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Original Article

Effect of Pitavastatin in Patients with Active Rheumatoid Arthritis Treated at a Tertiary Care Hospital

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, autoimmune in nature that predominately affects synovial joints. Being a crippling disease is a leading cause of disability that often reduces the quality of life and impairs patients ability to work.

Aims and Objectives: The aim of the study was to compare the effect of different treatment regimens on patients with active RA treated at a tertiary care hospital.

Materials and Methods: This was a prospective, open labeled, parallel arm, randomized, and single-center study performed in a tertiary care teaching hospital (Chennai Medical College Hospital and Research Centre [SRM Groups], Irungalur, Tiruchirapalli) and was conducted at outpatient clinics. Total duration of the study period was 24 weeks. All the patients were having active RA and were on oral methotrexate (first-line disease-modifying antirheumatic drug) at the time of recruitment.

Statistical Analysis: All the data were initially entered into Microsoft Excel 2010 and later these spreadsheets were used for analysis. Statistical analysis was done using SPSS version 20.0.

Conclusion: Combination therapy of pitavastatin and methotrexate is better than methotrexate monotherapy and combination therapy of rosuvastatin and methotrexate.

Key words: Combination therapy, Methotrexate, Pitavastatin, Rheumatoid arthritis, Rosuvastatin

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, autoimmune in nature that predominately affects synovial joints. Being a crippling disease is a leading cause of disability that often reduces the quality of life and impairs patient's ability to work.[1] The primary goal of managing the patient with RA is to maximize long-term health-related quality of life and to achieve remission as soon as possible. Pharmacotherapy of RA involves symptom-modifying antirheumatic drugs such as nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs) – small molecule non-biological agents, biological agents, and glucocorticoids.[2] RA, if not treated properly, may lead to permanent damage to joints and is the number one cause of early retirement, disability payments, and loss of employment.[3]

The pleiotropic effects of statins such as anti-inflammatory, immune-modulating, and anabolic effects strongly support the potential role of these drugs in the prevention and/or treatment of cardiovascular risk factors and joint damage associated with RA.[4] Pitavastatin, the seventh statin reduces elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglycerides and increases high-density lipoprotein (HDL) cholesterol levels.[5] Pitavastatin has anabolic effect on bone and prevents osteoporosis induced by RA. Substantial cardiovascular protection offered by it can reduce cardiovascular morbidity and mortality associated with RA.[6,7] Rosuvastatin is a hydrophilic statin with extensive first-pass metabolism.

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The absorption of rosuvastatin is not affected by food and maximum plasma concentration is reached in 3–5 h. The usual dose is 5–10 mg once daily.[8] Important side effects include myopathy and rhabdomyolysis. It is contraindicated in hepatic failure, pregnancy, and lactation. It should be used cautiously in patients with diabetes since it increases the hemoglobin A_1C levels.[8] As an adjunct to DMARDs, rosuvastatin can effectively bring out remission in active RA patients. Only a limited number of studies elaborate the effect of pitavastatin in RA. Hence, this study was done to evaluate the efficacy and safety of pitavastatin in patients with active RA.

MATERIALS AND METHODS

Study Setting

This study was conducted at the Medicine Outpatient Department at Chennai Medical College Hospital and Research Centre, Irungalur, Tiruchirapalli.

Study Design

This was a hospital-based analytical cross-sectional study performed in a tertiary care teaching hospital (Chennai Medical College Hospital and Research Centre, Tiruchirapalli).

Sample Size

A total of 90 active RA patients who fulfilled the inclusion and exclusion criteria were recruited in the study after obtaining written informed consent. Study subjects were divided into three groups of 30 each.

Inclusion Criteria

Active RA patients of both the sexes in the age group of 20–60 years according to the American College of Rheumatology (ACR) criteria and on a dose of methotrexate 7.5 mg weekly for the past 3 months were enrolled for this study. Criteria for active RA include patients with more than or equal to six swollen joints/six tender joints (from 68 joint counts), C-reactive protein (CRP) more than or equal to 1.5 mg/dl, erythrocyte sedimentation rate (ESR) more than or equal to 28 mm at the end of 1st h, and morning stiffness more than or equal to 45 min.

Exclusion Criteria

Patients on steroids therapy, Vitamin D3 therapy, patients with severe RA as per ACR Criteria-Stage IV, pregnant and lactating women, patients with liver failure, renal failure, myopathies, and pancytopenia were all excluded from the study.

Sample Size

A total of 90 active RA patients who fulfilled the inclusion and exclusion criteria were recruited to participate in the study.

Data Collection Tool

Data collection was done during working hours at a time feasible to the respondents. The study was conducted in the hospital premises after obtaining prior permissions from the concerned authorities. After obtaining informed consent from the participants, they were divided into three groups, based on their treatment schedules and observed. The first group consisted of patients with RA with active disease on tab. Methotrexate 12.5 mg weekly, the second group included patients with RA with active disease on methotrexate 7.5 mg weekly + Tab. Rosuvastatin 10 mg once daily and in the third group included patients with RA with active disease on methotrexate 7.5 mg weekly + Tab. Pitavastatin 1 mg once daily. The respondents were asked to fill a questionnaire which covered information on socio-demographic data, biochemical parameters were measured by drawing 5 ml venous blood, the samples were collected from the subjects in all the three groups on 0th day at the end of 4th, 8th, and 12th weeks of the study period.

