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Original Article Rheumatology

Real-life experience of tofacitinib in patients with treatment-resistant rheumatoid arthritis: A 5-year follow-up: Monocentric experience

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ABSTRACT

OBJECTIVE: The present study aims to assess the short- and long-term effects of tofacitinib (TOFA) therapy on efficacy, safety, and drug retention rate patients with rheumatoid arthritis (RA) refractory to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or biological disease-modifying anti-rheumatic drugs (bDMARDs).

METHODS: Thirty-five patients with RA who received TOFA therapy for at least 3 months in rheumatology outpatient clinic between December 2015 and December 2020 were included in the study. The prospectively follow-up results of the patients obtained on the 6th month and 5th year are presented. Demographic characteristics of the patients, the disease activity score-28 for RA with erythrocyte sedimentation rate (DAS 28-4 [ESR]), change in DAS-28, health assessment questionnaire score, patient visual analog scale score, and laboratory parameters were recorded. The data at 6 months and 5 years of treatment were compared with baseline data. All side effects were recorded at each follow-up visit. Wilcoxon signed-rank tests were used for analysis.

RESULTS: Of the 35 patients, 23 received TOFA treatment after receiving ≥1 bDMARDs, while the remaining 12 patients received TOFA therapy were biologic naive. On the 6-month follow-up, DAS 28-4 (ESR) score and DAS28 improvement significantly decreased at the 6th months from baseline ($p<0.001$ and $p<0.001$, respectively), and moderate disease activity was achieved in 13 patients. High disease activity persisted in four patients. DAS28 improvement according to the EULAR response criteria was good response in 86% of the patients. DAS 28-4 (ESR) score and DAS28 improvement significantly decreased at 5 years from baseline ($p<0.01$ and $p<0.001$, respectively), and the moderate disease activity was achieved in 10 patients. High disease activity persisted in two patients. Drug retention rate at 5-year follow-up was 54% and the daily glucocorticoid therapy could be discontinued in 9 patients (47%). Three patients (15%) were tested positive for COVID-19. None of them required hospitalization and no deaths were occurred due to COVID-19.

CONCLUSION: TOFA is effective and well-tolerated treatment options that reduce the need for steroids in patients with RA.

Keywords: Disease activity; real-life data; rheumatoid arthritis; tofacitinib.

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Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by widespread and symmetrical chronic inflammation in the joints. The treatment of RA focuses on the prevention of joint erosions and functional limitations caused by joint inflammation in such patients. The difficulties in parenteral administration of biological disease-modifying anti-rheumatic drugs (bDMARDs) have necessitated the development of effective oral therapies. Tofacitinib (TOFA) is the first oral, non-biological targeted synthetic disease-modifying

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anti-rheumatic drug (tsDMARD) and it was approved by the Food and Drug Administration in 2012 for the treatment of RA. TOFA exerts its effects by inhibiting Janus kinase 1/3 (JAK1-3) and, to a lesser extent, JAK2 enzymes that are involved in the transmission of extracellular information into the cell nucleus [1].

Cytokines play an important role in the pathogenesis of RA [2]. The JAK/signal transducer and activator of transcription (STAT) signaling pathway that transmits information from the cell membrane to the nucleus is activated on binding of cytokines to the receptors. The activated JAK phosphorylates STAT, which results in translocation of STATs to the nucleus to activate new gene transcription. The activated JAKs play a role in immune and inflammatory responses. New treatment approaches in the treatment of RA have targeted intracellular signaling pathways to suppress cytokine release. TOFA prevents transcription signaling to the cell nucleus by inhibiting JAK autophosphorylation and activation [3, 4].

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend the use of TOFA as the first-line oral therapy as an alternative to other biological therapies in the treatment of RA in patients with moderate-to-high disease activity that is refractory to methotrexate (MTX) and/or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) [5].

The present study aims to present the efficacy and the safety data of the patients with RA who received TOFA therapy in an outpatient clinic of a secondary center.

