ABSTRACT

Objective: To assess the real-life efficacy, retention rate and safety data of tofacitinib in rheumatoid arthritis (RA) patients.

Method: We analyzed all patients registered in the HURBIo database who received at least 1 dose of tofacitinib. Patients who received at least one dose included in retention analysis, with at least 1 control visit, were included in efficacy and safety analysis. Factors predicting good response at last follow-up visit were analyzed by the logistic regression analysis. Drug retention rates were calculated using the Kaplan-Meier method and predictors of drug retention was determined by Cox proportional hazard model. Adverse events, reasons of switching and discontinuation were also determined.

Results: 247 (210, 85.0% female) patients included in the study. Median duration of tofacitinib treatment was 10.2 (20.2) (med, (IQR)) months. 204 (82.6%) patients included in safety and efficacy analysis. 45.6% of patients was in low-disease activity (LDA) state (DAS28-CRP≤3.2). Predictors of LDA were being biologic-nave (aOR 2.53 (1.31-4.88); 95% CI) and RF negativity (aOR 2.14 (1.12-4.07); 95% CI). At 1 year, overall tofacitinib retention rate was 63.9% with no relevant predicting factor. Response and retention rates of tofacitinib were similar in patients with and without concomitant csDMARDs. Treatment failure was the most common cause of discontinuation. The most common infectious and laboratory adverse events were herpes zoster infection (3.9 per 100 patient-years) and elevation in ALT (x3UNL: 9.7 per 100 patient-years), respectively.

Conclusion: In conclusion, tofacitinib is an effective -as monotherapy or combination with csDMARDs- and well-tolerated treatment option in Turkish RA patients.
Keywords: Rheumatoid arthritis, tofacitinib, real-life, predictor

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated disease that characterized by systemic inflammation causing articular and extra-articular manifestations. Systemic inflammation is directly correlated with active disease and ongoing active disease may cause functional impairment, reduced quality of life, organ-system dysfunction and even death [1]. The main principal of RA treatment in the treatment of RA is to reach sustained remission or low disease activity (LDA) in every patient [2].

In the last 20 years, biologic agents re-designed the principles of RA management. Despite of the growing number of “biologic players”, there is still an unmet need in RA management. Approximately half of the patients did not respond sufficiently to conventional synthetic (cs) or biologic (b) disease modifying anti-rheumatic drugs (DMARD), revealing the need for alternative treatments [3].

Tofacitinib is an oral pan-Janus kinase (JAK) inhibitor. Phase II and III clinical trials revealed the efficacy of tofacitinib, either as a monotherapy or in combination with csDMARDs, in RA patients[4-7]. Comparative studies of tofacitinib and other bDMARDs resulted in similar efficacy and safety profiles[4,7-10]. Although the safety and efficacy have been evaluated in clinical trials, there is still need for real-life experience of tofacitinib to confirm its role in RA management.

In this study, our primary aim was to determine the real-life efficacy, retention rate and safety profile of tofacitinib in RA patients treated in our center.
METHODS

Study population

We conducted this retrospective longitudinal analysis with RA patients who received at least 1 dose of tofacitinib from March 2015 until the end of November 2019 and registered in the Hacettepe University biological database (HUR-BİO) which was settled in 2005 study [11]. Diagnosis of RA was established by treating physician with taking into account the history, physical examination, laboratory and imaging of the patients and all patients met the 1987 American College of Rheumatology (ACR) and/or 2010 European League Against Rheumatism (EULAR)/ACR classification criteria [12,13].

According to Turkish Social Security and Prescription rules, patients receiving biologic/targeted-synthetic DMARDs ought to be seen in every 3 months by treating physician, and by the aid of these regulations, many of the patients are in regular follow-up and we could identify whether the patients actually received the drug or not. If the patient had no control visit for 6 months after prescription, the treating physician made a constructed phone call with the patient or their relatives to confirm whether the patient received tofacitinib or not. A total of 275 RA patients were prescribed tofacitinib, 28 (10.2%) of them never received of tofacitinib. As a result, our main study population consisted from 247 patients who received at least 1 dose of tofacitinib.

Data collection

Demographic Data and Population Characteristics

We collected these following demographic data: gender, age, smoking history, body mass index (BMI), the frequency of hypertension and diabetes mellitus. Regarding RA, disease
duration rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) positivity, duration under tofacitinib, percentage of biologic naïve patients, distribution of previous bDMARDs in biologic-experienced group, concomitant DMARD [methotrexate (MTX), leflunomide (LEF), sulphasalazine (SLZ), hydroxychloroquine (HCQ)] and glucocorticoid (GC) use at last visit, baseline disease activity and functional status parameters [erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP) (mg/dl), tender and swollen joint count (28 joints), patient global-visual analogue scale assessment (VAS) (0-100mm) (PGA-VAS), disease activity score (DAS)28-ESR and health assessment questionnaire-disability index (HAQ-DI)] were recorded.

