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Title: The Effects of Conventional and Biological Drugs Used for the Treatment of Rheumatoid Arthritis on Quality of Life and Depression

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Objectives: The present research aims to investigate the effects of conventional and biological drugs, which are used for the treatment of rheumatoid arthritis (RA), on the patients' quality of life, depression and anxiety.

Patients and Methods: A total number of 80 patients with a diagnosis of RA based on American College of Rheumatology/Annual European Congress of Rheumatology (ACR/EULAR) 2010 diagnostic criteria were considered in the present study. Patients were classified into two groups as follows: Patients using conventional disease-modifying agents (csDMARDs) alone (Group 1, n=40) and patients using biological disease-modifying agents (bDMARDs) and csDMARD combination (Group 2, n=40). Demographical data of the patients were collected. Levels of rheumatoid factor (RF) and Anti-Cyclic Citrullinated Peptide (anti-CCP) were measured in both groups. All patients completed Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), Short Form-36 (SF-36), Beck Depression Scale (BDS) and Hospital Anxiety Depression Scale (HADS).

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Results: There was no significant difference between the two groups of patients regarding their demographical characteristics, autoantibody positivity or DAS scores ($p>0.05$). HAQ scores, all parameters and summary scores of SF-36, BDS and HADS scores were not significantly different between the two groups ($p>0.05$).

Conclusion: Results of the present study showed that csDMARDs and bDMARDs, which required a more invasive administration and were associated with serious side effects, were not superior to each other in terms of their effects on the patients' quality of life. CsDMARD and bDMARD were also not superior to each other regarding their effects on anxiety and depression among RA patients.

Keywords: Rheumatoid Arthritis, DMARD, Depression, Quality of Life

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder that is characterized by symmetrical, erosive synovitis and occasionally with multi-systemic involvement [1]. Being a chronic disease, RA can have significant effects on both physical and psychosocial health, to the detriment of the quality of life of the patient [2]. There are currently no curative therapy options for RA patients, although conventional disease-modifying agents (csDMARDs) and biological disease-modifying agents (bDMARDs) are essential in its medical treatment [3]. Failure to achieve complete disease control results in physical limitations with the potential of leading to psychological and social problems. In this regard, the main treatment goals should be to increase quality of life and reduce disability [4]. While the effects of RA itself on the patients' quality of life, depression and anxiety has been investigated in previous studies [5], there is only a limited number of studies in the literature demonstrating the effect of the drugs used in the treatment of RA on quality of life, depression and anxiety. Notably, most of the previous studies have compared the effects of two different csDMARDs and/or bDMARDs on the quality of life, depression and anxiety among RA patients, while there is a lack of studies involving homogenous patient populations that focus on the Disease Activity Score (DAS28) and the rate of autoantibody positivity (rheumatoid factor and Anti-Cyclic Citrullinated Peptide) (RF and anti-CCP).

bDMARDs have attained an important position in the treatment of RA in recent years and have become associated with functional status recovery and structural improvement [6]. That said, **This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Yayikci YI, Karadag A. The Effects of Conventional and Biological Drugs Used for the Treatment of Rheumatoid Arthritis on Quality of Life and Depression. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18018.**

the more invasive administration route of these therapies and their serious side effect profiles may have a negative effect on quality of life and depression among RA patients [7].

Additionally, there have to date been no studies involving all the csDMARDs and bDMARDs used in the treatment of RA that compare their effects on the quality of life, anxiety and depression in patients with RA.

This study may be considered unique, in the sense that it is the first in literature in which the groups of patients with RA included in the study are homogeneous in terms of DAS 28 scores and autoantibody positivity, and which includes all the csDMARDs and bDMARDs used in the treatment of RA. In this study, we investigate the effects of drugs used in RA treatment on quality of life, anxiety and depression.

Patients and Methods:

Study design

We conducted this study between 2016 and 2017 prospectively and single-blind in the our University School of Medicine Physical treatment clinic. The study sample comprised 80 patients, diagnosed with RA based on the American College of Rheumatology/ Annual European Congress of Rheumatology (ACR/EULAR) 2010 criteria [8], who had been undergoing medical treatment for the preceding six months and who consented to take part in the study. The RA patients were divided into two groups based on the medications they use: 40 patients using csDMARD alone constituted Group 1 and 40 patients using csDMARD in combination with bDMARD constituted Group 2.

Patients with histories of psychiatric disorder and those using antipsychotic medication, those with a concomitant inflammatory rheumatoid disease, those with a history of treatment with a biological agent who were not actively using this medication at the time of screening, pregnant or lactating women, and those aged < 18 were excluded from this study.

