Review article

Insights into methotrexate in rheumatoid arthritis: a clinical review

Genga EK[1,2], Oyoo GO[1, 2], Ezzi MS[1]

[1]*Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202, Nairobi, Kenya*
[2]*Nairobi Arthritis Clinic*

Corresponding author:
Dr EK Genga, Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202, Nairobi, Kenya. Email: eugenekalman@gmail.com

Abstract

Objective: To review the efficacy and safety profile of methotrexate in rheumatoid arthritis.
Data source: Published original research work and reviews were searched in English related to efficacy and safety profile of methotrexate in rheumatoid arthritis.
Study design: Only articles that emphasis on efficacy and safety profile of methotrexate in rheumatoid arthritis.
Data extraction: Online and library searches done.
Data synthesis: Data added and summarized.
Conclusion: Methotrexate (MTX) has been the mainstay of treatment of patients with Rheumatoid Arthritis (RA). It has been used for over 50 years as the backbone in the treatment in a number of rheumatic diseases and thus it remains a gold standard of therapy for RA. Clinical trial results indicate that weekly low dose MTX is generally safe and effective in the treatment of RA. Factors that favour a good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity. Folate supplementation has been shown to reduce the risk of adverse events.

Key words: Methotrexate, Rheumatoid arthritis, Efficacy, Safety profile

Introduction

Methotrexate was first used for the treatment of rheumatoid arthritis in 1951[1]. It emerged at the same time as glucocorticoids. It received little attention in the therapy of rheumatic diseases until retrospective reports appeared about 30 years later[2,3]. The initial short term studies in the mid-1980s demonstrated that it was more potent, efficacious and superior to placebo in patients with chronic severe RA. Long-term open prospective studies have since showed that the response is sustained and that toxicity is manageable. These insights have led to the evolution of methotrexate into its present status as the main stay of treatment of patients with RA. However, there is a large variability in the medical practice regarding the use of methotrexate for RA. The variability occurs mainly with regards to the starting dose, adjusting dosages, routes of administration and concomitant use of folic or folinic acid. The purpose of this article is to provide guidance on the use of methotrexate for the treatment of RA.

Mechanism of action

Methotrexate was introduced for the therapy of rheumatoid arthritis without any clear understanding of its mechanism of action. With methotrexate, studies are even more difficult to interpret because the effects of methotrexate are observed over weeks to months in patients. Another caveat is that studies in animals may be misleading because the doses of the drug used are not similar to those used in patients. It's important to note that the methotrexate effect in animals is seen over a shorter duration of time as compared to humans[4]. Despite these, there are a number of postulated mechanisms of action.

The first hypothesis, based on methotrexate's known anti-folate properties. Methotrexate is a structural analogue of folic acid that competitively inhibits the binding of dihydrofolic acid to the enzyme dihydrofolate reductase. Dihydrofolate reductase is enzyme responsible for reducing dihydrofolic acid to the active metabolite, folinic acid. Therefore, methotrexate decreases the amount of intracellular folinic acid available and affects the intra-cellular folinic acid dependent metabolic pathways. These pathways include purine and pyrimidine metabolism, as well as amino acid and polyamine synthesis. Its postulated by inhibiting these methylated reactions it inhibits proliferation of the pro-inflammatory cells and cytokines responsible for synovial inflammation in RA[5,6].

Other mechanism of action includes increasing T cell apoptosis and release of endogenous anti-inflammatory adenosine. It also alters the expression of cellular adhesion molecules thus reducing in expression of cellular adhesion molecules and anti-angiogenesis effects via indirect mechanisms such as disruption of macrophage interaction[7,8].

