Research Article (Araştırma Makalesi)

Factors Affecting Survival on Biologic Treatments in Patients with Rheumatoid Arthritis: A Single-Center Study From Turkey

Romatoid Artrit Tanılı Hastalarda Biyolojik İlaç Sağkalımını Etkileyen Faktörler: Türkiye'den Tek Merkezli Bir Çalışma

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Özet

Amaç: Çalışmanın amacı; erişkin romatoid artrit (RA) hastalarında biyolojik ajan tedavilerinde ilaçta sağkalımı etkileyen faktörleri belirlemektir.

Gereç ve Yöntemler: Çalışmamızda 2013-2016 yılları arasında Trakya Üniversitesi Tıp Fakültesi Hastanesi Romatoloji kliniğinde RA tanısı ile ayaktan ya da yatırılarak takip edilmiş 245 hastanın verileri retrospektif olarak incelendi. Otuz yedi hastanın verileri eksik olduğundan çalışmadan dışlandı. Kalan 208 hastanın verileri değerlendirildi.

Bulgular: Çalışmamızda ilerleyen yaşın ilaç sağkalım süresini 0.48 kat (%95 güven aralığı 0.23-0.97), kadın cinsiyetin 3 kat (%95 güven aralığı 1.09-10.3), hiperlipidemi varlığının 8 kat (%95 güven aralığı 2.12-32.5), tedavi öncesi eritrosit sedimantasyon hızı (ESH) yüksekliğinin 1.03 kat (%95 güven aralığı 1.01-1.04), Hepatit B yüzey antijen pozitifliğinin (HBsAg) 9.2 kat (%95 güven aralığı 2.4-35.3), sitrulinlenmiş proteine karşı oluşan antikor (Anti-CCP) pozitifliğinin 2.9 kat (%95 güven aralığı 1.3-6.4), glukokortikoid kullanımının 0.36 kat (%95 güven aralığı 0.17-0.76) kısalttığını gösterdik. Buna karşın; kronik böbrek hasarı olan hastalarda ilaçta kalma süresinin 0.18 kat (%95 güven aralığı 0.06-0.57) uzadığı gözlemlenmiştir.

Sonuç: RA hastalarına biyolojik ilaç başlarken bazı parametreler ilaçta sağ kalımı ön görmede yardımcı olabilir. Etki sırasına gore; HBsAg pozitifliği, hiperlipidemi varlığı, kadın cinsiyet, anti-CCP pozitifliği, ESH yüksekliği, ileri yaş ve glukokortikoid kullanımı ilaçta kalma süresi için negatif marker iken; kronik böbrek hasarı ise pozitif marker olabilir.

Anahtar kelimeler: Biyolojik Ajanlar, Romatoid artrit, Tümör Nekroz Faktör Alfa (TNF-α)

Abstract

Objective: In our study, we aimed to determine the factors affecting survival on biologic treatment in adult rheumatoid arthritis (RA) patients using biological drugs.

Materials and Methods: In our study, the data of 245 patients who were followed up with the diagnosis of RA in the Rheumatology Clinic of Trakya University Medical Faculty Hospital between 2013 and 2016 were analyzed retrospectively. 37 patients were excluded due to missing data. The data of the remaining 208 patients were evaluated.

Results: In our study, we found that drug survival was reduced by 0.48 times (95% CI 0.23-0.97) in elderly patients and 3 times (95% CI 1.09-10.3) in females. According to the results of our study, drug survival is shortened 8 times (95% CI 2.12-32.5) in patients with hyperlipidemia and 1.03 times (95% CI 1.01-1.04) in patients with high pretreatment erythrocyte sedimentation rate (ESR). In addition, we found that shorter drug survival 9.2 times (95% CI 2.4-35.3) in patients with Hepatitis B surface antigen (HBsAg) positivity, 2.9 times (95% CI 1.3-6.4) in patients with antibody positivity against citrullinated protein (ACPA), in patients using glucocorticoids 0.36 times (95% CI 0.17-0.76). Despite that; in patients with chronic kidney disease, drug survival was prolonged by 0.18 times (95% CI 0.06-0.57).

Conclusion: When starting biologic drugs in RA patients, some parameters may help to predict drug survival. According to the order of effect; while HBsAg positivity, presence of hyperlipidemia, female gender, ACPA positivity, high ESR, advanced age and glucocorticoid use were negative markers for drug survival; chronic kidney damage can be a positive marker.

