Current and future role of methotrexate in the therapeutic armamentarium for rheumatoid arthritis

Methotrexate (MTX) has been used for rheumatoid arthritis (RA) treatment since 1980. It is the most common effective disease-modifying antirheumatic drug (DMARD) for RA, and is considered to be the anchor drug, to which other DMARDS or biological agents are added to, in order to achieve an optimal therapeutic effect. MTX improves signs and symptoms to a similar degree as anti-TNF agents. However, it seems to inhibit radiographic progression less effectively than anti-TNF agents. The appropriate route of administration and optimal dose should be individualized depending on the profile and response of the patient. It seems to be one of the safest DMARDS, while there is evidence that patients treated with MTX have lower mortality, especially due to cardiovascular causes. Currently, there is no reliable way to predict which patients will respond to treatment with MTX, and who will experience side effects, the answer to which remains to be clarified.

**KEYWORDS:** biologic agents disease-modifying antirheumatic drugs methotrexate rheumatoid arthritis treatment

Methotrexate (MTX) is currently the most frequently used disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA). Since it was first administered to RA patients, its use has become more and more widespread and the doses applied have gradually increased from initial lower doses to the levels that are considered effective and safe today.

The development of MTX as a therapy for RA initially evolved from isolated case reports followed by uncontrolled case series, placebo-controlled studies and, finally, randomized double-blind active comparator studies [1–3]. The importance of MTX in the therapeutic armamentarium for RA has also been emphasized over the past few decades by the increased therapeutic efficacy observed, when synthetic or biologic DMARDS are added to MTX [1].

The importance of MTX in earlier and more aggressive management of RA patients cannot be overemphasized. MTX is one of the most flexible antirheumatic drugs, given that it can be used as a monotherapy, in combination with glucocorticoids, other synthetic DMARDS, and biologic agents to enhance their efficacy. The safety profile of the weekly low doses used for RA treatment has been studied for over 25 years with very few clinically relevant adverse events. Courses of MTX show some of the longest continuation rates reported in clinical medicine, owing to both its effectiveness and safety. This safety profile makes MTX one of the safest drugs available for the treatment of RA, as well as other forms of chronic inflammatory arthritis [4,5].

**Current situation**

Presently, MTX is considered as the anchor drug among the DMARDS and it is globally regarded as the first medical treatment option for RA [4]. The degree of appreciation that MTX receives has made it very difficult for authorities and ethical committees to allow pure placebo arms in randomized clinical trials of new agents tested for the treatment of RA. Thus, the treatment of patients who have been classified as MTX non-responders or insufficient responders is usually the first challenge for emerging drugs. The combination of MTX with biologic agents is probably the most effective therapy we currently have to treat RA [6].

MTX was shown to improve signs and symptoms of RA, disease activity and function to a similar degree as the TNF blockers in monotherapy [7]. It also inhibits radiographic progression [8,9], although to a smaller degree than anti-TNF agents [10]. However, a recent study using tocilizumab, an IL-6 receptor antagonist showed that tocilizumab monotherapy was superior as compared with MTX [11].

The use of MTX in early RA started in 1980 and its use has significantly increased in the last few years. Indeed, recent studies have shown an increased use of MTX from 5 to 90% in Finland [12] and from 25 to 90% in the USA [6].
RA is a systemic inflammatory arthritis that not only results in permanent joint damage, but is also associated with a higher morbidity and mortality compared with the general population. The use of MTX seems to prolong the overall survival of RA patients [13,14], probably owing to its beneficial effects on cardiovascular mortality [15,16]. The reason for this is related not only to the suppression of inflammation, but also to the atheroprotective effect of MTX. Indeed, recent studies showed that MTX may facilitate cholesterol outflow from foam cells of the artery wall involved in the atherosclerosis process [17].

Strategic trials have shown that independently of the medications employed, the early and effective suppression of inflammation is the most important target in RA treatment [18]. Hence, the ultimate therapeutic goal in the treatment of RA is remission or at least low disease activity, although this goal may not always be achieved with MTX monotherapy. Thus, over the last two decades various drug combinations based on MTX have been increasingly used to treat those patients with RA. DMARD combination therapy may be used initially or in a step-up strategy after MTX monotherapy in patients with persistently active disease. Drugs frequently used in combination with MTX background include leflunomide, cyclosporine A, sulfasalazine and hydroxychloroquine (HCQ).