Highlight key points

- Remission and low disease activity were achieved in 42% of patients in 6 months with TOFA treatment, while good response was obtained in 86% of patients and the rates were similar at 5 years.
- TOFA monotherapy retention rate was 45.5% at the 6th month and 32% at the 5th year.
- TOFA is a safe and effective agent in patients with RA, and also effectively reduces the patients' need for steroids.

MATERIALS AND METHODS

Study Design and Subjects

We conducted this retrospective longitudinal analysis with RA patients who received at least 3 months TOFA from December 2015 until the end of December 2020. The patients who were diagnosed with RA according to 2010 ACR/EULAR criteria [6], and followed up in rheumatology outpatient clinic of Istanbul Health Sciences University, Umraniye Training and Research Hospital were included in this prospective study. Thirty-five consecutive RA patients who had active disease refractory to conventional synthetic and/or biological (b) disease-modifying anti-rheumatic drugs DMARDs and treated with TOFA at a dose of 5 mg twice daily were selected and followed up for 5 years. The follow-up results of the patients acquired on the 6th month and 5th year visits are presented.

Demographic, clinical, and laboratory data including rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, serum erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels, whole blood count, kidney and liver function tests, uric acid, and serum lipid levels were documented at each visit. Side effects were noted to a pre-prepared questionnaire.

Disease Activity Assessments in Patients with RA

The joint involvement of the patients was evaluated on 28 tender and swollen joints at each visit. Disease activity was assessed with DAS28-4 (ESR) composed by total joint count, swollen joint count, visual analog scale (VAS), and ESR. Cutoff points of remission were defined as a DAS-28 score of ≤2.6, with higher scores indicating low disease activity (>2.6–≤3.1), moderate disease activity (>3.1–≤5.1), and high disease activity (>5.1). Disease activity score of 28 joints – ESR (DAS28-4 ESR), VAS, and health assessment questionnaire (HAQ) scores, was calculated at the initial evaluation, the 6-month and 5-year follow-ups of TOFA therapy [7]. DAS28 response according to the EULAR response criteria [8, 9] was recorded at the 6-month and the 5th-year follow-up visits. Patients were defined as responders or non-responders according to DAS28-4 ESR; DAS28 ≤3.2: Responders; and DAS28 >3.2: Non-responders. ESR and CRP were evaluated for laboratory disease activity.

Statistical Analysis

Statistical Package for the Social Sciences (IBM SPSS Statistics New York, USA) version 20.0 was used to perform statistical analyses. The clinical and the laboratory data were compared using Wilcoxon signed-rank test in TOFA tolerant and responder patients who completed the 5 years of therapy. Adverse events other than laboratory abnormalities were calculated per 100 patient-years.

Table 1. Demographic, clinical, laboratory, and treatment characteristics of 35 patients

Number of patients, n	35
Gender, F/M	30/5
Age (years), SD	55±13
Disease duration (months), SD	147±111
RF positivity	18/35
Anti-CCP positivity	25/35
Seropositivity (%)	28 (80)
DAS28-4 (ESR), SD	5.87±0.80
HAQ, SD	0.92±0.47
bDMARDs before TOFA therapy, n (%)	12 (35)
One bDMARD	7
Two bDMARDs	1
Three bDMARDs	2
Four bDMARDs	2
Glucocorticoid treatment users	34

RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; DAS28-4: Disease activity score calculated by evaluating 28 joints; ESR: Erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; bDMARD: Biological disease-modifying anti-rheumatic drug; the data are presented as mean±standard deviation (SD) unless otherwise indicated.

