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Title: Methotrexate for osteoarthritis: what does the evidence say?

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Abstract

Osteoarthritis (OA) is a leading cause of disability worldwide, characterised by chronic pain and reduced quality of life. Despite its prevalence, pharmacotherapy options remain limited. Inflammation has emerged as a promising target, with anti-inflammatory agents used in other rheumatological conditions, such as methotrexate (MTX), being explored for OA treatment. MTX is a cornerstone therapy in rheumatoid arthritis (RA), owing to its broad immunomodulatory properties and well-established clinical efficacy. This review summarises evidence from seven randomised controlled trials and two observational studies investigating MTX in knee and hand OA. Studies varied considerably in terms of sample size, study population, MTX dosage and follow-up duration. Overall, study outcomes were conflicting in terms of MTX effect on OA symptoms. However, trials with larger sample sizes and higher MTX doses (>15 mg/week) consistently reported benefits for pain in knee and hand OA, with a favourable safety profile, supporting MTX as a a potential OA treatment. There is still a need for further research to refine dosing strategies, assess longer term use and evaluate cost-effectiveness. Given the complex heterogeneity of OA, stratification by OA phenotype, particularly consideration of local and systemic inflammation, may also be important to underpin selection of a population most likely to respond to MTX treatment. Considerations for the use of MTX in older adults, where comorbidities and polypharmacy may impact use, will also be essential for clinical implementation.

Key points:

- Methotrexate (MTX) shows promise in osteoarthritis (OA) treatment, with higher doses (>15 mg/week) linked to pain reduction.
- The heterogeneous nature of OA necessitates phenotype-based treatment strategies. Consideration of local and systemic inflammation will be important to identify patient subgroups most likely to benefit from MTX.

- Further research is needed to optimise dosing protocols, assess long-term efficacy, evaluate cost-effectiveness, and address considerations for use in older adults with comorbidities and polypharmacy.

1 Introduction

Osteoarthritis (OA) is a major contributor to global disability and diminished quality-of-life, affecting over 500 million people and accounting for approximately 2.19% of all years lived with disability (YLDs) [1]. The knee is most commonly affected, with the lifetime risk of developing symptomatic knee OA estimated at 45% [2]. Prevalence is rising, driven by aging populations and increasing obesity rates, with projections indicating a 74.9% increase in knee OA by 2050 [3]. Clinically, OA is characterized by joint pain, stiffness, and functional impairment. Pain, the most debilitating symptom, affects up to 80% of individuals and limits daily activities in approximately 25% [4]. Symptoms often precede radiographic changes and may fluctuate over time.

Despite its burden, therapeutic options remain limited, and efforts to develop disease-modifying treatments have not yet resulted in a licensed therapy. Current management strategies primarily rely on non-pharmacologic approaches aiming at symptom relief, with first-line interventions including patient education, structured exercise programmes, and weight reduction. However, adherence and access remain suboptimal. Pharmacologic therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids, offer pain relief but are constrained by modest and short-term efficacy, and potential adverse effects. Many patients continue to experience persistent pain despite standard care and rising joint replacement rates highlight the inadequacy of current treatments in altering disease trajectory and symptom progression.

Traditionally, OA is viewed as a "wear-and-tear" condition, however, more recently, it has been recognized as a more complex, heterogeneous, whole-joint disease, with multiple causative factors resulting in several clinical phenotypes underpinned by a spectrum of molecular endotypes [5]. Various phenotypes have been proposed, including an inflammatory phenotype characterised by synovitis, which contributes to the symptoms and pathophysiology of progression in OA. Synovitis (detected by MRI, rather than clinically) can occur early in OA

development, with synovial infiltration of immune cells releasing pro-inflammatory cytokines that initiate and maintain a vicious cycle of tissue damage [6]. Synovitis and the activation of macrophages have been shown to correlate with cartilage loss, osteophyte formation, the severity of OA-related pain, loss of joint function and the likelihood of joint replacement [7]. In addition to local inflammation within the OA joint, low-grade systemic inflammation has also been suggested to play a role in OA pathogenesis, with biomarkers of systemic inflammation, such as highly-sensitive C-reactive protein (hsCRP) being directly associated with OA symptoms and progression [8, 9]. Systemic inflammation is also linked to a metabolic-syndrome phenotype [10], associated with obesity and comorbid conditions including hypertension and cardiovascular disease [11].

