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Safety profile of tofacitinib in rheumatoid arthritis: a single-center experience

Romatoid artrit hastalarında tofasitinibin güvenlik profili: tek merkez deneyimi

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Abstract

Objective: To assess the adverse events (AEs) of tofacitinib in rheumatoid arthritis (RA) patients and to present real-life experiences.

Methods: Data on the demographic characteristics, comorbidities, and the AEs of 71 RA patients using tofacitinib was collected. Coronary artery disease, cerebrovascular disease, pulmonary embolism, malignancy, and mortality were defined as serious AEs. The risk factors for serious AEs were defined.

Results: Infections were the most common drug-related AEs, most of which were upper respiratory and urinary tract infections. Malignancy was detected in 3 patients in follow-up. No significant difference was found in the rates of overall AEs except urinary tract infections, between patients <65 years and those ≥65 years of age. However, serious AEs were observed more frequently in patients aged ≥65 years (p=0.019). Older age, male gender, pre-existing hyperlipidemia, and the initial year of tofacitinib treatment were significantly associated with developing serious AEs. Four patients (median age= 65.9 years) died.

Conclusion: Real-life data on the safety profile of tofacitinib in RA was presented in this study. Male gender was an independent risk factor for serious AEs in subjects receiving tofacitinib. Patients with older age, male gender, those with hyperlipidemia, and those in their first year of treatment should also be closely monitored for serious AEs.

Keywords: Tofacitinib, adverse events, rheumatoid arthritis, older age

Öz

Amaç: Romatoid artrit (RA) hastalarında tofasitinibin yan etkilerini (YE) değerlendirmeyi ve gerçek yaşam verilerini sunmayı amaçladık.

Yöntem: Tofacitinib kullanan 71 RA hastasının demografik özellikleri, komorbiditeleri ve YE'leri değerlendirildi. Koroner arter hastalığı, serebrovasküler hastalık, pulmoner emboli, malignite ve mortalite ciddi YE olarak gruplandırıldı. Ciddi YE'ler için risk faktörleri tanımlandı.

Bulgular: Enfeksiyonlar ilaca bağlı en yaygın YE'ler olup, bunların çoğu üst solunum yolu ve idrar yolu enfeksiyonlarıydı. Takipte 3 hastada malignite tespit edildi. <65 yaş ve ≥65 yaş hastalar arasında idrar yolu enfeksiyonları dışındaki genel YE oranlarında anlamlı bir fark bulunmadı. Ancak 65 yaş ve üzeri hastalarda ciddi YE'ler daha sık görüldü (p=0,019). İleri yaş, erkek cinsiyet, hiperlipidemi varlığı ve tofasitinib tedavisinin ilk yılı ciddi YE'lerin gelişmesiyle anlamlı düzeyde ilişkiliydi. Ortanca yaşları 65,9 olan 4 hasta hayatını kaybetti.

Sonuç: Bu çalışmada tofasitinibin RA'daki güvenlik profiline ilişkin gerçek yaşam verileri sunulmuştur. Erkek cinsiyet, tofacitinib kullanan hastalarda ciddi YE'ler için bağımsız bir risk faktörüydü. İleri yaş, erkek cinsiyet, hiperlipidemisi olan ve tedavinin ilk yılında olan hastalar ciddi YE'ler açısından yakın izlenmelidir.

Anahtar Kelimeler: Tofasitinib, yan etkiler, romatoid artrit, ileri yaş

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease presenting with inflammatory arthritis and joint damage that can cause joint destruction, deformity, and progressive disability. The estimated prevalence is about 0.24-1%.[1,2] It is also associated with a wide variety of extra-articular features and comorbidities which can lead to lower quality of life, increased morbidity, and mortality.[3] Early diagnosis and early initiation of treatment are aimed to prevent irreversible damage to the joints. There are various therapeutic agents used in the management including glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic (b) DMARDs [tumor necrosis factor (TNF) inhibitors and non-TNF biologics], and targeted synthetic(ts) DMARDs [Janus kinase (JAK) inhibitors]. The 2015 American College of Rheumatology (ACR) RA