Table 2. Clinical and laboratory findings and DAS28-4 (ESR) scores before and after 6 months of TOFA treatment

n=29	Baseline (±SD)	At 6 months of TOFA (±SD)	p
HAQ	0.91±0.45	0.58±0.4	<**0.001**
Patient VAS	56.2±18	26.5±19	<**0.001**
Swollen joints	8.8±4	3.5±4	<**0.001**
Tender joints	8.06±4	1.8±2	<**0.001**
DAS28-4 (ESR)	5.84±0.78	3.59±1.17	<**0.001**
ESR	52.2±25	32.0±20	<**0.001**
CRP	3.1±2.6	0.71±0.7	<**0.001**
Leukocyte (x10^9/L)	8.506±2.703	8.002±3.477	NS
Neutrophils (x10^9/L)	5.582±2.101	4.583±1.954	NS
Lymphocytes (x10^9/L)	2.100±0.923	2.011±0.827	NS
Hemoglobin (mg/L)	11.85±1.50	11.92±1.40	NS
Platelets (x10^9/L)	302.685±83.16	282.593±74.81	NS
T-CHOL (mg/dl)	205.8±43	231.4±49	**0.004**
LDL-CHOL (mg/dl)	128.2±34	145.2±39	<**0.05**
HDL-CHOL (mg/dl)	49.0±10	58.3±15	**0.002**
TG	140.8±102	141.9±73	NS
UA	4.7±1.7	4.91±1.6	<**0.05**

VAS: Visual analog scale; HAQ: Health assessment questionnaire; DAS28-4: Disease activity score calculated by evaluating 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; T-CHOL: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; UA: Uric acid.

The study was approved by the Clinical Trials Ethics Committee (process no. 2020/244) and conducted in accordance with the Helsinki Declaration and Good Clinical Practices guidelines. Informed consent was collected before the inclusion.

RESULTS

Thirty-five patients with RA who prospectively followed up at least 3 months, in a single center were included in this study. Demographic and disease characteristics are presented in Table 1. Before TOFA treatment, while all patients received MTX (100%), other received hydroxychloroquine (74%), leflunomide (LEF) (65%), and sulfasalazine (42%) either as mono or combined treatment. Almost all patients (97%) were on glucocorticoid treatment. Sixty-five percent of patients (n=23) were b-DMARD-naïve before TOFA. TOFA therapy was applied as monotherapy in 13 (37%) patients. In addition, it was combined with MTX in 15 patients (43%) and with LEF in 7 patients (20%). Comorbidity was detected in 18 (51.4%) patients and there was hypertension 11.4%, chronic obstructive pulmonary diseases 11.4%, osteoporosis 11.4%, diabetes mellitus 8.6%, cardiovascular disease 2.9%, and interstitial lung disease 2.9%, respectively. Interstitial lung disease was detected in one patient secondary to RA.

While 34 patients (97%) had high disease activity, 1 (3%) had moderate disease activity before TOFA therapy, according to DAS 28. Initially, DAS28 was 5.87±0.80, and HAQ score was 0.92±0.47.

Eighty-two percent of RA patients (n=29) completed 6 months of TOFA therapy. Clinical and laboratory findings and DAS28-4 (ESR) scores at the 1st and 6th month follow-up visits for TOFA treatment are shown in Table 2. There were significant improvements in DAS 28-4 (ESR) scores and changes in the DAS 28 scores at 6 months after initiation of TOFA therapy ($p<0.001$ and $p<0.001$). DAS28-4 (ESR) improvement was achieved in 26 (90%) patients. Majority of patients (86%) were good EULAR (>1.2 improvement) responders. The response to therapy in terms of change in DAS28 according to the EULAR response criteria was good in 25 patients (>1.2 improvement), moderate in one patient (0.6–1.2 improvement), and poor in three patients (<0.6 improvement).

Table 3. Clinical and laboratory findings and DAS28-4 (ESR) scores before and after 5 years of TOFA treatment

