



## SPECIAL ARTICLE

# Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis<sup>☆,☆☆</sup>



I. Calvo<sup>a,\*</sup>, J. Antón<sup>b</sup>, J.C. López Robledillo<sup>c</sup>, J. de Inocencio<sup>d</sup>, M.L. Gamir<sup>e</sup>, R. Merino<sup>f</sup>, L. Lacruz<sup>g</sup>, M. Camacho<sup>h</sup>, M.J. Rua<sup>i</sup>, S. Bustabad<sup>j</sup>, G. Díaz Cordovés-Rego<sup>k</sup>

<sup>a</sup> Hospital Universitario y Politécnico La Fe, Valencia, Spain

<sup>b</sup> Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues de Llobregat, Barcelona, Spain

<sup>c</sup> Hospital Infantil Universitario Niño Jesús, Madrid, Spain

<sup>d</sup> Hospital Universitario 12 de Octubre, Madrid, Spain

<sup>e</sup> Hospital Universitario Ramón y Cajal, Madrid, Spain

<sup>f</sup> Hospital Universitario La Paz, Madrid, Spain

<sup>g</sup> Hospital Son Espases, Palma de Mallorca, Spain

<sup>h</sup> Hospital Universitario Virgen del Rocío, Sevilla, Spain

<sup>i</sup> Hospital Universitario Cruces, San Vicente de Barakaldo, Spain

<sup>j</sup> Hospital Universitario de Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife, Spain

<sup>k</sup> Hospital Materno Infantil del Hospital Regional Universitario de Málaga, Málaga, Spain

Received 2 March 2015; accepted 5 May 2015

Available online 3 February 2016

### KEYWORDS

Methotrexate;  
Juvenile idiopathic  
arthritis;  
Consensus

### Abstract

**Objectives:** To develop a consensus document of recommendations for the use of methotrexate (MTX) in patients with juvenile idiopathic arthritis (JIA).

**Material and method:** A group of eleven experts proposed several clinical questions on the use of MTX in patients with JIA. A systematic review was conducted and the evidence and recommendations for each question were extracted. The results were discussed and validated by the experts in a work session to establish the final recommendations.

**Results:** MTX is recommended as the first drug for inducing remission in JIA, and its indication should be made according to the clinical category of the patient. Prior to treatment, it is recommended to perform a complete blood count, including white cells, levels of liver enzymes, serum creatinine, and other analytical parameters according to specific risk factors. Treatment should be initiated with a dose of 10–15 mg/m<sup>2</sup>/week. In cases of uveitis or polyarthritis, an

<sup>☆</sup> Please cite this article as: Calvo I, Antón J, López Robledillo JC, de Inocencio J, Gamir ML, Merino R, et al. Recomendaciones para el uso de metotrexato en pacientes con artritis idiopática juvenil. An Pediatr (Barc). 2016;84:177.

<sup>☆☆</sup> This study was presented at the X Congreso de la Sociedad Española de Reumatología Pediátrica; November 14, 2013; Granada, Spain.

\* Corresponding author.

E-mail addresses: [calvo.inm@gva.es](mailto:calvo.inm@gva.es), [inmaculadacalvopenades@gmail.com](mailto:inmaculadacalvopenades@gmail.com) (I. Calvo).

**PALABRAS CLAVE**

Metotrexato;  
Artritis idiopática  
juvenil;  
Consenso

initial dose of 15 mg/m<sup>2</sup>/week should be considered. For a better bioavailability and tolerability, it is preferable to administer MTX parenterally if the dose is  $\geq 15$  mg/m<sup>2</sup>/week. It is necessary to periodically perform an analytical monitoring of the patient and to assess possible alterations in liver enzymes to make changes if necessary. Combinations with biological agents may be necessary, as well as the concomitant addition of folic or folinic acid.

**Conclusions:** This document describes the main recommendations for the appropriate use of MTX in JIA patients, according to scientific evidence and clinical experience.

© 2015 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. All rights reserved.

## Recomendaciones para el uso de metotrexato en pacientes con artritis idiopática juvenil

### Resumen

**Objetivos:** Elaborar un documento de recomendaciones consensuadas para el uso de metotrexato (MTX) en pacientes con artritis idiopática juvenil (AIJ).

