



Special Article

Recommendations for the Use of Methotrexate in Rheumatoid Arthritis: Up and Down Scaling of the Dose and Administration Routes[☆]



Jesús Tornero Molina,^{a,*} Francisco Javier Ballina García,^b Jaime Calvo Alén,^c Miguel Ángel Caracuel Ruiz,^d Jordi Carbonell Abelló,^e Antonio López Meseguer,^f José Vicente Moreno Muelas,^g Trinidad Pérez Sandoval,^h Jesús Quijada Carrera,ⁱ Pilar Trenor Larraz,^j Antonio Zea Mendoza^k

^a Servicio de Reumatología, Hospital de Guadalajara, Guadalajara, Spain

^b Servicio de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Spain

^c Servicio de Reumatología, Hospital Universitario Sierrallana, Torrelavega, Cantabria, Spain

^d Servicio de Reumatología, Hospital Reina Sofía, Córdoba, Spain

^e Servicio de Reumatología, Hospital del Mar, Barcelona, Spain

^f Servicio de Reumatología, Hospital Gutiérrez Ortega, Valdepeñas, Ciudad Real, Spain

^g Servicio de Reumatología, Hospital Vall d'Hebron, Barcelona, Spain

^h Servicio de Reumatología, Complejo Asistencia Universitario de León, León, Spain

ⁱ Servicio de Reumatología, Hospital Virgen del Rocío, Sevilla, Spain

^j Servicio de Reumatología, Hospital Clínico Universitario de Valencia, Valencia, Spain

^k Servicio de Reumatología, Hospital Universitario Ramón y Cajal, Madrid, Spain

ARTICLE INFO

Article history:

Received 2 October 2013

Accepted 28 February 2014

Available online 13 June 2014

Keywords:

Methotrexate

Rheumatoid arthritis

Up and downscaling of the dose

Consensus

ABSTRACT

Objectives: To describe the optimal therapeutic strategy for use of methotrexate in RA patients over the initial dose, route of administration, dose increase and decrease, patient monitoring, and use of folic/folinic acid.

Materials and methods: Eleven clinical experts proposed some questions to be solved. A systematic literature search was conducted. The contents were selected in a work session and subsequently validated via email to establish the level of agreement.

Results: The initial dose of methotrexate should not be <10 mg/week, preferably orally, but the parenteral route is considered as an alternative due to compliance, non-effectiveness of treatment or gastrointestinal side effects, polypharmacy, obesity (if required doses are >20 mg/week), patient preference, very active disease or to avoid administration errors. Changing to a parenteral administration is proposed when the oral route is not effective enough, gastrointestinal toxicity appears, there is non-compliance or due to cost-effectiveness reasons before using more expensive drugs. On the contrary, due to patient preferences, intolerance to injections, dose reduction <7.5 mg/week, non-effectiveness of the route, poor compliance or gastrointestinal side effects. There should be a rapid dose escalation if inadequate responses occur up to 15–20 or even 25 mg/week in about 8 weeks, with increments of 2.5–5 mg. The reduction will be carried out according to the dose the patient had, with decreases of 2.5–5 mg every 3–6 months. Patient monitoring should be performed every 1–1.5 months until stability is reached and then for every 1–3 months.

Conclusions: This document pretends to solve some common clinical questions and facilitate decision-making in RA patients treated with methotrexate.

© 2013 Elsevier España, S.L.U. All rights reserved.

[☆] Please cite this article as: Tornero Molina J, Ballina García FJ, Calvo Alén J, Caracuel Ruiz MÁ, Carbonell Abelló J, López Meseguer A, et al. Recomendaciones para el uso del metotrexato en artritis reumatoide: incremento y reducción de dosis y vías de administración. Reumatol Clin. 2015;11:3–8.

* Corresponding author.

E-mail address: jtorneromolina@ser.es (J. Tornero Molina).

Recomendaciones para el uso del metotrexato en artritis reumatoide: incremento y reducción de dosis y vías de administración

R E S U M E N

Palabras clave:
Metotrexato
Artritis reumatoide
Incremento y reducción de dosis
Consenso

Objetivos: Describir la estrategia terapéutica óptima de uso de metotrexato en AR sobre dosis inicial, vía de administración, incremento y disminución de dosis, seguimiento del paciente y uso de ácido fólico/folínico.

