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RESEARCH ARTICLE

THE USE OF ATORVASTATIN IN RHEUMATOID ARTHRITIS AND ITS EFFECT ON DAS28 AND ACUTE PHASE REACTANTS

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Abstract

Background: Rheumatoid arthritis is a chronic inflammatory arthopathy associated with rapid onset of clinically significant functional impairment, and is associated with accelerated vascular risk with attendant early mortality and excess morbidity. Atorvastatin the well known anti-dyslipidemic have a plausible bioactivity profile in vitro and in vivo that makes them possible therapeutic agents in rheumatoid arthritis to target both vascular risk and synovial inflammation.

Objective: The present study was performed to evaluate the effect of atorvastatin on disease activity score and acute phase reactants (ESR, CRP) in rheumatoid arthritis, apart from their lipid lower properties.

Study Design: A prospective, hospital based, open labeled, randomized, case control study in which 100 patients of active rheumatoid arthritis, age group between 20-70 years and both sexes were included. The patients were randomized into cases and controls by lottery method. Cases received 40mg of atorvastatin daily and controls received placebo (vitamin B complex capsules) as an adjuvant to existing disease modifying antirheumatic drugs for 6 months. All were clinically evaluated and disease activity score (DAS), ESR, CRP, lipid profile, LFT were measured at 0 and 6 months.

Results: Rheumatoid arthritis patients received atorvastatin showed a significant (p value < 0.05) reduction in ESR and CRP as compared to those who received placebo, but without improving DAS-28 ($p > 0.05$).

Conclusion: Atorvastatin significantly suppressed acute phase variables, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in patients with active rheumatoid arthritis despite ongoing therapy with disease modifying anti-rheumatic drugs without significantly improving DAS-28.

Keywords: Atorvastatin, CRP, ESR, DAS-28.

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory arthropathy associated with rapid onset of clinically significant functional impairment, and is also associated with accelerated vascular risk with attendant early mortality and excess morbidity.[1,2,3,4,5] It has an annual incidence of 0.5 per 1000 persons per year in United States, with peak incidence in fourth and fifth decade of life.[2,6,7]

Atorvastatin the well known anti-dyslipidemic have a plausible bioactivity profile in vitro and in vivo that makes them possible therapeutic agents in rheumatoid arthritis to target both vascular risk and synovial inflammation. Statins reduce cardiovascular morbidity and mortality by inhibiting HMG-CoA (3-hydroxyl-3-methyl glutaryl co-

enzyme A) in patients without inflammatory disease,[5,8,9] but many studies have found that they have broader properties including alteration of inflammatory pathways. Ex-vivo activities of statins include suppression of adhesion molecule expression, leucocyte cytokine release, MHC class-II expression, lymphocyte and macrophage cognate interaction and effects on reactive oxygen and nitrogen intermediate production statins also modify apoptosis in smooth muscle and endothelial cells leading to altered vascular function and neovascularization.[5,8,9] These properties offer the potential to modify chronic inflammatory disease states with drugs that shows minimal toxic effects in both the short and long term.[5] The present study was performed to evaluate the effects of statins on disease activity score and acute phase reactants (ESR, CRP) in rheumatoid arthritis, apart from their lipid lower properties.

MATERIAL AND METHODS

This was a prospective, hospital based open labeled, randomized case control study conducted in the Department of Medicine, SMHS Hospital Srinagar (J&K), a teaching hospital from April 2011 to Oct. 2011. One hundred patients between age group of 20-70 years and both sexes with active rheumatoid arthritis (According to 1987 Criteria for Classification of Rheumatoid Arthritis) were included and divided into two groups to receive 40mg of atorvastatin or placebo (vitamin B complex capsules).

Eligible patients had confirmed rheumatoid arthritis according to the 1987 American College of Rheumatology (ACR) Criteria[8] for at least one year with ongoing activity (active disease defined as at least two of the following three (a) $\geq$ six tender joints, (b) three swollen joints, and (c) $\geq$ 45 minutes of morning stiffness. The exclusion criteria included patients who were taking statins, pregnancy, lactation, hypersensitivity to statins, renal or hepatic impairment and age below 20 years. An informed consent was taken from all patients.

Clinical and Laboratory Evaluation

All cases were clinically evaluated for tender and swollen joints by a specialized Rheumatologist at 0, and 6 months, and disease activity score measured using DAS28 which is a validated composite. Blood samples were collected and analyzed at baseline, and 6 months for the measurement of CRP and ESR, lipid profile and liver function.

Statistical Analysis

Statistical software was used for input and analysis. Continuous variables were presented as mean $\pm$ SD and discrete variables as numbers and frequencies. Chi-square and other applicable statistical tests were used to analyze inferences and p value of < 0.05 was taken as statistically significant.

