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METHOTREXATE AN OLD DRUG WITH NEW TRICKS

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Abstract

Methotrexate (MTX) is the first line drug for the treatment of a number of rheumatic and non-rheumatic disorders. It is currently used as an anchor disease, modifying anti-rheumatic drug in the treatment of rheumatoid arthritis (RA). Despite the development of numerous new targeted therapies, MTX remains the backbone of RA therapy due to its potent efficacy and tolerability. There has been also a growing interest in the use of MTX in the treatment of chronic viral mediated arthritis. Many viruses—including old world alphaviruses, Parvovirus B19, hepatitis B/C virus, and human immunodeficiency virus—have been associated with arthritogenic diseases and reminiscent of RA. MTX may provide benefits although with the potential risk of attenuating patients' immune surveillance capacities. In this review

Keywords: methotrexate, arthritis, inflammation, alarmin, virus, chikungunya, rheumatoid arthritis, innate immunity, pharmacology

Introduction

Methotrexate (4-amino-10-methylfolic acid, MTX), an analog and antagonist of folic acid, is commonly used in the treatment of a wide range of malignant and non-malignant diseases [1].

Originally developed as an anticancer medication, MTX is currently the first-line disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriasis, and is useful in inflammatory bowel diseases, multiple sclerosis, vasculitis, systemic lupus erythematosus and other connective tissue diseases, and transplantation due to its beneficial anti-inflammatory and immunomodulatory activities [1,2,3].

MTX has also prompted a growing interest in the treatment of viral mediated arthritis [4]. Many viruses—including old world alphaviruses, Parvovirus B19, hepatitis B/C virus (HBV/HBC), and human immunodeficiency virus (HIV)—are associated with arthritogenic diseases [5]. Chronic viral arthritis can clinically mimic RA and last for months to years [6]. Given pathogenic similarities with RA, MTX may provide benefits in the treatment of chronic viral associated rheumatic disorders, although the potential risk to compromise patients' immune surveillance to prevent viral reactivation may need to be considered [7].

MTX is considered an essential medication by the World Health Organization (WHO) and is incontestably one of the pharmaceuticals greatest success stories as it found indications widely distinct from its original intention [8,9]. Despite the introduction of a number of effective biological agents for the treatment of autoimmune inflammatory diseases and mainly RA, MTX remains one of the most efficient and most commonly used therapies against which the efficacy of new DMARDs is judged [1]. MTX can be used both as first-line monotherapy in DMARD-naive patients [10], and as an anchor drug, in MTX-insufficient responders, in combination with other conventional or biological DMARDs to maximize therapeutic effects [11,12]. Low and more infrequent doses of MTX are used to treat inflammatory diseases and compared with the 5 g/week doses used in the treatment of malignancy, once-weekly administration of MTX at 10 to 25 mg provides optimal clinical outcomes in RA, the commonest prototype of low-dose MTX indications [13].

Fundamental mechanisms underlying the therapeutic effect of high doses MTX on malignant diseases are currently well established; MTX as a folate antagonist, competitively inhibits the activity of folate-dependent enzymes and synthesis of purine and pyrimidine required for DNA and RNA production in rapidly dividing malignant cells [14]. However, mechanisms by which low-dose MTX exerts its therapeutic effect in inflammatory disorders are not completely elucidated.

MTX is known to have highly favorable cost-effectiveness and efficacy/toxicity ratios but toxicity is still a concern. The potential adverse events associated with MTX attract considerable attention as they represent the main cause of drug withdrawal [15,16,17]. There are two broad subsets of MTX associated adverse events; Symptomatic but rarely life-threatening adverse events such as nausea, headaches, fatigue, mucositis and hair loss, and potentially life-threatening adverse events including cytopenias, interstitial lung disease (or MTX pneumonitis), and MTX related liver disease (fibrosis and cirrhosis) [8].

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MTX, formerly known as amethopterin, is one of several folic acid antagonists originally synthesized in the 1940s for the treatment of malignancies and structurally designed to inhibit dihydrofolate reductase (DHFR), an essential enzyme for purine and pyrimidine synthesis in cell proliferation [18,19,20].