As our understanding of OA pathophysiology has evolved, numerous clinical trials have attempted to target specific phenotypes. Within the inflammatory phenotype, synovitis has been identified as a potentially promising target. Repurposing anti-inflammatory agents utilised in other rheumatological conditions has gained interest. Methotrexate, an immunomodulatory and anti-inflammatory agent effective in rheumatoid arthritis (RA), has therefore been explored as a potential OA treatment. This review evaluates the current evidence supporting the use of methotrexate in OA.

2 Mechanisms of Action of MTX in Rheumatoid Arthritis

Methotrexate (MTX) is a synthetic folate antagonist with antiproliferative, antimetabolic, and anti-inflammatory properties, originally developed as a chemotherapeutic agent. MTX inhibits dihydrofolate reductase (DHFR), reducing nucleotide synthesis and exerting anti-proliferative effects. In the 1980s, MTX was repurposed at lower doses for RA, a chronic form of arthritis characterized by persistent synovial inflammation, hyperplasia, and progressive joint destruction and associated with autoantibodies [12]. “Low-dose” MTX (compared to traditional cancer chemotherapeutic doses) therapy (typically 15-25 mg weekly) is associated with significant improvements in RA symptoms, including reductions in joint pain, stiffness,

swelling, and radiographic progression [13]. Its efficacy is now well-established, and MTX is considered the first-line treatment for RA, administered either as monotherapy or in combination with other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as hydroxychloroquine, sulfasalazine, and leflunomide. In more severe disease, MTX is used in combination with biological DMARDs such as tumour necrosis factor (TNF)-α inhibitors; or targeted synthetic DMARDs. MTX is also used in other inflammatory diseases such as vasculitis and polymyalgia rheumatic as a corticosteroid-sparing drug. Approximately one-third of patients achieve low disease activity with MTX monotherapy, with an additional 30% benefitting from combination therapy [12, 14, 15]. Even in cases of inadequate monotherapy response, MTX is typically continued alongside biologics, as evidence suggests improved outcomes, including reduced joint replacement rates [16-18] and decreased resistance to biologic agents [19].

The anti-inflammatory mechanisms of MTX in RA are multifaceted and not yet fully elucidated. Emerging evidence highlights several biochemical and cellular pathways, as well as distinct effects across immune and stromal cell types, many of which diverge from its classical antifolate activity. A key pathway involves inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase/inosine monophosphate cyclohydrolase (ATIC), leading to intracellular accumulation of AICAR and elevated extracellular adenosine. Adenosine, (via cell surface purinergic receptors A2A and A3), suppresses pro-inflammatory cytokines (e.g., tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-6), promotes anti-inflammatory cytokines (e.g., IL-10) [20] and inhibits the activation of nuclear factor-κB (NF-kB). MTX also downregulates matrix metalloproteinases (MMPs) and adhesion molecules such as E-selectin and VCAM-1, limiting immune cell infiltration, and antagonizes the mitogenic effects of platelet-derived growth factor (PDGF) and interleukin-1β (IL-1β), restoring expression of tumour suppressor genes such as limb bud and heart development *(LBH),* p21 (*CDKN1A)*, and p53 (*TP53*), and inducing G1 phase cell cycle arrest [21, 22]. Adenosine's

central role is supported by animal studies, with MTX-mediated adenosine accumulation reversed by adenosine receptor antagonists [23].

MTX reduces tetrahydrobiopterin (BH_4) levels, a nitric oxide synthase (NOS cofactor), leading to NOS uncoupling, reactive oxygen species (ROS production), and activation of JUN N-terminal kinase (JNK), p53 and p21, enhancing apoptosis sensitivity and inhibiting NF-κB [15, 24, 25]. Recent data also implicate MTX in the regulation of long non-coding RNAs via DNA-dependent protein kinase (DNA-PK) activation, including inducing expression of long intergenic non-coding RNA p21 (lincRNA-p21), which binds the RELA proto-oncogene (NF-κB Subunit, RELA) mRNA and suppresses NF-κB activity.

