Early, Structured Disease Modifying Anti-rheumatic Drug (DMARD) Therapy Reduces Cardiovascular Risk in Rheumatoid Arthritis- A Single Centre Study Using Non-Biologic Drugs

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Abstract

**Background**: Rheumatoid arthritis, being a chronic disease requires long-term management of patients with drugs. The increasing cost of biologics in this era of disease management led us to devise a treatment regime, optimal for use in a developing country like India, which was economical as well as effective in controlling disease activity. **Objective**: To investigate if combination therapy with DMARDs can reduce cardiovascular risk in early Rheumatoid Arthritis, besides controlling disease activity. **Methods**: A small cohort of early Rheumatoid subjects with disease duration less than 1 year were treated with a structured DMARD regime and were followed up over a year. Disease activity score, C-reactive protein (CRP) and cardiac risk markers like lipid panel and carotid intima-medial thickness were monitored at 6 months and 1 year. **Results**: A significant reduction (p<0.001) of disease activity as well as cardiac risk parameters were observed. **Conclusion**: Our study showed that treatment of early rheumatoid arthritis with a combination regime of traditional DMARDs is highly effective in controlling disease activity as well as cardiovascular risk.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology, characterized by persistent synovitis, usually involving peripheral joints along with various extra-articular manifestations like rheumatoid nodules, neuropathy, anemia, Sjögren’s syndrome, osteoporosis, amyloidosis and pulmonary fibrosis.1,2

The prevalence of RA is about 0.5-1% in industrialized nations with 5-50 new cases per 100,000 population annually.1 It predominantly occurs in female and elderly people.1 In India prevalence of RA was found to be 0.5-0.75%.3,4

The concept of early therapeutic intervention has drastically changed the management of RA in last few years. The classification criteria, used for diagnosis of RA have been updated by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) in September 2010.5 Early diagnosis of rheumatoid arthritis (RA) is an important challenge for clinical rheumatologists. There is substantial evidence that early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs) can lead to a better outcome.6

Incidence of cardiovascular disease (CVD) risk is significantly increased in RA, particularly that of coronary artery disease. Cardiovascular mortality is increased by almost 50% in RA compared to general population.7

The present study was aimed to find out, if early DMARD therapy can reduce CVD risk in RA, besides controlling disease activity.

Materials and Methods

The present prospective cohort study was conducted for a period of one year from October 2010 to September 2011 in Rheumatology out-patient clinic of our Institute. Fifty Three subjects between 16-65 years of age, attending Rheumatology clinic and satisfying ACR and EULAR 2010 criteria for RA,5 with disease duration less than one year were enrolled for the study. The subjects were normotensive, nondiabetic, nonsmoker, euthyroid and had no history of prior intake of DMARD, systemic steroids or any other medications, adversely affecting lipid profile. Ethical Committee approval and informed consent were taken from each subject before participation. Fifty Three apparently healthy age and sex matched controls were also selected from general population.

Investigations

Focused history and thorough clinical examination of involved joints were performed in each subject and following investigations were done: 1) Fasting lipid profile 2) Erythrocytic Sedimentation rate (ESR) 3) C-reactive protein (CRP) 4) Carotid Intima-Medial Thickness (CIMT) of Internal and Common Carotid arteries using B mode Ultrasonography. Disease activity score (DAS) of 28 joints were determined based on following four parameters: a) Total number of swollen joints (SW), b) Total number of tender joints (TEN), c) ESR (after one hour in mm), d) Severity of the pain (General health assessment during last seven days) as determined by Visual analogue scale (VAS). DAS was calculated as 0.56×√ (TEN) + 0.28×√ (SW) + 0.70×ln (ESR) +0.014×VAS. Patients with DAS more than 3.2 were only selected as subjects for the present study. Fasting lipid profile and CIMT were also measured in the control group.

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Treatment Regimen

On the basis of preliminary studies done at our clinic, following combination of DMARD therapy was offered to the subjects depending on their DAS:

1. DAS 3.2 – 5.1: Tablet (tab) Methotrexate 10mg (one tab once weekly), tab Hydroxychloroquine 200 mg (one tab two times daily) and tab Sulfasalazine: 1-2 g daily. 2. DAS > 5.1: Injection Methotrexate 15mg (intramuscular once weekly), tab Sulfasalazine 3-4 g daily, tab Hydroxychloroquine 200 mg (one tab two times daily) and tab Methylprednisolone 16 mg every Sunday and 8 mg on Monday, Wednesday, Friday. Treatment failures (DAS not improved by 50% after 6 months of therapy) were considered for injection Methotrexate 15mg along with tab Leflunomide. Biologics (infliximab) were offered to all the patients however only 4 patients could afford the therapy.

