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Efficacy and Safety of Tofacitinib in Patients with Rheumatoid Arthritis

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Abstract

Objective: The aim of our study is to show the efficacy and side effects of tofacitinib in patients with rheumatoid arthritis (RA).

Methods: 66 Patients who were followed up in the rheumatology outpatient clinic, were older than 18 years, and used tofacitinib for at least three months were included. Blood count, liver transaminase levels, cholesterol and triglyceride levels, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR) were determined before and at the third and sixth months of the tofacitinib treatment. Before and after treatment, DAS 28-ESR, morning stiffness duration, and VAS score were also calculated

Results: The mean age was 54.7±12.0 years, and 84.8% were women. The mean duration of tofacitinib use was 19.0±13.5 months. Duration of morning stiffness, VAS and DAS 28-ESR scores decreased significantly after tofacitinib ($p<0.001$). The leukocyte count after treatment also decreased significantly compared to before treatment. Side effects related to tofacitinib were seen in 33.3% of the patients. Rash, cough, and nausea were the most common side effects. Tofacitinib-associated Herpes Zoster infections were seen in 13.6% of the patients. Tofacitinib treatment was discontinued in 48.5% of patients due to adverse effects, drug ineffectiveness, and disease activation.

Conclusion: There was statistically significant decrease in RA disease activity with tofacitinib treatment. It was noteworthy that 33.3% of the patients developed adverse effects and 48.5% developed a condition requiring discontinuation of tofacitinib treatment.

Keywords: Rheumatoid Arthritis, tofacitinib, efficacy

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic and inflammatory autoimmune disease characterized by erosive synovitis and causes progressive damage to cartilage and bone (1). The interaction between the innate immune system and the acquired immune cells (CD4+ T and B lymphocytes) and the resulting cytokines and autoantibodies play a fundamental role in the pathogenesis of the disease (2). Synovitis, which occurs as a result of synovial intimal cell hyperplasia and microvascular damage, forms the basis of the disease (3). Rheumatoid arthritis can be seen in all populations, and its prevalence is approximately 1-2%. Although its incidence increases with advanced age and female gender, it can be seen at any age. The onset of the disease peaks at the age of 4-5 decades (4).

The goals of treating rheumatoid arthritis are to suppress inflammation and prevent joint damage and extra-articular involvement. Analgesic agents, glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and immunosuppressive agents are used in the pharmacological treatment of RA. Disease-modifying anti-rheumatic drugs (DMARDs) are divided into synthetic or biologic DMARDs. Synthetic DMARDs consist of two groups: conventional synthetic (cs) DMARDs (Leflunomide, Sulfasalazine, Methotrexate, Hydroxychloroquine) and targeted synthetic (Tofacitinib, Baricitinib). Biological DMARDs consist of original biological (Tumor Necrosis Factor-Alpha blockers) and biosimilar agents(5).

Tofacitinib is a Janus tyrosine kinase (JAK) inhibitor and is in the targeted synthetic DMARD group. Tofacitinib exerts its efficacy by inhibiting JAK1 and JAK3 and, to a lesser extent, JAK2. As a result of Janus tyrosine kinase inhibition, cytokine signaling is inhibited, and a cytokine-dependent immune response is suppressed(6). Tofacitinib was licensed in the United States on 6 November 2012 to be used with moderate and active RA patients who have an inadequate response or intolerance to methotrexate(MTX). Phase III studies have shown that Tofacitinib 5mg and 10mg orally twice daily can be safely used as monotherapy or in combination with MTX and other non-biological DMARDs (7).

Our aim in this study is to evaluate the effect of tofacitinib on RA disease activity and the adverse effects of the drug.