Material y método: Once expertos plantearon los interrogantes clínicos a resolver. Se realizó una búsqueda bibliográfica sistemática. Los contenidos fueron seleccionados en una sesión de trabajo y el nivel de acuerdo se estableció posteriormente en una ronda de consenso vía correo.

Resultados: La dosis de inicio de metotrexato no debe ser < 10 mg/semana, preferentemente por vía oral, considerando la vía parenteral como alternativa según el cumplimiento, ineficacia o efectos secundarios gastrointestinales, polimedicación, obesidad (si requiere dosis > 20 mg/semana), preferencias del paciente, enfermedad muy activa o para evitar errores de medicación. Se cambiará a la vía parenteral cuando haya ineficacia, toxicidad gastrointestinal, incumplimiento o por coste-efectividad antes de pasar a fármacos más caros; y a la inversa, según preferencias del paciente, intolerancia a inyectables, reducción de dosis < 7,5 mg/semana, ineficacia, bajo cumplimiento o efectos adversos gastrointestinales. Se realizará escalada rápida de dosis si la respuesta es inadecuada hasta los 15-20 o, incluso, 25 mg/semana en unas 8 semanas, con incrementos de 2,5-5 mg. La reducción se realizará según la dosis a la que estuviera el paciente, con disminuciones de 2,5-5 mg cada 3-6 meses. El seguimiento del paciente deberá realizarse cada 1-1,5 meses hasta la estabilidad y luego cada 1-3 meses.

Conclusiones: Este documento pretende resolver algunos interrogantes clínicos habituales y facilitar la toma de decisiones en la AR tratada con metotrexato.

© 2013 Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The correct use of disease-modifying antirheumatic drugs (DMARDs) has improved the prognosis of RA based on its early use and setting a specific therapeutic goal, aiming to reach remission or the lowest possible degrees of inflammatory activity.¹⁻³ In this sense, EULAR recommends that DMARD treatment should begin as soon as the diagnosis of RA is made.⁴

Methotrexate (MTX) has been used for over 20 years in the treatment of rheumatoid arthritis. The features that make the MTX as the DMARD of first choice are related to its low price, its favorable safety profile, its slowing of radiographic progression, clinical experience with high response rates, therapeutic continuity, availability and versatility of doses and routes of administration. Thus, after the diagnosis of the disease, it is indicated as the first-line treatment for early and in clearly defined RA, as recommended by different societies⁴⁻⁶, and it is also suitable as an anchor drug for combination therapies.⁷

However, there is a large variability in the clinical practice in our country with regard to the starting dose, the rate and pattern of dose escalation, selection of routes of administration and dosing with concomitant use of folic acid or folinic acid in patients with RA. This is because the clinical practice may not be clearly supported by appropriate clinical trials.

The objective of this study is to establish recommendations for decision-making in the treatment of adult RA with MTX, based on scientific evidence.

Materials and Methods

For the preparation of the consensus document a group of experts, who drafted the recommendations (ER), was made up by 11 rheumatologists from hospitals of the Spanish National Health System. The ER worked according to the methodological basis given by the Quality Plan of the Ministry of Health, in its reference document "Development of clinical practice guidelines in the National Health System".⁸

The ER work in the context of the use of MTX in the treatment of adult RA was performed with a participatory and structured methodology, in which ER members identified 3 major blocks: (a) indication criteria; (b) initial dose and route of administration and

changes along the treatment; (c) criteria for dose modification and withdrawal of MTX. A detailed index was established to solve clinical questions, to which they later applied the PICO methodology, in order to facilitate and manage the process of literature search and the subsequent development of specific recommendations developed in response to each issue raised. The systematic review of the literature was used as the basic source of the original query, clinical trials, cohort studies, protocols, review articles and clinical guidelines. Filter criteria and the search limits were established by the ER panel. The objective of all of this was to make feasible an updated and critical reading of the key aspects of the scientific evidence available. A search for articles published since 1995 was conducted, both in English and Spanish, in databases such as PubMed, Cochrane Bookseller, Trip data base and abstracts of the congresses of the Spanish Society of Rheumatology (2005-2012), *The European League Against Rheumatism* (2012) and the *American College of Rheumatology* (2010-2011) and in the latest update available for MTX data sheets for both oral and parenteral formulations (Fig. 1).

