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CONSENSUS STATEMENT

Guidelines on the Use of Methotrexate in Psoriasis

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Abstract
Psoriasis, a chronic multifactorial inflammatory disease that develops in genetically predisposed individuals, affects approximately 1.5% of the Spanish population. This disease has a negative impact on patients' quality of life, and long-term therapy is often required to control the symptoms. In addition to the classical systemic treatments (methotrexate, acitretin, cyclosporine, and ultraviolet light), the group of drugs known as biologics (etanercept, infliximab, adalimumab, and ustekinumab) provides the dermatologist with an expanded therapeutic armamentarium, thereby improving the likelihood of controlling psoriasis in patients with severe and/or extensive disease. Methotrexate, a classic

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antipsoriatic drug, is still very useful either as single-drug therapy or in combination with other systemic drugs, particularly as a rescue therapy or combined with biologics. This article aims to establish the role of methotrexate in the treatment of psoriasis. We considered it of interest to develop guidelines for using methotrexate in the management of psoriasis with a view to ensuring the safe and proper use of this drug in the management of psoriasis. This document was developed by consensus among members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology.

PALABRAS CLAVE
Metotrexato;
Guía;
Tratamiento;
Psoriasis

Metotrexato: guía de uso en psoriasis

Resumen
La psoriasis es una enfermedad inflamatoria crónica, de predisposición genética y origen multifactorial, que afecta aproximadamente al 1,5% de la población española, repercutiendo negativamente de forma importante en la calidad de vida de los pacientes, los cuales requieren frecuentemente tratamientos de larga duración, para controlar sus síntomas. Los tratamientos sistémicos clásicos (metotrexato, acitetrino, ciclosporina, luz ultravioleta), junto con las denominadas terapias biológicas (etanercept, infliximab, adalimumab, ustekinumab), permiten al dermatólogo disponer de un arsenal terapéutico más amplio y disponer, por lo tanto, de mayores posibilidades de control de pacientes con psoriasis severa y/o extensa. El metotrexato, un fármaco clásico en la terapia antipsoriásica, sigue siendo de gran utilidad tanto en monoterapia como asociado a otros fármacos sistémicos, en especial como rescate o combinación con los biológicos. El objetivo de este artículo es establecer el papel del metotrexato en el tratamiento de la psoriasis. Por ello hemos creído de interés elaborar una guía de uso de metotrexato en psoriasis, consensuada entre varios componentes del Grupo de Psoriasis de la Academia Española de Dermatología y Venereología, que facilite la utilización segura y precisa de este fármaco en el manejo de pacientes con psoriasis.

Introduction

Methotrexate (MTX) ($C_{20}H_{22}N_8O_5$) is an antimetabolite analog of folic acid (4-amino-10-methylfolic acid) derived by N^{10} methylation of its precursor amethopterin (Figure 1).

MTX competitively inhibits dihydrofolate reductase, an enzyme that catalyzes the reduction of dihydrofolic acid (FH_2) to tetrahydrofolic acid (FH_4). Aminopterin was used empirically for the first time in 1951 to treat psoriasis and rheumatoid arthritis.[1] The first published reference to its use specifically in the treatment of psoriasis was in 1958.[2]

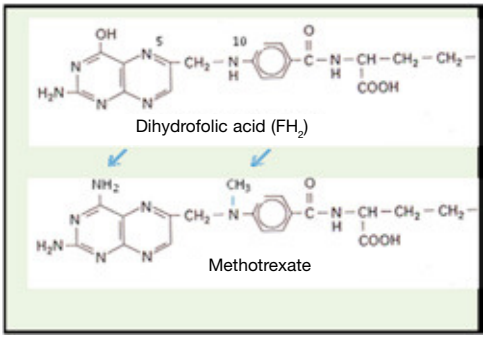


Figure 1 Chemical formula of methotrexate.

In 1972, methotrexate was approved by the US Food and Drug Administration for this indication.

Mechanism of Action

MTX has a triple anti-inflammatory, antiproliferative and immunosuppressant action. It interferes with the metabolic pathway of folic acid, competitively inhibiting the enzyme dihydrofolate reductase and consequently the activation of folinic acid. This inhibition blocks the synthesis of deoxythymidylic acid, which is required for DNA synthesis. MTX binds strongly to the enzyme. However, as the bond is reversible, a large number of drug molecules must be in contact with the enzyme to maintain inhibition. Otherwise, the bond breaks and the enzyme regains its activity;it is precisely this constraint that determines how MTX must be prescribed and administered. MTX also partially, and with less sensitivity, inhibits the formation of the purine ring of inosinic acid, the precursor of all DNA and RNA purine nucleotides. High concentrations of MTX can even directly inhibit protein synthesis.

It seems clear that at high doses the chief effect of MTX is its antifolate effect but the mechanism of action at low doses is still poorly understood. It has been suggested that the effects of low-dose MTX may be due more to the formation of intracellular polyglutamates (polyglutamation)

and the increased formation of adenosine, a potent endogenous anti-inflammatory mediator.[3,4]

Some authors have suggested that the chief mechanism of action of low-dose MTX in psoriasis and other inflammatory diseases may result from the induction of apoptosis in activated lymphocytes or from the inhibition of these cells' activation and expression of certain adhesion molecules.[5-8]

Pharmacokinetics

At doses under 30 mg/m^2, MTX is entirely absorbed in the gastrointestinal tract by active transport. At higher doses, absorption is incomplete because of transport saturation. Once absorbed, the drug is partially inactivated in the intestinal tract and the liver, which means that its bioavailability is low. It is distributed throughout the body but penetrates pleural and cerebrospinal fluid slowly and with difficulty such that the peak concentrations are 30 times lower at these sites than in plasma. The drug is eliminated practically unchanged (90%) in urine by both filtration and active secretion. MTX clearance is therefore reduced when elimination depends on creatinine clearance. The bioavailability achieved with oral and intravenous routes is comparable but highly variable (25%-70%). Peak levels in serum are achieved 1 to 2 hours after oral administration and 30 to 60 minutes after intramuscular injection.

