Chapter 11
Biochemical Markers of Rheumatoid Arthritis and Osteoarthritis: Clinical Utility and Practical Considerations

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Introduction

Biochemical markers of bone and cartilage turnover and degradation are quantitative and dynamic tests that may detect early joint damage, disease progression, and response to therapy and therefore have the potential to be used to evaluate the chondroprotective activity of novel therapies for rheumatoid arthritis (RA) and osteoarthritis (OA). Inclusion of such markers in clinical development programs can provide information for their later use as adjuncts to diagnosis and treatment monitoring. The ultimate hallmark of both RA and OA is joint destruction, and there is a need for rapid, real-time markers to guide therapy.

There are now several biochemical biomarkers with emerging clinical utility and for which robust assays have been developed; these markers can be recommended for inclusion in pharmaceutical clinical trials. Markers specific for articular cartilage and synovium include peptide fragments of type II collagen and procollagen, accessory proteins present within cartilage, and products from synovial membranes. In addition, markers of bone turnover are useful in RA and OA because of the prominence of bone erosions, osteophytes, and/or subchondral sclerosis.

The inclusion of biochemical markers of joint disease in preclinical and clinical development programs for arthritis adds value by providing additional information about the mechanism of action of the investigational drug and by identifying cohorts at baseline that will progress and thus potentially identifying subgroups with a significant treatment response. Moreover, use of biomarkers can potentially differentiate novel drugs in the market after approval.

In this chapter, we provide an overview of biochemical markers currently available for use in clinical trials, including practical considerations. Readers are also directed to Chapter 16 in this volume for a more complete review of the biochemistry and clinical utility of markers for joint disease, with an emphasis on OA.
Pathogenesis of RA and OA

Rheumatoid Arthritis

RA is a chronic systemic inflammatory disease characterized by a destructive polyarthritids. Although extra-articular involvement is common (e.g., vasculitis, which can be life-threatening), the ultimate hallmark of RA is joint destruction. RA is regarded as an autoimmune disease with a polygenic basis, but the precise etiology and specific precipitating events are unknown. The immuno-inflammatory process involves a T-cell activation cascade with a strong \( T_H^1 \) bias, which by means of proinflammatory cytokines (such as TNF-\( \alpha \), IL-1, IL-6, IL-18, and IFN-\( \gamma \)) activates macrophages, synovial fibroblasts, osteoclasts, and chondrocytes. These activated cells degrade cartilage and bone in and around synovial joints, in part by secretion of matrix metalloproteinases (MMPs) [1].

There is a strong association between RA and several types of autoantibodies, the most important being rheumatoid factor (RF) but which also include antibodies to citrullinated proteins. Hence, B cells and autoantibodies, as well as immune complexes and complement activation, may play an important role in RA [1].

Osteoarthritis

OA is the most prevalent form of arthritis and is characterized by progressive loss of articular cartilage and by alterations of periarticular bone and synovial metabolism [2]. Although the damage to articular cartilage is progressive and apparently irreversible in late OA, there is evidence for increased cartilage turnover in early OA, with increased synthesis of the two main structural proteins, type II collagen and aggrecan [3, 4]. Moreover, bone may play an important role in the pathogenesis of OA, in that abnormalities in subchondral bone may result in the release of destructive factors, such as metalloproteinases, that damage the articular cartilage [2].

Role of Biomarkers in RA and OA

Rheumatoid Arthritis

The immuno-inflammatory component of the pathogenesis of RA is generally accepted, and the use of laboratory tests for markers of the activated immune and inflammatory systems is well established; for example, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), B and T cell counts, Ig levels, complement, and autoantibodies such as antinuclear antibody (ANA) and RF. Standard immunology testing will not be discussed further in this overview. Among the autoantibodies,