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USE OF BIOMARKERS IN PROGNOSIS AND MONITORING OF DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS IN COMMON CLINICAL PRACTICE

Rheumatology

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ABSTRACT

Rheumatoid arthritis appears to be a major health hazards in growing environment affecting the quality of life. There are several biomarkers like CRP, ESR, RA factor, Anti CCP & DAS-28 that helps to determine and monitor disease activity and treatment response. The study was carried out on 27 RA patients, there shows significant reduction in value following treatment. RA Factor changes are not significantly correlate with treatment. Exacerbation of symptoms or acute presentation is commonly presented with elevated level of CRP and ESR, post treatment it reduced to 8.36 and 37.85. DAS score changes also significant from 3.5 (moderate severity) to 3.1 (low disease activity). High anti CCP value is associated with increased risk of joint destruction. Biomarkers hold a significant value in diagnostic, prognostic and monitoring of the disease in Rheumatoid arthritis in common clinical practices.

KEYWORDS

Rheumatoid Arthritis, Biomarkers, CRP, RA factor, AntiCCP, DMRD, DAS

INTRODUCTION

Rheumatoid arthritis is a chronic, inflammatory, multisystem involved autoimmune disorder that causes synovial joint damage leading to inflammation, pain and later into disability. Though it involves mainly joint but extra-articular involvement is common like skin, eye, lung or renal involvement. Rheumatoid arthritis (RA) is three-times more common in women than in men and can begin at any age.[1] The resultant disability due to pain and joint destruction leads to loss of work and decreased quality of life contributing burden in socio-economic life.

RA remains a clinical diagnosis although the use and discovery of biomarkers helps to assist with the diagnosis and prognosis. The 2010 RA Classification Criteria developed by the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) define a scoring system that includes elements of history, physical exam, and biomarkers that identify patients with RA for the purpose of clinical trial standardization.[2] In RA pathology cellular events that occurs alters protein biomarkers, reflecting the process in cell signaling. Progression and disease activity can be monitored with these markers, and appropriate treatment also changes the biomarkers. In clinical practice most commonly encountered biomarkers are Rheumatoid Factor, Autoantibodies against Citrullinated Proteins (ACPA), Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP); sometimes Multi-biomarker disease activity (MBDA) also plays a role. Rheumatoid factor (RF) is an IgM antibody which targets the fragment crystallisable (Fc) portion of the immunoglobulin G (IgG) forming an immune complex that promotes inflammation.[3] Among ACPA most commonly found one is Anti CCP2 and they have excellent diagnostic and prognostic value. CRP and ESR works as an inflammatory marker. MBDA score helps to assess the prognosis of the disease. 14-3-3n is unique RA bio marker but we didn't include in study because it's not readily available. In this study we tried to understand role of the following biomarkers: ESR, CRP, RF, antiCCP and DAS28 Score in the diagnosis and treatment prognosis of RA and to assess the effectiveness of monitoring this routinely.

METHODS:

The present study was carried out on 27 RA patients, who have fulfilled the 2010 ACR/EULAR criteria. All cases were selected from orthopedic and medicine OPD of a tertiary hospital and followed up for around 12 months. We have checked the biomarkers every 12 weeks for follow up and the effectiveness of treatment. Every patients have active RA and on DMRD. The study was institution based prospective study. The study had local Research Ethics Committee and Research and Development approval, and all participants gave their written informed consent. Among 27 RA patients 2 patients have lost follow up so they are not included in final result. DAS 28 Score is calculated obtaining clinical examination data using a online calculator.

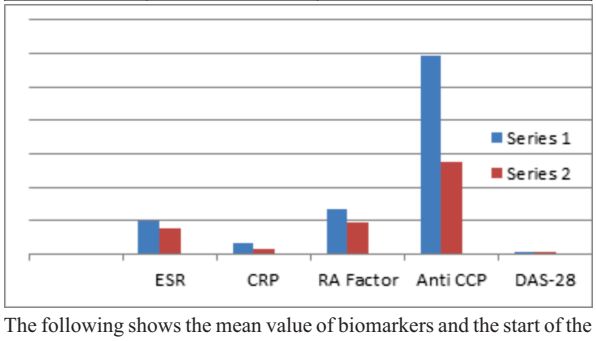
Inclusion Criteria: 1. Active RA (2010 ACR/EULAR) 2. Patients managed through OPD (without any severe co-morbidity 3. On oral DMRD

Exclusion Criteria: 1. Pt on injectables DMRD 2. Patient on clinical remission. 3. IPD patients

RESULTS:

Presenting the demographic data the mean age of patients is 45.57 and the patient group was compromised of 6 males and 19 females. The mean value of the morning stiffness is 80.23 minutes. When enquired about family history it shows 11 patients shows positive family history. RA is closely associated with a family history of arthritis, though most of the patients can't differentiate between specific arthritis. In co-morbidity history 9 was found diabetic and 11 among them are suffering from hypertension.

