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ORIGINAL ARTICLE

Comparison of the safety profile of tofacitinib and etanercept in rheumatoid arthritis patients aged 60 years and over: The real-life data from the HUR-BIO registry

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ABSTRACT

Objective: To investigate the safety profile of tofacitinib in rheumatoid arthritis (RA) patients aged 60 and over and to compare these findings with etanercept.

Materials and methods: HUR-BIO (Hacettepe University Rheumatology Biologic Registry) is a single-center registry for biological and targeted synthetic DMARDs since 2005. We included RA patients aged ≥ 60 years who were prescribed tofacitinib or etanercept as their first bDMARD or tsDMARD and had at least one control visit. MACE (major adverse cardiovascular event), VTE (venous thromboembolism), malignancy, herpes zoster, and infections requiring hospitalization were recorded for the safety profile. Incidence rate (IR) and incidence rate ratios (IRR) per 1000 patient years were calculated for all safety data.

Results: This study consisted of 123 RA patients (tofacitinib n=70, etanercept n=53). In the overall population, the mean age was 67.9 ± 6.2 years and the median follow-up period was 2.1 years. Among the traditional cardiovascular risk factors, smoking history and hyperlipidemia were more common in the tofacitinib group. The IRR per 1000 patients years for MACE, herpes zoster, and infections requiring hospitalization was similar between the groups. All three patients who diagnosed with DVT or PE were in the tofacitinib group, and the significance level of the increase in IR was close to the statistical threshold (p=0.057). There was only one patient who developed non-melanoma skin cancer, and that patient was in the tofacitinib group.

Conclusion: The incidence of MACE, herpes zoster, and infections requiring hospitalization was comparable between tofacitinib and etanercept. However, the occurrence of VTE exclusively in the tofacitinib group suggests that this issue needs careful evaluation for these patients.

Keywords: tofacitinib, rheumatoid arthritis, safety profile.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that predominantly affects peripheral joints by targeting synovial tissues [1]. Modern treatment guides recommend adding biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic (ts) DMARDs in patients whose treatment goal is not accomplished with conventional synthetic DMARDs (csDMARDs) [2, 3]. However, the findings of the ORAL Surveillance research have caused some concerns about the safety profile of tofacitinib, one of the tsDMARDs [4].

Tofacitinib is known a pan-JAK inhibitor that inhibits the JAK family, which plays a pivotal role in inflammation by participating intracellular signal transduction. JAK inhibitors suppress inflammatory mediators by inhibiting the autophosphorylation and activation of JAK [5]. The United States Food and Drug Administration (FDA) approved tofacitinib for the treatment of moderate-to-severe RA patients in 2012, and the European Medicines Agency (EMA) authorized it in 2017 [6]. In Turkey, it was approved by the Ministry of Health in 2015 and subsequently implemented.

Although there are no discuss about the effectiveness of tofacitinib, concerns about safety have increased significantly. The FDA's post-marketing safety study in 2019 stated that the incidence of pulmonary embolism and all-cause death in the tofacitinib 10 mg group was higher than in the TNF inhibitor (TNFi) group [7]. Then, the ORAL Surveillance trial displayed that the risk of malignancy and major adverse cardiovascular events (MACE) was increased in the tofacitinib group among RA patients aged 50 and over who had at least one cardiovascular risk factor. Moreover, the incidences of opportunistic infections and all herpes zoster infections were higher in this group [4]. Therefore, the European Alliance of Associations for Rheumatology (EULAR 2022) update prioritized the use of bDMARDs in patients who have failed csDMARDs. It was stated that relevant risk factors should be taken notice when prescribing JAK inhibitors [8].

Following the ORAL Surveillance trial, many researches containing safety data of tofacitinib were published [9-14]. Assumed the augmented risk of adverse events (AEs) in elderly patients, our study aimed to examine safety profile in RA patients aged 60 and over who were using tofacitinib, and to compare with those in patients who were using etanercept as their first bDMARD.

MATERIALS AND METHODS

This study was a observational cohort study of prospectively registered RA patients from the Hacettepe University Rheumatology (HUR-BIO) database, conducted at a primary referral center in central Türkiye. In the HUR-BIO database, established in 2005, patient data are recorded distinctly for each patient and there are no repeat patient records [15]. RA was diagnosed regarding to the doctor desicion and/or 2010 EULAR/ACR criteria [16]. We screened RA patients who received tofacitinib or etanercept as first b/tsDMARDs and had at least one visit from the date it became available in Türkiye until January 2022. The exclusion criteria for the study were being under 60 years of age, having used another bDMARD or tsDMARD before the use of tofacitinib/etanercept, not attending any visits after the prescription of tofacitinib/etanercept, and being unable to reach patients who did not attend their routine follow-ups by phone. Our study was performed according to the Helsinki Declaration and approved by the Ethical Committee (Number: GO 21/1251).