Thus, the use of MTX in combination with other DMARDs represents another option for patients who fail on DMARD monotherapy. However, in patients at risk for rapid disease progression, the early use of biologics may also be considered [19].

Regarding comparisons of efficacy and safety between MTX and biologic agents, plenty of clinical trials, including a total of four biologics, have been published so far. Three TNF inhibitors (etanercept [20–22], adalimumab [23] and golimumab [24]) and the IL-6 receptor inhibitor tocilizumab [25] have been investigated in MTX-naive patients using a parallel design. These trials had three treatment arms: MTX monotherapy, biologic compound monotherapy and the combination of both. Other biologics (infliximab [25,26], certolizumab pegol [27], rituximab [28] and abatacept [29]) were tested in patients who had experienced an inadequate response to MTX, and were treated with a combination of MTX plus a biologic agent or MTX plus placebo (Table 1). However, that particular design does not provide a true comparison between MTX and the biologics, but may provide indirect clues on the relative efficacy of the different biologic agents. In all trials involving a head-to-head comparison, MTX and biologics were similarly effective as measured by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) response criteria including remission. In general, improvement started sooner with the biologic treatment than with MTX therapy. Inhibition of radiographic progression was greater with biologics, probably because TNF inhibitors, apart from their anti-inflammatory effects, directly reduce osteoclast activity. The efficacy of biologics was significantly augmented when they were combined with MTX. Furthermore, based solely on trial results, the efficacy of MTX may be underestimated: the initial doses of MTX were too low and were perhaps increased too gradually. The trial design with intention-to-treat and last observation carried forward analysis may have been unfavorable for MTX, since more patients treated with MTX withdrew and thus had less time under treatment. Folic acid (FA) supplementation may have suppressed MTX efficacy by interfering with its mechanism of action. Nevertheless, all trials showed a good performance of MTX in comparison with biologics [30].

**Mechanism of action**

Although MTX was initially introduced as a chemotherapeutic agent for the treatment of malignancies, it is clear that, in the doses used, the mechanism of action in the suppression of inflammation differs from simply suppression of purine and pyrimidine metabolism, resulting in the inhibition of cellular proliferation [31].

MTX was designed to be a close analog of FA and to block the folate-dependent steps in *de novo* purine and pyrimidine biosynthesis (Figure 1).

MTX’s mechanisms of action in RA are most likely associated to its antiproliferative and immunosuppressive effects [32,33]. Thus the possible effects of MTX are: decrease of cell proliferation; increase of T-cell apoptosis; increase of endogenous adenosine release; alterations in the expression of adhesion molecules; and influence on cytokine production and other humoral responses, as well as effects on bone formation [6].

However, the most likely mode of MTX action in the therapy of RA is that MTX stimulates adenosine release and adenosine suppresses the inflammatory functions of neutrophils, macrophage/monocytes, dendritic cells and lymphocytes in the pathogenesis of joint inflammation [34,35].
The transportation mechanisms through which MTX reaches its pharmacodynamic target are an important part of MTX pharmacology and the effectiveness and/or toxicity of the drug may be strongly influenced by its concentration in various tissues, such as RA synovial membrane or the liver. Plasma protein binding of MTX to albumin is important for MTX distribution throughout the body, while relatively high concentrations of the drug are found in the liver. Drug delivery directly into inflamed joints and enhanced antiarthritic efficiency can be achieved by covalent coupling of MTX \textit{ex vivo} to human serum albumin or \textit{in vivo} to endogenous albumin through the MTX prodrug AWO54. High levels of expression of the folate receptor $\beta$ (FR$\beta$) on the synovial macrophages of patients with RA and its capacity to mediate the binding and uptake of MTX has been shown. To further improve drug treatment of RA, FR$\beta$-specific drugs have been developed that are characterized for their therapeutic efficacy in synovial inflammation. Consequently, different approaches to improve folate inhibitory and FR$\beta$-specific therapy of RA beyond MTX are being developed [36].