Efficacy for rheumatoid arthritis

Methotrexate can be given by oral, intramuscular, and subcutaneous routes. The oral route has a variable absorption and has less serum levels when compared to parenteral administration [9, 10]. This may have therapeutic implications, as some patients may seem to respond better to parenteral therapy, presumably because more drugs reaches the circulation especially when higher doses within the therapeutic range are used. The liquid MTX formulation (prepared for parenteral use) may be consumed orally by mixing it with juice; this preparation is cheaper than tablets and may be used if expense is a serious issue and if the patient can be relied upon to measure the precise volume of drug. It is not recommended for patients with decreased finger dexterity, limited vision, or impaired cognition. Research has shown that better disease activity scores can be attained from switching to parenteral administration with patients on maximally tolerated oral doses of MTX. Toxicity has been noted to be higher in the parental group[11,12].

Its use in rheumatoid arthritis is well known. Apart from improving disease activity scores, it also has benefits of reducing mortality, improving quality of life and reducing radiographic joint damage[13,14]. With the introduction of biologics, data from Kleinert's study, Gruppo Italiano Studio Early Arthritis (GISEA), British Society for Rheumatology Biologics Register (BSRBR), and Research in Active Rheumatoid Arthritis (ReAct) still show that methotrexate is still the anchor for rheumatoid arthritis management[15-17]. Despite its popularity in rheumatoid arthritis, the dose and route of administration has been varied. To determine the best dose and route of administration, we looked into data from previous studies.

The starting dose has been an area of contention. Furst *et al*[18] compared starting doses of 5-10mg weekly, 12.5-20mg weekly and 25-35mg weekly vs placebo in RA patients who had the disease for a long duration and had failed other Disease Modifying Antirheumatic Drugs (DMARDs). The best response in terms of tender joint counts, pain and global status versus the placebo was noted in the 12.5-20mg group. The 25-35mg group had the highest adverse events as measured by gastrointestinal and mucocutaneous toxicities.

In early RA DMARD naïve patients, Verstappen *et al*[19] looked at two groups. First group started at 7.5mg per week and increased it per month by 5mg up to a maximum of 25mg weekly. The second group had a slower increment of 5mg every 3 months to a mean of 18mg weekly. Patients in the group with the fast increment achieved better disease control as measured using tender and swollen joint counts, pain and global status. Interestingly both groups had similar records of adverse events. The general recommendations are start patients on 15 mg weekly orally, escalating 5 mg per month to 25-30 mg weekly as tolerated depending on disease activity, size, and age of the patient, the presence of comorbidities, and renal function. If response is inadequate, one should consider switching to SC where available[20].

The response to any DMARDs be it synthetic or biologic varies from one RA patient to another. This is due to the unique and complex pathogenesis of RA which causes varied clinical presentation. The next frontier in management is being able to predict the responders to drugs used in RA treatment. A novel biomarker of response has been methotrexate polyglutamate. These are the active MTX metabolites that produce the anti-inflammatory effects and their levels have been found to correlate to disease activity[21,22]. Higher levels are associated with good responses, while lower levels might indicate the need for either more MTX, or the possibilities of poor adherence to the treatment regimen or poor absorption of the dose inhibit enzymes of folate metabolism[21,22]. Data is still limited and more research is needed before this can be applied to routine clinical use. The known clinical and biological factors that predict good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity[22-23].

Safety profile

MTX use has been associated with a variety of adverse effects. The range of severity is influenced by the MTX dose and treatment regimen. The major side effects are reviewed here.

Common minor adverse events

Gastrointestinal

The common side effects include nausea, loose stools and stomatitis. Stomatitis can occur at any dose of MTX but is more likely to be seen at higher doses. These are mainly due to sub-optimal supplementation of folic acid. Patients with mild to moderate stomatitis, one can gradually increase the folic acid dose from 1 mg daily increments up to a maximum of 5 mg until the toxicity is controlled. Patients presenting with severe oral ulcers may require both a lowering of the MTX dose and an increase of folic acid[24].