n=19	Baseline (±SD)	At 5 years of TOFA (±SD)	p
HAQ	0.74±0.40	0.64±0.34	**0.012**
Patient VAS	23.33±17.48	30.52±15.08	NS
Swollen joints	9.68±4.11	3.94±3.50	<**0.001**
Tender joints	8.79±4.41	2.21±2.67	<**0.001**
DAS28-4 (ESR)	5.99±0.76	3.70±1.44	<**0.001**
ESR	50.11±23.91	28.00±16.70	<**0.001**
CRP (mg/dL)	2.27±2.14	0.83±0.80	**0.004**
Leukocyte ($\times10^9$/L)	8.007±2.645	7.902±2.261	<**0.001**
Neutrophils ($\times10^9$/L)	4.983±1.851	5.021±1.816	<**0.001**
Lymphocytes ($\times10^9$/L)	2.187±0.946	2.086±0.865	<**0.001**
Hemoglobin (mg/L)	12.23±1.59	12.67±1.34	NS
Platelets ($\times10^9$/L)	304.631±89.42	315.421±100.596	NS
T-CHOL (mg/dL)	207.44±43.62	223.70±41.58	NS
LDL-CHOL (mg/dL)	128.94±34.10	131.00±40.75	NS
HDL-CHOL (mg/dL)	48.06±10.81	61.00±15.50	<**0.001**
TG	128.94±34.10	154.17±114.62	NS
UA	4.99±2.14	5.02±1.31	NS

VAS: Visual analog scale; HAQ: Health assessment questionnaire; DAS28-4: Disease activity score calculated by evaluating 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; T-CHOL: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; UA: Uric acid.

Table 4. The reasons for the discontinuation of TOFA therapy

Reason for discontinuation	(n=16) %
Primary inefficacy	25
Secondary inefficacy	37.5
Allergic reaction	7
Malignancy	13
Death	7
Dropouts	14

After 6 months of TOFA therapy, 11.4% of the patients (n=4) had high activity, 37.1% (n=13) of the patients had moderate activity, 14.3% of the patients (n=5) had low activity, and 20,1% of the patients (n=7) were in remission. On the 6th month follow-up visit, the observed seropositivity rate was 82.9% among patients with high activity, 11.4% with moderate activity, 14.3% with low activity, and 20% in patients at remission. Of those in remission, 85.7% of the patients were biologic-naive, 58% of patients (n=17) were non-responders. Seropositivity rate was 58.3% in responders and 65% in non-responders.

Total cholesterol (T-CHOL), low-density lipoprotein cholesterol (LDL-CHOL), high-density lipoprotein cholesterol (HDL-CHOL), and UA levels (p=0.004, p=0.014, p=0.002, and p=0.03) were elevated significantly at the 6 months of therapy. There was no significant change in complete blood count and triglyceride (TG) levels (p>0.05).

Thirteen patients (45%) continued as TOFA monotherapy for 5 years. Ten patients (35%) received MTX and 6 patients (20%) received combination therapy with LEF. After 6 months of TOFA therapy, 12 patients (41%) were no longer required glucocorticoid treatment; subsequently, glucocorticoid treatment was discontinued. Out of 12 patients, six were receiving only TOFA, two were receiving TOFA+MTX, and five were receiving TOFA+LEF.

Patients were reevaluated at the 5th year follow-up visit. Fifty-four percent of RA patients (n=19) completed the 5 years of TOFA therapy. The mean duration of TOFA therapy was 30.89±18.32 months. Clinical and laboratory findings and DAS28-4 (ESR) scores before and after 5 years of TOFA treatment are shown in Table 3. Five years after initiation of TOFA therapy, a drastic difference was observed in DAS28-4 (ESR) scores (p<0.001). DAS28 improvement was achieved in 18 (94%) patients. Majority of patients (89%) were good (>1.2 improvement) responders. DAS28 components other than patient VAS displayed significant decrease. (p<0.001). The improvement in DAS28 components following TOFA therapy shown in Figure 1A–C.

The response to therapy in terms of change in DAS28 according to the EULAR response criteria was good in 17 patients (>1.2 improvement), moderate in one patient (0.6–1.2 improvement), and poor in one patient (<0.6 improvement).

After 5 years of TOFA therapy, 10.5% of the patients (n=2) had high activity, 52.6% (n=10) of the patients had moderate activity, 5.3% of the patients (n=1) had low activity, and 31.6% of the patients (n=6) were in remission in accordance to DAS28. Of the patients in remission, 50% were biologic-naive and 50% were seropositive. Sixty-three percent of patients were non-responders. Seropositivity rate was 57.1% in responders and 83.3% in non-responders. In non-responders, RF positivity was found in 66.5%, anti-CCP positivity in 75%, and biological-naive 58.3%.

