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Review Article

Japan College of Rheumatology guidance for the use of methotrexate in patients with rheumatoid arthritis: Secondary publication

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ABSTRACT

Methotrexate (MTX), the anchor drug in the current treatment strategy for rheumatoid arthritis (RA), was first approved for the treatment of RA in Japan in 1999 at a recommended dose of 6–8 mg/week. The approved maximum dose of MTX has been 16 mg/week since February 2011 when MTX was approved as a first-line drug in the treatment of RA. Recent evidence of MTX-polyglutamate concentration in the red blood cells of Japanese patients with RA justifies the current daily use of MTX in Japan. Additionally, after a nationwide clinical trial, a subcutaneous MTX injection formula (7.5–15 mg/week) was approved for RA treatment in September 2022. Therefore, in March 2023, a subcommittee of the Japan College of Rheumatology updated the guidance (formerly 'guidelines') for the use of MTX in Japanese patients with RA. This article, an abridged English translation summarizing the 2023 update of the Japan College of Rheumatology guidance for the use of MTX and management of patients with RA, will be helpful to both Japanese and global rheumatology communities.

KEYWORDS: Guideline; methotrexate; rheumatoid arthritis; subcutaneous injection

Introduction

Methotrexate (MTX) is the anchor drug currently used to treat rheumatoid arthritis (RA) [1–3]. In Japan, MTX was first approved for refractory RA in adults in 1999 at a recommended dose of 6–8 mg/week. In February 2011, MTX was approved for adult RA at a maximum dose of up to 16 mg/week as the first-line conventional synthetic disease-modifying antirheumatic drug (csDMARD). The Japan College of Rheumatology (JCR) subcommittee on the guideline for the use of MTX in patients with RA published the first Japanese version of the guidelines in 2011 and updated them in 2016 [4]. Since then, evidence supporting the use of MTX in Japanese patients with RA has accumulated. For example, erythrocyte MTX-polyglutamate concentrations of ∼80–100 nmol/l have been suggested as the optimal target, which is usually reached with MTX 10–12 mg/week in Japanese patients with RA [5]. The association between the expression of MTX-related genes, including drug transporter genes, and clinical response to MTX in MTX-naïve patients has been demonstrated [6]. Furthermore, lymphoproliferative disorders (LPD), as well as pneumocystis pneumonia (PCP), are adverse events during MTX treatment, more frequently observed in Japan than in other countries, and have been addressed by multi-institutional retrospective studies [7, 8]. Recently, a randomized clinical trial performed in Japan, South Korea, and Taiwan demonstrated the non-inferiority of reduced (6–8 mg/week) versus maximum tolerated MTX dose concomitant with tumour necrosis factor (TNF) inhibitors in patients with RA [9].

Under these circumstances, a nationwide clinical trial comparing subcutaneous MTX injection (7.5–15 mg/week) and oral administration demonstrated similar efficacy with numerically lower gastrointestinal manifestations, which was approved for RA in September 2022 in Japan [10]. In March 2023, the JCR subcommittee published updated guidance [formerly 'guidelines', and the name was changed according to the JCR policy whether the procedure had been based on the GRADE (Grading of Recommendations

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Assessment, Development and Evaluation: https://www.gradeworkinggroup.org) approach or not] for the use of MTX in Japanese patients with RA [11]. This article is an abridged English translation that summarizes the 2023 update of the JCR guidance for the use of MTX and management of patients with RA [11].

Methods

The update of the 2016 version of the JCR guidelines for the use of MTX in patients with RA was endorsed by the approval of subcutaneous injection of MTX (7.5–15 mg/week) in Japan [10], as well as the recent evidence of MTX-polyglutamate concentration in red blood cells in Japanese patients with RA, confirming the validity of the approved MTX dose (6–16 mg/week) in Japan [5].

The process began with a virtual meeting of the subcommittee members (H.K., K.Y., Y.Y., M.T., R.K., A.N., M.F., and T.F.) in February 2022 for them to define the scope and methods of the update. The assignment of the parts for intensive literature review and writing was determined. The GRADE approach was waived again because of the evidence gap between Japan and Western countries in terms of MTX dosage and unique adverse event profiles, such as PCP and LPD [4]. Recommendations and subsequent explanations were presented and fully discussed at virtual meetings in July 2022 and August 2022. Thereafter, minor email-based discussions and modifications were performed. A consensus was reached in a virtual meeting in January 2023, and the Japanese version of the 2023 update of the JCR guidance for the use of MTX and management of patients with RA was issued in March 2023.

Results and discussion

Indications, contraindications, and precautions

MTX should be considered as a first choice among csDMARDs to maintain a balance between risk factors associated with MTX treatment, such as advanced age and comorbidities and benefits obtained by prompt control of disease activity (Table 1, Recommendation 1 [11]). Additionally, MTX should be used as far as possible in patients who are likely to develop a functional disorder or its progression, despite the optimal dose of other csDMARDs for 2–3 months (Table 1, Recommendation 2 [11]).

