SIR, We read with interest the paper by Karie et al. on the MATRIX study. 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.

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 into 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 pancytopaenia, with an admission creatinine of 196 μmol/l. We presume that the episode of 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 pancytopaenia, 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 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 8 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].

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

SIR, We appreciated the letter from Bateman and colleagues. 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 haematoctoxicity. 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
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.

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