Original Article

# Comparison of the Effect of Disease: Modifying Antirheumatic Drugs Alone or in Combination with Biologic Drugs in the Outcome of Patients with Rheumatoid Arthritis

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## Abstract

**Background:** Rheumatoid arthritis (RA) is a rheumatic disease that could be disabling if not treated. The aim of RA therapy is to resolve tenderness and swelling in the joints. The present study was conducted to compare two methods of RA treatment with disease-modifying anti-rheumatic drugs (DMARDs) and DMARDs with biologic drugs in two groups of patients. **Materials and Methods:** The present study was a nonrandomized clinical trial which was conducted from July to September 2017 on 110 patients who were selected based on the American College of Rheumatology (2010) criteria for RA. Patients were divided into two groups of 55: Groups A and B. For the treatment of Group A, prednisolone along with one or two drugs from the DMARDs combinations was used. Group B received one biologic drug besides with the drugs of the group A. *T*-test and covariance analysis was used to compare the outcomes of both groups. **Results:** Disease activity score (DAS-28) at the beginning of the study was 4.23 (0.81) in Group A and 4.51 (0.7) in Group B ($P = 0.05$). At the end of the study, DAS-28 was 3.52 (0.79) in Group A and 3.75 (0.85) in Group B ($P = 0.1$). DAS-28 activity index had a significant difference between both two groups at the beginning of the study ($P = 0.05$), but at the end of the study, the difference was not statistically significant ($P = 0.1$). **Conclusions:** Simultaneous use of DMARDs and biologic drugs in RA patients could lead to improvement the disease symptoms and decrease the severity and activity of the disease.

**Keywords:** *Biologic, disease activity score-28, disease modifying anti-rheumatic drugs, rheumatoid arthritis*

## Introduction

Rheumatoid arthritis (RA) is the most common disease of the joints affecting about 1% of the world population.[1] It involves not only the joints, but also all body systems such as the eyes, the respiratory system, and the heart. If left untreated, RA may develop into a crippling disease the treatment of which imposes heavy costs on the community and it might affect the economy of the society and its treatment and recovery also would annually impose great costs on the government.[2] Significant advancements have been made for treatment of this disease during the recent years that is majorly consisted of simultaneous use of old and new disease-modifying drugs. The common treatment of RA is the triple method that involves administration of hydroxychloroquine, methotrexate, and prednisolone.[3,4] Disease-modifying anti-rheumatoid drugs (DMARDs) are drugs that would prevent joint destruction. There are many kinds of drugs that all would act through suppression of the immune system. DMARD's contains hydroxychloroquine (HCQ), methotrexate (MTX), leflunomide, and sulfasalazine (SSZ). Biologic drugs are in fact a type of DMARDs that would block the production of cytokines and was first used for the treatment of RA in 1998.[5] If the RA is not severe, one type of DMARDs would be used at first for the treatment. If significant improvement is not occurred, the dosage of the drug would be increased to full-dose or another drug from the same category would be combined with it and the patient would be monitored after 3 months. If the aim of the treatment, which is to resolve tenderness and swelling in the joint, is not achieved yet, biologic



**How to cite this article:** Mousavi M, Karimzadeh H, Pakzad B, Mirrokni F. Comparison of the effect of disease: Modifying antirheumatic drugs alone or in combination with biologic drugs in the outcome of patients with rheumatoid arthritis. Adv Biomed Res 2019;8:32.

**Received:** December, 2018. **Accepted:** February, 2019.

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**Access this article online**

**Website:** www.advbiores.net

**DOI:** 10.4103/abr.abr_247_18

**Quick Response Code:**

drugs would be added to the treatment. To determine the intensity of the disease, Disease Activity Score (DAS-28) was used. In this scale, the elements of the number inflamed joints, the number of swollen joints, erythrocyte sedimentation rate (ESR), and pain intensity rate in clinical examination (physical assessment) are used. Some studies report the use of biological DMARDs.[6,7] This study investigated the effect of DMARDs along with biologic drugs in the early stages of this disorder to show that the integrated use of these two drug categories may hasten the recovery of RA.

