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ORIGINAL ARTICLE

# Retention Rate of Etanercept in Patients with Rheumatoid Arthritis Is Better Than That of Monoclonal Antibody

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ABSTRACT

Background: In routine practice, observational registries may show retention rates of tumor necrosis factor inhibitor drugs in rheumatoid arthritis. The objective of this study was to comparetumor necrosis factor inhibitor regarding the drug survival rate in RA patients.
Methods: Hacettepe University Rheumatology Biologic Registry is a single center biological registry since 2005. Data collected includes demographic data, switch ratio, baseline and follow-up disease activity parameters (if available). Patients with lost of follow-up searched regarding to last tumor necrosis factor inhibitor prescription date either local computer system or national social security institution database. Beginning and last date of tumor necrosis factor inhibitor were noted from those systems. First tumor necrosis factor inhibitordrug switch date (either adverse event or inefficacy) was accepted as main variable for drug survival. Kaplan-Meier plots and log rank tests were used to assess drug survival.
Results: Hacettepe University Rheumatology Biologic Registry includes 653 patients 77.9% was female. Mean age was 50±13 years and mean disease duration was 10.5±8.2 years. First tumor necrosis factor inhibitor drugs were etanercept 318 (48.7%), adalimumab 219 (33.5%) and infliximab 116 (17.8%). Patients were divided as regularly follow-up (either first biological drugs or another biological drugs) 455 (69.7%), lost of follow-up 144 (22.1%), drug cessation 36 (5.5%), exitus 18 (2.7%) Patients with etanercept had better drug retention than monoclonal antibodies (log rank p=0.014).
Conclusion: In this single center observational registry, etanercept had better drug retention rate than monoclonal antibodies. On the other hand, certain confounder factors such as baseline disease activity, functional status, and socioeconomic status were not known in whole patients, thus our results should evaluate in this limitation.
Key Words: Rheumatoid arthritis, Tumor necrosis factor inhibitor tumor necrosis factor inhibitor drugs, drug retention rate.

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## INTRODUCTION

According to the generally accepted view, observational studies are behind randomized controlled trials (RCTs) in the evidence hierarchy [1]. On the other hand, data collection methods have both advantages and disadvantages. The superiority of observational registries over RCTs is as follows. They display external validity, have longer-term follow-up time, include a higher number of patients, and have lower cost [1]. Another advantage is that no drug sponsor is needed, since an observational registry can be planned and conducted by the academy [1].
An important parameter showing drug efficacy in registries is the rate of drug continuity. This parameter is considered the indicator of the efficacy in real life. Drug continuity can be affected by other factors not associated with drugs, as well as drug efficiency and significant frequency of side effects. However, while evaluating the rate of drug continuity as an efficiency criterion, we should be careful. In fact, many other factors, including concomitant medications, cost, drug accessibility, and patient's choices, may be responsible for the cessation of drug. Moreover, discontinuity of drug use should not be always evaluated negatively. Drug therapy can be stopped because of patients' remission.
It has been demonstrated in RCTs and meta-analyses

that each tumor necrosis factor alpha blocker (anti-TNF) drug is effective in rheumatoid arthritis (RA) [2]. However, one-to-one comparisons of these drugs in RCTs have not been published yet. In meta-analyses, no significant difference has been revealed among anti-TNFs in terms of their efficiency, or this issue is controversial [2]. On the other hand, there are many national registry systems in which the continuity of biological drugs is evaluated for RA patients [3-9]. These registry systems generally include registries of multiple centers, often at the national level. The primary aim of this study was to determine the ratios of drug continuity for patients who were followed in a single center and who used anti-TNF drugs for RA. The secondary aim was to identify associated factors in the case of the presence of any difference with regard to continuity of the drug.

# METHODS

## Design of the Study

Demographic data of 32 RA patients who were receiving biological treatment in our center in May 2005 were retrospectively recorded into an Excel file. Since then, the demographic data of each patient who planned to be initiated on biological treatment have continued to be recorded prospectively.