In addition, MTX modulates the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, inhibiting JAK1–STAT3 and JAK2–STAT5 signalling in macrophages and other immune cells. This inhibition appears to be folate-independent and cell-type specific [26]. Paradoxically, MTX has been shown to induce pro-inflammatory cytokines such as IL-1 and IL-6 in a human monocytic cell-line and promote apoptosis, potentially explaining how MTX may contribute to adverse effects including mucositis and pneumonitis [25, 27-29]. MTX also inhibits the enzyme methionine-adenosine transferase, hence reducing the availability of the methyl donor for DNA-methylation. Mechanistically, MTX is therefore believed to exert its effects at several levels by interfering not only with DNA-synthesis, but also with DNA-methylation (possibly associated with the dosage used), hence having potential effects on resetting gene expression programmes. Global DNA-methylation levels are reduced with MTX response, but individual CpG sites showed more gene specific responses [30-33].

Through these diverse mechanisms, MTX remains the corner stone of early treatment in RA, suppressing inflammation, mitigating synovitis and protecting against bone and joint destruction. Its use has also been extended to other autoimmune arthritides, including

psoriatic arthritis and systemic lupus erythematosus. With increased understanding of the role of synovitis in OA symptoms and disease progression, MTX is therefore a major candidate for evaluation in OA.

3 Clinical evidence for the use of methotrexate in osteoarthritis

Two recent systematic review meta-analyses have summarised the evidence for the use of MTX as a treatment for OA [34, 35]. In addition to the 6 trials included in these reviews, we identified one recently published randomised controlled trial (RCT) of MTX in knee OA [36], and two open-label observational studies, one in knee OA and one in hand OA [37, 38]. A summary of all studies is included in Table 1.

3.1 Effect of MTX on OA Symptoms

In total, five RCTs and one observational study focused on knee OA (KOA), while two RCTs and one observational study targeted hand OA (HOA). Considerable heterogeneity exists between these studies, both in terms of methodological design and population characteristics. Sample sizes ranged from 21 to 215 participants, with a cumulative total of over 700 patients. The mean age of participants varied between 52 and 67 years, and in all studies, the majority of participants were female. MTX dosing regimens differed considerably, ranging from 7.5 mg to 25 mg per week, with intervention durations from 2 to 12 months.

3.1.1 Pain outcomes

For KOA, both meta-analyses found that MTX significantly reduced pain in OA patients (for individual trial outcomes, see Table 1). Wong et al. [34] reported a standardised mean difference (SMD) for visual analogue scale/numerical rating scale (VAS/NRS) pain of −0.47 (95% CI: −0.88 to −0.06, $p = 0.024$), indicating moderate efficacy (at or above that of NSAIDs). Queiroz et al [35] corroborated these findings, noting significant NRS pain reduction for KOA at 6 months but not at longer follow-up intervals. Western Ontario and MacMaster Universities Arthritis Index (WOMAC) pain scores showed inconsistent results in both meta-analyses, with

high heterogeneity and limited statistical significance. In the recent RCT, Zhu et al [36] found no significant difference in either pain outcome with 15 mg/week MTX treatment compared to placebo arms, whilst the KOA observational study reported a significant reduction in VAS and WOMAC pain at 6 months with 20 mg/week MTX. Differential responses using NRS and WOMAC have been reported before in other trials, and it is possible given the different questions employed that these tools measure slightly different constructs of OA pain or have different thresholds for efficacy. A recent meta-epidemiological study indicated that the VAS pain score may demonstrate marginally greater sensitivity compared to the WOMAC pain subscale [39].

For HOA, Wong et al [34] reported similar efficacy to KOA in terms of VAS pain, with a SMD of −0.36 (95% CI: −0.67 to −0.05, $p = 0.022$), however Queiroz et al [35] found no significant differences in VAS pain for HOA. A significant reduction in pain VAS was noted by Pavelka et al [37], following 2 months treatment with 10 mg/week MTX.

3.1.2 Functional outcomes

Data reported were mixed. For KOA, Wong et al. [34] observed significant improvement in WOMAC function scores in KOA (WMD −7.36, 95% CI: −14.34 to −0.38, $p = 0.045$). However, Queiroz et al. [35] found no consistent effect across studies. Similarly, in the separately reported RCT and observational study, no significant effects on function were observed. For HOA, the two RCTs and one observational study did not identify significant functional gains, with FIHOA and AUSCAN scores showing minimal change with treatment.

