In the name of God

Shiraz E-Medical Journal
Vol. 12, No. 4, October 2011

http://semj.sums.ac.ir/vol12/apr2011/89034.htm

A Comparative Study on Atorvastatin Versus Methotrexate in Rheumatoid Arthritis in a Double Blind Placebo Control Trial.

Sandooghi M*, Zakeri Z**, Almasy S***, Dashipour AR¤.

*Assistant Professor, ** Associate Professor, Section of Rheumatology, Department of Internal Medicine, Ali-Ebn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran, *** Assistant Professor, Section of Rheumatology, Department of Internal Medicine, Firoozgar Hospital, Tehran University of Medical Sciences, Tehran, Iran, ¤ MSc in Nutrition , Zahedan University of Medical Sciences, Zahedan, Iran.

Correspondence: Zahra Zakeri, Department of Internal Medicine, Zahedan University of Medical Sciences, Zahedan, Iran. Tel: +98(541) 341-4575, Fax: +98(541)341-4563, Email: zah_zakeri@yahoo.com

Received for Publication: September 26, 2010, Accepted for Publication: October 1, 2011.

Abstract:

Background: The therapeutic effects of methotrexate (MTX) are well-known in rheumatoid arthritis(RA).Also,anti inflammatory effects of atorvastatin have already been reported, but no study has compared the effects of these two drugs on RA.Therefore we designed this study to compare the effects of these drugs on patients with active RA.
Method: The study was conducted on 54 patients with active RA who had been undergoing Disease – Modifying -Anti Rheumatic- Drugs therapy for at least 3 months that included 7.5 mg methotrexate weekly. They were allocated into two groups. In addition to the 7.5 mg of MTX, one group received another 7.5 mg of MTX weekly and placebo daily and the other group received atorvastatin 40 mg daily and placebo weekly. They were followed up for 12 weeks. Some clinical aspects and the disease activity score (DAS) were evaluated at the beginning of the study and then at the weeks of 6th and 12th.
Results: After multiple comparisons by repeated measures, disease activity score and other variables showed a significant reduction in both groups at 12th week after treatment; however, the effect of both interventions was similar in change of DAS and other variables except for duration of morning stiffness, that it decreased more in statin than MTX group. No significant side effects causing to exclude the patients from the study were observed in any of the two groups.
Conclusion: we concluded that statin, can serve an important role in treatment of RA.

Keywords: Rheumatoid arthritis, Atorvastatin, Methotrexate, Disease activity score.

Introduction:

Rheumatoid arthritis is a chronic systemic disease which primarily involves the synovial tissues. This disease can potentially lead to substantial disability and premature death; therefore, early and aggressive treatment is essential important. Observational trials have clearly identified that methotrexate (MTX) is the synthetic Disease Modifying Anti Rheumatic Drugs (DMARDS) that is most often selected for initial therapy.[1] The patients with suboptimal response to MTX, combination therapy and or biologic agent should be applied. However, biologic agent is expensive; Hence, searching for other alternatives of DMARDS in treatment of RA seems to be highly demendnding. Several studies have confirmed the effects of statins in decreasing atherosclerosis through anti inflammatory mechanism [3], since RA patients are more susceptible to cardiovascular diseases and the most common cause of mortality in RA is cardiovascular complications [2]; an increasing interest has aroused to study the effects of statins in improving RA.

Statins prevent the formation of Isoprenoids. Inhibition of Isoprenoid intermediates may contribute to the pleiotropic effects of statin therapy.[4,5] Anti inflammatory effects of statins in innate and acquired immune system established in several studies.[3,4,6,7,8,] Also, statins modify apoptosis in smooth muscle, endothelial cells and synovial cells [3, 9] and bones[5,10], for instance, statins may have preserving effects on periarticular bone in RA joints.[11] Moreover, several reports have revealed that therapeutic use of statins in treatment of multiple sclerosis[3,6,5], autoimmune encephalomyelitis[3,6], cardiac and renal transplantation[3,6], in murine collagen-induced arthritis [12,13], refractory rheumatics disease.[14] And Antiphospholipid syndrome in animal models.[15] The first placebo controlled study named TARA Study was conducted to investigate therapeutic effects and vascular risk factor modification of statin in RA patients.[16] TARA Study showed a significant reduction in the disease activity score in atorvastatin group compared to placebo group in patients with RA. Some other studies, also, revealed similar results.[17, 18,19).

However, some other studies did not confirm any significant improvement in the measures of clinical activity by statins.[20, 21] Overall, no significant side effects were seen in use of statin; for example, increased risk of serious infections [10] and an elevated cancer risk.[10]

The brief review of literature in this field reveals that so far there is or little information available to make a comparison between MTX and statins directly. The aim of the present study is to examine the effect of atorvastatin on disease activity in RA patients and compare it with MTX .

