INTRODUCTION

Rheumatoid arthritis (RA) is a progressive disease that mainly influences the joints. While RA has been a disease associated with permanent joint damage and physical disability in the past, today it has become a disease that remission is an achievable target with early diagnosis, new treatments and improvements in treatment strategies (1-6). Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs) have been the mainstay of disease management in with RA patients (7-9). However, despite the various treatment methods, therapeutic targets are not achieved in many patients, which increases the need for additional treatments (9,10).

A better understanding of the relationship between immune receptors and signal pathways has admitted to the investigation of small molecule anti-rheumatic drugs that target these important pathways (9,11). The Janus kinase (JAK) family is important for the signaling of cytokines responsible for inflammatory processes in RA pathogenesis. For this reason, JAKs have become optimal targets for treatment in rheumatic diseases (9,12). Tofacitinib, the first JAK inhibitor, is a mainly JAK1 and JAK 3 (to a lesser extent JAK 2) inhibitor. Tofacitinib was allowed for the treatment of RA by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (13,14). Tofacitinib can be used in patients with active RA who have not responded to standard therapy. In this study, we aimed to analyze the drug survival rate in patients with RA receiving tofacitinib treatment at the 6th month and to investigate the factors affecting the discontinuation of tofacitinib.
**MATERIALS and METHODS**

**Study Design**

Approval from the Firat University Ethics Committee of Non-Interventional Studies for the study was obtained. The data of RA patients admitted to Firat University rheumatology outpatient clinic between January 2018 and January 2020 and receiving tofacitinib (5mg twice daily, oral) were analyzed retrospectively.

Patient’s age, gender status, levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), whether they used csDMARD together, whether they continued tofacitinib treatment at sixth months if they don’t continue treatment at sixth month which treatment was switched to and whether they used bDMARD before tofacitinib treatment were recorded.

**Statistical Analyses**

All statistical evaluations were made with Statistical Packages for Social Sciences Version 22.0 program (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). Descriptive values are stated as number, percentage, and mean ± standard deviation. The chi-square test was used in the comparison of categorical variables, and the Mann Whitney U test was used in the comparison of continuous data. The p-value<0.05 was statistically significant.

**RESULTS**

Tofacitinib treatment was initiated in 38 (35 female, 3 male) RA patients who followed by the rheumatology clinic between January 2018 and January 2020. Eight of these patients were excluded from the study, as tofacitinib treatment was used less than 6 months. The mean age of 30 (29 female, 1 male) patients included in the study was 50.5 ± 11.3 years. The mean disease duration was 11.6 ± 6.9 years. The rates of CCP and RF positivities were 76% and 70%, respectively. While 24 (80%) of the patients received a csDMARD treatment with tofacitinib treatment, 6 (20%) patients received tofacitinib treatment as monotherapy. Nineteen (63%) patients received at least one bDMARD treatment before tofacitinib treatment (bDMARD resistant).

In the 6th month of treatment, 15 (50%) of patients were continued tofacitinib treatment, while 15 of the patients were discontinued tofacitinib treatment. In terms of disease duration, no significant difference was found between those who continued tofacitinib treatment and discontinued (p = 0.68). There was no significant difference between CCP positive and negative patients in the drug survival rate (p = 0.92). Similarly, there was no significant difference between RF positive and negative patients in terms of the drug survival rate (p = 0.90). In patients receiving and not receiving co-treatment at least one csDMARD (combined vs. monotherapy), the drug survival rates were similar (p = 0.36). No significant difference was found between biological naive patients and bDMARD resistant patients in terms of drug survival rates (p = 0.70) (Table 1).

### Table 1. Factors affecting the drug survival in the 6th month of tofacitinib treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Tofacitinib is Continue (n=15)</th>
<th>Tofacitinib is Discontinue (n=15)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Disease Duration, years</td>
<td>12.1±7.5</td>
<td>11.6±5</td>
<td>0.68</td>
</tr>
<tr>
<td>RF +, n (%)</td>
<td>10 (66.6)</td>
<td>11 (73.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>CCP +, n (%)</td>
<td>11 (73.3)</td>
<td>12 (80)</td>
<td>0.92</td>
</tr>
<tr>
<td>Co-treatment with csDMARD, n (%)</td>
<td>11 (73.3)</td>
<td>13 (86.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Biologic DMARDs Resistants, n (%)</td>
<td>9 (60)</td>
<td>10 (66.6)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

RF = rheumatoid factor; CCP = cyclic citrullinated peptide; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying antirheumatic drug

**DISCUSSION**

In our study, 7 (46%) of 15 patients was discontinued to tofacitinib in the first 3 months. The reasons for discontinuation tofacitinib treatment included patient-reported lack of efficacy (7 patients, 46%), patient decision (5 patients, 33%), and patient-reported adverse events (3 patients, 20%). In 15 patients who did not continue tofacitinib treatment switched to other biological agents; tocilizumab was started in 5 (33.3%) patients, rituximab in 4 (26.6%) patients, etanercept in 2 (13.3%) patients, abatacept in 2 (13.3%) patients, adalimumab in 1 (6.6%) patient, and golimumab in 1 (6.6%) patient. Moreover, these patients continue their treatment.