**Pharmacokinetics of MTX**

The relationship between intracellular MTX concentration in erythrocytes and clinical efficacy has recently been reported [37]. There is a significant variability in patients’ response to MTX, both in terms of efficacy and toxicity. Moreover, the pharmacokinetics of polyglutamated forms of MTX with up to five glutamate moieties (MTXGlu1–5) has recently been studied in much detail [38]. The median time for the MTXGlu1–5 to reach steady state in erythrocytes (defined as 90% of the maximal concentration) in red blood cells was between 6 and 149 weeks, the median half-life of accumulation for erythrocyte MTXGlu1–5 was between 2 and 45 weeks and the median half-life of elimination for erythrocyte MTXGlu1–5 was 1–4 weeks. The authors concluded that there is a wide interpatient variability of erythrocyte MTXGlu1–5 concentration in adult patients with RA.

MTX enters cells through the reduced folate carrier and exerts part of its effects after polyglutamation to MTX polyglutamates (MTXPGs) and then by the inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase and thymidylate synthase. The dose was not always associated with the effects of MTX. These data imply that measuring erythrocyte MTXPG levels and/or the common polymorphisms in the folate–purine–pyrimidine pathway may help to monitor MTX therapy [39]. Although MTX response improves at higher MTXPG levels, there is no absolute correlation between level and effect. Besides, overlapping MTXPG levels between clinical responders and nonresponders limits the clinical utility of this measurement [40].

**Pharmacogenetics**

Recent advances in genetics, particularly pharmacogenetics, may permit the prediction of an individual patient’s response to MTX. Currently available data demonstrate the potential, but also the limitations of genetic polymorphism analyses [41,42]. At present, there are no reliable means to predict an individual patient’s response to MTX, although pharmacogenetics seems to have a promising role [43].

Genetic variations (single nucleotide polymorphisms) in enzymes associated with MTX metabolism and regeneration of reduced folates have been studied, while a pharmacogenetic index has been calculated [44] as a function of homozygous variant genotypes. However, although genetic polymorphisms in the folate metabolic pathway and MTX transporters...
modify MTX toxicity, they do not seem to influence MTX efficacy [6].

**Optimal route of administration & dosage of MTX**

Although it has long been recognized through pharmacokinetic studies that the bioavailability of MTX is higher when administered parenterally rather than orally, the clinical implications of this had not been formally tested. However, in a recent randomized clinical trial, the two routes of administration were directly compared [45]. The finding that the patient group who received subcutaneous MTX had a better clinical outcome than the group who had been treated with oral MTX is a verification of the initial hypothesis on clinical grounds. Even though this does not mean that all patients should be treated with parenteral MTX, it suggests that patients with an inadequate response and/or intolerance to oral MTX may benefit from a trial with parenteral MTX [46].

A recent systematic review of the literature concerning the best dosage and route of MTX administration in RA showed that the optimal evidence-based dosing regimen is to start with MTX 15 mg/week orally (0.2 mg/kg), to gradually escalate by 5 mg/month up to 25–30 mg/week or the highest tolerable dose (0.3 mg/kg) according to the patient’s response.
and tolerance and to subsequently switch to subcutaneous administration in the case of an insufficient response [47]. However, a study by Lambert et al. in RA patients showed no higher efficacy when switching to intramuscular MTX, after the failure of oral MTX [48]. Moreover, in patients in remission, the dose of MTX should be reduced according to patients’ response, usually no less than 7.5 mg/week.

**Optimal time to start MTX**
While there is a consensus that treatment with DMARDs should be started early in patients with RA [49,50], confirmation that radiographic progression is inhibited with an early treatment start is scarce. Another concern is that no one can precisely define how early is early enough. Current studies showed that 3 months should be the maximum delay from diagnosis to the initiation of DMARD treatment [51,52].

The initiation of DMARD therapy within the first 3 months of disease onset is now the standard care for RA, with MTX being the most common DMARD of choice [49].

**Side effects of MTX**
Diverse side effects are the major reason for MTX withdrawal and changing treatment. However, patients with RA treated with MTX show a relatively good tolerability to MTX compared with other DMARDs [53]. Minor gastrointestinal side effects, mild transaminase elevation and stomatitis are frequent but reversible effects after dose reduction or discontinuation of treatment. Serious side effects include cystopenia, hepatotoxicity and interstitial pneumonitis, and in such cases MTX should be withdrawn. The main side effects according to incidence rates are shown in Box 1.

