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Anti-tumour necrosis factor (TNF)-α therapy (etanercept)

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Keywords

Etanercept, MMP, Rheumatoid arthritis, Tumour Necrosis Factor-α

Context

The role of tumour necrosis factor (TNF)-α in rheumatoid arthritis (RA) pathogenesis is clearly recognised as is the benefit of its blockade. Its effects include release of enzymes involved in extracellular matrix degradation (matrix metalloproteinases or MMPs), such as stromelysin 1 (MMP-3) and collagenase 1 (MMP-1). Tissue inhibitor of matrix metalloproteinase (TIMP)-1 partly regulates MMP action. In RA an imbalance between MMP and TIMP activity has been suggested.

Infliximab was previously shown to reduce serum levels of MMP-1 and MMP-3. In the current study the authors studied whether etanercept (25mg subcutaneously twice weekly) similarly modulated serum MMP as well as TIMP levels, and also whether it modulated synovial expression of these mediators.

Significant findings

Of the 60 patients studied 78% achieved ≥ ACR20 response (some on additional Disease-modifying antirheumatic drugs [DMARDs]). ELISA measurements showed that median serum MMP-3 and MMP-1 levels were significantly decreased at 8 and 12 weeks after treatment. TIMP-1 was downregulated only after 8 weeks. Hence the significant reduction at 12 weeks in MMP-1:TIMP-1 and MMP-3:TIMP-1 ratios can only be attributed to the downregulation of serum MMP-1 and -3 respectively rather than significant changes in TIMP levels. Baseline serum levels of MMP-3 and TIMP-1 correlated with baseline C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Additionally, baseline MMP-3 correlated with change in DAS28 score after 12 weeks of therapy.

Synovial MMP-1, MMP-3 and TIMP-1 expression showed no change with therapy.

Comments

The authors have concentrated on examining the effect of TNF-blockade on MMPs, which are known to exert a significant role in bone and cartilage destruction.

Details on how many patients were on oral prednisolone, which can also modulate disease, was not given. A standard ELISA method, which did not discriminate between active and inactive MMP was employed. Computerised image analysis was undertaken to evaluate stained synovial biopsy specimens, and the authors have published well-recognised studies using this technique.

The significant reduction in serum MMP-1 and MMP-3 levels, and fall in MMP:TIMP-1 ratios may relate to the retardation in structural damage that has been documented clinically following TNF blockade. On the other hand, the lack of change in synovial expression is somewhat surprising. Possible explanations include: a 'lag' period between synovial and serum expression changes; the synovium not being the dominant source of serum MMP; other MMPS/TIMPs being responsible for joint damage in RA; total MMP measurements not necessarily reflecting biologically active enzyme; and the fact that measurements made in one joint may not fully reflect changes elsewhere.

The data linking baseline serum MMP-3 levels and subsequent changes in DAS score was of only borderline significance and requires replication.

Methods

ELISA, Immunohistochemical analysis, Computerised image analysis.

References

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