The initial search result yielded 1241 articles. Relevant articles were selected in 2 phases. The first prioritized titles and abstracts (177), and the second prioritized consensus statements, specific systematic reviews and most recent articles (46). The ER panel considered necessary, in very specific cases, a complementary search in certain areas of therapeutic care, which were not sufficiently defined in the initial search strategy (Table 1). Because of the predominance of review articles and clinical guidelines, references to the summary report of the literature were expanded to a total of 182 citations.

The categorization of levels of evidence (LE) and degrees of recommendation (DR) was performed from system criteria *Scottish Intercollegiate Guidelines Network* (SIGN)⁹ themes that used diagnostic criteria of the "Center-based medicine evidence of Oxford" (CMBE). For recommendations that already had NE and/or in other previous documents DR originals are kept, referencing it in each case.

The executive summary of the evidence was assessed in a participatory classroom session, in which 37 recommendations and 14 were proposed evidence. This document was sent to the ER members for their individual assessment and to vote on their agreement, to regard these recommendations as appropriate responses to the clinical questions posed. Finally, 12 recommendations reached an

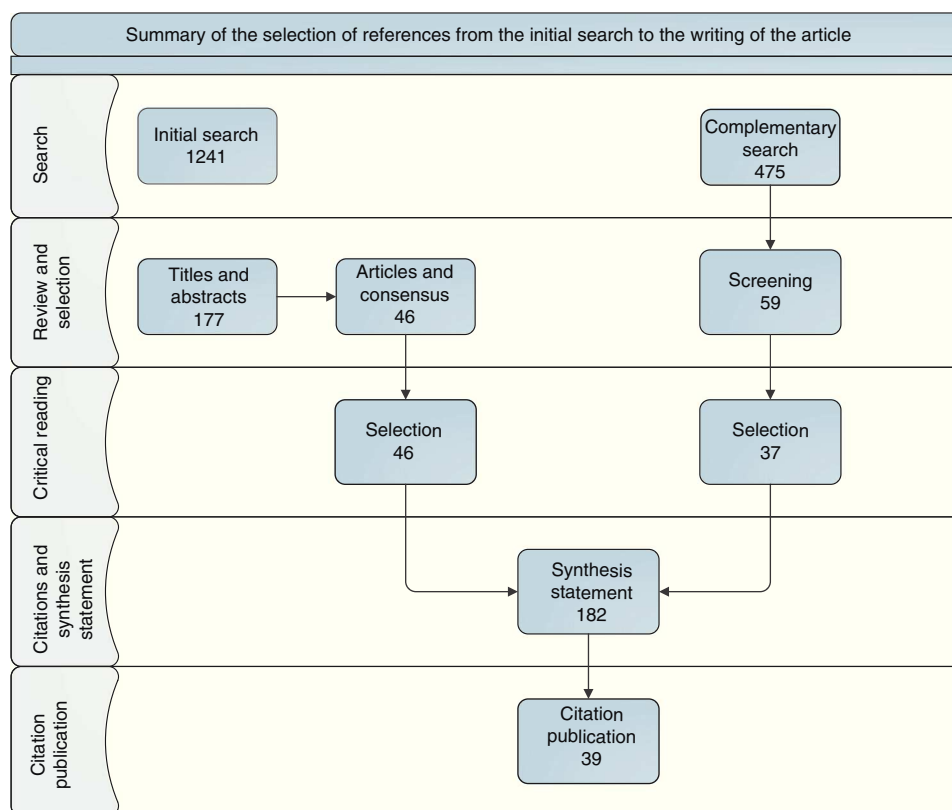


Fig. 1. Selection of citations made from the initial search to the writing of the article.

agreement (A) greater than 70% were established as validated formal recommendations.

Results

From the literature search and the articles referred, prioritized by the ER members specifically, this document regarding answers to clinical questions raised was developed, with the objective to reduce the variability in the use of MTX in the treatment of adult RA. The 12 recommendations that reached greater agreement among members of the ER panel are here presented. Of these, 10 have their scientific basis in 28 of the references cited, while 2 correspond to recommendations based from experience and expert opinion of the ER panel.

What Dose Methotrexate Should be Initiated in the Treatment of Rheumatoid Arthritis?