Indications

MTX is indicated as a systemic treatment in moderate to severe plaque psoriasis, psoriatic erythroderma, generalized pustular psoriasis, nail psoriasis, palmoplantar psoriasis, and, especially, in psoriatic arthritis. It is a good therapeutic choice for the treatment of psoriasis that has failed to respond to topical therapies, acitretin, broadband and narrowband psoralen-UV-A (PUVA) and UV-B, or when these therapies are unavailable or have been rejected by the patient. It is indicated as a rescue therapy in the event of loss of efficacy or a rebound flare in patients treated with antipsoriatic biologic agents. MTX is also used in combination with other systemic drugs to maintain efficacy while reducing the adverse effects of the drugs with which it is combined.

Low-dose MTX therapy is particularly useful in combination with infliximab because it suppresses or reduces the development of antibodies against the biologic agent thereby maintaining its efficacy.[9,10]

MTX is approved by the FDA for the treatment of rheumatoid arthritis in children. It is usually well tolerated, and the protocol for monitoring toxicity risk in children is similar to that used in adults. MTX has also been used in combination with etanercept in the treatment of pediatric psoriasis.[11] Etanercept is approved for the treatment of plaque psoriasis in children over 8 years of age.

Contraindications

When considering treatment with MTX, the clinician must carefully evaluate all the contraindications and special precautions relating to the use of this drug (Table 1). If treatment is deemed necessary, the presence of a relative contraindication should be taken into account in the selection of the appropriate dose (test dose and subsequent adjustment) and the monitoring and safety protocol used.

Table 1 Contraindications to the Use of Methotrexate

Relative
- Renal insufficiency (reduce dose)[a]
- Persistently abnormal liver enzymes[b]
- Active or recurrent hepatitis[b]
- Cirrhosis
- Excessive alcohol intake[a,b]
- Drug interactions[a,b]
- Concomitant use of organ-toxic drugs[a,b]
- Active infectious disease (especially chronic infections, such as tuberculosis and human immunodeficiency virus)
- Immunosuppression or current use of immunosuppressive agents (other than biologics)
- Pregnancy. Likewise, conception should be avoided during treatment and following withdrawal for at least 3 months in men and 1 ovulatory cycle in women.
- Recent vaccination with a live vaccine
- Active gastric ulcer
- Obesity (body mass index >30)
- Diabetes mellitus[b]
- Hyperlipidemia[b]
- Hypoalbuminemia[a]
- Low intake or deficiency of folic acid[a,b]
- An uncooperative patient who does not follow instructions or does not adhere to the treatment regimen[a]
- Advanced age[a]

Absolute
- Pregnancy or breastfeeding in women/conception in men
- Marked anemia, leukopenia, or thrombocytopenia
- Alcohol abuse
- Acute peptic ulcer
- Severe respiratory failure
- Immunodeficiency

[a]Factors associated with hematologic toxicity.[13]
[b]Factors associated with liver toxicity.[13]

Since MTX is an abortifacient and a teratogen associated with a specific pattern of malformations (FDA category D teratogenicity), its use is contraindicated in pregnancy. Nor should it be prescribed for nursing mothers, given what is known of its ability to cause fetal skeletal, cardiac, and nervous system abnormalities.[12] Women of childbearing age taking MTX must use an effective method of contraception. If MTX is prescribed to a pregnant woman who is unaware of her condition, any subsequent decision should be made taking into account that the minimum teratogenic dose of MTX is 10 mg/wk and the critical period for the development of malformations is between the sixth and eight weeks of pregnancy.[13] In addition to its direct mutagenic potential, MTX also has a toxic effect on dividing cells, such as spermatocytes, and may produce oligospermia, which can be intense and persistent and affect male fertility. While the minimum interval after

MTX treatment before conception can be safely planned has not been clearly established, in light of the drug's pharmacological properties and mechanism of action, it can be suggested that men should avoid fertilization for at least 3 months after completing treatment (since a single cycle of spermatogenesis lasts 74 days) and women should avoid conception for at least 1 complete ovulatory cycle following the end of treatment.[13]

Patients on MTX should avoid vaccination with live vaccines, such as oral polio, measles, mumps, rubella, chickenpox, and yellow fever. MTX is also contraindicated in patients with active viral hepatitis.

Dosage and Route of Administration

MTX is sold in 2.5-mg tablets for oral use and in preloaded syringes containing 7.5, 10, 15, 20, or 25 mg for parenteral administration (subcutaneous or intramuscular). Also available are 50-mg vials for intramuscular injection. These can be fractioned into smaller doses, although in such cases it should be remembered that the handling and disposal of MTX are problematic, owing to its toxicity.

A low weekly dose is the MTX regimen that has been used since the drug was first prescribed for the treatment of psoriasis.[14] The weekly dose of 7.5 to 30 mg is administered on a single day or divided into 3 doses and administered at 12-h intervals over 2 consecutive days.[15] The reason for dividing the dose is to prevent or reduce potential adverse gastrointestinal effects, although there is no evidence to support this practice. Subcutaneous administration of MTX may reduce the gastrointestinal effects and enhance the therapeutic efficacy of the drug, although this has only been demonstrated in patients with rheumatoid arthritis[16] and no evidence relating to psoriasis is yet available.

Efficacy in Psoriasis

The therapeutic effect generally appears slowly and gradually within the first 4 to 8 weeks following start of treatment. The efficacy of MTX monotherapy for psoriasis has not been evaluated in clinical trials. Available evidence relates to trials that compared diverse doses of MTX with other drugs.[17-20] The results of those studies lead to the conclusion that treatment with MTX is associated with the following dose-dependent improvement at 12 weeks: with low-dose therapy (increasing from 7.5 to 15 mg/wk), 25% of patients achieved a 75% improvement in the psoriasis area severity index (PASI 75) and 11% achieved PASI 90;[18] with higher doses (from 15 to 22.5 mg/wk), 60% of patients achieved PASI 75 and 40% PASI 90[17,19,20] (Table 2). The same studies show that MTX was less effective than ciclosporin,[17,18] adalimumab,[19] and infliximab.[20] Furthermore, an analysis of the subgroup of patients treated with MTX in one trial[19] revealed that, when no adequate response was achieved within 12 weeks with a dose of 20 mg/wk, no improvement was obtained by increasing the dose to 25 mg/wk (Saurat, presentation at the European Association of Dermatologists and Venereologists, Berlin, 2009). The superior efficacy of biologic agents over MTX appears to be clearly established according to the most recent meta-analyses and reviews published.[21-23]

Table 2 Efficacy of Methotrexate in Psoriasis (PASI Improvement at 12 Weeks)

Increasing doses	PASI 75 (%)	PASI 90 (%)
7.5-15 mg/wk[18]	25	11
15-22.5 mg/wk[17,19,20]	60	40

Abbreviation: PASI, psoriasis area severity index.