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treatment guidelines recommended the primary use of TNF inhibitor treatments instead of tofacitinib in early RA patients with moderate to high disease activity despite DMARDs.[4] On the other hand, the European Alliance of Associations for Rheumatology (EULAR) 2019 guidelines and 2021 ACR guideline recommend either bDMARDs or tsDMARDs in combination with methotrexate (MTX) in patients who do not respond to the first csDMARD strategy and have poor prognostic factors.[5,6] Subsequently, the 2022 update of EULAR recommendations for RA patients reported the priority use of bDMARDs in patients with poor prognostic factors and failure to the first csDMARDs. It was stated that JAK inhibitors may be used, taking into account the relevant risk factors.[7]

The EULAR also established recommendations for the management of patients with difficult-to-treat RA in 2021.[8] In patients unresponsive to at least two b/tsDMARDs, especially two TNF inhibitor treatments, the use of b/tsDMARDs with a different target was suggested.[8]

The Janus kinase-signal transducer and activator of transcription signaling pathway has a crucial role in RA pathogenesis. JAK inhibitors inhibit the activity of the JAK family that lead to suppression of the effect of cytokines. Tofacitinib is one of the JAK inhibitors approved in many countries worldwide in the treatment of RA.[9,10]

Tofacitinib is generally well tolerated, although adverse events (AEs) have been reported in some patients. Infections are the most commonly reported AEs. In addition, malignancy, cardiovascular events, thrombosis, laboratory abnormalities (neutropenia, lymphopenia, elevated liver enzymes, increase in serum creatinine concentration, or changes in lipid levels), and gastrointestinal perforations are some of the other reported AEs.[11-13] The malignancies and major adverse cardiovascular events (MACE) risk of tofacitinib were evaluated and compared to TNF inhibitors in a study including patients ≥50 years of age with at least one additional cardiovascular risk factor (ORAL Surveillance study).[14] The risk of MACE and cancers were found to be higher in the tofacitinib group. We aimed to review the AEs in RA patients using tofacitinib and present our single-center real-life experience in this study.

Materials and Methods

Seventy-one RA patients who were on tofacitinib between January 2014 and April 2022 were included in the study. The 2010 ACR/EULAR classification criteria was used to diagnose RA.[15] Gender, age at diagnosis, follow-up time, tofacitinib treatment duration, smoking status, co-morbidities, body mass index, and the laboratory examinations [hemoglobin, leukocyte, platelet, alanine aminotransferase (ALT), creatinine, and aspartate aminotransferase (AST)] at the beginning of the tofacitinib treatment, at the 3rd month, and at the last visit were evaluated retrospectively. The treatment regimen was tofacitinib 5 mg twice a day.

The presence of AEs was reviewed from the medical records of patients. Detailed analysis and severity of AEs were assessed according to symptoms, physical examination findings, and laboratory findings. Serious AEs were described as any AEs that were life-threatening, causing death, need for hospitalization, or causing disability. Coronary artery disease, cerebrovascular disease, pulmonary embolism, malignancy, and mortality were defined as serious AEs. The associated infectious AEs were detailed and suspected AEs such as pretibial edema, tinnitus, and ecchymosis were also noted. The frequency of AEs in patients <65 and ≥65 years of age were also compared. We used age 65 years as a threshold value to compare variables and evaluate risk factors for severe AEs in patients receiving tofacitinib. Age over 65 years was identified as a risk factor for the use of tofacitinib by the European Medicines Agency (EMA) and also stated as a risk factor in the 2022 update of the EULAR recommendations for patients with RA.[7,16]

Statistical Analysis

Descriptive statistics were presented as frequency, median (minimum-maximum), mean and standard deviation. Visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk's test) were used to decide whether a variable had a normal distribution. The chi-square test or Fisher's exact test (if the data did not meet the assumptions of the chi-square test) were used to examine the differences between categorical variables. Friedman test, Wilcoxon test, ANOVA, and paired samples t-test were also used for statistical analyses. Univariate and multivariate logistic regression analyses were used to report risk factors for severe AEs in patients receiving tofacitinib and to define the independent risk factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value of less than 0.05 was used as the cutoff for statistical significance. The SPSS (version 20.0) was used in the statistical analyses.

