We read with interest the paper by Karie et al. [1]. We wish to highlight an issue regarding MTX prescribing and toxicity in chronic kidney disease (CKD) in patients with RA and report a case that has changed clinical practice in our unit [2].

A 77-yr-old female with a 40-yr history of RA, was stable on MTX therapy (original dose 15 mg once weekly). Following a gradual rise in serum creatinine (up to 170 µmol/l) MTX was stopped. It was later restarted at lower dose at the patient’s request (following a consultant renal physician opinion and investigations including the cause of the renal impairment). Her disease was then well controlled on a low dose of MTX 10 mg once a week. Other disease-modifying drugs (DMARDs) were considered but had failed in past. At the MTX restart her estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft–Gault formula to be 24 ml/min (Stage 4 CKD, creatinine 200 µmol/l). The patient went on to regular blood monitoring over the next 15 months on 10 mg MTX once weekly with a normal full blood count and stable renal function. She was admitted with non-specific malaise having had diarrhoea ~2 weeks earlier. Parameters recorded 16 days prior to her admission revealed a normal full blood count (white blood cell, differential platelet count) and static renal function. Her admission blood tests revealed a pancytopenia, with an admission creatinine of 196 µmol/l. There had been no dosing error (tablet count), no new concomitantly prescribed medications and the tablet strength was checked by the hospital pharmacy. Bone marrow biopsy showed evidence of bone marrow failure with no other specific diagnostic features.

Despite intravenous folinic acid, anti-microbial treatment and multi-organ support treatment in our Critical Care unit she died 7 days into her admission. Post-mortem showed no other major abnormalities and cause of death was reported as MTX toxicity.

Although there is limited published data on MTX clearance in CKD, trial data suggests that with an eGFR of <45 ml/min the expected h level for a 10 mg dose is 0.11 µmol/l, with a half-life (t1/2) of 22 h [3]. On admission, the free MTX level (30 h post dose) was 0.13 µmol/l. We presume that the episode of diarrhoea and vomiting prior to her admission had resulted in dehydration with a subsequent drop in renal clearance of MTX, leading to MTX/metabolite accumulation and subsequent toxicity.

This case highlights the dangers of MTX in CKD, even at reduced dose, and what can be falsely reassuring blood monitoring leading up to an adverse event. Following on from this experience we have instigated a number of changes to our clinical practice.

First, we now give written advice to all patients on MTX who have a significant inter-current illness, particularly those with CKD, to omit MTX until a full recovery has ensued. This will hopefully reduce accumulation of MTX and toxicity.

Second, we have arranged for the EGFR [calculated by the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation as recommended by the UK Chronic Kidney Disease Guidelines] to be added to our computerized DMARD blood monitoring system. We are also asking for routine EGFR measurements on all our patients on blood monitoring for MTX.

Finally, we have reviewed our computerized monitoring system to identify all patients on MTX who have reduced eGFR and we are currently undertaking a case note review. To date, we have identified 18 patients with CKD Stage 4 (of 879 patients on MTX) under follow-up in our unit, on a reduced dose of MTX (the age range is 61–77, prevalence 2%). This is significant as Karie et al. describe no patients with CKD Stage 4 in their study. We suspect MTX is being used more commonly in an increasing elderly group of patients with added comorbidities.

The Renal Association provide both an online calculator for eGFR and have produced helpful online (and downloadable) eGFR tables that are practical and easily used by both Specialist Nurses and Rheumatologists in satellite clinics, etc [4]. This information can be used to make judgements on MTX dosage. There are a number of conflicting sources of advice for MTX dosing in CKD and there is a need for national guidelines for the dosing of MTX in CKD [5, 6].

Disclosure statement: The authors have declared no conflicts of interest.

J. Bateman, R. Penfold, S. P. Rigby
Department of Rheumatology, Warwick Hospital, Warwick, UK
Accepted 10 April 2008

Correspondence to: J. Bateman, Department of Rheumatology, Warwick Hospital, Lakin Road, Warwick CV34 5BW, UK. E-mail: James.Bateman@SWH.nhs.uk


Advance Access publication 25 May 2008

Comment on: Kidney disease in RA patients: prevalence and implication on RA-related drugs management: the MATRIX study

SIR, We appreciated the letter from Bateman and colleagues [1]. The case they report emphasizes the risk of MTX use in patients with reduced renal function. In fact, their patient with a Stage 4 renal insufficiency at baseline presented with an episode of functional acute renal failure due to dehydration secondary to diarrhoea. In this particular patient with baseline deeply reduced renal function, the further reduction in glomerular filtration resulted in accumulation, overdosage of MTX and metabolites, resulting in a severe haematotoxicity. In addition, we had previously collected and analysed 10 cases of severe or even fatal MTX toxicity in end-stage renal disease (ESRD) patients after very low MTX doses (<7.5 mg/week) [2], which further emphasize the risk of MTX in RA patients with renal insufficiency.