In addition to loss of effect, the increase in drug intolerance of the patient, and the decrease in treatment compliance lead to discontinuation of treatment. However, there is no appropriate method that determines which patient will continue a particular therapy. Understanding the factors affecting treatment duration and persistence rate is important for the long-term outcome in RA patients. The results of observational studies performed in this regard may differ from randomized controlled studies. As an example, using MTX in patients with RA patients as the first choice in the therapy process is mostly the result of observational studies. Similarly, the relationship between the use of tumor necrosis factor-alpha inhibitor (TNF-i) and increased risk of opportunistic infection is the result of an observational study. In this respect, the contribution of real-life data to science is important.
In a study on tofacitinib, the rate of using tofacitinib as monotherapy was found to be 53.1% (15). Iwamoto et al. (16) reported that 68.6% of the patients used tofacitinib in combination with MTX. Another study following these studies found that 34.2% of patients receiving tofacitinib, 21.7% of patients receiving adalimumab, and 26.5% of patients receiving etanercept used these agents as monotherapy (17). According to the Corrona registry, monotherapy usage rate was 61% in patients receiving tofacitinib; however, it was 31% in patients using TNF-i. In terms of remission rates in patients receiving both tofacitinib and TNF-i was not determined significant difference between monotherapy and combination therapy groups. (p = 0.473 for tofacitinib, p = 0.222 for TNF-i) (18). In our study, 20% of patients were using tofacitinib as monotherapy, and there was no difference between combined and monotherapy use of tofacitinib in terms of the drug survival rates.

Patients who use more than one different DMARD are considered to have low treatment responses and are more resistant to treatment. Mori et al. (19) compared the efficacy of tofacitinib in patients who are bDMARD naive and bDMARD resistant. Remission rates were 41.7% in the bDMARD naive group and 11.7% in the bDMARD resistant group. However, in our study, it was found that drug survival rate of tofacitinib was alike in patients who used tofacitinib as the first advanced treatment agent and in patients who used after at least one bDMARD.

The analysis of two long-term studies on patients with RA showed that the median drug survival of tofacitinib was 4.9 years. The patients on tofacitinib monotherapy continued the treatment slightly longer than patients receiving combination therapy (20). The 2- and 5-year treatment continuation rates were 75.5% and 49.4%, respectively. In the long term extension period, 50.7% of patients drop out of tofacitinib treatment. Of these, 47.2% were due to adverse events and 7.1% for ineffectiveness. The presence of diabetes and hypertension, negative anti-CCP and RF, and non-response to TNF-i therapy were associated with an elevated risk of discontinuing the drugs. The persistence of tofacitinib treatment was lower in our study than anticipated persistence rates. One of the reasons for this finding can be the individual differences of the patients included in the cohorts.

A study by Pope et al. (21) on patients with RA, who received tofacitinib treatment, found that the median drug survival was approximately two years in bDMARD naive patients. The persistence of tofacitinib treatment in the first and second years was 62.7% and 49.6%, respectively. The likelihood of discontinuing the drug was lower in bDMARD naive patients than the patients who were bDMARD resistant. Also, patients over 56 years of age were less likely to discontinue the drug than patients younger than 45. They showed that 33.3% of patients discontinued tofacitinib therapy. The most common argument for treatment discontinuation was a loss of efficacy (35.7%), adverse events (26.9%), and patient's decision (12%). Bird et al. (22) investigated the efficacy, persistence, and the patterns of use of tofacitinib therapy in RA patients. That study found that the median treatment persistence for tofacitinib was 34.2 months, which was similar to that found in patients receiving treatment with other bDMARDs (33.8 months). Another observational study found that the rate of tofacitinib monotherapy (43.4%) was higher than that of monotherapy with bDMARDs (33.4%).

In another study on 2000 RA patients; while the risk of drug discontinuation was higher in the group receiving TNF-i than in the group receiving tofacitinib (p=0.03), the risk of drug discontinuation was not different between patients receiving non-TNFi biologics and patients taking tofacitinib (p=0.76). The rate of drug discontinuation was found high in patients previously treated with more than one type of bDMARDs and in patients with high body mass index (13).

The limitations of our research are the small sample size and the retrospective study design.

CONCLUSION

The 6th-month drug survival rate in RA patients was calculated as 50% in our study. We thought that the low rate of treatment continuation in our study might be associated with long disease duration and previous use of bDMARDs in the patients included in our study population. The rates of continuing tofacitinib therapy were found not to be associated with disease duration, autoantibodies, concomitant csDMARD therapy, and previous treatment with bDMARDs. Considering the growing incidence of tofacitinib therapy for RA patients in Turkey, further long-term studies with a large sample size are warranted to evaluate the factors acting on the length of treatment continuation and drug survival.

Competing Interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Ethical Approval: This study was performed with the approval of Firat University Non-Interventional Research Ethics Committee (approval reference number 2020/08-01).
REFERENCES