All data were performed from the HUR-BIO database. Patients with at least one visit who did not attend their follow-up visits were contacted by the physician via phone to inquire about their continuation of the medication and any AEs. With the patients' consent, information obtained from the Turkish Ministry of Health National Electronic Database, E-pulse was utilized to check for the presence of metabolic comorbidities and AEs. The demographic data and disease features included gender, age, body mass index (BMI), smoking status, disease duration, follow-up time, seropositivity status, accompanying DMARD usage (methotrexate or leflunomide), current prednisolone dose, disease activity score (DAS)-28, and health assessment questionnaire-disability index (HAQ-DI).

Safety outcomes contained MACE, malignancies (excluding non-melanoma skin cancer [NMSC]),

NMSC, venous thromboembolism (VTE), herpes zoster, and all infections requiring hospitalization. Adjudicated MACE was described as myocardial infarction (MI), stroke, and/or cardiovascular death after 60 days of drug exposure and within 28 days after drug discontinuation. Cardiovascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, low HDL level) and coronary artery disease at an early age in first-degree relatives were also recorded. All safety profile data were investigated during the period of drug exposure.

Statistical analysis

Statistical analyses were performed using SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA). Both visual methods (histogram, probability plots) and analytical techniques (Kolmogorov-Smirnov, skewness, and kurtosis) were employed to assess the normality of variable distributions. For continuous data, either the median (interquartile range, IQR) or the mean (standard deviation, SD) was reported, while categorical data were presented as percentages. Categorical variables were examined using the Chi-square or Fisher's exact test, and continuous variables were evaluated using the Mann-Whitney U test or Student's T test. Incidence rates (IR) and incidence rate ratios (IRR) per 1000 patient-years were calculated for all safety data. Drug retention rates were analyzed with the log-rank test, and Kaplan-Meier survival estimates were generated. A p value of less than 0.05 was deemed statistically significant.

RESULTS

A total of 123 patients were included in this study. In the overall population, the mean age was 67.9 ± 6.2 years and 96 (78.0%) patients were female. The median (IQR) disease duration was 13 (12) years and the median (IQR) follow-up duration under tofacitinib or etanercept was 27 (45) months. The treatment of 72 (58.5%) patients receiving tofacitinib or etanercept was discontinued for various causes. The most frequent causes for discontination the drug were: secondary failure (n=25), primary failure (n=14), patient's preference (n=9) and allergic reaction/rash (n=6). The mean baseline DAS-28 (ESR) score of patients was 4.8 ± 1.2 and the rate of concomitant methotrexate (MTX) or leflunomide (LEF) usage was 57.7%. There was no distinction between the groups in terms of age, gender, and BMI. Ever smoking condition was more common in the tofacitinib group (47.1% vs 24.5%, p=0.010). While the median disease duration was longer in the etanercept group (18 years vs 10.5 years, p<0.001), the median duration under tofacitib or etanercept use was similar. In the tofacitinib group, 55.7% of patients continued treatment; this rate was significantly higher than the etanercept group (55.7% vs 22.6%, p<0.001). Additionally, both the mean baseline DAS-28 (ESR) score (4.6 vs 5, p=0.021) and the rate of concomitant MTX or LEF use (48.6% vs 84.1%, p<0.001) were lower in this group (Table 1).

Comorbidities and safety outcomes of the groups were displayed in table 2. Hyperlipidemia (58.6% vs 25%, p<0.001) was significantly higher in the tofacitinib group, whereas the distribution of metabolic comorbidities such as hypertension, diabetes mellitus, and obesity was similar for both groups. The results for safety data were as follows: coronary heart disease (CHD) (n=7), cerebrovascular disease (CVD) (n=2), NMSC (n=1), VTE (n=3), herpes zoster (n=8), and infection requiring hospitalization (n=9). One patient who developed NMSC was in the tofacitinib group and her diagnosis was squamous cell carcinoma (SCC) of the skin. The time from tofacitinib initiation to SCC development was 18 months. In the tofacitinib group, one patient was diagnosed with DVT and 2 patients were diagnosed with PE. Tofacitinib exposure durations were 63 months, 15 months, and 4 months, respectively. Reasons for hospitalization were pneumonia (n=3), COVID-19 disease (n=3), gastrointestinal infection (n=2) and soft tissue infection (n=1). Six patients deceased under the medication. The reason of death of the patient in the etanercept group was CVD, the cause of death of one of the 5 patients in the tofacitinib group was pneumonia, and the others was unknown.