There is further evidence on the prevalence of renal insufficiency in RA patients. In our MATRIX study, we identified only one patient with Stage 4 kidney disease (Cockcroft and Gault...
formulas) among 106 RA patients treated with MTX (0.9%). Bateman and colleagues reported a prevalence of around 2% of Stage 4 kidney disease among a population of 879 RA patients treated with MTX. As a result, the estimation of renal function on a regular basis in patients with RA, and especially in patients receiving MTX, is crucial.

We agree that clinical guidelines should be released on how to manage those patients on MTX regarding the dosage and the specific monitoring.

Disclosure statement: The authors have declared no conflicts of interest.

S. Karie1, V. Launay-Vacher1, F. Gandibakhi2, N. Janus3, S. Rozenberg2, P. Bourgeois2, G. Deray1

1Department of Nephrology and 2Department of Rheumatology, Pitie-Salpetriere Hospital, Paris, France

Accepted 2 June 2008

Correspondence to: S. Karie, Department of Nephrology, Pitie-Salpetriere Hospital, Paris, France.

E-mail: svetlana.karie@psl.aphp.fr


Rheumatology 2008;47:1260
doi:10.1093/rheumatology/ken228
Advance Access publication 17 June 2008

Comment on: Sparing of the thumb in Raynaud's phenomenon

Sir, I read with interest the article by Chikura et al. [1]. In their conclusion, they confirm that the thumbs are spared in patients with RP, both primary and secondary, as demonstrated by both symptoms and thermography. A distal–dorsal difference (DDD) in temperature at 23°C of −1°C or less was considered to be clinically relevant. The DDD of the thumb compared with that of the other fingers was used to establish that outcome.

Thermography as a test exhibits considerable temporal variations in the measured values, which are due to both technical factors and physiological characteristics of the blood flow. It often lacks reproducibility and has a wide inter-observer variability [2].

Although DDD specificity and sensitivity have been examined in other fingers affected with RP [3], we do not have database or previous studies that define a cut-off point or normal value nor a reference pattern for thumb DDD that we can use to assess sparing of the thumb with confidence. The study test did not control for finger length, or width being unique characteristics of the thumb that could influence test specificity and sensitivity.

The use of control groups has one major purpose: to allow discrimination of patient outcomes. By using a concurrent group in this study (primary vs secondary RP) and adopting poorly constructed new (thumb) DDD test made it difficult to discriminate the degree of change when the test result is unidirectional (normal thumb DDD).

A three-arm trial including an active control as well as a normal-control group can readily assess whether a failure to distinguish the test group from normal controls implies sparing was due to non-involvement by the pathological process or is simply the result of a trial test that lacked the ability to discriminate between a lower degree of involvement.

The comparison of normal with RP groups in such a trial provides evidence of test sensitivity. It is possible to make the active groups larger than the normal group in order to improve the precision of the test comparison, if this is considered important.

I find it difficult to accept the conclusion statement that the thumbs are spared based on the test method adopted in this study.

Disclosure statement: The author has declared no conflicts of interest.

K. A. BINYMIN

Southport and Formby District General Hospital – Rheumatology, Southport, UK.

Accepted 15 May 2008

Correspondence to: K. A. Binymin, Southport and Formby District General Hospital – Rheumatology, Kew, Southport, PR8 6PN, UK. E-mail: khalid.binymin@southportandormskirk.nhs.uk


Rheumatology 2008;47:1260
doi:10.1093/rheumatology/ken221
Advance Access publication 11 June 2008

Comment on: Sparing of the thumb in Raynaud’s phenomenon: reply

We thank Dr Binymin for his interest in our article [1]. We fully agree that although useful in the assessment of patients with RP, thermography has its limitations and we too have reported that there are concerns about reproducibility [2]. However, we believe that Dr Binymin’s concern [3] about not including healthy controls in our cross-sectional study examining thumb involvement in patients with RP is unfounded: the reason for not including a control group was because the comparison was ‘within-subject’. Including healthy controls, who do not experience RP and who do not demonstrate temperature gradients along their fingers, would not have been meaningful.

Digit length or width may well be the explanation for the apparent thumb sparing as discussed, and adjustment for this would be inappropriate. We used both objective (thermography) and subjective (symptom reporting by patients) measures to assess thumb sparing in patients with RP. Thumb sparing found using thermography was confirmed by symptoms reported by patients.

Disclosure statement: The authors have declared no conflicts of interest.

B. CHIKURA1, T. MOORE2, J. MANNING2, A. VAIL3, A. L. HERRICK2

1The Royal Liverpool University Hospital, Liverpool, 2Rheumatic Diseases Centre, University of Manchester, Hope Hospital, Salford and 3Biostatistics Group, University of Manchester, Manchester, UK

Accepted 14 May 2008

Correspondence to: B. Chikura, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK. E-mail: docbatsi@aol.com