Keywords: Biological Agents, Rheumatoid arthritis, Tumor Necrosis Factor Alpha (TNF-α)

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by persistent synovitis in small joints, systemic inflammation and the presence of autoantibodies (1,2). It is known that RA affects approximately 0.5-1% of the adult population in developed countries (2). RA is a disease that reduces the quality of life of patients due to joint involvement, causes loss of work force, as well as can cause extra-articular involvements and cause mortality with cardiovascular events. Therefore, our goal should be to achieve and maintain remission or low disease activity in RA patients (3).

Generally, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, DMARDs (Disease Modifying Anti-Rheumatic Drugs and these are methotrexate, leflunamide, sulfasalazine, hydroxychloroquine) are used in the treatment of RA (4,5). Biological agents have also been added to this group of drugs, as the role of tumor necrosis factor-α (TNF-α) and interleukins in the pathogenesis of RA has been better understood in the last two decades (6). TNF-α inhibitors (adalimumab, infliximab, etanercept, golimumab, certolizumab pegol), rituximab (CD20 antibody), abatacept (cytotoxic T lymphocyte antigen 4 immunoglobulin), tocilizumab (IL-6 antibody), tofacitinib and baricitinib started to be used in last 20 years (4,5). Biological drugs have revolutionized the treatment of RA and have been effective in patients who do not respond to synthetic DMARDs (3). However, there are some difficulties in the use of biologic drugs. Issues such as which biological treatment will be preferred for which patient and managing side effects are very important (7). In addition, the cost of biologic drugs and the difficulties in accessing the drug should be considered (3). Therefore, in order to use biological agents more rationally, survival in treatment and the factors affecting them should be examined (8). To date, the factors affecting the survival of biologics in treatment, such as the clinical characteristics of the patients and the course of the disease, have been investigated (9).

Although there are guidelines for the use of biological DMARDs by the European Rheumatism Association (EULAR) and the American Rheumatology Society (ACR), the use of biological drugs may differ between countries (10). These differences may cause the factors affecting survival in biological drugs to differ according to populations (11). For example, although a study conducted in the United States showed that previous use of glucocorticoids and concomitant use of synthetic DMARDs affected the survival time of biologic drugs (12). The effect of factors such as age, low socio-demographic status, and the presence of comorbidities was determined in a study conducted in Japan (13). Therefore, in our study, we aimed to reveal the factors affecting the survival of biologic drugs in a center from Turkey. In our study, we hope to provide rheumatologists in our country with more information about the selection or switch of biologic drug therapies.

MATERIALS AND METHODS

Our study included 245 patients who were followed up with the diagnosis of RA in the Department of Internal Medicine, Division of Rheumatology, between 2013 and 2016. Thirty seven patients were excluded due to insufficient data. In our study, we retrospectively analyzed the data of 208 patients. Ethics Committee approval was obtained for our study with the protocol number of Trakya University Scientific Researchs Ethics Comittee (TÜTF-BAEK) 2018/55 dated 19/02/18. Our study complies with the provisions of the Declaration of Helsinki. This article was produced from a medical specialty thesis. We retrospectively scanned the composite indices associated with demographic data, laboratory findings, disease activity and treatment responses of the cases included in the study from the hospital information system and recorded them in the data collection form.

Inclusion Criteria

1. Be over 18 years of age.
2. To be followed up for at least 36 months with the diagnosis of RA between 2013 and 2016, to be evaluated at least once every 3 months and twice.
3. Using biologic agents for the treatment of RA.

Exclusion Criteria

1. Be under the age of 18
2. Pregnancy or breastfeeding

Demographic data were recorded as gender, age and year of diagnosis. Disease duration was considered as months after diagnosis. Type 1 and Type 2 diabetes mellitus, hypertension, coronary artery disease, chronic kidney damage, and hyperlipidemia were recorded as comorbidities. We recorded the patients' C-reactive protein (CRP), ESR, pre-biological rheumatoid factor (RF), ACPA, hepatitis B and hepatitis

C test results before biologic therapy, at the time of initiation of therapy, and every 3 months while under biologic therapy. Serum CRP and RF levels were measured using the original kits in the nephelometer device in the central laboratory of our hospital. Serum ACPA levels were measured in the Central Laboratory using an autoanalyzer and original kits. The erythrocyte sedimentation rate was also measured in the Central Laboratory.

Composite indices used in our study are HAQ: health assessment questionnaire, VAS pain: visual analog scale pain, VAS physician: visual analog scale physician, VAS global: visual analog scale global, DAS-28: Disease Activity Score-28 and CDAI: Clinical Disease Activity Indices . The data obtained as a result of the measurements were recorded in the data collection form at certain intervals. We used Boolean remission criteria for remission assessment. In the evaluation of biological DMARDs, at least two visits were required. By evaluating the data of all visits for each patient, the duration of drug use was calculated in months as the time from the date the drug was prescribed to its discontinuation or switching. The patients were followed up for an average of 72 months (min 48-max 108 months). Treatment response assessment was done by changing the final DAS 28 score from the baseline DAS 28 score. No decrease in DAS 28 score was recorded as unresponsiveness, increase as worsening. At the last evaluation of all patients, those who were still on treatment were recorded.

