ORIGINAL ARTICLE

The effects of conventional drugs in the treatment of rheumatoid arthritis on the serum lipids

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Background: Rheumatoid arthritis (RA) is a common chronic autoimmune disorder that leads to damage of human joints. There are various treatment approaches in which different drugs are prescribed which have several alterations in serum lipids. This research aimed to study the effect of RA treatments on the serum lipids. **Materials and Methods:** Two hundred randomly selected patients with RA were randomly assigned to three different groups. The first group of patients was treated with a combination of prednisolone (PRD) and hydroxychloroquine (HCQ). The second group was treated with three drugs including PRD, HCQ, and methotrexate (MTX). The third group was treated with four medications including PRD, HCQ, MTX, and sulfasalazine. Within each group, the lipid factors such as triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), erythrocyte sedimentation rate, and visual analog scale were measured at the beginning of the experiment and 6 months after exposing the treatments. For each group, we also calculated the Disease Activity Score-28 (DAS-28). The analysis of variance revealed that the overall DAS-28 was significantly different among the three groups. **Results:** In the first group, the level of TG and TC significantly decreased ($P = 0.015$ and $P \leq 0.001$, respectively). In the second group, the level of TG and LDL significantly decreased ($P = 0.009$). In the third group, the LDL level increased considerably ($P < 0.001$). The HDL level significantly increased in all three groups ($P = 0.012$, $P = 0.014$, and $P = 0.028$, respectively). **Conclusion:** The treatment PRD + HCQ + MTX was more effective in reducing the LDL level and increasing the HDL level. To reduce the risk of cardiovascular diseases in patients with RA, it is important to prescribe the combination of drugs which leads and normalizes the lipid profile levels.

Key words: Hydroxychloroquine, methotrexate, prednisolone, rheumatoid arthritis, sulfasalazine

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic auto-inflammatory disease that can cause systemic inflammation and joint damages.[1-4] It can be identified by its specific pattern in the destruction of bones and joints.[5-9] The prevalence of RA almost considered from 0.5% to 1% in the world.[1]

The main cause of death is related to cardiovascular diseases (CVD) among patients with RA[10] so that these patients are more susceptible to CVD, especially atherosclerosis compared to others.[1,10,11] On the other hand, plasma lipids are considered significant predictors of CVD.[10] Thus, measuring and determining these indicators could be useful in disease prognosis.

The previous studies on patients with RA showed that the level of triglyceride (TG), total cholesterol (TC), and low-density lipoprotein (LDL) was higher than the general population and the level of high-density lipoprotein (HDL) was lower.[12,13] On the other hand, some other studies indicated that the TG level was higher than the control group, and the HDL level was lower than the baseline. These studies showed no significant difference in the serum level of LDL and TC.[14,15] It seems

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that the role of treatment and the effect of medication in treating patients with RA have a significant impact on the level of the serum lipids.[15] hydroxychloroquine (HCQ), methotrexate (MTX), corticosteroids, and sulfasalazine (SSZ) are examples of these drugs.

HCQ is a drug derived from 4-aminoquinoline which is used as a malaria treatment. This is one of the disease-modifying antirheumatic drugs (DMARDs) that is used in the treatment of RA. This drug has a positive effect on the level of serum lipids so that it can lead to increasing the level of HDL and decreasing the level of TG, LDL, and TC.

SSZ is a combination of salicylate and sulfapyridine that is used in the treatment of RA.[16] The previous study shows a decrease in the level of HDL after exposing this therapy. SSZ alone or in combination with MTX and prednisolone (PRD) has a positive effect on HDL level. MTX is a drug which acts as a folic acid analog and binds to the dihydrofolate reductase enzyme and prevents the formation of folic acid.[13] Some studies showed that using the combination therapy by DMARDs, MTX, HCQ, and SSZ have no significant effect on the serum level of any serum lipids.[17]

PRD plays an essential role in decreasing the inflammation and its related complications. In fact, PRD at a low-dose over long periods of the time changes the blood pressure, lipid profiles, and insulin resistance. This drug can lead to increasing the risk of heart attack.[18,19] Results from some studies suggest that the combination of MTX and PRD as a treatment of RA can lead to a significant increase in the level of HDL and TC. These results did show no substantial change in the level of LDL and TG.[20,21]

In the present study, with the existing controversy, we decided to investigate the effect of three commonly used methods of RA treatments on the level of TG, TC, LDL, and HDL.