METHODS

In the present study, those patients who were followed up in Ankara Yıldırım Beyazıt University- Ankara City Hospital Rheumatology Clinic had RA in accordance with the 2010 American Rheumatology Society (ACR) classification criteria and were diagnosed with RA and used tofacitinib at any period of their medical treatment, even if tofacitinib treatment was discontinued afterward were included. The group consists of

66 patients between the ages of 25 and 78 who used tofacitinib 5 mg twice a day for at least three months or were still using tofacitinib. Each patient's age, age at diagnosis, gender, baseline rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP), anti-nuclear antibody (ANA) values, and comorbidities were determined. Before tofacitinib treatment, the duration of morning stiffness, Disease Activity Score (DAS 28-ESR), Visual Analogue Scale (VAS) score, hemoglobin level, leukocyte count, platelet count, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride level, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, erythrocyte sedimentation rate (ESR) and CRP levels were noted.

According to The European League Against Rheumatism (EULAR), disease activity and treatment response criteria are based on disease activity scores (DAS). The DAS28 assesses swelling and tenderness in 28 joints. A patient global health assessment is performed. In addition, the ESR or CRP value is measured. Calculating the DAS score is a complicated process that requires the help of a calculator or computer:

$$DAS28(ESR)=0.56\times\sqrt{(TJC28)}+0.28\sqrt{(SJC28)}+0.70\times\ln(ESR)+0.014\times GH(range,0–9)$$

EULAR (The European League Against Rheumatism) disease remission criteria were used for disease activity score (DAS 28-ESR). According to EULAR disease remission criteria, a DAS 28-ESR score below 2.6 was accepted as remission, 3.2-5.1 as moderate disease activity, and above 5.1 as high disease activity.In patients who used tofacitinib treatment for 3-6 months, baseline and third-month values were compared. In patients using tofacitinib for longer than six months, baseline values were compared with the third and sixth-month values. In our study, DAS 28-ESR, VAS score, and duration of morning stiffness were used to evaluate disease activity.

A visual analog scale (VAS) score was used to assess the patient's pain. DAS 28-ESR, VAS score, and duration of morning stiffness were calculated and compared before and after tofacitinib use. Statistically, significant decreases were evaluated as clinical response and increase as clinical non-response-disease activity. Adverse effects during tofacitinib use (such as rash, cough, nausea, leukopenia, pneumonia, genito-urinary infection, Cytomegalovirus (CMV) retinitis, deep vein thrombosis, right heart failure-lung edema, acute coronary syndrome), and additional diseases that developed during tofacitinib use were investigated. It was examined how many patients discontinued tofacitinib treatment due to adverse effects and which treatment was started afterward. In addition, it was investigated how many patients developed

herpes zoster and herpes simplex infections with the use of tofacitinib.

STATISTICAL ANALYSIS

Research data was evaluated by means of "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". Descriptive statistics were presented as mean±standard deviation (minimum-maximum), percentage, and frequency distribution. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). Wilcoxon Signed Ranks Test was used as a statistical method for the variables that were not found to fit the normal distribution, for statistical significance between two dependent groups, and the Friedman Test was used as a statistical method between three dependent groups. The statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 66 patients who were diagnosed with RA and were given tofacitinib for three months or longer were analyzed retrospectively. The clinical and descriptive characteristics of the patients examined are presented in Table 1. The additional disease was present in 69.7% of the patients (46 patients). A total of 83 additional diseases were reported in these 46 patients. The most common comorbidity was essential hypertension, which was present in 31.8% of the patients.

Table 1. Dermographic and Clinical Characteristics of Patients with RA

	(n=66)
Age, mean±SD	54.7±12.0
Gender, n (%)	
Female	56 (84.8)
Male	10 (15.2)
Complaint Onset Age, mean±SD	42.9±11.8
Diagnosis Age, mean±SD	45.0±12.1
Time to Diagnosis, mean±SD (min-max)	2.1±3.2
ANA	
Negative	39 (59.1)
+	26 (39.4)
++	0
+++	1 (1,5)
RF n (%)	32 (48.5)
Anti-CCP Positivity, n (%)	32 (48.5)

n: Number of patients; %: Percent; SD: Standard deviation; ANA: Anti-nuclear antibody Anti-CCP: Anti cyclic citrulline protein RA: Rheumatoid Arthritis, RF: Rheumatoid factor, min: minimum, max:maximum

This was followed by diabetes mellitus at 30.3% and allergic asthma at 12.1%.