**Prevention of side effects**
According to a recent review, supplementation with FA is an effective measure to reduce hepatic adverse effects associated with MTX treatment [54]. Both FA and folinic acid supplements have been demonstrated to reduce the toxicity of MTX when used in RA therapy. The effect of folate supplementation on MTX efficacy, however, still needs to be studied. FA supplementation has been found to exert a beneficial effect on homocysteine metabolism and may prevent the formation of the less effective metabolite 7-hydroxy-MTX. The cost of FA supplements is substantially less than that of folinic acid supplements [55].

The latest British Society for Rheumatology guidelines suggested that alcohol consumption by patients treated with MTX should be “well within national limits”. However, this is in contrast with the summary of product characteristics for MTX that recommends avoiding alcohol [56].

Moreover, MTX has to be avoided in patients at risk of liver damage or with pre-existing lung disease. Patient monitoring by means of clinical and laboratory tests prior to and during MTX therapy is necessary to diminish the potential serious toxicities of MTX.

On the other hand, in patients with various comorbidities such as diabetes mellitus, renal failure and obese patients, a lower dose of MTX is used to avoid toxicity and severe adverse events. In addition, patients should be tested for hepatitis B and C before starting MTX treatment. In these conditions, close monitoring is required and DNA viral load should be performed when indicated. Moreover, all patients should be tested for latent tuberculosis before the commencement of MTX treatment. However, there are no international guidelines for tuberculosis prophylaxis in patients treated with MTX.

**Preoperative use of MTX**
In spite of the widespread use of MTX and the frequent need of elective orthopedic or other types of surgical procedures in RA patients, there is some confusion concerning the use of MTX perioperatively. There is some evidence that treatment with MTX is safe prior to and

### Box 1. Side effects of methotrexate.

#### More frequent
- Transaminasemia (10–43%)
- Gastrointestinal (20–65%)
- Stomatitis (10–15%)
- Anemia (10–15%)
- Leucopenia (12%)
- Thrombocytopenia (12%)

#### Less frequent
- CNS (8–10%)
- Hair loss (8%)
- Pneumonitis (2.1–8%)
- Infections (5%)
- Subcutaneous nodules (2–6%)

#### Rare
- Nephrotoxicity
- Dermatitis (1.4%)
- Photosensitivity (0.8%)
- Gynecomastia (0.6%)
- Oligospermia (0.5%)
- Lymphoma?

Data taken from [2,6,7,53,70,73].
after elective surgical procedures. On the other hand, discontinuation of MTX 1 week before and 1 week after surgery might be a compromise for surgeons and patients who are concerned about complications during or after operations. Moreover, disease activity is better controlled when MTX is not interrupted.

**Use of MTX in the elderly**

The absorption and distribution of MTX are similar in the elderly and younger RA patients. However, as both metabolism and renal or biliary excretion of MTX might be affected by age, these parameters should be considered when using this drug. Neither hemodialysis nor peritoneal dialysis effectively clears MTX, while high-flux dialysis may be effective. MTX efficacy is equivalent in the young and elderly. The side-effect profile includes a higher frequency of gastrointestinal, liver and hematological toxicities in older patients, even though the overall profile is not qualitatively different. By contrast, a population-based study indicated that increasing age was associated with a greater tendency for discontinuation of MTX in patients with newly diagnosed RA. The potential for renal toxicity should always be considered when determining which dosage of MTX to use for RA therapy, and there is modest doubt that the dosage of MTX is especially critical in the elderly.

**Drug combinations with MTX in RA**

The ultimate therapeutic goal in RA treatment is remission or at least low disease activity, which unfortunately is not always achieved with MTX monotherapy. DMARD combination therapy may be used from the beginning or after a patient has failed initial MTX monotherapy. Plenty of different MTX-based combination regimens have been studied. The most frequently used combinations include: MTX plus leflunomide, MTX plus cyclosporine A, MTX plus sulfasalazine, MTX plus HCQ and triple therapy with MTX plus sulfasalazine plus HCQ. Less common and presently outdated combinations include MTX plus azathioprine and MTX plus gold. Together, the use of MTX in combination with other DMARDs still represents a valuable therapeutic option in patients who fail DMARD monotherapy or for whom initial combination therapy is considered a better option than a ‘step-up’ strategy. However, in patients at risk for rapid radiographic progression, the early use of biologics – again in combination with MTX – may be considered.