Parameters Measured

(i) Disease activity score (DAS): DAS was calculated according to the standard formula based on tender joint count, swollen joint count, ESR, and assessment of general health based on the scores between 0 and 100 from the patient. The joints involved and include shoulders, metacarpophalangeal joints, proximal interphalangeal joints, elbows, wrists, and knees of both sides contributing to a score of 28. Estimation was done at every visit. (ii) Rheumatoid factor (RF) test: RF test detects immunoglobulin M (IgM) antibodies to immunoglobulin G (IgG) antigen. The purified antigen is bound to a solid phase microassay well. Patient serum samples are diluted and added to each well. If antibody is present in the patient's serum, antigen-antibody complexes are formed. The absorbance of the solution, measured at 450 nm, is directly related to the concentration of IgM antibody. Values more than 7.7 IU are considered to be positive, with the presence of detectable antibodies. (iii) Anti-cyclic citrullinated peptide (CCP): Intended for the quantitative determination of IgG class antibodies directed against CCPs, present in human serum, or plasma. Procedure was the same as estimation of RF. The lowest concentration of anti-CCP detected is 1.12 U/ml with 98% confidence value. The immunological parameters, namely, RF and anti-citrullinated protein antibody were estimated by enzyme-linked immunosorbent assay. (iv) ESR: ESR was measured by Westergren method as the method of choice. The Westergren method uses ethylenediaminetetraacetic acid as an anticoagulant. The reference range is for men <15 mm/h–20 mm/h and for women <20 mm/h–30 mm/h. (v). Lipid profile: Lipid profile included total cholesterol, triglycerides, HDL, and LDL.

Statistical Analysis

The data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) (version 21.0) software package. Descriptive statistics were used to define the study population. Categorical and ordinal variables were expressed as frequency/percentages. Continuous variables were expressed as mean and standard deviation. Appropriate tests of significance (analysis of variance) were applied to the study variables to establish the relationship between the study variables. $P < 0.05$ was considered to be statistically significant.

RESULTS

Our results showed that among the study participants, more than half were female 59 (65.6%). Majority of the sample population, 37 (41.1%) respondents were in the age group of 41–50 years followed by 32 (35.6%) who were between the age group 51–60 years. The mean age group of the respondents was 48.32 ± 7.49 [Table 1].

Table 1: Age and gender distribution of the respondents (*n*=90)

Variable	Frequency	Percentage
Gender		
Male	31	34.4
Female	59	65.6
Age distribution		
30–40	19	21.1
41–50	37	41.1
51–60	32	35.6
>60	2	2.2
Mean age (±SD)	48.32±7.49	

Distribution of DAS Across the Three Groups at Various Time Periods

Our results showed that among the study participants the mean reduction in DAS were seen from the baseline at 4th, 8th, and 12th weeks of the study in all the groups and a significant reduction is seen in Group 3, having baseline value of 6.54–3.03 at the end of the study [Table 2]. This decrease in the DAS was found to be statistically significant ($P = 0.001$).

Distribution of Serum RF Levels Across the Three Groups at Various Time Periods

A mean reduction in RF was seen from the baseline to 12th week of study in all the groups and a significant reduction ($P = 0.003$) is seen in Group 3, having baseline value of 88.5–42.3 at the end of the study [Table 2].

Distribution of Serum Anti-CCP Levels Across the Three Groups at Various Time Periods [Table 2]

We found a mean reduction in anti-CCP level was seen from the baseline to 12th week of study in all the groups. In the third group, we found that the anti CCP values had decreased from 38.06 (at the begining of the study) to 18.33 (at the end of the study). There decrease in the serum anti-CCP levels was found to be statistically significant ($P = 0.001$).

ESR Across the Three Groups at Various Time Periods

As seen in Table 2, there has been a mean reduction in the ESR values among all the three groups. It has also been observed that only in the third group this reduction was found to be statistically significant.

Table 2: Distribution and comparison of various parameters among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Disease activity score				
0 weeks	6.86±0.76	6.49±0.8	6.54±0.6	*P*=0.001
4 weeks	6.34±0.73	5.96±0.7	5.39±0.5	
8 weeks	5.96±0.75	5.56±0.7	4.14±0.5	
12 weeks	5.60±0.91	5.11±0.7	3.03±0.5	
Serum rheumatoid factor levels				
0 weeks	94.3±97.3	93.5±98.3	88.5±73.8	*P*=0.003
4 weeks	74.3±79.4	84.3±87.3	64.3±67.3	
8 weeks	64.2±68.5	66.3±69.3	54.3±57.5	
12 weeks	52.8±43.6	52.5±44.7	42.3±35.5	
Serum anti-CCP levels				
0 weeks	41.61±44.3	48.84±43.5	38.06±34.4	*P*=0.001
4 weeks	36.3±79.4	44.3±42.3	29.3±30.3	
8 weeks	28.2±68.5	32.3±29.3	23.4±26.5	
12 weeks	21.7±17.2	29.8±24.1	18.3±14.8	
ESR				
0 weeks	49.0±19.7	52.1±21.3	49.7±11.7	*P*=0.001
4 weeks	39.0±18.0	44.8±19.0	37.7±10.7	
8 weeks	34.2±16.2	39.7±17.8	27.6±8.4	
12 weeks	29.7±14.4	34.1±18.4	17.1±3.5	