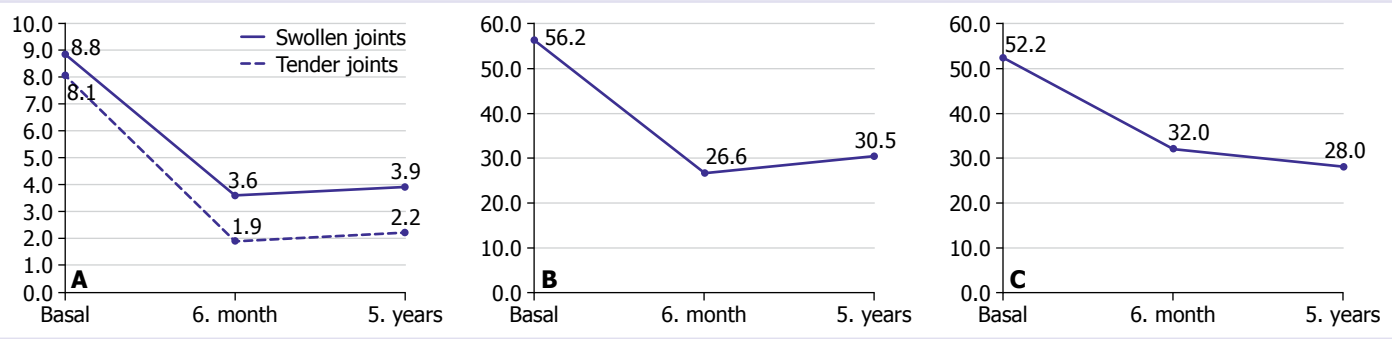

FIGURE 1. The improvement in DAS28 components following tofacitinib therapy. **(A)** Tender-swollen joint, **(B)** visual analog scale, and **(C)** erythrocyte sedimentation rate (mm/h).

HDL-CHOL was elevated significantly at the 5 years of TOFA therapy ($p<0.001$). There were no significant changes in LDL-CHOL, TG, and UA levels ($p>0.05$). T-CHOL and HDL-CHOL ($p=0.004$ and $p=0.002$) were elevated significantly in the 5th year of therapy. According to the 5th year result, a significant decrease has been detected in level of leukocyte and lymphocytes ($p<0.001$) compared to baseline data. Moreover, an increase was detected in neutrophil count. There was no meaningful difference in the number hemoglobin and platelet.

Six patients (32%) continued as TOFA monotherapy. Six patients (32%) received MTX, and 7 patients (36%) received combination therapy with LEF. Glucocorticoid treatment could be discontinued in 9 patients (47.4%) after TOFA therapy. After 5 years of TOFA therapy, 9 patients (47.4%) were no longer needed to glucocorticoid treatment; subsequently, glucocorticoid treatment was discontinued. Out of nine patients, four were receiving only TOFA and five were receiving TOFA+LEF.

The reasons for discontinuation of therapy in 16 patients are shown in Table 4. One patient who died at the 6th month of TOFA at home was elderly RA patient with pulmonary involvement and comorbid conditions. One had incidentally detected papillary thyroid carcinoma and the other had diffuse B-cell lymphoma presented with skin involvement, discontinued TOFA at their 36th and 27th month of TOFA therapy, respectively. The malignancy rate was 1.14/100 patient-years.

One patient (3%) complicated with severe pulmonary infection at the 13th month and the other had non-disseminated herpes zoster (HZ) infection at the 26th month of TOFA. HZ infection rate was 0.55/100 patient-years and the rate of infection requiring hospitalization was 0.55/100 patient-years. Among 19 patients receiving TOFA therapy during COVID-19 pandemic, 3 patients (15%) had COVID-19. Two of those had mild disease and one proceeded asymptomatic. None of them required hospitalization, mechanical ventilation, and no deaths were occurred due to COVID-19.