## Selection of Patients

The first biological treatment registered in the Rheumatology Biological Registry System (HUR-BIO) of Hacettepe University was in 2001. Since then, the data of 817 RA patients who were prescribed a biological drug at least once in our department have been recorded. In this study, 157 patients having a relatively shorter follow-up period and taking rituximab, abatacept, golimumab, and tocilizumab were excluded (Figure 1). Furthermore, 7 patients who had been prescribed an anti-TNF drug during the last 3 months but whose control examination had not been performed yet in May 2014 were also ruled out. The diagnosis of RA was established by the physicians following the patients in daily routine care. No diagnosis criterion was used. Twelve different physicians deciding on the initiation of biological treatment for RA patients worked in our center between the years of 2001 and 2014. By 2014, 6 physicians have still been deciding on the treatment actively.

## Study Medications

In Turkey, infliximab has been licensed since 2000, etanercept has been licensed since 2003, and adalimumab has been licensed since 2004 for the diagnosis of RA. In this study, biological drugs were prescribed considering the recommendations of the national social security institution. Drug continuity rates of the patients using infliximab, adalimumab, and etanercept due to their sufficient number and follow-up time were evaluated. The biological drugs administered in this study were prescribed in accordance with daily routine care. Disease modified antirheumatic drugs (DMARD) and/or corticosteroid were given in addition to biological drugs with approval of the rheumatologist who followed the patient.

## Data Collection

All patients who had decided to start biological treatment were evaluated by two study nurses responsible for the registry. A local database was used. Demographic information (age, gender), duration of RA disease, comorbidities (hypertension, diabetes mellitus, amyloidosis, coronary artery disease, hepatitis B, hepatitis C, and history of operations), tuberculosis screening results, starting date of the biological drug, the biological agent used first, and history of DMARD were recorded for all RA patients between the years of 2005 and 2012. Before the treatment of the disease, acute phase reactants [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], rheumatoid factor, and anti-citrullinated peptide antibodies were registered, if any. Since 2012, our center has been involved in the TURK-BIO registry system using DAN-BIO. Owing to this system, smoking histories, educational levels, body mass indexes, count of swollen and tender joints, pain, fatigue and global VAS scores, DAS-28 score, and HAQ score had also begun to be recorded. Accordingly, the distribution of patient rates, whose baseline values were recorded before anti-TNF therapy, in accordance with the parameters was as follows: ESR in 89% patients, CRP in 88% patients, DAS-28 in 26% patients, and HAQ in 23% patients.

## Measurements

The data of this study were collected at May 2014. The cessation time of anti-TNF drug was estimated considering the dates for discontinuance of the initial drug and/or switching to another biological drug or the last prescription. According to this, the patients were classified as follows: the patients who had been prescribed biological drugs for the last 6 months were defined as "patients regularly taking biological drugs," and the patients who had not been prescribed biological drugs for longer than 6 months were defined as "patients with loss of follow-up." The patients with loss of follow-up were divided into three groups. The first group included patients who had not been prescribed in the last 6 months and whose medical condition was unknown. The second group consisted of patients whose anti-TNF drug therapy was discontinued by the physicians in our center. The third group included patients who were exitus based on the information obtained from the social security network.

For the patients whose anti-TNF drug was switched to another biological drug or whose drug therapy was discontinued, the reasons for cessation of the drugs were recorded. Inefficiency (in accordance with the rheumatologist's opinion) and/or side effects were noted as the causes of discontinuance.

Other possible causes (pregnancy, surgery, and remission, demand of the patient or physician) were also mentioned. In case of multiple reasons, all of them were taken into account.

### Statistics

Statistical analyses were performed using the SPSS software version 21.0. Descriptive analyses were presented as means and standard deviations for normally distributed variables and median and ranges for the non-normally distributed variables. Chi-square test or Fisher's exact test, where appropriate, was used to compare proportions in the groups. To determine independent predictors of patient outcome, the logistic regression analysis was performed using the possible factors identified with univariate analyses. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit.

