A study of high sensitive C-reactive protein in rheumatoid arthritis patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is not only merely limited to joints but has many extraarticular features. The major cause of mortality in RA is cardiovascular disease (CVD). Inflammation in RA predispose them to succumb to CVD. The aim of this study to observe whether therapy with disease-modifying anti-rheumatic drugs (DMARD) decreases inflammation and if it does so then it can be said that decrease the risk to develop CVD. Aim and objectives were to assess hs-CRP level in early and established RA both at diagnosis and again at 3 months of DMARD therapy and compare between them.

Methods: Total 58 early RA (group A) and 58 established (group B) DMARD naïve RA patients were included in the study. Age, BMI, haemoglobin, random blood sugar, lipid profile, ESR, hs-CRP, RA factor and anti-CCP were measured. All of them were treated with DMARD and hs-CRP was again assessed after 3 months.

Results: The mean hs-CRP level at diagnosis was 6.14±1.90 mg/l in group A while it was 10.39±3.13 mg/l in group B. The mean hs-CRP level after 3 months of DMARD was 2.56±1.35mg/l in group A while it was 7.91±3.13 mg/l in group B. The mean reduction in hs-CRP level in early RA (3.58±0.99 mg/l) was statistically significantly (p<0.001) higher than that in established RA (2.48±0.09 mg/l).

Conclusions: DMARD decreases level of inflammation in RA more efficiently if initiated early in the course of the disease.

Keywords: Rheumatoid arthritis, High sensitive C-reactive protein, Disease modifying anti-rheumatoid drugs

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting the synovial joints that also often lead to extra articular manifestations which greatly hampers the quality of life of patients and in some cases may even prove fatal in the absence of proper interventions.

The extra-articular manifestations are diverse which includes subcutaneous nodules, pleuropulmonary involvement, ocular involvement, renal disease, cardiovascular disease, peripheral neuropathy, vasculitis, and hematologic abnormalities. These manifestations occur almost exclusively in patients who are seropositive for rheumatoid factor, and they often cluster together. The extra-articular manifestations of RA are usually related to uncontrolled inflammation and associated with increased cardiovascular (CV) mortality suggesting that processes intrinsic to RA pathogenesis may play important role in CV damage and its clinical consequences.

The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes,
and cigarette smoking. Furthermore, congestive heart failure occurs at an approximately two-fold higher rate in RA than in the general population.

The presence of elevated serum inflammatory markers appears to confer an increased risk of CV disease in this population. Inflammation plays a central role in the pathogenesis of atherosclerosis. Marker of inflammation, such as C-reactive protein (CRP) is predictive of future cardiovascular (CV) events in healthy individuals and may be useful in identifying patients with coronary artery disease (CAD) who are at risk for recurrent CV events.5,6

In 2015, American College of rheumatology (ACR) has made distinction in the treatment of patients with early (<6 months of disease duration) and established disease (>6 months of disease duration).3 Early treatment is more beneficial than delayed therapy. Patients with prolonged arthritis have more atherosclerosis than patients of the same age with more recent disease onset.9 However, even patients with early RA show evidence of increased subclinical atherosclerosis, as assessed by carotid intima media thickness (CIMT) and coronary calcification.5 This suggests that atherosclerosis accelerates after the onset of RA.

So, if treatment is initiated early, we can decrease the risk of CVD in RA patients.

**Aims and objectives**

1) To assess hs-CRP level at diagnosis of disease modifying anti-rheumatic drugs (DMARD) naïve rheumatoid arthritis patients. 2) reassess hs-CRP after three months of DMARD therapy in DMARD naïve rheumatoid arthritis patients. 3) correlate the changes in the two parameters. 4) to compare the same parameter between early and established RA patients.