As a statistical method, we checked the assumptions of normal distribution with the Shapiro-Wilk test. We used the t-test for group comparisons when the assumption of normal distribution was satisfied. Otherwise, we used the Mann-Whitney U test for group comparisons. We investigated the relationships between categorical variables using the Pearson Chi-Square test. We compared multivariate categorical data with the Kruskal-Wallis test. We used Cox-Regression test to determine the factors affecting the survival times of biologic drugs. We evaluated the potential factors that may affect the duration with univariate analyses. We performed multivariate analysis by including variables of comparisons with a P value less than 0.2 in the model. We gave the mean standard deviation or median and quartiles as descriptive statistics. We determined the level of significance as 5% in all statistical analyzes. Using the Kaplan Meier test, we analyzed the time to biologic drug replacement. We used the SPSS.20 (Statistical Package for the Social Sciences) package program for statistical analysis.

RESULTS

Epidemiolojical Data

Of the 208 patients included in our study, 158 were female and 50 were male. The female/male ratio was 3.16. The median age of the patients was 59 years (25-75 percentile 49-67), the median age at which they were diagnosed was 52 years (25-75 percentile 42-61), and the median disease duration was 72 (25-75 percentile 48-108) months.

Comorbidities and treatment data

We grouped the patients according to diabetes mellitus, hypertension, chronic kidney injury (CKD), hyperlipidemia and coronary artery disease (CAD) and congestive heart failure (CHF). We included hyperlipidemia patients whose low density lipoprotein (LDL) level was above 160 mg/dl for at least 6 months, not using statins, and chronic carrier and/or chronic hepatitis B patients with HBsAg positivity older than 6 months. The distribution of patients with comorbidity in our study is as follows. 24 patients (11.5%) with type 2 diabetes mellitus, 68 patients (32.7%) with hypertension, 24 patients (11.5%) with CKD, 14 patients (%6.7) with hyperlipidemia, 49 patients (23.6%) with CAD and CHF.

The distribution of patients using conventional DMARDs is as follows: Hydroxychloroquine 88 patients (42.3%), leflunomide 53 patients (25.48%), methotrexate 130 patients (62.5%), sulfasalazine 109 patients (52.4%), NSAIDs 73 patients (35.09%), colchicine 1 patient (0.48%), glucocorticoid 155 patients (74.5%). The distribution of biological drugs used by the patients included in our study is as follows; 39 (18.8%) patients were treated with abatacept, 44 (21.2%) patients with adalimumab, 30 (14.4%) patients with etanercept, 19 (9.1%) patients with golimumab, 26 (12.5%) patients with infliximab, 24 (11.5%) patients were treated with rituximab, 5 (2.4%) patients with certolizumab, 12 (5.8%) patients with tocilizumab and 9 (4.3%) patients with tofacitinib (**Table 1**).

Laboratory and disease activity data

We analyzed the changes in laboratory values, clinical indexes, and physical examination findings according to gender and comorbidities of patients 12 months after biologic treatments (**Table 2**). Since these

Table 1. Demographic, comorbid, clinical and laboratory data of the patients

	Total number of patients (208)
Age (year)	*59 (49- 67)
Age of diagnosis (year)	*52 (42-61)
Disease duration (month)	*72 (48-108)
Female (n%)	158 (%76)
Male (n%)	50 (%24)
Diabetes mellitus (n%)	24 (%11.5)
Hypertension (n %)	68 (%32.7)
Chronic kidney damage (n%)	24 (%11.5)
Hyperlipidemia (n%)	14 (%6.7)
Coronary artery disease and congestive heart failure (n%)	49 (%23.6)
Hydroxychloroquine (n%)	88 (%42.3)
Leflunomide (n%)	53 (%25.48)
Methotrexate (n%)	130 (%62.5)
Sulfasalazine (n%)	109 (%52.4)
**NSAID (n%)	73 (%35.09)
Colchicine (n%)	1 (%0.48)
Glucocorticoid (n%)	155 (%74.5)
Dosage of glucocorticoid (mg/day)	†7 (2.5-32)
Abatacept (n%)	39 (%18.8)
Adalimumab (n%)	44 (%21.2)
Etanercept (n%)	30 (%14.4)
Golimumab (n%)	19 (%9.1)
Infliximab (n%)	26 (%12.5)
Rituximab (n%)	24 (%11.5)
Certolizumab (n%)	5 (%2.4)
Tocilizumab (n%)	12 (%5.8)
Tofacitinib (n%)	9 (%4.3)
‡ACPA pozitive §RF pozitive	68 (%32.6)
‡ACPA pozitive §RF negative	10 (%4.9)
‡ACPA negative §RF pozitive	10 (%4.9)
‡ACPA negative §RF negative	120 (%57.6)
¶HbsAg	12 (%5.76)
††Anti-HCV	61 (%29.32)

