Evaluation of Rosuvastatin Effect as Adjuvant Therapy to Methotrexate on Lipid Profile and the Possibility of its Cardioprotective Effect in Iraqi Patients with Active Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a common inflammatory disease that associated with increased morbidity and mortality due to accelerated atherosclerosis. Rosuvastatin is a unique hydroxy methyl glutaryl Co A (HMGCoA) reductase inhibitor that has anti inflammatory effects.

The aim of this study was to evaluate the effect of rosuvastatin as adjuvant therapy to methotrexate (MTX) on lipid profile and its possible cardioprotective effect in RA patients. A double blinded placebo controlled clinical trial with 8 weeks follow up periods at which 40 patients with active RA using MTX were randomized into 2 groups to receive either rosuvastatin 10mg or placebo as adjuvant therapy to MTX. In addition to twenty healthy subjects as control group. Lipid profile and erythrocyte sedimentation rate (ESR) was assessed at the start and at the end of the study. At the start of the study total cholesterol (TC), low density lipoprotein cholesterol (LDLc) and high density lipoprotein cholesterol (HDLc) values were not significantly different between RA patients and control group. At the end of the study rosuvastatin significantly reduced ESR, TC and LDLc after 8 weeks of treatment.

It can be concluded that MTX has the ability to normalize lipid profile in RA patients. Rosuvastatin effectively reduce ESR, TC and LDLc; Moreover, Rosuvastatin might have a possible cardioprotective effect in RA patients.

Keywords: Active rheumatoid arthritis, Methotrexate, Rosuvastatin.

تقييم تأثير الروسوفاستاتين كعلاج مضاف للميثوتركسيت على الدهون وتأثيره القلبي الوقائي المحتمل للمرضى العراقيين المصابين بالتهاب المفاصل الرثوي الفعال

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الخلاصة

التهاب المفاصل الرثوي هو مرض التهابي شائع ويتميز بزيادة نسبة المراضة والوفيات بسبب زيادة سرعة تصلب الأوعية الدموية . يعتبر الروسوفاستاتين مثبطا فريدا لإنزيم هايدروكسي مثيل كلوتاريل كو اي (HMGCoA) كما إن له خاصية مضادة للالتهاب.

ان الهدف من هذه الدراسة هو لتقييم فائدة الروسوفاستاتين كعلاج إضافي للميثوتركسيت على الدهون وتأثيره المحتمل لوقاية القلب عند مرضى التهاب المفاصل الرثوي الفعال.البحث سريري مزدوج الإعماء شمل أربعون مريضا بالتهاب المفاصل الرثوي الفعال والذين يستخدمون للميثوتركسيت تمت مراقبتهم لمدة أسابيع بعد تقسيمهم عشوائيا لمجموعتين لاستعمال روسوفاستاتين ١٠ ملغرام أو العلاج الواهم. بالإضافة إلى عشرين شخصا كمجموعة مقارنة.

تم قياس نسبة الدهون ونسبة ترسيب كريات الدم الحمر عند البدء وعند الانتهاء من هذه الدراسة. عند بدء هذه الدراسة تبين إن نسبة الكولسترول والكولسترول منخفض ومرتفع الكثافة لاتختلف بين المرضى المصابين بالتهاب المفاصل الروماتويدي عن نظرائهم بالمجموعة المقارنة وعند انتهاء الدراسة قلل الروسوفاستاتين وبشكل معنوي ملحوظ من نسبة ترسب كريات الدم الحمر والكولسترول, والبروتين المرتبط بالكولسترول منخفض الكثافة.

نستنتج من ذلك إن للميثوتركسيت قابلية تعديل مستوى الدهون عند مرضى التهاب المفاصل الرثوي الفعال والروسوفاستاتين له القابلية على تقليل مستوى ترسب كريات الدم الحمر, الكولسترول, والبروتين المرتبط بالكولسترول منخفض الكثافة إضافة إلى تأثيره الوقائي المحتمل للقلب عند مرضى التهاب المفاصل الرثوي الفعال.

الكلمات المفتاحية: التهاب المفاصل الرثوي الفعال, ميثوتركسيت, روسوفاستاتين.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology characterized by articular and extra articular features [(1)]. The atherogenic lipid profile and subclinical atherosclerosis are features of early RA [(2).]

Rheumatoid arthritis is associated with increased mortality, which is predominantly due to accelerated coronary artery atherosclerosis [(3)]. Cardiovascular (CV) morbidity and mortality are increased twofold in RA patients compared to those of the general population [(4, 5)]. This increased CV risk may be due to systemic inflammation and its interplay with traditional CV risk factors like smoking, personal and family history of ischemic heart disease, hypertension, hyperlipidemia, higher body mass index and diabetes mellitus (DM) [(6)].