The duration lasting from the first day of drugs to its discontinuation from any cause or the last contact to patient was

## RESULTS

### Population of the Study

The HUR-BIO/RA registry system included 817 RA patients. Of these patients, 157 were excluded from the study because of use of other biological agents, and 7 patients were ruled out, since they did not come to the center for

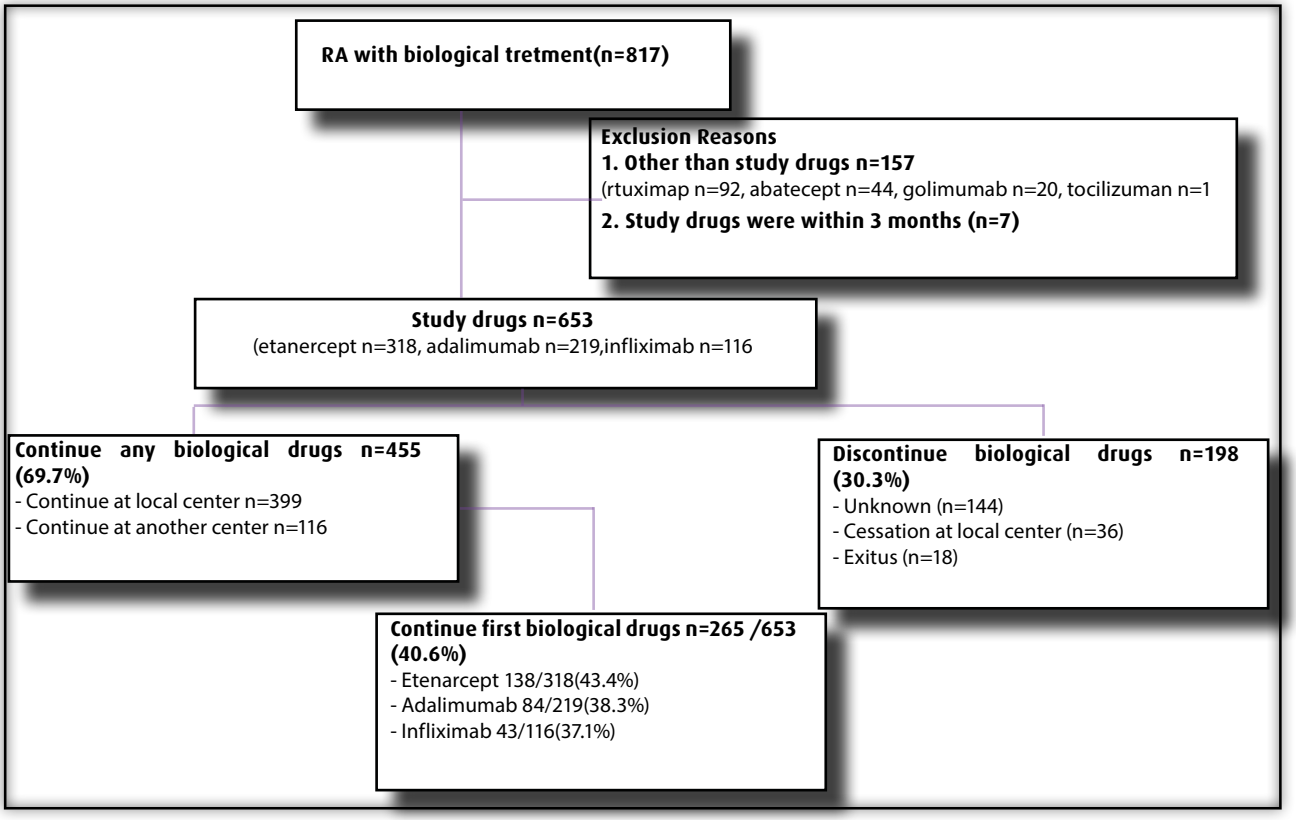


Figure 1: Flow Chart of Study Design

### Characteristics of the Patients

The study included 653 RA patients. Among them, 318 patients used etanercept (48.7%), 219 used adalimumab (33.5%), and 116 used infliximab (17.8%). The baseline demographic features of the patients are shown in Table 1. According to these baseline features, the patients using infliximab were slightly older than the ones using adalimumab. The patients using adalimumab had more frequent rheumatoid factor positivity than the ones using etanercept. The patients using etanercept had higher baseline CRP levels and a more common history of diabetes mellitus compared to the patients using adalimumab (Table 1).