* Variables are given as median (25-75 percentile) values,**NSAID: Non-steroidal anti-inflammatory drugs
† Variables are given as mean and standard deviation. ‡ACPA: Against citrullinated protein
§RF: Rheumatoid factor, ¶HbsAg: Hepatitis B virus surface antigen, ††Anti-HCV: Hepatitis C antibody

Table 2. Change of laboratory, clinical index and physical examination status of patients according to gender and comorbidities

At the end of 12 months in biological therapy	Total number of patients (208)	Female	Male	*p value	Presence of type 2 diabetes mellitus	Absence of type 2 diabetes mellitus	*p value	Presence of hyperlipidemia	Absence of hyperlipidemia	*p value	Presence of stage 1 and 2 chronic kidney damage	Absence of chronickidney damage	*p value	HbsAg positive patients	HbsAg negative patients	*p value
**ESR (mm/sa)	30 (0-104)	32 (2-104)	20 (0-79)	**0.01**	32 (7-60)	29 (0-104)	0.65	41 (14-60)	29 (0-104)	0.34	38 (2-104)	29 (0-100)	0.12	54 (11-104)	29 (0-100)	0.28
†CRP (mg/dl)	1 (0-20)	0.82 (0-18)	0.4 (0-20)	0.16	1 (0-18)	1 (0-20)	**0.01**	2 (0-18)	1 (0-20)	**0.01**	1 (0-10)	1 (0-20)	0.2	1 (0-9)	1 (0-20)	0.72
‡DAS-28	3 (1-14)	3 (1-9)	2 (2-14)	**0.03**	3 (2-7)	3 (1-14)	0.65	5 (2-6)	3 (1-1)	0.1	4 (2-6)	3 (1-14)	0.59	3 (2-9)	3 (1-14)	0.44
§CDAI	7 (2-63)	7 (2-63)	7 (2-38)	**0.01**	7 (6-55)	7 (2-63)	0.5	32 (6-42)	7 (2-63)	0.1	10 (5-42)	7 (2-63)	0.34	9 (7-53)	7 (2-63)	0.43
¶HAQ	1 (0-20)	1 (0-3)	0 (0-20)	0.12	2 (0-3)	1 (0-20)	0.13	2 (0-3)	1 (0-20)	0.18	2 (0-3)	1 (0-20)	0.1	2 (1-3)	1 (0-20)	**0.04**
††VAS pain	40 (0-100)	40 (0-100)	30 (0-70)	0.28	40 (10-70)	40 (0-100)	0.68	50 (10-60)	0 (0-100)	0.34	60 (20-90)	40 (0-100)	**0.03**	50 (50-70)	40 (0-100	**0.05**
§§VAS physician	30 (0-80)	30 (20-80)	30 (0-60)	0.31	30 (20-80)	30 (0-60)	0.7	40 (20-40)	30 (0-80)	0.24	30 (30-40)	30 (0-80)	**0.03**	30 (30-40)	30 (0-80)	0.4
‡‡VAS global	40 (20-80)	40 (20-80)	40 (20-80)	**0.01**	40 (30-80)	40 (20-80)	0.8	40 (40-60)	40 (20-80)	0.13	40 (40-80)	40 (20-80)	0.1	50 (40-60)	40 (20-80)	0.07
Number of swollen joints	0 (0-28)	0 (0-28)	0 (0-14)	0.38	0 (0-24)	0 (0-28)	0.72	12 (0-16)	0 (0-28)	0.1	1 (0-16)	0 (0-28)	0.52	0 (0-22)	0 (0-28)	0.8
Number of tender joints	0 (0-28)	0 (0-28)	0 (0-14)	0.12	0 (0-24)	0 (0-28)	0.59	12 (0-16)	0 (0-28)	**0.04**	1 (0-16)	0 (0-28)	0.59	1 (0-22)	0 (0-28)	0.4

