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The safety of low-dose methotrexate for rheumatic diseases: looking beyond blood monitoring

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Low-dose weekly methotrexate (MTX) revolutionised clinical outcomes in rheumatoid arthritis (RA) and remains a cornerstone of modern management of RA. MTX blood monitoring protocols, comprising periodic checks of haematological, liver, and renal parameters, are now a familiar part of rheumatology clinical practice, The approved safety information for the UK is hosted on the Electronic Medicines Compendium (medicines.org.uk). However, MTX is not licenced for polymyalgia rheumatica (PMR). The Sponsor of the ongoing randomised clinical trial of MTX in relapsing PMR, STERLING-PMR (ISRCTN17828080), is required to write a detailed Annual Development Safety Update Report, following the E2F guideline set out by the European Medicines Agency EMA/CHMP/ICH/309348/2008, including a summary of all new information about MTX safety since the date of regulatory approval. A scoping review of safety-relevant information was therefore conducted on low-dose MTX, covering 4.10.2023 to 3.10.2024. 1,242 hits yielded 405 abstracts and 131 full-texts were reviewed (Supplementary Information). Drawing on our recent sample of the literature on MTX safety, in this commentary we ask: is it time to update our ideas about how often MTX blood monitoring tests are needed?

The literature review included a study within eight linked administrative databases from Ontario, Canada to identify predictors of early MTX toxicity in patients with renal impairment. They identified a cohort of 4,618 individuals starting either MTX or hydroxychloroquine (HCQ) who had a baseline eGFR<60ml/min/1.73m^2; propensity score matching to control for bias by indication. The primary outcome, serious adverse event during the first 90 days after starting the medication (admission with myelosuppression, sepsis, lung or liver toxicity) was seen in 80/2309 (3.55%) patients starting MTX compared to 40/2309 (1.73%) patients starting HCQ. Overall in the matched cohort 82/4,618 (1.78%) had lung toxicity, 32/4,618 (0.69%) had sepsis, 27/4,618 (0.58%) had myelotoxicity and <6/4,618 (<0.13%) had hepatotoxicity. Lung toxicity (risk difference: 1.39%) and myelosuppression (risk difference: 0.74%), but not sepsis, were significantly more common in MTX users than HCQ users. The risk differences all progressively increased at lower eGFR, and when starting higher doses of MTX (15-35mg weekly). .[1] The study was well-conducted and considered multiple possible sources of bias using a series of sensitivity analyses and a negative control outcome as well as E-value calculation. However, an important limitation was the reliance on administrative codes for outcome ascertainment, which

likely led to over-estimation of outcome event rates; for example, the ICD-10 codes used to define pneumotoxicity included J13 (pneumococcal pneumonia) and various other types of pneumonia.

During the COVID-19 pandemic, the requirement for three-monthly blood monitoring for MTX in rheumatic diseases was relaxed in the UK without reported untoward effects.[2] It has been questioned whether three-monthly monitoring should still be mandatory for all patients on stable doses of MTX, with a risk-stratified approach having been suggested instead.[3] Overly frequent blood monitoring schedules in low-risk patients might be costly, burdensome for patients and could lead to unnecessary breaks in therapy and flares of disease. On the other hand, higher-risk patients may need more frequent blood monitoring. In a study of patients on stable MTX therapy for >1 year in UK primary care the major risk factors for MTX discontinuation were CKD, diabetes, and a prior history of abnormal blood monitoring tests.[3]

Well-publicised national patient safety alerts pointed to potential confusion between the different strengths of available tablets that had led to dosing errors; as a result of these patient safety alerts it is recommended in the UK that only the 2.5mg MTX tablets should be prescribed/dispensed, whereas Australian rheumatologists have access to both 2.5mg and 10mg MTX tablets. In the abovementioned study from Ontario, the highest MTX-associated myelosuppression risk was seen in those with eGFR<45 ml/min/1.73m^2.[1] In a case series from Dresden of 12 patients taking long-term, low-dose MTX who were hospitalised with severe myelosuppression, dosing error was suspected in only one patient. [4] All 12 patients in that series were over 70 years old and many had acute kidney injury on admission. Previous routine blood monitoring tests had not identified any concerns. 6 had a prior history of grade 2 CKD and 4 had a history of grade 3 CKD.[4]

Daily dosing of MTX can lead to an acute MTX toxicity syndrome within 2 weeks (Figure 1). Case reports of MTX toxicity tend to feature concurrent severe myelosuppression and acute kidney injury, frequently accompanied by sepsis and/or mucocutaneous ulceration and rapid physical deterioration. Patients often had pre-existing CKD, and some were taking loop diuretics, highlighting that MTX may accumulate in third-space fluids (Figure 1). MTX is excreted via the kidneys; the

most consistent risk factor for MTX-related adverse effects in the studies identified was CKD.