For main analyses, we grouped patients as “biologic-naïve vs biologic-experienced” and “tofacitinib monotherapy vs tofacitinib + concomitant csDMARDs”.

**Assessment of Efficacy**

Patients who had at least 1 control visit under tofacitinib and complete baseline disease activity data were included in efficacy analysis. To test the overall effectiveness of tofacitinib, we compared the ESR, CRP, PGA-VAS, tender and swollen joint counts, DAS28 and HAQ-DI scores at the visit just before the starting of tofacitinib and the last visit of the patient under tofacitinib therapy. As the physician global assessment has not been recorded in our database, we could not compare Clinical Disease Activity Index (CDAI) or Simple Disease Activity Index (SDAI) scores. Also, we had no missing values of DAS28 at last visits of patients, so, we decided to take this time point for comparison instead of 3rd or 6th mouth of therapy and adjusted the final model for duration of tofacitinib therapy. Patients were categorized into 4 according to DAS28 score at last follow-up visit: Remission (DAS28 ≤2.6), low (2.6-3.2), moderate (3.3-5.1), high (>5.1)[14]. Patients were
further grouped as “responder” or “non-responders” according to DAS28 at last follow-up visit: DAS28≤3.2: “Responders’’; DAS28>3.2: “Non-responders’. We also used the EULAR Response Criteria to assess efficacy of tofacitinib[15]. In this assessment, patients were categorized into 3 groups: “good response” (DAS28 improvement regarding baseline > 1.2 and DAS28 at last visit ≤3.2), “moderate response” (DAS28 improvement regarding baseline > 1.2 and DAS28 at last visit > 3.2 or DAS28 improvement regarding baseline > 0.6 to ≤1.2 and DAS28 at last visit ≤5.1) and “no response” (DAS28 improvement regarding baseline ≤ 0.6 irrespective from DAS28 at last visit or DAS28 improvement regarding baseline > 0.6 to ≤1.2 and DAS28 at last visit >5.1). Besides evaluating disease activity, HAQ-DI scores at first and last visits (calculated for patients with baseline HAQ-DI score>0.5) were compared to determine the effects of tofacitinib on functional status of patients. A minimal clinical difference of HAQ-DI score has been proposed as 0.22 (calculated for patients with baseline HAQ-DI score>0.5), and functional remission has been defined as HAQ-DI ≤ 0.5 in earlier studies[16,17]. We defined percentage of patients who met these definitions.

**Assessment of Retention Rate**

Patients who had at least 1 dose of tofacitinib were included into drug retention analysis. To calculate the drug retention more precisely, patients whom tofacitinib was prescribed and who have not had a control visit in following 6 months, they were considered in “ tofacitinib-continue group” if they had not prescribed another biologic treatment. Besides, if the patients have not had a control visit longer than 6 months and they had not prescribed tofacitinib by another institution, they were considered in “ tofacitinib-discontinue group”.
**Tofacitinib Discontinuation and Adverse Events**

Tofacitinib discontinuation and adverse event analysis were done over patients who had at least 1 control visit under tofacitinib and complete baseline data. Discontinuation rates and causes of discontinuation were analyzed for biologic- naïve and experienced groups.

For safety issues, adverse events attributable to tofacitinib (neutropenia (<1500/mm³), leukopenia (<4000/mm³), transaminitis (alanine aminotransferase (ALT) > 3 X UNL [upper normal limit, UNL = 40 IU/ml]), changes in lipid profile (calculated for patients who had baseline and follow-up values), herpes zoster (HZ) infection and infections other than HZ, hepatitis reactivation, tuberculosis, cancer) were analyzed. Adverse events other than laboratory abnormalities were calculated as “per 100 patient-years”.

Our study is compliant with the Helsinki Declaration and approved by Hacettepe University ethical committee (Approval number: GO 19/1088).

