

Disease-specific biomarkers for early diagnosis of rheumatoid arthritis and other chronic arthritic conditions

Abstract

Despite recent advances in the treatment of rheumatoid arthritis (RA), including the introduction of biologic therapies and employment of combination disease-modifying anti-rheumatic drug (DMARD) strategies, remission rates remain suboptimal and patients with RA are still missing a significant number of work days. Early diagnostic criteria are needed to ensure that appropriate treatment is initiated early to prevent joint damage. Better prognostic markers are also needed to identify patients with the potential for poor outcomes, in whom more aggressive strategies can be applied at the outset. Because of stringent inclusion criteria and heterogeneous definitions of remission, results seen in clinical trials of RA are not necessarily generalizable to results seen in clinical practice. As a result, existing guidelines may not adequately reflect current practice. In the absence of biomarkers to predict the course of disease, methotrexate remains the standard of care initially for most patients with RA. The ability to predict the course of disease could allow more appropriately targeted therapy and higher rates of remission.¹

It is clear that there is a current unmet medical need for a novel diagnostic kit which will diagnose more accurately and earlier, the presence of chronic arthritic conditions. Two biomarkers, expressed during early stages of the establishment of the inflammatory conditions, discovered by us; galectin and CD44 proteins, has a potential to provide the missing tools for development of robust diagnostic and prognostic assays that will guide treatment choices and leading to improved patient care. The clinical and business advantages of such novel diagnostic kit are huge, especially for the benefit of the RA patients.

Keywords: rheumatoid arthritis, diagnosis, inflammatory disease, rheumatoid factor

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Abbreviations: RA, rheumatoid arthritis; RF, rheumatoid factor; MSDs, musculoskeletal disorders; GDP, gross domestic product; T2T, treatment to target

Introduction

The social problem to overcome and the resulting business opportunity

RA is a chronic, disabling autoimmune condition which predominantly impacts upon the joints, but can also affect other organs, such as the heart and lungs. The Fit for Work study showed that over 44 million (one in six) members of the European Union (EU) workforce now have a long-standing health problem or disability that affects their ability to work, and musculoskeletal disorders (MSDs) account for a higher proportion of sickness absence from work than any other health condition: 9.5 million were lost in one year in the UK alone. It is estimated that up to 2% - €240 billion - of European gross domestic product (GDP) is accounted for by the direct costs of MSDs each year.² Over 2.9 million people in Europe have rheumatoid arthritis (RA), many are of working age. On average, every third person with RA becomes work disabled and up to 40% leaves work completely within 5 years of diagnosis. Many people with RA want to stay in work but are unable to because their condition is not diagnosed or treated early enough, or with the right treatment. In the UK, the National Audit Office has calculated that a 10% increase in people with RA being treated within 3 months of diagnosis could result in productivity gains of £31m for the economy due to reduced sick leave and lost employment.³

Costs related to RA are generally those arising from disability, medical expenses and reduced quality of life. Although MSDs costs tend to be related to high morbidity rates, in some cases, such as RA, there is also increased mortality. A survey conducted by Arthritis Ireland provides further insights into the impact of the condition on employment. In 2008 a survey of people with RA showed that 70% were not able to work outside the home because of their condition and that the annual cost of lost productive time due to RA was estimated at €1.6 billion.⁴ A second survey, including Irish people with other forms of arthritis, showed that 67% of those who did not work or worked part-time stated it was because of their condition and that almost half had changed or left employment because of arthritis. The damaging impact, of RA, on the health and labour market participation of working age people in many other European and Western countries is very similar, for example;

- Lithuania: 16% of RA patients withdraw from the labour force after 1 year of disease diagnosed and almost 50% withdraw after 10 years of the onset of the disease.⁵
- Germany: 42% of female RA patients are employed, whereas 58% of male RA patients are employed.⁶
- Greece: one study reports that the prevalence of RA, in Greece, is 0.68. The prevalence rate increased significantly as age increased up to the 50-59 year old age group. Individuals aged 50-59 years had the highest prevalence rate of 1.2%.⁷
- Czech: data reveals that the annual incidence for RA was 31 per 100,000 adults aged 16 or above. The prevalence rate of RA was shown to be 610 per 100,000 among adults aged 16 and over.

There are approximately 20,000 new cases of rheumatoid arthritis in the UK every year.⁸ These data show that most people who acquire RA do so when they are of working age and are productive, contributing members of society. It is obvious from the above that the incidence of RA amongst productive members of society in the European Union is causing significant distress, economic costs, and loss of productivity which affects Europeans quality of life in addition to placing additional burden on health care systems and health budgets across the EU.

Therefore the economic impact of early intervention will be significant

Recent studies have indicated that early intervention can significantly reduce the clinical impact of the condition. Treatment choices for RA patients include corticosteroids and disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate. For patients who fail to respond to these conventional therapies, the additional use of biologic TNF inhibitors offers greater opportunities for disease management and these drugs represent an important step forward in the treatment of RA.

However, TNF inhibitors are not curative and may therefore require years of therapy resulting in high costs (approximately €12,000 per annum per patient) and the potential for serious infections, cancer and other adverse outcomes. In addition, about a third of patients fail to respond adequately to anti-TNF therapy (primary non-response) and in a significant proportion of patients who initially respond well, there is a progressive loss of efficacy (secondary non-response). Additional biological therapies include anti-CD20, CTLA4-Fc, and anti-IL-6R and, in general, patients who exhibit an inadequate response to one or more TNF inhibitors will be offered treatment with one of these biologics. Treatment to target (T2T) is a relatively new approach to the treatment of RA that involves measurement of disease activity and adjustment of therapy accordingly in order to optimise outcomes. Increasingly, and in line with patient expectations, the treatment target is remission, which is defined as the absence of signs and symptoms of significant inflammatory disease activity.