MATERIALS AND METHODS

Design and participants

This study is an experimental study. We conducted a completely randomized design of analysis on 200 randomly selected patients with RA from the Outpatient Rheumatology Clinics of Alzahra and Noor Hospital affiliated with Isfahan University of Medical Sciences from January 2015 to January 2016. The sampling method was a simple random sampling method. Out of 200 sampled patients with RA, we randomly assigned 67 patients to the first treatment PRD + HCQ, 93 patients to the second treatment PRD + HCQ + MTX, and 40 patients to the third treatment PRD + HCQ + MTX + SSZ. The Ethics Committee of Isfahan University of Medical Sciences investigates and approves this study (ethics code 395690). A written informed consent was obtained from all patients in this study. In this study, the randomly selected patients with RA were diagnosed and classified based on the American College of Rheumatology (ACR) criteria 2015. It should be noted that the medication of patients who were under treatment of RA was recorded before entering into this study. When one of these drugs PRD, HCQ, MTX, or SSZ was added to the existed treatment, the type of medicine and the related dose were recorded. In this way, we could determine the effect of these drugs on the level of TG, TC, LDL, and HDL factors. We re-examined patients after 6 months of receiving treatments and calculated the Disease Activity Score-28 (DAS-28) and the level of factors above.

Instruments and procedures

Inclusion criteria were patients with the body mass index <30 and were willing to participate in the study. Patients were excluded if they fall into the following categories: smoking, alcohol consumption, diabetes mellitus, CVD, atherosclerosis, hyperlipidemia, hypothyroidism, liver and kidney disease, Cushing's and nephrotic syndrome, taking insulin, metformin, the lipid-lowering drugs and anticholesterol drugs in the last 6 months, beta-blockers, estrogen, progesterone, atorvastatin, levothyroxine, current pregnancy, and failure to visit at the appointment or prematurely, discontinued treatment for any reason.

Patients were advised not to eat any high-fat foods and red meats 3 days before testing and referred them to the reference laboratory, while they were for 12 h in fasting status. After taking samples, we put them in the form of a blood clot (blood clots at room temperature). The sampled blood was centrifuged at 35,000 rpm for 10 min. Two hundred lambdas of these serum samples placed in the cup of the machine (depending on the BT1500 or BT3000). Based on the type of kit (BIOLAB or Pars Azmoon), we measured the level of factors TG, TC, LDL, and HDL. On each patient, the score DAS-28 was used to assess the disease activity of RA (tender and swollen joint count [0–28], patients' assessment of disease activity visual analog scale [VAS] [0–100 mm], and erythrocyte sedimentation rate [ESR]). To evaluate the condition of RA patient and the level of prognosis, we used a published survey which has been verified by European League Against Rheumatism. Under the supervision of investigators and according to the ACR criteria 2015 guidelines, we treated patients with RA.

Statistical analysis

The collected sampled data on 200 RA patients and all related information were entered into a statistical software SPSS (ver. 20, IBM, Armonk, NY, United States

of America). Some statistical analyses such as mean, standard deviation, frequency, and the percentage of the rate of changes are reported in Tables 1, 2 and Figure 1. All tests were performed at the significant level of $\alpha = 0.05$. As part of the statistical analysis, we conducted an analysis of variance (ANOVA) to compare the score of DAS-28 on each of these treatments. The related ANOVA to this experimental design revealed that the overall DAS-28 was significantly different among the three groups [Table 1; $P < 0.001$]. A simple paired sample *t*-test within each group was employed to test the effect of three commonly used methods of RA treatments on the serum lipids [Table 2]. The normality assumption of the data was tested by the Shapiro–Wilk test.