**Statistical analyses**

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 25.0; IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov, skewness and curtosis) to determine whether they are normally distributed or not. The data of descriptive analysis were expressed as either mean ± standard deviation (SD) or the median, interquartile range (IQR). Categorical variables were compared with the Chi-square test or Fisher’s exact test where appropriate. The Student-t test and Mann-Whitney U test was used to compare the normal and non-normally distributed continuous data between two groups, respectively.
The univariate effects of age, gender, disease duration, smoking history, BMI, history of biologic treatment, RF and CCP positivity, baseline ESR-CRP levels, status of concomitant DMARD and glucocorticoid use identified with univariate analyzes (p<0.20), were further entered the logistic regression analysis to determine independent predictors of “remission or low disease activity” based on DAS28 at last follow-up visit. Same method also used to determine independent predictors of “good EULAR response” at last follow-up visit. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit.

Possible factors (same factors tested for ‘remission or low disease activity’) on tofacitinib retention were investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. The possible factors identified with univariate analyzes (p<0.20) were further entered into the Cox regression analysis, with the backward selection, to determine independent predictors of tofacitinib retention. Among correlated factors with similar effects on tofacitinib retention, only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual (Schonfeld and Martingale) analysis.

Adverse events other than the lipid profile were estimated for 100 patient-years.

A 5% Type-I error level was used to infer statistical significance.

RESULTS

i. Study population and Patient Characteristics

A total of 247 patients included in the study. Mean age was 53.1±12.6 years and 210 (85.0%) of patients were female. Mean disease duration was 11.4 ± 8.0 years. Current smoking ratio was 25.5%. Hypertension, diabetes mellitus and obesity (BMI>30) were prevalent in 30.1%, 13.0%, 47.0% of patients, respectively. RF, anti-CCP, RF and/or anti-CCP positivity rates were
66.7%, 65.2% and 79.7%, respectively. Rate of concomitant synthetic DMARD and GC use, and disease activity parameters at first visit were similar between biologic-naïve and biologic-experienced groups. Details were given in Table 1.

Overall, 137 (55.5%) of patients were bDMARD- naïve. In bDMARD-experienced group (n=110, 44.5%), number of previous bDMARDs was (med, IQR) 3 (2-4). Of 110 patients, 44 (40.0%) had only anti TNF, 23 (20.9%) had only non-anti TNF and 43 (39.1%) had at least one anti TNF and non-anti TNF bDMARDs before tofacitinib. Distribution of former bDMARD therapies: 59 (53.6%) adalimumab, 51 (46.4%) etanercept, 45 (40.9%) abatacept, 41 (37.3%) tocilizumab, 27 (24.5%) certolizumab, 23 (20.9%) rituximab, 21 (19.1%) infliximab and 15 (16.6%) golimumab.

ii. **Tofacitinib efficacy and retention rate**

(a) **Efficacy**

Of 247 patients, 27 (10.9%) patients had missing first visit data and 16 (6.5%) did not have a first control visit yet by the date of data analysis. Patients with at least one control visit after the starting of tofacitinib and have complete baseline data (204, 82.6%) were included to further analyzes to compare the effectiveness of the drug (see Figure 1). Median follow up of these patients when they have been receiving tofacitinib was 11.6 (20.7) [med, (IQR)] months. Baseline vs. last follow-up visit values for these parameters as follows: ESR: 28 (29) vs. 22 (22); CRP: 1.2 (1.6) vs. 0.6 (0.8); SJC: 2 (4) vs. 0 (2); TJC: 5 (7) vs. 1 (5); PGA-VAS: 70 (30) vs. 50 (30); DAS28: 4.7±1.4 vs. 3.6±1.5; HAQ-DI: 1.02 (1.10) vs. 0.65 (1.01); p<0.001 for all parameters.

Distribution of patients into DAS-28 categories (remission, low, moderate, high) were 26.0%, 19.6%, 37.3% and 17.2%, respectively. The percentage of patients fitting in different
disease activity categories according to their concomitant DMARD use (monotherapy (±GCs) vs. combination) were similar. Details of patients distribution were given in Figure 2.

Overall, 45.6% of patients were in “responders” group and 54.4% of patients was in “non-responders” group. Predictors of response (DAS28-CRP≤3.2 at last follow-up visit) were determined by logistic regression analysis. Predictors of good response to tofacitinib were (in multivariate analysis, *adjusted for follow-up duration under tofacitinib, RA disease duration and baseline DAS-28 score*): *being biologic-naïve* (OR 2.53 (1.31-4.88); 95% CI) and *RF negativity* (OR 2.14 (1.12-4.07); 95% CI) (Table 2). Model fit was tested by Hosmer-Lemeshow test (p=0.46). Response (DAS28-CRP≤3.2) rates were 53.3% vs. 34.5% in biologic-naïve and biologic-experienced patients, respectively, 56.9% vs. 40.4% in RF negative and RF positive patients. Anti-CCP status or seropositivity status (RF and/or anti-CCP positivity or absence of both) were statistically insignificant when they entered into the model one by one instead of RF status.

