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Additional diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis

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Abstract

In the past decade significant advantages have been made in the treatment of rheumatoid arthritis (RA) and therapeutic strategies have changed a lot. These days, highly effective disease modifying anti-rheumatic drugs enable intervention early in the disease process, in order to prevent major joint damage.

For years, serological support in the diagnosis of RA has been limited to the presence of rheumatoid factors, although not very specific for RA. During the last years a variety of circulating non-RF antibodies have been discovered and reported to be of potential diagnostic value. CCP2 proved to be a very disease-specific and even sensitive marker for RA. In addition to the diagnostic properties, CCP showed to be a good prognostic marker, CCP helps to predict the erosive or nonerosive progression of the disease, and CCP is already present early in the disease. This diagnostic tool enables the clinician to choose the optimal therapeutic management for each single RA patient.

Keywords: Rheumatoid arthritis; Rheumatoid factor isotypes; Anti-cyclic citrullinated peptide antibodies

Contents

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; AKA, antikeratin antibodies; APF, antiperinuclear factor; CCP, cyclic citrullinated peptide; DMARD, disease modifying antirheumatic drug; ELISA, enzyme-linked immunosorbent assay; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.

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1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, affecting 1–2% of the world population and causes annual medical care and lost productivity costs of approximately US$65 billions [1]. It is a systemic, inflammatory autoimmune disease of unknown origin, characterized by chronic joint inflammation that often leads to destruction of bone and cartilage. Apart from pain, RA is associated with reduction of functional capacity, and increased comorbidity and mortality [2,3].

For decades, the diagnosis RA has been primarily based on clinical manifestation. However, especially during the first few months of the disease, the 1987 revised criteria of the American College of Rheumatology (ACR) [4] are rarely met. About one third of the patients with persistent arthritis do not fulfill the classification criteria, so it is often difficult to diagnose RA in very early stages of the disease. On the other hand, numerous studies have shown that substantial irreversible joint damage occurs within the first 2 years [5,6]. In the last few years, significant therapeutic advances have been made and there is growing evidence that only therapeutic intervention early in the course of RA leads to earlier disease control, less joint damage, and a better prognosis [7,8]. Since the current therapeutic strategies in RA recommend increasingly aggressive treatment regimens early in the course of disease, it is mandatory to differentiate between persistent erosive RA, self-limiting disease and other forms of arthritis early after symptoms onset. The highly variable and unpredictable course of disease implicates the need for a serological marker which allows to predict, in early course of RA, the erosive or nonerosive progression of the disease. A diagnostic test with high specificity and sensitivity would be desirable to choose the optimal therapeutic management, since the use of disease modifying anti-rheumatic drugs (DMARDs) can only be justified if their efficacy and benefits outweigh risks and costs [9].

2. Antibodies in RA

2.1. Rheumatoid factors

So far, serological support in the diagnosis of RA was mainly based on the presence of rheumatoid factors (RF) [10]. The rheumatoid factor was first described more than 75 years ago. Since then a vast amount of work has been performed on the incidence, nature and specificity of RF [10–12]. Specificity and sensitivity of RF have been improved by the development of enzyme-linked immunosorbent assays (ELISA), which permit the detection and quantitative measurement of RF in various immunoglobulin classes (IgG-, IgA-, IgM-RF). RF can be detected in up to 70–80% of RA patients [12], with the IgM class being the most common. Indeed, the American College of Rheumatology criteria for RA diagnosis include the presence of RF, a decision that has contributed to the widely routine use of this test as a diagnostic marker for RA in most clinical laboratories. However, these antibodies, directed to the Fc part of IgG, are not very specific for RA and can also be detected in other rheumatic diseases, infectious diseases, and even in 3–5% of apparently healthy individuals [10,13].

2.2. Anti-cyclic citrullinated peptide antibodies

During the last years a variety of circulating non-RF antibodies have been discovered and reported to be of