Contraindications for MTX (Table 1, Recommendation 3 [11]) include pregnancy; hypersensitivity to MTX; severe infection; severe haematological and lymphatic disorders, namely, myelodysplasia, aplastic anaemia, pure red cell aplasia, LPD within the last 5 years, and severe leucopenia or thrombocytopenia [white blood cell (WBC) count <3000/μl; platelet count <50,000/μl] [12]; hepatic disorders, including acute or chronic active viral hepatitis B or C and liver cirrhosis; severe renal disorders, including end-stage kidney disorder requiring dialysis and severely impaired renal function with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 [12]; severe respiratory disorders diagnosed with hypoxaemia (PaO_2 <70 Torr in room air) or severe pulmonary fibrosis as seen on chest radiographs; and massive ascites/pleural effusion that requires therapeutic intervention.

In addition to the above contraindications, the conditions under which MTX should be administered with caution have been raised. For example, MTX should be administered to elderly patients with caution. Patients with infectious diseases or those susceptible to them may require appropriate vaccinations and/or prophylactic medications. Patients with mild leucopenia (3000/μl ≤ WBC < 4000/μl), thrombocytopenia (50,000/μl ≤ platelet < 100,000 /μl) or those with a history of drug-induced bone marrow disorder should receive a reduced dose of MTX therapy. A reduced dose of MTX should also be considered for patients with hypoalbuminaemia (<3 g/dl) because these patients are susceptible to dose-dependent adverse events, such as pancytopenia due to the delayed clearance of MTX [13]. Patients with habitual alcohol consumption should be instructed to avoid alcohol, as much as possible. Patients who test positive for hepatitis B surface antigen (HBs-Ag) or hepatitis B virus (HBV)-DNA should receive antiviral therapy before starting MTX treatment after consulting with a hepatology/gastroenterology expert [14]. Patients with positive test results for hepatitis C virus (HCV) antibodies (HCV-Ab) should be referred to a hepatology/gastroenterology expert to discuss the risks and benefits of MTX treatment. When the levels of liver transaminases [aspartate aminotransferase (AST) or alanine aminotransferase (ALT)] and alkaline phosphatase (ALP) are >2-fold the upper limit of normal without any positive tests for hepatitis viruses, intensive evaluation should be performed before commencing MTX therapy. Renal function should be evaluated by estimating eGFR, creatinine clearance, or cystatin C, and in patients with renal dysfunction (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2 or equivalent), therapy should be started with a reduced dose of MTX. Consultation with a respiratory expert should be considered for patients whose chest radiographs show possible signs of interstitial pneumonia, chronic obstructive pulmonary disease, or nontuberculous mycobacterium (NTM) infection. Additionally, patients with nonmassive ascites or pleural effusion should be monitored with caution because of possible retention of MTX in third-space fluids [15].

Dosing of MTX

Based on global evidence regarding the use of MTX, it has been recommended that the initial optimal dose of MTX should be 10–15 mg/week [2, 16], although this is not the case in Japan [3]. An initial study conducted in Japan demonstrated that a dose of 2 mg/week of MTX was less effective than 6 or 9 mg/week, while leucopenia and liver dysfunction were more frequently observed in patients receiving 9 mg/week than in those receiving 6 mg/week. This led to the maximum approved MTX dose of 8 mg/week for patients with RA in 1999 [17]. After the approval of 16 mg/week as the maximum dose in 2011 [4], the Certolizumab-Optimal Prevention of joint damage for Early RA (C-OPERA) trial was conducted, in which MTX therapy was started at a dose of 8 mg/week and escalated by 4 mg every fourth week up to 16 mg/week by Week 8 [18]. The mean dose of MTX throughout the 52 weeks was 11.6 mg/week (0.2 mg/kg), and ∼30% of the patients participating in the study received 16 mg/week per protocol at Week 52. Additionally, a 76-week multicentre prospective study, in which MTX was started at a dose of 8 mg/week with 5 mg/week folic acid and increased by 4 mg every 4 weeks until 16 mg/week, also showed that the maximum average dose of MTX was 11.7 mg/week, which was achieved at Week 8, followed by a slight decrease to 10.7 mg/week by Week 76 [5].

Based on these studies and with respect to the treat-to-target (T2T) strategy aiming to achieve the therapeutic goal

Table 1. 2023 update of the JCR guidance for the use of MTX and management of patients with RA [11].