Neurotoxicity

Manifestations include severe headaches, fatigue, and problems in concentrating which may require reducing the MTX dose or discontinuation in some patients. The exact mechanism is still unclear. Some have suggested it may be related to the accumulation of adenosine due to the inhibition of purine synthesis[25].

Fever

MTX can induce fever either directly or indirectly through infections. Infections are rare but commonly occur with co-administration of glucocorticoids, azathioprine and tumour necrosis factor inhibitors. Pneumocystis jiroveci, herpes zoster and fungi can occur. Infections are a common cause of drug withdrawal among those administered MTX for prolonged periods[26].

Potential severe adverse effects

Hepatotoxicity

Low dose methotrexate can have adverse effects on the liver. These include reversible transaminase elevation (most common), liver fibrosis and liver cirrhosis (rare). Risk factors include alcohol and preexisting liver disease. Other risk factors for elevated transaminases include obesity, untreated high cholesterol, Aspartate Transaminase (AST) or Alanine Transaminase (ALT) elevations above the upper limit of normal at baseline (before starting MTX) use of a biologic agent in addition to the MTX, and lack of folic acid supplementation[27]. Some authors suggest that folate supplementation may help prevent MTX induced hepatotoxicity. Methotrexate depletes the folate hepatic stores and supplementation either folic acid 1 mg per day or folinic acid 2.5 mg per week is associated with a reduced incidence of serum transaminase elevation[28]. However, more research is needed to establish the relationship between folate depletion and hepatic toxicity.

Data from the CORRONA database that 1953 RA and 151 psoriatic arthritis patients, showed there was an increased risk of transaminase elevations with a combination of MTX and leflunomide compared with either drug used alone[29]. The overall incidence of elevations in aminotransferase enzymes in patients with RA receiving MTX, leflunomide, MTX plus leflunomide, and neither was 22, 17, 31, and 14%, respectively. Elevations > 2 x ULN occurred in 1-2% of patients on MTX or LEF monotherapy compared to 5% with the combination. After multivariable adjustment and compared with either monotherapy, combination MTX + LEF was associated with greater risk according to MTX dose used as part of the combination.

Data from the SMILE cohort (Safety of Methotrexate and Leflunomide in RA trial) over a period of 12 months examined transaminase abnormalities in 2975 patients. The overall incidence of elevations in aminotransferase enzymes in patients receiving MTX (52.2%), Leflunomide (7.3%), MTX plus Leflunomide (13.9%), and neither (26.6%) was 12, 16, 19, and 14%, respectively[30]. No reports of liver fibrosis or cirrhosis were recorded. Only a small number of patients had to stop taking MTX and/or LEF cessation due to AEs.

The above results are reassuring that rarely do serious liver abnormalities occur in patients using low dose. Other novel non-invasive methods are under investigation to detect hepatic injury and fibrosis. As an example, ultrasound-based transient elastography has been used in preliminary studies of patients receiving MTX for inflammatory arthritis, psoriasis, and gastroenterologic disorders but has not been evaluated for its utility in monitoring patients with RA receiving MTX in clinical practice[31].

Recommendations dictate that, in patients on a stable dose of MTX, monitoring at an interval of every 8 to 12 weeks is appropriate after three months of therapy and monitoring every 12 weeks can be performed beyond six months of therapy. Liver biopsies are no longer recommended on all patients on MTX but only done based upon the presence of risk factors for hepatotoxicity[32]. A pre-treatment biopsy is considered only for patients with a history of excessive prior alcohol consumption, persistently abnormal baseline AST values, or chronic hepatitis B or C infection [32].