## Materials and Methods

This nonrandomized clinical trial was conducted on the secondary data obtained from filed records of patients presenting to Rheumatology Clinic of Alzahra Hospital in Isfahan, Iran, in 2017. The diagnosis of RA was established by a rheumatologist and patients enrolled the study if they fulfilled the criteria on the basis of the American College of Rheumatology 2010 (ACR). The sample size was determined as 110 patients by a statistician with 95% confidence interval and error index of 0.05%. All the patients were under the baseline combination therapy (7.5 mg of MTX/week, 200 mg of HCQ/week, and 15 mg of prednisone/day and they were adjusted in sex, age, body mass index, and treatment duration. They were divided into two groups of 55 named Group A and Group B. Group A received prednisolone 15 mg/day along with one or two drugs of the DMARDs drugs (MTX and HCQ) for the treatment of RA. Group B received the drugs of Group A plus one biological drug (Subcutaneous Adalimumab 40 mg, per 2 weeks). The DMARDs include hydroxychloroquine, methotrexate, sulfasalazine, and leflunomide. The biological drugs include infliximab, adalimumab, and etanercept. In this study, parameters including age, gender, prednisolone dose, ESR, and C-reactive protein (CRP) were measured and recorded before and after pharmaceutical intervention and compared. Moreover, the two variables of physical assessment and global assessment were assessed and recorded before and after intervention and compared. Patients Global Assessment was ranged from 0 to 100 mm, although it was reported from 0 to 10 cm. Higher scores represent a higher level of disease activity or a worse global health. The proposed definition of "low global assessment" is ≤2.0 (scale 0–10). DAS-28 criteria were used to compare RA activity. The patients were divided into three groups on the basis of this scale:

1. Low disease activity with DAS-28 = 2.6–3.2
2. Moderate disease activity with DAS-28 = 3.30–5.10
3. High disease activity with DAS-28 >5.01.

The data were analyzed with SPSS (Chicago: SPSS Inc. IBM Corp.) using descriptive statistics including frequency, standard deviation, and mean. *T*-test and analysis of covariance were used to compare the data between the two groups ($P < 0.05$).

## Results

The mean age was 52.6 ± 11.9 years in Group A and 49.3 ± 11.9 years in Group B. Group A included 15 (27.3%) men and 40 (72.7%) women.

The ESR and CRP values and 100 mg Prednisolone dose before and after intervention are presented in Table 1. Physical assessment, global assessment, and DAS-28 values are shown in Table 2. Table 3 compares global assessment, physical assessment, and DAS-28 before and after intervention between the two groups. The *P* value was adjusted for age, gender, and duration of treatment. As it can be observed in Tables 1 and 2, ESR was statistically significant between the two groups before intervention ($P = 0.03$); yet, the difference was not significant after intervention ($P = 0.4$). This is also true with CRP (before intervention, $P = 0.01$ and after intervention, $P = 0.1$). In addition, prednisolone dose was not significantly different between the two groups before and after intervention (before intervention, $P = 1$; after intervention, $P = 0.8$); however, global assessment and physical assessment was significantly different between the two groups before and after intervention (physical assessment, before intervention, $P = 0.01$, after intervention, $P \leq 0.001$; global assessment, before intervention, $P \leq 0.001$, after intervention, $P \leq 0.001$). DAS-28 was significantly different between the two groups before intervention ($P = 0.05$); yet, the difference was not significant after intervention ($P = 0.1$).