The study was approved by the Aydın Adnan Menderes University Ethics Commission (approval number: 2022/110, date: 10.06.2022) and was conducted according to the guidelines of the Declaration of Helsinki.

Results

There were 71 RA patients (62 female, 9 male) receiving tofacitinib. The median age was 60.0 (29.6-77.4) years while the median age at diagnosis was 47.5 (19.4-72.0) years. The

median duration of tofacitinib treatment was 23 (1-66) months. At the enrollment of the study, tofacitinib treatment was discontinued in 45.1 percent of patients (n=32). Of those, the reasons for medication discontinuation were lack of (or poor) response to drugs (n=8), AEs (n=17), and patient's decision (n=7). The demographics and clinical features were summarized in Table 1.

Infections were the most common drug-related AEs (n=45), most of which were upper respiratory and urinary tract infections. The treatment agents used in the combination treatment were leflunomide (n=22), hydroxychloroquine (n=18), MTX (n=17), sulfasalazine (n=3), and methylprednisolone (n=38, with a median dose of 4 mg). In addition, twenty patients (29%) had a history of coronavirus disease-2019 (COVID-19) infection during tofacitinib. Intensive care unit admission was required for COVID-19 pneumonia in two of them. Malignancy was detected in three patients; one had squamous cell carcinoma of the skin, one had prostate cancer, and the other had lung cancer. They were diagnosed with cancer at 56 months, 8 months, and 21 months, respectively, after starting tofacitinib. Four patients with a median age of 65.9 years, two of whom were male, died. Two of them died from COVID-19 pneumonia, one from lung cancer, and one from acute myocardial infarction. The median time from initiation of tofacitinib to death was 7.5 (3-23) months. Apart from these patients, sudden cardiac death occurred five months after stopping tofacitinib in one patient. Reported AEs during tofacitinib were listed in Table 2.

Serious AEs occurred in 10 patients (14.0%). There was no statistically significant difference in comparison of the observed AEs rates in patients <65 and ≥65 years of age, except for urinary tract infections, which were significantly more common in those <65 years of age. In addition, serious AEs were more frequently encountered in patients 65 years or older (31.6% vs. 7.7%, p=0.019).

The median leukocyte number at treatment initiation was 9.120 (4.880-21.900) which was significantly higher than that at the 3rd month and at the last visit (p=0.01, p=0.001; respectively). Platelet levels showed an increasing tendency at the last visit, from 313.3 (±77.8) 10^3/μL at the initiation of treatment to 333.1 (±93.3) 10^3/μL at the last

Table 1. The demographics and clinical characteristics of the patients with rheumatoid arthritis

	Rheumatoid arthritis (n=71)
Sex, n (%)	
Female	62 (87.3)
Male	9 (22.7)
Age, years, median (min-max)	60.0 (29.6-77.4)
Age at diagnosis, years, median (min-max)	47.5 (19.4-72.0)
Time interval between diagnosis and onset of tofacitinib, years, median (min-max)	6.2 (0.1-39.4)
Median follow-up time, years, median (min-max)	8.7 (0.8-41.6)
Status of tofacitinib treatment, n (%)	
Ongoing	39 (54.9)
Discontinued	32 (45.1)
Duration of tofacitinib treatment, month, median (min-max)	23.0 (1-66)
Body mass index, median (min-max)	28.9 (16.5-47.7)
Overweight, n (%)	25/66 (37.8)
Obesity, n (%)	25/66 (37.8)
Smoking status, n (%)	
Smoker	9/68 (13.2)
Ex-smoker	9/68 (13.2)
Non-smoker	50/68 (73.5)
Pre-existing co-morbidities, n (%)	
Hypertension	24 (33.8)
Diabetes mellitus	15 (21.1)
Hyperlipidemia	11 (15.5)
Coronary artery disease	6 (8.5)
Cerebrovascular disease	2 (2.8)
Pulmonary embolism	2 (2.8)
Deep vein thrombosis	1 (1.4)