DISCUSSION

The real-life data of RA patients from Turkey were presented in this study. Thirty-five patients under TOFA therapy for at least 3 months were observed prospectively, and efficacy, safety, and retention rate of TOFA therapy were evaluated. Twelve patients (42%) in the present study were in remission and had low disease activity at 6 months while this rate was calculated 7 patients (36%) in 5 years. According to EULAR response criteria based on the changes in DAS 28 score, good response was achieved in 25 (86%) patients at the 6th month visits whereas 17 patients (89%) had good response at the 5th year visits. Drug retention rate was 54% in 5 years; moreover, approximately half of the patients were no longer required steroid therapy, the rates of continuing drug therapy, infections, and malignancies were similar to those reported in the literature.

Randomized controlled trials suggest that TOFA therapy reduces disease activity and improves the patient's functional status [10–14]. Studies have found different remission rates between 7 and 25% with TOFA [10–14]. In the ORAL Sync study, the remission rate at 6 month was 7.2% and it was shown that TOFA reduces the disease activity at 12 months [11]. In the ORAL Start study, in which TNF inhibitors resistant patients were recruited, the remission rate was found to be 14.6% in 6 months [13]. In the long-term results of the ORAL Sequel study of Wollenhaupt et al. [15], it was observed that the remission rates continued as 25% in 8 years. In our study, we

showed a higher percentage of remission at both month 6 and year 5 than all these studies. Although TOFA is used in patients with high disease activity, the patient populations are slightly different due to the preconditions required in these studies, such as the number of tender and swollen joints more than 4 and an increase in acute phases. Furthermore, real-life data have also shown that biologically naive patients achieve greater remission and lower disease activity [16–18]. Therewithal, RF negativity along with biological naivety was associated with low disease activity, and in our study, the majority of our patients in remission were biologic-naïve and seronegative. There was a significant improvement in DAS28-4 (ESR) scores at 6 months compared to baseline values in all our patients. Likewise, the results of the 5th year visits had shown the same statistically significant improvement.

Although more than half of the patients in our study were non-responder, more than 90% of the patients had improvement in DAS 28 scores based on EULAR response criteria at 6 months and 5 years, which continued in the long term. Most of these non-response patients were seropositive, which is known to have higher disease activity than seronegative patients. While we were not considered as responders according to DAS28-4 (ESR) criteria after treatment in these patients, we showed that disease activity decreased significantly in both the short term and the long term compared to baseline.

The Phase 3 clinical trials of Oral SOLO and ORAL Strategy found an improvement in disease activity parameters following TOFA therapy. The results of the present study also support these clinical trials [10–14, 19, 20]. Especially, the continuation of the improvement in DAS-28 indicates that the response to treatment is long term.

When DAS28-4 (ESR) compounds were evaluated separately, the mean ESR, number of tender and swollen joints, and pain score significantly decreased at both 6th month and 5th year visits. In the 5th year, except for the VAS score, the significant decline continued in other compounds according to the baseline. The mean HAQ score evaluating the functionality of the patients significantly decreased at 6 months and 5 years after initiation of TOFA therapy compared to baseline values, and this finding was consistent with those of large-scale Phase 3 clinical trials [10–14, 19, 20].

TOFA monotherapy retention rate was 45.5% at the 6th month and 32% at the 5th year. When 5 mg and 10 mg TOFA doses were compared with placebo in the TOFA monotherapy study, an ACR20 response was achieved, and a significant decrease was noted in DAS28 and HAQ scores at 3 months. Similar to these findings, approximately one-third of the patients in the present study received monotherapy [10]. It was reported in arm of the open-label, multicenter ORAL sequel study that combination therapies were discontinued in patients in remission who had low disease activity, and the rate of discontinuation was 11.6% for MTX and 35.7% for glucocorticoids [21]. Similarly, the rate of steroid discontinuation in the present study was 34% at the 6th month visits and 47% at the 5th year visits. Consequently, long-term follow-up showed higher rates of steroid discontinuation. However, in our study, the rate of discontinuation was higher for cDMARD in our study at the 6th month (13/35, 37.1%). It is considered that the patients discontinued csDMARD therapy due to high efficacy of TOFA monotherapy. In consideration of long-term effects of monotherapy, the drug monotherapy rate was calculated as 32% in the 5th year results.