It is known that the effectiveness of MTX is dose dependent. Results of some studies indicate that an initial dose of 7.5 mg/week was often ineffective and, in many cases required an increase in dose after 6 weeks.^{10,11} In addition, a starting

dose of 12.5–20 mg/week was more effective than 5–7.5 mg/week, with no differences in safety.¹² Therefore, some experts recommend a minimum initial dose of at least 10 mg/week, although it is more complicated to establish agreement on what to recommend as an optimal initial dose. However, a systematic review¹³ defends the optimal initial dose of 10–15 mg/week orally, taking into account the specific characteristics of each patient. Based on these evidences, a dose not lower than 10 mg/week is recommended; but also lower doses may be considered depending on the circumstances of the patient (comorbidities, low weight, age, renal function, liver).

Recommendation 1: For RA, a starting dose of MTX not less than 10 mg/week should be determined, based on the severity of the disease and prognostic factors associated with the patient¹⁴ (LE: 1b/2 [Shekelle],¹⁵ DR: C [Shekelle],¹⁵ A: 82%).

What Route of Administration Should Methotrexate be Initially Delivered Through?

The selection of the initial route of administration may be agreed upon between the doctor and the patient. Generally, the patient

Table 1
Results of the Expanded Search for Specific Topics.

Block	Matrix	Screening	Independent selection
1. Definitions and Interpretation. The efficacy and toxicity of DMARDs (hydroxychloroquine, and leflunomide) with MTX	84	20	16
2. Use of aspirin at antiplatelet doses in combination with MTX	16	7	
3–5. Use of MTX when desiring pregnancy, during pregnancy and lactation	166	9	4
6. Use of MTX in intercurrent infection, HCV, HBV, HIV, and tuberculosis	42	14	1
7. Use of MTX in minor and major surgery	123	5	1
8. MTX use in vaccination	13		
9. Downscaling: in association with a biological, what should be reduced first?	17	1	1
10. MTX dose fractioning	14	1	0
Total articles	475	59	37

usually prefers the oral route. Different studies show that the relative bioavailability of oral MTX compared to the intramuscular MTX is good at low doses but decreases at higher doses (Table 1).^{16–18} Considering that the relationship between oral bioavailability and parenteral dosage is 1 for total doses of 7.5 mg, it becomes 0.85 (range 0.77–0.93) when the total dosage reaches 10–15 mg and drops to 0.64 (range 0.21–0.94) at doses of 15–20 mg. Therefore, a dosage under 20 mg/week, ease of handling and low cost of oral MTX position it as the preferred route of administration in RA¹⁴; however, after 15 mg/week there is no evidence that the oral route is better than parenteral.

However, there are situations in which to consider the parenteral route as the route of choice from the start: polypharmacy patients who are overweight or obese (as administered doses are higher), low compliance, per patient preference in order to reduce certain gastrointestinal adverse effects or to avoid medication errors. In addition, experimental data seem to indicate that the subcutaneous (sc) onset is especially useful in patients with active, longstanding disease (DAS 28 \geq 4).¹⁹

Recommendation 2: In patients with RA it is recommended to start treatment with MTX preferably through an oral route. However, consideration should be given to sc or intramuscular routes in patients with poor compliance, insufficient effectiveness or gastrointestinal side effects (LE: 4 [SIGN],⁹ DR: D [SIGN],⁹ A: 91%).

When Should the Clinician Change the Route of Administration?

Change From Oral to Subcutaneous

Some studies have suggested that patients with poor compliance, inadequate effectiveness and/or gastrointestinal side effects (when MTX was administered orally) should be considered when switching to injection^{20–23} because better results and effectiveness may be achieved. Changing to sc from oral in patients with a lack of response or toxicity has proven useful, with responses reaching 30% higher in the ACR20 criteria.¹⁹ In addition, this change in patients with inadequate response could be cost-effective because it can prevent or delay therapy with biological agents.^{23–25}

Recommendation 3: In patients with RA treated orally with MTX, available evidence justifies the change to sc route of administration when a lack of therapeutic response is expressed against the activity of the disease, or gastrointestinal toxicity or therapeutic failure are present, since the sc is associated with better treatment response²⁵ (LE: 4 [SIGN],⁹ DR: D [SIGN],⁹ A: 100%).

Recommendation 4: Its better cost-effectiveness in studies suggest the suitability of changing from oral administration to parenteral MTX in patients with an inadequate response, as the evidence shows that this prevents or delays subsequent therapy with biological agents^{23,25,26} (LE: 4 [SIGN],⁹ DR: D [SIGN],⁹ A: 82%).