Min-max: Minimum-maximum

visit (p=0.013). However, leukopenia or thrombocytopenia was not observed in any patient. There was no statistically significant difference in the levels of hemoglobin, creatinine, ALT, and AST between the beginning of the tofacitinib, at the 3rd month, and at the last visit (Table 3).

Older age (aged ≥65 years), male gender, pre-existing hyperlipidemia, and the initial year of tofacitinib treatment were associated with developing serious AEs (OR: 5.538; 95% CI: 1.358-22.589; p=0.017, OR: 7.467; 95% CI: 1.567-35.577; p=0.012, OR: 1.159; 95% CI: 1.159-22.823;

Table 2. Reported adverse events in patients with rheumatoid arthritis treated with tofacitinib

	Total number of patients, n (%)	Age <65 years, n (%)	Age ≥65 years, n (%)	p value
Hypertension	6 (8.5)	3 (5.8)	3 (15.8)	0.332*
Coronary artery disease	3 (4.2)	1 (1.9)	2 (10.5)	0.173*
Cerebrovascular disease	2 (2.8)	0 (0)	2 (10.5)	0.069*
Pulmonary embolism	1 (1.4)	1 (1.9)	0 (0)	1.000*
Malignity	3 (4.2)	2 (3.8)	1 (5.3)	1.000*
Infection				
COVID-19 infection	20 (29.0)	15 (28.8)	5 (26.3)	0.834
Upper respiratory tract infections	20 (29.0)	15 (28.8)	5 (26.3)	0.834
Urinary tract infections	17 (24.0)	16 (30.8)	1 (5.3)	0.029*
Pneumonia	4 (5.6)	3 (5.8)	1 (5.3)	1.000*
Bronchitis	3 (4.2)	3 (5.8)	0 (0)	0.559*
Herpes zoster infection	2 (2.8)	2 (3.8)	0 (0)	1.000*
Other infections				
Cellulitis	1 (1.4)	0 (0)	1 (5.3)	0.268*
Periodontal abscess	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinea incognito	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinea pedis	1 (1.4)	1 (1.9)	0 (0)	1.000*
Gastrointestinal symptoms				
Nausea	3 (4.2)	3 (5.8)	0 (0)	0.559*
Abdominal pain	2 (2.8)	1 (1.9)	1 (5.3)	0.466*
Diarrhea	2 (2.8)	1 (1.9)	1 (1.9)	0.466*
Constipation	1 (1.4)	1 (1.9)	0 (0)	1.000*
Elevated liver function tests	1 (1.4)	1 (1.9)	0 (0)	1.000*
Others				
Skin discoloration	1 (1.4)	0 (0)	1 (5.3)	0.268*
Pretibial edema	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinnitus	1 (1.4)	0 (0)	1 (5.3)	0.268*
Itching	1 (1.4)	1 (1.9)	0 (0)	1.000*
Bruising, ecchymosis	1 (1.4)	0 (0)	1 (5.3)	0.268*
Erythematous lesion on the leg	1 (1.4)	1 (1.9)	0 (0)	1.000*
Dizziness	1 (1.4)	1 (1.9)	0 (0)	1.000*
Death	4 (5.6)	2 (5.4)	2 (10.5)	0.289*

**: Fisher's exact test, COVID-19: Coronavirus disease-2019*

Table 3. Laboratory characteristics of the patients at the beginning of the tofacitinib, at the 3rd month and at the last visit