Systemic reviews and meta-analysis reported a decrease in hemoglobin, neutrophil count, and lymphocyte count of patients receiving TOFA therapy [22]. A randomized, controlled, Phase 3 ORAL Sync study reported that the decrease in leukocyte and neutrophil counts were more remarkable than in the placebo group, and this effect was found to be dose dependent [23, 24]. There was a decrease in neutrophil and lymphocyte counts of patients with RA receiving TOFA therapy, even though they remained within the normal reference ranges along the course of TOFA therapy [25]. Similarly, the present study did not note a significant change in neutrophil and lymphocyte counts and hemoglobin values at the 6th month visits. However, leukocyte and lymphocyte counts were found significantly decreased at the 5th year visits corresponding with the current literature findings.

An increase in T-CHOL, LDL-CHOL, and HDL-CHOL levels was observed in patients receiving TOFA therapy in a Phase 2 clinical trial [26]. Subsequent Phase 3 clinical trials observed an increased in HDL-CHOL and LDL-CHOL levels after the therapy [10, 20, 25, 27]. There is an increased risk of cardiovascular events in patients with active RA. A study on patients with active RA receiving TOFA therapy found a significant decrease in carotid intima media thickness [28]. TOFA therapy increases cholesterol levels but suppresses the inflammation. There was no increase in the T-CHOL-to-HDL-CHOL ratio, which is a marker of atherosclerosis [29], because both T-CHOL and HDL-CHOL increased proportionately in patients receiving TOFA therapy.

Particularly long-term data of our study indicate similar results; T-CHOL/LDL-CHOL ratio and triglyceride levels did not change from baseline, while there was an increase in HDL-CHOL levels. One of the largest studies on JAK inhibitors and increased cardiovascular risks found that major adverse cardiovascular events were more common with TOFA than TNF inhibitors. However, in this study, included patients were older than 50 years of age and had at least one cardiovascular risk factors. In the same study, another important result was that deep venous thrombosis (DVT) and venous thromboembolism (VTE) were observed in 0.8% and 1.2% of the patients, respectively [30]. In our study, no major cardiovascular event, DVT and VTE were observed in any of the patients, probably due to the more younger and small study population.

Some studies observed that an increase in UA levels is related to an increased risk of metabolic syndrome and that increased UA level is an independent risk factor for atherosclerosis [31]. Among the components of metabolic syndrome, hyperglycemia and weight gain were observed in some studies involving the use of TOFA therapy [32, 33]. The finding of a significant increase in UA levels gives rise a question of whether UA levels could serve as a marker in predicting atherosclerosis at the 6th month but this significant difference in UA level did not persist over 5 years. The parameters of metabolic syndrome and other risk factors for atherosclerosis were not evaluated in our study. There is a need for controlled studies on a larger number of patients.

There is a significant increase in the risk of infections in patients receiving TOFA therapy and particularly in those with high disease activity. Meta-analyses report an incidence rate of 2.5–3 for severe infections [34]. In our study, there was only one elderly patient with lung involvement who was found to have a lung infection requiring hospital admission. A multicenter study using TOFA therapy identified tuberculosis as the most common opportunistic infection associated with the therapy [35]. No patient in our study had tuberculosis or opportunistic infections. This might be associated with small number of study patients and the fact that all patients with a positive PPD test (>5 mm) received prophylactic isoniazid therapy.

It was observed that the incidence of HZ is higher than expected in patients with RA treated with JAK inhibitors. A large-scale study reported a rate of 5% [36]. HZ infection was observed in 1 patient (3%) in the present study. This figure can be related to genetic diversity of HZ and small number of study patients.