Follow up

The subjects were followed up every month for first 3 months and then at six months according to the dates of their respective initial visits. Regimes were upgraded or downgraded as per symptoms. At 6 months, 14 subjects were excluded, out of which, 7 subjects were on irregular medications due to financial reasons/ non-compliance and they developed disease flare-up. Three subjects developed adverse drug reaction (decreased peripheral symptoms. at 6 months, 14 subjects were excluded, out of which, 3 subjects were lost to follow up. So the final subject pool at the end of six months was 39. These 39 subjects then underwent the same clinical examinations and laboratory investigations like that of their initial visit. They were again followed up after another six months or one year after initiation of therapy. At that time 4 subjects did not turn up for follow up and were excluded. All the subjects’ addresses and contact numbers were recorded whenever applicable and they were contacted prior to their follow-up visit to minimize loss to follow-up. Since final sample size got reduced from 53 to 35 or 66 % of the initial sample size, number of controls was also considered as 35 at the end of one year. Results found in controls were compared with the baseline parameters of the subjects.

Statistical Analysis

Results were analyzed using statistical model STATISTICA 5.1 and SPSS. Descriptive data were represented as mean and standard deviation (SD). Baseline parameters of subjects were compared to controls by student t test (inter-group analysis). Comparisons between Baseline parameters and results measured at six months and one year of therapy in subjects (intra-group analysis) were done by analysis of variance (ANOVA) with Newman-Keuls multiple comparison tests (post-hoc analysis).

Results

Baseline characteristics of the patients (Table 1) revealed mean age of onset was 40.26 years. Sixty five percent subjects were between the age group16 to 45 years and remaining 35% between 46 to 65 years. Eighty percent of the subjects were female. Seventy four percent subjects had positive rheumatoid factor. Disease activity of RA, as measured by CRP and DAS was found to be decreasing significantly over one year after initiation of combined DMARD therapy (p value< 0.001) on intra-group comparison or post hoc analysis. (Table 2) CVD risk, as reflected by dyslipidemia and increased CIMT was found to be significantly increased in RA subjects as compared to controls (p value< 0.001). CVD risk was also shown to be reduced significantly (p value<0.001) after one year follow up on intra-group comparison. Although CIMT had shown a decreasing trend over one year, intra-group comparison between values measured at six months and one year of therapy were comparable on post-hoc analysis.

Discussion

Inclusion Criteria

Many previous studies have used various cut offs for defining early disease onset. The basis being that, diagnosis of RA made as early as possible can lead to early therapeutic intervention and thereby reduce joint related morbidity. Hence some researchers are now using the term very early RA, as joint erosions start appearing by 2 years of disease onset. In the present study, RA less than 1 year was considered as early disease and patients were selected according to the ACR criteria 2010 which have been especially designed to detect early RA. It has been shown

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient (N=35)</th>
<th>Controls (N=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.26 ± 11.41</td>
<td>39.49 ± 10.73</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/28</td>
<td>6/29</td>
<td>NS</td>
</tr>
<tr>
<td>RF positivity</td>
<td>26</td>
<td>3</td>
<td>0.000</td>
</tr>
<tr>
<td>Duration 6 weeks to 6 months</td>
<td>19</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean CIMT (mm)</td>
<td>0.6 ± 0.1</td>
<td>0.39 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>213 ± 22</td>
<td>166 ± 23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>38 ± 8</td>
<td>49 ± 8.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>5.83 ± 1.35</td>
<td>3.51± 0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>143.7 ± 11.04</td>
<td>100± 19.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>177.7 ± 17.66</td>
<td>137.1± 13.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CIMT Carotid intima medial thickness, HDL High density lipoprotein, LDL Low density lipoprotein, NA Not applicable, NS Not significant, RF Rheumatoid factor, TC Total cholesterol, Values indicate mean ± standard deviation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>0 months</th>
<th>6 months</th>
<th>12 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>29 ± 9</td>
<td>16 ± 6</td>
<td>10 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS 28</td>
<td>6.29 ± 0.63</td>
<td>5.12 ± 0.40</td>
<td>4.58 ± 1.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cardiovascular Risk markers

Mean CIMT (mm) | 0.6 ± 0.1 | 0.53 ±0.1 | 0.52 ± 0.1 | <0.001 |
TC (mg/dl)     | 213 ± 22  | 187 ± 25  | 163 ± 18  | <0.001 |
HDL Cholesterol (mg/dl) | 38 ± 8 | 42.7± 7.38 | 48 ± 5.91 | <0.001 |
TC/HDL ratio   | 5.83 ± 1.35 | 4.5± 1.07  | 3.45 ± 0.53 | <0.001 |
LDL Cholesterol (mg/dl) | 143.7 ± 11.04 | 123.7± 11.23 | 104.2 ± 12.30 | <0.001 |
Triglycerides (mg/dl) | 177.7 ± 17.66 | 158.5± 15.77 | 134.8 ± 14.1 | <0.001 |

CRP C-reactive protein, DAS Disease activity score, other abbreviations as in Table 1 Values indicate mean ± standard deviation.
that subclinical atherosclerosis starts even earlier than the joint related symptoms in RA, a slightly higher cut-off however facilitated in determining expression of dyslipidemia in the subjects. Moreover the usual delayed diagnosis due to lack of awareness both among the patients as well as providers in developing countries makes one year a reasonable cutoff.11

Baseline demographic profile of patients

Incidence of RA increases with age, but in our study, subjects between ages of 16-45 years had higher incidence than between age group 46-65 years. This discrepancy found may be due to geographical variation or increased awareness among the young or middle aged population to seek medical help for early joint related symptoms.

