Intramuscular methotrexate in inflammatory rheumatic disease

We read with great interest the recent letter entitled "Is parenteral methotrexate worth trying?" by Osman and Mulherin.[1] There has been an increased use of intramuscular methotrexate (IM-MTX) in our department in the past two years, leading to an increased workload in the nurse-led monitoring clinics and in the cost. This has prompted us to review the clinical utility of switching patients to IM-MTX. In addition, we have recorded patients' experiences, focusing chiefly on patient satisfaction, with this treatment.

Medical case notes of 31 patients who had started treatment with IM-MTX, identified from our database, were examined. The clinical diagnosis, previous drug treatment, reason for changing to IM-MTX, efficacy, and side effects were noted. In addition, the patients were asked to complete a questionnaire, looking at patient satisfaction and preferred venue for injections (monitoring clinic or local doctor's surgery/home).

Our patient cohort was made up of 24 patients with rheumatoid arthritis, four with seronegative spondyloarthritis, two with systemic lupus erythematosus, and one with undifferentiated connective tissue disease. Most patients had been receiving a previous disease modifying antirheumatic drug (DMARD), including 24 patients taking oral MTX. Reasons for changing to IM-MTX treatment were as follows: side effects in 11 patients, loss of efficacy in 12, and poor oral compliance in eight. The median starting and maintenance doses were 10 mg weekly (range 5–17.5) and 15 mg weekly (range 10–17.5), respectively. During the study, five patients discontinued IM-MTX: two because of side effects, one developed multiple nodulosis, one did not attend for follow up, and one died from an unrelated cause. Median duration of treatment in the remaining 26 patients was 10 months (range 1–20). Significant improvement in disease activity, as measured by erythrocyte sedimentation rate and C reactive protein, was seen after three months ($p<0.01$), with improvement maintained after nine months ($p<0.01$) of IM-MTX treatment. Twenty four of the 26 current patients completed the questionnaire. On a satisfaction scale of 1–5, the average rating was 4.2, indicating that patients were either very or extremely satisfied with their IM-MTX treatment. Fourteen patients preferred their injections in the monitoring clinic, five patients preferred their local doctor's surgery, and five patients expressed no preferences. Only three patients stated that weekly clinic visits were inconvenient.

In conclusion, we found that IM-MTX was effective and well tolerated. In addition, our observations further support the switch to parenteral MTX in those patients previously intolerant or who have failed to respond to oral MTX.[2] Surprisingly, most patients preferred to have their injections in the monitoring clinic. The reason for this is not clear. Possibly, the patients felt more confident if cytotoxic drugs were given by a trained healthcare professional, although a previous study by Arthur *et al* has found that self injection of DMARDs is safe, convenient, and time and cost saving to the patient.[3] We are currently comparing the administration of parenteral MTX in the monitoring clinic with self administration in the community. Regardless of the outcome, the role of parenteral MTX in rheumatic diseases is likely to expand and the cost and resource implications of continuing with this treatment need to be discussed.

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Author's reply

It is gratifying that Drs Burbage, Gupta, and Lim have also demonstrated efficacy and high levels of patient satisfaction associated with parenteral methotrexate in their study. There remains a surprising dearth of reported information about this useful and widely prescribed development in rheumatology practice. Because of the burgeoning number of patients being treated in this way, it is creating increasing logistical difficulties. It represents an unlicensed use of this drug, which can cause anxiety among less experienced practitioners. Issues related to the appropriate disposal of the residual cytotoxic waste have also caused considerable difficulties. Although weekly oral methotrexate, prescribed and monitored within primary care, is an extremely cheap and effective treatment for rheumatoid arthritis, this is certainly not the case for parenteral methotrexate if it is necessary for it to be prescribed and administered in a costly secondary care setting. As primary care buckles under increasing demands on its resources, cost and logistical issues, rather than issues of efficacy, may curtail the deserved role of parenteral methotrexate in current and future rheumatology practice.

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LETTERS TO THE EDITOR

Epidemiology of vasculitis in Europe

We recently compared the annual incidence of primary systemic vasculitis (PSV) in two different regions of Europe (Norwich, UK (latitude 52°N) and Lugo, Spain (latitude 43°N)).[1] Wegener's granulomatosis (WG) was more common in Norwich (10.6/million) than in Spain (4.9/million), though the overall incidence of PSV was similar. This supports the idea that environmental factors may be important in the aetiopathogenesis of PSV. To extend our observations we have now studied the incidence of PSV in northern Europe (Tromsø, Norway (latitude 70°N)). The same methodology was used as in the previous study.[1] All new patients presenting with PSV between 1 January 1988 and 31 December 1998 were identified in the three centres. WG, Churg-Strauss syndrome (CSS), and polyarteritis nodosa (PAN) were classified by the American College of Rheumatology (1990) criteria,[2–4] and microscopic polyangiitis (MPA) and classical PAN by the Chapel Hill consensus definition.[5] Incidence figures were calculated using the Poisson distribution for the observed number of cases.