For drug retention, survival rates of the tofacitinib and etanercept was similar in our study population (log rank, p=0.194) (Figure 1). The IRR per 1000 patients years for MACE was not different between the groups [IRR:0.8 (0.07–7.01), p=0.837]. One of the 2 patients in the tofacitinib group had MI (smoking and hyperlipidemia history) and the other had CVD (smoking and hypertansion history). One of the 3 patients in the etanercept group died due to CVD. Two others had experienced MI; one had

Table 1. Comparison of the demographic and disease characteristics of tofacitinib and etanercept groups

Variables*	Tofacitinib (n=70)	Etanercept (n=53)	p
Age (mean, SD)	67.5 (6.3)	68.5 (6)	0.387
Gender (female)	59 (84.3)	37 (69.8)	0.055
BMI (kg/m^2)	28.9 (8)	30.1 (8.1)	0.446
Smoking status			
- Ever smoker	33 (47.1)	13 (24.5)	**0.010**
- Never smoker	37 (52.9)	40 (75.5)	
Disease duration, years	10.5 (11)	18 (13)	**<0.001**
Duration under tofacitinib or etanercept, months	25 (30.5)	26.5 (57.2)	0.341
Total follow-up time, months	37.5 (30.2)	105 (68.5)	**<0.001**
Current tofacitinib or etanercept status			
- Ongoing	39 (55.7)	12 (22.6)	**<0.001**
- Discontinued	31 (44.3)	41 (77.4)	
RF and/or anti-CCP positivity	58 (82.9)	38 (73.1)	0.192
Glucocorticoids use at last visit	49 (74.2)	26 (59.1)	0.095
Glucocorticoids dose at last visit	5 (5)	2.5 (5)	0.110
Concomitant MTX or LEF use	34 (48.6)	37 (84.1)	**<0.001**
Baseline DAS-28 (ESR) (mean, SD)	4.6 (1.3)	5 (1.1)	**0.021**
Baseline HAQ-DI (mean, SD)	1 (0.7)	1.1 (0.7)	0.440

*n (%) for categorical values and median (IQR) for numeric values, if not otherwise specified

BMI: Body mass index, CCP: cyclic-citrulinated peptide, DAS28: disease activity score 28, ESR: erythrocyte sedimentation rate, HAQ: health assessment questionnaire, IQR: interquartile range, MTX: Methotrexate, LEF: Leflunomide, RF: rheumatoid factor, SD: Standart derivation.

Table 2. Comorbidities and safety outcomes of tofacitinib and etanercept groups

Variables*	Tofacitinib (n=70)	Etanercept (n=53)	p
Hypertension	40 (57.1)	26 (51)	0.501
Diabetes mellitus	15 (21.4)	10 (21.7)	0.968
BMI ≥30 kg/m^2	29 (42)	27 (50.9)	0.327
Hyperlipidemia	41 (58.6)	11 (25)	<0.001
HDL level (<40 mg/dl)	2/62 (3.2)	1/16 (6.2)	0.617
Family history of early CHD	8 (11.9)	4 (8.5)	0.557
CHD	3 (4.4)	4 (7.5)	0.464
Myocardial infarction	1 (1.5)	2 (3.8)	0.581
Cerebrovascular disease	1 (1.9)	1 (1.5)	0.999
NMSC	1 (1.4)	0	NA
Family history for cancer	11 (16.2)	12 (27.9)	0.137
DVT or PE	3 (4.5)	0	NA
Herpes zoster	4 (5.9)	4 (9.1)	0.521
Infection requiring hospitalization	6 (8.8)	3 (6.7)	0.678
Exitus	5 (7.1)	1 (1.9)	0.327

*n (%) for categorical values

BMI: Body mass index, CHD: Coronary heart disease, DVT: Deep vein thrombosis, HDL: High density lipoprotein, NMSC: Non-melonom skin cancer, PE: Pulmonary embolism

only hypertension as a risk factor, while the other had risk factors including smoking, hypertension, diabetes mellitus, and hyperlipidemia. Similar to MACE, the IRR for herpes zoster and infection displayed no significant difference between the groups [herpes zoster IRR:1.2 (0.22–6.46), p=0.798; infections IRR:2.4 (0.51-14.89), p=0.223]. All three patients who developed DVT or PE were in the tofacitinib group, and the significance level of the increase in IRR was close to the statistical threshold (p=0.057) (Table 3).