Change From Subcutaneous Oral Route

There are reasons for the change from SC to oral: sc administration intolerance, patient preferences, dose reduction to less than 7.5 mg or therapeutic failure.

Furthermore, it has been observed that if after switching to oral from sc, one desires to return to the sc route, the response rate may be lower compared to the first batch of parenteral MTX.^{19,21}

Recommendation 5: Some clinical-care criteria can justify changing the route of administration from sc to oral MTX in RA patients: patient preferences, intolerance to the sc route of administration, dose reduction to levels <7.5 mg/week, or low compliance¹⁴ (LE: 4, [SIGN],⁹ DR: D/ $\sqrt{}$ [SIGN],⁹ A: 82%).

How Should the Increase in Dose of Methotrexate be Made? Pattern and Timing

Some studies show that initial doses of 25 mg/week orally or rapid initial dose escalation therapeutic strategies of 5 mg/month

to 25–30 mg/week are associated with greater efficiency; although with increased toxicity compared to the initial patterns of 5–15 mg/week or slow escalation strategies of 5 mg/3 months.^{12,27,28} These results support that achieving high doses (25–30 mg/week) in a short period of time is effective, but may produce more adverse events.¹³ It should also be noted that other studies with more aggressive strategies versus conventional increase patterns showed no statistically significant differences in therapeutic response.^{29,30}

Moreover, in the dose range of 2.5–30 mg/week of MTX, it is easy to reach the dose titration with small increments of 2.5 mg offering even new formulations for parenteral administration. These are useful for problems of tolerance due to rapid dose escalation for lack of efficacy with the oral formulation.^{31,32}

After evaluating this evidence, the panel of experts validated 2 recommendations:

Recommendation 6: Once the initial dose of MTX has been established, if an adequate response in patients with RA is not achieved, proceed to a rapid increase of the dose up to 15–20 or even 25 mg/week in about 8 weeks. Before making a dose increase, one should establish a clinical-therapeutic 4-week observation period, with the preceding dose to determine whether or not it is effective. In case of insufficient clinical response, increments of 2.5–5 mg every 2–6 weeks are recommended, depending on the clinical severity, up to a maximum of 25 mg weekly²⁴ (LE 5 [Oxford],³³ DR: D [Oxford],³³ A: 100%).

If no response is seen after 8 weeks with a high dose of MTX, treatment should be discontinued, as indicated by the MTX insert.

How Should the Clinician Reduce the Dose of Methotrexate? Pattern, Timing and Route of Administration

Due to the paucity of evidence related to MTX dose reduction, the experts agreed to develop their own recommendations. The aim of downscaling is reaching the minimum effective dose to maintain a complete remission (DAS 28<2.6).

Recommendation 7: Downscaling is recommended when complete remission is maintained for a period of time, depending on the dose:

- Dose \geq 25 mg/week: dose reduction will begin when there is sustained remission for at least 6 months.
- Doses <25 mg/week: dose reduction will begin when there is sustained remission for at least 6–12 months (LE: 4 [SIGN],⁹ DR: D/ $\sqrt{}$ [SIGN],⁹ A: 91%).

Recommendation 8: In patients with RA, as a general guideline for the downscaling of MTX, recommended reductions of 2.5–5 mg every 3–6 months should be carried out (LE: 4 [SIGN],⁹ DR: D/ $\sqrt{}$ [SIGN],⁹ A: 91%).

As mentioned above, previous studies¹⁹ show the consequences that could result from changes in route of administration. Therefore, it is agreed that:

Recommendation 9: We recommend keeping track of the patient at the time of decision making (LE: 4 [SIGN],⁹ DR: D/ $\sqrt{}$ [SIGN],⁹ A: 100%).

However, doses below 15 mg are candidates for oral treatment. Therefore, it is agreed:

Recommendation 10: Arriving at doses of <15 mg, it is considered appropriate to provide a change from sc to oral, except in the case of prior intolerance to oral or when there is suspected improvement in the efficiency related to the route of administration (LE: 4 [SIGN],⁹ DR: D/ $\sqrt{}$ [SIGN],⁹ A: 91%).

However, on downscaling during a change of parenteral to oral administration, it may be necessary to increase the oral dose to 2.5–5 mg/week with respect to the parenteral dosage to maintain the effectiveness of the treatment.

