# Romatoid artrit ve Ankilozan Spondilit Tedavisinde Biyolojik Ajanların Değişimlerinin Analizi

# Analysis of Switching Biological Agents in Treatment of Rheumatoid Arthritis and Ankylosing Spondylitis

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***ÖZ***

***GİRİŞ ve AMAÇ:*** *Hastalığı modifiye edici biyolojik antiromatizmal ilaçlar (bDMARDs), romatoid artrit (RA) ve ankilozan spondilit (AS) tedavisinde kullanılmaktadırlar. Bu çalışmada, bDMARDs değişim paternlerinin, ilaç tedavisinde kalım sürelerinin ve RA ile AS hastalarında ilaç değişim nedenlerinin gerçek dünya verileri ışığında araştırılması amaçlandı.*

***YÖNTEM ve GEREÇLER:*** *Çalışma, retrospektif, tek merkezli, gözlemsel bir çalışma olarak dizayn edildi. Çalışmaya, en az 1 kez bDMARDs değişimi yapmış 102 hasta (55 RA ve 47 AS) dahil edildi. İlaç tedavisinde kalım süreleri ve bDMARDs değişim nedenleri kaydedildi. Her biyolojik ajan için ilaç devamlılık sürelerini analiz etmek ve gruplar arası karşılaştırma yapmak için Kaplan-Meier analizi ve Log-Rank testi kullanıldı.*

***BULGULAR:*** *Ellibeş (%53.9) hasta RA iken, 47 (%46.1) hasta AS idi. İlk değişim oranı RA hastalarında %23.7 iken, bu oran AS hastalarında %21.5 idi. İkinci ilaç değişim oranları RA hastalarında %5.5 ve AS hastalarında %4.3 bulundu. En sık görülen üç ilaç değişim nedeni sırası ile; ilaç etkinliğinin kaybı, yeni gelişen klinik durumlar ve yan etkilerdi. Kaplan-Meier analizie göre, ilk biyolojik ilaç tedavisinde kalım süresi, AS'de RA'ya göre daha yüksekti (p=0.039, Log-Rank test). İlk seçilen bDMARD'lar arasında, Etanercept ile ilaç tedavisinde kalım süresi AS'de RA hastalarından daha uzundu (p=0.036, Log-Rank test).*

***TARTIŞMA ve SONUÇ:*** *bDMARDs'ların ilk ve ikinci ilaç değişim oranları ve değişim nedenleri gruplar arasında benzerdi. İlk bDMARD tedavisinde kalım süresi, AS hastalarında RA hastalarından daha uzundu.*

***Anahtar Kelimeler:*** *Ankilozan spondilit, antiromatizmal ajanlar, romatoid artrit, değişim*

***ABSTRACT***

***INTRODUCTION:*** *Biological disease-modifying anti-rheumatic drugs (bDMARDs) have been used in the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS). The aim of the study was to investigate the switching patterns of bDMARDs, the drug survival rates and the reasons for switching in patients with RA and AS by means of Real-World data.*

***METHODS:*** *The study was designed as retrospective, single-center, and observational. One hundred and two patients (55 RA, 47 AS) who switched at least one biologic agent were included in the study. The drug survival time and causes of switching bDMARDs were recorded. The Kaplan-Meier analysis and Log-Rank tests were performed to analyze the survival curves of each biological agent and compare the results between groups.*

***RESULTS:*** *Of 102, 55 patients (53.9%) were RA, 47 patients (46.1%) were AS. First switching ratio of RA was 23.7% whilst it was 21.5% in AS. Second switching rates were 5.5% and 4.3% in RA and AS patients, respectively. The most three causes of switching were loss of efficacy, the occurrence of new clinical conditions, and adverse events. In the Kaplan-Meier analysis, the higher continuance of using the first bDMARD was observed in AS than in RA (p=0.039, Log-Rank test). Among the first bDMARDs, the drug survival rate of Etanercept was higher in AS patients than in RA. (p=0.036, Log-Rank test).*

***DISCUSSION AND CONCLUSION:*** *The first and second switching ratios of bDMARDs, and switching causes were similar between groups. The drug survival rate was longer in AS than in RA.*

***Keywords:*** *Ankylosing spondylitis, anti-rheumatic agents, survival, rheumatoid arthritis, switch*

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, and autoimmune disease characterized by joint and systemic involvement (1). Ankylosing spondylitis (AS) is a long-lasting disease generally depicted as inflammation in the axial skeleton, especially in sacroiliac joint (2). Even though the immunopathogenesis of RA and AS are different from each other (3,4), the treatment approach is partially similar.