For KOA, only Queiroz et al. [35] evaluated stiffness outcomes, finding significant improvements in WOMAC stiffness scores at 6 months (MD −0.78, 95% CI: −1.18 to −0.39) and at study endpoints (MD −0.62, 95% CI: −0.99 to −0.25). For HOA, a statistically significant improvement in AUSCAN stiffness was reported in the RCT by Wang et al, as well as the observational study [37, 40].

3.1.3 Quality of life (QoL)

QoL outcomes were assessed in two KOA studies. Wong et al. [34] reported no significant differences between MTX and placebo groups (SMD −0.74, 95% CI: −1.53 to 0.05, $p = 0.07$), with high heterogeneity. Queiroz et al. [35] noted a transient improvement in SF-12 scores at 6 months in one KOA RCT, but this was not sustained. Overall, evidence for QoL improvement with MTX treatment remains weak.

3.2 Effects of MTX on Inflammation in OA

3.2.1 Imaging-assessed synovitis

The clinical efficacy of MTX in RA is associated with a reduction in imaging-detected synovitis. Two of five KOA RCTs included imaging-detected synovitis as an inclusion criterion, one defined by US [41] and the other by MRI [36]. Kingsbury et al [42] did not use an imaging-detected synovitis phenotype for participant selection, although did incorporate an MRI substudy. No relationship between baseline imaging-assessed synovitis/effusion and treatment effect was reported in any of the three studies, whilst in the two RCTs which included follow-up MRI assessment, MTX treatment was not associated with significant change in synovitis/effusion volume compared to placebo. The observational study, which used US-synovitis as an inclusion criterion, similarly reported no change in US-synovitis associated with MTX treatment.

In HOA, one study (Ferrero et al) [43] included MRI-assessment of synovitis at baseline and follow-up. Despite inclusion requiring >1 joint with radiographic erosion, MRI-detected synovitis was only observed in 29 of 1024 assessed joints at baseline. Perhaps related to this frequency of synovitis, there was no significant effect of 10 mg MTX treatment on synovitis. In the MTX group, although the study had a negative symptom/pain outcome, joints showed a significantly greater transition to the radiographic remodelling phase over 12 months, and joints exhibiting space loss appeared to undergo less erosive progression. The progression

from an erosive to a remodelling phase is characteristic of the natural history of erosive HOA, with evidence suggesting that the remodelling phase typically follows the resolution of inflammation [44, 45]. A well-established association between inflammation and erosive changes exists in other inflammatory rheumatic diseases, and similar mechanisms may operate in HOA, though a larger study would be required to evaluate this. In the other two HOA studies, which both required evidence of inflammation for inclusion (MRI-confirmed synovitis of grade ≥1 in at least 1 joint for the RCT by Wang et al [40] and at least one clinically swollen proximal interphalangeal (PIP) joint for the observational study [37], symptomatic improvement with MTX was reported. Whilst measurement of synovitis was not included as an outcome measure, these findings support the hypothesis that MTX may be effective in treating HOA pain and active synovitis.

3.2.2 Inflammatory biomarkers

Only three studies reported biomarker data. A post-hoc analysis by Kingsbury et al [42] reported a significant MTX treatment interaction in patients with elevated baseline hsCRP, perhaps suggesting a systemic anti-inflammatory effect in a subset of patients. In addition, changes in the levels of various inflammatory markers (C3M, TNF-α, IL6, IFN-γ, hsCRP) were associated with MTX treatment. Ghosh et al [46], in KOA, noted a significant reduction in mean serum ESR and CRP levels associated with MTX, although did not correlate this with symptom response. In the observational HOA study, a non-significant trend for a decrease in CRP following treatment with 10 mg MTX for 2 months was observed. These studies provide further evidence that MTX may exert an anti-inflammatory effect in OA, and that in a subset of people, this may be associated with an effect on OA symptoms. Future trials may incorporate the measurement of inflammatory markers to define a trial population more likely to respond to treatment.

