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Effect of Rosuvastatin on Rheumatoid Arthritis Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire-Disability Index (HAQ-DI)

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Abstract
Objective: To evaluate the effect of rusovastatin on the clinical disease activity index(CDAI) and health assessment questionnaire disability index(HAQ-DI) in rheumatoid arthritis patients(RA).
Methods: A single center randomized double-blind placebo-controlled trial of 8 weeks duration was performed. Patients had RA according to the 1987 American College of Rheumatology (ACR) criteria. Disease activity was measured by CDAI and functional disability by HAQ-DI. They were treated by rusovastatin 10mg tablet or identical placebo (PBO).
Results: Of 74 randomly assigned patients, 40 completed 8 weeks. Twenty from the rosuvastatin group and 20 from the PBO. No significant difference between the change of CDAI produced by rusovastatin compared to that of PBO after 8weeks (-45.95±42.14 (-30.87%) versus -26.15±48.05 (-19.03%), p= 0.174) although it was clinically relevant. Also no statistical significant difference between the change of HAQDI produced by rusovastatin compared to that of PBO after 8weeks (-0.48±0.40 (-27.74%) versus -0.36±0.36 (-22.09%), p= 0.477).
Conclusions: Rusovastatin has no statistical significant effect on CDAI and HAQDI, however clinically may be relevant. Large long prospective study is needed.
Key words: Rusovastatin, Rheumatoid arthritis, CDAI, HAQDI.

1. Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown etiology characterized by articular involvement and extra articular involvement [1]. Additionally it is a progressive disease that cause damage and disability [2,3].

Many studies have reported an increased risk of mortality in patients with RA [4-6]. So the primary goal of treating the patient with rheumatoid arthritis is to maximize long-term health-related quality of life which can be achieved through reduction of inflammation; Moreover treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA [7]. Clinical disease activity index CDAI is a purely clinical score and it is a valid measure of disease activity with greatest merits in clinical practice rather than research, since it may facilitate immediate and consistent treatment decisions and help in improving patient outcomes in the longer term [8]. Whereas Health assessment questionnaire – disability index (HAQ-DI) is very responsive to change, and usually is the most sensitive to change of the available outcome measures [9]

Rosuvastatin is a unique HMGCoA reductase inhibitor that used to treat dyslipidemia [10]. It also exerts important anti-inflammatory effects in addition to its lipid-lowering actions [11].This study was designed to evaluate the possible benefit of low dose rosuvastatin on RA disease activity (CDAI) and patient functional disability(HAQDI).

2. Methods

2.1 Study design

This was an 8-week randomized double blind placebo-controlled single center study conducted at Rheumatology Unit, Baghdad Teaching Hospital, Baghdad, Iraq from August 2011 till May 2012. Patients were randomly allocated to receive each day either rosuvastatin 10mg tablet or capsule prefilled with glucose as placebo (PBO). Rosuvastatin was bought from Unipharma Company, Syria whereas glucose was bought from SDI, Iraq. Patients were evaluated at baseline and at week 8.

Informed consent was obtained from all participants and this study was approved by the ethical committee of Baghdad University, College of Medicine - Medical Department.

2.2 Sample selection

Eligible patients had confirmed RA according to the 1987 American College of Rheumatology (ACR) criteria with moderate to highly active disease defined as CDAI greater than 11 at baseline. For inclusion, patients also were required to have taken methotrexate (MTX) regularly for at least 3 previous consecutive months. The exclusion criteria included patients who were taking lipid-lowering therapy, had hypersensitivity to statin,

pregnancy, breast feeding, renal and liver impairment, patients younger than 18 years old and those using high dose steroids.

2.3 **Clinical evaluation**

Clinical evaluation of patients for tender and swelling joints was done by specialized rheumatologist who was blinded to treatment at zero time (baseline) and after 8 weeks.

RA disease activity was measured using CDAI which was calculated by simple summation of tender and swelling joint count, visual analogue scale (VAS) as stated by the patient (VAS) and physician or evaluator (EGA) [8] , whereas functional disability was measured by HAQDI [9].

2.4 **Statistical analysis**

Statistical software (SPSS v. 12, Chicago, IL, USA) was used for data input and analysis. Continuous variables were presented as mean ± standard deviation (SD) and discrete variables were presented as frequencies and percentages. Chi square test for independence was used to test the significance of association between discrete variables. Continuous variables were tested by a web version of Shapiro Wilk test to determine if they were normally or abnormally distributed.

Paired T test was used to test the significance of difference in means of pre and post treatment in normally distributed continuous variables.

Unpaired T test was used to test the significance of difference in the mean of two independent samples in normally distributed continuous variables and Mann Whitney test for abnormally distributed data.

All P values used were asymptotic and two sided. Findings with P value less than 0.05 were considered significant whereas P values less than 0.01 considered highly significant. Statistical power was not calculated since it is a pilot study.

3. Results

Of 74 patients randomized in this double-blind study, 40 completed the 8weeks of treatment (20 from the rosuvastatin group and 20 from the PBO). The two groups did not differ significantly in the baseline characteristics (Table 1).