Variables are given with median, minimum and maximum values.
*p<0,05 : significant
**ESR (mm/hour): Erythrocyte sedimentation rate, †CRP (mg/dl): C-reaktive protein, ‡DAS-28: Disease Activity Score-28, §CDAI: Clinical Disease Activity Index
¶HAQ: Health evaluation questionnaire, ††VAS pain: Visual analog scale pain, §§VAS physician: Visual analog scale physician, ‡‡VAS global: Visual analog scale global

parameters were not in the normal distribution, minimum and maximum values were determined by using the median. According to this calculation, the median ESR of all patients was 30mm/h (min 0-max 104), median CRP was 1 mg/dl (min 0-max 20), DAS-28 median was 3 (min 1-max 14). ESR, DAS-28, CDAI and VAS values were significantly higher in women. We found that CRP values increased in patients with type 2 DM (Diabetes Mellitus), CRP and number of sensitive joints increased in patients with hyperlipidemia, and VAS pain and VAS physician values increased in patients with stage 1 and 2 CKD. HAQ and VAS pain values were higher in patients with HBsAg positivity. 68 patients (32.6%) included in our study had RF and ACPA positivity. RF and ACPA were negative in 120 patients (57.6%). 12 (5.76%) patients had HBsAg positivity (**Table 1**).

Factors affecting the drug survival

When we examined the switch status of the drugs, we found that 142 patients (68.3%) continued their first biologic drugs. The most frequent switch was made within the first 12 months of treatment, and the number of patients whose biologic drug was changed once was 52 (25%). When the follow-up period of 36 months was completed, the number of patients who had more than one switch was found to be 14 (6.7%). The number of patients whose treatment was switched due to ineffectiveness and adverse events was equal; it was 21 (10.1%). Treatment non-compliance, which occurred in 24 (11.53%) patients, was the most common cause of switch. Serious infections observed in 10 (4.8%) patients were the most common side effects (**Table 3**).

When we examined the relationship between the survival times of drugs and comorbidities, the duration of rituximab use was prolonged in Type 2 DM patients without CAD (**Table 4**). The duration of infliximab use was shortened in patients with CAD and CHF. The duration of use of golimumab was increased in patients with stage 1 and 2 CKD. Etanercept was used as the first biological agent in stage 3 and above CKD (**Figure 1**). The survival times of adalimumab and infliximab were shortened in the presence of respiratory tract diseases.

We found that drug survival duration was reduced 0.48 times (95% CI 0.23-0.97) in elderly patients and 3 times (95% CI 1.09-10.3) in women. In patients with hyperlipidemia, drug survival was reduced 8 times (95% CI 2.12-32.5). On the other hand, we observed that drug survival duration was increased by 0.18 times (95% confidence interval 0.06-0.57) in patients with chronic kidney disease. In our study, drug survival duration decreased in case of high ESR levels before biological treatments (1.03 times), HBsAg positivity (9.2 times), ACPA positivity (2.9 times), use of glucocorticoid (0,36 times) (**Table 5**).

Table 3. Drug change and reasons for change according to the follow-up period of the patients

Frequency of drug change	Total number of patients (208)
Never changed (%n)	142 (%68.3)
Patients whose drug was changed once at the end of the first 12 months (%n)	52 (%25)
Patients who changed more than one times drug at the end of 36 months (%n)	14 (%6.7)
Ineffectiveness (%n)	21 (%10.1)
Non-compliance with treatment (%n)	24 (%11.53)
Adverse effects (%n)	21 (%10.1)
Serious infection (%n)	10 (%4.8)
Allergic reaction (%n)	5 (%2.4)
Parapsoriasis (%n)	3 (%1.44)
*İBD (%n)	1 (%0.48)
Uveitis (%n)	1 (%0.48)
Hyperlipidemia (%n)	1 (%0.48)

*İBD: İnflammatory bowel disease

Table 4. Changes in patients' comorbidities and duration of drug use			
Months±Standard Deviation	**Presence of Tip 2 diabetes mellitus (absence of CAD)**	**Absence of Tip 2 diabetes mellitus**	***p value**
Rituximab usage time	52 ±16.3	34.8±17	0.01
	Presence of **stage 3 CAD-CHF	**Absence of **CAD-CHF**	***p value**
Infliximab usage time	24 ±16.9	52±19.5	0.005
	Presence of †stage 1 and 2 CRD	**Absence of †CRD**	***p value**
Golimumab usage time	48±0	33.4±12.7	0.00
	Presence of respiratory diseases	**Absence of respiratory diseases**	***p value**
Infliximab usage time	28±18.3	53.2±19.3	0.043
Adalimumab usage time	23.5±17.3	47±29.7	0.05

*p<0,05: significant
**CAD-CHF: coronary artery disease - congestive heart failure, †CRD: chronic kidney damage

