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Rheumatoid Arthritis

Effects of disease modifying anti-rheumatic drugs on subclinical atherosclerosis and endothelial dysfunction which has been detected in early rheumatoid arthritis: 1-year follow-up study ☆

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ABSTRACT

Objective: The study was designed to explore the effect of disease modifying anti-rheumatic drugs (DMARDs) on synovial inflammation as well as on atherosclerotic indices in patients with early rheumatoid arthritis (RA).
Methods: The study included 35 early RA patients (disease duration <12 months). Inflammatory variables, like erythrocyte sedimentation rate (ESR) and high sensitivity C-reactive protein (hsCRP) were measured. Carotid intima-media thickness (cIMT) and endothelial dependent flow-mediated vasodilatation (ED-FMD) were measured by high-resolution ultrasonography. Disease activity of RA was assessed by disease activity score (DAS28) and quality of life was determined by Health Assessment Questionnaire-Disability Index (HAQ-DI) Score. All the above parameters were assessed both at baseline and follow-up after 1 year. Patients were treated with methotrexate (MTX), hydroxycholoroquine (HCQ) and sulfasalazine (SSZ) depending on their disease activity.
Results: After a year of treatment, variables like ESR, hsCRP, DAS28 and HAQ-DI showed significant improvement ($p < 0.0001$ for each variable). However, there was no such significant change observed in the lipid profile after 1 year from the baseline. Average body mass index (BMI) of patients remained same at the one year follow-up. The cIMT values after 1 year decreased significantly [0.43 ± 0.08 mm] from the baseline [0.50 ± 0.16 mm] [$p = 0.002$]. Similarly, in case of FMD%, the post-1-year treatment values [7.57 (4.04–13.03)] improved significantly from the baseline [5.26 (2.9–10.6)] [$p = 0.041$].
Conclusion: Subclinical atherosclerosis and endothelial dysfunction are demonstrable features even in early RA which improved after therapy. Early intervention of RA with DMARDs not only controls the disease but also retards the atherosclerotic progression.

Introduction

In the last two decades there have been several studies showing premature coronary heart disease and cardiovascular disease (CVD) as major causes of morbidity and mortality in patients with rheumatoid arthritis (RA) [1–5]. In general, CVD in RA leads to an excess 35–50% of the mortality rate in comparison to general population and reduces life expectancy by 5–10 years [3,5]. Prevalence of CVD was observed in 13% of the RA patients in general compared to 5% of the normal population [6]. In a recent study [7], the overall incidence rate ratio (IRR) of myocardial infarction in RA was 1.7 (95% CI 1.5–1.9), which was similar to the risk in type 2 diabetes mellitus [1.7 (95% CI 1.6–1.8)].

The etiopathogenesis of the excess risk of CVD in RA is postulated to be multifactorial. The traditional cardiovascular (CV) risk factors like hypertension, diabetes and hyperlipidemia are identified, in part, as common confounders. However, of recent interest is the fact that RA itself is a major cause for higher CV mortality and morbidity due to underlying inflammatory process [8]. Few therapeutic drugs like corticosteroids and non-steroidal anti-inflammatory drugs may accelerate the risk of atherosclerosis in RA [9,10]. Contrary to what may be expected there are reports claiming improvement of atherosclerosis due to decrease in inflammation with the use of corticosteroids [11,12].

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The initiation and progression of atherosclerosis occurs in very early stages of RA and it can be easily detected by high-resolution ultrasonography as already shown by few recent studies [13–16]. In this respect, carotid artery intima-media thickness (cIMT) and endothelial dependent flow-mediated vasodilatation (ED-FMD) are two simple, noninvasive tools used for detecting subclinical atherosclerosis and endothelial dysfunction [17–19].

As already known, disease modifying anti-rheumatic drugs (DMARDs) are quite effective in lowering the disease activity and halting the progression of joint damage [20]. Recent therapeutic strategy suggests that early diagnosis and early use of DMARDs are more effective in controlling inflammatory activity in RA [21–23]. According to the "2008 American College of Rheumatology (ACR) Recommendations for Rheumatoid Arthritis Treatments", the combination of DMARDs [Methotrexate (MTX), Hydroxychloroquine (HCQ) and Sulfasalazine (SSZ)] was recommended for patients with moderate to high levels of disease activity [24].

Earlier studies have shown that DMARDs can improve cardiovascular risk in RA by influencing the traditional risk factors of atherosclerosis directly or through controlling inflammation [25,26]. However, studies showing the effect of DMARDs on CVD are limited, most of which predominantly focus on the role of MTX only [27]. In view of the recommendations suggesting treatment with combination of DMARDs for such patients as stated earlier, we chose to conduct our study involving three combination DMARDs.

