Chapter 1

Introduction & aim of the thesis

Marcel D. Posthumus
INTRODUCTION & AIM OF THE THESIS

Rheumatoid arthritis (RA) is a complex inflammatory auto-immune disease associated with considerable disability, morbidity, and mortality. Early identification of patients with aggressive destructive disease is important, not only for prognostic, but also for therapeutic reasons. Novel, more aggressive therapies are currently developed and the need for clinically feasible means for assessing the prognosis in the individual patients is becoming increasingly important.

Cytokines play a major role in local inflammation and destruction, as well as in the systemic acute phase response. The relationship between acute phase proteins such as C-reactive protein (CRP) on the one hand, and disease activity and radiological progression on the other, has been demonstrated in several studies. Although CRP appears to be a good marker for prognostic purposes and for monitoring treatment effects, it is an indicator of inflammation in general which may be influenced by other stimuli of the acute phase response.

The matrix metalloproteinases (MMPs), which are locally produced and activated within the affected joint as a result of cytokine mediated stimulation, could be more specific markers for joint inflammation and especially destruction in rheumatic diseases. In RA matrix metalloproteinase 3 (MMP-3=stromelysin 1) is of interest because it is thought to play a prominent role in the pathogenesis of matrix destruction in the inflamed joints. MMP-3 is capable of degrading many components of the matrix in the synovial joint, and has been localized in fibroblast-like synoviocytes of rheumatoid synovium and in RA cartilage. The enzyme is secreted as a latent pro-enzyme resulting in elevated levels in local tissue and synovial fluid. In RA, serum MMP-3 is thought to originate from the inflamed joint because there are significant correlations between MMP-3 levels in synovial fluid and in serum, and between serum MMP-3 levels and the number of clinically active inflamed joints. Furthermore local therapies, such as intra-articular corticosteroid injections, cause significant reductions in serum MMP-3 levels in synovial fluid and in the systemic circulation of patients with RA.

The relative balance between activated MMPs and their inhibitors such as the tissue inhibitors of matrix metalloproteinases (TIMPs) and α2-macroglobulin (α2-M) eventually determines the fate of the matrix. In synovial fluid the levels of activated MMP-3 are increased but measurement of activated MMP-3 in the systemic circulation is very difficult, if not impossible, because of the high levels of α2-M in the systemic circulation which encloses the activated enzyme completely.
Elevated systemic levels of MMP-3 (probably mainly pro-MMP-3) have been found in several other rheumatic diseases such as SLE, systemic sclerosis, ankylosing spondylitis, crystal induced arthritis, and psoriatic arthritis. Nevertheless, in RA the systemic levels of MMP-3 are considered to be a direct reflection of local synthesis and as such, serum MMP-3 could be a useful marker of disease activity and destruction in early RA.

The **aim of the thesis** was to investigate the significance of serum MMP-3 in relation to disease activity, and in particular in relation to radiological progression, in patients with early RA. The data were derived from a prospective follow-up study in patients with recent onset RA (disease symptoms < 1 year).

In **chapter 2** a general review is provided on matrix metalloproteinases, in particular in rheumatoid arthritis.

In **chapter 3** the significance of serum MMP-3 in relation to the development of radiological damage in early RA is evaluated and in particular its prognostic value at an early time-point.

In **chapter 4** the clinical significance of serial measurements of serum MMP-3 levels in relation to markers of disease activity and radiological progression in early RA is analyzed, during a follow-up of three years.

In **chapter 5** the effects of treatment with sulphasalazine, or the combination methotrexate and sulphasalazine, on the serum MMP-3 levels in patients with early RA is investigated. Changes in serum MMP-3 were also compared to changes in CRP levels.

In **chapter 6** serum MMP-3 levels in periods with and without progression of radiological damage in patients with early RA are evaluated and compared to CRP.

In **chapter 7** functional (at least in *in vitro* experiments) promoter polymorphisms in MMP genes are evaluated. In this study the significance of MMP-1 and MMP-3 promoter polymorphisms in relation to disease activity and radiological damage in patients with early rheumatoid arthritis is analyzed.

In **chapter 8 & 9** a summary, the general conclusions and future perspectives are given.
Chapter 1

REFERENCES
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