1. MTX should be considered the first choice among csDMARDs based on the risk-benefit balance in patients with RA.
2. MTX should be actively considered in patients who do not reach their treatment target, despite the optimal dose of other csDMARDs for 2–3 months.
3. MTX is contraindicated in pregnancy, in cases of hypersensitivity to MTX, massive pleural effusion or ascites, severe infection or severe haematological, lymphatic, hepatic, renal, or respiratory disorders. MTX should be administered with caution in elderly patients and those with hypoalbuminemia or less severe organ disorders.
4. MTX should be started at an oral dose of 6–8 mg/week. The initial dose should be determined based on risk factors for adverse events, disease activity, and poor prognostic factors. A dose of 8 mg/week of MTX is recommended, especially for nonelderly patients with poor prognostic factors. Subcutaneous MTX should be started with 7.5 mg/week.
5. MTX dose should be increased for patients who do not reach their treatment target. Usually, the dose of oral MTX is escalated by 2 mg/week. The dose of oral MTX may be increased by 2 mg/week every 2 weeks or by 4 mg/week every 4 weeks in non-elderly patients with high disease activity and poor prognostic factors. The dose of subcutaneous MTX may be escalated by 2.5 mg/week every 4 weeks as a guide.
6. The dose of oral MTX should be escalated to 10–12 mg/week in tolerable patients without risk factors for adverse events. The dose of MTX may be escalated maximally to 16 mg/week (15 mg/week for subcutaneous injection) in patients showing an insufficient response, although the addition of other csDMARDs, biological DMARDs (bDMARDs), or Janus kinase (JAK) inhibitors may also be considered.
7. When switching from oral to subcutaneous MTX dosing, the recommended doses are as follows: oral 6 mg/week to subcutaneous 7.5 mg/week, oral 8 or 10 mg/week to subcutaneous 7.5 or 10 mg/week, and oral 12–16 mg/week to subcutaneous 10 or 12.5 mg/week. Thus, 15 mg/week should not be selected as the initial dose for subcutaneous injections. After switching from oral to subcutaneous MTX, therapeutic monitoring should be performed at the same frequency as the initiation or dose escalation of MTX.
8. A weekly MTX dose can be administered as a single dose or divided into 2–3 doses every 12 h for 1–2 days. Divided dosing is preferable to non-divided dosing for >8 mg of MTX per week. Subcutaneous injection should be administered as a single dose once a week.
9. The addition of other csDMARDs to MTX therapy is a therapeutic choice for patients who do not reach their treatment target despite continuous and sufficient dose of MTX.
10. The addition of bDMARDs to MTX therapy is a therapeutic choice for patients who do not reach their treatment target, despite continuous and sufficient dose of MTX. The addition of bDMARDs to MTX therapy, rather than switching to bDMARDs alone, has been recommended because of their effectiveness.
11. Although their long-term safety profiles have not been established, the use of JAK inhibitors should be considered in patients who do not reach their treatment target, despite continuous and sufficient doses of MTX.
12. The dose of MTX may be kept unchanged with the addition of other csDMARDs, bDMARDs, or tsDMARDs up to 16 mg/week, which is the same dose used in monotherapy. The MTX dose can be reduced in patients with risk factors for adverse events.
13. Folic acid supplementation is recommended for all patients receiving MTX, irrespective of the dose. It is particularly effective in preventing liver dysfunction, gastrointestinal symptoms, and stomatitis.
14. Folic acid (Foliamin®) 5 mg/week should be given after 24–48 h after the latest MTX administration. Folinic acid (Leucovorin®), instead of folic acid, should be used for the treatment of severe MTX-related adverse events.
15. Prior to MTX therapy, RA activity and risk factors for MTX-related adverse events should be assessed by history taking, physical examination, blood tests for complete blood cell count (CBC), blood chemistry, inflammatory biomarkers and immunological tests, urinalysis, chest and joint radiography, and screening tests for hepatitis viruses and tuberculosis (TB).
16. After the initiation of MTX therapy, a general physical examination, joint evaluation, and blood, urine and imaging tests should be performed regularly to monitor the effectiveness of MTX and confirm its safety. Laboratory tests, including CBC, blood chemistry, inflammatory biomarkers, and urinalysis, should be performed every 2–4 weeks within three months of initiation or dose escalation of MTX. The aforementioned laboratory tests should be repeated every 4–12 weeks (the interval should be cautiously determined) in patients receiving maintenance dosing after confirmation of the effectiveness of MTX and its safety. Chest and relevant joint radiographs should be preferably performed annually. The effectiveness of MTX should be assessed based on clinical measures of disease activity, blood tests, joint images, and physical function.
17. MTX discontinuation is not required during the perioperative period in patients undergoing elective orthopaedic surgery.
18. Before starting MTX, patients should be informed of its adverse effects on pregnancy and foetal life so that they can use effective contraceptive measures during MTX treatment. MTX is contraindicated for (possibly) pregnant patients. Therefore, female patients of childbearing age should be instructed to avoid pregnancy during MTX therapy and to have at least one menstrual cycle after the latest dose of MTX. Moreover, MTX is contraindicated during lactation.
19. When starting MTX therapy, its unique weekly dosing and major adverse effects should be well explained to patients in an interprofessional manner for the prevention, early recognition, and treatment of these effects. Patient education as described above should be repeated during MTX therapy. The evaluation of risk factors and subsequent prophylactic measures for serious side effects, such as bone marrow disorders, interstitial pneumonia, infections, and lymphoproliferative disorders (LPD) should be performed, and these should be promptly and appropriately managed when they develop.
20. Overdose of MTX should be avoided because bone marrow disorders associated with MTX are often fatal. The initial MTX dose should be reduced in high-risk patients, such as elderly patients and those with renal insufficiency. Skipping MTX when patients show signs and symptoms of dehydration or multiple stomatitis should be considered.