Toxicity and Adverse Effects

Although the efficacy of MTX in moderate to severe psoriasis is not in doubt, it is important to remember that approximately 30% of patients will be affected by some type of MTX toxicity. The toxic effect is generally moderate[24,25] but in rare cases may be fatal; the mortality rate is 1.2 per 100 000 patients treated.[26] Consequently, risk avoidance measures must be scrupulously observed (Table 3).

MTX-induced toxicity depends on the extracellular drug concentration and the duration of exposure. Thus, in the case of a fixed dose, toxicity is proportional to duration of exposure. Most of the adverse events associated with low weekly doses of MTX are mild (gastrointestinal and mucocutaneous). The most important major adverse events (hematologic, hepatic, and pulmonary effects) are infrequent and often associated with predisposing factors.

Mild or Moderate Secondary Toxicity

The adverse events most often reported in patients taking weekly doses of MTX are fever, joint pain, and

Table 3 Measures to Reduce the Risk of Methotrexate (MTX) Toxicity

Interventions
- Appropriate prescription after evaluation of contraindications
- Dose reduction after evaluation of contraindications
- Folic acid supplementation
- Provision of written information on risks to patients
- Written instructions concerning drug regimen
- Monitoring

Drugs that increase the toxicity of MTX[a]

NSAIDs	*Others*
• Salicylates	• Ciclosporin
• Naproxen	• Colchicine
• Ibuprofen	• Dipyridamole
• Indomethacin	• Ethanol
• Phenylbutazone	• Phenytoin
Antibiotics	• Probenecid
• Trimethoprim + sulfamethoxazole	• Sulfonylurea
• Sulfamides	• Thiazide
• Tetracyclines	• Furosemide
• Ciprofloxacin	• Barbiturates

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
[a]List of common medications (not exhaustive).[13]

gastrointestinal reactions. They tend to be mild and reversible and do not generally require withdrawal of treatment. They can be minimized by reducing or dividing the dose, taking a folic acid supplement, and by taking the dose at bedtime or injecting it subcutaneously.[27] Adverse events generally appear 24 to 48 hours after administration. Although they are mild, the occurrence of these adverse events is one of the most frequent causes for discontinuation of treatment.[28]

Gastrointestinal Toxicity

Some 60% of patients develop signs of gastrointestinal toxicity: stomatitis, nausea, vomiting, dyspepsia, abdominal pain, indigestion, diarrhea, anorexia and weight loss.[27] Aphthous ulcers occur with higher doses of MTX and their course improves with folic acid supplementation.[28]

Serious Primary Toxicity

The most serious adverse events associated with MTX treatment involve specific organs: the blood, liver, and lungs, with mortality decreasing in that order.[29] Since their appearance is often associated with the presence of risk factors that were insufficiently evaluated prior to treatment,[13] we must pay careful attention to all relevant risk factors when screening candidates for MTX therapy and to tailoring our prescription (Table 1). Other very important factors in the prevention of serious toxicity are the prescription of folic acid supplementation in situations involving excessive depletion, careful consideration of possible drug interactions, and ensuring that no mistakes are made in the regimen prescribed (the most common cause of acute myelosuppression is inadvertent overdose due to medication errors).

Because of the serious consequences of errors in MTX prescription, the Spanish body responsible for ensuring patient safety (the Agencia Española del Medicamento y Productos Sanitarios) has issued a drug warning on the subject.[30] In the United Kingdom, the National Patient Safety Agency in conjunction with the British Society of Rheumatology and the British Academy of Dermatology have published a drug alert leaflet that must be given to all patients taking MTX.[31]

Pharmacokinetic research has opened up an interesting line of enquiry concerning the evaluation of toxicity and clinical response in patients on MTX. In oncology, it is established practice to use genetic testing to determine the drug's rate of metabolism in the individual so as to minimize the risk of toxicity.[32] As mentioned above, the mechanism of action of low-dose MTX in psoriasis is still poorly understood, but it appears to be related to polyglutamation, a process that plays a key role in the drug's anti-inflammatory action. This pharmacokinetic process varies greatly from one individual to another, and it has been shown in rheumatoid arthritis that patients with more extensive polyglutamation respond more effectively to MTX.[33] It should therefore be possible to reduce the dose of MTX in these patients and achieve equal efficacy with a lower risk of toxicity.

Other pharmacogenetic studies have revealed that several polymorphisms affecting the metabolic pathways of folate, pyrimidine, and purine or the intracellular transporters of MTX are associated with the efficacy and toxicity of the drug in psoriasis.[34,35] However, pharmacokinetic studies have failed to demonstrate any correlation between the efficacy of MTX and the concentration of polyglutamates in red blood cells.[36] When the dose is adjusted in accordance with the results of individualized pharmacokinetic testing, the use of a folic acid supplement (20 mg/wk) appears to reduce the efficacy of MTX.[37] This observation suggests an interesting line of future research.

Hematologic Toxicity

In the presence of certain risk factors (Table 1) or when high doses are taken owing to a prescription error or a high-dose therapeutic strategy (in the treatment of squamous cell carcinoma of the head and neck, for example), the most worrying and rapidly developing toxic effect of MTX is myelosuppression (leukopenia, thrombopenia, and anemia). This event is life threatening.

In most cases, myelosuppression is dose dependent and due to the direct toxic action of MTX on bone marrow although, in exceptional cases, it has been reported as a dose-independent idiosyncratic reaction. In such cases, it is usually associated with precipitating factors, such as renal insufficiency, advanced age, hypoalbuminemia, underlying bone marrow hypoplasia, persistent macrocytosis, low folate levels, or the use of concomitant medications.[38] It is this potential toxicity that justifies the practice of assessing the patient's reaction to MTX by administering an initial test dose before starting treatment.

