity of MTX.

#### FOLATE METABOLISM

Figure 1 gives an outline of folate metabolism and folate dependent pathways. Because humans are not capable of forming folic acid from their basic constituents, dietary intake is essential (26). Dihydrofolate-reductase (DHFR) catalyzes the conversion of dihydrofolate (DHF) into tetrahydrofolate (THF), which serves as a central component of folate dependent pathways (27,28). THF is also formed from 5-methyl-THF during the conversion of homocysteine (the methyl group acceptor) into methionine, and in the steps involved in purine synthesis. The biologically active folates are derivatives of tetrahydrofolates and participate in one carbon transfer reactions. In the cells, these folates are converted into polyglutamated forms and thereby retained intracellularly. Serum folate consists mainly of 5-methyl-THF, which is the predominant circulating form of folate. In rapidly dividing tissues,

5-methyl-THF and 10-formyl-THF are equally predominant. 5-Methyl-THF is more susceptible to both intra- and extracellular changes in folate status (29).

Folates are involved in several important metabolic routes: 5,10-methenyl-THF/10-formyl-THF, 5,10-methylene-THF, and 5-methyl-THF deliver one-carbon units for the synthesis of purines, pyrimidines and methionine respectively.

#### *Purine-Metabolism*

Purines are necessary for the synthesis of the nucleic acids adenosine monophosphate (AMP) and guanosine monophosphate (GMP), and finally deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The purine-metabolism is composed of a de novo synthesis and a salvage route (Fig 2). Complete purine de novo synthesis (PDNS) exists only in proliferating cells such as of bone marrow and liver and is partly performed in lymphocytes and mononuclear cells (30). The central enzyme is 5-phosphoribosyl-1-pyrophosphate (PRPP) synthetase. In PDNS the 5,10-methenyl-THF dependent enzyme glycylamide ribosyl-5-phosphate (GAR) formyltransferase and the 10-formyl-THF dependent enzyme amino-imidazolcarboxamide ribosyl-5-phosphate (AICAR) formyltransferase are involved. Salvage probably takes place in all body cells, but measurements have been done mainly in lymphocytes and erythrocytes. In the purine salvage route, the enzymes hypoxanthine-guanine phosphoribosyl transferase (HGPRT), purine nucleoside phosphorylase (PNP), adenosine deaminase (ADA), and purine-5' nucleotidase (5'NT) are involved.

AICAR and its metabolites inhibit adenosine kinase (AK) and ADA with the consequent increase of adenosine, which has antiinflammatory properties (31-33).

#### *Pyrimidine-Metabolism*

The 5,10-methylene-THF dependent enzyme thymidylate synthetase (TS), catalyzing the conversion of deoxyuridylylate (dUMP) to deoxythymidylylate (dTMP), forms a rate limiting step in DNA synthesis (26).

#### *Homocysteine-Methionine-Polyamine Pathway*

Homocysteine and folate status are inversely related. Homocysteine is probably an even better

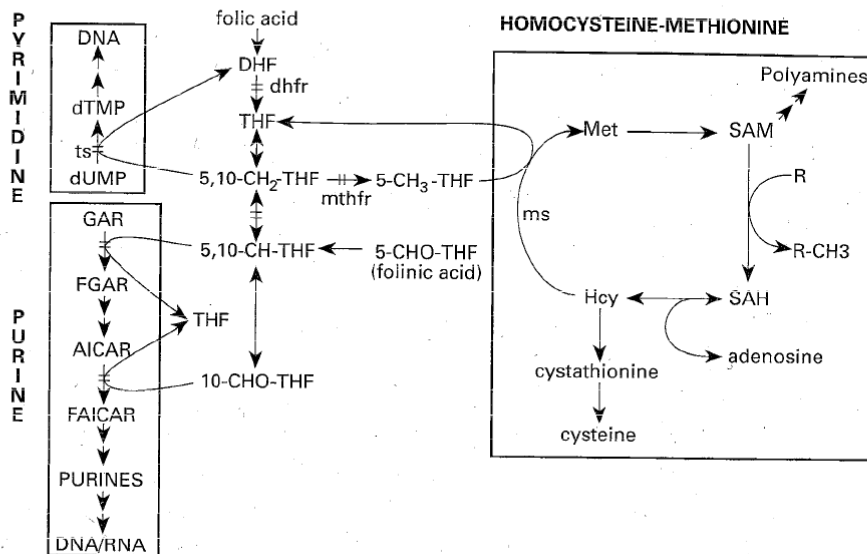


Fig 1. Simplified metabolic scheme illustrating folate metabolism and its relation to purine, pyrimidine, and homocysteine-methionine metabolism. Known inhibition of enzymes by methotrexate is indicated by —|— Abbreviations: DNA, deoxyribonucleic acid; dTMP, deoxythymidylate; ts, thymidilate synthetase; dUMP, deoxyuridylate; GAR, glycinamide ribosyl-5-phosphate; FGAR, form-glycinamide ribosyl-5-phosphate; AICAR, amino-imidazolcarboxamide ribosyl-5-phosphate; FAICAR, form-amino-imidazolcarboxamide ribosyl-5-phosphate; RNA, ribonucleic acid; DHF, dihydrofolate; dhfr, dihydrofolate-reductase; THF, tetrahydrofolate; 5,10-CH<sub>2</sub>-THF, 5,10-methylene tetrahydrofolate; 5,10-CH-THF, 5,10-methenyl tetrahydrofolate; 10-CHO-THF, 10-formyl tetrahydrofolate; mthfr, methylene-tetrahydrofolate reductase; 5-CH<sub>3</sub>-THF, 5-methyl tetrahydrofolate; 5-CHO-THF, 5-formyl tetrahydrofolate (folinic acid); Met, methionine; SAM, S-adenosyl-L-methionine; ms, methionine synthetase; Hcy, homocysteine; SAH, S-adenosyl-L-homocysteine; R, methyl-acceptor; R-CH<sub>3</sub>.

parameter for measuring the effective capacity of folate metabolism than folate blood levels (34-38).

Homocysteine is not derived from the diet but from transmethylation of methionine. It is reused by remethylation to methionine and transsulfuration to cysteine, regulated by methylene-tetrahydrofolate reductase (MTHFR) and cystathionine-β-synthase (CS) respectively (39). 5-Methyl-THF is necessary as a methyl donor for the conversion of homocysteine to methionine, which in turn can be converted into S-adenosyl-L-methionine (SAM) by adenosine triphosphate (ATP). SAM is the most important methyl group donor in the cell; during these methyltransferase reactions, SAM is

converted into S-adenosyl-L-homocysteine (SAH). SAH is degraded by SAH-hydrolase into homocysteine and adenosine. Homocysteine is an inhibitor of methyltransferases. Therefore, the ratio between SAM and SAH is an important determinant of intracellular transmethylation capacity (40,41).

SAM is not only converted into SAH, but also into decarboxy-SAM, which is the substrate for the synthesis of polyamines. In polyamine synthesis, the decarboxylation of SAM by SAM-decarboxylase is a rate-limiting step (41,42). The polyamines putrescine, spermidine, and spermine are essential for cell functions including proliferation, differen-

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