(continued)

Table 1. (Continued)

21. Education on the initial signs and symptoms of interstitial pneumonia is crucial. Patients should be instructed to consult a doctor immediately when they develop dry cough, shortening of breath, or dyspnoea without apparent causes. MTX pneumonitis tends to develop within 2–3 years of MTX initiation, although it may develop at any time during MTX therapy. Prompt exclusion of possibilities other than MTX pneumonitis is necessary, and treatments, including moderate-to-high doses of glucocorticoids, should be initiated when needed.
22. Screening tests to evaluate the risks of infectious diseases must be performed prior to starting MTX therapy, and adequate prophylactic treatment, such as anti-TB therapy or administration of trimethoprim/sulfamethoxazole (TMP/SMX), should be provided. Patients should be educated about the signs and symptoms of infectious diseases, drug cessation, and early return visits, with the aim of early diagnosis and prevention of deterioration. Patients should be monitored with special attention to respiratory infections and herpes zoster, which are frequent and account for almost half of all infectious events. Non-live vaccines against influenza, pneumococcus, and SARS-CoV-2 should be actively considered to prevent infectious diseases and their progression.
23. Possible gastrointestinal adverse events, such as stomatitis and nausea should be communicated at the commencement of MTX therapy. An increase in dosage of supplementary folic acid and administration of antiemetic drugs may be effective for treating these events.
24. Lifestyle history related to chronic liver diseases, liver function tests (total bilirubin, AST, ALT, alkaline phosphatase, γ-GTP, etc.), and screening tests for hepatitis viruses (HBs-Ag, HBs-Ab, HBc-Ab, and HCV-Ab) must be performed before starting MTX therapy. Adequate monitoring should be performed subsequently. Folic acid supplementation is recommended for all patients receiving MTX to prevent liver toxicity.
25. When the signs and symptoms or laboratory investigations suggest LPD during MTX treatment, MTX and concomitant immunosuppressive drugs should be immediately withdrawn. Since LPD in patients with RA undergoing immunosuppressive therapy (other iatrogenic immunodeficiency-associated LPD; OIIA-LPD) frequently results in extranodal lesions, referral to the division of haematology or related departments should be made when needed for soft tissue masses and refractory stomatitis. The treatment of RA after the remission of OIIA-LPD should not include immunosuppressive drugs as far as possible, and MTX rechallenge should be avoided.
26. The development and exacerbation of adverse events should be monitored during the concomitant use of drugs known to interact with MTX. Accordingly, dose adjustments for MTX and/or concomitant drugs should be considered when managing adverse events.

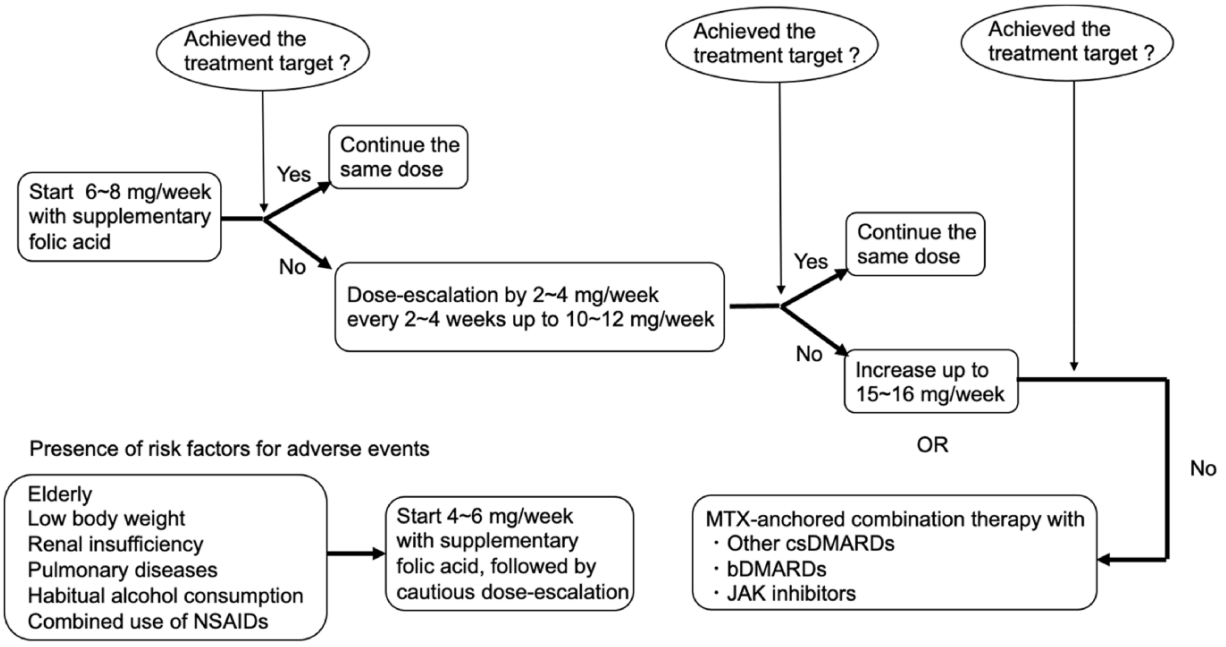

Figure 1. Dosing algorithm of MTX in Japanese patients with RA [11].

within 6 months [19], 6–8 mg/week of MTX was recommended as an initial dose for Japanese patients (Table 1, Recommendation 4 [11]). The initial dose should be determined based on risk factors for adverse events, disease activity, and poor prognostic factors. A dose of 8 mg/week of MTX is recommended, especially for nonelderly patients with poor prognostic factors. However, starting with 2 mg/week was not indicated, even in patients with multiple risk factors (Figure 1 [11]). Subcutaneous MTX should be started with 7.5 mg/week.