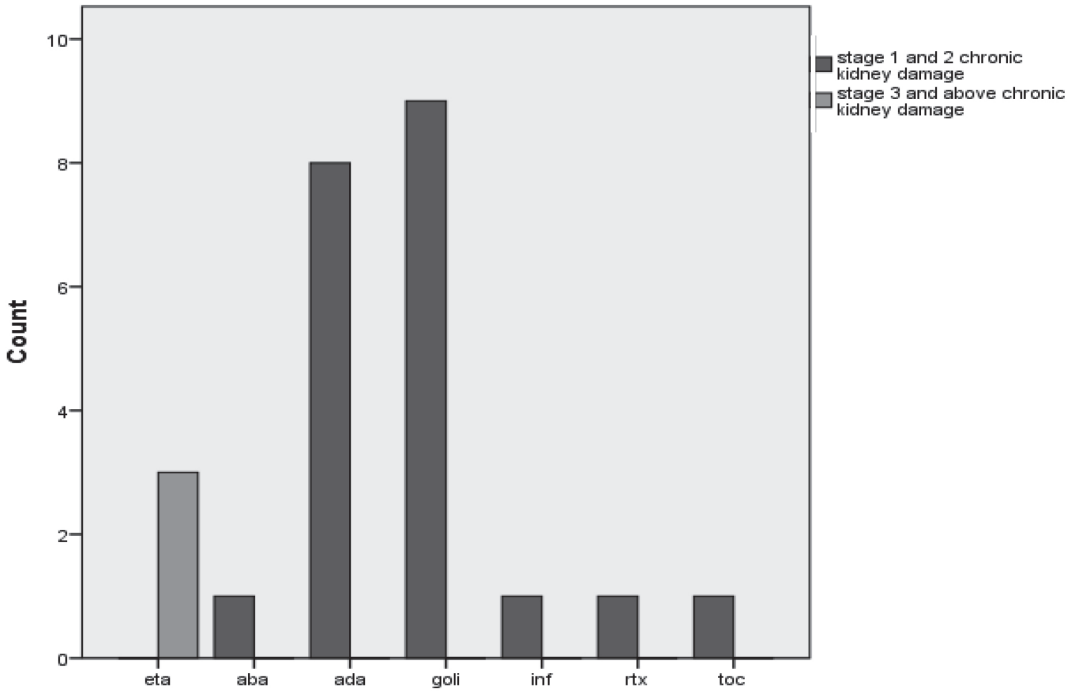

Figure 1. Biological drug distribution according to chronic kidney damage stages

Eta: Etanercept, **Aba:** Abatecept, **Ada:** Adalimumab, **Goli:** Golimumab **Inf:** Infliximab, **Rtx:** Rituximab, **Toc:** Tocilizumab

DISCUSSION

We examined the reasons for the switch in RA patients using biological drugs with regression analyses according to the clinical characteristics of the patients and the course of the disease. We showed that there is a relationship between drug survival times and older age, female gender, presence of hyperlipidemia, presence of chronic kidney damage, steroid using, pretreatment ESR elevation, HBsAg positivity, and ACPA positivity.

In a meta-analysis by Souto et al., a relationship was found that the female gender shortens drug survival (14). They attributed this to the increase in DAS-28 and HAQ values due to the increased frequency of fibromyalgia in women, and to changing the biological drug, which is assumed to be ineffective. In our study, although VAS global, ESR, DAS-28, and CDAI values were found to be higher in women at the end of 12 months when biologic therapy was most frequently changed, this was not associated with RA exacerbation.

Table 5. Multivariate COX regression analysis associated with variables affecting drug retention		
	Odds Ratio (%95 confidence interval)	***p value**
Age	-0.48 (0.23-0.97)	0.043
Female gender	-3.3 (1.09-10.3)	0.034
Presence of hyperlipidemia	-8.3 (2.12-32.5)	0.002
Chronic kidney damage	0.18 (0.06-0.57)	0.004
**ESR value before treatment	-1.03 (1.01-1.04)	0.000
†HbsAg pozitivity	-9.2 (2.4-35.3)	0.001
¶ACPA positivity	-2.9 (1.3-6.4)	0.005
Glucocorticoid using	-0.36 (0.17-0.76)	0.008

*p<0,05 : significant
**ESR: Erythrocyte sedimentation rate
†HbsAg: Hepatitis B virus surface antigen
¶ACPA: Against citrullinated protein

When we completed our study, we understood that the frequency of fibromyalgia was higher in women and this situation masked the remission and caused the change in medication and thus shortened drug survival.