Rescue with Folinic Acid

When acute hematologic toxicity develops, the priority objective is to neutralize and counteract the activity of MTX by supplying FH_4. This rescue treatment involves the intravenous administration of folinic acid (N^5-formil-FH_4). Once introduced into the folate cycle, folinic acid is transformed into active FH_4 molecules, thereby obviating the need for the conversion of FH_2 to FH_4.

This treatment should be administered whenever plasma levels of MTX remain above 10^{-8} M for more than 48 hours; the dose of folinic acid should be increased in proportion to the concentration of MTX to be neutralized. Rescue therapy is not necessary when low doses are used (15-10 mg/m^2) because plasma levels drop below 10^{-8} M within 48 hours. The amount of folinic acid required is proportional to the MTX plasma concentration determined 24 hours after administration (Table 4), and the rescue treatment should be continued until MTX levels fall below $5x10^{-8}$ M. Obviously, MTX levels must be measured every 12 to 24 hours throughout the rescue period.

Table 4 Rescue with Intravenous Folinic Acid

[MTX] every 24h	Dose of Folinic Acid
1.5×10^{-6} M	10-15 mg/m^2/6 h
1.5 and 5×10^{-6} M	30 mg/m^2/6 h
$>5\times10^{-6}$ M	60 mg/m^2/6 h

Hepatotoxicity

A small percentage of patients may present elevated transaminase levels as an expression of acute drug toxicity. This elevation is seen during the initial weeks of treatment, and the values generally return to normal over the following weeks without requiring any reduction in the dose. Once again, the abnormality is generally related to the presence of other relative hepatic risk factors (Table 1) and is another situation that justifies the use of an initial test dose. Obviously, the appearance and above all the persistence of abnormal liver test results necessitates more frequent monitoring of both clinical and laboratory parameters and/or a dose reduction. Liver function tests should be performed the day before MTX is taken to rule out the mild and transient elevation of transaminase values that appears in some patients on the day they take the drug but which is not an indication of real toxicity.

Historically, however, chronic hepatotoxicity (fibrosis, cirrhosis) has been the greatest problem associated with the long-term use of MTX. The principal motive for intermittent, or interrupted, treatment regimens is to prevent cumulative hepatotoxicity. Traditionally, the risk of liver damage was assessed by performing serial liver biopsies after a certain cumulative dose threshold had been reached (as low as 1-1.5 g, a level reached within 2 years at a dosage of 15 mg/wk), and treatment would be continued or withdrawn depending on the biopsy results.[39,40] The issue of the supposed hepatotoxicity of MTX has been more important in the dermatology literature[39] than in the rheumatology literature,[40] possibly because of the presence of a number of confounding factors in the assessment of liver toxicity in patients with psoriasis, which has led some authors to reconsider the need for liver biopsy in this group.[41,42] The greater hepatotoxicity observed in patients with psoriasis may be due to the presence of nonalcoholic steatohepatitis, which has a prevalence of close to 50% in psoriasis patients,[43] in conjunction with metabolic syndrome and glucose intolerance.[44] Moreover, clinicians must always check whether the patient is taking another hepatotoxic medication that would increase the toxicity of MTX.

MTX-induced hepatotoxicity is more common in patients with pre-existing risk factors (Table 1), and particularly in obese or diabetic patients, in those whose alcohol intake is high or who have a history of liver disease or persistently elevated transaminase levels. The current consensus is that preventive measures must be more rigorous in patients with risk factors; in those who have a lower risk profile, very similar to that described in guidelines for patients with rheumatoid arthritis, measures may be less strict.[40] The cumulative dose threshold has been increased to between and 3.5 to 4 g in the low-risk group.[25]

Liver Biopsy

Liver function test results have not traditionally been considered to be a good marker of MTX-associated hepatotoxicity in patients with psoriasis. However, recent studies indicate that candidates for liver biopsy can be identified using serial measurements of alanine aminotransferase and γ-glutamyl-transferase (taking alcohol intake into account as a risk factor). This method is a also recommended in patients with rheumatoid arthritis.[45] In recent years, the possibility of devising an indirect approach to measuring liver damage through serial measurement of serum aminoterminal propeptide of type III procollagen (PIIINP) has been investigated.[45] Once this method has been standardized, it may eventually replace, or at least reduce, the need for liver biopsy in patients requiring long-term treatment with MTX.[46] Patient anxiety about the procedure and the risk associated with biopsy (1.5 complications per 1000 biopsies, including subcapsular hemorrhage, perforated gallbladder, pneumothorax, and hemoperitoneum) would thereby be reduced.[39] Liver biopsy would be unnecessary in patients with normal PIIINP levels and a cumulative dose of MTX of less than 3 to 4 g (Table 5).[46,47] However, it should be remembered that PIIINP levels may be elevated in patients with active psoriatic arthritis and steatohepatitis. Other noninvasive tests that can predict the presence (Fibrotest) or absence (Fibroscan) of clinically significant liver fibrosis are very useful in the selection of liver biopsy candidates.[48,49]

In our opinion, the use of serial liver biopsies corresponds to a time when there were fewer therapeutic options for patients with psoriasis. The risks and cost associated with routine liver biopsy are no longer justified, and the practice can be replaced by using a cumulative threshold dose of 3.5 to 4 g, liver enzyme abnormalities, and variations from stable PIIINP levels as hepatotoxicity indicators in patients receiving long-term MTX therapy (Table 5).[50] When the possibility of liver toxicity is identified (PIIINP levels >4.2 μg/L), a biopsy should be considered or the patient should be switched to an alternative therapy and the liver condition managed in conjunction with specialists in the liver unit.