*P<0.05 was taken to be statistically significant. ESR: Erythrocyte sedimentation rate, CCP: Citrullinated peptide, ANOVA: Analysis of variance

Table 3: Distribution and comparison of mean lipid profile values and Vitamin D values among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Total cholesterol levels				
0 weeks	160.13±24.24	169.47±17.87	156.13±18.89	*P*=0.001
4 weeks	159.67±23.77	168.95±17.91	154.93±18.65	
8 weeks	159.33±23.68	168.18±18.17	153.65±18.68	
12 weeks	159.73±23.81	167.35±18.57	152.63±18.30	
TGL levels				
0 weeks	170.3±23.0	189.0±33.2	182.9±24.0	*P*=0.001
4 weeks	169.3±22.3	188.5±33.7	180.4±23.9	
8 weeks	168.9±22.9	187.7±34.5	178.0±23.2	
12 weeks	168.3±22.0	186.6±35.5	175.5±23.4	
LDL levels				
0 weeks	124.5±21.8	119.7±36.3	132.3±19.2	*P*=0.001
4 weeks	123.8±22.0	118.1±36.0	129.6±18.4	
8 weeks	123.8±21.7	115.7±35.0	126.6±18.0	
12 weeks	124.5±21.9	113.0±34.5	123.2±17.1	
HDL levels				
0 weeks	33.33±1.77	37.73±23.04	35.79±3.41	*P*=0.001
4 weeks	32.87±1.78	37.76±23.08	36.45±3.03	
8 weeks	32.90±1.94	37.78±23.08	37.00±3.15	
12 weeks	32.83±1.74	37.89±22.99	37.87±2.91	

*$P<0.05$ was taken to be statistically significant. TGL: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Comparison of Mean Lipid Profile Values [Table 3]

Our results showed a uniform reduction in all the lipid profile values across all the three groups in the progressive weeks, except for HDLs which showed a significant increase. There was a significant reduction in total cholesterol, triglyceride, and LDL levels in all the three groups in the progressive weeks, as shown in Table 3.

DISCUSSION

RA is a chronic inflammatory, autoimmune disease which leads to rapid onset of clinically significant functional impairment, particularly if not controlled properly by DMARDs. Statins, because of their pleiotrophic effects, have been used in various trials to prove their efficacy in RA. The present study was conducted to find out the effect of pitavastatin in active RA patients along with methotrexate, compared to methotrexate monotherapy and methotrexate, rosuvastatin combination therapy.

The reduction in mean DAS was maximum among the subjects under pitavastatin + methotrexate group. Hence, pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the DAS scores. This result is comparable with the result of Kumar *et al*.,[9] but against the studies conducted by Mikhael[10] McCarey *et al*.[11] and Das *et al*.[12]

The reduction in mean RA factor levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. This correlates with the studies conducted by Abeles and Pillinger[13] Chan *et al*.,[14] and Niwa *et al*.[15]

The reduction in mean anti-CCP levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. Hence, pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the mean anti-CCP levels. This correlates with the findings from studies conducted by Abeles and Pillinger[13] Chan *et al*.,[14] and Niwa *et al*.[15]

The reduction in mean ESR levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. This shows that pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the mean ESR levels. This reduction in the ESR levels can be compared with the studies done by Kumar *et al*.,[9] Mikhael[10] McCarey *et al*.,[11] and Das *et al*.[12]

The LIVES study,[16] CHIBA study,[17] and PATROL trial[18] have shown a significant reduction in total cholesterol levels, triglyceride levels, and LDL levels with the combined therapy of pitavastatin + methotrexate. The have also documented a significant increase in the HDL levels. These findings are similar to the findings from our study. The highlight of the present study is the identification of superiority of pitavastatin as an adjuvant therapy along with

methotrexate in the management of patients with active RA with marked inflammation.

CONCLUSION AND RECOMMENDATIONS

Pitavastatin decreases the DAS and improves the well-being of patients with active RA by lowering the RFs and anti-CCP levels. It significantly reduces inflammation in active RA which is evident from the decrease in the ESR and CRP levels. Further the side effects such as myopathy and precipitation of diabetes seen with others statins are not that much pronounced while using pitavastatin. Further it raises the HDL level, lowers TG, TC, and LDL levels and has a favoring effect in reducing the cardiovascular risk factors. Considering the increasing morbidity and mortality in crippling disease-RA, particularly involving the cardiovascular system, addition of a potent statin like pitavastatin as an adjuvant to DMARDs can improve the quality of life of patients suffering from RA.

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