Materials and Methods:

According to the American College of Rheumatology criteria were fifty four patients with RA diagnosis recruited from rheumatology clinic of Ali- Bn-Abitaleb hospital in Zahedan, city of Iran from January 2006 through March 2007.

The age of all the patients were above 18 years old , signed a written informed consent. Recruitment was done in patients with active inflammatory disease

who had been undergoing Disease – Modifying -Anti Rheumatic- Drugs (DMARD) therapy that included for at least 3 months 7.5 mg methotrexate.

Our definition of the disease activities were as three swollen joints or joint groups plus two of the following:

i) Three tender joints

ii) Early Morning stiffness for more than 30 min and 3)an erythrocyte sedimentation rate of greater than 30 mm/ hr .

Exclusion criteria included: not signing the written informed consent, Current lipid - lowering therapy or indication for lipid lowering therapy , previous history of adverse reaction to statins, clinically significant renal disease or aspartate aminotransferase and alanine aminotransferase more than twice the upper limit of laboratory normal rang ,recent corticosteroid injections and finally every patient who was required to receive a high dose of corticosteroid to suppress his disease activity. (for instance pulse therapy with corticosteroid)

Patients remained on all previous DMARD therapy, and were asked to maintain their DMARD dose while in the study, unless the researchers prescribed a different dose. We modified and recorded the prednisolone or NSAID dose during the study. Patients included in the study were introduced to an independent study administrator by rheumatologist, then, every other one received box A that including methotrexate 7.5 mg/weekly (in capsule) and one placebo capsule every day (group a) or box B including atorvastatin 40 mg/daily (in capsule) and one placebo capsule every week (group b).That is, after the first patient was placed in group a, the second patient was allocated to group b. The patients refer to researcher who was blinded to the allocations. Therefore, both patients and doctors were blinded to medication.

The primary outcome was a change in DAS 28 (a validated composite disease activity score, Components of DAS 28 are erythrocyte sedimentation rate (ESR), patient assessed global score, visual analogue score (pain, 0-100) and swollen and tender joint counts (both 0-28)) [15]; also, secondary outcome holds variables including duration of early morning stiffness, ESR, swollen and tender joint counts, change in prednisolone, sulfasalazine, and Hydroxychloroquine dose.

After screening, patients were visited on o, 6th and 12th weeks. The same researcher, who was blinded to the allocations, evaluated and recorded all clinical variables at study entry and at 6th and 12th weeks .Also, Hematology and biochemical screening for liver and renal function was done at baseline and 6th and 12th weeks ,and significant side effects including, weakness, rash, fever, headache or abdominal pain were recorded by the researcher. Patients who failed to take the drugs properly and those who had hematologic, kidney or liver dysfunction and significant side effects during the study, were excluded from the study. The monitoring was carried out through telephonic conservation to the patients if they failed to visit at the appropriate time; moreover, they were introduced back to the researcher if they visited the rheumatologist directly. Moreover, regarding ethical aspects, every

patient could discontinued the study due to lack of efficacy or adverse events, and we also, could exclude patients without any response (change in duration of morning stiffness, swollen and tender joint counts, patient assessed global score, visual analogue score of pain)

Statistical analysis:

Calculation of sample size was based on variation in mean value of DAS for every group in TARA study and study by Fransen J and et al.(22) α=0.05, ß=o.o5 power=0.95,and using the following formula:

μ1=variation in mean DAS before and after treatment of statin (TARA study)

μ2= variation in mean DAS before and after treatment of MTX (Fransen study)

Z1-α/2 and Z1-β are standard normal distribution values corresponding to two-side test

S1= standard deviation in statin group (TARA study)

S2= standard deviation of MTX group (Fransen study

Baseline data were summarized as mean ±SD for continuous variables, number and percent of patients for categorical variables . Statistical analysis was made for multiple comparisons by repeated measures .We used k2 test for categorical variables. We used SPSS software (version 11.5) and P value less than 0.05 was evaluated as statistically significant.

Results:

Fifty four patients with RA received either increased dose of MTX from 7.5 mg to 15 mg (group a) or 7.5 mg MTX plus 40 mg atorvastatin (group b) .Each group consisted of 27 patients, of whom 26 (96.13%) and 25 (92.6%)were females in group a and group b respectively. Mean age was 43.96±13/9 in group a and 48.5±11 in group b. (P=0.18) Mean duration of disease was 4.2±3.2 years in group a and 5.5±5.3 years in group b (p=0.26). After multiple comparisons by repeated measures, disease activity score and other variables including number of swollen and tender joints , ESR, duration of morning stiffness showed a significant reduction in both groups at 12th week after treatment; however, the effect of both interventions (add of 7.5 mg MTX or 40 mg atorvastatin) was similar in change of DAS and other variables except for duration of morning stiffness. Although both groups have shown decrease in duration of morning stiffness, further decrease was observed in statin group.