What Are the Recommendations for Evaluation and Monitoring for Patients With Rheumatoid Arthritis Receiving Methotrexate?

Intensive monitoring of inflammatory activity and safety of treatment of RA in the early stages of its evolution is related to better results in remission and control of inflammatory disease activity.^{13,34,35} From the ACR³⁶ guidelines regarding the appropriate periodicity in the monitoring of these patients, Visser et al.¹³ established parameters to review treatment as well as its periodicity, although for the latter there is less evidence.

Recommendation 11: To initiate the process of increasing MTX dose, analytical control of ALT with/without AST, creatinine and CBC should be performed every month or month and a half until a stable dose is reached. From the clinical and therapeutic standpoint, monitoring is recommended every 1–3 months, with possible side effects and changes in risk factors monitored at each visit¹³ (LE: 4 [Oxford],³³ DR: C [Oxford],³³ A: 91%).

What Should Folic Acid Supplementation be in Patients With Rheumatoid Arthritis Treated With Methotrexate?

MTX reduces inflammation by a mechanism related to folic acid metabolism. In some people treated with MTX there may be a deficiency in folic acid, so supplementation with folic acid or folinic may improve tolerability and safety of MTX (oral ulcers, gastrointestinal upset, diarrhea, hematological disorders, elevated transaminases). Folic or folinic acid is administered as one tablet of 5 mg a week separating the drug at least one day with regard to the administration of MTX.^{37,38}

Routine supplementation with folic/folinic acid generally does not affect the effectiveness of MTX, although the data of one study suggest that the use of these supplements could lead to a slight increase of the dose of MTX to maintain efficacy.³⁹

Recommendation 12: In patients with RA treated with MTX, administration of 5 mg of folic or folinic acid/week is recommended, separating the intake of it from MTX by 24 h¹⁴ (LE: 1a/1b [Shekelle],¹⁵ DR: A [Shekelle],¹⁵ A: 100%).

Discussion

This consensus has been undertaken with the intent to facilitate decision making in the clinical practice of physicians involved in the management of patients with RA treated with MTX, the cornerstone of treatment of RA. Optimization is a process used to modify a system in order to increase its efficiency with the use of available resources. This has clearly been the goal of our consensus, trying to raise the profile of clinical use of this drug.

Based on previous clinical questions, we have found evidence available on the initial dose of MTX used,^{10,19–26} the route of administration (and possible exchangeability)^{14,19}, therapeutic scaling,^{12,14,24,27,28,31,32,35} and optimal patient monitoring with MTX.^{13,36} Based on these reports, the panel of experts has made the appropriate recommendations, emphasizing issues such as who should start at full doses and quickly scale back to quickly gain control of the disease. We also emphasize the usefulness of the proper evaluation of the route of administration, at all times adapting to the characteristics of the individual and the clinical status of the disease.

In conclusion, this paper gives some recommendations on the management of MTX in RA patients, and especially in the process

of dose decreasing, which may facilitate clinical decision making and standardize the different ways to proceed.

Ethical Responsibilities

Protection of people and animals. The authors declare that this research did not perform experiments on humans or animals.

Data confidentiality. The authors declare that they have followed the protocols of their workplace on the publication of data from patients and all patients included in the study have received sufficient information and gave written informed consent to participate in the study.

Right to privacy and informed consent. The authors state that no patient data appears in this article.

Funding

The study has been developed through an unrestricted grant offered by Gebro Pharma SA.

Conflicts of Interest

Dr. Jesus Tornero Molina has received payments for research projects and conferences from Abbvie, Gebro, Pfizer and Roche.

Dr. Jordi Carbonell states having an advisory contract with Gebro.

The remaining authors declare that they have no conflict of interest related to the article.

Acknowledgments

We thank Manel Alepuz and Veronica Albert, of Gestió Organització Comunicació, SA for their support in conducting the methodology used to prepare the study.