RESULTS

In this study, 100 patients were included and randomly assigned to receive atorvastatin or placebo. Half of them received atorvastatin and the other half placebo. Patients in both groups had similar baseline and demographic characteristics (Table 1,2). Patients were predominantly middle aged women (80% atorvastatin group versus 82% control group) with disease duration of more than one year. Table 3 shows the mean $\pm$ SD value of indices used to evaluate the progression of the patients in two study groups. It shows statistically insignificant difference in ESR, CRP and DAS28 of both groups, at pretreatment stage [p value 0.073 (ESR), 0.59 (CRP), 0.089 (ESR – mean $\pm$ SD 43.22 $\pm$ 11.45 (Atorvastatin group versus 39.06 $\pm$ 11.49 (placebo group) p value 0.073. CRP – mean $\pm$ SD 26.18 $\pm$ 18.71 atorvastatin group versus 25.24 $\pm$ 7.09, p value 0.59], but there was a progressive and significant reduction in ESR and CRP levels in atorvastatin group compared to placebo group at 6 months (ESR 28.68$\pm$9.27 atorvastatin group versus 35.60$\pm$11.46 (p value 0.001), (CRP- 18.90$\pm$8.034 atorvastatin group versus 23.62$\pm$7.036 (p value 0.002), though there was no improvement in DAS28 (p value 0.666).

Table – 1
Age (years) distribution in the studied patients

Group	Minimum	Maximum	Mean	SD	Percentage
Cases	32	60	46.44	7.265	0.143
Controls	24	66	43.88	9.860	

Table – 2
Sex distribution in the studied patients

Group	Male		Female		p value
	No.	%	No.	%	
Cases	10	20	40	80	0.50
Controls	9	18	41	82	

Table – 3
Mean ± SD of Indices Used in the Studied Subjects

Test	Group	At 0 months		At 6 months	
		Mean	SD	Mean	SD
ESR	Atorvastatin	43.22	11.45	28.68	9.27
	Placebo	39.06	11.49	35.60	11.56
	p value	0.073		0.001	
CRP	Atorvastatin	26.18	8.71	18.90	8.03
	Placebo	25.24	7.09	23.62	7.03
	p value	0.59		0.002	
DAS28	Atorvastatin	4.91	1.09	4.38	0.93
	Placebo	4.55	1.01	4.30	0.86
	p value	0.089		0.666	

DISCUSSION

This study was designed as randomized, open labeled case control study to decrease the possibility of bias.[10] Because it is ethically unaccepted to use atorvastatin alone, adjuvant therapy to DMARDS is implemented, this also avoid risks in patients who remain untreated for study duration.[11] Though all studies show statins to improve individual markers of inflammation,[12,13,14,15,16] the picture remains mixed as to the effect of statins in rheumatoid arthritis disease progression. The studies which demonstrated statistically significant improvement[12,13,15] (p 0.004, p 0.002 and $p < 0.001$) in DAS28 with adjuvant statins use, are the studies conducted by McCarey DM et

al, Maki-Petaja KM et al, and El-Barbary AM et al. The other studies demonstrated either a statistically insignificant improvement ($p > 0.05$)[14], or almost no statistical difference (p 0.98)[16].

While not all studies demonstrated a statistically significant decrease in DAS28, they all showed improvement in one or more individual markers of inflammation. Four studies[12,13,15,16] found statins to improve CRP ($p < 0.001$, p 0.002, $p < 0.001$ and $p < 0.001$) respectively and three studies showed improvement in ESR (p 0.005, p 0.006 and $p < 0.001$).[12,13,15] In this respect our study showed improvement in both inflammatory markers at 6 months (p 0.002) and p (0.001).

The study results do not appear to depend upon specific statins or its dosages. Of the studies demonstrating statistically significant improvement in DAS28, McCarey et al[12] and El-Barbary et al[15] used atorvastatin 40mg which is same what we used in our study, but without any improvement in DAS-28 ($p < 0.066$), while Maki Petaja et al[13] compared simvastatin, 20 mg daily and ezetemide 10mg daily. On the other hand, of the two studies showing statistically insignificant improvement, Charles-Schoeman et al[14] used atorvastatin 80mg daily and Okamoto et al[16] did not differentiate between statin drugs or dosages.

Interestingly, differences in DAS28 outcomes may be related to study, quality. Those studies that demonstrated a benefit to adjuvant statin use in rheumatoid arthritis disease progression were of higher study quality than those that did not.

CONCLUSION

It can be concluded that 40mg of atorvastatin is a safe and well tolerated drug that can significantly suppress acute phase reactants (CRP and ESR) in patients with active rheumatoid arthritis despite ongoing therapy with DMARDS, without significantly improving DAS28.

RECOMMENDATION

Large scale multicenter trials are required to support the reported data, and longer period of follow up is required to evaluate long term benefit of atorvastatin in rheumatoid arthritis disease activity.

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