According to EULAR response criteria, 45.6%, 22.1% and 32.4% of patients met the good, moderate and no response criteria, respectively, at last follow-up visit. Predictors of good EULAR response criteria were (in multivariate analysis, *adjusted for follow-up duration under tofacitinib, RA disease duration and baseline DAS-28 score*): *being biologic-naïve* (OR 2.70 (1.40-5.25); 95% CI) and *RF negativity* (OR 2.17 (1.13-4.16); 95% CI). Anti-CCP status or seropositivity status (RF and/or anti-CCP positivity or absence of both) were statistically insignificant when they entered into the model one by one instead of RF status. Model fit was tested by Hosmer-Lemeshow test (p=0.30).

At first visit, 26% of patients had HAQ-DI score ≤0.5, while 45% of patients had HAQ-DI score ≤0.5 at last follow-up visit (p<0.001). Mean difference of HAQ-DI scores and HAQ-DI drop
≥ 0.22 at last follow-up visit compared to the first visit were calculated for 150 (74%) patients who had baseline HAQ-DI score > 0.5. Mean difference was 0.40 (95% CI, 0.30-0.40, p<0.001) and HAQ-DI decrease ≥ 0.22 was valid for 83/150 (55.3%) patients.

(b) Retention

Tofacitinib retention rate was calculated over the whole study population (n=247, 100%). Median duration of tofacitinib treatment was 10.2 (20.2) (med,(IQR)) months and similar among biologic-naïve and biologic-experienced groups. At 1 year, overall tofacitinib retention rate was 63.9% (Figure 3A). Median tofacitinib retention was 24.9 (16) (med,(IQR)) months. Unadjusted tofacitinib retention rates were similar in patients receiving tofacitinib as monotherapy (±GCs) or combination with DMARDs (1-year retention: monotherapy (±GCs) vs. combination: 59.7% vs. 64.8%, p=0.76, Figure 3B). Unadjusted tofacitinib retention rates were similar in bDMARD-naïve and experienced patients (1-year retention: bDMARD-naïve vs. bDMARD-experienced: 59.6% vs. 65.2%, p=0.26, Figure 3C). In multivariate analysis, we found no relevant factor predicting better tofacitinib retention.

iii- Tofacitinib discontinuation and adverse events attributable to tofacitinib

Tofacitinib was discontinued in 86 (42.2%) of 204 patients; discontinuation rates were similar for biologic-naïve and biologic-experienced groups (38.3% vs. 47.7%, respectively; p=0.23, log-rank). Treatment failure (primary and secondary) was the most common cause of discontinuation and seen in similar rates among biologic-naïve and biologic experienced groups (primary:36.9% vs. 32.5%, secondary: 21.9 vs. 17.5%, total: 58.8% vs. 50.0%, respectively). Rates of adverse events causing treatment discontinuation were 10.8% and 20% among biologic-naïve and experienced groups, respectively, and the difference was not statistically significant (p=0.28).
These adverse events were; in biologic-naïve group: 2 allergic skin reaction, 1 coronary artery disease, 1 gastrointestinal bleeding, 1 knee prosthesis infection and in biologic-experienced group: 4 allergic skin reaction, 1 urinary tract infection, 1 pneumonia, 1 leukopenia, 1 herpes zoster. Details of therapy switch were given in Figure 1.

The most common laboratory abnormality during the treatment course was elevation in ALT (>3xUNL: 9.7 per 100 patient-years). Leukopenia was prevalent in 2% of patients, severe leukopenia causing drug cessation was seen in 1 patient. Neutropenia was seen in 0.5% of patients, and it was not severe to cause tofacitinib cessation. Lipid profile at beginning of tofacitinib and last follow-up visit under tofacitinib was available for 37 patients. HDL levels were higher in the last follow-up visit compared to the beginning of tofacitinib in significant levels (p=0.03); LDL, total cholesterol and triglyceride levels were similar. Incidence rates for herpes zoster and other infections were 3.9 (11 patients) and 1.4 (4 patients) per 100 patient-years, respectively. All HZ cases were monophasic and one of 11 (9.1%) patients discontinued tofacitinib. 3 of 4 patients who had hospitalization-requiring infections discontinued tofacitinib. Details of adverse events that can be attributed to tofacitinib were given in Table 3.