**Material y método:** Un grupo de 11 expertos planteó diversos interrogantes clínicos en el uso de MTX en pacientes con AIJ. Se realizó una revisión sistemática y se extrajeron las evidencias y recomendaciones para cada pregunta. Los resultados fueron valorados y consensuados por los expertos en una sesión presencial para establecer las recomendaciones finales.

**Resultados:** Se recomienda el MTX como primer fármaco inductor de remisión en AIJ, cuya indicación se realizará según la categoría clínica del paciente. Previo al tratamiento se recomienda evaluar un hemograma que incluya recuento leucocitario, niveles de enzimas hepáticas y creatinina sérica, así como otros parámetros analíticos conforme a factores de riesgo específicos. El tratamiento se iniciará con dosis de 10–15 mg/m<sup>2</sup>/semana. En casos de uveítis o poliartritis se valorará una dosis inicial de 15 mg/m<sup>2</sup>/semana. Para una mejor biodisponibilidad y tolerabilidad, se administrará preferentemente por vía parenteral si la dosis es  $\geq 15$  mg/m<sup>2</sup>/semana. Se deberá realizar un seguimiento analítico del paciente periódicamente y evaluar posibles alteraciones en enzimas hepáticas para realizar cambios si fuera preciso. La combinación con biológicos puede ser necesaria, además del uso concomitante de ácido fólico o folínico.

**Conclusiones:** Este documento recoge las principales recomendaciones para el empleo adecuado de MTX en pacientes con AIJ, de acuerdo a la evidencia científica y a la experiencia clínica.

© 2015 Asociación Española de Pediatría. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

## Introduction

Juvenile idiopathic arthritis (JIA) is an inflammatory arthropathy that comprehends 7 subtypes based on the classification of the International League of Association for Rheumatology (ILAR).<sup>1</sup> These subtypes differ in their pathophysiology, clinical features, and treatment.

Juvenile idiopathic arthritis is a chronic disease that impairs the functional capacity and quality of life of affected individuals, and thus it is important that it be diagnosed and treated early.

The pharmacological treatment of JIA depends on the subtype and severity of the disease, with frequent use of disease-modifying antirheumatic drugs (DMARDs) as monotherapy or in combination with oral and intra-articular non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). Early introduction of DMARDs—methotrexate (MTX) being one of them—may help prevent disease progression.

The use of MTX in patients with JIA is recommended due to its proven efficacy and safety profile.<sup>2</sup> However, despite being the DMARD most frequently used for JIA<sup>3</sup> and having been available for many years, certain points pertaining to its management in clinical practice are still in question. Thus, the aim of this study was to establish consensus-based clinical and therapeutic recommendations for the management of MTX in patients with JIA.

## Methods

We set up a guideline-developing group (GDG) consisting of three coordinators and eight specialists in paediatric rheumatology, all members of the Sociedad Española de Reumatología Pediátrica (Spanish Society of Paediatric Rheumatology [SERPE]). The GDG formulated the clinical questions pertaining to MTX management applying the PICO framework (patient, intervention, control and outcome).

## Strategy for literature search and selection

We carried out a systematic search in Medline and the Cochrane Library for human studies published in English or Spanish in the past 15 years for which an abstract was available. The keywords used in the search were “idiopathic juvenile arthritis”, “methotrexate”, “routes of administration”, “dosage”, “tapering”, “discontinuation” and other, more specific terms based on each particular clinical question. Finally, we completed the search with articles provided directly by the GDG and the summaries of product characteristics for methotrexate.

Of the resulting list of publications, we selected review articles, consensus documents, guidelines by scientific associations and articles that explicitly addressed specific aspects of the proposed questions, and proceeded to summarise the evidence.

## Consensus process

We used the nominal group technique. The experts discussed the contents of the evidence summary in a structured fashion during a work session. Based on the conclusions reached at the session, we drafted a document with the agreed-on recommendations and determined the level of evidence (LE) and grade of recommendation (GR) for each of them, either adhering to the system employed in the source (if any had been used) or applying the grading system of the Scottish Intercollegiate Guidelines Network (SIGN).<sup>4</sup> Lastly, the resulting document was presented to the group of experts for a final review.