RESULTS

This study included 200 patients with RA. Among them, 67 (33.5%) patients were under treatment of PRD + HCQ, 93 (46.8%) patients were under treatment of PRD + HCQ + MTX, and 40 (20%) patients were under treatment of PRD + HCQ + MTX + SSZ. These three groups showed no differences regarding the gender and age with $P = 0.237$ and $P = 0.861$, respectively [Table 1]. The mean of the duration of RA disease and its severity DAS-28 suggested a significant difference among these three groups ($P = 0.036$). Patients with more involvement of joints, length, and a severity score of RA (DAS-28) showed a substantial increase in the number of this score with a $P < 0.001$ [Table 1]. After 6 months of treatment, the mean

Table 1: Baseline characteristics of the patients with rheumatoid arthritis in three treatment groups

Characteristics	PRD + HCQ (*n*=67), *n* (%)	PRD + HCQ + MTX (*n*=92), *n* (%)	PRD + HCQ + MTX + SSZ (*n*=40), *n* (%)	*P*
Gender				
Female	58 (86.6)	71 (77.4)	30 (75)	0.237
Male	9 (13.4)	22 (22.8)	10 (25)	
Age (year)	50.51±8.67	51.37±9.69	50.98±11.05	0.861
Duration of disease (year)	2.33±2.19	3.36±3.07	4.36±2.84	0.036
DAS-28	5.37±0.21	5.83±0.20	6.33±0.15	<0.001

Data are shown mean±SD or *n* (%). DAS-28=Disease Activity Score in 28 joints. *P* values are used for the comparison between three groups at 5% significant level. SD=Standard deviation; PRD=Prednisolone; HCQ=Hydroxychloroquine; MTX=Methotrexate; SSZ=Sulfasalazine

Table 2: Comparison of mean change from baseline at month 6 in metabolic factors in the patients with rheumatoid arthritis in three treatment groups

Factors	PRD + HCQ (*n*=67)	PRD + HCQ + MTX (*n*=92)	PRD + HCQ + MTX + SSZ (*n*=40)	*P**
Triglyceride (mg/dl)				
Baseline	160.29±36.99	153.08±73.59	163.30±62.73	0.666
At month 6	136.11±58.08	120.32±45.85	124.00±55.53	0.173
*P***	0.015	<0.001	0.065	
Total cholesterol (mg/dl)				
Baseline	191.65±27.47	200.39±33.08	198.22±42.85	0.432
At month 6	181.81±28.27	204.11±44.29	200.25±24.99	0.001
*P***	<0.001	0.560	0.018	
LDL (mg/dl)				
Baseline	102.59±25.18	113.10±31.02	118.52±20.34	0.121
At month 6	100.07±22.60	105.48±40.30	121.67±29.20	<0.001
*P***	0.120	0.009	<0.001	
HDL (mg/dl)				
Baseline	56.39±20.03	54.88±13.21	52.42±18.02	0.500
At month 6	75.11±77.73	81.59±100.06	58.35±14.09	0.329
*P***	0.012	0.014	0.028	
ESR (mg/dl)				
Baseline	26.26±13.82	31.82±15.52	46.47±28.99	<0.001
At month 6	12.93±6.45	15.38±8.87	20.00±13.16	0.001
*P***	<0.001	<0.001	<0.001	
VAS				
Baseline	50.00±18.89	55.71±10.86	80.00±3.27	<0.001
At month 6	9.00±9.51	5.74±4.58	18.76±15.06	0.001
*P***	<0.001	<0.001	<0.001	

Data are shown mean±SD. *P* value is used to test if the difference between baseline and 6 months is significant within each group. *Level of significance in the comparison between three groups, **Level of significance in the comparison between admission and 6 months in each of groups. LDL=Low-density lipoprotein; HDL=High-density lipoprotein; ESR=Erythrocyte sedimentation rate; VAS=Visual analog scale; SD=Standard deviation; PRD=Prednisolone; HCQ=Hydroxychloroquine; MTX=Methotrexate; SSZ=Sulfasalazine

score of DAS-28 in PRD + HCQ group showed a decline from 5.37 ± 0.21 to 2.62 ± 0.71, in which 52 patients (77.6%) had a good response and 15 patients (22.4%) had a moderate response to this treatment. In PRD + HCQ + MTX group, also the mean score decreased from 5.83 ± 0.20 to 3.24 ± 0.84 in which 34 (36.6%) patients had a good response and 59 (63.4%) patients had a moderate response to the treatment. In PRD + HCQ + MTX + SSZ group, the mean score also decreases from 6.33 ± 0.15 to 3.64 ± 0.81 in which 6 (15%) had an excellent response and 34 (85%) patients showed a moderate response to the treatment. The improvement of severity and symptoms among these three groups is statistically significant with a $P < 0.001$ [Figure 1].