In our study, 62.1% of patients had previously used csDMARD, 37.9% had used a biologic or biosimilar DMARD in combination with csDMARD (21.2% had one, 9.1% had two, 4.5% had three, and 3.0% had four different DMARD use). When the biological biosimilar agents used before tofacitinib are examined, Etanercept was in the first place with 23.2%, followed by Abatacept with 18.6% and Tocilizumab with 10.6%. Infliximab was found to be the least used biological agent, with 3.0%. The mean duration of using tofacitinib was 19.0±13.5 (min:3-max:50) months. When the treatment regimens were examined, it was observed that 80.3% of the patients received tofacitinib in combination with at least one csDMARD and the remainder as monotherapy.

Among the combined therapy protocols, the most commonly used combination was MTX, Prednisolone, and Tofacitinib, with 15.2%, followed by Leflunomide and Tofacitinib with 12.1%. The number of patients using the combination of Tofacitinib and MTX and the combination of prednisone and tofacitinib was equal (10.6%)

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Before and after tofacitinib treatment, DAS 28-ESR, VAS score, and duration of morning stiffness were compared, and a statistically significant difference was found for all three ($p<0.001$). The duration of morning stiffness, VAS scores, and DAS 28-ESR were significantly reduced after tofacitinib treatment (Table 2).

Table 2. Comparison of the duration of morning stiffness, DAS28 -ESR and VAS values before and after Tofacitinib treatment

(n=66)	**Before Tofacitinib Treatment** **mean±SD** (min-max)	**After Tofacitinib Treatment** **mean±SD** (min-max)	**p[1]**
Morning Stiffness (minute)	53.1±35.7 (0-120)	31.1±27.4 (0-120)	**<0,001****
DAS28-ESR	5.4±0.6 (4.2-6.7)	4.3±1.3 (2.0-7.0)	**<0,001****
VAS	72.0±14.4 (20-90)	53.9±22.7 (10-90)	**<0,001****

n: Number of patients; %: Percent; SD: Standard deviation min: minimum max :maximum VAS: visual analog scale, DAS28-ESR: disease activity scores- Erythrocyte Sedimentation Rate

ESR, CRP, leukocyte count, hemoglobin platelet, AST and ALT values were obtained in 57 of 66 patients examined before and after treatment at 3 and 6 months. Total cholesterol, HDL, LDL and triglyceride values of 24 patients were present at all three times. The leukocyte count value in the sixth month after the treatment was significantly lower than before the treatment. On the other hand, the changes in hemoglobin level, platelet count, AST, ALT, ESR, CRP, total cholesterol, HDL, LDL, and triglyceride values between the measurement times were not statistically significant ($p>0.05$) (Table 3). It was observed that 33.3% of the patients examined developed adverse effects related to tofacitinib. A total of 27 adverse events were reported. Rash was observed in 6% of the patients, cough in 4.5%, and nausea in 3%. During tofacitinib treatment, 28.8% of the patients developed Herpes Simplex and 13.6% of them developed Herpes Zoster infection. None of the patients had a previous vaccination for Herpes Simplex and Herpes Zoster infection (Table 4).

Tofacitinib treatment was discontinued in 48.5% of the patients. Treatment was discontinued in 16.7% of patients due to clinical unresponsiveness, in 12.1% of disease activation, 3% of leukopenia, and 3% of acute coronary syndrome (Table 5).