Table 1: Demographic and clinical features of patients

| | Whole Patients n=653 | Etanercept n=318 | Adalimumab n=219 | Infliximab n=116 |
|---|---|---|---|---|
| Age mean (SD) | 50 (13) | 51 (13) | 48 (13) | 52 (12) |
| Female Sex (%) | 77.9 | 76.0 | 82.5 | 75.8 |
| Disease duration years mean (SD) | 10.5 (8.2) | 10.8 (8.8) | 9.7 (6.9) | 11.5 (8.4) |
| RF (+) n (%) | 352/598 (59.1) | 165/298 (55.3) | 125/193 (64.7) | 62/109 (56.9) |
| ACPA (+) n (%) | 215/356 (60.4) | 89/154 (57.8 | 77/122 (63.1) | 49/80 (61.2) |
| Diabetes Mellitus (%) | 13,3 | 16.4 | 9.5 | 11.7 |
| Previous DMARDs (%) | | | | |
| Methotrexate | 92.2 | 92.2 | 92.6 | 91.6 |
| Hydroxychloroquine | 80.9 | 81.9 | 77.8 | 84.3 |
| Sulphasalazine | 75.6 | 77.3 | 73.1 | 75.9 |
| Leflunomide | 63.1 | 66.5 | 61.1 | 59.0 |
| Corticosteroid | 76.7 | 78.3 | 77.8 | 71.1 |
| Previous DMARDs count mean (SD) | 3.1 (1.0) | 3.2 (1.0) | 3.0 (1.0) | 3.1 (0.9) |
| Baseline DAS-28* | 5,23 (0,94) | 5,17 (0,89) | 5,20 (1,01) | 5,47 (0,88) |
| Baseline HAQ* | 1,14 (0,66) | 1,17 (0,66) | 1,06 (0,67) | 1,21 (0,63) |
| Baseline ESR* | 41 (26) | 43 (27) | 38 (23) | 42 (26) |
| Baseline CRP* | 3,8 (5,4) | 4,3 (6,4) | 3,1 (4,0) | 4,0 (4,3) |

* The complete number of cases with available information are: ESR; 583, CRP; 573, DAS-28; 173 and HAQ; 153. Infliximab vs adalimumab, age (p=0.024). Adalimumab vs Etanercept; RF (p=0.039), DM history (p=0.043), baseline CRP (p=0.020)

## Retention Rate of the First Anti-TNF Drug

Of these 653 patients, 455 (69.7%) were continuing to receive any biological treatment, and 265 (40.6%) were continuing to use the anti-TNF drug that was first initiated (Figure 1). The rates of the continuity of the same anti-TNF drug are presented in Figure 2 according to year. It was found that etanercept provided longer continuity compared to monoclonal antibodies (log-rank p=0.014). The difference in the continuity of the three anti-TNF drugs (etanercept 83%, adalimumab 79%, and infliximab 71%) in the first year became clearer as of the second year, and this difference lasted increasingly until the fifth year (Table 2).

Table 2: Retention rate according to different anti-TNF drugs

| | 1. year | 2.year | 3.year | 4.year | 5.year |
|---|---|---|---|---|---|
| Etanercept (%)<br>- Our Study<br>- Literature Review10 | 83<br>82,1 | 76<br>71,5 | 68<br>64,6 | 62<br>58,5 | 59<br>52,2 |
| Adalimumab (%)<br>- Our Study<br>- Literature Review10 | 79<br>74,4 | 65<br>63,6 | 55<br>57,6 | 53<br>47,2 | 48<br>47,5 |
| Fliximab (%)<br>- Our Study<br>- Literature Review10 | 71<br>69,0 | 54<br>55,8 | 51<br>47,0 | 45<br>42,4 | 40<br>37,1 |