Considering an inhibitory effect on cytokine release syndrome, tofacitinib is applied to COVID-19 patients in a randomized clinical trial. Thus, it demonstrated a significant decrease in the mortality rates among COVID-19 patients [37]. In our study, three out of 19 patients who were not vaccinated yet had COVID-19 and none of them need hospitalization. Furthermore, no mortality rates detected due to COVID-19.

Malignancies are 10% more common in patients with RA than in general population. There is also an increased prevalence of lymphoma, and lung and renal cancers [38]. The disease activity in RA and the use of immunosuppressive therapies contribute to increased prevalence of cancers. In a review including both real-world data and clinical studies on safety profile of TOFA, malignancy rates were 1.15/100 patient-years. Therefore, no correlation was found between TOFA use and increased malignancy rates [36]. Similarly, one meta-analysis did not find a significant difference in the development of malignancies between TOFA therapy and bDMARD therapy [39]. Malignancy rates were found 1.14/100 patient years and were similar to those documented in the current literature. One patient (2.8%) in the present study had diffuse large B-cell non-Hodgkin lymphoma, who was seropositive and had an erosive disease course, and had received bDMARD for a prolonged period before TOFA therapy. Lymphoma was detected after a 1-year course of TOFA therapy. This effect cannot be suggested to be directly related to TOFA therapy. There is a need for prospective studies to identify isolated effect of TOFA therapy. Another multicenter study involving 486 patients detected malignancy in 19 patients (3%), one of whom had thyroid cancer [40]. Similarly, thyroid cancer was detected incidentally in 1 patient (2.8%) in our study who received TOFA therapy for 3 years and intermittent MTX therapies.

A multicenter TReasure registry evaluated drug survival rates in 407 patients receiving TOFA therapy. The rate of drug survival at the end of 50 months was 71.9%. The treatment was discontinued due to primary inefficacy in 39 patients (45.3%), secondary inefficacy in 19 patients (22.1%), and side effects in 17 patients (19.8%). The primary inefficacy rate in this study was higher than our results, possibly due to the higher number of patients who started TOFA after multiple biologics [41]. In the Oral SEQUEL study, the rate of continuation to ther-

apy was 49% [15]. In a long-term study of 6194 patients, 2489 (40.2%) continued therapy at 48 months [42.] In a study from Turkey with 210 participants, overall TOFA retention rate detected in 1 year was as 63.9% [43]. In this study, drug survival was 82% at 1 year and 54% at 5 years. Considering the retention rates of other biological treatments, a higher rate than abatacept was observed in the 5th year, while similar rates were found to TNF inhibitor treatments [44, 45].

This study had some limitations. First, the study is single centered. Furthermore, some patients skipped a few periodic appointments which were arranged according to the biologic/targeted synthetic DMARDs prescription rules designed by Ministry of Health. This study was done with real-life data. Follow-ups in real-life practice are not as frequent or consistent as in clinical studies. Another limitation was cardiovascular risk factors such as BMI, smoking habits were not included in the study. In addition, rates of mild infections were not recorded, in contrast to recorded severe infections requiring hospitalization, due to the missing periodic appointments.

Although the number of participants was relatively small; signifying the data of efficacy and safety of TOFA in RA patients from Turkey and presentation of prospective 5-year follow-up findings, including COVID-19 history and its prognosis, were advantages of our study. Although there are studies with larger patient groups on TOFA, there are few studies showing 5-year results in which long-term outcomes such as malignancy are important. On the other hand, more female patients enrolled in the study, possibly due to female predominance in RA and higher disease activity in females.

Conclusion

Our study presents the results of real-life short and long-term data of patients who received TOFA therapy after bDMARD and/or csDMARD therapy. It was observed that the disease activity remained moderate to high in approximately half of the patients. The change in the disease activity, however, was consistent with good response in most patients. The rate of infections requiring hospitalization, malignancy, and HZ infection was similar to that reported in other studies. The drug survival rate was also consistent with those reported in other studies. Cardiovascular event or thromboembolism was not observed. In conclusion, TOFA is an effective and safe oral treatment option in RA.

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