Outcome of rheumatoid arthritis following adjunct statin therapy

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ABSTRACT

Objective: Rheumatoid arthritis (RA) is characterized by symmetric peripheral polyarthritis, inflammatory synovitis, and articular destruction. Statins, 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors, mediate significant vascular risk reduction in patients with coronary artery disease by promoting reduction in plasma levels of low-density-lipoprotein cholesterol. Extensive in vitro data, experimental studies and more recently few clinical trials have strongly suggested statins to possess an important role in RA mainly mediated by their anti-inflammatory and immunomodulatory properties. The objective of this study was to evaluate the effect of adjunct statin therapy in comparison to standard disease modifying antirheumatic drugs (DMARD) therapy in patients with RA.

Materials and Methods: In this observational study, diagnosed RA patients of age group between 40 and 60 years were selected as per the inclusion criteria from the rheumatology outdoor. From the selected patients, we identified two separate groups of patients. Group 1 included 30 patients of RA currently under DMARD therapy with adjunct statin medication. Group 2 included 30 patients of RA currently under DMARD therapy. Patients were followed up over 6 months. Standard parameters such as disease activity score (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded for comparing the outcome of RA in both groups.

Results: Out of a total of 60 patients who took part in the study, significant beneficial role of adjunct statin medication was found in this study when prescribed along with conventional DMARDs in active RA patients. The mean DAS28, considered by far as the most important index of clinical disease activity in RA, was found to be significantly lower ($P < 0.05$) in the adjunct statin-treated group (group 1) than that of the conventional DMARD treated group (group 2) after 6 months of continuous therapy. Other two important biochemical markers of RA disease activity, that is, ESR and CRP were also found to be significantly lower ($P < 0.05$) in RA patients who were on adjunct statin medication (group 1) than in group 2 comprising RA patients only under conventional DMARDs therapy without statin medication.

Conclusion: The results suggest an adjunct and potentially beneficial role of statin therapy in active cases of RA, producing significant clinical and biochemical improvement.

KEY WORDS: 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors, disease activity score 28, disease modifying antirheumatic drugs, rheumatoid arthritis, statins
Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease that affects joints and other tissues. The hallmark of the disease is symmetric peripheral polyarthritis, inflammatory synovitis, and articular destruction. The disease is characterized by inflammation of synovial tissues, joint swelling, stiffness and pain, which may progress to joint and bone erosion. It leads to rapid onset of clinically significant functional impairment. Along with causing significant morbidity and mortality, RA results in substantial use of medical resource and costs. Pharmacotherapy for active RA at present includes one or a combination of the following four classes of drugs: Nonsteroidal anti-inflammatory drugs, analgesics, corticosteroids (prednisolone and methylprednisolone), and disease modifying antirheumatic drugs (DMARDs). Modern RA management stresses the importance of early diagnosis and aggressive treatment with DMARDs, particularly methotrexate, hydroxychloroquine, and sulfasalazine. In spite of the availability of so many conventional DMARDs, favorable outcomes are frequently not achieved with combination DMARDs resulting in persistent active disease. Of late, however, newer biologic therapies are the order of the day for successful management of active RA. Leflunomide, etanercept, and adalimumab are the popular biologics which are frequently used either alone or in combination with methotrexate. A number of trials have shown that these newer drugs to be more effective than traditional agents because of their ability to alter joint remodeling as well as attenuate disease symptoms. Despite promising and successful outcome with these newer biologic agents, its benefit largely remains confined to the small subset of patients moreover, in a resource poor country like India, very few can afford the high cost of these therapy. Thus, it is apparent that further therapeutic advances are required for better treatment of RA for those patients who do not respond to conventional DMARDs combination therapy and particularly for those who cannot afford the costly new biologic treatments. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, mediate significant vascular risk reduction in patients with coronary artery disease by promoting reduction in plasma levels of low-density-lipoprotein cholesterol. Although the action of statins is primarily via this mechanism, recent studies suggest they have broader properties, including alteration in inflammatory pathways and immunomodulatory functions. Statins have been shown to be of some benefit in both, suitable animal models of RA and in the randomized clinical trial. Statins, therefore, have a plausible bioactivity profile that makes them possible adjunct therapeutic agents in addition to standard antirheumatic treatment to target both vascular risk reduction and synovial inflammation. With this background knowledge the current study was undertaken with the objective of assessing the effectiveness of adjunct statin with conventional DMARDs in active RA patients in comparison to standard DMARDs therapy alone.

Materials and Methods

Study Design and Patient Selection

A prospective observational study was conducted in the Rheumatology out-patient department during July 2013 to July 2014. Participants of 40–70 years of age, diagnosed as cases of RA (as per 2010 ACR-EULAR criteria, no limit on disease duration) and having active RA disease activity despite ongoing DMARD therapy were included in the study. The patients having composite 28 joints disease activity score (DAS28) of 3.2 or higher were taken as having active disease. Exclusion criteria included the inability to give informed consent; history of allergy to statins, chronic liver disease, active infection, or any concurrent renal disease. From the patients satisfying the inclusion criteria, we identified two separate groups of patients. Group 1 included all patients of RA currently under standard DMARD therapy with an adjunct statin (i.e., atorvastatin, rosuvastatin, etc.) medication. Group 2 included all patients of RA currently under standard DMARD therapy.