Table 3. Incidence rate and incidence rate ratios for safety outcomes of tofacitinib and etanercept groups

	Tofacitinib (n=70)		Etanercept (n=53)			
	n	IR (95% CI	n	IR (95% CI)	IRR (95% CI)	P value for IRR
MACE	2	12 (1.46-43.55)	3	15 (3.09-43.528)	0.8 (0.07-7.01)	0.837
NMSC	1	6 (0.15-33.56)	0	0	NA	0.272
DVT or PE	3	18.1 (3.73-52.81)	0	0	NA	0.057
Herpes zoster	4	24.1 (6.57-61.7)	4	20 (5.45-51.21)	1.2 (0.22-6.46)	0.798
Infection requiring hospitalization	6	36.1 (13.26-78.67)	3	15 (3.09-43.84)	0.51-14.89	0.223

IR: Incidence rate and IRR: Incidence rate ratios were calculated per 1000 patient years. DVT: Deep vein thrombosis, MACE: major adverse cardiovascular event; NA: not applicable, NMSC: Non-melonom skin cancer, PE: Pulmonary embolism

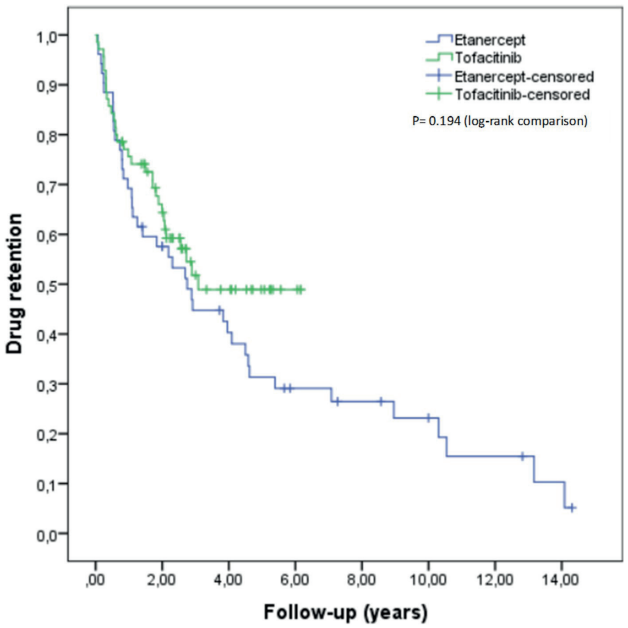

Figure 1. Kaplan–Meier analysis of tofacitinib and etanercept for drug retention

DISCUSSION

In this study, we compared the real-world safety data of tofacitinib and etanercept as the first bDMARD/tsDMARD used in RA patients aged 60 and over. Although the presence of smoking history and hyperlipidemia was more common in the tofacitinib group, we found the risk of MACE to be similar in both groups through a median follow-up time of 25 months. Additionally, the risk of herpes zoster and infections requiring hospitalization were not distinct between the groups. One patient who developed non-melanom skin cancer and three patients who diagnosed VTE were in the tofacitinib group.

Patients with RA have an elevated risk of cardiovascular disease compared to the general population. This increased risk is attributed not only to traditional risk factors but also to endothelial dysfunction related to the inflammation and the medications used in treatment, particularly glucocorticoids [17, 18]. A study conducted on RA patients who experienced MI demonstrated that cardiovascular risk increased in association with both the current and the cumulative glucocorticoid dose [19]. Therefore, current guidelines for RA treatment advise administering the minimal effective dose of glucocorticoids for the shortest feasible duration [3, 8]. Similar apprehension for cardiovascular disease risk was enhanced for tofacitinib in the ORAL Surveillance (A3921133) study [4]. This research focused on patients aged 50 and above with at least one cardiovascular risk factor, and the safety profile comparison between tofacitinib and TNFi (adalimumab or etanercept) did not show non-inferiority for MACE. The post-hoc analysis of the ORAL Surveillance study revealed that MACE risk was higher in the tofacitinib (2x5 mg) group compared to the TNFi group among patients with a history of atherosclerotic cardiovascular disease (ASCVD). In contrast, the risk of MACE was similar for patients without a history of ASCVD but with common cardiovascular risk factors [20]. The STAR-RA study outcomes in the United States did not provide any evidence of an elevated risk of cardiovascular outcomes for tofacitinib compared to TNFi. However, RA patients with cardiovascular risk factors or a history of cardiovascular disease showed an observed, yet not statistically significant, elevated risk of cardiovascular events. Additionally, the subgroup analysis of patients over 65 years of age with cardiovascular risk factors showed that the tofacitinib group had a higher cardiovascular risk, although this tendency did not attain statistical importance [21]. Similarly, the German observational RABBIT registry, which included 8000 RA patients, stated that the incidence of MACE did not increase in RA patients when comparing JAKi therapy with TNFi therapy [22]. Results from the French national health system comparing JAK inhibitors and adalimumab revealed reassuring

outcomes for MACE and these results were also valid for patients ≥ 65 years with at least one cardiovascular disease risk [23]. Consistent with previously published studies, we also indicated that MACE risk was not raised in the tofacitinib group compared to the etanercept group. Since data from large cohorts also include patients without cardiovascular disease risk, the necessity for careful monitoring of cardiovascular events in older patients and those with cardiovascular disease risk is evident.