DISCUSSION

In this study, we reported the real-life efficacy, drug retention and safety of tofacitinib in Turkish RA patients. Low disease activity (DAS-28 ≤ 3.2) was achieved in 45.6% of patients at last follow-up visit, in addition, being biologic-naive and absence of RF were the independent predictors of low disease activity. At 1 year, overall tofacitinib retention rate was 63.9%. Disease
activity at last follow-up visit and tofacitinib retention were similar in patients receiving tofacitinib as monotherapy or combination with csDMARDs. Rate and distribution of adverse events were similar to current literature.

Real-life data of JAK kinase inhibitors such as tofacitinib in RA is growing. Remission and LDA with tofacitinib has been studied largely in clinical trials [4,10,18-20]. Long-term extension (LTE) studies of phase-3 randomized clinical trials of tofacitinib make up the main body of real-life tofacitinib evidence. One of the largest of LTE studies was the ORAL Sequel LTE study that includes 4290 patients. In this study, LDA (DAS28 ≤ 3.2) rate was 46.8% at the end of 96th month [21]. A recent study from Switzerland, low-disease activity (DAS28 ≤ 3.2) was achieved by 58.2% of 144 RA patients on tofacitinib after 1.2-years follow up [22]. These data are in line with our study and the efficacy of tofacitinib also demonstrated in small observational studies [23-25]. Besides its efficacy on disease activity, it was also shown in clinical trials that tofacitinib improves functional status of RA patients. In this present study, mean HAQ-DI difference was 0.40 HAQ-DI decrease ≥ 0.22 was valid for 55.3% of patients. These improvements were in parallel with the LTE studies of tofacitinib [21]. We found that being biologic-naive and absence of rheumatoid factor were independent predictors of good response to tofacitinib after adjusting for disease duration and baseline disease activity. Previous biologic agent use had a 4.5 times higher risk of nonresponse to tofacitinib in a prospective observational study from Japan including 113 RA [26], similar association was also demonstrated by different studies [22]. Effects of serologic status on the treatment outcomes have been studies in LTE studies of tofacitinib RCTs. In that analysis, response rates were higher in seropositive patients compared to seronegative patients (response rates: anti-CCP+/RF+ > anti-CCP-/RF-, anti-CCP+/RF- > anti-CCP-/RF-, anti-CCP-/RF+ > anti-CCP-
However, this association has not been fully approved in real-life data. Similar to our study, there was no difference of anti-CCP positivity among responders and non-responders in studies by Mori, Iwamoto, Mueller and colleagues. Mori and colleagues did not report RF status, the others reported no relationship between RF status and response rates [19,22,26]. Also, there is conflicting data regarding the RF status and response to TNF inhibitors. Some of these studies suggesting that the RF positivity is a risk factor for poor response to TNF inhibitors [28-32]. Data regarding the link between serologic status and response to tofacitinib is scant and conflicting. Further studies are needed to enlighten the mechanism and clinical application of this link.

Overall tofacitinib retention rate at 1 year was 63.9%. This rate was similar across other tofacitinib real-life data [22,25], however, slightly lower than the retention rate of anti-TNF agents [33]. For tofacitinib, being a late player in the field of RA may be an explanation of these reduced retention. However, when anti-TNF agents were compared with tofacitinib when all the treatments were started in the same time period, retention rates were similar. Even higher for tofacitinib when the adjustments for potential confounders were done [25]. We found no predictor of better tofacitinib including the status of previous biologic DMARD use and using tofacitinib as monotherapy or combination with csDMARDs. However, a real-life data from Israel reported inverse relationship between the number of previous bDMARDs and tofacitinib retention -similar to anti-TNF agents- and they found no other relevant factors [34,35].

We found a similar response and retention rates of tofacitinib in patients with and without concomitant csDMARDs. There are many studies demonstrating efficacy and safety of tofacitinib monotherapy. The ORAL Solo trial showed the efficacy of tofacitinib monotherapy in reducing RA signs and symptoms and improving physical function in patients with inadequate
response to disease-modifying drugs [5]. In ORAL Standard trial, tofacitinib add-on to methotrexate was superior to adalimumab add-on to methotrexate therapy [8]. The results of ORAL Strategy trial for tofacitinib monotherapy were defined statistically inconclusive because non-inferiority of tofacitinib 5mg b.i.d. to either adalimumab and MTX or tofacitinib and MTX was not shown [10]. Concomitant csDMARDs were found to be required for optimal treatment results for TNFi but not for tofacitinib and non-TNFi in SCQM cohort [25]. A systematic review and meta-analyses showed that tofacitinib monotherapy was neither statistically no clinically different from TNF inhibitors in efficacy [36,37]. In addition, we noticed that our csDMARD strategies were different from literature. Leflunomide (LEF) and hydroxychloroquine (HCQ) utilization rates were higher in present data. For instance, Mueller and colleagues reported LEF and HCQ rates were 17.3% and 7.6%, respectively, in their cohort [22]. Also, participants of ORAL Solo trial were allowed to use HCQ, and the rate was 18.5% [5]. Although cohort is relatively small to conclude it, LEF seems an important player just behind MTX. Also, further assessments are needed if there was a possible cardiovascular protective contribution of HCQ to neutralize cardiovascular adverse effects. Prospective, large-scaled studies are needed to reveal these important points.