## Discussion

DMARDs other than MTX include SSZ, HCQ, and leflunomide. These agents are listed in ACR guidelines and European league against rheumatism recommendations. However, little information has been obtained for other csDMARDs compared with MTX because most instances involve the addition of a biologic agent to existing DMARD therapy. Hence, studies investigating the efficacy of other csDMARDs for combination with a bDMARD are lacking.[8]

In this study, the patients in Group A had a milder disease and received DMARDs. The moderate intensity and activity of the disease was DAS-28 = 4.23 (0.81). The patients in both groups were followed up for 3 months. The DAS-28 was 3.52 (0.79) for Group A after intervention which was statistically significant ($P < 0.001$). Group B included patients with a more severe disease compared to Group A with DAS-28 = 4.51 (0.7). The patients in this group received Group A drugs plus biological medicines. Their DAS-28 increased to 3.75 (0.85) after 3 months at the end of intervention indicating a significant change ($P < 0.001$); nonetheless, changes in Group B were greater than Group A using paired *t*-test. A study by Dewitt *et al*. compared the biological and nonbiological drugs in RA patients and found that biological drugs combined with Methotrexate exerted

**Table 1: Demographic information of the groups**

| Variable | A | | B | | Crude *P* |
|---|---|---|---|---|---|
| | *n* (%) | Mean±SD | *n* (%) | Mean±SD | |
| Gender | | | | | |
| Male | 15 (27.3) | | 9 (16.4) | | 0.166 |
| Female | 40 (72.7) | | 46 (83.6) | | |
| Age (year) | | 52.6±13.2 | | 49.3±11.9 | 0.175 |
| Duration of treatment (year) | | 14.9±7.01 | | 17.4±7.66 | 0.063 |
| $CRP_0$ (beginning of the study) | | | | | |
| - | 34 (66.7) | | 22 (40) | | 0.012 |
| +1 | 5 (9.9) | | 15 (27.3) | | |
| +2 | 10 (19.6) | | 10 (18.2) | | |
| +3 | 2 (319) | | 8 (14.5) | | |
| $CRP_1$ (end of the study) | | | | | |
| - | 44 (86.3) | | 39 (70.9) | | 0.158 |
| + | 6 (11.8) | | 14 (25.5) | | |
| +2 | 1 (2) | | 2 (3.6) | | |
| *P* vlaue for CRP (within group) | <0.05 | | <0.05 | | |
| The dose of prednisolone at the beginning of the study (mg) | | 8.7±4.05 | | 8.7±2.58 | 0.1 |
| The dose of prednisolone at the end of the study (mg) | | 5.3±2.85 | | 5.2±1.91 | 0.804 |
| $ESR_0$ (beginning of the study) (mm/h) | | 33.01±22.2 | | 41.7±20.9 | 0.037 |
| $ESR_1$ (end of the study) (mm/h) | | 17.1±13.9 | | 19.1±13.1 | 0.44 |
| *P* value for ESR (within groups) | | <0.05 | | <0.05 | |

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SD: Standard deviation

**Table 2: Compare results of disease activity score-28**

| Variable | Mean±SD | | Crude *P* |
|---|---|---|---|
| | Group A | Group B | |
| Global assessment (beginning of the study) | 50.8 | 40±11.5 | <0.001 |
| Global assessment (end of the study) | 65.8±10.2 | 55.2±12.45 | <0.001 |
| Physical assessment (beginning of the study) | 44.5±12.02 | 39.2±10.15 | 0.018 |
| Physical assessment (end of the study) | 71.2±9.59 | 62±16.37 | 0.001 |
| DAS-28 (beginning of the study) | 4.23±0.65 | 4.51±0.7 | 0.035 |
| DAS-28 (end of the study) | 3.52±0.79 | 3.75±85 | 0.117 |

Comparing the score of Global assessment and physical assessment between two groups. DAS: Disease activity score, SD: Standard deviation

an effect similar to nonbiological drugs used as triple therapy.[9] Another study carried out in the Netherlands compared the effect of biological drugs and DMARDs on RA patients for 2 years. The results indicated that recovery was faster in the group that received biological drugs plus Methotrexate.[10] Another study was done on 10396 RA patients in Manchester University. The treatment began with biological medicines and continued with DMARDs.[11] After 1 year, it was observed that recovery was very significant in these patients. Moreover, another study was performed on 632 RA patients in the Netherlands and compared the effect of etanercept and methotrexate. The findings suggested faster and greater healing of the patients who received etanercept.[12] Our study demonstrated that DAS-28 criteria were not significantly different between the two groups after intervention meaning that although the patients who received biological drugs were those who had a more severe disease compared to Group A patients, the severity of their disease was not significantly different from Group A after intervention on the basis of DAS-28 criteria. This indicates greater and more effective recovery of the group that received DMARDs plus biological drugs simultaneously.