Table 1 shows the results obtained. The overall incidence and pattern of vasculitis was similar in the three regions, but there were some differences. MPA was less common in Tromsø than in the other two regions, and there was a trend for WG to be more common in the north. CSS was more common in Norwich than in the other two regions. In all areas and all disease categories the incidence was greater in men than women and showed a peak incidence at age 65–74. Overall, WG is the most common type of PSV and classical PAN the rarest.

These results support the notion suggested by doctors interested in vasculitis that there are geographical differences in the incidence of WG, MPA, and CSS, and, in particular, there is an inverse relation between the incidence of WG and MPA. In clinical practice MPA and WG can be difficult to distinguish. Possibly, despite our best attempts to harmonise the application of classification criteria/definitions, there were still differences in approach. The reason for the apparent excess of CSS in Norwich is unclear

Table 1 Annual incidence of primary systemic vasculitis in three regions of Europe

	Criteria/ definition	Tromsø		Norwich		Lugo	
		n	*/million (95% CI)*	*n*	*/million (95% CI)*	*n*	*/million (95% CI)*
WG*	ACR†	43	10.5 (7.6 to 14.2)	48	10.6 (7.8 to 14.0)	11	4.9 (2.4 to 8.8)
CSS*	ACR	2	0.5 (0.06 to 1.8)	14	3.1 (1.7 to 5.2)	2	0.9 (0.1 to 3.2)
MPA*	CHCC†	11	2.7 (1.3 to 4.8)	38	8.4 (5.9 to 11.5)	26	11.6 (7.6 to 17.0)
PAN*	ACR	18	4.4 (2.6 to 7.0)	44	9.7 (7.0 to 13.0)	14	6.2 (3.4 to 10.5)
PAN	CHCC	2	0.5 (0.06 to 1.8)	0	0.0 (0.0 to 0.8)	2	0.9 (0.1 to 3.2)
Total		56	13.7 (10.3 to 17.8)	86	18.9 (15.1 to 23.4)	41	18.3 (13.1 to 24.8)

n = number of patients fulfilling each criteria in each centre, 18 Tromsø patients, 24 Norwich patients, and 12 Lugo patients fulfilled more than one set of classification criteria. Total represents the number of patients seen in each centre.
*WG = Wegener's granulomatosis; CSS = Churg-Strauss syndrome; MPA = microscopic polyangiitis; PAN = polyarteritis nodosa.
†ACR = American College of Rheumatology; CHCC = Chapel Hill Consensus definition.

but might reflect local environmental factors. The aetiopathogenesis of PSV is unknown, but both genetic and environmental factors are likely to be important. The clinically observed differences between MPA and WG may reflect interaction of varying trigger factors on a heterogeneous genetic background. It should therefore not be assumed that the same triggers operate in all regions of Europe.

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Anti-U3 snRNP antibodies in localised scleroderma

Localised scleroderma (LScl) is a connective tissue disorder usually limited to the skin and subcutaneous tissue, but it sometimes affects the muscle beneath the cutaneous lesions. The absence of Raynaud's phenomenon, acrosclerosis, and internal organ involvement differentiates LScl from systemic sclerosis (SSc).[1] LScl has been reported to be accompanied by a variety of abnormal immune reactions, such as the presence of antinuclear antibody, rheumatoid factor, anti-single-stranded DNA antibody (anti-ssDNA), and antihistone antibody.[2–5]

In our laboratory an indirect immunofluorescent study showed nucleolar staining in the serum samples of some patients with LScl. Although autoantibodies to nucleolar antigens have been well described in patients with SSc,[6 7] these antibodies have not been determined in patients with LScl, and the incidence of anti-U3 snRNP antibodies has not been described previously. In this study we investigated the prevalence of anti-U3 snRNP antibodies using RNA immunoprecipitation,[8] and examined the clinical and laboratory features of patients with LScl. In addition, we examined the serum samples of patients with SSc and control subjects matched for age and sex with the patients with LScl.

