Methotrexate in Rheumatoid Arthritis: Optimizing Therapy Among Different Formulations. Current and Emerging Paradigms

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ABSTRACT

Background: Methotrexate (MTX) is currently considered the drug of choice, among the disease-modifying antirheumatic drugs, for the treatment of rheumatoid arthritis (RA) because of its favorable risk/benefit ratio, good safety profile, and low costs. Despite MTX's widespread use and large experience accumulated over the many years since its introduction into clinical practice, specific guidelines have not been published.

Objective: We report here the available research regarding the optimal dosage and route of MTX administration.

Methods: MEDLINE and the Cochrane Library were systematically searched for articles published between 1990 and 2013, using terms related to RA and MTX. The search was conducted by using both MeSH terms and free text. The references of the retrieved studies were also screened manually for additional articles.

Results: For the treatment of rheumatic diseases, the antimetabolite drug MTX can be administered weekly by different routes: oral, subcutaneous, or intramuscular. One of the goals of treatment is to minimize acute and chronic toxicity. A starting dose of 15 mg/week orally, escalating to 25 to 30 mg/week or the highest tolerable dose (with a subsequent switch to parenteral administration in cases of insufficient response), seems to be the optimal evidence-based strategy for MTX treatment of RA. Oral MTX is widely preferred because of its low costs and patient preferences; the bioavailability of parenteral MTX is higher, however. This is supported by data from observational studies, in which patients switching from parenteral to oral MTX at an equal dose had disease exacerbations. In several trials, the subcutaneous formulation of MTX was considered, by both physicians and patients, to be more advantageous in terms of discomfort and compliance. In addition, a significant proportion of patients reported that this formulation led to greater independence, with a resulting improvement in quality of life.

Conclusions: Although MTX treatment can be initiated by using the oral administration route, parenteral administration of MTX is indicated in those patients with poor compliance toward the oral form. The subcutaneous route seems to be more effective than the oral route for MTX administration based on the results of several studies, and this route may be preferred because of better usability and absence of pain at the infusion site. (*Clin Ther.* 2014;36:427–435)

Key words: Methotrexate, disease-modifying antirheumatic drugs, rheumatoid arthritis, therapeutic strategy.

INTRODUCTION

The use of immunosuppressive agents in the treatment of rheumatoid arthritis (RA) began in the 1950s after the introduction of NSAIDs and corticosteroids. In 1951, the use of an antifolate, aminopterin, and a nitrogen mustard, mechlorethamine, were proposed for the treatment of RA.[1] Other drugs were subsequently introduced, including cyclophosphamide, 6-mercaptopurine, azathioprine, and methotrexate (MTX). The latter was synthesized in 1948 and first used in the therapy of RA 15 years later.[2,3] Due to the

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reported higher incidence of adverse effects, including the onset of severe infections, any kind of immunosuppressive therapy was used cautiously. Therefore, for almost a decade, immunosuppressive drugs were used as rescue therapy, after repeated failure of all other possible therapeutic options. In 1972, Hoffmeister demonstrated both the availability and safety of MTX, at low doses, with a single weekly administration.[4] After publication of this article, this strategy became the first choice in the treatment of RA.

Among the disease-modifying antirheumatic drugs (DMARDs), MTX is currently considered the "anchor drug" for the treatment of RA[5]; it is administered in up to 70% of patients with this disease. In patients naive for DMARDs, MTX should always be considered the first-line therapy based on its favorable risk/benefit ratio, good safety profile, and low costs. It may be considered both in monotherapy, in which it is possible to obtain good control or a clinical remission, as well as in combination therapy,[5,6] for those patients in whom different DMARDs or biologic drugs are needed to control the disease.[7,8] Over the past 50 years, MTX has been proven effective not only in RA but also in various immunologic disorders such as psoriasis, psoriatic arthritis, polymyositis, dermatomyositis, systemic lupus erythematosus, and granulomatosis with polyangiitis (Wegener's granulomatosis).[9] In addition, MTX is recommended because of its steroid-sparing activity for the treatment of diseases such as giant cell arteritis and polymyalgia rheumatica.[10,11] Recently, the usefulness of MTX therapy in achieving remission in patients with Crohn's disease whose condition is refractory to treatment with corticosteroids has been reported.[12]

We report here the available research regarding the optimal dosage and route of MTX administration.

MATERIALS AND METHODS

The bibliographic team (Drs. Cipriani, Ruscitti, Carubbi, and Liakouli) and the scientific organizer (Dr. Giacomelli) first selected the following areas of interest: optimal dosage and route, use of folic acid, safety monitoring, adverse effects, long-term safety (2 years), management in the perioperative period and before/during pregnancy, and oral versus parenteral administration. MEDLINE and the Cochrane Library were systematically searched for articles published between 1990 and 2013, and a systematic literature review, including adult and pediatric RA, was performed following the updated guidelines of the Cochrane Collaboration.[13]

All selected articles were reviewed by the bibliographic team, on the basis of language (only English-written articles were evaluated, except for 2 historical articles in the Introduction and 1 article in which the Italian recommendations about MTX administration are reported), title, abstracts review, and study design. The selected articles were graded according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine.[14] Table I shows the results of the systematic literature review, and Table II reports the level of evidence regarding the references analyzed.

RESULTS

Mechanism of Action

MTX is an antimetabolite drug used in the treatment of some cancers; it acts on the intermediate metabolism of proliferating cells at higher doses than those used in rheumatology.[15,16] MTX acts as an antagonist of folic acid by binding to the catalytic site of dihydrofolic acid–reductase, interrupting the synthesis of thymidylate, purine nucleotides, serine and methionine, and inhibiting the production of DNA, RNA, and proteins. MTX's inhibitory activity on several enzymes involved in purine base metabolism, through the accumulation of adenosine, may determine its therapeutic effect. These effects modulate the function of lymphocytes and macrophages, reducing the chemotaxis of polymorphonuclear cells and decreasing the production of both immunoglobulins and pro-inflammatory cytokines.[15–17]

After ingestion, MTX is rapidly absorbed in the small bowel. A large part of the adsorbed drug is bound to plasma proteins, particularly albumin, and is released in all body compartments. A direct relationship between dose and plasma concentration has been described. Concomitant use of certain drugs such as sulfonamides and tetracyclines or clinical conditions may interfere with the binding to plasma proteins, thus leading to adverse effects.[15,16]

Once absorbed, MTX is metabolized to a hydroxylated compound that has less activity. The serum half-life is generally 6 to 9 hours. However, MTX is transported intracellularly via the reduced folate carrier and is retained within cells long after it has been eliminated from serum, thus permitting weekly dosing.[15–17] The frequency of weekly MTX dosing was derived from dermatology experiences in the early