## Results

### Literature search

We obtained 344 references in the literature search. Through a subsequent screening, we selected 67 articles, 6 clinical practice guidelines and 9 summaries of product characteristics for critical reading. After evaluation by the GDG members and the implementation of the structured and participatory consensus methodology, we validated sixteen recommendations (Table 1).

### Initiation of methotrexate treatment

#### Efficacy of methotrexate in juvenile idiopathic arthritis

Most clinical trials and prospective cohort studies demonstrate that MTX is efficacious for the treatment of active JIA.<sup>8–13</sup>

Several studies have demonstrated the impact of MTX on the quality of life of patients with JIA, regardless of the dose used. Depending on the form and severity of the disease, MTX treatment is administered in combination with local and/or systemic NSAIDs and GCs or even with biologics.<sup>9,12–14</sup> Given the extensive experience with the use of MTX for JIA, MTX is considered the first-line DMARD and is the mainstay of long-term therapy in these patients.<sup>2</sup>

- Recommendation 1: MTX is recommended as the first-line treatment for remission induction in JIA due to its proven efficacy and safety profile<sup>2</sup> (IA; Feldman<sup>5</sup>).

#### Indication for methotrexate

Several international publications have established recommendations for the use of MTX,<sup>1,7,8</sup> based on which we developed our own recommendations. We found variability in the criteria applied to certain aspects, consistent with the variability that exists in everyday clinical practice. Thus, we agreed on a set of minimum criteria that would allow for a uniform decision-making process as pertains to the indication of MTX (Table 2).

- Recommendation 2: MTX will be indicated based on the clinical classification of JIA as presented in Table 2 (4D√; SIGN<sup>4</sup>).

#### Evaluation of the patient prior to receiving methotrexate

If MTX is indicated, the clinical evaluation of patients with JIA must include at least certain diagnostic tests and other parameters depending on the risk factors.

- Recommendation 3: prior to initiation of treatment with MTX, performance of a complete blood count, differential blood count, liver enzyme level and serum creatinine<sup>7</sup> tests is recommended (D; Oxford<sup>6</sup>).
- Recommendation 4: depending on the existing risk factors, the patient’s condition and previous diagnostic tests, testing for acute phase reactants (ESR-CRP) and hepatitis B and C serology (HBV and HCV) will be considered. In female adolescents, a potential pregnancy should be ruled out by means of an appropriate test. Confirmation of a negative Mantoux skin test in the past six months is recommended (4D√; SIGN<sup>4</sup>).

#### Initial dose and maximum dose

A study by Giannini et al.<sup>16</sup> showed that an initial MTX dose of 5 mg/m<sup>2</sup> is no more efficient than placebo. A study conducted by PRINTO<sup>10</sup> showed that patients with polyarticular JIA responded to MTX within nine months of starting treatment at standard doses of 8–12.5 mg/m<sup>2</sup> (administered by the oral, subcutaneous and intramuscular routes). Thus, we have determined the following:

- Recommendation 5: the following doses are recommended<sup>8</sup>: initial dose, 10–15 mg/m<sup>2</sup>/week; maximum total dose: 25 mg/week (IA; Niehues<sup>8</sup>).

While additional randomised controlled trials are needed, several studies suggest that MTX is useful for the treatment of chronic uveitis in patients with JIA, preventing its onset,<sup>17</sup> and improving disease activity in a significant percentage of patients.<sup>18</sup> Thus, we agreed on the following initial dose:

- Recommendation 6: in patients with uveitis or polyarthritis, an initial dose of 15 mg/m<sup>2</sup>/week is recommended (4D; SIGN<sup>4</sup>).