We found anti-U3 snRNP antibodies in 2/70 (3%) serum samples from the patients with LScl (fig 1). One of the 28 patients (4%) with linear scleroderma and one of the 20 patients (5%) with morphoea had anti-U3 snRNP antibodies (table 1). This prevalence was smaller than that in patients with SSc,[9] but there was no significant difference. RNA immunoprecipitation using silver staining of the RNA is not as sensitive as other methods—for example, probing with a labelled U3 snRNP probe. Possibly, some anti-U3 snRNP positive serum samples might have been missed. The three patients with SSc and with anti-U3 snRNP antibodies were diagnosed as having diffuse cutaneous SSc, and they tended to be older and have disease of longer duration than patients with LScl; the difference was not significant. In this study the titres of antinucleolar antibodies in the two patients with LScl with anti-U3 snRNP antibodies were 1/320 and 1/640, respectively. The titres of this antibody did not change in a follow up study. A previous study reported that 43/46 patients with SSc and anti-U3 snRNP antibodies produced bright nucleolar staining with titres >1/640.[10] Taken together, the titres of antinucleolar antibodies in patients with LScl were as high as those in SSc. Patients with LScl and with anti-U3 snRNP antibodies did not have sclerodactyly or nailfold bleeding. Raynaud's phenomenon did not occur at any time in the course of their disease. These results suggest that anti-U3 snRNP antibodies occur in patients with LScl as well as in those with SSc.

The patients with LScl and anti-U3 snRNP antibodies tended to be younger, have shorter disease duration, have fewer sclerotic lesions, and have fewer affected areas than those without, but there was no significant difference. We could not find any correlations with clinical manifestations, probably because of the small number of patients. In earlier investigations of systemic sclerosis, anti-U3 snRNP antibodies did not seem to have any distinctive clinical and laboratory correlation. A large group of patients with SSc was assembled and the clinical features of the patients with anti-U3 snRNP antibodies investigated; various clinical associations were reported.[9] A large group of patients with LScl might similarly disclose clinical associations of patients with LScl with anti-U3 snRNP antibodies.

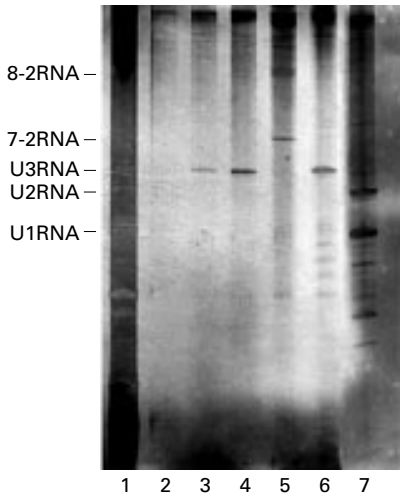

Figure 1 RNA immunoprecipitation. Urea (7 M/10% polyacrylamide gel electrophoresis of phenol-extracted immunoprecipitates from HeLa cell extracts were stained with silver. Total nucleic acids, with 7-2RNA, 8-2RNA, and the U snRNA regions are indicated. Serum samples used for immunoprecipitation included: lane 1, total RNA; lane 2, healthy control serum; lanes 3–4, patients with LScl and with anti-U3 snRNP antibodies; lane 5, patient with SSc and anti-Th/To ribonucleoprotein antibodies; lane 6, patient with SSc and anti-U3 snRNP antibodies; lane 7, patient with systemic lupus erythematosus and anti-Sm antibodies.

Table 1 Frequencies of antibodies to U3 small nuclear ribonucleoprotein (snRNP), detected by immunoprecipitation, in patients with localised scleroderma (LScl), systemic sclerosis (SSc), and control subjects

	Anti-U3 snRNP antibodies (%)
Patients with LScl	2/70 (3)
GM	0/22 (0)
LS	1/28 (4)
M	1/20 (5)
Patients with SSc	3/30 (10)
Control subjects	0/40 (0)

LScl = localised scleroderma; GM = generalised morphoea; LS = linear scleroderma; M = morphoea; SSc = systemic sclerosis.

Previous studies have shown that anti-U3 snRNP antibodies rarely coexist with other autoantibodies.[9] Okano *et al* reported that each distinctive serum antibody is associated with its own unique combination of clinical features.[9] In our study antihistone antibodies or anti-ssDNA did not coexist with anti-U3 snRNP antibodies, and no other autoantibodies were detected by RNA immunoprecipitation. LScl may be a heterogeneous condition with diverse autoantibodies, and these antibodies may have a mutually exclusive status.

In conclusion, we showed for the first time that anti-U3 snRNP antibodies are found in patients with LScl by RNA immunoprecipitation. We found no correlations between clinical and laboratory manifestations in the present study. Our study suggests that the presence of anti-U3 snRNP antibodies is one of the serological abnormalities in LScl. A study of more patients may assist in showing a distinctive association between anti-U3 snRNP antibodies and the clinical and laboratory features of patients with LScl.

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