Although the effect of RA treatment on serum lipids indicates that the level of TG decreased in all three groups, statistical analysis showed a significant reduction in the two groups of PRD + HCQ and PRD + HCQ + MTX with $P = 0.015$ and 0.001, respectively. The level of TC in PRD + HCQ group showed a decline of − 9.84 mg/dl but in other groups showed an increase in TC level. This study indicated that the increase in PRD + HCQ + MTX + SSZ group with a mean of + 2.03 mg/dl was significant (P = 0.018). The LDL level in the group with SSZ showed a significant increase. The level of LDL in the first and second groups showed a significant decrease (P = 0.009). Furthermore, the HDL level had a significant increase in all three groups with P = 0.012, 0.014, and 0.028, respectively. Finally, the ESR level and the pain scores of these patients over the time and after 6 months showed a significant decrease (all $P < 0.001$). In addition, the level of ESR and VAS after treatment suggested a marked reduction among the three groups. PRD + HCQ + MTX group has been more efficient in reducing the level of LDL and increasing the level of HDL factor. Needless to say that the most pain reduction observed in PRD + HCQ + MTX + SSZ group as it is reported in Table 2 and Figure 2.

Participant flow diagram

As an evidence-based reporting the findings of randomized trials, we address a flow diagram which shows the flow of participants through each stage of our study. This Consolidated Standards of Reporting Trials statement is essential when some participants did not receive the treatment as allocated or were excluded from the analysis [Figure 3].

DISCUSSION

In this study, patients with RA were allocated into three groups. The severity of RA disease in patients had no significant connection to the age and gender. However, based on these results, the severity of disease had more effect on the older patients. DAS-28 was related to the severity of sickness which was treated by multiple drug therapy.[22] After 6 months of treatment, 77.6% of patients in the group treated by PRD + HCQ showed a decreasing 2.75 scores in the mean of DAS-28. We also observed that the two groups under treatments PRD + HCQ + MTX and PRD + HCQ + MTX + SSZ had a significant improvement. In agreement with our results, the previous study reported a significant decrease in DAS-28 after prescribing the treatments MTX and prednisone. It showed that the early treatment of a patient with RA reduced the CVD risk significantly. A systemic review showed the improvement of lipid profiles and DAS-28 after treatment of patients with RA.[23]

The present study demonstrated that treatment of RA (with three methods) resulted in a significant reduction in TG levels. In contrast, HDL level was increased substantially in all three treatment groups. The patients treated with PRD + HCQ had a significant reduction in TC and LDL levels. In a group containing SSZ, there was an increasing

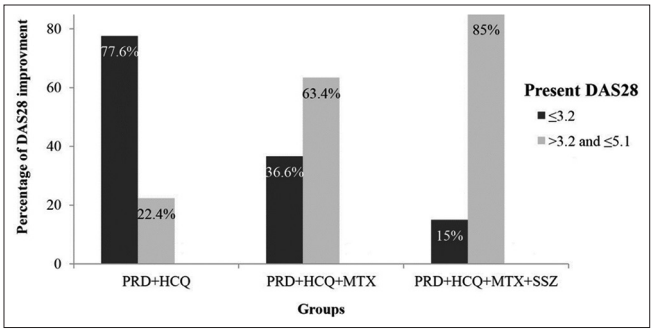

Figure 1: Comparing the Disease Activity Score-28 at two different time points, possible to define improvement or response (the EULAR response criteria)