Procedure

At the start of the study, baseline demographic details such as age, gender, and body weight were noted. A worldwide accepted clinical outcome variable of RA, that is, composite DAS28 was determined from patient clinical examination data such as swollen joint count, tender joint count, patient global assessment, and provider global assessment. Among biochemical variables erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and other routine values such as serum hemoglobin%, total leukocyte count, serum creatinine, fasting blood sugar, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase were also noted. Patients of both groups were followed up after 6 months of initial observation. Both the clinical and biochemical variables were also noted during follow-up visits. After follow-up, analysis of the collected data was done to study the outcome of RA patients between group 1 and group 2 in terms of various biochemical parameters such as ESR, CRP and also in clinical parameter of DAS28 score. CRP was measured by the immunoturbidimetric method, ESR by Westergreen method. DAS28 was determined by standard formula given by the following equation:

\[
\text{DAS28} = 0.56 \times \sqrt{t(28)} + 0.28 \times \sqrt{\text{sw}(28)} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{VAS}
\]

Statistical Analysis

Data were expressed as mean ± standard deviations. Data analysis was carried out using GraphPad Prism version 5.01 (for Windows, GraphPad Software, San Diego California USA) as software for statistics. Independent sample t-test was done for intergroup comparison of various parameters such as ESR, CRP and DAS28 score with 95% confidence level.

Ethical Issues

The study protocol and design was approved by the Institutional Ethical Committee. Written informed consent was also obtained from all the patients who agreed to participate in the study.

Results

Out of total 70 patients enrolled for the study involving effectiveness of adjunct statin given alongside DMARDs; 5 patients did not follow-up, 3 patients were excluded as they could not adhere to the study protocol, and 2 of them opted out of the study. From the rest, 30 patients were identified in group 1, that is, with adjunct statin and 30 patients were identified in group 2 (without statin and only under DMARDs).
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All of the participants belonging to both the groups were female patients. Independent sample t-test ($P < 0.05$ taken as significant, 95% confidence interval) was done to compare the baseline demographic data like age, weight; and baseline clinical and biochemical disease activity status like composite DAS28 and ESR among the two groups [Table 1].

As evident from this table, all RA patients belonging to both group 1 and group 2 had a comparable age, body weight and sex distribution with no statistically significant difference in between the two groups. When compared in terms of biochemical outcome parameter; that is, mean ESR and clinical outcome parameter; that is, mean DAS28, there was no statistically significant difference at baseline. After 6 months of continuing the same treatment, it was seen that the mean ESR (27.0 ± 6.136) in RA patients with adjunct statin (group 1) was lower than the mean ESR (53.47 ± 18.17) of RA patients without adjunct statin (group 2). The difference was statistically significant ($P < 0.05$) [Figure 1].

The mean CRP value (2.437 ± 0.626) as evident in our study was also found to be significantly lower in RA patients of group 1 (with adjunct statin) as compared to (4.443 ± 1.791) group 2 (without adjunct statin) ($P < 0.05$) [Figure 2].

The means of the principal clinical outcome measurement in our study, that is, DAS28, were found to be 3.386 ± 0.286 and 4.657 ± 1.083 in group 1 and group 2 respectively. On comparison a significant ($P < 0.05$) difference was followed in the DAS28 score between group 1 and group 2 [Figure 3].

The principal RA disease outcome parameter in our study, that is, the mean DAS28 score, when plotted against time in both the groups, it is observed that the mean level of DAS28 in group 1 is significantly lower ($P < 0.05$) than the mean level of DAS28 in group 2 [Figure 4].

Discussion

In our observational prospective study, it was observed that RA patients who were on adjunct statin therapy, had markedly reduced mean level of acute phase reactants like ESR and CRP than the patients who were on DMARDS at the end of 6 months of follow-up. Although there is a modest change in mean DAS28 level at the end of 6 months, yet the significant reduction supports the concept that pathways targeted by statins offer therapeutic opportunity in RA.\(^{[11]}\) Many data indicate effects for statins in innate immune response, manifest on endothelial activation,\(^{[12]}\) macrophage, natural killer cells, and neutrophil effector function.\(^{[13]}\) Similar effects on acquired immune responses via suppression of antigen presentation\(^{[14]}\) and T-cell polarization have been shown in vitro and in vivo.\(^{[15,16]}\)