Another factor that we investigated in our study was the age of the patients. In the study of Min Jung et al. with 682 Korean patients, it was stated that advanced age shortens the survival duration of biologic drugs. In this study, side effects, including drug-related infections, were more common in advanced age, and although it was not statistically significant, it was considered among the reasons for drug discontinuation (15). In a cohort study conducted by Mathieu et al. in France, they reported that the duration of etanercept use increased, but the duration of adalimumab use decreased in the elderly (16). In our study, a relationship was found between advanced age and biological drug survival, and adalimumab survival shortened with increasing age. This result is similar to the study of Mathieu et al. The reason for this is the discontinuation of biologic drugs due to the increasing frequency of life-threatening infections with advancing age.

Marchesoni et al. reported that comorbidities increase the drug survival (17). On the other hand, Markenson et al. reported in their study that comorbid conditions reduce the duration of etanercept treatment (18). The reason for this may be that other DMARDs are preferred over etanercept in conditions such as inflammatory bowel disease and uveitis (19). Soo Kyung Cho et al. showed that comorbidities such as diabetes, chronic pulmonary disease, mild liver disease, and baseline depression do not affect drug survival, while peptic ulcer disease reduces the risk of discontinuation of TNF inhibitors. They explained this as the fact that patients using TNF inhibitors do not want to use oral medication (20). In our study, comorbidities affected the survival of drugs. We have demonstrated that drug survival is reduced in patients with LDL levels above 160 mg/dl for more than 6 months. The reason for this situation is that some biological agents cause hyperlipidemia more and therefore treatment change is needed. The reason for this situation is that some biological agents cause hyperlipidemia more and treatment change is needed because of this side effect. The most common biological drugs causing hyperlipidemia are Janus Kinase (JAK) inhibitors (21). Another remarkable biological drug in our study was tocilizumab. Singh et al. reported the relationship between tocilizumab and a significant increase in cholesterol levels (22). In addition, Alsulaim et al. also mentioned an increased cardiovascular risk due to tocilizumab-induced hyperlipidemia, although there is no clear evidence (23). In our study, we also observed a significant increase in the number of sensitive joints and CRP values in these patients, and we found that the drugs were switched due to ineffectiveness. In a study by Attar et al. in Saudi Arabia evaluating the relationship between hyperlipidemia and CRP values and disease activity in RA patients, they concluded that hyperlipidemia develops as a result of increased disease activity and inflammation. There are limited studies on this subject in the literature, some studies have shown a relationship between lipid profile and disease activity, and some have not found this relationship (24).

When we evaluated on a drug basis, we saw the effects of some comorbidities on the survival of some drugs. For example, the mean survival duration of rituximab was found to be significantly higher in patients with type 2 DM without CAD than in patients with concomitant CAD. This may be due to trying to control the increased disease activity due to high CRP levels in patients with type 2 DM without CAD. Stage 3 congestive heart failure is one of the reasons for discontinuation of biologic drugs and in our study, it resulted in discontinuation of infliximab treatment. The duration of adalimumab and infliximab use was shortened in the presence of respiratory tract diseases. The reason for this may be the necessity of changing the medication when lung involvement develops in RA.

Another comorbidity that affects drug survival, which we found in our study, is chronic kidney disease. In the presence of CKD, drug survival is prolonged. In the study of Soo Kyung Cho et al., etanercept was reported to be safe and effective in CKD patients (25), Don BR. et al. reported that etanercept clearance in patients with end-stage renal disease was the same as in patients with normal renal function, and they observed no side effects (26). Therefore, etanercept survival time was prolonged in CKD cases in both studies. In accordance with the literature, etanercept has been used more frequently in our patients with stage 3 CKD. We explain this situation by the fact that safety and side effects concerns come to the fore in patients with advanced CKD. On the other hand, in our earlier stage CKD cases (stages 1 and 2), the treatment was changed due to non-compliance, and golimumab was preferred as the second biologic drug, as the patients demanded a drug with a longer dose range. We found that golimumab, which is used as a second drug in stage 1 and 2 CKD patients, prolongs the survival time significantly. VAS pain and VAS physician evaluation results were found to be significantly higher in patients with stage 1 and 2 CKD, and a significant relationship was found between unresponsiveness and switches.

Since hepatitis viruses play a role in the etiology of RA and affect the course of the disease and the drugs used (27,28), we also discussed hepatitis B and hepatitis C. In our study, we determined that HBsAg positivity lasting longer than 6 months shortens drug survival. In the literature, in a multicenter, retrospective study conducted by Carlino et al. on 486 patients, it was stated that the carrier of Hepatitis B cor antigen significantly reduced the survival time of the first biological drug. The reason for this was considered to be higher ESR and DAS-28 values in patients with hepatitis B core antigen positivity and unresponsiveness due to high disease activity (29). In our study, HAQ and VAS pain values were higher in patients with chronic HBsAg positivity. Therefore, drug change due to primary unresponsiveness was high in these patients. However, Zou et al. showed in their study that chronic hepatitis B infection did not have a significant effect on disease activity, synovitis or joint destruction in RA (30). Studies on the relationship between hepatitis B and RA are limited in the literature.