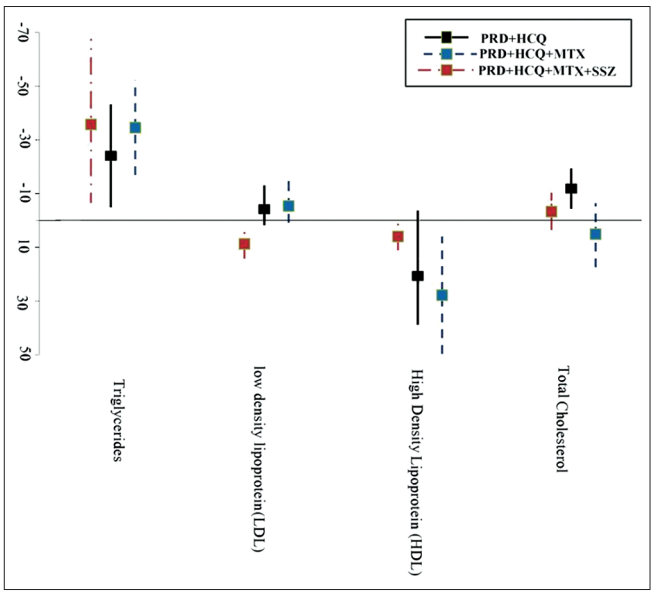

Figure 2: Treatment effect on the change of low-density lipoprotein, high-density lipoprotein, triglycerides, and total cholesterol in three treatment groups

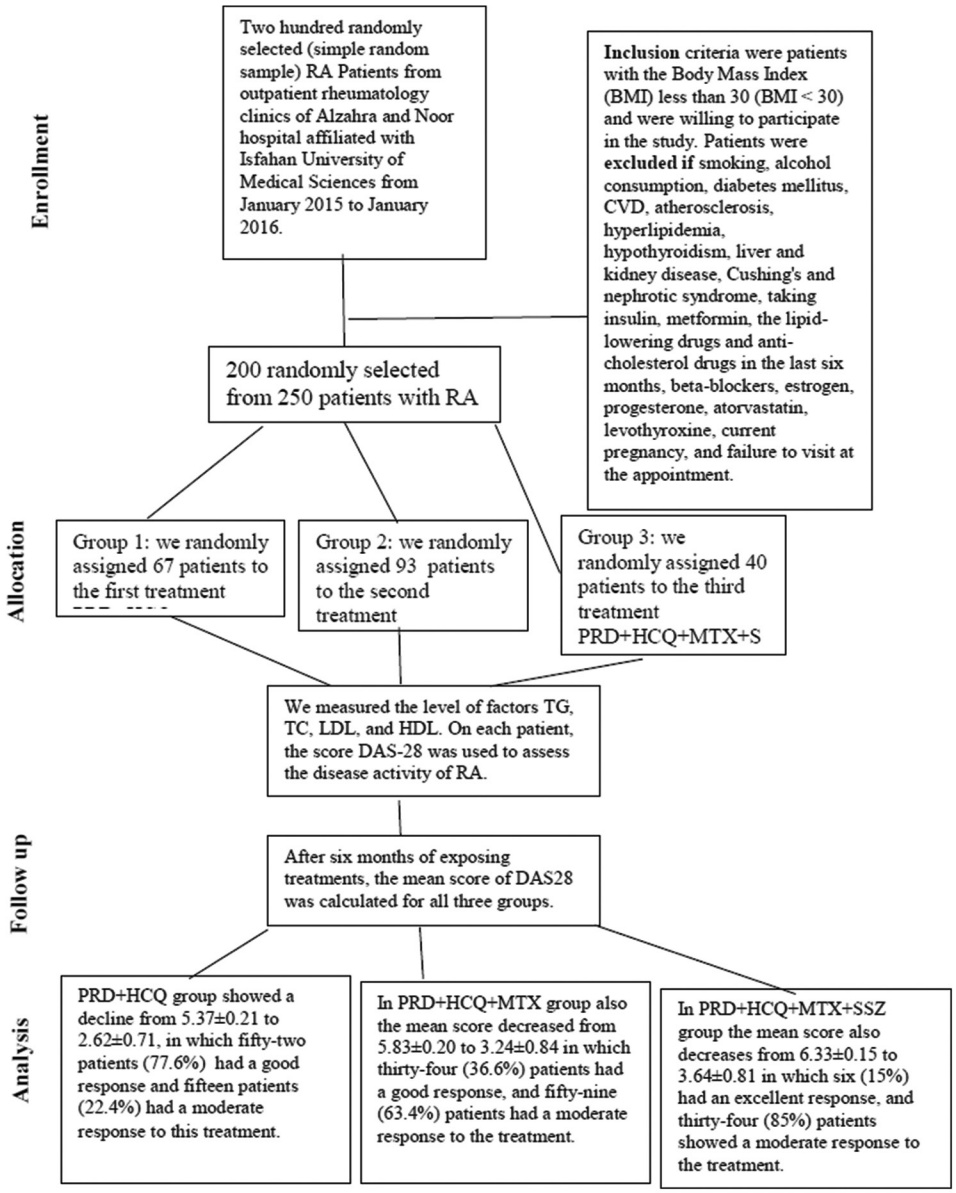

Figure 3: The progress through the phases of a three-group parallel randomized trial

level of both TC and LDL. In the treated group with PRD + HCQ + MTX, we did not find significant changes in TC level, while the LDL level decreased. Therefore, TG and HDL level more affected by treatment in all three groups of RA patients.