**Table 1** Recommendations for the use of methotrexate (MTX) in patients with juvenile idiopathic arthritis (JIA).

#	Recommendation	LE	GR	Grading system	Ref.
1	MTX is recommended as the first-line treatment for remission induction in JIA, due to its demonstrated efficacy and safety profile	I	A	Feldman <sup>5</sup>	Dueckers et al. <sup>2</sup>
2	MTX will be indicated based on the clinical classification of JIA as presented in Table 2	4	D✓	SIGN <sup>4</sup>	
3	Prior to initiation of treatment with MTX, performance of a complete blood count, differential blood count, liver enzymes and serum creatinine tests is recommended for all patients	NA	D	Oxford <sup>6</sup>	Beukelman et al. <sup>7</sup>
4	Based on the existing risk factors, the patient's condition and previous diagnostic tests, testing for acute phase reactants (ESR-CRP) and hepatitis B and C serology (HBV and HCV) will be considered. In female adolescents, a potential pregnancy should be ruled out by means of an appropriate test. Confirmation of a negative Mantoux skin test in the past six months is recommended.	4	D✓	SIGN <sup>4</sup>	
5	The following doses are recommended <sup>8</sup> : Initial dose, 10–15 mg/m <sup>2</sup> /week Maximum total dose: 25 mg/week	I	A	Niehues <sup>8</sup>	Niehues et al. <sup>8</sup>
6	In patients with uveitis or polyarthritis, an initial dose of 15 mg/m <sup>2</sup> /week is recommended	4	D	SIGN <sup>4</sup>	
7	For doses $\geq 15$ mg/m <sup>2</sup> /week, parenteral administration is recommended due to a higher bioavailability and tolerability	III	C	Niehues <sup>8</sup>	Niehues et al. <sup>8</sup>
8	For initial doses of 10 mg/m <sup>2</sup> /week, a choice will be made between oral or subcutaneous administration, deciding on whichever is most suitable based on the circumstances of the patient	4	D✓	SIGN <sup>4</sup>	
9	It is recommended that laboratory testing of baseline parameters is repeated 1 month after initiating MTX or 1–2 months after any dose increases	2+	D✓	SIGN <sup>4</sup>	
10	In patients receiving stable doses and with no previous test abnormalities, surveillance laboratory testing is recommended every 3–4 months	4	D	SIGN <sup>4</sup>	
11	In response to liver enzyme elevation between 1 and 2 times the upper limit of normal, no specific action will be taken, or liver enzymes will be rechecked at a shorter interval until the levels normalise	NA	C	Oxford <sup>6</sup>	Beukelman et al. <sup>7</sup>
12	In response to liver enzyme elevation more than twice the upper limit of normal, decreasing the dose of methotrexate or temporarily withholding methotrexate administration is recommended	NA	C	Oxford <sup>6</sup>	Beukelman et al. <sup>7</sup>
13	If liver enzymes remain at levels more than 3 times the upper limit of normal following a decrease in the methotrexate dose, discontinuation of methotrexate is recommended	NA	C	Oxford <sup>6</sup>	Beukelman et al. <sup>7</sup>
14	We recommend considering the use of MTX in patients treated with biologic agents to improve the response and/or reduce the development of antibodies to certain biologics	4	D	SIGN <sup>4</sup>	
15	To prevent side effects such as dyspepsia and nausea, the use of either folic or folinic acid is recommended as an adjuvant to MTX therapy. Folic or folinic acid will be given in tablet form in doses of 5 mg/week at least one day apart from the administration of MTX or, alternatively, in doses of 1 mg/day skipping the day that MTX is administered	4	D	SIGN <sup>4</sup>	

GR, grade of recommendation; NA, not available; LE, level of evidence; Ref, source reference.

**Table 2** Indication of MTX based on the clinical classification of JIA.

Category	Criteria for indication of MTX	Exceptions
Oligoarticular	MTX recommended as first-line treatment	Monoarticular presentations that are easy to manage and assess and respond well to intra-articular GCs
Polyarticular (RF[+] and [-])	MTX recommended for all cases alone or combined with other medication such as NSAIDs or oral or intra-articular GCs	
Psoriatic arthritis	Oligoarticular: MTX recommended as first-line treatment Polyarticular: we recommend the use of MTX in all cases, combined with oral and/or intra-articular GCs and with or without NSAID therapy.	Monoarticular presentations that are easy to manage and assess and respond well to intra-articular GCs.
Enthesitis-related arthritis (ERA)	Peripheral: we recommend the use of MTX or sulfasalazine combined with oral and/or intra-articular GCs Axial: a therapeutic trial with MTX or sulfasalazine is recommended when initial treatment with full-dose NSAID has failed after 4 weeks	
Systemic arthritis	The use of MTX may be considered in patients with active joint involvement and no systemic component	
Presence of uveitis	MTX is recommended in cases of uveitis associated with JIA that do not respond to first-line topical treatment <sup>15</sup>	

NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; GC, glucocorticoid; MTX, methotrexate.