Sociodemographic data of the patients (i.e., age, gender, marital status, level of education, smoking history, body mass index, disease duration, dose and duration of treatment with drugs used for RA) was recorded, and the serum RF and anti-CCP levels of patients in both groups were measured. Anti-CCP and RF low-high positivity limits were classified based on a level of 3-fold of the

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normal upper limit as defined by the 2010 ACR/EULAR criteria [8]. All patients completed a DAS28, Health Assessment Questionnaire (HAQ), a Short Form-36 (SF-36), a Beck Depression Scale (BDS) and a Hospital Anxiety Depression Scale (HADS). The questionnaires of all patients and the DAS 28 scores were assessed through a blind evaluation by the same physician.

The study was approved by the Ethics Committee of our University (2016-09/04) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each of the study participants.

Disease Activity Score 28 (DAS28): The DAS 28 score was used to assess disease activity and was calculated using the following formula: $0.56 \times \sqrt{\text{Number of tender joints (NTJ28)}} + 0.28 \times \sqrt{\text{Number of swollen joints (NSJ28)}} + 0.014 \times \text{General health assessment (GHA)} + 0.70 \times \text{Estimated sedimentation rate (ESH)}$ [9].

Health Assessment Questionnaire (HAQ): The HAQ consists of 20 items and assesses eight activities, including dressing, standing up, eating, walking, hygiene, cognition and daily activities. Each answer is graded on a scale of 0–3. The HAQ scale reflects functional status and its scores are shown to be correlated with the markers of disease activity [10]. The reliability and validity study of the Turkish HAQ was carried out by Kucukdeveci et al. [11].

Short Form (SF) 36: The SF has been developed to assess quality of life in clinical practice and research studies. The SF-36 consists of 36 questions relating to eight sub-scales: physical functioning, physical role limitations, body pain, overall health, vitality, social functioning, emotional role limitations and mental health [12]. The Turkish validation study of the SF-36 was carried out by Kocyigit et al. [13].

Hospital Anxiety and Depression Scale (HADS): HADS is a self-assessment scale that is used to determine a patient's risk of anxiety and depression, and to measure the level and change in intensity of anxiety and depression [14]. The validity and reliability study of the Turkish version of HADS was carried out by Aydemir O. [15].

Beck Depression Scale (BDS): The BDS is useful for screening the frequency of depression among patients, and is used to determine the risk of depression and measure the level and change

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in intensity of depressive symptoms [16]. The validity and reliability study of the Turkish version of BDS was carried out by Hisli [17]. We used the BDS to support the reliability of the study, as HADS does not fully cover the depressive symptoms specified in the DSM-IV anxiety and depression scale.

All statistical analyses were performed using SPSS version 22 software. As appropriate to the nature of the parameters in the dataset, analyses were made using frequency tables, descriptive statistics, difference tests and Chi-square tests. Since the non-categorical variables of the study were not found to be significant in a Kolmogorov-Smirnov Z test ($p>0,05$), the analyses continued with parametric tests. Accordingly, an Independent Samples t-test was used to calculate the differences between bi-categorical variables and an F-test was used to calculate the differences between multi-categorical variables. In cases where the F-test indicated a significant difference, the Least Significant Difference (LSD) method was used post-hoc to determine which pair resulted in the significant difference. The level of statistical significance was considered as 95 percent. In the study, when $\alpha=0.05$ $\beta=0.10$ $(1-\beta)=0.90$, it was decided to take 40 individuals for each group, and the power of the test was found to be $p=0.9017$. The statistical analysis was performed by a statistician who was completely blind to the groups.

Results

A total of 80 RA patients, including 40 RA patients who used csDMARD alone (Group 1) and 40 RA patients who used a csDMARD and bDMARD combination (Group 2) took part in the study. The age, gender, educational status, marital status and concomitant diseases of the groups were similar ($p>0.05$). Table 1 presents the sociodemographic characteristics of the two groups.

There was no significant difference in the disease duration between the two groups ($p>0.05$) and the DAS28 scores, as well as the mean Anti-CCP and RF levels, were not significantly different between the two groups ($p>0.05$). Table 2 presents the mean DAS 28 scores, the disease duration Anti-CCP and the RF levels of both groups.

The mean HAQ scores of Group 1 and 2 were 0.81 ± 0.73 and 0.91 ± 0.73 , respectively, revealing no significant difference between the two groups ($p>0.05$). Figure 1 shows the mean HAQ scores of both groups.