**METHODS**

The study protocol was approved by the Ethics Committee of S.M.S. Medical College and Attached hospital, Jaipur, India. This was a hospital based prospective observational study carried out in the Upgraded Department of Medicine, Jaipur, India from April 2018 to March 2019. After informed consent, 58 early RA patients and 58 established RA patients who were newly diagnosed and DMARD naïve were taken in the study. Patients having diabetes, hypertension, dyslipidemia, liver, kidney, thyroid dysfunction, any documented previous or current cardiac illness or family history of coronary artery disease or hyperuricemia, pregnancy, or with coexisting disease associated with high uric acid levels e.g., malignancy, chronic renal failure, active chronic infections e.g. Tuberculosis were excluded. Known smoker or alcoholics were also excluded. Patients were diagnosed of having RA using ACR 2010 criteria.

hs-CRP was estimated by automated cartridge based specific protein analyser Mispa i3. This is based on latex-enhanced turbidimetric in-vitro immunoassay. CRP in the sample binds to specific anti-CRP antibodies, which had been adsorbed to latex particles and agglutinates. The agglutination is detected as an absorbance change. The magnitude of the change is proportional to the concentration of CRP in the sample. The actual concentration is then detected by interpolation from a calibration curve prepared from calibrators of known concentration.

**Statistical analysis**

The collected the data were transformed into variables, coded and entered in Microsoft excel sheet. Data were analysed and statistically evaluated using statistical package for social sciences (SPSS)-PC-20 software (version 20, SPSS, Inc, Chicago, IL, USA). Data are presented as mean and standard deviation (SD) for normally distributed continuous variables and as frequencies for categorical variables. Pearson’s chi-square test was performed for the comparison of categorical variables, and the means of normally distributed continuous variables were compared by Student’s t-test. Correlation was tested with Pearson’s analysis, where appropriate. P value of<0.05 was considered to be significant.

**RESULTS**

Baseline clinical characteristics at diagnosis is depicted in table 1. Total number of participants were 116. They were grouped as group A (n=58) with early RA and group B (n=58) with established RA. There were 35 male subjects and 81 (69.8%) female subjects.

| Table 1: Baseline characteristics of subjects at diagnosis. |
|-----------------------------------------------------------|
| **Group A (early RA) (n=58)** | **Group B (established RA) (n=58)** | **P** |
| Age (kg) | 36.62±5.87 | 39.34±6.02 | 0.171 |
| BMI (kg/m²) | 23.47±1.62 | 20.04±0.99 | <0.001 |
| RBS (mg/dl) | 102.4±22.29 | 98.02±9.57 | 0.171 |
| ESR (mm/hr) | 69.21±24.40 | 100.43±24.33 | <0.001 |
| Hemoglobin (gm/dl) | 11.56±1.64 | 9.40±1.03 | <0.001 |
| Platelet counts (lakh/mm³) | 2.33±0.86 | 3.62±1.00 | <0.001 |
| HDL (mg/dl) | 45.31±8.23 | 37.97±5.59 | <0.001 |
| LDL (mg/dl) | 47.90±8.57 | 66.74±10.87 | <0.001 |

Continued.
Mean age of the study population was 37.97±6.12 years. There were significant differences in age, BMI, ESR, haemoglobin, platelet count, HDL, LDL, triglycerides between group A and group B.

The mean hs-CRP level at diagnosis was 6.14±1.90 mg/l in group A while it was 10.39±3.13 mg/l in group B (Table 1) and (Figure 1). This difference in mean hs-CRP was found to be statistically significant (p<0.001). This suggests that a higher level of inflammation is present in patients with established RA as compared to early RA patients. The mean hs-CRP level after 3 months of DMARD was 2.56±1.35 mg/l in group A while it was 7.91±3.13 mg/l in group B (Figure 2).

Figure 1: Distribution of hs-CRP (mg/l) level at diagnosis.

Figure 2: hs-CRP level at 3 months.

Figure 3: Reduction of mean hs-CRP (mg/L) level after treatment.