## Route of administration

The study of Niehues et al.<sup>8</sup> reviews several studies<sup>19–22</sup> on the bioavailability of MTX. The conclusion is that for doses of up to 15 mg/m<sup>2</sup>/week, the bioavailability after parenteral and oral administration is similar; at higher doses ( $\geq 15$  mg/m<sup>2</sup>/week) parenteral administration is recommended for its higher bioavailability and tolerability.

- Recommendation 7: for doses  $\geq 15$  mg/m<sup>2</sup>/week, parenteral administration is recommended due to a higher bioavailability and tolerability<sup>8</sup> (IIC; Niehues<sup>8</sup>).

The criteria for making decisions regarding the initial dose and route of administration are variable and subject to the preferences of the patient and/or family members and the required doses.

- Recommendation 8: for initial doses of 10 mg/m<sup>2</sup>/week, a choice will be made between oral or subcutaneous administration, deciding on whichever is most suitable based on the circumstances of the patient (4D $\checkmark$ ; SIGN<sup>4</sup>).

## Tapering and discontinuation of methotrexate

We did not find sufficient evidence to make a recommendation. However, the data of a clinical trial<sup>23</sup> show similar results whether MTX is discontinued six or twelve months after achieving remission. Thus, in principle, MTX could be discontinued six months after achieving remission.

The panel of experts found a wide variability in the tapering off and discontinuation of MTX doses in everyday clinical practice: from withdrawal of treatment to tapering down in steps of 2.5 mg in each visit (every 6–8 weeks). Other strategies consisted of increasing the interval between doses without changing the dose itself; that is, for example, giving the same dose every 15 days as opposed to every week, and so on, until discontinuation.

In gradual tapering schemes, it is acceptable to choose to switch to oral administration once a dose of 10 mg is reached, applying the previously noted criteria regarding the route of administration.

## Safety of methotrexate

Based on the review of the summaries of product characteristics, the most significant adverse effects of MTX involve the suppression of the haematopoietic system and gastrointestinal disorders. Specifically, the most frequent adverse reactions ( $\geq 1/10$ ) are gastrointestinal (stomatitis, dyspepsia, nausea and loss of appetite) and hepatobiliary (elevated transaminases); with less frequent effects ( $\geq 1/100$ ,  $< 1/10$ ) including involvement of the gastrointestinal tract (mouth ulcers and diarrhoea), cutaneous and subcutaneous tissues (exanthema, erythema and pruritus), nervous system (headache, fatigue and sleepiness), respiratory system, thorax and mediastinum (pneumonia and interstitial alveolitis/pneumonitis, often associated with eosinophilia) and the blood and lymphatic system (leukopenia, anaemia and thrombocytopenia). Hair loss, while being rare ( $\geq 1/1000$ ,  $< 1/100$ ), is usually a source of concern for the families.<sup>24</sup>



The development and degree of severity of adverse reactions depend on the dose and frequency of administration. Since severe adverse reactions may occur even at the lowest doses, it is imperative that physicians monitor these patients at regular intervals (every 3–4 months).

We recommend the subcutaneous administration of MTX, as it is well tolerated at the site of injection. Only mild local skin reactions have been observed, and these diminish over the course of treatment. Intramuscular administration has led to reports of local adverse reactions (burning feeling) or lesions (formation of sterile abscesses or destruction of fatty tissues) at the site of administration.<sup>24</sup>

The contraindications for MTX need also be considered<sup>24</sup>: hypersensitivity to MTX or any of the excipients; liver failure, alcohol abuse, or kidney failure; pre-existing blood dyscrasias such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; severe acute or chronic infection, such as tuberculosis or HIV infection; mouth ulcers or known active gastrointestinal ulcerative disease; pregnancy and breastfeeding; and concurrent vaccination with live or live-attenuated vaccines, although the evidence-based recommendations of a panel of experts of the EULAR<sup>25</sup> recommend the live-attenuated vaccine if the dose used is less than 15 mg/m<sup>2</sup>.