Very little is known as to how these DMARDs affect subclinical atherosclerosis and endothelial dysfunction while controlling joint inflammation in RA. Few sporadic studies have shown the effect of DMARDs on cIMT and FMD separately. Georgiadis et al. have shown the positive effect of MTX and Prednisolone on cIMT in early RA patients ($n = 40$) at the 1-year follow-up [13]. Similarly, Hannawi et al. have shown improvement in FMD of early RA patients ($n = 20$) with combination of MTX, HCQ and SSZ [15]. However, no such study, till date, has reported the effect of these three DMARDs on both cIMT and FMD in early RA patients.

In this background, the present study was undertaken to investigate as to how the control of disease activity and inflammatory burden in RA with combination of DMARDs (MTX, HCQ and SSZ) could affect the atherosclerotic progression in early RA patients.

Materials and methods

Subjects

Thirty-five consecutive early RA patients of age between 18 and 60 years, who attended the "early arthritis clinic" of the rheumatology department at the Institute of Postgraduate Medical Education and Research (IPGME&R), SSKM Hospital, Kolkata, India between December 2009 and May 2010, were included. All patients fulfilled the American College of Rheumatology (formerly, The American Rheumatism Association) 1987 criteria for RA [28], had a disease duration of less than 1 year and had no prior use of disease modifying anti-rheumatic drugs (DMARDs) or corticosteroids.

Exclusion criteria

At baseline, patients with history of coronary artery disease and cerebrovascular accident, smokers or patients suffering from comorbid conditions/diseases such as diabetes, obesity (body mass index ≥ 30), familial dyslipidemia (primarily hyperlipidemia), peripheral vascular disease, hypothyroidism, renal disease (serum creatinine ≥ 3.0 mg/dl or creatinine clearance ≤ 30 ml/min), liver disease, Cushing syndrome were excluded. In addition patients receiving medications that affect lipid metabolism such as lipid lowering drugs, beta blockers, oral contraceptives, estrogens, progestin, thyroxin, vitamin E were excluded from the study. Female patients having current or recent (within the past 3 months) pregnancy were also excluded.

Written informed consent was taken from all study participants and the study protocol was approved by the Institutional Ethics Committee.

Study design

Patients were evaluated at baseline and after 12 months by TJC, SJC, HAQ-DI [29] and VAS. A composite DAS28 [30] was calculated in both cases. Patients were treated with MTX (7.5–20 mg/week) along with HCQ (200–400 mg/day) and SSZ (0.5–2 g/day) and titrated as per disease activity indices. Short-term, low-dose corticosteroids (≤ 7.5 mg/day for < 3 months) were used to control disease severity. All patients were followed up every 3 months for review of symptoms and signs and for need of change of drugs' doses. The subjects were also followed up for any change in diet or lifestyle with a questionnaire. The body weight and body mass index were also recorded.

Laboratory investigations

Patients were followed up every 3 months for routine examinations like hemogram and liver enzymes. Overnight fasting (12 h) blood samples were obtained at baseline and after 12 months of follow-up from the patients. The blood samples were immediately centrifuged and the sera were collected and stored at $-70\ ^{\circ}C$ until analyzed. All sera analysis was performed within 1 month of blood collection and storage. Serum levels of cholesterol (Ch), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and lipoprotein (Lp) (a) were determined using a semi-auto analyzer (Randox Laboratory India Private Limited, Mumbai, Maharashtra, India). High sensitivity C-reactive protein (hsCRP) was measured by nephelometry (BN Prospec, Siemens Healthcare Diagnostic Limited, Deerfield, IL, USA). Erythrocyte sedimentation rate (ESR) was measured by the modified Westergren method.

Radiological investigations

Flow-mediated vasodilatation of brachial artery

The procedure was performed by a single radiologist. The subjects were asked to abstain from alcohol, caffeine and smoking at least 8 h prior to the procedure. The subject was made to lie in a supine position for 10 min. The right brachial artery was scanned in longitudinal section 2–15 cm above the antecubital fossa with B-mode ultrasonography images using 7–12 MHz broadband linear array transducer in an Acuson Antares ultrasound system premium edition (Siemens Healthcare Diagnostic Limited, Deerfield, IL, USA). The center of the artery was identified where clearest picture of anterior and posterior intimal layers was available. Depth and gain settings were optimized to obtain a clear picture of lumen-intima interface. In this suitable transducer position, which was kept constant throughout the procedure (by noting the relation of the artery with adjacent anatomical landmarks like veins and fascial planes), a resting scan was obtained. The luminal diameter of the brachial artery was measured by pulsed Doppler. A sphygmomanometer cuff placed around forearm distal to the scanned region was inflated to 200 mmHg for 4.5 min and then released which induced increased flow. A second scan was taken at this stage and again luminal diameter of the artery was measured 60 s after cuff deflation. Endothelial