The results of statical analysis are tabulated in Table 1.It is obvious from this table that there is no significant difference was not observed in interaction effects except for use of prednisolone ,while in the study, dose of prednisolone decreased in statin group and increased in MTX group. (table 1) Eight patients (14.8%) achieve remission (DAS<2.6) in both groups, 5 patients (18.1%) in group a and 3 patients (11.1%) in group b. (p=o.4)

No patients were excluded and there were not withdrawals due to lack of efficacy or adverse events.

Although patients had been asked to adhere to concomitant already prescribed drugs unless the rheumatologist decides so, dose of prednisolone was increased by 2 patients in group a and 3 patients in group b and also decreased in 15 patients in group b from about 10mg to 5mg. In addition to methotrexate, two patients in group b received both Hydroxychloroquine and sulfasalazine, also, 17 and 16 patients in group a and b respectively received Hydroxychloroquine alone and 6 patients received sulfasalazine alone in both groups. Three patients in both groups (11.7%) decreased 200 mg doses of Hydroxychloroquine and 4 patients in group b decreased 500mg doses of sulfasalazine. The effect of NSAID dose was not analyzed because it was used neither in anti inflammatory dosage nor continuously.

Discussion and conclusion /Summary and conclusion:

To address the objectives of the present research in order to compare the effects of MTX and statin directly, ethically no group was asked to receive MTX, therefore, after both groups had received MTX for at least three months which seems to be enough time to have responded to MTX, we administered Statin to group b and added the dose of MTX in group a; meanwhile, we would like to mention that in our area patients receiving 7.5mg to 15mg MTX show usually a good respond.

In present study, patients with active RA ,with both increase dose of MTX from 7.5 mg to 15 mg weekly and adding 40 mg atorvastatin daily to MTX 7.5 mg /weekly reduced DAS in similar degree, although patients in atorvastatin group(.at this junction of the investigation it is difficult to justify) had a longer duration of morning stiffness at baseline. Also, duration of morning stiffness showed a more reduction in patients who used atorvastatin and patients in statin group decreased dose of prednisolone.

The results of our study were compatible with the TARA's findings; in that, showed a significant reduction in DAS 28 ,CRP,ESR and swollen joint count in atorvastatin group compared to placebo in patients with RA presenting with active disease despite undergoing DMARD therapy. In TARA Study more patients in the placebo group than in the atorvastatin group received intra –articular or intramuscular administration of triamcinolone .Authors in TARA study believed that the improvement seen in statin therapy is comparable with cyclosporine and minocycline , but they did not directly compare statin and MTX. As well, Kanda and et al. showed that 10 mg of simvastatin for 12 weeks improves clinical, laboratory and immunological parameters of RA patients.[17] Beside, a large observational cohort in daily practice and real life setting showed Patients taking statin had significantly lower disease activity assessed by CRP ,pain assessment, physician assessment, swollen and tender joint count, but no statistical differences were noted in DAS 28 or HAQ.[19]

However, our findings were not well-matched with some studies Van Doornume and et al detected arterial stiffness, lipid profile and inflammatory marker in RA patient before and after 20 mg atorvastatin therapy.[20]

Lipid profile and arterial stiffness improved significantly after atorvastatin therapy but inflammatory marker remained unchanged during the study. Similar observation was made by Charles - Schoeman and et al with 80 mg atorvastatin in double blind placebo control trial.[21] The changes in measures of clinical activity were not significant but there was a trend for a decrease in CRP during 12 weeks of treatment with statin .

on the other hand , some authors believed that , the effect of statin on inflammatory is due to cholesterol lowering per se and not pleotropism effect of statin .Mäki-Petäjä and et al in a study conducted in a randomized double - blind crossover manner , compared simvastatin with ezetimib (that neither is absorbed nor has systemic effects). In both groups, reduction in disease activity score is similar.[18]

In addition to the results of all mentioned studies that suggest a hopeful future for statins as a reliable drug to control RA, based on the findings of the present study we can also conclude that statin, can serve an potential benefit in treatment of RA. If statin can control the inflammation like MTX it may be a good choice in treatment of RA.However this study was limited to 54 patients with duration of 15 months .Whether or not statin can be used without MTX, needs much more investigations to be conducted in different situations, for example, to administer statin without MTX with/without other DMARDS especially in patients with mild forms of the disease and in much longer time study.

Acknowledgement:

We would like to express our gratitude to the authorities in university of Zahedan Medical Sciences for their cooperation, special thanks to Mr. Khazaei for his English editorial work . We are also grateful to Dr Rahimian for in collecting data.

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