The TICORA (TIght COntrol for Rheumatoid Arthritis) [20] and CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) [21] studies examining the T2T strategy demonstrated a higher remission rate and less radiographic progression in patients undergoing therapeutic adjustment every 4 weeks compared with those evaluated conventionally every 12 weeks. Patients should be assessed every 2–4 weeks after the commencement or dose escalation of MTX, followed by a dose escalation of 2 or 4 mg/week, if necessary and tolerable, up to the maximum targeted dose

within 8–12 weeks (Figure 1 and Table 1, Recommendation 5 [11]). Although the dose of MTX may ideally be escalated up to 16 mg/week, the primarily targeted dose is 10–12 mg/week because of the aforementioned evidence [5, 18] and average doses of MTX in Japanese MTX (or other csDMARDs)-IR (inadequate response to MTX or other csDMARDs) patients at baseline in recent clinical trials (10–12 mg/week) [22–27].

After reaching a dose of MTX 10–12 mg/week, several options are available, according to the risk-benefit in each patient: further dose escalation of MTX to 16 mg/week or addition of other csDMARDs, biological DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs) (Table 1, Recommendation 6 [11]). Additionally, a subcutaneous injection of MTX (7.5–15 mg/week) was approved for RA in September 2022 in Japan [10]. Some clinical parameters have been shown to reach a plateau at >15 mg/week [28], and parenteral MTX showed better efficacy with fewer adverse gastrointestinal events than oral MTX at doses >15 mg/week [29]. Therefore, switching from oral to subcutaneous MTX is a new option for patients with RA showing an inadequate response to 10–12 mg/week of oral MTX (Table 1, Recommendation 7 [11]).

Although a single-dosing regimen is simple and globally popular for MTX therapy in RA, the bioavailability of oral MTX is not comparable between single and divided dosing [30–33]. Subcutaneous MTX is more effective than oral administration of 15 mg/week MTX [34]. Furthermore, the bioavailability of subcutaneous MTX is 25% higher than that of oral MTX, even at a dose of 10 mg/week, and much higher at doses >15 mg/week [35]. Thus, the fact that a 10–15-mg/week dose of oral MTX is less effective than subcutaneous MTX may be explained by differences in the bioavailability of the respective forms of MTX. Additionally, it has been reported that the bioavailability of oral MTX is similar between single and divided dosing at ≤8 mg/week, while a 25–35-mg/week dose of oral MTX has better bioavailability in divided dosing than in single dosing [36]. Therefore, single dosing is appropriate for ≤8 mg/week of oral MTX, although two to three divided dosing every 12 h for 1–2 days may be an option (Table 1, Recommendation 8 [11]). Divided dosing or switching to subcutaneous injection may be beneficial when using 10 mg/week or greater doses of oral MTX in terms of less gastrointestinal toxicity and higher bioavailability. As a matter of fact, 15 mg/week of subcutaneous MTX was tolerated by two-thirds of Japanese patients with RA in a Phase III study of subcutaneous MTX injection [10].

Hence, subcutaneous MTX is recommended for patients with intolerance or insufficient response to oral MTX [37]. When switching from oral to subcutaneous MTX, the recommended doses were as follows: oral 6 mg/week to subcutaneous 7.5 mg/week, oral 8 or 10 mg/week to subcutaneous 7.5 or 10 mg/week, and oral 12–16 mg/week to subcutaneous 10 or 12.5 mg/week (Table 1, Recommendation 7 [11]). After switching from oral to subcutaneous MTX, therapeutic monitoring should be performed with the same frequency as the start or dose escalation of MTX because of the possible increased bioavailability of MTX, even at the same dose between oral and subcutaneous MTX.

MTX combined with other DMARDs

MTX is the anchor drug for the management of RA, and it may be used as a monotherapy or combination therapy with other csDMARDs, bDMARDs, or tsDMARDs [Janus kinase (JAK) inhibitors] [1–3]. However, the long-term safety profiles of JAK inhibitors have not been established, and currently, there are issues with specific concerns [38–40] (Table 1, Recommendation 9–11 [11]). The dose of MTX may be kept unchanged up to 16 mg/week, with the addition of other csDMARDs, bDMARDs, or tsDMARDs, which is the same dose used in monotherapy. The dose of MTX can be reduced in patients with risk factors for adverse events (Table 1, Recommendation 12 [11]).

Folic acid supplementation

A meta-analysis examining the effects of folic acid supplementation on the outcome of MTX therapy showed a decrease in the rate of development of gastrointestinal symptoms, liver dysfunction, and MTX discontinuation [41–45]. However, folic or folinic acid supplementation may exacerbate RA in some patients receiving MTX [46–48]. Nevertheless, folic acid supplementation is recommended for all patients with RA receiving MTX because, nowadays, the MTX dose may be increased to 16 mg/week orally or 15 mg/week subcutaneously (Table 1, Recommendation 13 [11]).