3.3 MTX dosing and duration

MTX is used at doses up to 25 mg per week in RA, with a known dose-response, and it is known to take many weeks (12-15 or more) to manifest its full antirheumatic effects [13]. A dose-response relationship may be at play in OA as well, with lower doses of MTX and short duration of treatment being insufficient to produce detectable clinical benefits in OA. Ferrero et al. [43] used a 10 mg/week dose in patients with erosive hand OA for 12 months and found no benefit in pain, function, or structural outcomes. In the trial by Zhu et al [36], which administered up to 15 mg mg/week for 6 months, there were also no significant improvements in pain or function, although a trend toward symptom improvements was noted in participants with severe pain (VAS ≥ 80mm). These findings contrast with studies employing higher doses, such as Kingsbury et al. [42], which escalated MTX to 25 mg/week (for 12 months), and observed statistically significant symptom relief at 6 months with a mean reported dose of 20.2 mg, and Wang et al. [40], which used 20 mg/week (for 6 months) and reported clinically meaningful reductions in pain and stiffness in HOA with MRI-confirmed synovitis. Kingsbury et al [42] also noted an enhanced treatment effect in both a treatment adherence analysis (with adjustment based on a priori definition of adherence of <4 missed weekly doses in 3 months) and an exploratory complier average causal effect analysis, that adjusted for mean recent dose ≥17 mg MTX/week, whilst at 12 months when the mean dose dropped to 16.9 mg the treatment effect was no longer significant. These observations support the hypothesis that MTX's therapeutic effect in OA may be dose-dependent, with higher doses of 20 mg/week or greater more likely to achieve the anti-inflammatory threshold necessary for clinical improvement. However, long-term use of MTX at these doses may be limited by reduced adherence linked to intolerance, with studies in RA suggesting increased intolerance with higher MTX dosage of 15 mg/week or greater [47].

3.4 Safety Profile

The long-term safety profile of methotrexate (MTX) in RA is well established, alongside folate supplementation to reduce minor side effects. In a systematic review of 88 studies involving MTX monotherapy, discontinuation due to toxicity ranged from 10–37%, with 72.9% of patients

experiencing at least one adverse event (AE) over an average of 36.5 months, predominantly gastrointestinal symptoms and elevated liver enzymes [48]. Adverse event data from the OA MTX studies, suggests similar AE profiles in an OA population. Wong et al. [34] reported no significant increase in AEs (RR 0.88, 95% CI: 0.75 to 1.02) or serious adverse events (SAEs, RR 1.57, 95% CI: 0.37 to 6.78) between MTX and placebo, whilst Queiroz et al. [35] reported similar findings, with gastrointestinal symptoms being the most common AEs. Only two RCTs reported SAEs, with similar distribution across MTX and placebo arms, and none treatment-related. Consistent with data in RA, common AEs observed in these studies were nausea, vomiting and loss of appetite, and abnormal liver enzyme profiles, with slightly higher incidence in MTX groups compared to placebo. Overall, most AEs were mild and self-limiting. In the meta-analysis by Wong et al [34], no significant difference was found in the withdrawal rate due to AEs (RR, 1.75; 95% CI, 0.65 to 4.72, P = 0.27) and no treatment-related deaths were reported. As per standard treatment regimens for RA, all but one of the OA trials included concomitant folic acid use (at varying doses) to reduce MTX-related hepatotoxicity.

4 Potential mechanisms of action of MTX in OA

Given the broad immunomodulatory effects of MTX in RA, and the heterogeneous pathological processes underlying OA, MTX likely acts through multiple biochemical and cellular pathways (Figure 1). Inflammation in OA is typically chronic and low-grade, with modest elevations in inflammatory plasma proteins and less pronounced synovial histopathology than RA [49]. While cellular profiles differ between OA and RA in terms of severity, synovial infiltration of macrophages and T- or B-cells as well as their organisation in tissue architecture (aggregates or germinal-like centres), and autoantibody production are observed in both diseases [50, 51].

No studies found a correlation between imaging-detected synovial volume changes and treatment response. Similar findings in trials of intra-articular corticosteroids and knee brace in OA suggest clinical benefit may occur independently of measurable changes in the volume

of synovial hyperplasia in OA [52, 53]. The absence of a direct association between morphologic synovial volume reduction and clinical symptomatic response therefore does not exclude the possibility of sub-morphological anti-inflammatory effects of MTX on synovitis. In the PROMOTE trial [42], serum C3M (a biomarker of type III collagen degradation) was significantly reduced in the MTX group compared to placebo [54]. Turnover of type III collagen, a key component of the synovial membrane, is upregulated during inflammatory processes, tissue repair, and synovitis [55]. Elevated systemic C3M levels in RA reflect active synovial tissue remodelling and are known to decline following treatment with IL-6 receptor antagonists [56, 57]. However, as discussed below, the effects of MTX on pain may be mediated by systemic rather than local factors.

