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How to Effectively Use Methotrexate in Rheumatoid Arthritis?☆

Samuel Hernandez-Baldizon

Servicio de Reumatología, Hospital de Cruces, Baracaldo, Vizcaya, Spain

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ABSTRACT

Methotrexate (MTX) is the first choice disease modifying anti-rheumatic drugs for rheumatoid arthritis. In spite of its generalized use by rheumatologists worldwide, there is a general lack of agreement regarding the route of administration, the start-up dose and the way to increase the same. In this article, we propose a simplified outline for the use of the drug that should be individualized, based on it's pharmacological aspects, guidelines and recommendations published in high impact factor journals during the past few years. Adverse reactions and side effects, as well as their follow up are also reviewed.

¿Cómo hacer buen uso del metotrexato en artritis reumatoide?

Palabras clave:
Artritis reumatoide
Metotrexato
Práctica clínica
Dosis
Efectos secundarios
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RESUMEN

El metotrexato (MTX) es el fármaco modificador de la enfermedad de primera elección en artritis reumatoide. A pesar del uso casi generalizado por reumatólogos en todo el mundo, hay mucha discordancia entre la forma de iniciar la dosis, la vía de administración y la forma de realizar el incremento de dosis. En este artículo se planteamos un esquema simplificado del uso de este fármaco a individualizar en cada caso, basado en los aspectos farmacológicos, guías y protocolos de manejo publicados en revistas de impacto de nuestra especialidad en los últimos años. Se revisa además las reacciones adversas y efectos secundarios y cómo realizar el seguimiento de éstos.

Rheumatoid arthritis (RA) is an autoimmune systemic disease characterized primarily by symmetric, episodic, chronic, erosive, deforming polyarthritis that produces long-term joint disability if uncontrolled. Currently, methotrexate (MTX) is the disease-modifying drug most commonly used in RA and the first treatment choice.[1–3] Despite its almost universal therapeutic application, there is much disagreement on the part of rheumatologists in terms of the starting dose, how to increase it and the route of administration (Fig. 1).

In this article we propose a simplified clinical setting which may serve to identify general recommendation for each individual case. Our proposal is based on the analysis of review articles, meta-analysis, consensus and clinical practice guidelines published in the last five years in influential journals of our specialty.

How Does It Work?

MTX is an antimetabolite that competitively inhibits dihydrofolate reductase. This enzyme participates in the formation of tetrahydrofolate, necessary for the formation of the nucleoside thymidine, required for the synthesis of DNA, RNA, thymidylate and proteins. It partially inhibits the immune response[4] and, although through a poorly understood mechanism, autoimmune joint inflammation is reduced in the long term.

What Pharmacological Aspects Must Be Taken into Account?

Oral absorption of MTX is dose dependent and varies significantly according to intestinal transit. Meals, diarrhea and

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E-mail address: samuel.hernandezbaldizon@osakidetza.net

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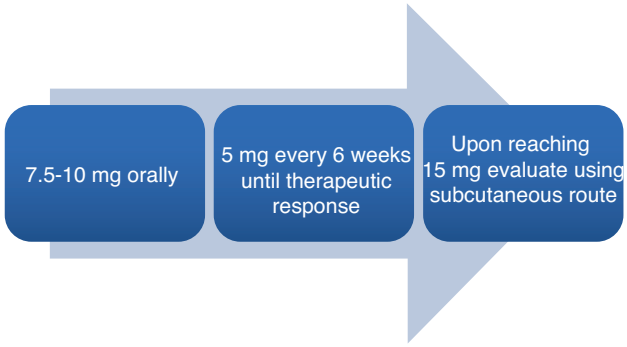

Fig. 1. Onset and dose increase.

non-absorbable antibiotics decrease its absorption, while constipation increases it. The oral mean bioavailability is 33% and parenteral is 77%. Once in the serum, 50% circulates bound to proteins, with a half life of 3–10 h. Excretion is 90% renal and 10% gastrointestinal.[5] These are issues that we must take into account when assessing the risk of adverse reactions and side effects of the drug, as their frequency increases in proportion to plasma levels (Table 1).

When to Start Treatment?

One should begin treatment with disease modifying drugs as soon as the diagnosis is carried out.[2] Diagnosis is mostly based on the history and physical examination, and less on the classification criteria. The patient will usually complain of pain, morning stiffness and swelling. Physical examination reveals symmetrical swelling and joint tenderness. However, these findings are not unique to RA in its early stage and a differential diagnosis is necessary. The RA classification criteria published in September 2010 by the ACR/EULAR[6] aim to classify patients who may benefit from treatment in the initial stages of the disease.