Furthermore, in the case of insufficient response to a single DMARD or to a DMARD combination, a biologic should be added to MTX. To date, the most frequent biologic treatment is TNF inhibition (with etanercept, adalimumab, infliximab or the newer inhibitors, certolizumab pegol and golimumab). However, most studies have shown that all biologics (with the exception of anakinra) have comparable efficacy. The combinations of MTX plus abatacept, MTX plus rituximab and MTX plus tocilizumab are very effective in both producing clinical improvement, and inhibiting radiographic progression. The efficacy of biological therapy is generally better using MTX combination than monotherapy. The safety of MTX combination treatment with DMARDs is not significantly lower than that of the individual drugs; therefore, the respective safety measures should be taken.

**Underestimation of MTX**

There are several reasons suggesting that the use of MTX in RA is underestimated in regard to its efficacy, and overestimated in regard to adverse events. Based on a current review, ten reasons are outlined:

- Meta-analyses of clinical trials suggest that MTX is similarly effective to other DMARDs;
- Information in textbooks and websites may overemphasize adverse events and drug interactions associated with MTX;
- Information presented to patients when prescribing MTX understates ‘effects’ of RA and overstates those of MTX;
- Suggestions made to patients to refrain entirely from alcohol while on MTX may be unnecessary;
- The frequency of blood testing of patients who take MTX may be exaggerated;
- Only a small minority of patients are eligible for clinical trials to compare biologics and MTX;
- Step-up design in most comparisons of biologics with MTX only includes patients who had experienced an inadequate response to MTX;
- In parallel design trials, biologic agents are not substantially more efficacious than MTX;
- Low, inflexible dosing regimens of MTX and the requirement for withdrawal after minimal liver function disturbances in many clinical trials may underestimate efficacy and safety;
- The clinical significance of lower radiographic progression in patients treated with biologic
agents versus patients treated with MTX may be overemphasized.

**Long-term safety of MTX**

The profile of side effects of MTX has been studied over 25 years, with very few clinically important adverse effects in the weekly low doses used for RA therapy. Indeed, MTX courses show some of the longest continuation rates reported in clinical medicine, obviously as a result of both its efficacy and safety [69]. The safety profile of MTX indicates that it is among the safest of all drugs used for the treatment of chronic inflammatory arthritis [70].

The incidence of cancer and the mortality due to cancer have been studied in a group of 789 randomly selected RA patients between 1999 and 2005, and compared with the general population [71]. The standardized incidence ratio of cancer in RA was 1.23 (95% CI: 0.78–1.85). An increased risk of leukemia, non-Hodgkin's lymphoma and lung cancer was found in patients with RA, but the overall standardized mortality ratio of cancer was not higher than expected. RA patients, however, with kidney or lung cancer had a higher mortality than expected. Male gender, elderly age, longstanding disease and having used cytotoxic drugs other than MTX were identified as predictive factors for cancer. The authors concluded that the overall incidence and mortality of cancer in RA was not greater than expected, although an increased risk of hematopoietic and lung cancer in RA was found [72].

In another study of 23,810 patients with RA from Quebec (Canada) over the period 1980–2003 [70], hematologic malignant neoplasms developed in 619 patients, including lymphoma in 346 patients, leukemia in 178 patients and multiple myeloma in 95 patients. The unadjusted rate ratios for hematologic malignancies after drug exposure were: MTX 1.18 (95% CI: 0.99–1.40); azathioprine 1.44 (95% CI: 1.01–2.03); and cyclophosphamide 2.21 (95% CI: 1.52–3.20). Apart from cyclophosphamide, which is clearly associated with an increased risk of neoplasia, such an association was less convincing for azathioprine and even less for MTX.

There is no evidence that MTX worsens interstitial lung disease in RA patients [73].