	Beginning of tofacitinib	3rd month	Last visit	p value
Hemoglobin (g/dL)	12.1 (9.4-14.7)	12.2 (9.4-15.2)	12.1 (8.8-14.7)	0.263
Leukocyte (10^3/μL)	9.050 (4.880-21.900)[a, b]	7.990 (1.049-21.140)[a]	8.225 (4.530-19.530)[b]	0.002
Platelet (10^3/μL)	313.3±77.8[c]	310.0±74.1[d]	333.1±93.3[c, d]	0.008
Creatinine (mg/dL)	0.7 (0.5-2.7)	0.7 (0.5-2.7)	0.7 (0.5-2.8)	0.119
Alanine aminotransferase (U/L)	17.0 (7.0-45.0)	16.0 (1.0-40.0)	18.0 (7.0-92.0)	0.133
Aspartate aminotransferase (U/L)	16.0 (9.0-81.0)	18.0 (9.0-33.0)	17.0 (9.0-66.0)	0.202

Median (min-max) or mean (± SD); [a, b, c, d]: Significant differences between parameters in the same letters, SD: Standard deviation

p=0.031, and OR: 4.219; 95% CI: 1.053-16.901; p=0.042; respectively). On the other hand, age, obesity, smoking, pre-existing hypertension, pre-existing diabetes mellitus, and pre-existing coronary artery disease were not risk factors. The male gender was also detected as an independent risk factor for serious AEs in patients receiving tofacitinib in multivariate analysis (OR: 6.868; 95% CI: 1.140-41.356; p=0.035) (Table 4).

Discussion

We retrospectively evaluated the safety profile of tofacitinib in RA patients in a tertiary rheumatology center in Turkey and defined the risk factors for serious AEs as male gender, older age, pre-existing hyperlipidemia, and the initial year of the tofacitinib treatment. Tofacitinib safety assessment in RA was investigated in phase II-IV and long-term extension studies previously.[17-22] In line with our findings, the rate of serious AEs was stated to be higher in elderly patients than in younger patients.[23] In the long-term safety analysis, male gender and older age were also reported as risk factors for serious infection events.[24] The presence of traditional risk factors at baseline (eg. older age, higher body mass index, and elevated blood pressure) and higher baseline triglyceride levels were identified as risk factors for MACE. With these caveats kept in mind, the relationship between RA and increased cardiovascular morbidity and mortality should be taken into account.[25] The presence of traditional risk factors also increases the risk of cardiovascular disease in RA patients.[26]

The integrated analysis of trials and long-term safety profile of tofacitinib up to 8.5 years was reported in 2017.[27] Afterward, the long-term analysis results up to 9.5 years was published in 2020.[24] Analysis of 7061 patients' data revealed serious infections in 576 patients, herpes zoster infections in 782 patients, malignancies [excluding non-melanoma skin cancer (NMSC)] in 177 patients, NMSC in 129 patients, MACE in 85 patients, arterial thromboembolism in 84 patients, venous thromboembolism in 59 patients, and deep venous thrombosis in 36 patients.[24] Tofacitinib safety assessment was found to be similar to bDMARDs except for herpes zoster infection. We also reported most of the aforementioned AEs in our cohort and infection was the most common among them. The rate of serious AEs of tofacitinib was reported as 26.3% in a follow-up period of up to 9.5 years.[24] We found it as 14% at a median follow-up of 8.7 years.

EMA recommended using tofacitinib with caution due to possible AEs. One of the recommendations was to use tofacitinib in patients over 65 years of age only if there is no alternative treatment available.[16] However, the comparison of the two treatments (tofacitinib versus biologic DMARDs) for the incidence of infections and serious infections in RA patients aged 65 years or older and less than 65 years revealed a similar risk of serious infection events in patients receiving tofacitinib 5 mg twice daily (BID) and adalimumab. Also, the increased risk with tofacitinib 10 mg BID in older patients was reported.[28] We did not find any difference in the rate of infections or AEs in older patients (aged ≥65) compared with younger patients (<65 years) except for the increased frequency of serious AEs in patients receiving tofacitinib 5 mg BID.