After 8 weeks of treatment, rosuvastatin reduced very highly significantly CDAI while placebo reduced CDAI significantly .Also, both rosuvastatin and placebo reduced very highly significantly HAQDI score (Table 2, 3)

However, there was no statistical significant difference between the effect of rusovastatin and placebo on CDAI and HAQDI (p>0.05, table 4).

Table1: Baseline characteristics of 76 RA patients

Parameter	Rosuvastatin	Placebo	P
Age, years	43.35 ± 9.96	44.4 ± 13.53	0.781
Female: Male Ratio	14:6 (70%)	16:4 (80%)	0.465
Disease duration, years	7.55 ± 5.38	6.65 ± 4.96	0.586
Dose of MTX, mg	13.88± 4.40	13.25 ± 3.54	0.624
Family Hx of +ve RA	2 (10%)	7 (35%)	0.058
Positive RF n (%)	13 (65%)	12 (60%)	0.743
Sc nodule n (%)	2 (10%)	0 (0%)	0.147
CDAI	149.6±45.79	137.45±47.63	0.416
HAQDI	1.73± 0.74	1.63±0.65	0.633

Data are mean±SD; n, number; %, percentile; Sc, subcutaneous; CDAI, clinical disease activity index; HAQDI, health assessment questionnaire disability index. P> 0.05 not significant

Table2: Effect of treatment on CDAI

Group	CDAI Pre-treatment (at Baseline)	CDAI Post-treatment (After 8weeks)	Change (Percent of change)	P value
Rosuva-statin	149.6±45.79	103.65±58.12	-45.95±42.14 (-30.87%)	0.000*
Placebo	137.45±47.63	111.3±47.69	-26.15±48.05 (-19.03%)	0.025**

Data are mean ±SD; *p<0.01, highly significant;** p<0.05, significant; CDAI, clinical disease activity index.

Table3: Effect of treatment on HAQDI

Group	HAQDI Pre-treatment (at Baseline)	HAQDI Post-treatment (After 8weeks)	Change (Percent of change)	P value
Rosuva-statin	1.73±0.74	1.25±0.74	-0.48±0.40 (-27.74%)	0.000
Placebo	1.63±0.65	1.27±0.73	-0.36±0.36 (-22.09%)	0.000

Data are mean±SD; HAQDI, health assessment questionnaire disability index; *p<0.01, highly significant**.**

Table 4: Comparison of the change produced in CDAI and HAQDI after 8 weeks of treatment

Parameter	Rosuvastatin	Placebo	P value
CDAI	-45.95±42.14	-26.15±48.05	0.174
HAQDI	-0.48±0.40	-0.36±0.36	0.477

Data are mean±SD; CDAI, clinical disease activity index; HAQDI, health assessment questionnaire disability index. P> 0.05 not significant

4. Discussion

Approaches to management of RA disease activity, functional capacity, and outcome have evolved because of the availability of an increasing number of effective disease-modifying anti-rheumatic drugs (DMARDs) [12].Assessing RA disease activity regularly is a very important aspect in the management but this aspect is often neglected. Recently, CDAI has come up for assessing the disease activity [13]. It is simple, completely clinical score, and easy to calculate. Hence, it is possible to determine the disease activity immediately in a physician's chamber especially when a patient visits for the first time or turns non-compliant to the laboratory investigations advised, which is so common in this chronic disease. Additionally, HAQ-DI, a type of patient reported outcome, has become an established approach to assess health outcomes in RA patients [14].

This study showed that the reduction of CDAI in RA patients after 8 weeks of treatment with rosuvastatin was clinically relevant compared to that by placebo (-45.95±42.14 versus -26.15±48.05), however the effect was statistically not significant.

According to the current evaluation of the literature, there were no other studies (in addition to the current one) that focus on the effect of statin on RA disease activity as measured by CDAI and it is the 1st time to get such result, but instead there were 2 other studies examining the effect of rosuvastatin on RA disease activity by disease activity score of 28 joints (DAS28) [15,16], the results of these studies showed that rosuvastatin was not able to significantly reduce RA disease activity when compared to placebo, which agreed with the finding of this study since there is a direct and positive correlation between DAS28 and CDAI as shown in other clinical studies [17,18].

Moreover rosuvastatin was no more effective than placebo to reduce HAQDI score. Similar finding was reported by Kumar et al who studied the effects of rosuvastatin on RA patients in a pilot randomized double-blind placebo-controlled trial conducted on 50 patients from rheumatology clinics throughout Tayside in Scotland. [15] where they found rusovastatin does not improve the overall rheumatoid disease activity including HAQDI [15].

The absence of statistical significant improvement in both disease activity and functional ability by rosuvastatin may be attributed to the small sample size and to the use of low dose of rusovastatin. Ghaisas *et al* [19] reported that there was a dose-dependent antioxidant, analgesic, and anti-inflammatory activities of rosuvastatin.

The small sample of the study, short period of follow up, and small dose of the rusovastatin used might be a limitation of this study. However, this may be improved and solved by a large, long duration prospective study with higher doses of rusovastatin.

5. Conclusions

Rosuvastatin has no statistical significant effect on disease activity and functional disability in active RA patients although it was clinically relevant. This may suggest that rusovastatin can be beneficial and may be used as adjuvant therapy to other medications for treatment of RA. A large long prospective study is needed.

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