23% of our patients discontinued tofacitinib due to ineffectiveness. Clinical trials or their LTE studies did not report clearly on this issue. A recent real-life data reported thr drug discontinuation rate due to the ineffectiveness as 15.9% [22]. This rate is a bit lower than ours, however differences of these two cohorts regarding demographics, disease and treatment characteristics may explain this discrepancy.

Safety profile including infections and laboratory anomalies of our cohort is consistent with the current literature [21,22,38,39]. We had no HBV reactivation and tuberculosis, which
may be due to the strict surveillance and prophylaxis regimen of Turkey. None of the patient had a cancer diagnosis under tofacitinib, however, follow-up duration was not enough to take a decision. Herpes zoster was the most common infection in our cohort. We found a HZ incidence rate similar to that reported from USA and global data; however, we found a lower incidence rate that reported from far East Asia [38]. Most of the patients had HZ in only one dermatome (92%), and 8% of patients with HZ discontinued tofacitinib permanently, similar to current study [21,40].

The main limitation of our study was its one-centre design. Our results should be validated in larger and multicenter studies. We could not test the cardiovascular risk of tofacitinib properly. Besides, we did not examine the effect of tofacitinib on radiographic progression. Also, as we could not clearly assess the drug compliance of the patients (eg. we accepted the patients with control visit within 6 months in “tofacitinib-continue group” but the patients might step-down to csDMARDs without informing the treating physician, patients might use the drug irregularly) and these issues may cause under/over estimation of drug retention. However, with 3-month regular follow-up regulation of our Social Security System has been minimized the bias caused by the 6-month cut-off.

In conclusion, tofacitinib is an effective -as monotherapy or combination with csDMARDs- and well-tolerated treatment option in Turkish RA patients. Safety profile is consistent with current literature.

**Funding:** None
REFERENCES


Table 1. Demographic and baseline disease characteristics of all patients, comparison of these variables among biologic-naïve and experienced patients