Folinic acid is the active form of folic acid that does not require enzymatic activation by dihydrofolate reductase. Therefore, the administration of folinic acid, instead of folic acid, has been recommended for severe MTX adverse events (Table 1, Recommendation 14 [11]). Generally, 10 mg of folinic acid is administered orally every 6 h or 6–12 mg is administered intramuscularly (or intravenously when unavoidable) every 6 h (the daily dose of folinic acid is approximately three times the weekly dose of MTX) concomitantly with hydration and urinary alkalinization until improvement in adverse events is observed.

Screening tests before MTX therapy

Prior to MTX therapy, RA activity and risk factors for MTX-related adverse events should be assessed by history taking and physical examinations (Table 1, Recommendation 15 [11]). Complete blood count (CBC), blood chemistry [total bilirubin, AST, ALT, ALP, γ-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), albumin, creatinine, and blood urea nitrogen], and urinalysis are required for general laboratory tests (Table 2 [11]). Immunological and disease activity assessments, including immunoglobulin (Ig)G, IgM, and IgA, rheumatoid factor, anti-cyclic citrullinated peptide antibody, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3, should be completed in advance. Renal dysfunction is the most important risk factor for MTX-related adverse events and should be evaluated with reference to eGFR or cystatin C in elderly patients, in those with elevated serum creatinine levels, and in those with low body weight [49]. It has been reported that some patients manifest replication of HBV during or after immunosuppressive therapies or chemotherapies, followed by the development of hepatitis, including fatal fulminant hepatitis, which is also the case with MTX therapy [50, 51]. Therefore, screening and monitoring of HBV, according to the guidelines for preventing HBV reactivation [52], are needed along with referral to a hepatology/gastroenterology expert. All patients should be screened for HBs-Ag and HCV-Ab before commencing MTX therapy. If HBs-Ag is positive, suggesting an HBV carrier, the patient should be referred to a

Table 2. Screening procedure before starting MTX therapy [11].

For all patients	Blood tests	CBC (including leucocyte differentiation and mean corpuscular volume); blood chemistry (total bilirubin, AST, ALT, ALP, γ-GTP, LDH, albumin, creatinine, and blood urea nitrogen); inflammatory biomarkers (CRP, ESR, and matrix metalloproteinase-3); immunological tests (IgG, IgM, and IgA, rheumatoid factor, and anti-cyclic citrullinated peptide antibody); hepatitis virus tests (HBs-Ag/antibody and core antibody, HCV-Ab)
	Urine tests	Protein, blood, and glucose
	Image tests	Chest and joint (hand, foot, and other involved areas) radiography
	TB tests	IGRA or tuberculin skin test
For patients with any suspected pulmonary disease, such as ILD, chronic obstructive pulmonary disease, and nontuberculous mycobacterial disease	Pulmonary diseases-associated tests	Consider saturation of percutaneous oxygen, lung function test, HRCT of lung, biomarker for ILD (KL-6/SP-D), β-D-glucan, and anti-MAC-GPL core IgA antibody

hepatology/gastroenterology expert for prophylactic antiviral therapy before the initiation of MTX therapy. If HBs-Ag is negative, high-sensitivity testing for hepatitis B core antibody (HBc-Ab) and HBs-Ab should be performed to investigate the possibility of resolved HBV infection. If HBc-Ab and/or HBs-Ab are positive, the screening test for HBV-DNA should be performed every 1–3 months except for vaccinated patients who show negative reports for HBc-Ab. Additionally, when ≥20 IU (1.3 Log IU)/ml of HBV-DNA is observed in 1 ml of the sample, the patient should be referred to a hepatology/gastroenterology expert for prophylactic antiviral therapy alongside continuation of MTX therapy.

History taking, chest radiography, interferon-gamma releasing assay (IGRA), tuberculin skin test, and chest computed tomography (CT), if needed, should be performed to investigate the possibility of tuberculosis (TB) infection. Two types of IGRAs, QuantiFERON®-TB Gold Plus and T-SPOT®.TB, have been approved in Japan for this purpose. In principle, patients who meet the following criteria should receive prophylactic chemotherapy for TB before initiating MTX therapy:

(1) An abnormal shadow in chest images compatible with a previous TB infection.
(2) History of TB diagnosis (including extrapulmonary TB and excluding those who had completed standard chemotherapy).
(3) Probable latent TB infection (LTBI) based on IGRA and/or tuberculin skin test.
(4) Close contact with patients with active TB.

Chest radiography is helpful in the screening of interstitial pneumonia and other lung infections, which is also helpful in comparison with that obtained for the diagnosis of lung diseases that develop during MTX therapy. When interstitial pneumonia or other pulmonary complications are suspected, percutaneous oxygen saturation (SpO_2), high-resolution CT (HRCT) of the lung, tests for detecting β-D-glucan, and biomarkers of interstitial pneumonia [sialylated carbohydrate antigen (KL-6)/surfactant protein D (SP-D)] should be considered, in addition to physical examination of the chest. Although pre-existing lung disease may be a risk factor for MTX pneumonitis, MTX may be administered to RA patients with mild and stable lung disease because of its important role as an anchor drug. However, informed consent regarding the risk of MTX pneumonitis is necessary before initiating MTX [2]. The serum anti-*Mycobacterium avium* complex (MAC)-glycopeptidolipid (GPL) core IgA antibody test can be helpful in patients suspected of having NTM infection with *M. avium/intracellulare* [53].