The association between lipids and CV risk in RA appears to be more complex than in the general population, with systemic inflammation being a notable contributor to the lipid profile changes [(7)]. Inflammation leads to pro-atherogenic changes of the lipoprotein metabolism and an increased disease activity is associated with lower total cholesterol (TC) levels and even more depressed high density lipoprotein – cholesterol (HDLc) levels and lowered apolipoprotein-A1 (apo-A1) levels (4). Beside that active inflammation increases oxidized fatty acids in circulating lipoproteins, promoting low density lipoprotein (LDL) oxidation and HDL dysfunction, thereby increasing atherosclerotic risk [(8)].

Rosuvastatin is a unique hydroxy methyl glutaryl CoA (HMGCoA) reductase inhibitor that used to treat dyslipidemia [(9)]. It also exerts important anti-inflammatory effects in addition to its lipid-lowering actions [(10)].

Aim of the study

Evaluating the effect of rosuvastatin as adjuvant therapy to MTX on lipid profile and its possible cardioprotective effect in Iraqi patients with active RA.

Methods

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. Methotrexate ampoules from Ebewe Company/ Austria. Patients were evaluated at baseline and at week 8.

Sample selection

Eligible patients had confirmed to have active RA according to the 1987 American College of Rheumatology (ACR) criteria and had ESR values greater than 20 mm/hr for men and greater than 30 for females(11). Additionally all patients included were selected to be users of 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 steroids.

Additionally 20 healthy individuals with age and sex matched were considered as a control group.

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

Blood sample collection and laboratory evaluation

Blood specimen collection: 5 ml of venous blood was obtained from forearm for doing laboratory analysis (at baseline and after 8 weeks). 3 ml was transferred to plane test tube and left to be coagulated then centrifuged at 3000 rpm for 10 minutes and then serum obtained for biochemical measurements of total cholesterol, LDLc, HDLc, and triglyceride (TG) and measuring Rheumatoid factor. Lipid profile tests were done by specialized laboratory workers who did not participate in this study using specialized kits from Randox ® company.

Total cholesterol was measured by cholesterol oxidase - peroxidase aminophenazone (CHOD-PAP) enzymatic colorimetric method [(12)].

TG estimation was done by Glycerol-3-phosphate oxidase – peroxidase (GPO-PAP) enzymatic colorimetric method under the principle of Bucolo and David 1973 [(13)].HDLc was measured by Polyethylene Glycol (PEG) / CHOD – PAP method , according to the principle of Lopes [(14)].

Whereas LDLc level was estimated according to the Friedewald formula [(15)]. ESR was measured by Westergren method and also was done by blinded non interested laboratory worker [(16)].Rheumatoid factor was measured qualitatively just at start of study by serological agglutination test through antigen antibody reaction using specialized kit from spectrum company/ Egypt [(17)].

Statistical analysis

Statistical package for social sciences (SPSS) version 12, was used for data input and analysis. Continuous variables were presented as mean ± standard deviation (SD) and discrete variables were presented as numbers and frequencies. 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. Analysis of variance (ANOVA) test was used to test the significance of difference in the mean of 3 independent samples in normally distributed continuous variables.

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

Results

Of the 74 patients who were randomized in this double-blind study, only 40 patients completed the 8weeks of treatment (20 from the rosuvastatin group and 20 from the PBO). The two groups did not differ significantly in baseline characteristics. Another 20 healthy controls aged and sex matched were also participated (figure1, table 1).

Baseline lipid profile (table 2) showed that there was a non significant difference at baseline level of TC, LDLc and HDLc between RA patients and control subjects and only TG level was significantly higher in RA patients of PBO group than that in the control group. But unfortunately there was a significant difference at a baseline level of TC, LDLc, and TG between rosuvastatin and PBO group (table 3).

Additionally baseline ESR was higher in RA patients, but with no any significant difference between rosuvastatin and placebo group (Table 2, 3).

After 8 weeks of starting adjuvant treatment with either rosuvastatin or placebo, TC, LDLc and ESR decreased significantly by rosuvastatin ($p<0.05$) while other parameters showed no any difference between the effect of rosuvastatin and placebo ($p>0.05$, table 4).