In erosive HOA, imaging findings (limited to a single study) suggest MTX may facilitate progression from the erosive to the remodelling phase, indicating a potential localized anti-inflammatory effect of MTX, possibly promoting bone repair and reducing the duration of the erosive phase. Similar structural benefits have been reported with TNF-α inhibitors in erosive OA, where modulation of inflammation was associated with improved joint structure, though not with benefit on symptoms [58, 59].

Animal studies suggest MTX may also modulate neuroinflammation and neurotrophin-mediated pain processing. In a rat OA model, oral administration of MTX improved pain-related behaviours and inhibited the upregulated mRNA expression of transient receptor potential cation channel, subfamily V, member 1 (TRPV-1) and brain derived neurotrophic factor (BDNF) in the dorsal root ganglia and nerve growth factor (NGF) in knee joint tissue [60]. TRPV1 has been highlighted as a potential target for OA pain treatment, with preclinical data suggesting a key role in maintenance of established OA pain [61].

Although chronic, low-grade inflammation in OA is well-established, postulated to be the result of interactions between the immune system and factors including local tissue damage and

metabolic dysfunction, the interplay between systemic and local inflammation remains unclear. Systemic inflammatory markers such as hsCRP are linked to increased OA pain, supporting a role for both local and systemic inflammatory processes in joint nociception, but further work is needed to fully define the molecular pathways mediating the low-grade inflammation in OA. Notably, the study populations of Kingsbury and Wang [40, 42] which both demonstrated significant symptom effects in response to MTX, had higher mean BMIs compared to the two large RCTs (Zhu, Ferrero), that failed to show a treatment effect [36, 43]. Taken together with the post-hoc analyses from the CANTOS trial, which enrolled individuals with elevated hsCRP, and showed reduced incident total joint replacements and OA-related adverse events following IL-1β inhibition over 3.7 years [62], these findings suggest that systemic inflammation associated with metabolic dysfunction and obesity, may contribute to OA pathophysiology and symptom burden. The presence of systemic inflammation may identify an OA subset more likely to respond to treatment with anti-inflammatory therapies such as MTX.

CRP is produced by the liver in response to pro-inflammatory cytokines including IL-6, IL-1β or TNF-α. Reductions in IL-6 and TNF-α were associated with pain relief in PROMOTE [42], while Ferrero et al. [43] reported that IL-6 expression was linked to a higher risk of erosive progression. TNF-α is associated with OA disease progression [63, 64], and is a known MTX target in RA. Although TNF-α inhibitor trials in OA have failed to demonstrate efficacy, subgroup analyses in erosive hand OA suggest modest symptomatic and structural benefits in patients exhibiting active inflammation [65]. Both TNF-α and IL-6 contribute to bone remodelling by promoting osteoclast and osteoblast differentiation, both processes modulated by interferon-gamma (IFN-γ). MTX has been shown to activate the IFN-γ receptor signalling cascade in osteoclasts, enhancing osteoclastogenesis and mitigating glucocorticoid-induced bone loss. Additionally, MTX suppresses intracellular IFN-γ production in helper T-cells, further influencing inflammatory and bone turnover pathways [66]. Findings from the PROMOTE [42] study support the involvement of these pathways in MTX's clinical effects in OA. Reductions in IL-6 and TNF-α levels were associated with pain improvement, and greater pain reduction

was observed in individuals with higher baseline IFN-γ. These data suggest that MTX may exert therapeutic effects in OA through modulation of multiple inflammatory mediators, including TNF-α, IL-6, and IFN-γ, particularly in patients with an inflammatory phenotype.

5 Challenges of MTX use in an OA population

Whilst AE profiles appear similar within the context of published RCTs, the OA population is in general older than the RA population, with increased associated comorbidities and polypharmacy which may require additional considerations for the use of MTX. The mean age across the OA clinical trials included in Wong et al's [34] meta-analysis was 59 years, however UK general practice data indicates that 34% and 8% of OA patients are aged ≥75 years and ≥85 years, respectively [67]. Previous reports have highlighted the under-representation of the elderly in OA clinical trials[68], raising the question of generalisability of trial findings to these populations. Comorbidities are highly prevalent in people with OA and increase with age [69]. Approximately two-thirds of individuals with OA have at least one comorbidity, and one-quarter have three or more. A recent systematic review meta-analysis found the most prevalent comorbidities to be hypertension and dyslipidaemia, with pooled prevalences of 50% and 48% respectively, whilst the prevalence of cardiovascular disease was 56% higher in those with OA than in those without [70]. The pooled prevalence of renal disease, which may preclude MTX use, was 6%. Depression, anxiety, and gastrointestinal disorders were also frequently reported. OA is also associated with increased mortality, primarily through cardiovascular and metabolic comorbidities [71].