Table 3. Comparison of Laboratory Values Before and After Tofacitinib Treatment

	n	**Before Tofacitinib Treatment mean±SD** (min-max)	**3th Month of Tofacitinib Treatment mean±SD** (min-max)	**6th Month of Tofacitinib Treatment mean±SD** (min-max)	**p**[1]
Esr	57	39.0±25.2 (3-110)	38.8±22.5 (1-90)	36.7±22.8 (3-98)	0.724
Crp	57	18.4±18.7 (2.6-83.4)	14.3±17.0 (2.0-93.0)	17.2±18.7 (1.2-83.7)	0.247
Leukocyte Count	57	8.4±2.8 (3.3-15.8)[c]	8.3±2.5 (4.4-16.6)	7.5±2.5 (2.6-17.1)	**0.022***
Hemoglobın	57	12.3±1.9 (7.8-16.9)	12.3±1.6 (9.2-16.0)	12.1±1.8 (8.0-16.5)	0.296
Platelets	57	291.6±71.6 (185-534)	295.8±69.2 (168-480)	297.5±79.5 (163-569)	0.612
Ast	57	19.2±10.1 (8-68)	20.1±7.9 (11-47)	19.1±7.0 (10-44)	0.995
Alt	57	20.4±12.8 (5-82)	20.6±12.7 (7-87)	19.5±13.7 (7-87)	0.162
Total Cholesterol	24	199.2±57.9 (113-369)	210.6±50.5 (114-295)	226.7±68.3 (144-419)	0.124
Hdl	24	54.6±21.6 (29-138)	51.7±12.2 (33.4-76.0)	66.0±28.6 (38.7-175)	0.149
Ldl	24	119.9±54.3 (37-296)	125.5±49.8 (12.5-204)	138.0±68.8 (24-332)	0.137
Trıglycerıde	24	133.4±50.2 (81-262)	149.9±82.2 (68-459)	132.7±48.0 (72-267)	0.545

n: Number of patients; %: Percent; SD: Standard deviation; [1]Friedman Test; ESR: Erythrocyte Sedimentation Rate CRP: C-Reactive Protein, AST: aspartate amino transferase, ALT : alanine amino transferase, HDL: high-density lipoprotein, LDL:), low-density lipoprotein

Table 4. Adverse event rates were seen with Tofacitinib treatment

(n=66)	**n (%)**
Adverse Event Development	
No	44 (66,7)
Yes	22 (33,3)
Adverse Events	**n %**
Skin Rash	4(6,0)
Cough	3(4,5)
Nausea	2(3,0)
Acute Coronary Syndrome	2(3,0)
Leukopenia	2(3,0)
Discoid Lupus Erythematosus	1(1,5)
CMV Retinitis	1(1,5)
DVT	1(1,5)
Increase In The Number Of Rheumatoid Nodules	1(1,5)
Weakness	1(1,5)
Transaminase Elevation	1(1,5)
Anemia	1(1,5)
Pulmonary Thromboembolism	1(1,5)
Right Heart Failure And Pulmonary Edema	1(1,5)
Creatine Kinase Elevation	1(1,5)
Malignancy	1(1.5)
Pneumonia	1(1.5)
Proteinuria	1(1.5)
Genito-Urinary İnfection	1(1.5)

Table 5. Reasons for Discontinuation of Tofacitinib

(n=66)	**n (%)**
Tofacitinib Treatment	66 (100)
Continued	36 (51.5)
Discontinued	32 (48.5)
Conditions Leading to Treatment Discontinuation	
Clinical Unresponsiveness	11(16.7)
Disease Activation	8(12.1)
Leukopenia	2(3)
Myocardial Infarction	2(3)
Discoid Lupus Erythematosus	1(1.5)
Malignancy	1(1.5)
With Own Request	1(1.5)
Anemia	1(1.5)
Creatine Kinase Elevation	1(1.5)
Pneumonia	1(1.5)
Increased Number of Rheumatoid Nodules	1(1.5)
Heart Failure	1(1.5)
Proteinuria	1(1.5)

n: Number of patients; %: Percent;

DISCUSSION

In this study, we aimed to show the effect of Tofacitinib on RA patients and the adverse effects that may occur due to its use. In our study, significant improvement was observed in VAS score, DAS28-ESR, and duration of morning stiffness after tofacitinib use. These decreases in disease activity indices are an indication of the efficacy of tofacitinib on the disease, but adverse events developed in 33.3% of the patients and the treatment had to be discontinued in 48.5%.

In The European League Against Rheumatism (EULAR) guideline updated in 2021, it is recommended to start treatment with conventional synthetic DMARDs, and to use a biological/biosimilar DMARD or a targeted synthetic DMARD in patients who do not respond to conventional synthetic DMARDs (8).

