MATTERS ARISING

Effects of methotrexate on cartilage metabolism

We read with interest the report by Neidel *et al*¹ on the effects of methotrexate (MTX) on articular cartilage in vitro and in vivo. The relevance of these findings to patients with rheumatoid arthritis (RA) and other diseases who are receiving MTX is of considerable interest.

In a previous study² we reported that treatment of RA patients with MTX resulted in reduced numbers of leucocytes and reduced concentrations of interleukin 1 β (IL1 β) in the synovial fluid (SF) relative to placebo control patients.

Sequential specimens of SF were available in four control patients and in eight patients treated with MTX who participated in that study.² The SF keratan sulphate concentrations at baseline and at days 7, 28, and 56 were determined as previously described³ and are shown in figure 1. A progressive and statistically significant reduction in SF keratan sulphate was observed in the MTX group (mean (SEM) 206 (76) μ g/ml at baseline versus 108 (15) μ g/ml at eight weeks ($p < 0.02$, Wilcoxon matched pairs signed rank test), but not in the controls. Reductions in concentration of keratan sulphate in the SF were observed in all of the eight patients treated with MTX. Among the controls, two

Figure 1 Keratan sulphate concentrations in serial specimens of synovial fluid from patients with RA who were treated ($n=8$) or not treated ($n=4$) with MTX. Results are expressed as mean (SEM).

patients showed an increase and two showed a decrease in the concentrations of keratan sulphate in SF. Comparison of the keratan sulphate concentrations in the MTX and control groups showed no statistically significant difference at any time point other than at eight weeks when the SF keratan sulphate concentrations in the MTX group were significantly lower than those in the control group. These data are consistent with reduced cartilage proteoglycan degradation in MTX recipients.

Like Neidel *et al* we were concerned that MTX may have affected proteoglycan metabolism directly. Accordingly we examined the effect of MTX on proteoglycan release in pig cartilage explants. The concentrations of MTX tested in these experiments were commensurate with and in excess of those achieved in vivo. MTX had no effect on either basal proteoglycan release or that stimulated by maximal concentrations of IL1.

As MTX was found to have no effect on proteoglycan release in vitro, it is unlikely that MTX directly inhibits the enzymes responsible for proteoglycan catabolism. Effects of MTX on proteoglycan clearance from the joint cavity have not been studied, but it is unlikely that MTX increases clearance as it has "anti-inflammatory" rather than "pro-inflammatory" effects. Overall the findings suggest that with suppression of rheumatoid synovitis, cartilage proteoglycan degradation is attenuated at least temporarily. Reduced production of pro-inflammatory/pro-catabolic cytokines such as IL1 and perhaps tumour necrosis factor α , LIF and OSM may explain the observed effects of MTX on proteoglycan release.

In summary our findings are in accord with and support those of Neidel *et al*.¹ They are consistent with the view that MTX does not have a toxic effect on proteoglycan metabolism in human articular cartilage in vivo. Furthermore in RA our collective findings suggest that the favourable effect of MTX on overall disease control is accompanied by reduced loss of proteoglycan from the articular cartilage during the first two months of treatment.

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2 Thomas R, Carroll GJ. Reduction of leukocyte and interleukin-1 beta concentrations in the synovial fluid of rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1993;36:1244–52.
3 Carroll GJ, Bell MC, Laing B, McCappin S, Bulmer S, Leslie A. Reduction of the concentration and total amount of keratan sulphate in synovial fluid from patients with osteoarthritis during treatment with piroxicam. *Ann Rheum Dis* 1992;51:850–4.

Authors' reply

We agree with the conclusion of Carroll and Bell that reduced keratan sulphate concentrations in the synovial fluid (SF) of RA patients receiving MTX treatment most probably reflect an attenuation of synovitis with subsequent reduction of cartilage proteoglycan breakdown rather than a direct inhibition by MTX of proteoglycan release from the cartilage matrix.

In a similar experiment as the one described by Carroll and Bell, MTX in concentrations exceeding those found in RA SF in vivo under a usual treatment regimen did not change the rate of proteoglycan release from bovine articular cartilage explants in vitro in the presence or absence of IL1 β .¹ Moreover, in a rabbit model of osteoarthritis, weekly pulse treatment with MTX led to a better preservation of the cartilage structure than did placebo treatment (determined by histological analysis using the Mankin score).² The latter findings may suggest the absence of MTX related adverse effects on damaged cartilage, as in RA affected joints that are no longer inflamed but where the clinical picture is dominated by post-arthritic changes.

We agree with the view of Carroll and Bell, that MTX most probably lacks toxicity on the proteoglycan metabolism of human articular cartilage in vivo. The reported reduced loss of proteoglycans from cartilage of RA patients receiving MTX treatment is consistent with findings in animal models of RA.¹

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2 Neidel J, Schroers B, Sintermann F. The effects of high-dose methotrexate on the development of cartilage lesions in a lapine model of osteoarthritis. *Arch Orthop Trauma Surg* 1998;117:265–9.