Fatal attraction: chemokines and rheumatoid arthritis
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Chapter 1

GENERAL INTRODUCTION
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease which has as its primary target the synovial tissue (ST) in the joints. Despite recent advances in the treatment of this disease, not all patients respond and a substantial number of patients suffer from (severe) side effects and adverse events associated with treatment.

Although the etiology of RA is still unknown it is thought of as an autoimmune disease which often leads to substantial disability and premature death when untreated (1). The disease affects between 0.5 and 1% of adults in most western countries, in a female: male ratio of 3:1 (2). RA can occur at any age, but it is most common among those aged 40-70 years. The geographic distribution is worldwide and it appears to afflict people of all races equally (2:3).

The activation of auto-reactive T cells and B cells is thought to be a central event in the initiation of the immune response, which may evolve into massive inflammation and cell recruitment in the involved tissues (4;5). The immune response, although systemic, is mainly directed at the synovium which under normal circumstances is a thin membrane that attaches to skeletal tissues at the bone-cartilage interface. The inflammatory process targets the ST, articular cartilage, as well as the peri-articular and sub-chondral bone causing largely irreversible deformities and subsequent disability. The microscopic appearances of inflamed ST in RA patients include marked intimal lining layer hyperplasia due to increased numbers of fibroblast-like synoviocytes and intimal macrophages, and the accumulation of macrophages, T cells, B cells, plasma cells, dendritic cells, mast cells, natural killer cells and neutrophils in the synovial sublining layer (6).

Macrophages play a central role in the perpetuation of inflammation and joint destruction. They accumulate in the synovium and produce cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and proteolytic enzymes including matrix metalloproteinases (MMPs) (7-9).

Improved knowledge of the pathogenesis and recognition of key proteins in the regulation of inflammation and destruction, like TNF-α and IL-1, have led to the identification of targeted therapies, such as anti-TNF-α treatment (infliximab, etanercept and adalimumab) and IL-1 receptor antagonist treatment (anakinra) (10). Although these treatments are effective in many patients, not all patients respond and (severe) side effects have been described (11-13).

In addition to these key pro-inflammatory cytokines, a new subfamily of chemotactic cytokines, so-called chemokines, has recently been recognized as central players in the inflammatory process (14). Since the discovery of their existence, chemokines have been considered therapeutic targets in a wide range of (inflammatory) disorders. Although research has focused on the application of chemokine blockade in many different disorders since the early 1990’s, the therapeutic potential is still unclear. The aim of this thesis was to further elaborate the use of chemokine blockade in chronic inflammatory joint disorders, especially in RA.

CONTENTS OF THIS THESIS

Part One of this thesis reviews the available knowledge on the characteristics, expression and role of chemokines and chemokine receptors in the pathogenesis and inflammatory process in RA and other joint disorders (Chapter 2). In addition, suitable candidates for therapeutic intervention are identified and discussed (Chapter 3).

Part Two of this thesis focuses on methodological issues with regard to the analysis of synovial tissue in small randomized controlled trials. The evaluation of histologic changes in
serial synovial tissue biopsies obtained from patients treated with new (targeted) drugs has facilitated studies on the mode of action of many (new) therapeutic strategies (15-21). Therefore, reliable quantification of the characteristics of synovial inflammation is pivotal. The reliability of digital image analysis in this setting is investigated in Chapter 4. Chapters 5 and 6 address the question which features in RA synovial tissue samples could be used as a biomarker for clinical efficacy in relatively small studies of short duration. The increase in the development of a variety of new, targeted therapies clearly raises the need for sensitive biomarkers, which could be used for selection purposes during the development process.

**Part Three** combines the gathered knowledge of parts 1 and 2 and presents two randomized controlled trials (Chapter 7 and 8), including analysis of serial synovial biopsies with evaluation of biomarkers by digital image analysis, investigating the feasibility, safety and efficacy of biomarkers in RA.

In Chapter 9 the main findings of the studies are summarized and discussed, including its limitations, and this chapter provides suggestions for future research.

**SCOPE OF THIS THESIS**

1. To identify suitable targets for therapeutic intervention among chemokines and chemokine receptors in RA.
2. To validate the used methods for the evaluation of serial synovial biopsies by digital image analysis.
3. To identify possible synovial tissue biomarkers for clinical efficacy in relatively small studies of short duration.
4. To test the feasibility, safety and (clinical) efficacy of blockade of selected chemokines and chemokine receptors in randomized controlled trials including serial synovial tissue analysis.

**Reference List**

Chapter 1


