Actas Dermosifiliogr. 2014;105(6):583–589

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

NOVELTIES IN DERMATOLOGY

Methotrexate: New Therapeutic Approaches☆

L. Puig

Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

Received 12 October 2012; accepted 29 November 2012
Available online 12 June 2014

KEYWORDS
Psoriasis;
Methotrexate;
Clinical trials;
Pharmacokinetics;
Mechanism of action;
Cost-effectiveness

Abstract Although the first study on the efficacy of methotrexate in the treatment of psoriasis was reported in 1958, scientific evidence for this indication has been scant until quite recently. We now have new data on the pharmacokinetics and mechanism of action of methotrexate and new subcutaneous formulations that have improved the bioavailability, efficacy, and ease of administration of the drug. The results of recent clinical trials comparing methotrexate with several biologic agents have shown it to be the first-line therapy among the classic systemic treatments for psoriasis. Moreover, the incremental cost-effectiveness ratio for subcutaneous methotrexate has been shown to be superior to that of ciclosporin, adalimumab, and infliximab.

PALABRAS CLAVE
Psoriasis;
Metotrexato;
Ensayos clínicos;
Farmacocinética;
Mecanismo de acción;
Coste-eficacia

Metotrexato: novedades terapéuticas

Resumen Pese a que el primer estudio sobre la eficacia de metotrexato en el tratamiento de la psoriasis se remonta a 1958, hasta no hace mucho ha sido escasa la evidencia científica disponible sobre su uso en esta indicación.

Disponemos de nuevos datos acerca de la farmacocinética y el mecanismo de acción del metotrexato, así como de nuevas presentaciones por vía subcutánea que mejoran la biodisponibilidad, la eficacia y la conveniencia de la administración de este fármaco. La reciente publicación de ensayos clínicos comparativos con diversos biológicos permite considerar al metotrexato como el estándar terapéutico dentro de los tratamientos sistémicos clásicos de la psoriasis, con un cociente coste-eficacia incremental favorable al metotrexato subcutáneo si se compara con ciclosporina, adalimumab o infliximab.

Introduction

Methotrexate (MTX, *4-amino-4-deoxy-N10*-methyl pteroylglutamic acid) is an analog of aminopterin (*4-amino*-pteroylglutamic acid), a folic acid antagonist that was introduced in 1948 to treat acute leukemia in children but later replaced by MTX as this had a more favorable toxicity profile. The first study of the efficacy of MTX in the

☆ Please cite this article as: Puig L. Metotrexato: novedades terapéuticas. Actas Dermosifiliogr. 2014;105:583–589.

E-mail address: lpuig@santpau.cat

1578-2190/$ – see front matter

treatment of psoriasis was published in 1958,[1] and the first guidelines on its use in dermatology appeared in 1972.[2] Until quite recently, however, there was relatively little evidence to support the use of MTX in the treatment of psoriasis.

Among the advances that justify this review are new efficacy data that have led MTX to be considered the first-line therapy among the classic systemic treatments for psoriasis and new subcutaneous formulations that offer improved bioavailability and convenience of administration.

Pharmacokinetics

MTX can be administered orally, subcutaneously, intramuscularly, or intravenously. In the case of psoriasis, the standard dose (7.5-25 mg/wk) is nearly always administered orally or subcutaneously. The bioavailability of low-dose oral MTX is high (70%),[3] although it varies from patient to patient. At doses of more than 15 mg/wk bioavailability drops to 30%, as the uptake of MTX by the gastrointestinal tract is mediated by a saturable transporter, reduced folate carrier 1 (RFC1).[3] The preferred route of administration in such cases is thus generally parenteral, which is also associated with better gastrointestinal tolerability,[4] although the use of split doses of oral MTX can improve bioavailability.[5] The absorption of oral MTX, which primarily occurs in the proximal jejunum, is not affected by food intake, but is decreased in cases of malabsorption or inflammatory bowel disease. The bioavailability of parenteral MTX is similar regardless of the administration route used.

