a group of 24 patients with a mixture of diagnoses found that i.m. MTX was effective and well tolerated, and most patients were either very or extremely satisfied with their therapy [5]. In addition, the same group found that the majority of patients preferred to receive their injections in the monitoring clinic rather than at the general practice surgery or at home despite the inconvenience.

We have conducted an open prospective safety and

5 and 25 mg of oral MTX per week. Another review of

efficacy study of switching to parenteral administration in a group of patients with active RA despite high-dose oral MTX who had not experienced any toxicity. The patients in this study had severe RA and had been referred for assessment for biological therapies in our 'Resistant RA' clinic. Consecutive patients who had failed at least 17.5 mg/week of oral MTX without toxicity were enrolled; parenteral MTX was commenced at 7.5 mg/week and increased by 2.5 mg in alternate weeks up to 25 mg/week, unless limited by toxicity. A relatively low initial dose was used because of concern that increased bioavailability may lead to increased toxicity. The doses of any concomitant disease-modifying agents (usually sulphasalazine or hydroxychloroquine) were stable for the preceding 4 weeks and were continued unchanged. The prednisolone dose was reduced when clinically indicated. All patients received concomitant folic acid (5 mg/day except on the day of the MTX dose). Blood test monitoring was performed at 2 weeks and then 4-weekly. In most cases the MTX was administered by our clinical nurse practitioners (AP and JW). All patients who entered the study were assessed at 12 weeks and all those who continued beyond 12 weeks were assessed at 24 weeks. Disease activity was assessed using the modified disease activity score (DAS28) and C-reactive protein (CRP). The incidence of therapy discontinuation and the reason for discontinuation were noted.

Therapy was switched in 33 patients (mean age 51 yr, range 29–70 yr; mean disease duration 8 yr, range 1–26 yr), and the mean number of previous disease-modifying anti-rheumatic drugs (DMARDs) was 4 (range 1–7). The mean baseline dose of oral MTX was 21 mg/week (range 17.5-25 mg/week). Patients had active disease with a mean baseline DAS28 of 6.4 (range 3.79–8.49) (Table 1). After 12 weeks of parenteral MTX, the mean DAS28 had decreased to 5.8 (P = 0.015) and at 24 weeks mean DAS28 was 5.7 (P = 0.014). Mean CRP also decreased, although this only reached significance at 24 weeks (P=0.022). The mean dose of MTX was comparable at each time point (Table 1), whereas the mean dose of prednisolone had decreased by 24 weeks (P = 0.108; Table 1). At 12 weeks, 29 (88%) patients continued therapy, two stopped due to toxicity (one with systemic symptoms and one with oral-pharyngeal malignancy) and two stopped due to inefficacy. In four patients the dose escalation of MTX was limited by toxicity (one each with nausea, abnormal taste, and systemically unwell and itchy rash), but the patients continued therapy. At 24 weeks, 19 patients continued therapy (58% of those studied), four stopped due to toxicity (one

Rheumatology 2003;42:1009–1010 doi:10.1093/rheumatology/keg246

Parenteral methotrexate should be given before biological therapy

Methotrexate (MTX) is the most commonly used diseasemodifying agent and is considered to be the gold standard treatment for therapy of rheumatoid arthritis (RA). The British Society for Rheumatology/National Institute for Clinical Excellence guidelines stipulate that patients must have failed therapy with MTX for at least 6 months (unless limited by toxicity) in order to be considered for anti-tumour necrosis factor α therapies [1]. In many cases MTX is efficacious and in general is well tolerated [2]. However, some patients do not respond to high-dose oral MTX. The absence of systemic side-effects in many of these patients suggests that this might be due to impaired gastrointestinal absorption, and Hamilton and Kremer showed increased bioavailability of MTX following switching from oral to intramuscular (i.m.) MTX [3]. Previous small studies have shown increased efficacy of i.m. MTX. A retrospective case-note review showed an improvement in 20 of 24 patients (mainly with RA) who switched from oral to i.m. administration [4]. The patients in this study were receiving between

Rheumatology 42 © British Society for Rheumatology 2003; all rights reserved





Table 1. Comparison of disease activity, MTX dose and prednisolone dose between baseline and 12 and 24 weeks of i.m. MTX

	Baseline $(n=33)$ Mean	12 weeks $(n=33)$		24 weeks (n = 29)	
		Mean	P*	Mean	P**
DAS28	6.43	5.84	0.015	5.67	0.014
CRP (mg/l)	47.9	34.4	0.200	26.0	0.022
MTX dose (mg/week)	20.8	19.6	0.169	19.4	0.313
Prednisolone dose (mg/day)	4.1	4.1	0.945	2.9	0.108

^{*}Paired t-test between baseline and week 12 data.

each with rash, systemic symptoms, upper respiratory tract infections and mouth ulcers) and five stopped due to inefficacy. One patient was lost to follow-up.

In this open prospective study, switching to i.m. administration in patients with active disease despite high-dose oral therapy was safe and efficacious. Disease activity was reduced and 58% of patients continued therapy for more than 24 weeks. A low incidence of adverse events was seen and no serious toxicity occurred. It is unlikely that the malignancy seen at 12 weeks can be attributed to the switch in the route of MTX administration. We feel that a trial of parenteral MTX is warranted in patients with severe RA prior to commencing biological therapies.

S. J. Bingham, M. H. Buch, S.Lindsay, A. Pollard¹, J. White¹, P. Emery

Rheumatology Research Unit, University of Leeds and ¹Rheumatology Department, Leeds General Infirmary, Leeds, UK

Accepted 11 December 2002

Correspondence to: S. J. Bingham, Old Nurses Home, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK. E-mail: s.bingham@leeds.ac.uk

- 1. British Society for Rheumatology. Guidelines for prescribing $TNF-\alpha$ blockers in adults with RA. London: British Society for Rheumatology, 2001.
- Kremer JM, Lee JK. A long-term prospective study of the use of methotrexate in rheumatoid arthritis: update after a mean of 53 months. Arthritis Rheum 1988;31:577–84.
- Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol 1997;36:86–90.
- 4. Osman A, Mulherin D. Is parenteral methotrexate worth trying? Ann Rheum Dis 2001;60:432.
- 5. Burbage G, Gupta R, Lim K. Intramuscular methotrexate in inflammatory rheumatic disease. Ann Rheum Dis 2001;60:1156.

^{**}Paired t-test between baseline and week 24 data.