A review of RA patients followed-up over 14 years at the hospital for Special Surgery in New York (NY, USA) [74] indicated that 3.4% of 182 patients with RA who had ever been treated with MTX had abnormal liver function tests. One hundred and fifty-two patients (83.5%) with 2007 evaluations had no abnormal results, compared with 30 patients (16.5%) who had at least one abnormal liver function result over 784 tests. Twenty-two out of the 30 patients with at least one abnormal test (73.3%), however, continued treatment without biopsy or other further evaluation or change in treatment, while subsequent

**Box 2. 3E multinational evidence-based recommendations for the use of methotrexate in rheumatoid arthritis.**

- Before starting methotrexate (MTX), patients should be assessed for risk factors for MTX toxicity: including alcohol intake, patient education, complete blood count, serum transaminase, albumin and creatinine levels, and chest x-ray; other tests to be considered are serology for HIV, hepatitis B or C, blood fasting glucose, serum lipid profile and pregnancy test.
- Oral MTX should be started at 10–15 mg/week, with gradual escalation every 2–4 weeks by 5 mg up to the dose of 20–30 mg/week, depending on response and tolerance; parenteral administration should be considered in cases of inadequate clinical response or poor tolerance.
- Supplementation with at least 5-mg folic acid weekly is strongly recommended.
- When starting MTX or increasing dose, alanine aminotransferase (ALT) with or without aspartate aminotransferase (AST), creatinine and complete blood count should be checked every 1–5 months, until a stable dose is attained and then every 1–3 months; clinical assessment for adverse effects and risk factors should be performed at each visit.
- MTX should be discontinued, if there is a confirmed increase in ALT/AST larger than three-times the upper limit of normal (ULN), but may be reintroduced at a lower dose after normalization. If the ALT/AST levels are persistently elevated up to three-times the ULN, then the MTX dose should be adjusted; diagnostic procedures should be considered, if elevated ALT/AST more than three-times the ULN persist after discontinuation.
- Given its acceptable safety profile, MTX is appropriate for long-term use.
- In disease-modifying antirheumatic drug (DMARD)-naive patients, the efficacy/toxicity ratio favors MTX monotherapy over combination with other synthetic DMARDs; MTX should be considered as the anchor drug for combination therapy, when MTX monotherapy does not achieve sufficient disease control.
- In RA patients undergoing elective orthopedic surgery, MTX can be safely continued in the perioperative period.
- Both men and women should not use MTX for at least 3 months before planned pregnancy and women should not use MTX during pregnancy or breast feeding.

Adapted from [6], with permission from BMJ Publishing Group Limited.
liver function assessments were within normal limits. Only three patients had leucopenia, the lowest 2300/µl, while MTX was discontinued in only one case. Twenty two patients had mild hypoalbuminemia, which resulted in no change of the MTX dose. The most common cause for discontinuation was inadequate response, not adverse events.

**MTX is the first choice for the treatment of RA**

Various drugs with different risk–benefit ratios have been claimed to decrease the intensity and frequency of flares and to slow the radiographic progression of RA. Among them, MTX is the best assessed DMARD, and the one that rheumatologists are most experienced with. At doses between 7.5 and 25 mg weekly, MTX relieves pain, reduces the number of tender and swollen joints and improves function. Some of its adverse effects are common to most immunosuppressive drugs, particularly gastrointestinal and hematological disorders. Treatment withdrawals due to adverse events are infrequent at the doses used in RA. Other DMARDs, such as azathioprine, antimalarials, cyclosporine A, cyclophosphamide, D-penicillamine, leflunomide, gold salts and sulfasalazine are not more effective than MTX. Some are less effective or even more toxic. Within clinical trials, some TNF antagonists (in particular etanercept and adalimumab) when used in monotherapy were no more effective than MTX monotherapy on clinical grounds after 1 or 2 years. Over a total of ten comparative trials, the combination of MTX with a TNF antagonist were more effective than MTX monotherapy in terms of reducing disease activity and improving function. The use of TNF antagonists is also far more expensive and less convenient, as periodic injections or intravenous infusions are necessary. There is no firm evidence that combinations of TNF blockers with other DMARDs are more effective than TNF antagonist–MTX combinations. In patients in whom treatment with TNF antagonists has failed, a combination of rituximab or abatacept or tocilizumab or golimumab plus MTX is more effective than MTX alone [78]. However, efficacy in patients in whom other treatments have failed is uncertain.