### Followup and monitoring of patients undergoing treatment with methotrexate

A study by Ortiz-Álvarez et al.<sup>26</sup> assessed the utility of the ACR guidelines for monitoring patients with JIA, and estimated a probability of 11% for having significantly abnormal blood tests at three months, compared to 10% probability of having an abnormal test by chance alone. Consequently, they deemed that periodical routine blood tests were unnecessary. The conclusions of a different study<sup>27</sup> suggested that the adult standard of surveillance laboratory testing every four to eight weeks might not be necessary in children treated with MTX, especially if certain risk factors are absent. Other studies suggest the need to monitor for potential and usually reversible liver function test abnormalities, especially if the dose needs to be increased or large doses of MTX are required.<sup>28</sup> There seems to be no question that testing should be performed to confirm normal levels one month after initiation of MTX treatment.

- Recommendation 9: it is recommended that laboratory testing of baseline parameters is repeated one month after initiating MTX or one to two months after any dose increases (2 + D<sub>✓</sub>; SIGN<sup>4</sup>).
- Recommendation 10: in patients receiving stable doses and with no previous test abnormalities, surveillance laboratory testing is recommended every 3–4 months (4D; SIGN<sup>4</sup>).

Hashkes et al.<sup>29</sup> analysed the relationship between hepatotoxic risk factors and liver histology in patients with JIA treated with MTX. They found that biochemical abnormalities were associated with liver damage based on the Roenigk classification and the presence of liver fibrosis, which concurred with studies of patients with rheumatoid arthritis (RA). This suggests that the guidelines for monitoring MTX

hepatotoxicity in AR may be applicable to JIA. These data along with further evidence extrapolated from adults with RA<sup>27–30</sup> justified the recommendations of the ACR<sup>7</sup>:

- Recommendation 11: in response to liver enzyme elevation between 1 and 2 times the upper limit of normal, either no specific action or rechecking liver enzymes at a shorter interval until the levels normalise is recommended<sup>7</sup> (C; Oxford<sup>6</sup>).
- Recommendation 12: in response to liver enzyme elevation more than twice the upper limit of normal, decreasing the dose of methotrexate or temporarily withholding methotrexate administration is recommended<sup>7</sup> (C; Oxford<sup>6</sup>).
- Recommendation 13: if liver enzymes remain at levels more than 3 times the upper limit of normal following a decrease in the methotrexate dose, discontinuation of methotrexate is recommended<sup>7</sup> (C; Oxford<sup>6</sup>).

Other possible causes of elevated liver enzymes unrelated to the administration of MTX must be investigated, and tapering off can be considered if these levels are abnormal or elevated.

### Combination therapy

More evidence is needed to establish the indications for combination therapy with MTX, be it with conventional or biologic DMARDs, in order to simplify decision-making.

The recommendations of the ACR<sup>7</sup> propose the addition of a TNF $\alpha$  inhibitor for patients receiving MTX as monotherapy and with persistent JIA activity, recommending that treatment with MTX be continued or not depending on the patient's previous response to it. Other authors recommend exhausting the time frame to observe the response to MTX therapy and achieve the maximum effective doses of MTX by the parenteral route before considering initiation of combination therapies.<sup>31,32</sup>

In recent years, several studies have demonstrated that in some patients clinical worsening and a diminished response to treatment with certain TNF inhibitors is associated with the development of anti-drug antibodies.<sup>33,34</sup> On the other hand, other studies have shown how the concomitant use of MTX reduces the immunogenicity of these drugs.<sup>35,36</sup> For all of the above, we recommend considering the use of MTX in patients treated with biologic agents to improve the response and/or reduce the development of antibodies to certain biologics.

- Recommendation 14: we recommend considering the use of MTX in patients treated with biologic agents to improve the response and/or reduce the development of antibodies to certain biologics (4D; SIGN<sup>4</sup>).

### Supplementary use of folic or folinic acid

Methotrexate reduces inflammation by a mechanism related to the metabolism of folic acid. The prescription of folic or folinic acid can improve the tolerability and safety of MTX (mouth ulcers, gastrointestinal complaints, diarrhoea, haematologic changes, elevation of transaminases, etc.).

Folic or folinic acid is given at least one day apart from the administration of MTX.<sup>8,12</sup>

Some expert-consensus guidelines state the need of supplementing MTX treatment with folic acid.<sup>37</sup>

- Recommendation 15: to prevent side effects such as dyspepsia and nausea, the use of either folic or folinic acid is recommended as an adjuvant to MTX therapy. Folic or folinic acid will be given in tablet form in doses of 5 mg/week at least one day apart from the administration of MTX or, alternatively, in doses of 1 mg/day, skipping the day that MTX is administered (LE, 4; GR, D; SIGN<sup>4</sup>).