Pulmonary abnormalities

The incidence of pulmonary abnormalities remains low. A systematic review on 21 prospective studies reported that only 15 (0.43%) out of 3463 RA patients on MTX treatment on follow up for 36.5 months developed MTX pneumonitis[33]. The authors concluded MTX pneumonitis be considered as an acute hypersensitivity reaction, occurs early in the course of MTX, thus it does not seem to be a problem of long-term treatment by MTX. Factors that have been associated with MTX- induced lung injury include higher weekly doses of methotrexate, preexisting interstitial lung diseases, abnormal pulmonary function tests prior to therapy, decreased elimination of methotrexate (e.g., as seen in renal insufficiency or with the presence of third-space fluid collections such as ascites), hypoalbuminemia (either before or during therapy), diabetes mellitus previous use of disease-modifying antirheumatic drugs, cigarette smoking, and low body weight[34]. The mechanism by which some of these factors may confer excess risk is unclear. There is data supporting hyperinsulinemia, which may occur with treatment for diabetes mellitus, is associated with increased polyglutamation of methotrexate. The previous use of disease-modifying antirheumatic drugs may be a marker for more severe rheumatoid arthritis, and hypoalbuminemia could potentially result in a lower degree of protein binding and higher free levels of methotrexate[34-36]. The acute presentation typically includes fever, chills, malaise, nonproductive cough, dyspnea, and chest pain; the subacute presentation is characterized by a more insidious onset of dyspnea, cough, and fever. The majority of patients who develop methotrexate pulmonary toxicity do so within the first year of therapy[33].

Myelosuppression

This is commonly seen when using MTX in high doses. With low dose MTX therapy, anaemia, neutropenia and lymphopenia are the commonest abnormalities encountered in RA. Thrombocytopenia is rare now that Felty's syndrome isn't common[37]. A more serious problem is pancytopenia which has been associated with elderly, those with concomitant use of dihydrofolate reductase inhibitors, and patients with renal impairment[38].

In a study by Bird *et al*[30] where they reported a lower incidence of neutropenia rate of neutropenia was higher in patients not taking MTX, than those taking MTX as monotherapy. They defined neutropenia as neutrophil count of < 2.0 x 10^9/L and found that 2.3% of the MTX monotherapy group, 5.5% of the LEF monotherapy group, 3.9% of the MTX/LEF combination group and 4.2% of the group taking neither drug. They however concluded that these values did not correspond to an increased incidence of infection.

Guidelines recommend that a routine peripheral complete blood count should be performed every four weeks during the first three months of therapy, every 8 to 12 weeks from three to six months, and every 8 to 12 weeks thereafter, depending upon the nature and/or severity of abnormalities noted during monitoring[32].

Risk of malignancy

The incidence of cancer and mortality by cancer are slightly higher in RA cohorts as compared to the general population[39,40]. Hematopoietic and lung cancers make up the majority of numbers[39]. Rarely, lymphoproliferative "malignancies" may develop after long-term therapy but regress spontaneously after MTX is withdrawn. They are usually of B-cell origin and some are associated with latent Epstein Barr virus infection[41]. Chemotherapy should be withheld until MTX has been stopped, since some of these tumours regress within four weeks after MTX has been discontinued. Continued vigilance is necessary in those who regress, since relapse has been reported[42,43]. Drug therapy does not confer a direct risk to developing cancer. A Canadian study of 23810 patients followed up between 1980 - 2003 reported 619 haematological malignancies (lymphoma in 346, leukaemia in 178 and myeloma in 95). Analysis performed to assess the effect of DMARD therapy showed that the unadjusted ratios for haematologic malignancy after drug exposures 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)[44]. There is an increased risk for malignancy, but the above data reassures that the numbers are still low.

Conclusion

Methotrexate is still the anchor for rheumatoid arthritis management. Clinical trial results indicate that weekly low dose MTX is generally safe and effective in the treatment of RA. Factors predictors of good response to MTX are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and HLA-DRB1 shared epitope (SE)-negativity. It has advantages in long term treatment due to cost and is generally well tolerated due to its favourable adverse effect profile. The most commonly observed side effects of MTX at doses typically used for the treatment of RA are rarely life-threatening. Folate supplementation has been shown to lower the risk of adverse events. Physicians need to know the risks associated with its use and monitor accordingly.

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