The rationale for the introduction of MTX for the treatment of RA was assumed on its capacity to inhibit inflammatory and proliferative response of connective tissue. The closely related antifolate aminopterin, a synthetic derivative of pterin, was shown to suppress exudative and proliferative changes in experimental formaldehyde arthritis [21]. Aminopterin was gradually replaced by MTX due to its less toxic nature and the first documented clinical use of MTX for the treatment of RA was in 1951 [22]. MTX clinical potential as a RA treatment was suggested by Gubner, after studying the effects of MTX in RA patients, and was confirmed by well designed, blinded, placebo controlled studies conducted during the 1980s [23]. RA patients treated with MTX demonstrated improved global assessments of disease activity, joint scores, and marked decreases in pain. Since then, the use of weekly low doses of MTX has expanded to involve additional inflammatory and autoimmune diseases.

In 1986, MTX was licensed by the US Food and Drug Administration (FDA) for the treatment of RA [24].The US FDA first approved the use of MTX only in life-threatening neoplastic diseases, or in patients with psoriasis or RA with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy [25]. Based on the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) recommendations, MTX should be started early in recent and/or undifferentiated arthritis evocative of RA [26], in order to prevent joint destruction and disability.

Improved understanding of the pathogenesis of RA led to the introduction of biologic treatment in 1998 [27] and despite the development of several targeted biologic treatments such as TNF blockers, MTX remains the cornerstone of RA treatment, alone or in combination [28].

Continuous efforts are devoted to derivatives of MTX in order to improve the pharmacological parameters of the parent MTX. MTX derivatives bearing dihydro-2H-1,4-benzothiazine or dihydro-2H-1,4-benzoxazine applied on human synovial cells and human peripheral blood mononuclear cells (hPBMC) have been reported to have enhanced antiproliferative activity and increased DHFR binding affinity compared with MTX. In vivo, benzothiazine and benzoxazine derivatives exhibited antirheumatic activity in a rat adjuvant arthritis model [29]. Similar activities were observed with MTX derivatives containing enantiomerically pure L-*erythro*- or L-*threo*-γ-fluoroglutamic acid [30]. Didodecyl-MTX in lipid nanocarrier was found to reduce inflammation when administered via the intra-articular route into rabbits [31]. An optimized conjugate of MTX and hyaluronic acid (HA) was assessed on human fibroblast-like synoviocytes (FLS) and a synovial sarcoma cell line (SW982) and proved to be more efficient than the parent compounds to retrieve synovial inflammation in rat models [32].

Pharmacokinetics of MTX

In the treatment of inflammatory autoimmune diseases, MTX is commonly administered orally as a single weekly dose. In clinical practice, treatment is initiated at the dose of 10 mg/week, with an increase of 5 mg every 2–4 weeks up to a maximum dose of 20–30 mg/week, depending on clinical response or intolerance [33,34]. The use of parenteral MTX, particularly in the form of subcutaneous (SC) injection, has recently gained great interest and is of greater benefit over the oral route. SC MTX, was shown to have greater clinical efficacy and improved tolerability compared to the oral form. SC MTX administration is currently recommended in cases of insufficient clinical response or intolerance with oral MTX [34,35]. In Juvenile Idiopathic Arthritis (JIA), MTX is proved to be efficient at the dose of 10 to 20 mg/m^2.

A modest fraction of MTX may be metabolized to 4-amino-4-deoxy-N10-methylpterroic acid through intestinal bacteria [37]. MTX bioavailability is relatively high, in the range of 64–90%. However, bioavailability varies widely among patients and decreases with increasing dose with a plateau effect at doses above 15 mg/week, suggesting saturation of the intestinal transporters [38,39,40]. MTX maximum plasma concentrations (Cmax) range between 0.3 and 1.6 µmol/L, and occur at a T max of 0.75 to 2 h after administration [37]. Several studies have demonstrated higher bioavailability with SC MTX than with oral MTX [38,39,41]. SC MTX injection will lead to a linear, dose-proportional increase in the blood circulation and no plateau effect [39]. Around 50% of circulating MTX is bound to plasma proteins [42,43,44,45]. MTX can distribute to the synovial fluid with comparable levels to those found in plasma [43]. MTX is subject to first-pass metabolism in the liver and is converted to 7-hydroxymethotrexate (7-OH-MTX), which is a major metabolite of MTX [46]. Renal excretion constitutes the major elimination route of MTX. The drug is filtered by the glomeruli, and additionally, undergoes active tubular secretion and reabsorption. A small proportion of MTX is excreted in the bile and some enterohepatic recycling also occurs [33,37,46,47]. The plasma half-life of low dose MTX varies from 4.5 h to 10 h [43,48]. MTX elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of MTX treatment [45,48,49].

After oral administration, MTX is absorbed in the proximal jejunum by the proton-coupled folate transporter (PCFT/SLC46A1), which transports reduced folates and MTX [36]

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