A better understanding of the pathogenesis of RA; with a clearer awareness of the effects of cytokines, chemokines, and lymphocytes on joint damage, tofacitinib has taken its place in the guidelines as a targeted synthetic DMARD (9).

In our study, the duration of morning stiffness, which is one of the parameters for evaluating the clinical efficacy of tofacitinib treatment and a subjective measurement, was found to be decreased in 68.2% of the patients. While the mean duration of morning stiffness was 53.1±35.7 minutes before treatment, it decreased to 31.1±27.4 minutes after tofacitinib.

Among other parameters used to evaluate the efficacy, a mean decrease of 20.3% in the DAS 28-ESR score and 25.1% in the VAS-patient score was found. Similar to our study, in the Phase III study of Hall et al., a significant decrease was found in the first and third month DAS28-ESR scores of the RA patients who received tofacitinib compared to the placebo group. When tofacitinib was added to the placebo group in the 3rd month and re-evaluated in the 12th month, a significant decrease was observed in the DAS28-ESR scores (10). In the study of Mueller et al., similar to our study, after tofacitinib use, 53% of patients had low disease activity and 48% had remission according to the DAS28-ESR score (11). In the retrospective study of Bird et al. on patients with RA, 1300 patients using biological DMARDs and 650 patients using tofacitinib were compared. At the 18th month of treatment, 52.4% of the patients using biological DMARDs and 57.8% of the patients using Tofasitinib achieved remission in the DAS28-ESR score, and there was no statistically significant difference between the two groups in terms of remission (12).

In our study, there was a higher decrease in the duration of morning stiffness, VAS and DAS28-ESR scores of patients who did not receive a biological-biosimilar DMARD before tofacitinib; Patients who received one or more

biologic DMARDs prior to tofacitinib had a lesser reduction in these parameters. Patients who have not previously achieved remission with biologic DMARDs may have had a lower response to tofacitinib, possibly due to greater disease severity and drug resistance.

In our study, no significant change was found in hemoglobin and thrombocyte values after treatment compared to pre-treatment. There was a significant decrease in the leukocyte values in the sixth month compared to the pre-treatment level. This decrease may be an indicator of a reduction in inflammation associated with tofacitinib use. When we evaluated the other laboratory values, there were not any significant changes in liver transaminase (AST-ALT) and lipid levels. In the study of Wollenhaupt et al. 4481 RA patients using tofacitinib were retrospectively analyzed. In the follow-up of the patients, no significant changes were detected in total cholesterol, LDL, ALT, AST and serum creatinine values. During follow-up, serum creatinine phosphokinase increased by 7.6%, ALT by 4.1%, and creatinine in 3.9% of the patients(13).

In some studies in the literature, many adverse effects related to tofacitinib have been shown. These adverse effects include non-serious drug reactions (such as rash, nausea, and cough), infections due to opportunistic microorganisms, cardiovascular adverse events, thromboembolic events, and malignancies. In our study, adverse effects developed in 33.3% (22 patients) of the patients. The most common adverse effect is rash at 6%; cough at 4.5%, nausea at 3%, fatigue at 1.5%, and genito-urinary system infection at 1.5%. In a long-term study (0-9.6 years) conducted by Cohen et al. on 7061 patients receiving tofacitinib with the diagnosis of rheumatoid arthritis, the most common adverse event in patients was infections. In the study, viral upper respiratory tract infection 17.3% (1221/7061), upper respiratory tract infection 17.2% (1214/7061), urinary tract infection 11.8% (832/7061), and bronchitis 11.3% (800/7061) were detected. Serious infection events were observed in 8.2% of the patients. These included pneumonia, urinary system infection, cellulitis and herpes zoster infection(14).