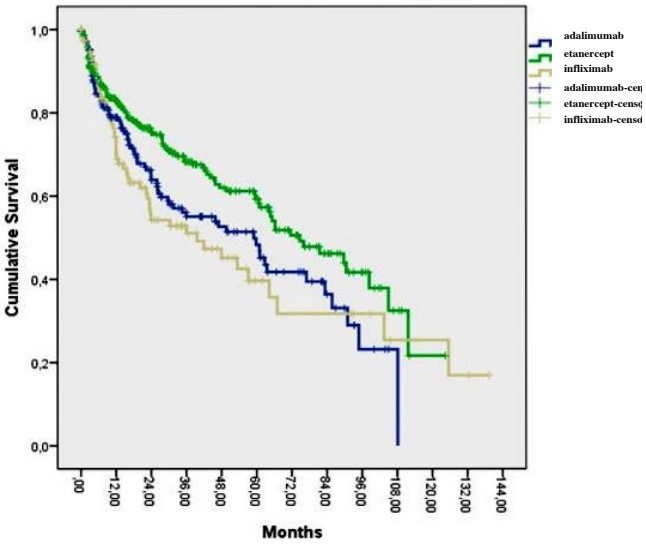


Figure 2: The rates of the continuity of the same anti-TNF drug

## Factors Affecting Continuity of the First Anti-TNF Drug

In patients using the anti-TNF drugs initiated first anti-CCP antibodies (52% vs. 66%, p=0.008), and rheumatoid factor (53% vs. 63%, p=0.014) were found at less frequency. The continuity ratio of the first anti-TNF drug was higher in patients without any comorbid disease [(80/137 (58.4%) vs. 112/267 (41.9%), p=0.002]. Between patients continuing to use the first anti-TNF drugs or not, there was no difference in terms of baseline acute phase response or DAS-28 and HAQ scores. The rate of last corticosteroid use (48% vs. 65%, p<0.001) and the dosage of corticosteroid were lower for patients continuing the first drug (1.9±2.5 vs. 3.5±3.9 mg/day, p<0.001). Moreover, a difference was found between the count of concomitant DMARD and the continuity of the first drug [41.7% for DMARD= 0 vs. 50.2% for DMARD=1, p=0.003]. In the multivariate analysis, the factors affecting continuity of the drug were found to be steroid use (OR 2.60, 95% CI 1.62-4.19), count of concomitant DMARD [for DMARD 0 vs. 1 (OR 2.53, 95% CI 1.19-5.36)], and presence of a comorbid disease (OR 0.47, 95% CI 0.29-0.76).

3.5. Causes of the Cessation of Anti-TNF Drugs

The reasons for the cessation of the first biological treatment were known in 203 patients. In 49.8% of these patients, the cause was inefficiency. The drugs were discontinued due to demand of the patient or physician or pregnancy in 7.9% of the patients and side effects in 42.3%. In 5.5% of these side effects, a life-threatening infection (tuberculosis, Pneumocystis pneumonia, sepsis, and empyema) was present, and 0.8% had a malignancy. No difference was found among three anti-TNF drugs in terms of the cessation that resulted from inefficiency or side effects.