Monitoring during MTX therapy

Safety monitoring aims to adequately manage potentially serious or frequently observed adverse events during MTX therapy (Table 1, Recommendation 16 [11]). In Japan, pancytopenia, lung injury, severe infection, and LPD are serious MTX-related adverse events that are of special concern [54]. Laboratory blood tests and urinalysis should be performed every 2–4 weeks within 3 months of starting MTX therapy or MTX dose escalation. The frequency of these tests may be reduced to every 4–12 weeks in patients receiving a constant MTX dose. However, patients with risk factors for MTX-related adverse events, such as renal disorders, should be monitored more closely [55]. Monitoring of CBC should include differential leucocyte count to rule out the possibility of granulocytopenia or lymphocytopenia and estimate the mean corpuscular volume. Blood chemistry includes estimation of total bilirubin, AST, ALT, ALP, γ-GTP, LDH, albumin, creatinine, and blood urea nitrogen. Transaminase elevation is the most frequently observed abnormal finding during laboratory investigations, and sustained elevation suggests a possibility of chronic liver diseases [56]. Sustained hypoalbuminaemia is a risk factor for the development of cytopenia, various infectious diseases, and MTX pneumonitis [57]. Chest radiography should be performed regularly (e.g. annually) to investigate opportunistic infections, such as TB, RA-associated interstitial lung disease (ILD), and malignant lung diseases. Additionally, chest CT should be considered in patients with lung comorbidities, such as interstitial pneumonia, and tests for the detection of biomarkers of interstitial pneumonia (KL-6 and SP-D) and fungal infection (β-D-glucan) may be considered. Serum anti-MAC-GPL core IgA antibody test can be helpful in patients with suspected MAC infection.

Assessment of the effectiveness of MTX should be based on a comprehensive assessment of disease activity, including joint examination and estimation of inflammatory biomarkers such as CRP and ESR. Disease activity should be initially

evaluated every 4–8 weeks after MTX dose adjustment, followed by more extended intervals, such as every 12 weeks, in patients with sustained remission or low disease activity. Additionally, relevant X-ray images of the joints should be monitored annually.

Perioperative management

Discontinuation of MTX is not needed in the perioperative period for patients undergoing elective orthopaedic surgery (Table 1, Recommendation 17 [11]) because the majority of the evidence suggests that continuation of 5–12.5 mg/week of MTX in the perioperative period of elective orthopaedic surgery does not have any impact on postoperative complications and wound healing, but it reduces the flare rate of RA [58–61]; however, some reports indicated an increase in the rate of postoperative infections [62, 63]. Since there is a lack of evidence concerning surgeries other than elective orthopaedic surgery, assessment regarding the continuation, discontinuation, and restart of MTX therapy should be based on the perioperative condition of patients (e.g. the status of renal function, bleeding volume, and hypoalbuminaemia) and MTX dose.

Management during pregnancy and lactation

Exposure to MTX during pregnancy may lead to MTX-related embryopathies, including central nervous system deformity, skull bone deformity, growth deficiency of the extremities, and cleft palate [64]. A report from the European League Against Rheumatism (currently, European Alliance of Associations for Rheumatology) task force on the use of DMARDs before and during pregnancy and lactation recommends discontinuation of MTX 1–3 months before conception [65]. As stated in the package insert of MTX in Japan, female patients of childbearing age should be instructed to avoid pregnancy during MTX therapy and at least one menstrual cycle after the latest dose of MTX (Table 1, Recommendation 18 [11]). MTX is contraindicated during lactation because it has been detected in human breast milk [66–68].

Management of MTX-related adverse events

When MTX therapy is initiated, major adverse effects and their prevention, early recognition, and treatment should be well explained to patients (Table 1, Recommendation 19 [11]). Patient education, as described earlier, should be repeated by doctors and other medical staff during MTX therapy.

Blood disorders (pancytopenia or myelosuppression) were the cause of death in 221 of 851 (26.0%) fatal cases [54]. Risk factors include renal disorders, advanced age, folic acid deficiency, use of multiple concomitant drugs, hypoalbuminaemia, and dehydration (Table 1, Recommendation 20 [11]) [69–72].

MTX pneumonitis develops in 1–7% of patients with RA [73, 74], and 13% of cases are fatal [75]. MTX pneumonitis was the cause of death in 35 of 238 (14.7%) fatal cases in a recent decade [54]. MTX pneumonitis tends to develop within one or a few years after the commencement of MTX therapy in Japan and other countries, although it may occur abruptly at any time during the therapy (Table 1, Recommendation 21 [11]). Risk factors for MTX pneumonitis include pre-existing rheumatoid lung disease, advanced age, diabetes mellitus, hypoalbuminaemia, and previous use of DMARDs [76, 77]. When patients develop interstitial pneumonia, MTX should be immediately discontinued, and a differential diagnosis should be made to rule out other possibilities. MTX pneumonitis is indistinguishable from PCP based on chest HRCT images alone. A publication by the Japanese Respiratory Society Committee on the formulation of a consensus statement is helpful in the diagnosis and treatment of drug-induced lung injuries [78]. Because PCP is sometimes fatal, antibiotics, such as trimethoprim/sulfamethoxazole (TMP/SMX) 6–12 g/day, are administered along with glucocorticoids until PCP is ruled out. Re-exposure to MTX should be avoided because 25% of such patients develop repeated MTX pneumonitis [75].