It was found in our study that 74% of the subjects were rheumatoid factor positive. Positive rheumatoid factor may be a confounding factor for atherosclerosis in RA, but the patients who satisfied the inclusion criteria were chosen randomly to eliminate this bias.

Role of DAS (ESR) and CRP in monitoring disease activity in RA

Studies have recommended DAS as a measure of disease activity in RA, disease activity monitoring as well as DMARD regimen for each subject was decided based on DAS (ESR) in the present study. In addition to DAS disease activity had also been determined by ESR and CRP.

Role of fasting lipid profile and CIMT in CVD risk assessment in RA

CVD risk was determined in our study by measuring lipid profile parameters and CIMT. In accordance to the previous studies, which have already established higher incidence of dyslipidemia in RA; all the lipid profile parameters, measured in case of our study, were found to be significantly higher in RA subjects as compared to the controls. Some studies were previously done to demonstrate increased CIMT in RA. In our study, significantly higher CIMT in RA subjects therefore had given substantial evidence of the fact that there is an increased CVD risk and enhanced chance of atherosclerosis in RA.

Effectiveness of an early combined DMARD therapy in disease remission

Recent studies and trials have established increased effectiveness of combined DMARD therapy in early RA compared to monotherapy. Addition of prednisolone to the regimen may be better in severe disease. In our study, subjects were classified into two groups based on their DAS. DAS 3.2-5.1 were considered as moderately severe and DAS >5.1 as highly severe disease. In accordance to recent clinical data available, triple therapy regimen were offered to the subjects, with steroid added in case of severe disease (DAS >5.1).

The treatment regime offered to the subjects in our study was based on ACR guidelines 2008. In the present study, effectiveness of combined DMARD therapy in reducing disease activity of RA was monitored by measuring DAS and CRP in subjects on follow-up visits at six months and one year of therapy. Significant decrease that was found in DAS and CRP on early triple DMARD therapy in our study had similar evidence from various other trials and studies done on combined DMARD therapy.

Effectiveness of early combined DMARD therapy in reducing CVD risk in RA

Significant decrease that had been found in CIMT as well as significant improvement in dyslipidemia after one year of early DMARD therapy in the present study had similar evidence from some previous research. In the study conducted by Georgiadis AN et al significant improvement (p<0.01) was found in HDL and TC/HDL ratio as well as a decrease in CIMT (p<0.001) upon one year of treatment with methotrexate and steroid. Similar to our present study, Das-28 in their study too got reduced significantly (p<0.03) along with improvement in CVD risk. Case control study conducted by van Halm VP et al have also established that combined therapy of methotrexate, hydroxychloroquine and sulfasalazine was most effective in controlling both inflammation as well as CVD risk. In the study conducted by Turiel M et al, 18 months treatment with DMARD in very early disease (mean disease duration 6.24 ± 4.1 months) had shown significant reduction in DAS (p<0.0001) as well as improved coronary flow reserve (p<0.01). However they could not find any significant reduction in CIMT on DMARD therapy, probably due to monotherapy with methotrexate.

Cost-effectiveness of the regime

ACR guidelines 2008 has recommended combined use of traditional DMARD therapy including methotrexate in early Rheumatoid and biologics are used only when it fails to respond to conventional non-biologics. Overall, biologic therapies cost considerably more than traditional DMARDs but produced more quality-adjusted life-years (QALYs). Clinical guidelines currently recommend the use of biologics as step therapy after failure of traditional DMARDs. Many studies have failed to demonstrate the benefit and cost-effectiveness of biologics in early Rheumatoid when compared to combined DMARD therapy. Moreover high cost of biologics is a major limitation for its widespread use in developing countries like India. Since India has a considerable burden of tuberculosis, chance of reactivation of latent tuberculosis due to biologics also limited its use in our setting. So we developed a structured regime that was economical and cheap for our subjects and was equally effective in controlling disease activity.

Study limitations

A small sample size due to difficulties in follow-up and using traditional DMARDs for treatment of the patients due to financial constraints were the limitations. Coronary angiogram or arterial flow-mediated studies (marker of endothelial dysfunction) would have made our study more informative. These could not be performed due to lack of upgraded facilities.

Conclusion

Our study shows that a cost-effective structured regime using traditional DMARDs is highly effective in controlling disease activity as well as CVD risk in patients of rheumatoid arthritis.

References


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