as inducible, endothelial, and neuronal isoforms of nitric oxide synthase (iNOS, eNOS, and nNOS) were examined by semiquantitative reverse transcriptase-polymerase chain reaction. Densitometry readings were standardised against the housekeeping gene β-actin. Data were compared using Spearman rank order correlation test.

There was a consistent pattern of cytokine mRNA expression in the subacromial bursal samples. All 17 samples expressed IL6, IL8, and 15 out of 17 expressed GM-CSF as well, but there was no detectable mRNA expression for IL1β, and only in one sample for TNFα. Positive, significant correlations were found between IL6 and GM-CSF (r_s=0.7, p<0.05), and IL6 and IL8 (r_s=0.5, p<0.05), demonstrating a concomitant expression of these cytokines.

iNOS and eNOS mRNA expression was detected in all samples, while nNOS was found in five out of 17 samples (fig 1). Significant correlation was found between the mRNA expression of eNOS and IL8 (r_s=0.7, p<0.05). This study was unable to detect correlations between the expression levels of cytokines or NOS isoforms and patient age, duration of symptoms, and shoulder pain scores.

In systemic immune response, proinflammatory cytokines tend to increase together. A temporal sequential expression of cytokines has been reported during wound healing. IL1 and TNF are expressed mainly in the early (inflammatory and proliferative) phase of wound healing,[5] whereas IL6 levels are highest at a later (revascularisation) stage.[4] Increase in IL6 and decrease in IL1 levels have been reported in cultured human tendon fibroblasts subjected to repetitive motion.[3] It may be, therefore, that the pattern of cytokine expression, which we observed in the subacromial bursae, may reflect a dominance of reparative processes, or a response to altered mechanical stimuli rather than inflammatory or destructive processes.

In joint cartilage, production of NO has generally been implicated as a pathogenetic factor. However, increased local NO production seems to be essential for normal tissue healing.[6] The expression of NOS isoforms in the subacromial bursa is a new finding and generates interesting questions.

The molecular events involved in the subacromial space are likely to be complex. Whether induction or inhibition of certain cytokines and NOS isoforms impairs or enhances the overall healing processes remains to be answered.

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Is parenteral methotrexate worth trying?

Methotrexate is widely accepted as a useful disease modifying drug for the management of rheumatic diseases, against which new treatments are often compared.[1–3] However, apart from those who are intolerant of oral methotrexate despite folate supplementation, some patients simply do not respond. This may relate to compliance, but may also reflect pharmacokinetic variables, which influence the absorption of oral methotrexate.[4 5] To overcome compliance and pharmacokinetic problems, some units have begun using parenteral methotrexate, either intramuscular or subcutaneous, the latter providing the potential for self treatment.[6] However, although some authors have shown that parenteral methotrexate works,[7] and many have examined the theoretical aspects of such treatment,[4 5] hardly any have examined the clinical utility of switching patients from oral to parenteral methotrexate.

In this small cross sectional study we examined the case notes of all 24 patients (17 female) who had started treatment with intramuscular methotrexate at this rheumatology department. The indication for methotrexate treatment was mostly rheumatoid arthritis (RA), except for one patient with polymyositis and one with juvenile arthritis. Mean (range) age was 56 (9–70) years. Median (range) dose of oral methotrexate was 17.5 (5–25) mg a week before the initiation of intramuscular methotrexate. At the time that the case notes were reviewed, 20 patients had improved, one patient was worse, and three were unchanged—an assessment reached by reviewing their clinicians' most recently recorded observations. Median (range) duration of parenteral treatment was 5 (1–55) months and dose of parenteral methotrexate at the time of this review was 15 (7.5–25) mg a week. Mean (range) C reactive protein fell from 53 (5–122) measured at the time parenteral methotrexate was started to 34 (7–111) mg/l when the case notes were reviewed.

It seems inevitable that the role of parenteral methotrexate will expand as institutions resolve the issues related to delivery of treatment and disposal of the cytotoxic waste it engenders. It also seems highly unlikely that a substantial clinical trial comparing continued oral treatment with initiation of parenteral methotrexate in patients unresponsive to oral methotrexate will ever be performed. At least this small study suggests that not only is it a development that ought to work but also it actually seems to improve disease control for these patients.

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