Infectious diseases were the cause of death in 163 of 851 (19.2%) fatal cases [54]. The risk factors for infectious diseases to be evaluated prior to MTX therapy include age, pre-existing lung disease, extra-articular manifestations, diabetes mellitus, glucocorticoid use, and serious infection within the past 3 years [79, 80], in addition to chronic infectious complications, renal disorders, bone marrow disorders, and a history of opportunistic infections. Adequate prophylaxis includes complete antibiotic therapy for active infection or necessary vaccination, such as against pneumococcus, influenza viruses, and SARS-CoV-2; isoniazid for LTBI; TMP/SMX, pentamidine isethionate inhalation, and atovaquone for those with an elevated risk for PCP; and consultation with an expert in pulmonary medicine for patients with possible NTM infection (Table 1, Recommendation 22 [11]).

Possible gastrointestinal adverse events, such as stomatitis and nausea, should be communicated at the commencement of MTX therapy. An increase in the dose of supplementary folic acid and administration of antiemetic drugs may be effective for treating these events (Table 1, Recommendation 23 [11]).

MTX-related liver disorders are classified as dose-dependent, principally hepatotoxic liver dysfunction and viral hepatitis, which are reactivated or aggravated by MTX. Alcoholic or nonalcoholic fatty liver disease causes liver dysfunction following MTX therapy. It is important to obtain information on alcohol consumption and other lifestyle factors (Table 1, Recommendation 24 [11]). When patients with positive test results for HBV or HCV develop liver dysfunction, they should be referred to a hepatology/gastroenterology expert for management, including discontinuation of MTX administration. When patients without viral hepatitis show elevated AST and/or ALT levels, not >3-fold of the upper limit of the normal levels, a reduction in the dose of MTX or an increase in the dose of folic acid (up to 10 mg/week) should be considered; however, for those showing elevated AST and/or ALT levels >3-fold of the upper limit of normal, dose reduction or discontinuation of MTX and an increase in the dose of folic acid are encouraged. Patients failing the aforementioned approaches should be evaluated for nonalcoholic fatty liver diseases and other possibilities and may be referred to a hepatology/gastroenterology expert.

A 2–6-fold increased risk of malignant lymphoma has been reported in patients with RA compared with that in the general population [81–84]. LPD including malignant lymphoma was the cause of death in 167 of 851 (19.6%) fatal cases [54]. In a multicentre study conducted between 2000 and 2017 in eight hospitals in Japan, 232 patients with LPD were included and analysed [85]. The median age was 67 years;

77.1% of the patients were females, and 94.8% were MTX users. Extranodal involvement was observed in 51.9% of the patients, and the major extranodal sites were the lungs and oral/oropharyngeal mucosa. Diffuse large B-cell lymphoma (40.5%) was the most common pathological LPD subtype.

A large study in Japan enrolled 9815 patients between April 2011 and July 2011 to investigate the risk factors and clinical characteristics of LPD in Japanese patients with RA [7]. At baseline, 79.4% of the patients were females, the median age was 63 years, the median disease duration was 7 years, and the prevalence of MTX use was 60.0%. Sixty-eight (0.69%) patients developed LPD during a 3-year observation period. Multivariable analysis using a Cox proportional hazard model showed that age by decade [hazard ratio (HR), 1.47] and MTX use at baseline (HR 2.35 for $\leq$8 mg/week and HR 4.39 for >8 mg/week versus nonuse) were significant risk factors of LPD. The 5-year mortality of patients with LPD was 24%.

MTX should be discontinued when LPD manifestations develop (Table 1, Recommendation 25 [11]). Approximately two-thirds of RA-LPD spontaneously regress upon discontinuation of MTX, and complete or partial regression is achieved within 4 weeks after discontinuation of MTX [86]. Therefore, if no regressive tendency is observed within 4 weeks, a biopsy and consultation with the related clinical department should be considered. Additionally, it should be noted that in many cases of spontaneous regression, lymphocyte count increases 2 weeks after MTX discontinuation [87].

Drug interactions

Possible development and exacerbation of adverse events should be monitored during concomitant use of drugs known to interact with MTX (Table 1, Recommendation 26 [11]) [54]. Accordingly, dose adjustments for MTX and/or concomitant drugs should be considered when managing adverse events.

Conclusion

This abridged English-language translation summarizes the 2023 update of the JCR guidance for the use of MTX and management of patients with RA [11]. We believe that this guidance will be helpful for both the Japanese and global rheumatology communities for the understanding and proper use of MTX in Japanese patients with RA.

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Conflict of interest

None declared.

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