Bio markers	Presentation	During treatment follow up
ESR	49.375	37.85
CRP	16.64	8.36
RA Factor	67.22	48.5
Anti CCP	296.03	138.22
DAS-28	3.5	3.1



The following shows the mean value of biomarkers and the start of the treatment or presentation and during fellow up. At presentation mean value of ESR was 49.375 and during treatment it significantly reduced. CRP is an acute phase reactant and present in inflammatory. We found that Mean level of CRP 16.64. RA factor is autoantibody that reacts with FC portion of IgG. IgM RAF is most commonly measured in clinical practice. Average value of RAF in our study is 67.22. Anti CCP has excellent diagnostic and prognostic value.

DISCUSSION:

The results of our study show that inflammatory markers are elevated in RA. In the RA synovium, there is an overabundance of pro inflammatory cytokines that stimulate the production of CRP by the liver, thus making it an attractive candidate as a disease activity biomarker.[4] In our study it is commonly found that exacerbation of symptoms or acute presentation is commonly presented with elevated level of CRP and ESR. During treatment it significantly settles down. Post treatment average CRP is8.36 and ESR is 37.85. This value correlates with study of Srivastava et al where they found the mean level of hs-CRP was high, significantly increased in RA cases (8.58 ± 5.99 mg/L) as compared to the healthy controls.[5] The 2010 ACR/EULAR Classification Criteria for RA includes CRP and ESR value for diagnosis. Even CRP <1mg/dl is suggestive of remission.[6] In the systemic review of 23 studies of 2020 and 2021 it shows high CRP >7.1 mg/dl during DMRD shows poor outcome.[7] We considered regimen change from csDMRD to biological DMRD and addition oral/systemic steroid in that instances. Studies show significant correlation with functional outcome RA with ESR and CRP. Elevated ESR is better predictor in early RA whereas CRP in late stage.[4] Though ESR and CRP are normal in about 40% of patients with RA.[8] Furthermore, even in those patients with baseline elevation; values may remain stable despite clinical improvement with treatment.[2]

Though most commonly advised 30% of RA patients may present with sero negative RA.[9] In our study we found decrease in level from 67.22 to 48.5, but it's far above the normal level. The level of RA factor though inconclusive but provide some indication to the prognosis, rather poor one in this variable disease.[10] Serial monitoring of RA factor is not at all recommended.[11] But presence of sero positivity influence treatment while using biological DMRD showing increased response to B Cell depleting monoclonal antibody (MAB).

Both RA Factor and AntiCCP have same sensitivity but later is more specific.[12] It is not only a important diagnostic marker but also contributes in pathogenesis. High titers of anti CCP with positive RF contribute highly as diagnostic marker. Prognosis is also indicated, in our study we found those with high value anti CCP having aggressive disease and frequently complaining of large and small joint pain. Patient with high anti CCP value is associated with increased risk of joint disease as predicted in our study also supports the finding of study of Meyer et al, Rönnelid J et al. [13,14,15] High titer anti-CCP2 is associated with better clinical response to certain biologics (rituximab, abatacept) and thus may aid clinicians in personalizing therapy for the greatest chance of response.[2]

In the study of Takeuchi T, et al concluded that patient with csDMRD bone erosion and cartilage destruction could be predicted by positive RF, antiCCP and high CRP level. Incidence was 29.4% in new cases increased to 38.4% in presence of antiCCP and further increased to 48.4% when two factors come together.[16]

The ACR has allowed 6 disease activity measures to evaluate RA burden; DAS using CRP / ESR is one of them. DAS-28 score has a strong association with anti CCP and Rapid Radiological Progression (RRP) of joint erosion. In our study we found DAS-28 ESR average was 3.5 which is suggestive of moderate disease activity at presentation, after treatment with DMRD it shows 3.1 which is suggestive of low disease activity and among them 7 patients' shows moving towards remission as per DAS score. The MBDA score correlates with the 28-joint disease activity score using C-reactive protein (DAS28-CRP).MBDA is now considered as the best indicator of RA monitoring and clinical response.[17] Monitoring RA disease activity and gauging treatment response using DAS score depends upon physician patient response and ESR/CRP count. The key disadvantage using DAS-28 is reliability, recent studied have shown inconsistencies.[18]

CONCLUSION:

The biomarkers in RA have significant utility in clinical practice. They correlates with disease activity and act as a potential predictor of response to treatment.

Whereas RA and AntiCCP acts as a diagnostic biomarker, high titers of RA and anti CCP , along with CRP can also use as a prognostic marker in clinical practice.[19] In treat the target recommendation DAS 28 score along with SDAI and CDAI acts as a tool to monitor disease activity. In several studies DAS score demonstrated its performance in measuring treatment response & disease activity.[20] Biomarkers in the prediction of treatment response commonly present with csDMRD, but with newly available tsDMRD studies are not available. Using 14-3-3 eta protein, MBDA might find the answer but not easily available right now.

So, as per existing evidence these biomarkers are important tools in our clinical practice. However there are lacks of literature exploring biomarkers are which are resistant to treatment before starting the therapy and there also lack of specificity in easily measurable biomarkers.

Ethical Statement:
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Ethical Approval: taken

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