Although RF and/or ACPA positivity are associated with poor prognostic factors in RA, their effects on biologic drugs are not clear (31). Although Lin et al found that abatacept survival increased in the first 3 years in ACPA positive patients, they reported that TNF-a inhibitors and tofacitinib's survival time decreased. Lin et al. could not prove the effect of ACPA positivity on rituximab survival (31). However, Sellam et al. stated that RF and ACPA positivity were associated with the survival of rituximab (32). On the other hand, Mulligen et al. showed that biologic drug survival increased in ACPA positive patients due to the inability to tapering the biologic treatments (33). In our study, it was determined that the survival time of infliximab was significantly reduced in these patients, especially in the first 2 years. In addition, we found that the number of seropositive patients using TNF inhibitors decreased in the first 2 years, and abatacept and rituximab were preferred as the second biologic agent in these patients. The fact that the most common cause of switch was unresponsiveness in our study suggested that seropositivity is a factor that reduces drug efficacy and causes switch.

Another poor prognostic factor affecting the prognosis of RA is high acute phase reactants (34). When we examined the effects of poor prognostic factors on the survival of biological drugs, we noticed that high ESR values shorten the duration of drug use. Marchesoni et al. reported that biological drug survival times were shortened due to side effects and ineffectiveness in patients with high ESR values (17). On the other hand, Flouri et al. reported that high CRP values before treatment prolong drug survival (35). Moreover; Kristensen et al. reported that patients with high CRP values were under control with biologic drugs, and accordingly, drug survival increased as treatment compliance increased (36). Relationships between drug

survival times and the number of synthetic DMARDs used, glucocorticoids and NSAIDs in RA continue to be investigated. Marchesoni et al. reported that the use of 4 or more DMARDs and 5 mg/day or more corticosteroids per day reduced the survival of biologic drugs. They reported that patients using multiple DMARDs had more resistant RA, which would be associated with the ineffectiveness of biologic drugs. The development of serious infection has been shown as the reason for the decrease in drug survival with the use of corticosteroids (17). On the contrary, Flouri et al. reported that low-dose glucocorticoid use is a protective factor in terms of drug survival (35). Similarly, Du Pan et al. reached the same conclusion, and stated that infusion reactions were prevented by the use of low-dose glucocorticoids, especially in patients using infliximab (37). In our study, we found a significant relationship between 3 or more DMARD experiences and biologic drug change, and the most common switch reason was ineffectiveness. However, we could not prove an effect on drug survival. The reason for this may be the decision to continue treatment with acceptable well-being in order to avoid adverse effects, including infections, especially in patients aged 75 years and older. We found that the use of glucocorticoids over 5 mg/day decreased drug survival. This situation can be explained by the increase of adverse events and infections with the use of glucocorticoids together with biologic drugs.

Methotrexate (MTX), a synthetic DMARD, is used extensively with TNF inhibitors. Kristensen et al. found a higher drug survival rate in patients using MTX concomitantly with TNF inhibitors. When compared to MTX, it was noticed that drug survival time could not be prolonged in patients using concomitant leflunamide, hydroxychloroquine, sulfasalazine with TNF inhibitors. Among the reasons that make methotrexate different, it can be said that its anti-rheumatic activity is strong and that it prevents the formation of immunopathogenic antibodies that can develop against TNF inhibitors (36). In our study, we did not observe a significant relationship between the use of MTX and the survival time of the biologic drug. We explain this situation with the fact that the patients could not tolerate MTX and did not want to use it, and therefore MTX treatment had to be stopped early.

The limitation of our study is the insufficient number of patients. In addition, due to the structuring in our electronic registration system, we had to exclude many patients from the study because we could not fully access their data. Due to the difficulty in accessing patient information, patients who used biologic agents for the first time were included in the study. Therefore, the relationship between drug survival times, previous biological agent failure, and disease duration could not be evaluated.

CONCLUSION

It should be known that RA patients who cannot be controlled with synthetic DMARDs or who cannot use these drugs are switched to biological DMARD treatment and that RA is a difficult disease to manage. When starting biologic drugs in RA patients, some parameters may help predict drug survival. In the treatment of RA, achieving remission with the first biological therapy ensures the protection of the treatment options that we may need in the later stages of the treatment and increases the patient's comfort of life.

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