<table>
<thead>
<tr>
<th>Variables*</th>
<th>All patients (n=247)</th>
<th>Biologic-naïve (n=137, 55.5%)</th>
<th>Biologic-experienced (n=110, 44.5%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>210 (85.0)</td>
<td>116 (84.7)</td>
<td>94 (85.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>53.1±12.6</td>
<td>53.7±12.9</td>
<td>52.3±12.3</td>
<td>0.37</td>
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<tr>
<td>Disease duration, years (mean ± SD)</td>
<td>11.4 ± 8.0</td>
<td>9.5 ± 7.5</td>
<td>13.6 ± 8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Current smoker</td>
<td>63 (25.5)</td>
<td>31 (22.6)</td>
<td>32 (29.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>- Ex-smoker or never smoked</td>
<td>184 (74.5)</td>
<td>106 (77.4)</td>
<td>78 (70.9)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>116 (47.0)</td>
<td>63 (46.0)</td>
<td>53 (48.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (30.1)</td>
<td>38 (27.7)</td>
<td>36 (33.0)</td>
<td>0.36</td>
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<td>Diabetes</td>
<td>32 (13.0)</td>
<td>17 (12.4)</td>
<td>15 (13.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Positive RF (n=240)</td>
<td>160 (66.7)</td>
<td>93 (69.4)</td>
<td>67 (63.2)</td>
<td>0.31</td>
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<tr>
<td>Positive CCP (n=207)</td>
<td>135 (65.2)</td>
<td>81 (71.1)</td>
<td>54 (58.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Positive RF or CCP (n=236)</td>
<td>188 (79.7)</td>
<td>111 (83.5)</td>
<td>77 (74.8)</td>
<td>0.10</td>
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<td>Duration under Tofacitinib, months (med, IQR)</td>
<td>10.2 (20.2)</td>
<td>10.9 (19.8)</td>
<td>9.5 (16.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Monotherapy (±GC) (at last visit)</td>
<td>41 (16.6)</td>
<td>21 (15.3)</td>
<td>20 (18.2)</td>
<td>0.55</td>
</tr>
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<td>Glucocorticoids (at last visit)</td>
<td>182 (73.7)</td>
<td>106 (77.4)</td>
<td>76 (69.1)</td>
<td>0.15</td>
</tr>
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<td>Combination with at least one csDMARD (at last visit)</td>
<td>206 (83.4)</td>
<td>116 (84.7)</td>
<td>90 (81.8)</td>
<td>0.54</td>
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<td>- Methotrexate</td>
<td>61 (24.7)</td>
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<td>26 (23.6)</td>
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<tr>
<td>- Leflunomide</td>
<td>70 (28.9)</td>
<td>32 (23.4)</td>
<td>38 (34.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>- Sulphasalazine</td>
<td>9 (3.7)</td>
<td>4 (2.9)</td>
<td>5 (4.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>- Hydroxychloroquine</td>
<td>135 (55.8)</td>
<td>83 (60.6)</td>
<td>52 (47.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Disease activity (at first visit) (n=220)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ESR</td>
<td>27 (28)</td>
<td>26 (27)</td>
<td>28 (30)</td>
<td>0.91</td>
</tr>
<tr>
<td>- CRP</td>
<td>1.3 (1.5)</td>
<td>1.2 (1.4)</td>
<td>1.3 (1.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>- Tender joint count</td>
<td>4 (7)</td>
<td>4 (6)</td>
<td>4 (7)</td>
<td>0.64</td>
</tr>
<tr>
<td>- Swollen joint count</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>70 (30)</td>
<td>70 (30)</td>
<td>70 (30)</td>
<td>0.75</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Patient VAS global</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DAS28</strong></td>
<td>4.7±1.4</td>
<td>4.6±1.4</td>
<td>4.6±1.3</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>HAQ</strong></td>
<td>1.05 (1.15)</td>
<td>0.95 (1.10)</td>
<td>1.15 (1.05)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* n(%), if otherwise specified

BMI: Body mass index, CCP: Cyclic-citrullinated peptide, csDMARD: Conventional Synthetic Disease Modifying Antirheumatic Drugs, CRP: C-reactive protein, DAS28: Disease Activity Score-28, ESR: Erythrocyte sedimentation rate, GC: Glucocorticoids, HAQ: Health Assessment Questionnaire, IQR: Interquartile range, RF: Rheumatoid factor, TOFA: Tofaicitinib, VAS: Visual analogue scale,
Table 2. Predictors of good response* to tofacitinib

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analyses</th>
<th>Multivariate Analysis †,‡</th>
<th>Final Multivariate Model †,§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Adjusted Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>1.98 (0.90-4.36)</td>
<td>1.42 (0.57-3.58)</td>
<td>2.53 (1.31-4.88)</td>
</tr>
<tr>
<td>Smoking (Current vs. ex-never)</td>
<td>0.97 (0.51-1.84)</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (&gt;25 vs. &lt;25)</td>
<td>1.27 (0.66-2.41)</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>History of biologic treatment (naïve vs. experienced)</td>
<td>2.17 (1.22-3.85)</td>
<td>2.44 (1.22-4.87)</td>
<td>2.14 (1.12-4.07)</td>
</tr>
<tr>
<td>Rheumatoid factor (negative vs. positive)</td>
<td>1.94 (1.07-3.54)</td>
<td>1.89 (0.97-3.70)</td>
<td>0.062</td>
</tr>
<tr>
<td>Anti-CCP antibody (negative vs. positive)</td>
<td>1.41 (0.74-2.67)</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Baseline ESR (&gt;20 mm/h vs. normal)</td>
<td>0.61 (0.33-1.12)</td>
<td>0.87 (0.42-1.83)</td>
<td>0.73</td>
</tr>
<tr>
<td>Baseline C-reactive protein (&gt;0.8 mg/dl vs. normal)</td>
<td>0.74 (0.41-1.35)</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Concomitant csDMARD (yes vs. no)</td>
<td>1.04 (0.51-2.11)</td>
<td></td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Good response means DAS28≤3.2 at last follow-up visit.
†Adjusted for follow-up duration under tofacitinib, RA disease duration and baseline DAS-28 score;
‡Variables with p<0.20 in univariate analyses were included. This is the baseline model.
§Logistic regression with backward LR
Table 3. Adverse events attributable to Tofacitinib