Today, MTX is considered the anchor drug for the treatment of RA not only as monotherapy, but also in combination with other DMARDs or biologics. It should be started very early in the treatment of RA and its ‘survival’ is higher than other DMARDs after 5 years of therapy [69]. In addition, in regard to radiographic outcome, it seems that MTX inhibits radiological progression more than other DMARDs [8,9]. MTX has similar results in efficacy and radiological progression compared with biological monotherapy. Finally, MTX can be given with a considerable safety profile, and further manipulation of the MTX molecule may provide a better therapeutic profile for RA patients.

**Multinational recommendations for the use of MTX in RA**

A set of recommendations for the use of MTX in daily clinical practice focused on RA has been developed, which are evidence-based and supported by a large panel of rheumatologists (Box 2) [6].

**Future perspective**

Manipulation of the MTX molecule may provide a better therapeutic profile for RA patients. Thus, polyglutamation of the drug, a metabolic step that appears to play a role both in its therapeutic properties and hepatic side effects, might be a potential starting point. Moreover, methods of targeted drug delivery, in order to increase drug accumulation at the site of inflammation, may increase effectiveness and reduce toxicity. Albumin-coupled and liposomally conjugated MTX, both of which are more potent than MTX in inhibiting inflammation in animal models, are under preclinical evaluation. It has been recognized that activated synovial macrophages upregulate FR-β expression and that MTX can also become active by this pathway. This makes it possible to develop new FR-β-specific folate inhibitors with a greater specificity for this pathophysiologically important cell population [76]. Although current treatment approaches with MTX can provide significant benefits in patients with RA, future investigation is needed to target therapy more accurately, in order to determine which patients respond best not only to MTX, but all available synthetic and biologic drugs and their combinations.

**Conclusion**

MTX is one of the most commonly used and effective DMARDs for the treatment of RA, and is considered to be the anchor among these drugs to which other synthetic DMARDs or biological agents are added, in order to achieve an optimal therapeutic effect.

At present there are some studies to predict response to MTX monotherapy. More specifically, current smoking, female gender, long disease duration and young age may predict a worse response to MTX treatment [77]. On
the other hand, a close follow-up and monitoring every 3–6 months is the best predictor of response [78].

However, the current mainstream view, which will remain for the near future, is that all patients with RA should start with sufficient doses of MTX. If this treatment is not efficacious enough in a reasonable time frame or is poorly tolerated, dose adjustments and ultimately adding or replacing another DMARD or a biological agent should be considered, taking into account the individual patient and disease characteristics. The development of newer, more effective and better tolerated drugs that may also complete the convenient dosing regimen and reduce the cost of MTX is eagerly awaited.

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**Executive summary**

**Current situation & methotrexate is the first choice for the treatment of rheumatoid arthritis & long-term safety**

- Methotrexate is the anchor drug in the treatment of rheumatoid arthritis (RA).
- Its effectiveness/safety profile has allowed researchers to use it as the gold standard to which other drugs or treatment strategies are compared.

**Side effects of methotrexate: prevention, preoperative use, in the elderly & long-term safety**

- Its efficacy and safety has been proven both in the context of clinical trials and through real-life experience, since it has probably been the disease-modifying antirheumatic drug most commonly prescribed to RA patients during the past two decades.

**Optimal route of administration and dosage of methotrexate**

- It has a flexible dosing regimen, allowing for dose titration and alternative routes of administration.

**Drug combinations with methotrexate in RA**

- Even in cases of methotrexate inefficacy, the drug retains its value, since it may be coupled with other synthetic or biologic disease-modifying antirheumatic drugs in combinations that have been proven efficacious and safe.

**Pharmacokinetics of methotrexate & pharmacogenetics**

- Although its mechanism of action still remains obscure, further research on methotrexate biologic properties may offer new alternatives with a better effectiveness/safety profile for the treatment of RA.

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Papers of special note have been highlighted as:

- of interest
- of considerable interest

7 Study based on recommendations for the use of methotrexate (MTX) in rheumatoid arthritis.
15 Georgiadis AN, Papavasiliou EC, Lourida ES et al. Atherogenic lipid profile is a feature...


*Main study on the pharmacokinetics of MTX.*


*Very useful study, comparing subcutaneous and oral administration of MTX.*


Study examined the most appropriate route of administration, as well as the optimal dose of MTX.
Good review with regard to the use of MTX in the elderly population.


Important study which demonstrated that MTX is the anchor drug for combination therapy.


Long-term observational study showing that MTX has a high survival rate.


