Spotlight

Biomarkers in Rheumatology: The Present and Future Outlook

Introduction

Rheumatoid disorders ranging from Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) to ankylosing spondylitis (AS) have seen huge therapeutic advancements over the last decade. From the release of the groundbreaking anti-TNF products, through to the arrival of new biologic agents including interleukin inhibitors, JAK inhibitors and anti-TKY-2 inhibitors, patient experience has been significantly improved. These advancements have provided ever increasing convenience, efficacy and tolerability. However, diagnostic and predictive biomarkers remain one area within the rheumatoid conditions that have seen limited commercial development in recent years. Late diagnosis and unpredictability of patient response to biologic treatment remains a major unmet need within rheumatoid disorder causing both underdiagnosis and repeated treatment failures in patients.

A number of diagnostic biomarkers currently show promise for RA, and predictive biomarkers hold huge potential, particularly in PsA. This article will look to explore a number of different biomarkers currently under investigation and the potential influence this will have for pharmaceutical companies working within the space.

Diagnostic biomarkers

Several serological biomarkers form the basis of RA diagnosis, including C-reactive protein, Rheumatoid Factor and anti-CCP levels. Elevated levels result in a diagnosis of RA1. However, these biomarkers lack sensitivity and specificity to achieve early diagnosis in some patients, potentially leading to progression before disease is detected. Similarly, biomarkers used in AS such as HLA-B27 status, C-reactive protein and erythrocyte sedimentation rate may have only moderate diagnostic value2. The use of biomarkers for diagnosis in PsA has been even more limited, with few biomarkers available to differentiate the disease from PsO3.

Whilst diagnostic biomarkers are under investigation across rheumatological conditions, the greatest progress appears to have been made within RA. A recent study1 has shown that in a patient group with negative Rheumatoid Factor and anti-CCP readings (who would not receive a diagnosis of RA based on current biomarkers) a set of novel biomarkers could potentially have achieved an earlier RA diagnosis. The biomarkers of interest, which have been supported by past research, included:

01 **Angiotensinogen (AGT)4**

02 **Serum amyloid A-4 protein (SAA4)5**

03 **Vitamin D-binding protein (VDBP)6**

04 **Retinol-binding protein-4 (RBP4)7**

These biomarkers had distinguished seronegative patients from healthy controls1. Earlier diagnosis of RA patients via additional biomarker screening could hold huge future potential. The ability to identify, treat and manage RA patients earlier could have the potential to prevent progression to more systemic and severe disease, and further progression to skin involvement.

The implications to the rheumatoid space as a whole remain wide open. Improved disease detection creates opportunities for pharmaceutical companies to gain traction earlier in the treatment paradigm, potentially expanding their target patient population to include those with less severe disease. However, the complexity of rheumatoid disease is further underscored by the frequent need to utilise multiple different biologic treatments before achieving positive results, highlighting the importance of predictive biomarkers as well.

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Response prediction biomarkers

A number of studies are currently in progress across rheumatoid disorders to investigate potential predictability of treatment response. One disease area showing significant promise for predictive biomarkers is PsA. The PsA treatment landscape has evolved rapidly over the past decade, with a huge number of efficacious treatments entering the market, targeting different mechanisms of disease. One area that remains unknown is the expected response of individual patients to individual treatments.

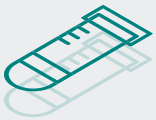
Decisions of expected treatment response are often based on grouped clinical trial data and physician experience with product/ future expectations of efficacy. A high unmet need exists for biomarkers that could accurately predict the responses of individual patients to varied treatments. Some biomarkers (DAS-28, CRP) have been utilised as a way of monitoring response to treatment, but this is often variable by patient type. Further investigation is under way for biomarkers in a variety of sites throughout the human body. These include genetic markers, as well as markers within the blood or within the tissue. A number of promising biomarkers have been identified in recent years:

Genetic

Two genetic polymorphisms have been identified that are associated with improved QoL at 3-month after initiation of an anti-TNF8

Further investigations are underway to investigate the link

Circulating biomarkers



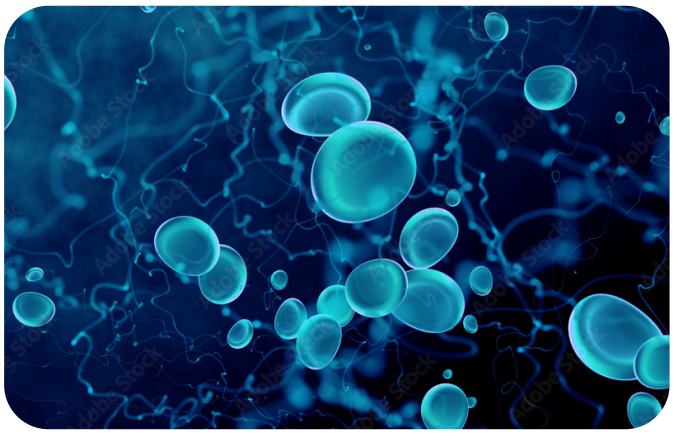
Complement component C3 was identified to associate with response to adalimumab and entanercept after 22 weeks of treatment9

A synovial-derived biomarker (14-3-3 eta) is associated to better response to adalimumab10

Tissue biomarkers

Haptoglobin, actin, serum albumin, annexin A2, serum amyloid P, Collagen 3 and fibrinogen have all shown potential associate to better response to treatment 11

Further investigations are underway to investigate the link



Additional work is required to investigate the potential of various biomarkers within PsA. 'Mulit-omic' approaches, those that consider the various factors causing PsA, can combine data from genetics, environmental factors and metabolites to further investigate the predictive biomarker potential.

The current trial-and-error process of selecting treatments for rheumatoid disorders can leave patients, and providers, feeling frustrated and discouraged. Predictive biomarkers thus could identify treatments with high potential efficacy, forgoing this process. While it remains to be seen, it will be interesting to watch for the impact of such tests on the approval process and potential 1L use.

Currently, many biologic medications require prior authorisations and step edits for patient use. Predictive biomarkers could theoretically be leveraged with payers to demonstrate value, ultimately placing these therapies earlier in the treatment paradigm and potentially decreasing the costs associated with worsening disease. Such tests could further drive volume of specific products, encouraging earlier use in individual patients who might otherwise fail on other medications first.

Conclusion

Diagnostic and predictive biomarkers hold a huge potential to revolutionise the diagnosis, treatment, and management of rheumatoid conditions and other autoimmune conditions. Both could act as a huge disruptive force to the current use of specific treatments, as various markers increase in importance. Pharma should continue to monitor and innovate within the space to further improve the quality of life of patients living with rheumatoid disorders.

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