Once absorbed, 10% of MTX is converted in the liver to its partly inactive metabolite, 7-hydroxymethotrexate (7-OH-MTX), thereby reducing plasma MTX concentrations. The ability to convert MTX to 7-OH-MTX via aldehyde oxidase varies greatly—relative interindividual differences ranging from 1 to 14 have been described—and exhibits a bimodal distribution in the population. Rapid metabolizers have a poorer therapeutic response to MTX; additionally, folic acid (unlike folinic acid) blocks the production of 7-OH-MTX and could therefore contribute to higher levels of MTX in these patients.[6] 7-OH-MTX competes with MTX for cellular uptake via RFCs, which also internalize reduced folates and folic acid, albeit with low affinity. Quantitative or qualitative alterations in RFCs, similarly to high levels of exogenous folates competing for the receptor, can result in transport-related resistance to the therapeutic action of MTX. A recent study described a single nucleotide polymorphism in the *RCF1* gene that predicts therapeutic response to MTX in Japanese patients with rheumatoid arthritis,[7] illustrating the role that pharmacogenetics may come to play in improving treatment outcomes.

MTX, like 7-OH-MTX, is metabolized intracellularly to produce monoglutamates and polyglutamates, which are the main inhibitors of a range of enzymes; the intracellular levels of these metabolites correlate with the therapeutic efficacy of MTX (which is actually a prodrug).[5] Both the bioavailability of MTX and its intracellular conjugation are partly determined by the administration route. In one study of patients with rheumatoid arthritis, switching from oral to subcutaneous administration resulted in a 37% increase in the concentration of very long-chain polyglutamates and a 31% reduction in disease activity.[8] Polyglutamates are released slowly from the interior of the cell by the action of active efflux carriers, which may contribute to prolonging the elimination of the drug and also reflect pharmacogenetic differences.[9] While no studies have demonstrated that genetic variability in the enzymes involved in MTX metabolism is of clinical relevance in psoriasis,[10] variations in the genes involved in polyglutamate efflux transporters have been associated with differences in treatment efficacy and the risk of toxicity.[11]

Between 35% and 50% of circulating MTX binds to albumin (compared with 91%-95% of 7-OH-MTX) and peak concentrations are reached in the kidneys, liver, gallbladder, spleen, skin, and red blood cells (RBCs). RBC MTX levels may indicate possible hematologic toxicity and hepatic accumulation of the drug. MTX tends to accumulate in the extravascular compartment, and therefore extra caution should be exercised in patients with pleural effusion, ascites, or massive edema due to the risk of toxicity from reabsorption of extravascular fluid.

Between 65% and 80% of MTX is eliminated unaltered by the kidneys (mainly in the first 12 hours after administration) and 20% to 35% undergoes biliary secretion and is metabolized or transferred to other compartments. Glomerular filtration is the main pathway of renal elimination; tubular secretion and reabsorption are also involved but to a lesser extent. Biliary secretion is an important factor in patents with renal insufficiency, who have reduced drug clearance and an increased risk of toxicity. Hemodialysis and peritoneal dialysis result in limited and transient reductions in serum MTX levels due to the drug's low-to-medium protein binding and high tissue distribution.

The terminal half-life of MTX in serum is approximately 7 to 10 hours, but it can be as long as 26 hours in some patients. RBC MTX concentrations remain stable for 9 days, while serum levels become undetectable after 52 hours.[12] Although individual MTX clearance rates can be established with just 2 tests (at 30 and 120 minutes after administration), they have not been found to be useful for defining an optimal treatment regimen in rheumatoid arthritis.[13] While many drugs interact with MTX, the use of various nonsteroidal anti-inflammatory drugs (NSAIDs) was not found to significantly alter MTX serum levels, as compared with levels in patients not treated with NSAIDs.[14] Nevertheless, it is very important to remember that dose reductions are necessary in older patients (> 65 years) and patients with renal insufficiency.[15]

Mechanisms of Action

Various mechanisms of action have been proposed for MTX. The most relevant in the case of inflammatory diseases is the promotion of adenosine release with subsequent suppression of inflammation.[3]

MTX inhibits the proliferation of neoplastic cells, blocking the de novo synthesis of purines and pyrimidines by irreversibly inhibiting dihydrofolate reductase, which is responsible for the production of tetrahydrofolate. Although high doses of folic or folinic acid can reverse this effect, folic and folinic acid supplementation in inflammatory diseases is not used for this purpose but rather to prevent MTX toxicity without significantly reducing treatment efficacy.[16]