C-reactive protein in early rheumatoid arthritis
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Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease of unknown etiology that is marked by synovial inflammation of joints, with pain, stiffness and swelling as the main local symptoms. The chronic synovitis often leads to a progressive destruction of cartilage and bone. Systemic features of inflammation may be prominent and include weight loss, muscle weakness, fever and anaemia. The inflammatory process may involve other organs, clinically characterized by nodules, serositis or vasculitis. The combination of pain, stiffness, muscle weakness and joint damage leads to physical disability, and the systemic features of the disease add up to the ultimate handicap by impairment of the general condition.

In most patients, the course of the disease is characterized by fluctuations in the severity of inflammatory activity. There is a large variation in the individual course of the disease from patient to patient. The spectrum may vary from a mild, non-destructive disease with long remissions, to a severe course with progressive joint destruction and disability, extra-articular manifestations, and reduced life-expectancy.

Many different quantitative measures are used to assess disease activity, monitor the course of the disease and predict the outcome of RA. A distinction has to be made between so called 'process variables' reflecting the disease activity at a specific point in time, and 'outcome measures', reflecting the result of the course of the disease over a given time period (1). Controversy still exists regarding the most appropriate measure to judge disease activity and outcome.

'Outcome' is defined as the suffering or loss of health experienced by an individual as result of the process of a disease (2). A comprehensive measure of outcome must therefore encompass all suffering throughout the course of the disease. It has been generally recognized that outcome in RA has different dimensions. Fries et al stated that an outcome measure should be relevant to the patient and proposed five dimensions of outcome: death, disability, discomfort (including pain, stiffness, fatigue, depression), iatrogenic effects and economic impact. Others have advocated that structural joint damage is the predominant cause of functional impairment in RA. Radiologically demonstrable joint damage is considered to be a direct and
objective outcome measure reflecting the results of chronic joint inflammation, including degradation of cartilage and erosion of bone. Radiological damage meets the requirements of a real outcome measure: it is the result of the course of the disease during the preceding period and it is independent of the current disease activity. Other outcome measures such as physical disability and functional tests may be largely influenced by disease activity, particularly in the early stage of the disease. This in contrast to advanced disease, where these measures are to a large extent determined by irreversible joint damage (3).

'Process variables' measure the actual activity of the disease, and include clinical variables, such as tender and swollen joints, and laboratory variables such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The ESR and CRP are both indicators of the 'acute phase response', the term used to describe the complex of systemic events which accompany inflammation. Elucidation of the role of cytokines in the pathogenesis of inflammatory arthritis has yielded a rationale for the use of markers of the acute phase response.

It is of importance to understand the interrelationship between process variables and outcome, and to determine which process variables do most adequately reflect those aspects of the disease which are representative for a specific outcome measure.

The increasing evidence that the process of irreversible joint damage may already start during the first months of the disease emphasizes the need of studies in the early stages of the disease. It is important to be able to identify at an early stage those patients at risk of a progressive course and a poor outcome and to have an instrument to monitor the effects of treatment aimed at preventing or limiting joint destruction.

The aim of the study was to investigate to what extent a direct measure of the acute phase response like CRP is a suitable process variable to monitor the course of inflammatory activity of rheumatoid arthritis with regard to progression of joint damage. This question was addressed by analysis of clinical, laboratory and radiological data which were obtained during a prospective follow-up study in patients with recent onset rheumatoid arthritis.
In chapter 1 a review is provided on the nature and the clinical relevance of the acute phase response, in particular for the rheumatic diseases.

In chapters 2 and 3 the relationship between the intra-articular cytokine profile and the systemic acute phase response is described. On the one hand, changes in local interleukin-6 (IL-6) levels are correlated with changes in the levels of other potentially destructive cytokines and mediators of inflammation. On the other hand, changes in local IL-6 levels appear to be related to changes in the systemic levels of IL-6 and acute phase proteins as well as other parameters of inflammatory activity.

In chapters 4 and 5 the global relationship is described between the progression of radiological damage, physical disability and the cumulative values of CRP and joint scores. A highly significant correlation was found between the acute phase response, number of swollen joints and the rate of progression of radiological damage. The use in individual clinical decision making remains limited due to a wide inter-individual variability.

In chapter 6 the significance of rheumatoid factor (RF) isotopes is discussed. The prognostic value of IgA-RF and IgG-RF appears to be limited compared to IgM-RF. Although the course of IgM-RF levels generally reflect the course of the disease, its clinical significance as a process variable is minimal compared to CRP.

In chapter 7 an attempt is made to construct a model describing the individual relationship between CRP and the progression of radiological damage. Using such a model in combination with the prognostic factors, a computer-based "decision support system" can be developed, which may be applicable in clinical practice for the individual treatment of early RA.

References