Like other immunomodulatory drugs used in the treatment of RA, opportunistic infections may develop in patients using tofacitinib. In addition, the patient's age, accompanying chronic diseases and other drugs used also play a role in the risk of infection. In our study, Herpes Simplex infection developed in 28.8% of the patients, Herpes Zoster infection developed in 13.6%. In the study of Winthrop et al., 5% (239) of 4789 RA patients developed tofacitinib-associated Herpes Zoster infection, and tofacitinib treatment was discontinued in 10% of these patients(15). In the study of Curtis et al., in 8030 (83.3% women) RA patients

receiving tofacitinib, age, female gender, and concomitant use of glucocorticoids with tofacitinib have been shown to increase the risk of Herpes Zoster infection (16). In our study, the mean age of patients with Herpes Zoster infection was 50.1 years, and 7 of these patients (77.7%) were women. Five of these patients were receiving tofacitinib and prednisolone treatment together. In addition, the remaining four patients had diabetes mellitus in one, major depression in one, and hypertension in one.

In our study, cardiovascular adverse events related to tofacitinib were remarkable. Cardiovascular adverse effects developed in three (4.5%) patients. Two patients developed acute coronary syndrome and one developed pulmonary edema due to right heart failure. In a study by Kivitz et al., cardiovascular adverse effects developed in 0.6% (15) of 2435 patients with a diagnosis of RA who received a combination of tofacitinib and csDMARD and in 0.59% of 1365 patients who received tofacitinib as monotherapy (17).

In the study of Ytterberg et al., patients using tofacitinib had a significantly higher rate of major adverse cardiovascular events (MACE) compared to patients using TNF inhibitors. The most common causes of MACE were nonfatal myocardial infarction with tofacitinib. The cumulative estimated probability of MACE with combined doses of tofacitinib was 5.8% and the cumulative predictive probability of nonfatal myocardial infarction was 2.2% (18).

The thromboembolic event rate in our study was 3%. In our study, pulmonary thromboembolism (PTE) developed in one patient and deep vein thrombosis (DVT) in one patient. In the study of Cohen et al., venous thromboembolism (DVT and/or PTE) was seen in 0.8% of 7061 patients (14). In the study of Mease et al., in the first three months of follow-up of 7964 rheumatoid arthritis patients who received tofacitinib, there was no significant difference in the development of DVT and PTE compared to the placebo control group. As a result of 24-month follow-up, no significant difference was found between Tofacitinib, adalimumab, and methotrexate in terms of the development of DVT and PTE (19). Desai et al. compared the risk of thromboembolism in RA patients receiving tofacitinib and anti-TNFα therapy and found no significant difference in thromboembolism risk between those receiving tofacitinib and anti-TNF-α agents (20).

One patient in our study developed endometrial adenocarcinoma during tofacitinib use and tofacitinib treatment had to be discontinued. The patient who developed endometrial adenocarcinoma was 60 years old and had been receiving tofacitinib treatment for four months. For this reason, no clear relationship was established between tofacitinib and the development of endometrial adenocarcinoma.

Tofacitinib treatment had to be discontinued in 45.5% (30 patients) of the patients.

Tofacitinib treatment was discontinued in 16.7% of patients due to clinical unresponsiveness and in 12.1% due to disease activation. The mean age of 19 patients whose treatment was discontinued due to clinical unresponsiveness and disease activation was 56.3 years. The mean age at diagnosis of these patients was 44.2. Of the 19 patients whose treatment was discontinued, 18 were women and 15 patients had comorbidities. In addition, these patients had not previously been in remission with a variety of conventional synthetic DMARDs, and ten patients had previously used one or more biological/biosimilar DMARDs. Age, age at diagnosis, female gender, comorbidity and unresponsiveness to DMARD therapy are poor prognostic factors for RA, and these patients may have a resistance not only to tofacitinib but also to other drugs.

Limitations of our study are firstly it is retrospective; secondly the number of patients is small and thirdly, the follow-up period is short. It is possible to reach more precise information with a higher number of RA patients and longer-term follow-up studies.

CONCLUSION

In our study, the efficacy, safety, and adverse effects of tofacitinib in Rheumatoid Arthritis were investigated. Tofacitinib, which is safe and effective in the treatment of RA, can be used orally and is preferred as a monotherapy, providing an advantage over other biologic agents. However, it is necessary to be careful in terms of adverse effects that may develop due to tofacitinib.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethics committee at Yıldırım Beyazıt University with file number 2019/64

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