Figure 4: Correlation between hs-CRP level at diagnosis with change after 3 months.
This difference in mean hs-CRP was also found to be statistically significant (p<0.001). The mean reduction in hs-CRP level in early RA (3.58±0.99 mg/l) was statistically significantly (p<0.001) higher than that in established RA (2.48±0.09 mg/l) (Figure 3). This indicates that early treatment reduces hs-CRP significantly. It was observed in present study that hs-CRP at diagnosis showed a negative correlation with change in hs -CRP level, that was statistically not significant (P>0.05) (Figure 4). The Pearson’s correlation coefficient ‘r’ found to be -0.017 established the strong negative correlation between two parameters. Although, not statistically significant, this study shows that hs-CRP level decreases after the start of DMARD.

**DISCUSSION**

We studied hs-CRP level in patients of RA who were DMARD naïve. We also studied the effect of DMARD on the above parameter in both early and established RA patients.

In our study, 30% (n=35) subjects were male and 70% (n=81) were female. The ratio of female to male was 2.3:1. Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2-3:1 ratio. In a cross-sectional and analytical study by Barragán-Martínez et al in which 1128 consecutive colombian patients with RA were assessed in which they found a high prevalence of RA in women with a ratio of 5.2 women per man.8

In our study, the mean hs-CRP level was significantly more in group B than in group A. As, CRP is an acute phase reactant, its level is increased in infection and inflammation. 356 We have excluded patients with infections from our study, so the increase in CRP level indicates that a higher level of inflammatory milieu was present at diagnosis in established RA patients than in patients with early RA. Orr et al did a observational study in 223 consecutive rheumatoid arthritis patients reporting knee arthralgia who underwent synovial sampling of the affected knee via needle arthroscopy.9 A statistically significant positive correlation was observed between CRP and the level of inflammation in the biopsy retrieved (n=197, rho=0.43, CI 0.30-0.54, p<0.0001).

Kervinen H et al measured baseline and pre-event CRP levels in patients who had myocardial infarction or coronary death and concluded that elevated CRP enhances the risks attributed to classic coronary risk factors.10 Koenig et al measured CRP and traditional cardiovascular risk factors at baseline in 3435 white men of German nationality and their results suggested that CRP enhances global coronary risk as assessed by the FRS.11 Thus, established RA patients with higher hs-CRP having higher degree of inflammation are more prone to develop CVD than those with lower hs-CRP.

Although, not statistically significant, this study shows that hs-CRP level decreases after the start of DMARD. In a similar study, Ismaili et al included 80 patients with active and newly discovered RA to study the impact of MTX therapy on CRP and disease activity and observed that after a year of therapy RA patients achieved significant decrease in the DAS28 (disease activity score) (p<0.01 and p<0.001), and CRP values (p<0.001).12

The evidence from trials using early intensive DMARD strategies introduced the concept of ‘window of opportunity’ and gave rise to early RA (ERA) clinics, supported by the long-term remission, as well as functional, radiographic and prognostic outcomes of starting treatment early.13 Early DMARD therapy during this ‘window of opportunity’ (that is within three months of onset) will more readily induce remission and delay progression.14 National and International recommendations address the importance of starting DMARD therapy as soon as the diagnosis of RA is made.15

The results of this study showed that DMARDs decreased the level of inflammation (hs-CRP) in RA. The possible role of inflammation in the pathogenesis of CVD in RA was beyond the scope of the present study, as the aim was to identify the parameter easily obtained in daily routine is an additional risk factor for cardiac involvement in RA. The limitation of our study was that we did not assess cardiovascular risk directly by measuring variables like carotid intima media thickness, coronary atherosclerosis, ankle-brachial index etc. There were no control group.

**CONCLUSION**

In this study we found that hs-CRP level correlates with the duration of RA in DMARD naïve patients. We also found that the initiation of DMARD significantly decreases the hs-CRP level thus serving as a risk reduction in cardiovascular disease. More importantly, early initiation of DMARD is a better treatment modality as it is observed to decrease the level of inflammation more significantly than delayed therapy. Thus, in short, it can be said that cardiovascular disease risk can be effectively reduced with prompt initiation of therapy in rheumatoid arthritis.

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