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia (&lt;4000 / mm$^3$)*</td>
<td>5.7</td>
</tr>
<tr>
<td>Neutropenia (&lt;1500 / mm$^3$)*</td>
<td>1.4</td>
</tr>
<tr>
<td>ALT &gt; 3 X UNL*</td>
<td>9.7</td>
</tr>
<tr>
<td>Lipid profile (med, Q1-4) (n=37)</td>
<td></td>
</tr>
<tr>
<td>- Total cholesterol</td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>213 (192-243)</td>
<td>232 (193-261)</td>
</tr>
<tr>
<td>- LDL</td>
<td></td>
</tr>
<tr>
<td>138 (123-156)</td>
<td>145 (120-167)</td>
</tr>
<tr>
<td>- HDL</td>
<td></td>
</tr>
<tr>
<td>57 (46-71)</td>
<td>64 (53-73)</td>
</tr>
<tr>
<td>- Triglyceride</td>
<td></td>
</tr>
<tr>
<td>129 (99-187)</td>
<td>136 (104-177)</td>
</tr>
<tr>
<td>Allergic reactions/rash*</td>
<td>3.2</td>
</tr>
<tr>
<td>Herpes Zoster*</td>
<td>3.9</td>
</tr>
<tr>
<td>Tuberculosis*</td>
<td>0</td>
</tr>
<tr>
<td>HBV reactivation*</td>
<td>0</td>
</tr>
<tr>
<td>Other infections*†</td>
<td>1.4</td>
</tr>
<tr>
<td>Diverticulitis*</td>
<td>0</td>
</tr>
<tr>
<td>Cancer*</td>
<td>0</td>
</tr>
</tbody>
</table>

*per 100 patient-years
† Requires hospitalization: 2 pneumonia, 1 knee prosthesis infection, 1 urinary tract infection

ALT: Alanine aminotransferase, HBV: Hepatitis B virus, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, UNL: Upper normal limit,
Figure 1. Flow chart of patient enrollment, causes of discontinuation

TOFA prescribed
n= 275

Never received TOFA
n= 28 (10.1%)

Patients ever received TOFA
n= 247 (100%)

Patients with missing first visit data: n= 27 (10.9%)

Patients without first control visit:
 n= 16 (6.5%)

Biologic-experienced
n= 84 (41.2%)

Biologic-naive
n= 120 (58.8%)

Median follow-up: 12.7 (5.5-26.2)

Median follow-up: 11.1 (4.2-25.4)

74 (61.7%) patients continued TOFA

46 (39.3%) patients discontinued TOFA
33 (27.5%) switched to another biologic
13 (10.85) discontinued permanently

- Primary failure: 17 (36.9)
- Secondary failure: 10 (21.9)
- Patients preference: 8 (17.5)
- Adverse events: 5 (10.8)
  - Allergic reaction/rash: 2 (4.3)
  - Coronary artery disease: 1 (2.1)
  - Gastrointestinal bleeding: 1 (2.1)
  - Knee prosthesis infection: 1 (2.1)
  - Unknown: 3 (6.5)
  - De-escalation to csDMARDs: 2 (4.3)
  - Pregnancy plan: 1 (2.1)

44 (52.3%) patients continued with TOFA

40 (47.6%) patients discontinued TOFA
34 (40.4%) switched to another biologic
6 (7.2%) discontinued permanently

- Primary failure: 13 (32.5)
- Secondary failure: 7 (17.5)
- Adverse events: 8 (20.0)
  - Allergic reaction/rash: 4 (10)
  - Leukopenia: 1 (2.5)
  - Urinary tract infection: 1 (2.5)
  - Herpes: 1 (2.5)
  - Pneumonia: 1 (2.5)
  - Unknown: 6 (15.0)
  - Patients’ preference: 5 (12.5)
  - Pregnancy: 1 (2.5)
Figure 2. Percentages of patients in four DAS-28 categories according to DAS-28 score at last follow-up visit. Left side represents overall group, right side represents data according to concomitant csDMARD use at last follow-up visit (Tofacitinib ± glucocorticoids vs. Tofacitinib + DMARDs ± glucocorticoids)
Figure 3. Retention analysis of tofacitinib (by Kaplan-Meier and log-rank comparison) A) Unadjusted tofacitinib retention in rheumatoid arthritis patients B) Unadjusted tofacitinib retention according to concomitant csDMARD use (Tofacitinib ± glucocorticoids vs. Tofacitinib + DMARDs ± glucocorticoids) C) Unadjusted tofacitinib retention according to concomitant previous biologic DMARD use