What Tests Should Be Performed Before Onset of Treatment?

Patients should be screened for assessment of potential toxicity risk factors (such as alcohol) and CBC, CRP and ESR, serum creatinine, transaminases, albumin, antibodies against hepatitis B and C, rheumatoid factor, anti cyclic citrullinated peptide antibodies, lipid profile, pregnancy test and chest, hands and feet X-rays carried out.[1,3] The application of the vaccine against pneumococcus and seasonal influenza virus[1] is also recommended. HIV serology[3] should also be assessed (Table 2).

The patient and the physician should assess pain and/or global disease activity scores (visual analog scale of 0–10). The doctor should perform a 28 joint count calculating a standard index of disease activity such as the DAS28. If positive for activity (DAS28 greater than 3), treatment is indicated.

Table 1
Main Interactions of Methotrexate.

Amoxicillin	Indomethacin
Trimethoprim	Nabumethone
Triamterene	Doxycycline
Omeprazole	Penicillin G
Tamoxifen	Flurbiprofen
Ketoprofen	Aspirin
Clotrimoxazole	Tazobactam
Piroxicam	Sulphamethoxazole
Diflunisal	Mercaptopurine
Ketorolac	Etodolac
Diclofenac	Acyclovir
Piperacillyn	Phenylbutazone
Naproxen	Citarabin
	Kanamycin

Modified from http://www.drugs.com/methotrexate.html.

Table 2
Tests That Must Be Performed Prior to Treatment.

Hemogram
Transaminases
CRP and ESR
Plasma creatinine
Hepatitis B and C serology
Plasma albumin
Simple X-rays of hands, feet and thorax

What Dose Should Be Used at Onset of Treatment?

There are multiple ways to approach treatment and each rheumatologist has his or her own way home, especially with regard to the route of administration and increasing the therapeutic dose. Here, we refer to treatment consensus and systematic reviews.[1–3,7] Traditionally, the recommended starting dose has been of 7.5–10 mg weekly for 4 weeks associated with folic acid in doses of 5–10 mg the day after taking MTX. Subsequently, a progressive increase between 2.5 and 5 mg every 2–4 weeks until a dose of 25 mg is reached between 3 and 6 months from the onset of treatment,[5] since high doses of 25–30 mg weekly are more effective as disease-modifying than 10–15 mg[3].

The starting dose recommended by GUIPCAR-SER typically varies between 7.5 and 15 mg weekly orally (4–6 tablets of 2.5 mg).[1] After 15 mg it is recommended to use the intravenous route to improve bioavailability (33% oral vs 77% parenteral).[1]

However, a systematic review of the literature on the use of MTX[3] recommended starting treatment with 10–15 mg orally, increasing 5 mg every 2 weeks up to 20–30 mg, depending on clinical response and tolerance. Parenteral administration of the drug should be considered in the case of poor response or intolerance.

Furthermore, the effectiveness of drug response, including a joint count, should be monitored,[8] for example using the DAS28, which has been validated and reviewed for this purpose in recent years.[9]

What Adverse Reactions and Side Effects Can We Foresee?

The evidence of risk factors for severe MTX toxicity suggests that a creatinine clearance of less than 79 ml/min increases the risk of pulmonary toxicity, and severe hypoalbuminemia in these patients is associated with liver and lung toxicity.[10,11] Abnormalities on chest x-rays, rather than respiratory function tests, are predictive of an increased risk of MTX pneumonitis.[12,13] The subgroups of patients with additional risk of developing liver failure secondary to the drug are mainly obese, diabetics and patients with viral or alcoholic hepatitis.[14,15] Adding this observational evidence to that of experts on the contraindications of the drug in randomized clinical trials in the last 15 years, it is not recommended to use MTX in the presence of significant renal disease, liver disease, leukopenia of less than 3000/mm^3, thrombocytopenia of less than 100,000/mm^3, age over 70 years, malignancy, pregnancy or fertility problems, a history of substance abuse/alcoholism, chronic lung disease and acute or chronic systemic infections (Table 3).

The toxicity of oral MTX is dose dependent, and initial doses of 20 mg have shown greater efficiency but a higher incidence of intolerance. Initial doses of 12.5–20 mg weekly compared to oral doses of 5–10 mg have shown to be more effective without increasing toxicity.[16] Regarding administration, the parenteral route has proven more effective in retrospective studies and shows