The present study showed that SSZ could increase the level of LDL and TC when combined with PRD + HCQ + MTX. The previous study showed that HDL level was significantly raised up during combination therapy with glucocorticoids and SSZ. Furthermore, the atherogenic index (cholesterol/HDL) in all treated groups was improved. In line with us, they also stated that the use of SSZ whether as monotherapy or combined with MTX and PRD caused an increase in the level of cholesterol and HDL. In another study conducted by Charles-Schoeman *et al.*,[13] they have been found that the disease activity and DAS-28 were significantly decreased and lipid profile was improved after treatment by MTX. The HDL level in monotherapy with MTX was considerably higher when it combined with the two- or triple-drug therapy treatment groups. The previous study showed that the treatment with MTX and PRD caused an increase in both HDL and cholesterol levels. We found similar results for HDL but not for cholesterol level. Navarro-Millán *et al*.[24] found that the treatment with MTX or combination therapy (MTX, HCQ, and SSZ) had a significant beneficial effect on lipid profile. All evidence suggested that the use of MTX was associated with the reduced risk of CVD in RA patients and could improve serum lipids in various stages of RA.[25] Although studies

have stated a beneficial effect of MTX to the reduction of CVD risk in RA patients, Saiki *et al*.[26] declared that using of the infliximab drug would be a better approach to lowering the level of TG than treating with MTX. The validity of the MTX in the multinational evidence-based study was recommended for the treatment of the RA patients with MTX.[27] The study of Kerr *et al*.[28] showed that the use of HCQ improved in the lipid profile except for HDL level which has remained unchanged after the treatment. Chopra *et al*.[29] also stated that using HCQ with new formulae (standardized Ayurveda formulation and HCQ sulfate) would help improvement in disease activity and can control the active RA. Peters *et al*.[30] found that the use of HCQ was in association with the improvement of lipid profile in RA patients. They found a considerable decrease in cholesterol and LDL levels and recommended using of infliximab with corticosteroid for treatment of RA patients. They found that the mean score of the DAS-28 was significantly reduced after the treatment and the lipid profile was improved. O'Dell *et al*.[31] reported that the combination of MTX, SSZ, and HCQ had a better outcome in RA patients compared with MTX and HCQ or MTX and SSZ although triple combination had no influence on pain relief in comparison with the other groups. Furthermore, the triple-drug combination did not have a significant effect on pain relief in comparison with other groups.[32] The efficacy of triple-drug therapy (MTX, HCQ, and SSZ) was better than using each separately regarding disease control. However, the biological treatment showed more efficient to inhibit progression of RA disease and triple therapy.[32]

Although we evaluated the standard drugs using for RA treatment, new studies have been working on other DMARDs and biological drugs such as tofacitinib and tocilizumab.[33] Moreover, the dose of drugs prescription play a significant role in the risk of CVD in RA patients.[34] The ESR was significantly decreased during treatment in all of the groups. The previous study showed a similarly reduced trend in ESR after treatment. Finally, the pain scores significantly decreased after 6 months of therapy, and PRD + HCQ + MTX + SSZ group was more efficient to reduce the pain score.

CONCLUSION

The results of this study showed that the level of factors TC, LDL, ESR, and VAS was significantly different between the three groups after exposing different treatments. It seemed that contrary to contained SSZ group, PRD + HCQ + MTX Group was more efficient in reducing the LDL level and increasing the HDL level. The PRD + HCQ + MTX + SSZ had a greater impact in reducing the patient's pain. Regarding the higher risk of CVD in RA patients, it was important to prescribe the combination of drugs which did lead to reduce the risk of CVD and normalize the lipid profile level.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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