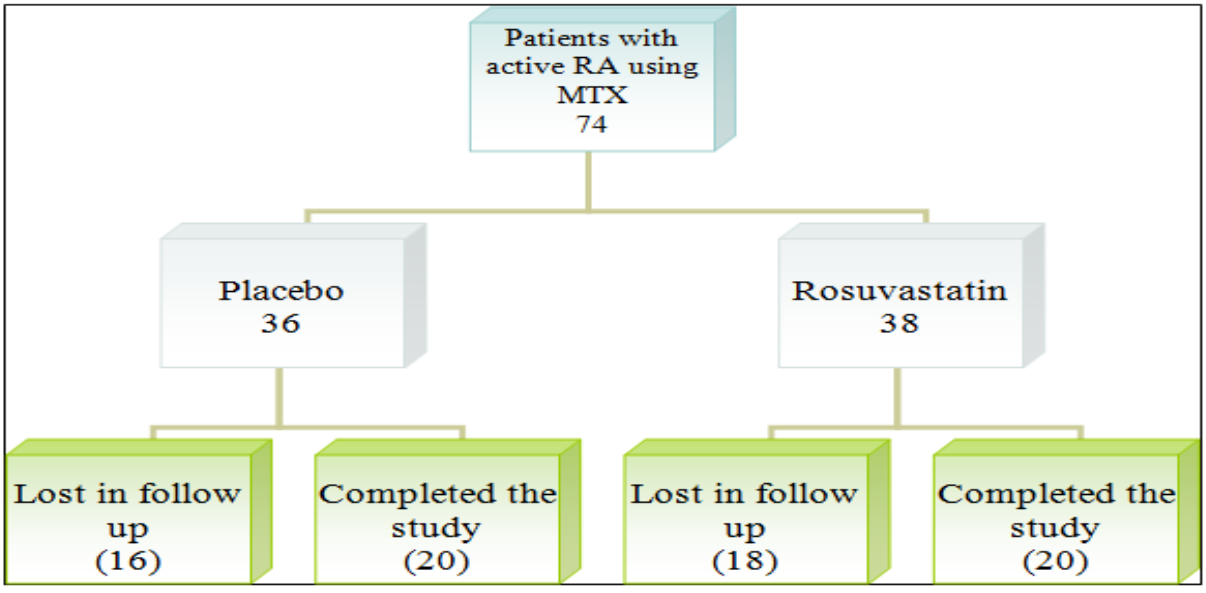

Figure 1: Schematic presentation for patient participating in the study

Table (1) Demographic data and baseline characteristics of both rheumatoid patients and control subjects

Parameter	Rosuvastatin	PBO	Control	P Value
Age (years)	43.35 ± 9.96	44.4 ±13.53	42.95±10.39	0.917
Female: Male Ratio	14:6 (70%)	16:4 (80%)	15:5(75%)	0.766
Dose of MTX	13.88± 4.40	13.25 ± 3.54	-	0.624
Smoking	3	2	5	0.431
Family Hx of CVD n (%)	3 (15%)	2 (10%)	3 (15%)	0.865
Hypertension n (%)	5 (25%)	5 (25%)	-	1
DM n (%)	5 (25%)	3 (15%)	-	0.429
Positive RF n (%)	13 (65%)	12 (60%)	-	0.743

Table (2) Comparison in baseline laboratory data of rheumatoid arthritis patients with control subjects

Parm	Rosuva	Control	P	PBO	Control	P
TC (Mg/dl)	168.9±38.22	180.05±54.29	0.457	202.85±28.68	180.05±54.29	0.105
LDLc (Mg/dl)	99.71±33.24	114.78±52.46	0.285	123.21±19.57	114.78±52.46	0.505
HDLc (Mg/dl)	42.25±9.42	43.45±6.06	0.635	43.6±10.34	43.45±6.06	0.956
TG (Mg/dl)	134.7±63.91	109.1±43.80	0.148	180.2±51.16	109.1±43.80	0.000
ESR (mm/hr)	48.95± 31.1	11.7±3.85	0.000	38.25±19.00	11.7±3.85	0.000

TC = Total cholesterol, normal range < 200mg/dl; LDLc = Low density lipoprotein cholesterol, normal range < 100mg/dl; HDLc = High density lipoprotein cholesterol, normal range 40 – 60mg/dl; TG = triglyceride , normal range < 150mg/dl; ESR = erythrocyte sedimentation rate, normal range < 20 for men and < 30 for females.

Table (3) Difference in baseline laboratory parameters between RA patients in rosuvastatin and placebo group

Parameter	Rosuva	PBO	P
TC	168.9±38.22	202.85±28.68	0.003
LDLc	99.71±33.24	123.21±19.57	0.01
HDLc	42.25±9.42	43.6±10.34	0.669
TG	134.7±63.91	180.2±51.16	0.017
ESR	48.95± 31.1	38.25±19.00	0.197

Table (4) Change produced in lipid profile and ESR after 8 weeks of treatment with either rosuvastatin or placebo

Parameter	Rosuvastatin (%)	PBO (%)	P value
TC	-39.3 ± 29.21 (-23.27%)	-6.25 ± 17.99 (-3.08%)	0.000
LDLc	-36.28 ± 27.10 (-36.39%)	-8.49 ± 21.61 (-6.89%)	0.001
HDLc	0.7 ± 8.71 (1.66%)	0.4 ± 4.28 (0.92%)	0.956
TG	-18.6 ± 33.11 (-13.81%)	9.2 ± 53.97 (5.11%)	0.096
ESR	-16.85 ± 28.66 (- 34.42%)	-0.55 ± 17.72 (-1.44)	0.012