Another safety issue that emerged from the ORAL Surveillance study was the increased frequency of cancer and the most frequent cancer was lung cancer in the tofacitinib group [4]. A meta-analysis examining the association between the JAKi class and malignancy found that JAK inhibitors were linked to a higher incidence of malignancy compared to TNFi. However, this result was mainly owing to the ORAL Surveillance study. When the ORAL Surveillance study was excluded from the analysis, the incidence of malignancy with JAK inhibitors remained higher compared to TNFi, but the statistical significance of this difference disappeared [24]. Likewise, the STAR-RA study found no evidence of a high risk of malignancy between tofacitinib and TNFi [25]. In the long-term safety results of tofacitinib, extending up to 9.5 years, the IRs for both NMSC and malignancies (excluding NMSC) were found to be similar to those informed in RA populations receiving bDMARD [9]. The fact that only one patient had squamous cell carcinoma in our study and no other malignancy (excluding NMSC) was detected makes it difficult to comment on this issue. However, the increased malignancy findings from the ORAL Surveillance study cannot be ignored and they remain up to date [26].

The other safety concern regarding tofacitinib is venous thromboembolism. VTE risk in RA patients is approximately twice as high compared to healthy controls and is closely related to disease activity [27]. In the ORAL Surveillance study, the most significant rise in VTE risk was in the tofacitinib 10 mg twice daily group. Although the signal for VTE was higher in the tofacitinib 5 mg twice daily group compared to TNFi, the difference did not reach statistical significance. Additionally, obesity, history of VTE in the past, advanced age, and chronic lung disease were risk factors for VTE [28]. Data from the French national health system also indicated that the risk of VTE was not elevated in the JAKi group compared to the TNFi group [23]. We identified three patients who experienced VTE, and all of them were in the tofacitinib group. This increase in the VTE signal in the tofacitinib group indicates that caution should be exercised in RA patients over 60 years of age.

Like most bDMARDs, the most prevalent adverse events for tofacitinib are infections. In the ORAL Surveillance study, opportunistic infections, particularly herpes zoster, were more frequent with all doses of tofacitinib compared to TNFi [4]. The long-term safety data of tofacitinib highlighted a high risk of serious infections, opportunistic infections, and herpes zoster [9]. Findings of the US Corrona RA registry indicated that the percentage of serious infections was similar for tofacitinib compared to adalimumab [29]. In a study that included all patients using tofacitinib from the HUR-BIO database, herpes zoster was shown to be more common in the tofacitinib group [13]. In our study, the incidence of both herpes zoster and infections requiring hospitalization was found to be similar in both groups. Clinicians need to be particularly vigilant regarding infections in all elderly RA patients receiving immunosuppressive therapy.

Study Limitations

Although all patients who discontinued follow-up were called and questioned by phone, disease activation data at the time when MACE and VTE developed were unknown. The study group included data from a single center, and the sample size was small. Particularly in the etanercept group, lipid levels were assessed in a small number of patients and we did not have any data on how blood sugar and blood pressure regulation was progressing in patients diagnosed with DM and/or HT. Finally, since patients who did not continue their follow-up and could not be reached by phone were excluded from the study, data on the drug safety profile could not be obtained in these patients. Despite all these limitations, the results we have presented in elderly RA patients provide to the understanding of the safety profile of tofacitinib.

CONCLUSION

Tofacitinib and etanercept had similar incidence for MACE, herpes zoster, and infections requiring hospitalization. The fact that all patients who developed VTE were in the tofacitinib group indicates that this situation warrants careful review. It is difficult to make a conclusive statement regarding cancer risk in this study. Large, observational, population-based controlled studies are needed to specifically investigate the safety profile of tofacitinib in RA patients and to evaluate factors that may be associated with adverse effects.

Author contribution

Study conception and design: UK, AIE, and SK; data collection: ES and EÜ; analysis and interpretation of results: ES, LK, ÖK; draft manuscript preparation: ES, LK, UK, and SK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no. GO 21/1251; Date 16 November 2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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