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# DISCUSSION

In this study, the continuity rates of three anti-TNF drugs that were first approved in the RA and biological treatment registry initiated about 10 years ago were compared. It was found that the continuity of etanercept was longer than that of monoclonal antibodies (adalimumab and infliximab). This difference began to occur within the first year. The rates for etanercept, adalimumab, and infliximab were 83%, 79%, and 71%, respectively. The difference increased prominently in the following years. Finally, the continuity of the first anti-TNF drug was detected as 59%, 48%, and 40%, respectively. It was observed especially in multi-center observational registries of European origin that etanercept displayed a higher rate of drug continuity than the other monoclonal antibodies [5-8]. On the other hand, in the American CORRONA registry, it was revealed that infliximab provided a higher rate of drug continuity [9]. This can be explained by the lower baseline disease activity in the registries in the USA and the use of a higher dosage of infliximab and cost [9]. In a review conducted recently, drug continuity rates of biologic-naive patients were measured with regard to these three anti-TNF drugs in biological medication registries [10]. The comparison of the results of this review and ours is shown in Table 2. Accordingly, our results are comparable with other biological drug registries for these three anti-TNFs. As a matter of fact, when evaluated for 5 years, it is seen that our data indicate 3%-5% higher drug continuity for three anti-TNFs, which can result from many reasons. First of all, while almost all of the biological registries are multi-center and national, we have published the results of a single registry, which is a reference center in our country. This may be the reason for the slight positive difference in the continuity of the drug. Another cause can be DMARD used concomitantly with other anti-TNF drugs. In biological drug registries, concomitant DMARDs and their effects on drug continuity have been emphasized in many studies. A Zink et al demonstrated that with regard to the continuity of etanercept during the first year, the continuity rates are 64.4% for the use of etanercept alone, 71.6% for the use of etanercept+methotrexate, and 74.6% when another DMARD was added [11]. For the continuity of infliximab, the rates for patients using infliximab alone, the ones using infliximab and methotrexate, and the ones using infliximab with addition of another DMARD are 44.2%, 66.2% and 72.1%, respectively [11]. A similar difference in the continuity of anti-TNF

drugs was also revealed by Heiberg MS et al. in 2008 [3]. According to their study, the use of anti-TNF drugs with methotrexate has a positive effect on the continuity of drug for RA and PsA patients (contrary to AS). Furthermore, in our study, one of the multivariate factors influencing the continuity of the first drug was found to be the use of a DMARD. Also, the effect of steroid was specified in our study.

Two main factors that affect drug continuity are inefficiency and side effects in biological registries. In our study, no difference was detected among the three anti-TNF drugs in terms of drug discontinuance due to inefficiency and side effects. However, it should be emphasized that 144 (22%) of our patients were not followed up, and the reason for the cessation of drug was not known for all patients. While the cause of drug discontinuance was side effects in approximately 42% of the patients, cessation or switch of anti-TNF due to inefficiency (primary or secondary) was seen in about 50% of the patients. In the biological registries published up to now, a consensus has not been reached on the causes of the cessation of anti-TNF drugs. For instance, in the DREAM [12] and Swiss studies [7], no difference was found among three anti-TNFs in terms of drug discontinuance because of inefficiency or side effects, but a difference was detected for etanercept and infliximab and/or adalimumab with regard to side effects or inefficiency in other registries [10].

This study has some strengths and limitations. The most important limitation is the lack of randomization and blindness. Therefore, some differences are observed in terms of baseline clinical features in the three groups (for instance, infliximab patients being older, etanercept patients having more frequent history of diabetes mellitus, etc.). The primary aim of our database is to determine whether anti-TNF drug is continued or not and also to identify any switching. Thus, although the continuity of drug is successfully specified in our database, the baseline features of the patients are not registered for all patients, and there is a remarkable loss of data. Nevertheless, disease activities of our center in the TURK-BIO database during the initial period after registry and follow-up in 2012 were collected successfully. As a result, the baseline disease activities of our database are not complete, and this limitation should be taken into consideration while evaluating the factors related to the continuity of anti-TNF drugs. On the other hand, this study has important strengths. The study design and data collection were conducted based on the academy, and no support was taken from drug companies for the establishment and maintenance of the database. Furthermore, the number of patients and follow-up duration are sufficient for the necessary evaluation.

In conclusion, in company with the limitations mentioned above, it is seen that etanercept provides a higher continuity of drug compared to monoclonal antibodies in this single-center, long-term biological RA registry. No significant difference was found among the three anti-TNF drugs in terms of the cessation of anti-TNF drugs due to inefficiency or side effects. The pharmacodynamics causes of the difference among these anti-TNF drugs should be emphasized.

## Conflict of Interest:

The authors declare they have no conflicts of interest.

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