In this study, mean level of CRP showed a decreasing trend after 6 months of follow-up in the patients of group 1 (with adjunct statin) than group 2. Mean level of DAS28 score and ESR were significantly lower in the RA patients on adjunct statin medication than RA patients without statin medication, which is similar to study reported by McCarey et al.\(^{[17]}\) in the TARA trial. Another important preclinical study that have found favorable effects of statins on animal models of chronic RA are those reported by Haruna et al.\(^{[18]}\) A study done by Leung et al.\(^{[19]}\) has also reported a favorable role of simvastatin on inflammatory arthritis in mice. A study by Abud-Mendoza et al. reported statins as an important therapeutic approach for the treatment of inflammatory rheumatic disease.\(^{[20]}\)

The standard treatment options for RA now involve a combination of DMARDs as the goal of therapy has shifted toward disease amelioration and remission induction together with tissue protection. A significant effect of adjunct statin on disease activity was noted in our study. The anti-inflammatory role of statins in RA, such as the inhibition of leukocyte-endothelial adhesion, effects on reactive oxygen and nitrogen intermediate production, the suppression of inflammatory cytokine release, inhibition of inflammatory signal pathways, activation of anti-inflammatory transcription factors and inhibition of T-cell activation and co-stimulatory molecules have been demonstrated by a series of molecular studies.\(^{[21]}\) Both anti-inflammatory and immunomodulatory actions of statins have been postulated to play an important role in RA. Statins have been shown to reduce the level of CRP in patients with RA independent of their cholesterol lowering effects.\(^{[22]}\) Statins have also been shown to decrease adhesion interaction between monocytes and vascular wall,\(^{[13]}\) reduce monocyte chemotaxis by interfering with monocyte chemotactic protein-1.\(^{[14]}\) Similarly, growth and proliferation of macrophages is also inhibited by statins therapy.\(^{[15,16]}\) Various statins such as fluvastatin,\(^{[17]}\) simvastatin,\(^{[18,19]}\) lovastatin, and atorvastatin\(^{[20]}\) have been reported to induce apoptosis and thus may be beneficial in killing of inflammatory cells in the RA. One study has suggested anti-inflammatory role of statin therapy by reduction of mRNA for cyclooxygenase-2.\(^{[21]}\)

Many studies have suggested immunomodulatory role of statins.\(^{[22]}\) Statins have been shown to decrease the T-cell proliferation.\(^{[23]}\) Atorvastatin, lovastatin, and pravastatin have been shown to reduce the expression of major histocompatibility complex-II (MHC-II) on antigen presenting cells and MHC-II mediated T-cell activation.\(^{[24]}\) Statins have been suggested to reduce inflammatory cytokines production like tumor necrosis factor-α and interleukin-1β (IL-1β), chemotactic cytokines like IL-8 and IL-6.\(^{[25]}\) As most of these above mentioned immunological events are central to the pathogenesis of RA, hence statins are expected to be beneficial in RA. In addition, it appears that statins can disrupt the oxidative stress/inflammation cycle\(^{[26]}\) by decreasing the release of inflammatory mediators and lipid peroxidation, since oxidative stress is recently recognized in inflammatory diseases like RA to perpetuate tissue damage. Chronic administration of statins can also inhibit peroxisome proliferator-activated receptor α and γ, which are known inflammatory mediators.

Table 1:
Mean values of different baseline parameters between group 1 and group 2

| Baseline parameters | Group 1 (n=30) | Group 2 (n=30) | P | Significance |
|---------------------|----------------|----------------|---|-------------|
| Age (years)         | 55.3±8.32      | 54.9±9.66      | 0.864 | NS         |
| Women               | 30             | 30             |     |             |
| Weight (kg)         | 61.6±8.46      | 59.0±6.96      | 0.1988 | NS         |
| ESR (mm/1 h)        | 47.7±8.924     | 52.8±15.11     | 0.1217 | NS         |
| DAS28               | 6.08±0.66      | 6.40±1.04      | 0.1594 | NS         |

Data expressed as mean±SD, P<0.05 taken as significant. NS=Nonsignificant, SD=Standard deviation, ESR=Erythrocyte sedimentation rate, DAS28=Disease activity score 28
We recognize important limitations of our study. The design chosen offers advantages in facilitating single-center observational study over a short period. However, the heterogeneous background of DMARD use, concomitant medication use and their dose modification as per individual patient requirement allow the possibility of statin-DMARD interactions that could confound outcomes. Though a sub-group analysis as per different DMARDs was not done in this study, however, hydroxychloroquine, methotrexate, sulfasalazine, leflunomide, and etanercept in very few cases were the mainly used DMARDs in our study. We observed patients under different statins irrespective of their dose and duration of usage to collect a statistically significant sample population of 30 patients in each group. Statins being not yet indicated for RA per se, the patients belonging to group 1 of our study were actually prescribed a statin for some other indication like dyslipidemia, etc. Further studies should, therefore, be designed to test statin activity in a strictly defined DMARD context and also based on an individual statin, their dose and duration, preferably in a multicenter trial.

Conclusion

The findings from our study reveal an adjunct and potentially beneficial role of statin therapy in active cases of RA; producing significant clinical and biochemical improvement. However, supporting data from large clinical trials are needed to conclusively establish the facts before statin therapy for RA can be recommended.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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