Table 4. Risk factors for serious adverse events in patients receiving tofacitinib

	B	S.E.	Wald	p	OR	95% CI
Risk factors for serious adverse events (univariate logistic regression analysis)						
Age ≥65 years	1.712	0.717	5.696	0.017	5.538	1.358-22.589
Male gender	2.010	0.797	6.370	0.012	7.467	1.567-35.577
Presence of obesity	0.218	0.906	0.058	0.810	1.243	0.211-7.338
Smoking	-1.190	0.770	2.386	0.122	0.304	0.067-1.377
Pre-existing hypertension	0.203	0.741	0.075	0.784	1.225	0.287-5.233
Pre-existing diabetes mellitus	0.080	0.850	0.009	0.925	1.083	0.205-5.733
Pre-existing coronary artery disease	-0.219	1.153	0.036	0.850	0.804	0.084-7.697
Pre-existing hyperlipidemia	1.638	0.760	4.639	0.031	1.159	1.159-22.823
First year of tofacitinib treatment	1.440	0.708	4.133	0.042	4.219	1.053-16.901
Risk factors for serious adverse events (multivariate logistic regression analysis)						
Age ≥65 years	1.264	0.808	2.445	0.118	3.539	0.726-17.254
Male gender	1.927	0.916	4.424	0.035	6.868	1.140-41.356
Pre-existing hyperlipidemia	1.165	0.860	1.833	0.176	3.204	0.594-17.295
First year of tofacitinib treatment	1.374	0.837	2.694	0.101	3.953	0.766-20.400

CI: Confidence interval, OR: Odds ratio, S.E.: Standard error

Pulmonary embolism was observed in one patient (1.4%) in our study group. In 2019, increased rates of pulmonary embolism and all-cause mortality were reported in patients receiving a 10 mg BID of tofacitinib compared to the tofacitinib 5 mg BID or TNF inhibitor regimens.[16] However, a meta-analysis of randomized controlled trials revealed a decreased rate of venous thromboembolism (VTE) in patients receiving both the 5 mg or 10 mg tofacitinib compared to the placebo group. In the subgroup analysis, the increased risk of VTE was reported in patients receiving 10 mg tofacitinib BID than those receiving 5 mg BID.[29]

Three (4.2%) of our patients were diagnosed with malignancy while on tofacitinib treatment. Association between tofacitinib and cancer is unclear. The result of a meta-analysis revealed no increased risk of cancer for tofacitinib compared with csDMARDs or TNF inhibitors.[30] Likewise, in the analysis of 5.671 patients with moderate-to-severe RA receiving tofacitinib, the incidence ratios of malignancies (excluding NMSC) were reported to be within the expected range.[31] On the other hand, the risk of cancer was reported to be higher in RA patients ≥50 years of age with at least one additional cardiovascular risk factor.[14] Tofacitinib should be used with caution in elderly RA patients.

Study Limitations

The main limitation is the retrospective design of the study. Another is that most of the patients were female. It might have affected our results. Besides, we did not assess disease activity and did not correlate it with the presence of AEs. However, we believe that our real-life data will contribute to the literature on the safety profile of tofacitinib. Knowledge and awareness of physicians are essential to monitoring carefully of patients and detecting AEs.

Conclusion

Adverse effects such as infections, cardiovascular disease, malignancy, and death may occur in patients using tofacitinib, similar to observations in patients receiving other biological agent treatments. Especially patients with older age, male gender, those with hyperlipidemia, and those in their first year of treatment should be closely monitored for serious AEs. Further multicenter studies with larger numbers of patients and real-life experience might provide additional insight into the safety profile of tofacitinib.

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Ethics Commission (approval number: 2022/110, date: 10.06.2022) and was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: T.A., C.D., G.S., S.Ç., T.Ş., Design: T.A., C.D., G.S., S.Ç., T.Ş., Data Collection or Processing: T.A., C.D., G.S., S.Ç., T.Ş., Analysis or Interpretation: T.A., G.S., S.Ç., T.Ş., Literature Search: T.A., C.D., G.S., S.Ç., T.Ş., Writing: T.A., C.D., G.S., S.Ç., T.Ş.

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