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In all subcomponents of SF-36, no statistically significant difference was found in either group in terms of the physical and mental health summary scores (physical functioning, physical role weakness, emotional role weakness, vitality, body pain, general health perception, social functioning, mental health). The mean SF-36, sub-scale scores and summary health scores of both groups are presented in Table 3.

The mean HADS anxiety scores in Groups 1 and 2 were 6.50 ± 3.93 and 7.08 ± 4.27 , respectively, indicating that the difference in the HADS anxiety scores between the two groups was not significant ($p > 0.05$). The HADS depression scores in Groups 1 and 2 were 7.03 ± 4.46 and 5.95 ± 3.54 , respectively, indicating that the mean HADS depression scores were not significantly different between the two groups ($p > 0.05$).

The mean BDS scores in Groups 1 and 2 were 12.35 ± 8.71 and 11.70 ± 7.16 , respectively meaning that the BDS scores were not significantly different between the two groups ($p > 0.05$).

Discussion

The present study found that the csDMARD and bDMARD therapies used in the treatment of RA did not differ in terms of their effects on the quality of life and depression. These findings are consistent with the findings of previously reported studies [18-20].

RA is associated with pain, weakness, functional limitation and mood disorders, and may result in irreversible structural and functional damage if treatment is delayed [21]. It has previously been shown that RA has a significant effect on the quality of life, and may result in unemployment, disability, increased medical and social costs, and a significant rate of morbidity and mortality [22-24].

In a study carried out by Direskeneli et al. [25], using a self-developed scale the authors found no significant difference between the quality of life of RA in patients treated with bDMARD or csDMARD. In another study of RA patients, Joensuu et al. [26] could find no significant difference between the DAS28 and HAQ scores of RA patients treated with or without bDMARDs. In line with these previous studies, we were unable to find any significant difference in the HAQ scores or quality of life between the RA patient groups in the present study [25,26].

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Gerhold et al. [27] reported that RA patients treated with csDMARDs had higher physical and mental health scores and a better quality of life than patients treated with bDMARDs. In contrast, Inotai [28] and Giacomelli et al. [29] demonstrated that RA patients treated with bDMARDs had a better quality of life, based on all parameters of the SF-36 and HAQ scores, than patients using csDMARDs. In all three studies, it can be seen that the group with the lower quality of life score had a higher DAS28 score than the other group, and we conclude that the inconsistencies between the results of these studies and the findings of the present study can be attributed to differences in the DAS28 scores of the study populations.

RA affects every aspect of a patient's life and has a deep effect on social, economic and psychological well-being [30,31]. Psychological factors, such as anxiety and depression, represent significant health problems among RA patients [32-34].

BDS was used to assess RA patients in a previous study conducted by Alkan et al. [19], in which the correlation analyses performed to compare the patients using csDMARD and bDMARD identified no significant relationship between the drugs and BDS. A study by Kekow et al. [20] reported no significant differences in the HADS depression and anxiety scores of groups treated with etanercept (Enbrel; Pfizer PFE) and methotrexate (MTX) (methotrexate sodium; Rheumatrex) in combination or with MTX alone. In line with the previous studies reported above, the depression and anxiety scores in the present study were not found to be significantly different between the two groups.

In their study of RA patients being treated with anti-tumor necrosis factor (anti-TNF) or csDMARD, Bae et al. [35] found depression and anxiety to be less common among those receiving anti-TNF (etanercept), although, unlike the present study, the one by Bae et al. [35] included RA patients with high disease activity and only one anti-TNF treatment was considered.

Despite the significant improvements in RA treatment, pain, long-term drug use, drug side effects, fatigue, incapacity to work and mood disorders still result in serious psychosocial outcomes in RA patients [4,36] and physicians should take these factors into consideration when treating patients with RA. There are several limitations to our study, including a limited number of patients,

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the lack of an RA-related deformity evaluation and radiological scores, evaluation of anxiety and depression by a non-psychiatrist and the non-cross-sectional nature of the study.

In conclusion, there is no superiority between csDMARD and bDMARD, in terms of the effect on the quality of life of patients with RA. That said, csDMARDs are easier and more comfortable to use as a treatment for RA, as bDMARDs require invasive administration in a hospital environment, have a serious side effect profile and are more difficult to use. Furthermore, there is no superiority between csDMARD and bDMARD in terms of the anxiety and depression in patients with RA. We believe that these results may assist physicians in the selection of medications for the treatment of patients with RA, although further clinical trials are needed to investigate the effects of drugs used in RA treatment on the quality of life, depression and anxiety of patients with RA.

Declaration of conflicting interests

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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