Pulmonary Toxicity

The chief form of pulmonary toxicity associated with MTX is acute interstitial pneumonitis characterized by nonproductive cough, dyspnea at rest, fever, and general malaise in conjunction with leukocytosis and radiographic evidence of diffuse bilateral interstitial involvement and alveolar infiltrate (Table 6).[51] While pneumonitis is rare, its incidence has been estimated to be 3.9 cases per 100 patient-years of MTX exposure and its prevalence to be 5.5%

Table 5 Guide to Serum Concentrations of Aminoterminal Propeptide of Type III Procollagen (PIIINP) in Patients Taking Methotrexate

PIIINP values, μg/L	Action
1.7-4.2	Normal in adults
>4.2 in at least 3 samples within a 12-month period	Consider the need for a biopsy
>8.0 in 2 consecutive samples	Consider the need for a biopsy
>10 in at least 3 samples within a 12-month period	Consider withdrawal of treatment

Table 6 Diagnostic Criteria for Methotrexate-Induced Pneumonitis[a]

Clinical criteri[a]
- Nonproductive cough
- Fever >38°C
- Dyspnea (<8 weeks)
- Tachypnea >28 breaths/min

Additional tests
- Oxygen saturation <90%
- Pulmonary or alveolar infiltrates (radiographic)
- White cell count <15000 mm^3
- Negative blood and bronchial aspirate cultures

[a]Adapted from Kremer,[51] Searles,[80] and McKendry.[81]

in exposed patients.[52] Although MTX pneumonitis appears to be much more frequent in patients with rheumatoid arthritis[53,54] than in patients with psoriasis, there have also been reports of cases in the latter group since the introduction of MTX use for psoriasis.[55] Pneumonitis is generally subacute, symptoms appear before the diagnosis is confirmed, and it does not appear to be related to the cumulative dose; a number of associated risk factors have been identified, although the findings are contradictory.[52] When pneumonitis is suspected, possible infectious causes (particularly *Pneumocystis jiroveci*) must always be ruled out . Treatment requires immediate withdrawal of MTX, the administration of systemic corticosteroids, and respiratory support. It is unclear whether MTX pneumonitis is caused by hypersensitivity or whether it is an idiosyncratic reaction. The associated risk of mortality has been estimated by some authors to be 20%.[56]

Pulmonary fibrosis is another adverse event traditionally associated with MTX therapy, but it appears to be related to the administration of high-doses and not with the weekly low-dose regimen used in psoriasis and psoriatic arthritis.[57] Other adverse pulmonary reactions have been reported in the rheumatology literature (bronchitis with bronchial hyperresponsiveness, bronchiolitis obliterans organizing pneumonia, pulmonary edema, pleuritis, and pleural effusion), but it is not clear whether these reactions are secondary to the use of MTX or related to the underlying disease (rheumatoid arthritis).[58]

Patient Screening and Treatment Management

Pretreatment Screening and Follow-up Monitoring (Table 7)

The prescription of MTX must be tailored on a case-by-case basis to maximize therapeutic benefit and minimize the risk of toxicity. The first step in the process is to obtain a complete medical history and perform a physical examination. The following should be assessed and recorded: the type and course of the disease; associated arthritis; severity measures (including PASI, body surface affected, physician's global assessment, and dermatology quality of life index); comorbidities; situations that may constitute

Table 7 Pretreatment Screening of Candidates for Methotrexate Therapy

Medical history
- Type of psoriasis
- Course
- Arthritis/arthralgia
- Response to prior treatment
- Contraindications/risks

Baseline assessment
- Physical and dermatologic examination
- Complete blood count
- Kidney and liver function
- Viral infections
- Purified protein derivative (Mantoux test)
- Chest radiograph
- Rule out and prevent conception

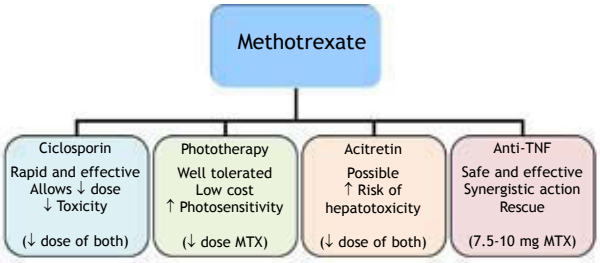
Monitoring
- Repeat physical and dermatological examination
- Complete blood count
- Kidney function
- Liver function
  - Hepatotoxicity
    - Risk factors
    - 3.5-4 g cumulative dose
    - Liver enzymes
    - PIIINP
    - Biopsy, not routinely
- Total protein
- Tuberculosis screening
- Levels
  - Folic acid (optional)
  - PIIINP (when available)
  - Methotrexate (optional)

Direct and easy access to the dermatologic nursing service

Abbreviations: PIIINP, aminoterminal propeptide of type III procollagen.

relative contraindications;[59] risk factors for hepatotoxicity or need to adjust the dose; and, in particular, information on the drugs the patient is taking for other indications (Tables 1 and 3).

The pretreatment workup should include a complete blood count and biochemistry, liver and kidney function tests, and a pregnancy test if appropriate. When indicated, serology for hepatitis B and C viruses and human immunodeficiency virus should also be ordered. A baseline chest radiograph and Mantoux test are also recommended (the tuberculin skin test should be repeated to identify a booster effect when necessary). The need for a skin test and chest radiograph to rule out the possibility of tuberculosis is not a generally accepted recommendation. However, in our opinion it should be performed as part of the overall assessment in patients who are candidates for systemic treatment for psoriasis, whether with a traditional drug or a biologic agent. Tuberculosis screening at baseline provides a reference in case pulmonary complications



TREATMENT MONITORING FORM — METHOTREXATE: — PSORIASIS — Episode No. =

NAME — (Date and physician's stamp) — Prior treatment — Reason for withdrawal: Treatment finished / Rotation / Adverse event / Other:

Diagnosis | Telephone | Code | Start | Finish

Inclusion Criteria	MONITORING	Baseline	1-2 wks	4 wks	12 wks	6 mo	9 mo	12 mo
Extensive disease Very frequent recurrence Impact on quality of life Poor control with topical treatment Special site or situation Rotational therapy Therapeutic strategy Other:	Date							
	Examination*							
	PASI/BSA							
	DLQI/PGA							
	HBV/HCV/HIV							
	Mantoux/Booster							
	Chest Rx (baseline)							
Main Toxicity	Complete blood count: Leuk(10^3/uL)							
	Complete blood count: Neut(10^3/uL)							
	Complete blood count: Lymphocytes (10^3/uL)							
	Complete blood count: Hb(g/dL)							
- Teratogenicity. Fetal death - Hepatotoxicity - Myelosuppression - Serious lung disease. Fibrosis - Severe cutaneous reaction - Severe opportunist infections - Lymphoproliferative disease - Gastrointestinal symptoms	MCV							
	Platelets							
	Bilirubin							
	AST/ALT (U/L)							
	LDH (U/L)							
	AP/GGT (U/L)							
Contraindications	Albumin							
	Urea/Uric Acid (mg/dL)							
Absolute - Pregnancy, breastfeeding and conception	Creatinine mg/dL							
	Adverse Event*							
	Folic Acid**							
Relative - Liver dysfunction - Renal insufficiency - Serious hematologic abnormalities - Immunodeficiency - Severe active infection - Alcohol abuse. - Diabetes mellitus - Obesity - Older Patients - Live vaccines	*Pregnancy test***							
	PIIINP assay**							
	*Other, case specific***							
	Consult NURSE*							
	Consult DOCTOR							
	Height/Weight/BP							
*Visit or phone call **Optional, case specific	**Dose**							

Decide between Rotation and Continuation (*Continuation Form*)

ADVERSE EVENTS RECORD (AE)

Date											
AE											
Date											
AE											

DRUG TYPE: Immunosuppressant

SIGNIFICANT ADVERSE EVENTS -Note: Adverse events may vary depending on dose and route of administration. Hematologic and/or gastrointestinal toxicity is common during chemotherapy. These reactions occur much less frequently with the intermittent regimens used in rheumatoid diseases and psoriasis

>10%
Central nervous system (with spinal administration or very high doses):
Arachnoiditis (acute reaction characterized by intense headache, stiff neck, vomiting, and fever; can be alleviated by reducing dose)
Subacute toxicity (limb paralysis, cranial nerve paralysis, epileptic seizure, or coma
Demyelinating encephalopathy (months after treatment)
Cutaneous: Reddening of the skin
Endocrine and metabolic: Hyperuricemia, defects in oogenesis and spermatogenesis
Gastrointestinal: Mouth ulcers, gingivitis, nausea, vomiting, diarrhea, anorexia, perforated intestinal tract, mucositis (dose dependent; appears within 3-7 days of administration and resolves within 2 weeks).
Potential emetic:
<100 mg: Moderately low (10%-30%)
≥100 mg and <250 mg: Moderate (30%-60%)
≤250 mg: Moderately high (60%-90%)
Hematologic: Leukopenia, thrombocytopenia
Renal: Renal failure, uremia, neuropathy
Respiratory: Pharyngitis

1%-10%
Cardiovascular: Vasculitis
Central nervous system: Vertigo, malaise, encephalopathy, epileptic seizure, fever, chills
Cutaneous: Alopecia, rash, photosensitivity, depigmentation or hyperpigmentation
Endocrine and metabolic: Diabetes
Urogenital: Cystitis
Hematologic: Hemorrhage
Myelosuppression: This (together with mucositis) is the dose-dependent factor limiting use; appears 5-7 days after start of treatment and usually resolves within 2 weeks.
Potential myelosuppression:
White blood cells: moderate/ Platelets: moderate/ Start: 7 days/ Plateau: 10 days/
Recovery: 21 days
Hepatic: Cirrhosis and portal fibrosis with long-term treatment, elevated liver enzymes; usually return to normal within 10 days.
Neuromuscular and skeletal: Joint pain
Ocular: Blurred vision
Renal: Kidney dysfunction (abrupt rise in creatinine and urea, and reduction in urine volume; occurs at high doses)
Respiratory: Pneumonitis (fever, cough, interstitial pulmonary infiltrate)

<1% (important or serious only):
Acute neurological syndrome, anaphylaxis, alveolitis, cognitive dysfunction, opportunist infections, erythema multiforme, liver failure, leukoencephalopathy, lymphoproliferative disease, osteonecrosis and soft tissue necrosis, pericarditis, erosion of psoriasis plaques, epileptic seizure, Stevens-Johnson syndrome, thromboembolism.

DRUG INTERACTIONS

Increase MTX toxicity	Reduces Efficacy of MTX	MTX modifies
- NSAIDs - Aminoglycosides - Azathioprine - Barbiturates -Ciclosporin - Cephalothin - Colchicine - Phenylbutazone - Penicillins - Pyrimethamine - Probenecid - Retinoids - Salicylates - Sulamides/Sulfones - Sulfasalazine - Tetracyclines - Trimethoprim/Sulfamethoxazole	- Cholestyramine	- Mercaptopurine - Cytarabine - Theophylline

ADVERSE EVENTS DURING TREATMENT
1.-

FOR MORE INFORMATION SEE SUMMARY OF PRODUCT CHARACTERISTICS

Figure 2 Treatment Monitoring Form.

should develop; moreover, due to the chronic nature of the disease, these patients are often switched to another antipsoriatic agent for which such screening is necessary, as other authors have suggested.[13]

Proper monitoring of MTX treatment requires the patient's cooperation and commitment. Patients must have easy access to the nursing service and the dermatology unit and attend regularly for monitoring and repeat laboratory tests following the usual protocol for patients with moderate to severe psoriasis.[59] Protocol-based monitoring is recommended (see Figure 2 for a sample monitoring form), but the protocol can be modified depending on the patient's test results and risk factors.

A complete blood count should be obtained 7 to 14 days after the initial test dose and every 3 months thereafter. Liver and kidney function should be assessed at baseline and every 3 months thereafter. In the presence of associated risk factors or changes from baseline results, more frequent monitoring of laboratory parameters may be necessary until the abnormalities are stable or have returned to normal. Both male and female patients receiving MTX therapy must take effective contraceptive measures. During treatment, the need to repeat the Mantoux test (or interferon-γ release assays when available) must be evaluated annually as long as the results remain negative in order to rule out the presence of latent tuberculosis, which would be indicated by a positive skin test. A meticulous record must be kept of the cumulative dose. Plasma concentrations of MTX should be measured when direct toxicity is suspected, when the cumulative dose in a patient with high alcohol consumption or steatohepatitis is above 1.0 to 1.5 g, or when liver toxicity is suspected on the basis of the results of PIIINP testing (when available).