It is important for readers to be aware of the potential for differential risks of drug toxicity that may arise from differences in genome or exposome (genetic or environmental backgrounds). RA is known to be associated with lymphoproliferative disease (LPD), but a subset of RA-LPD may be driven by MTX therapy; typically regressing after MTX cessation, without the need for chemotherapy. This has been labelled MTX-LPD and is mainly reported in the Japanese literature. Almost all cases of MTX-LPD arise in the context of RA.[5] The phenotype of MTX-LPD can range from a non-lymphomatous clonal expansion of lymphocyte subsets, that may not be discovered without extensive haematological testing, to macrophage activation syndrome with pancytopenia.[6]

Not all adverse effects are detected by blood monitoring. MTX has been reported to cause an osteopathy of lower limbs characterised by “meandering stress fractures”. This is mainly described in the European literature; reports remain rare, but it could be under-recognised.[7] MTX osteopathy presents with pain in lower limbs on weight-bearing, precipitated by minimal or no trauma; patients may have normal plain radiographs in which case diagnosis requires CT or MRI scans. The pain of MTX osteopathy is reported to improve following MTX cessation.[8]

For younger patients with normal renal function, three-monthly blood monitoring for MTX in might be more frequent than needed; but for patients with chronic kidney disease, enhanced monitoring might be considered. Safe MTX therapy is not only about getting blood tests on schedule; it is also about responding appropriately to intercurrent illness. Drug safety is not a property of a drug in isolation, but also a function of the context in which it is given, including the ability to detect changes in patient health status. In future, remote monitoring of rheumatic diseases and their treatments might also incorporate technologies such as biosensors, wearables or point of care blood testing targeted towards individuals at greater risk. MTX therapy is part of everyday practice in rheumatology and it is important that we continue to take safe MTX prescribing seriously, utilising all the tools available to us.

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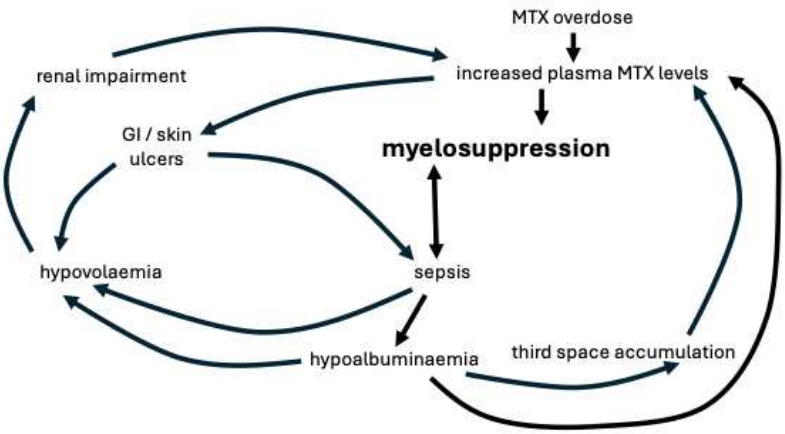
Data availability statement:
For transparency, all data underpinning this commentary has been included as Supplementary Information.

Figure 1.



Title and legend to Figure 1.
Acute methotrexate toxicity syndrome: interplay of infection and renal dysfunction most often triggered by intercurrent illness and/or dosing errors such as daily dosing. An illustration of themes identified from the one-year sample of case reports, including: C Barros TR, Ribeiro YP, Oliveira VC Jr, A Lopes M. A Case of Severe Organ Dysfunction and Skin Lesions Due to Methotrexate Toxicity. Cureus. 2024 May 9;16(5):e60008; Sawant R, Chaudhari P, Bardiya NA, Acharya S, Kumar S. From Treatment to Tragedy: Severe Methotrexate Toxicity With Mucocutaneous Ulcers, Myelosuppression, and Nephropathy. Cureus. 2024 Apr 8;16(4):e57797; Javed K, Wijeratne R, Bandaru SK. The Unseen Danger of Methotrexate Toxicity. J Community Hosp Intern Med Perspect. 2023 Nov 4;13(6):39-42; Abouzahir H, Belhouss A, Benyaich H. Acute methotrexate toxicity in a patient with psoriasis: a case report. Pan Afr Med J. 2024 Jan 17;47:19; Surapaneni D, Dasi SC, Sam N, M J. Methotrexate Toxicity-Induced Pancytopenia and Mucocutaneous Ulcerations in Psoriasis. Cureus. 2024 Aug 5;16(8):e66222; Akhdar G, Akpan I, Myles A, Atencah SE. Single Low-Dose Methotrexate and Vitamin B12 Deficiency-Induced Pancytopenia Causing Fatality: A Case Report. Cureus. 2024 Jun 30;16(6):e63528; 38277521.

Alt-text: A diagram composed of text and arrows summarising some mechanisms involved in acute methotrexate toxicity syndrome.

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