## Discussion

There have been advances in the knowledge of JIA in recent years, both in criteria regarding its classification, clinical improvement, remission and inactive disease, and in tools used to measure disease activity (JADAS)<sup>38</sup> and quality of life (JAMAR<sup>39</sup> and CHAQ<sup>40</sup>). This has made the follow-up of patients with JIA easier.

Although at present MTX is considered the most effective nonbiologic agent for induction remission in patients with JIA, there is great variability in the management of this drug in clinical practice. This called for the development of a consensus by a group of experts in paediatric rheumatology involved in the management of patients with JIA treated with MTX. Their contributions have resulted in a set of recommendations that will make it possible to improve the pattern of use of MTX for the treatment of children and adolescents with JIA by the integration of scientific evidence and clinical experience. These consensus-based recommendations aim at optimising the health and quality of life of patients with a JIA diagnosis, regardless of the stage and course of the disease.

Based on the clinical aspects that were deemed essential, we found scientific evidence pertaining to the selection and indication of MTX,<sup>1,7,8</sup> the choice of dosage<sup>8,10,16</sup> and route of administration,<sup>8</sup> criteria for dose reduction and discontinuation,<sup>23</sup> safety,<sup>24</sup> monitoring,<sup>7,26–30</sup> combined therapy<sup>7,31,32</sup> and adjuvant use of folic acid.<sup>8,12</sup>

The set of recommendations presented here addresses issues such as the use of MTX based on the clinical classification of JIA, the initiation of MTX at full doses to achieve remission quickly and subsequent tapering off, the importance of the subcutaneous route of administration, especially in cases of polyarticular disease or associated with uveitis, and the ongoing adjustment of MTX therapy to patient-related factors and clinical status. The panel of experts highlighted the importance of regular laboratory testing in the follow-up of patients treated with MTX and ongoing monitoring for adverse events and adherence to treatment, which requires increased watchfulness by the parents or guardians of the patient. On the other hand, the wide variability of clinical criteria for the discontinuation of MTX (with or without tapering off) sparked debates that did not ultimately lead to specific recommendations.

In conclusion, we found evidence of a marked variability in the therapeutic management of JIA with MTX. We believe that these recommendations for the management

of MTX in patients with JIA will facilitate decision-making and promote a more uniform follow-up of these patients.

## Funding

This project has received funding from Laboratorios Gebro Pharma, S.A.

## Conflict of interests

J. Antón has received honoraria for conferences organised by Gebro Pharma. The remaining authors have no conflicts of interest to declare.

## References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31:390–2.
2. Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, et al. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. *Clin Immunol*. 2012;142:176–93.
3. Beresford MW. Juvenile idiopathic arthritis: new insights into classification, measures of outcome, and pharmacotherapy. *Paediatr Drugs*. 2011;13:161–73.
4. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2014. (SIGN publication no. 50). [October 2014]. Available from URL: <http://www.sign.ac.uk>.
5. Feldman W. Evidence-based pediatrics. 1st ed. BC Deckers: Hamilton; 2000.
6. Oxford Centre for Evidence-Based Medicine. Levels of evidence. 2009 [accessed 9 Oct 2014]. Available from: <http://www.cebm.net/oxford-centre-evidence-based-medicinereviews-evidence-march-2009/>.
7. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken)*. 2011;63:465–82.
8. Niehues T, Horneff G, Michels H, Hock MS, Schuchmann L, Working Groups Pediatric Rheumatology. Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the Working Groups Pediatric Rheumatology Germany (AGKJR) and Pediatric Rheumatology Austria. *Rheumatol Int*. 2005;25:169–78.
9. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. *Clin Exp Rheumatol*. 2009;27:1017–25.
10. Ruperto N, Murray KJ, Gerloni V, Wulfraat N, de Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum*. 2004;50:2191–201.
11. Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ, et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. *Ann Rheum Dis*. 2008;67:309–14.