References

- Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwiderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med.* 2001;111:446–51.
- Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford).* 2004;43:906–14.
- Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? *Rheumatology (Oxford).* 2001;40:1211–20.
- Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69:964–75.
- Actualización de la guía de práctica clínica para el manejo de la artritis reumatoide en España. GuipCar 2007. Sociedad Española de Reumatología. Available from: http://www.ser.es/ArchivosDESCARGABLES/Proyectos/GUIPCAR_2007/GUIPCAR2007-Completa.pdf
- Saag KG, Teng GG, Patkar NM, Anuntiyoy J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762–84.
- Jurgens MS, Jacobs JW, Bijlsma JW. The use of conventional disease-modifying anti-rheumatic drugs in established RA. *Best Pract Res Clin Rheumatol.* 2011;25:523–33.
- Grupo de trabajo sobre GPC. Elaboración de guías de práctica clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC, Instituto Aragonés de Ciencias de la Salud-I+CS Guías de Práctica Clínica en el SNS: I+CS no. 2006/01; 2007.
- Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developers' handbook. Edinburgh: SIGN; 2004. Available from: <http://www.sign.ac.uk/guidelines/fulltext/50/>
- Williams HJ, Willkens RF, Samuelson CO, Alarcon GS, Guttadauria M, Yarboro C, et al. Comparison of low-dose oral pulse methotrexate and placebo in the

- treatment of rheumatoid arthritis. A controlled clinical trial. *Arthritis Rheum.* 1985;28:721–30.
11. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med.* 1985;312:818–22.
 12. Furst DE, Koehnke R, Burmeister LF, Kohler J, Cargill I. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. *J Rheumatol.* 1989;16:313–20.
 13. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. *Ann Rheum Dis.* 2009;68:1086–93.
 14. 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.
 15. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ.* 1999;318:593–6.
 16. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol.* 1993;20:1845–9.
 17. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol.* 2004;31:645–8.
 18. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. *Br J Rheumatol.* 1997;36:86–90.
 19. Braun J, Kastner P, Flaxenberg P, Wahrlich J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase iv trial. *Arthritis Rheum.* 2008;58:73–81.
 20. Wegrzyn J, Adeleine P, Miossec P. Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2004;63:1232–4.
 21. Rozin A, Schapira D, Balbir-Gurman A, Braun-Moscovici Y, Markovits D, Militianu D, et al. Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate. *Ann Rheum Dis.* 2002;61:756–7.
 22. Breslin A, Owen C. Improving tolerance and bioavailability of methotrexate by switching from oral to subcutaneous route of administration. *Rheumatology (Oxford).* 2005;44 Suppl. 1:i150.
 23. Bingham SJ, Buch MH, Lindsay S, Pollard A, White J, Emery P. Parenteral methotrexate should be given before biological therapy. *Rheumatology (Oxford).* 2003;42:1009–10.
 24. Actualización del Documento de consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la artritis reumatoide. *Reumatol Clin.* 2010;6:23–36.
 25. 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.
 26. Lindsay K, Shiela S, Lesley H, Sarah M. Subcutaneous methotrexate is an effective alternative to biologic agents: results of a review of service provided. *Rheumatology (Oxford).* 2006;45 Suppl. 1:i124.
 27. Schnabel A, Reinhold-Keller E, Willmann V, Gross WL. Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. *Rheumatol Int.* 1994;14:33–8.
 28. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, Ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer assisted management in early rheumatoid arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis.* 2007;66:1443–9.
 29. Jassim IAH, Al-Allaf A, Newton P. Methotrexate in rheumatoid arthritis, starting dose and dose escalation regimens. *Ann Rheum Dis.* 2007;66:S440–1.
 30. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose escalation of parenteral methotrexate in active rheumatoid arthritis that has been unresponsive to conventional doses of methotrexate: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:364–71.
 31. Bakker MF, Jacobs JWG, Welsing PMJ, van der Werf JH, Linn-Rasker SP, van der Veen MJ, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis. A post hoc analysis of the CAMERA study. *Ann Rheum Dis.* 2010;69:1849–52.
 32. Jacobs JW. Optimal use of non-biologic therapy in the treatment of rheumatoid arthritis. *Rheumatology (Oxford).* 2012;51 Suppl. 4:iv3–8.
 33. Oxford Centre for Evidence-Based Medicine. Levels of evidence; 2009. Available from: <http://www.cebm.net/index.aspx?o=1025> [accessed July 2013].
 34. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 2005;52:3381–90.
 35. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet.* 2004;364:263–9.
 36. Guidelines for monitoring drug therapy in rheumatoid arthritis. American College of Rheumatology ad hoc committee on clinical guidelines. *Arthritis Rheum.* 1996;39:723–31.
 37. 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.
 38. Niehues T, Horneff G, Michels H, Hock MS, Schuchmann L. 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.
 39. Van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 2001;44:1515–24.