The measurement of disease activity typically relies on binary measures, such as presence/absence of swollen and painful joints. There is, however, a lack of disease-specific and quantitative biomarkers of joint inflammation. C-reactive protein and erythrocyte sedimentation rate offer quantifiable measures of systemic inflammation but are a poor reflection of events in the joint. This makes the objective and accurate measurement of inflammatory disease activity difficult to achieve in practice. This question is of particular significance in the era of targeted therapy with biologics because of the extremely high costs involved and because of the potential for irreversible structural damage during the period in which ineffective drugs are prescribed. Hence, it is important to develop robust and sensitive measures of inflammatory joint disease activity, in particular when this is linked to local tissue destruction, in order to enable timely switching of drugs in the case of sub-optimal response to therapy.

Biomarkers for rheumatoid arthritis

Findings from the Best trial indicate that early therapeutic intervention can result in disease remission in a substantial proportion of RA patients.⁹ In practice, however, diagnosis, and hence therapeutic intervention, is frequently delayed, resulting in increased tissue damage. Even “early” diagnosis is currently made once erosion of cartilage and bone has already begun, a time at which the window

for optimal treatment may have been missed. Biomarkers that allow earlier diagnosis of RA in patients who present with undifferentiated arthritis are needed. The most significant progress in the diagnosis of RA over the last decade has been the development of assays for the detection of autoantibodies against cyclic citrullinated peptides (anti-CCP antibodies).¹⁰

Anti-CCP antibodies may be involved in the pathogenesis of RA¹¹ and, unlike the traditional RA biomarker rheumatoid factor (RF), are highly specific to RA.¹² However, the diagnostic sensitivity of anti-CCP antibody positivity in cohorts of early synovitis has been reported to range between 40% and 71%.¹³⁻¹⁵ This may partly be because approximately 30% of RA patients never develop anti-CCP antibodies.¹⁶ Thus, the search for biomarkers that provide greater sensitivity and specificity in the diagnosis of early RA continues.

Novel RA-specific biomarkers for early diagnosis of RA and other chronic arthritic conditions

Previous work, performed by us, demonstrated the importance of the CD44 pathway in the pathogenesis of arthritis¹⁷ and further studies identified a modified CD44 variant (designated CD44vRA) expressed on synovial cells from RA patients.¹⁸ Sequence analysis of CD44vRA cDNA (of 147 human patients with different arthritic conditions) revealed an additional intron-derived trinucleotide, CAG, which allows translation of an extra alanine residue in 75% of the patients. This insertion results in a conformational change in CD44vRA, generating an immunogenic epitope and facilitating the production of disease and inflammation specific antibodies.¹⁹ Subsequently, it was shown by affinity chromatography, flow cytometry, and surface plasmon resonance, that galectin-8, is a high-affinity ligand of CD44vRA.²⁰ It was further shown that synovial cells from RA patients express and secrete galectin-8, to a concentration of 25-65 nM.²⁰ Importantly, it was shown that galectin-8 causes apoptosis of synoviocytes and peripheral blood leucocytes (PBLs) of patients with RA and that administration of the arthritic-specific human galectin-8 protein has a therapeutic effect in established CIA in DBA/1 mice.²¹ Hence, CD44vRA and galectin-8 serve as quantifiable, process-related and disease-specific biomarkers for RA which we propose to use for early diagnosis of these inflammatory conditions.

In summary, significant progress has already been achieved; we have identified a modified human galectin-8 molecule in joint synoviocytes derived from rheumatoid arthritis and other arthritic patients-designated arthritic-specific human galectin protein. A provisional patent relating to its sequence was submitted in 2015. Modified CD44 molecule has been detected in joint synoviocytes derived from RA patients-designated CD44vRA, this discovery was protected also by patents. In addition, we successfully validated the CD44vRA protein as a specific biomarker for autoimmune inflammatory diseases; in different arthritic conditions and Crohn's disease during the participation in the FP7 European program.

The future R&D plan will involve the establishment of highly sensitive assays to quantify blood levels of CD44vRA and galectin-8 variants in patients with RA and other chronic arthritic conditions. This will allow us to relate serum levels of CD44vRA and galectin-8 to levels of disease activity, as measured by conventional parameters. More importantly, changes in serum levels of CD44vRA and galectin-8 in RA patients will be related to the clinical and histological response to therapeutic intervention with TNF inhibitors and other treatment modalities.

Summary

There is currently a marked lack of clinical useful disease - and process - specific biomarkers in the field of rheumatology which is hampering progress towards optimal approaches to treatment sequence and most effective management of these conditions. Our research provides unique opportunity to develop novel innovative diagnostic kit based on previously identified and validated biomarkers for early diagnosis of RA and other arthritic conditions within a clinical research setting. Such novel innovative product has huge commercial potential for short-term uptake (within five years) in the clinic and offers a platform for further diagnostic, biomarker and therapeutic developments for the benefit of human patients.

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Conflicts of interest

Author declares that there is no conflict of interest.

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