12. Gao JS, Wu H, Tian J. Treatment of patients with juvenile rheumatoid arthritis with combination of leflunomide and methotrexate. *Zhonghua Er Ke Za Zhi*. 2003;41:435–8.
13. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56:3096–106.
14. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. Rheumatoid Arthritis Clinical Trial Archive Group. *J Rheumatol*. 1995;22:218–23.
15. Bou R, Adan A, Borrás F, Bravo B, Calvo I, de Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. *Rheumatol Int*. 2015;35:777–8.
16. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med*. 1992;326:1043–9.
17. Papadopoulou C, Kostik M, Bohm M, Nieto-Gonzalez JC, Gonzalez-Fernandez MI, Pistorio A, et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr*. 2013;163:879–84.
18. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology (Oxford)*. 2013;52:825–31.
19. Balis FM, Mirro J Jr, Reaman GH, Evans WE, McCully C, Doherty KM, et al. Pharmacokinetics of subcutaneous methotrexate. *J Clin Oncol*. 1988;6:1882–6.
20. Balis FM, Savitch JL, Bleyer WA. Pharmacokinetics of oral methotrexate in children. *Cancer Res*. 1983;43:2342–5.
21. Oguey D, Kolliker F, Gerber NJ, Reichen J. Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum*. 1992;35:611–4.
22. Wallace CA. The use of methotrexate in childhood rheumatic diseases. *Arthritis Rheum*. 1998;41:381–91.
23. Hasija R, Pistorio A, Ravelli A, Demirkaya E, Khubchandani R, Guseinova D, et al. Therapeutic approaches in the treatment of juvenile dermatomyositis in patients with recent-onset disease and in those experiencing disease flare: an international multicenter PRINTO study. *Arthritis Rheum*. 2011;63:3142–52.
24. Ficha técnica de Metoject. [accessed 03.04.13]. Available from: <http://www.aemps.gob.es/cima/especialidad.do?metodo=verFichaWordPdf&codigo=71109&formato=pdf&formulario=FICHAS>
25. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis*. 2011;70:1704–12.
26. Ortiz-Alvarez O, Morishita K, Avery G, Green J, Petty RE, Tucker LB, et al. Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol*. 2004;31:2501–6.
27. Kocharla L, Taylor J, Weiler T, Ting TV, Luggen M, Brunner HI. Monitoring methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol*. 2009;36:2813–8.
28. Lahdenne P, Rapola J, Ylijoki H, Haapasaari J. Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. *J Rheumatol*. 2002;29:2442–5.
29. Hashkes PJ, Balistreri WF, Bove KE, Ballard ET, Passo MH. The relationship of hepatotoxic risk factors and liver histology in methotrexate therapy for juvenile rheumatoid arthritis. *J Pediatr*. 1999;134:47–52.
30. Wallace CA, Bleyer WA, Sherry DD, Salmonson KL, Wedgwood RJ. Toxicity and serum levels of methotrexate in children with juvenile rheumatoid arthritis. *Arthritis Rheum*. 1989;32:677–81.
31. Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61:46–51.
32. Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol*. 2004;31:179–82.
33. Kosmac M, Toplak N, Simonini G, Pagnini I, Cimaz R, Serbec VC, et al. Anti-drug antibodies are associated with diminished drug levels and treatment failure (abstract). *Arthritis Rheum*. 2012;64 Suppl. 10:2598.
34. Murias S, Alcobendas R, Pascual-Salcedo D, Remesal A, Peralta J, Merino R. Anti-adalimumab antibodies in paediatric rheumatology patients: A pilot experience. *Rheumatology (Oxford)*. 2014;53:2124–6.
35. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis*. 2012;71:1914–5.
36. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008;359:810–20.
37. Pavy S, Constantin A, Pham T, Gossec L, Maillefert JF, Cantagrel A, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine*. 2006;73:388–95.
38. Consolaro A, Ruperto N, Bazzo A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61:658–66.
39. Filocamo G, Consolaro A, Schiappapietra B, Dalpra S, Lattanzi B, Magni-Manzoni S, et al. A new approach to clinical care of juvenile idiopathic arthritis: The Juvenile Arthritis Multidimensional Assessment Report. *J Rheumatol*. 2011;38:938–53.
40. De Inocencio J, Garcia-Consuegra J, Merino R, Calvo I, Garcia JJ, Ruperto N, et al. The European Spanish version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol*. 2001;19:S141–5.