Considerations Regarding Use and Therapeutic Strategies

Traditionally, MTX has been prescribed as single-drug therapy in psoriasis and used particularly in patients with accompanying arthritis. However, the introduction of novel drugs and new treatment strategies has conferred a new role on MTX as interest has risen in using it in combination with other antipsoriatic drugs. We must remember, however, that psoriasis remains a chronic disease and that rotating, sequencing, and combining drugs with the aim of achieving an acceptable level of efficacy with the lowest doses and least risk possible will still be valid strategies, especially in the case of MTX since the most common form of toxicity of this drug is related to the cumulative dose. In patients with psoriasis, tailoring therapy to take into account all constraints related to the course of the disease and the patient's lifestyle is the key to maximizing efficacy.[60]

Test Dose

The prescription of a reduced initial test dose of MTX has become routine clinical practice because of the drug's potential toxicity and the possibility of serious idiosyncratic adverse reactions (especially hematologic) and even of reactions that are mild but nonetheless deserve consideration (mucositis, elevated transaminases). There is, however, no clinical evidence or consensus supporting the need for such a test dose. In fact, anaphylactic and hypersensitivity reactions have mainly been reported in patients with rheumatic disease who had previously taken high doses of MTX[38] and have not been reported in patients with psoriasis on low-dose MTX therapy. Leukopenia and pancytopenia have also been reported, especially in patients with underlying disease (in particular those with renal failure and patients on hemodialysis). In our opinion, the administration of a low test dose should receive particular consideration in patients with a relative contraindication (Table 1), in older patients, and whenever it is deemed clinically necessary. In such cases, a reasonable guideline is to administer 50% of the dose during the first 1 or 2 weeks of treatment. The summary of product characteristics for the oral preparation recommends using an initial test dose of 7.5 mg. The test dose recommended for the injectable preparation is 5 to 10 mg.[61]

In any case, the crux of the matter is not the size of the initial dose that should be used, but rather the need to assess the patient promptly after start of treatment (at 1 to 2 weeks) irrespective of the initial dose administered. This assessment should include both a clinical examination and blood tests. If no abnormalities are found in this early assessment, it is reasonable to increase the dose to a maintenance level and follow the normal monitoring protocol thereafter.

Supplemental Folic Acid

The impact of folic acid supplementation on the activity of MTX is paradoxical; it may reduce the therapeutic effect but has also been shown to reduce the potential adverse effects of the drug.[28] Evidence has suggested—with confirmation by a recent meta-analysis[62]— that folic acid supplementation tends to reduce blood, mucocutaneous, and gastrointestinal toxicities (and is therefore indicated when such effects are present) and significantly reduces liver toxicity, but neither prevents nor reduces pulmonary toxicity.[63,64]

However, the need for such supplementation is not universally accepted and neither has it been clearly established whether folic acid or folinic acid is the best choice or what the best doses and regimens might be.[65] There are opposing views about routine folic acid supplementation[66] and inconsistencies in reports of its impact on the therapeutic efficacy of MTX.[62] In patients with a certain metabolic profile, folic acid is preferable to folinic acid because it enhances the efficacy of MTX therapy.[67]

In our opinion, folic acid supplementation is required in patients being treated with MTX who have a folate deficiency or whose folate needs are high because of infectious disease or treatment with certain antibiotics, and in patients on high-dose MTX therapy (which is not used in psoriasis). In routine practice, the need for folic acid supplementation should be decided on a case-by-case basis depending on the presence or risk of adverse events. The physician must evaluate whether the better solution is to regularly measure folic acid blood levels or routinely prescribe supplements for patients on MTX. Note that a balanced diet normally supplies a sufficient daily intake

Table 8 Summary

Indications	• Psoriatic arthritis • Plaque psoriasis (vulgaris) • Psoriatic erythroderma • Palmoplantar psoriasis • Pustular psoriasis • Nail psoriasis • Loss of efficacy of other systemic medication • Loss of efficacy of UV-B/psoralen-UV-A • Combination with anti-TNF agent
Contraindications	• Pregnancy: category D teratogenicity (women and men) • Anemia, leukopenia, thrombocytopenia • Alcohol abuse, liver disease
Efficacy	• PASI 75 (12 wks): 25%-60% (dose of 7.5-22.5 mg/wk) • PASI 90 (12 wks): 11%-40% (dose of 7.5-22.5 mg/wk)
Dose regimen	• 7.5-25 mg/wk (oral or subcutaneous) • Split dose: every 12 h (on 1 or 2 consecutive days) • Initial therapeutic dose: 7.5-15 mg (adjust according to effects) • Reduce to minimum effective dose
Test dose	• New patient: 50% of standard dose (routine use not mandatory) • Repeat test dose: not mandatory unless there is risk or suspicion of toxicity or the patient is of advanced age (50% of standard dose) • Patients should always be assessed at 1-2 wks: complete blood count and transaminase levels (irrespective of the initial dose used)
Folic acid supplementation	• Prescribe at least 5 mg of folic acid 1 day a week (24-48 h after administration of MTX) • Assess supplementation needs individually in patients with a folate deficiency
Severe toxicity	• Bone marrow suppression • Hepatotoxicity • Interstitial pneumonia
Mild toxicity	• Headache, nausea, vomiting, loss of appetite • Mucositis, photosensitivity, erosion of psoriasis plaques
Special precautions	• Particular care should be taken to avoid medication errors, in both prescription and administration. • Risk of hepatotoxicity: avoid alcohol abuse and exposure to hepatotoxic drugs • Hypoalbuminemia • Renal insufficiency • Advanced age • Avoid conception (both women and men)
Strategies	• Rotational therapy • Sequential therapy • Intermittent therapy • Combination therapy
Combinations	• MTX + narrowband UV-B • MTX + ciclosporin • MTX + acitretin • MTX + anti-TNF agents
Reasons for rotation or switch	• Adverse events or intolerance • Total accumulated dose of 2.5-4 g (depending on risk profile) • Lack of efficacy (failure to meet treatment objective at 12 wks) • Treatment target achieved (reduce dose and/or change strategy)
Screening and monitoring	• Baseline physical examination and medical history • Baseline and regular follow-up screening for contraindications and comorbidities • Check the list of concomitant medications the patient is taking • Baseline and annual Mantoux test • Chest radiograph (baseline) • Serology for hepatitis B and C virus (HIV testing when indicated) • First assessment at 1-2 weeks (complete blood count and transaminases) • Protocol-guided baseline and follow-up workups (see Figure 2 for sample protocol)

Abbreviations: HIV, human immunodeficiency virus; MTX, methotrexate; PASI, psoriasis area severity index; TNF, tumor necrosis factor.

of folic acid. A useful indirect parameter to watch for indication that folic acid levels need to be monitored may be serial measurements of mean corpuscular volume done to rule out macrocytosis.