## Conclusions

It could be concluded from the results that simultaneous use of DMARDs and biologic drugs in RA patients could lead to better improvement of the disease symptoms and would decrease in the severity and activity of the disease.

### Limitations

The limitation of the present study was the short period of intervention execution.

### Recommendations

Although in the present study disease activity had a significant decrease following the used medicinal regimen, further studies are required to confirm this result.

### Financial support and sponsorship

Isfahan University of Medical Sciences

### Conflicts of interest

There are no conflicts of interest.

**Table 3: Results of covariance analysis**

| Variable | Mean±SD | | *P* (adjusted by age, gender, and duration of the disease) |
|---|---|---|---|
| | Group A | Group B | |
| Differ-ESR | 15.8±14.4 | 22.5±16.5 | 0.008 |
| $Differ_0$ P (physical assessment) | 26.6±8.8 | 22.7±11.9 | 0.979 |
| $Differ_0$ G (global assessment) | 15±6.1 | 15.2±7.4 | 0.174 |
| Differ-DAS-28 | 0.70±0.43 | 0.74±0.45 | 0.8 |

ESR: Erythrocyte sedimentation rate, DAS: Disease activity score, SD: Standard deviation

## References


1. Garys F, Ralph C. Kelly Text Book of Rheumatology. 10th ed. Philadelphia: Elsevier Saunders Publication: 2017. p. 1188-213.
2. Hochbergg MC, Silman A. Rheumatology. 5th ed. Philadelphia: Elsevier Mosby Publication: 2014.
3. Singh JA, Saag KG, Bridges SL Jr., Akl EA, Bannuru RR, Sullivan MC, *et al*. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26.
4. Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, *et al.* Safety of synthetic and biological DMARDs: A systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1101-36.
5. Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, Naredo E, *et al.* Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: Current evidence and future directions. Ann Rheum Dis 2016;75:1428-37.
6. Pavlovic V, Dimic A, Milenkovic S, Krtinic D. Serum levels of IL-17, IL-4, and INFγ in Serbian patients with early rheumatoid arthritis. J Res Med Sci 2014;19:18-22.
7. Aryaeian N, Djalali M, Shahram F, Djazayery A, Eshragian MR. Effect of conjugated linoleic acid, vitamin e, alone or combined on immunity and inflammatory parameters in adults with active rheumatoid arthritis: A randomized controlled trial. Int J Prev Med 2014;5:1567-77.
8. Inui K, Koike T. Combination therapy with biologic agents in rheumatic diseases: Current and future prospects. Ther Adv Musculoskelet Dis 2016;8:192-202.
9. Dewitt EM, Li Y, Curtis JR, Glick HA, Greenberg JD, Anstrom KJ, *et al.* Comparative effectiveness of nonbiologic versus biologic disease-modifying antirheumatic drugs for rheumatoid arthritis. J Rheumatol 2013;40:127-36.
10. Nurmohamed MT, Dijkmans BA. Are biologics more effective than classical disease-modifying antirheumatic drugs? Arthritis Res Ther 2008;10:118.
11. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL, *et al.* Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: Results from the British Society for Rheumatology biologics register. Ann Rheum Dis 2011;70:583-9.
12. Gallo G, Brock F, Kerkmann U, Kola B, Huizinga TW. Efficacy of etanercept in combination with methotrexate in moderate-to-severe rheumatoid arthritis is not dependent on methotrexate dosage. RMD Open 2016;2:e000186.