From a clinical perspective therefore, the enhanced risk of toxicity associated with common OA comorbidities and related polypharmacy, as well as potential drug interactions that may reduce MTX efficacy, need careful consideration. For example, long term angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, used for the treatment of conditions including hypertension and coronary heart disease, NSAIDs and proton pump inhibitors (lansoprazole, omeprazole or pantoprazole), can reduce renal

clearance of MTX and increase the risk of MTX toxicity. Concomitant use of statins (for example, atorvastatin or simvastatin) may increase the risk of liver toxicity. Further considerations include enhanced risk of MTX-associated pulmonary toxicity in patients with comorbid Chronic Obstructive Pulmonary Disease (COPD).

Conversely, contraindications to other OA therapies, such as NSAIDs, is commonplace in OA patients, and in these populations MTX may represent an attractive alternative. For example, the use of NSAIDs is contraindicated to the majority of elderly patients due to comorbidities. A study of low-dose MTX (7.5mg/week) use with a mean age of 78.8 years with RA reported an acceptable AE profile and concluded that with routine blood monitoring, MTX was a safe treatment option for the elderly RA population [72]. For the more elderly OA patients, consideration of reduced dosing may be necessary.

6 Conclusion and future considerations

MTX remains the cornerstone in the treatment of RA due to its broad immunomodulatory properties and well-established clinical efficacy. Whilst trial evidence for the use of MTX in OA remains limited by the heterogeneity in dosing regimens, short follow-up durations, and variability in study populations, studies with better design, including sample size greater than 50 per arm and doses over 15 mg/week, demonstrate benefits for pain in knee and hand OA, with a favourable safety profile. Future research should explore optional dosing protocols and extended follow-up periods to provide long-term safety, efficacy and cost-effectiveness data, and to understand the impact of comorbidities and polypharmacy. Stratification by OA phenotype, particularly consideration of systemic inflammation, will be essential to identify responsive populations. Considerations for the use of MTX in older adults, particularly in more elderly patients where comorbidities and polypharmacy may be more common, are also important. As per standard treatment regimens for RA, concomitant folic acid use should also be considered. Two further trials of MTX, one for erosive hand OA (NCT04579848, estimated completion 12/2026) and one for knee OA with US-synovitis (NCT07161336, estimated

primary completion 07/2026) are currently ongoing, which may yield further insights into MTX's efficacy in erosive hand OA and inflammatory OA phenotypes.

Declarations

Conflicts of interest: MDCF, FP, KF, PGC, SRK have no conflicts of interest related to this article.

Author contributions:

MDCF and SRK conducted the literature review and wrote the first draft of the manuscript. FP, KF and PGC critically revised and added extra text. All authors read and approved the final manuscript.

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Code availability: Not applicable.

Figure 1: Putative pathways for methotrexate effects on OA pathogenesis. Dashed lines represent pathways that have been shown to be involved in methotrexate (MTX) effects in RA, where pathways are also involved in OA pathogenesis. Solid lines represent pathways highlighted as potential modes of action for MTX in OA based on biomarker data from OA trials. ATIC: 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR)

transformylase/inosine monophosphate cyclohydrolase; BDNF: brain derived neurotrophic factor; BH4: tetrahydrobiopterin; C3M: biomarker of type III collagen degradation; DNA-PK: DNA-dependent protein kinase; hsCRP: highly-sensitive C-reactive protein; IL-6: interleukin-6; IFN-γ: interferon-gamma: JNK = JUN N-terminal kinase; lincRNA-p21: long intergenic non-coding RNA p21; MMPs: matrix metalloproteinases; NGF: nerve growth factor; NF-Kb: nuclear factor- κB; ROS: reactive oxygen species; TNF: tumour necrosis factor; TRPV-1: transient receptor potential cation channel, subfamily V, member 1; VCAM-1; vascular cell adhesion protein 1. Figure created in https://BioRender.com

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