There is no consensus on the optimum dose or regimen for folate supplementation. One option is to prescribe a daily dose of 5 mg of folic acid (except on the days when MTX is taken). Another is to prescribe 15 mg/wk of folinic acid to be taken 24 to 48 hours after administration of MTX. In order to simplify the treatment regimen, particularly in patients in good health with no associated disease or condition likely to deplete folic acid, a pragmatic strategy is to prescribe a single weekly dose of 5 mg to be taken 24 to 48 hours after administration of MTX (to avoid any interference with the therapeutic effect of the drug) and optionally and sporadically measure folic acid levels in blood during routine laboratory testing, modifying the dose or regimen of supplementation according to the results obtained.

Rotational, Sequential, and Intermittent Treatment

In light of the considerable therapeutic value of MTX not only as a first-line treatment for psoriasis but also as a rescue therapy during psoriasis flares in patients taking biologic agents, and given the limitations on MTX therapy imposed by cumulative toxicity, a policy of conservative use over the long term is recommended. Consequently, rotational, sequential, and intermittent strategies are important in the prescription of MTX. Combinations of MTX with other antipsoriatic drugs, such as acitretin and ciclosporin and even biologic agents bear careful consideration in the overall therapeutic approach to psoriasis.[68]

Dose Adjustment

In order to prevent toxicity and prolong the period during which MTX can be taken, once the therapeutic target has been achieved the dose should be reduced to the minimum required to effectively maintain the clearance achieved. Similarly, the adjusted dose should take into account the patient's age and kidney function as well as the presence of potential comorbidities associated with a risk of MTX toxicity.

Combination Therapies

Combinations of MTX and other drugs and therapies have been shown to be very useful in maintaining efficacy while minimizing the risk of toxicity (Figure 2). Combining MTX and ciclosporin reduces the dose and toxicity of both drugs with great effectiveness,[69,70] although the increased risk of immunosuppression must be taken into account. MTX has also been shown to be safe and effective in combination with narrowband UV-B therapy,[71] although it does increase phototoxicity in this situation. MTX can also be given in combination with acitretin at low doses,[72] although this combination is associated with an increased risk of liver toxicity.

However, the advent of biologic therapies for the treatment of psoriasis is perhaps the development that has most underscored the usefulness of MTX. The use of biologics has led to the introduction of new therapeutic strategies, including overlapping, switching, recovery of lost efficacy, and the inhibition of anti-TNF antibodies. MTX[73,74] and ciclosporin effectively fulfill these therapeutic targets.

Most experience with combining MTX and biologic agents is in rheumatoid arthritis and inflammatory bowel disease, settings in which this strategy has been shown to be particularly useful in optimizing therapeutic results and minimizing loss of response and infusion-related adverse events. Pharmacodynamic studies have shown that the addition of low-dose MTX (7.5 mg/wk) in patients being treated with infliximab reduces clearance of the biologic, perhaps by suppressing antibodies against infliximab.[75] The usefulness of combination therapy has not been explicitly demonstrated in dermatologic indications. The authors of a number of uncontrolled studies have suggested optimizing clinical results by prescribing MTX along with etanercept (a combination that produces no additional adverse events) or by prescribing MTX for short periods during fluctuations in the course of the psoriasis in patients taking etanercept.[76,77] Combining MTX with adalimumab can enhance the clinical effectiveness of treatment in both psoriasis and psoriatic arthritis according to the ADEPT trial comparing this combination to adalimumab monotherapy.[78]

Withdrawal of Treatment

MTX should be discontinued or the regimen modified in the presence of adverse events, intolerance, treatment failure, or insufficient response in terms of the initial treatment target, and also when the risk to benefit ratio is changed by new situations or comorbidities or when the cumulative dose is clinically significant (1.5-2g in patients at high risk and 3.5-4 g in patients at low risk for hepatotoxicity) and measurement of PIINP is not possible. Today, given the broad range of antipsoriatic treatments available, there no longer appears to be any justification for doing serial liver biopsies to monitor the safety of MTX therapy except in exceptional situations. Abrupt withdrawal of MTX treatment is not generally associated with a rebound effect.

Conclusions (Table 8)

MTX was the first systemic treatment for psoriasis. After more than 50 years of experience, oral MTX continues to be safe, effective, cheap, and easy to use. It can therefore be considered the standard systemic therapy,[39] especially for long-term antipsoriatic treatment with a classic systemic drug in carefully selected and monitored patients. Undoubtedly, there are currently other more effective treatments for psoriasis, in particular the biologic agents. Nonetheless, MTX continues to play an important role as a faithful ally that can be used in rescue strategies and combinations and to counteract loss of response. Its indication may become even more specific and effective in the near future when pharmacogenetic research makes it possible to identify patients with a better chance of response and lower risk of side effects. Another interesting advance is the possibility that liver biopsies may not be required to detect possible cumulative liver toxicity.

In line with other authors and after considering all the above reasons, we conclude that MTX has both a long history and a current relevance that will very probably be sustained in years to come.[79]

Conflict of Interest

The authors declare that they have no conflicts of interest with respect to these guidelines. However, all the authors currently have or have had diverse relationships with the pharmaceutical industry and have received financial remuneration for research, clinical trials, consultancy work, and conference participation. The annex at the end of this article includes the personal declarations of each author.

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