Discussion

The results of this study showed a non significant difference in TC, LDL-C and HDL-C level between RA patients using MTX and control subjects; the results of other studies were controversial: in one study it was found that both TC and LDL-C level were elevated in RA patients whereas HDL-C level was decreased in patients with early RA, and this atherogenic lipid profile can be improved by initiation of therapy [18]. Whereas other studies found that systemic inflammation was a notable contributor to the lipid profile changes. Growing evidences suggested that patients with active untreated RA have reduced TC, LDL-C and HDL-C levels [7,19]; and these abnormal lipid profiles were improved through suppression of inflammation by many disease modifying anti rheumatic drugs (DMARDs) [20]. Any how what ever the baseline level of lipid profile in Iraqi patients with RA, it seemed that the use of MTX could improve it.

The results of this study showed that there was a significant difference in the baseline level of both TC and LDLc between rosuvastatin and placebo group, which may be resulted by chance in such a randomized controlled trial of small sample size.

Results of this study showed that rosuvastatin produced a significant reduction in both TC and LDLc level; similar finding was reported in many other studies, comparing the effect of different statins, rosuvastatin [21], atorvastatin [22] and simvastatin [23] to placebo in patients with RA. Rosuvastatin reduced TC by more than 23% and LDL-C by more than 36% which was close to that found in UK survey for use of rosuvastatin in general practice (–28% for cholesterol and – 40% for LDL-C) [24]. Such result can be explained according to the fact that rosuvastatin is one of the HMG CoA reductase inhibitors which lower plasma cholesterol due to the inhibition of endogenous cholesterol synthesis in the liver, and subsequently increased expression of LDL receptors, resulting in an up-regulated catabolic rate for plasma LDL [25].

Moreover, the results showed that rosuvastatin was unable to significantly increase HDL-C despite its greater effect when compared to placebo; similar finding was observed in TARA study, at which 40mg atorvastatin failed to improve HDL-C [22]; however, rosuvastatin 10mg was sufficient to increase HDL-C significantly in RA patients after 1 year of therapy [21], this mean that short duration of follow up period in this study may be a limiting factor in achieving a real result regarding the effect on HDL-C.

The results of the current study showed that TG level was higher in active RA patients than those in the control group, and only those in placebo group were significantly higher than control group; similar finding was observed in patients with early active RA by Georgiadis *et al* [18].

Limitation in the current study may be related to the significant difference in baseline level of TG between patients in placebo and rosuvastatin group which may be caused by the small sample size; Any how only rosuvastatin significantly reduced TG from baseline level, this effect was not statistically significant when compared to that of placebo; similarly the use of low dose rosuvastatin in patients with mildly active RA failed to achieve significant reduction in TG level [21]. The absence of clinically significant effect on TG level may be attributed to the low dose of rosuvastatin that used in the current study, since Ooi et al. found that rosuvastatin effect to reduce TG level was dose dependent [26].

Regarding ESR which is sensitive for most types of inflammation, but cannot distinguish if the underlying cause is infectious, inflammatory, or paraneoplastic [27], however it provides a reliable means for discrimination between drugs that provide symptomatic relief only and those with a more profound effect in RA [28].

The results of this study showed that ESR level in RA patients who participated in this study was significantly higher than that in healthy control subjects, which was similar to the finding in the study of Yildirim K *et al.* [29] Since we included only patients with high ESR level.

More importantly, rosuvastatin (but not placebo) significantly reduced ESR level; similarly, in two other studies 40mg atorvastatin have the ability to reduce ESR significantly [22,30]. However, a study regarding the effect of 10mg rosuvastatin showed no any benefit, which may be explained in that patients who participated in that study had low initial ESR level since they have just mildly active RA disease [21], whereas this study excluded any patient with mild or inactive RA disease who had low ESR values (less than 20 mm/hr).

Myasoedova *et al* found that Inflammatory measures (particularly ESR) were significantly associated with the risk of CVD in RA [31]. In addition, it was found that controlling both RA disease activity and dyslipidemia is mandatory for minimizing the cardiac risk in RA patients [32].

This study showed that rosuvastatin significantly reduced both traditional (TC and LDLc) and non traditional (ESR) risk factors for CVD in RA patients which agreed with the recent EULAR recommendation for using statins for cardiovascular risk management in RA patients [33].

Conclusions

Methotrexate has the ability to normalize lipid profile in RA patients. Rosuvastatin effectively reduce ESR, TC and LDLc with little effect on TG and HDLc in RA patients; Moreover, Rosuvastatin might have a possible cardioprotective effect in RA patients.

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