The management of RA and AS has evolved over time (5,6). For almost 20 years, biological disease-modifying anti-rheumatic drugs (bDMARDs) including tumor necrosis factor inhibitors (TNFi) and non-tumor necrosis factor inhibitor agents (non-TNFi) have been taking part in treatment of RA and AS (7). Initially, these biologic drugs were used in patients with RA. Subsequently, they were begun to be used in AS, psoriatic arthritis, psoriasis, inflammatory bowel disease, and juvenile idiopathic arthritis. Etanercept (ETN) was the first TNFi approved for the treatment of RA in 1998. Then, Infliximab (IFX, 1999), Adalimumab (ADA, 2002), Abatacept (ABA, 2005), Rituximab (RTX, 2006), Certolizumab (CZP, 2008), Golimumab (GOL, 2009), Tocilizumab (TOC, 2010), Tofacitinib (TOF, 2012), Ustekinumab (2013), and Secukinumab (2016) were approved respectively (8). However, IFX was the first agent using in Turkey in 2002. Afterward, RTX (2002), ETN (2003), ABA (2009), GOL (2011), ADA (2012), CZP (2012), TOC (2012), TOF (2015), Ustekinumab (2017), and Secukinumab (2017) were started to be used, respectively (9).

Drug discontinuation including restarting, switching and stopping are fundamental problems in the way of management (10). Causes of switching drug include the lack or loss of efficacy, adverse effects, drug compliance and new clinical conditions (11). Reasons for discontinuation of treatment can be similar in both RA and AS. On the other hand, the switching rate has different ranges from study to study for both groups (11-15). Additionally, switching is related to drug survival rates defined long-term continuation of treatment. This rate indicates good treatment persistence and it is found to be associated with low healthcare costs. As a result of switching, drug survival rates may decrease (12-15).

Switching strategy includes cycling and swapping type. Cycling strategy is that changing treatment from the failure of the first-line TNFi to second-line TNFi, and swapping strategy is that choosing the non-TNFi agents (with a different mode of action) as the second-line treatment (11). According to EULAR recommendations for the management of RA and AS, TNFi can be used as second-line therapy after failing the first TNFi (5,6). On the other hand, some studies approved the superiority of the non-TNFi agents with a different mode of action as second-line treatment (16-19).

Real-World data is fundamental to clarify disease epidemiology, patterns of care, patients' conditions, treatment choices according to patients, and identification of treatment effectiveness and safety in clinical practice (20). Accordingly, we aimed to show Real-World switching patterns of bDMARDs, the drug survival rates and the reasons for switching in patients with RA and AS.

## METHODS

### Study Population

The study was designed as a retrospective, single-center, and observational study. The study was conducted according to the medical data of patients following between 1970 and 2017 at tertiary care hospital. The data was obtained from Çukurova university database, which contains medical history, demographic information, and records of taken medicines. Accordingly, 450 patients (232 RA, 218 AS) were screened and eligible patients were enrolled in the study. Inclusion criteria were as follows; i) the patients who were fulfilling the modified New York criteria for AS (21) and patients who met both the American Rheumatism Association 1987 revised criteria and American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA (22,23), ii) the patients switching at least one biologic drug. Fifty-five patients with RA and 47 patients with AS were included in the study. Local ethics committee of Çukurova University approved the study protocol (Date=7-JUL-2017, Ethical approval number=66).

The diagnosis, time interval between first symptoms and the diagnosis, laboratory outcomes, duration of using biologic drugs (drug survival),

adverse events causing of switching biological drugs, and new clinical conditions were recorded. During the follow-up of patients, emerging extra-articular manifestation such as uveitis and lung involvement was defined as new clinical conditions. Also, injection/infusion reactions, skin rash, infections, and malignancies were documented as adverse events. The medicines were noted as anti-TNFi (IFX, ETN, ADA, GOL, CZP), non-TNF biologics (ABA, TOC, RTX), and targeted synthetic DMARD (TOF). All bDMARDs were used at least 3 months after first administration. Conventional synthetic DMARDs including sulfasalazine, methotrexate, and hydroxychloroquine along with non-steroidal anti-inflammatory drugs (NSAIDs) were also recorded. The duration of using biologic drugs (drug survival data) was calculated for each patient (5,18). In addition, patients were evaluated in terms of the inefficacy of bDMARDs. Ineffectiveness consists of the lack of efficacy (primary treatment failure) and loss of efficacy (secondary treatment failure). While primary inefficacy is defined as the lack of expected effect from treatment, secondary inefficacy is accepted as the reduction in treatment effect over time (18).

**Statistical analysis**

Statistical analysis was performed by SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Clinical characteristics of the study population were assessed by the descriptive statistics. Continuous variables were checked for normality using the Shapiro-Wilk test. Mann-Whitney U test for continuous variables and Chi-Square test for categorical variables were used in order to test the differences in variables between groups. Kaplan-Meier analysis was used to estimate the drug survival of the bDMARD treatment. Cox regression models were used to estimate the Hazard Ratio (HR) of treatment discontinuation between groups. Results with p values less than 0.05 were reported as statistically significant.

**RESULTS**

After screening 450 patients (232 RA, 218 AS), 102 patients were included in the study. Of the study group, 55 patients (53.9%) were RA, 47 patients (46.1%) were AS. Sixty-one women (45 RA, 16 AS) and 41 men (10 RA, 31 AS) were included in the study. The median age was 54 years for RA and 39 years for AS. The median diagnosis delay was 1 month in RA and 30 months in AS. When compared the diagnosis delay between groups, it was statistically higher in AS patients (p=0.001). The median time of using conventional synthetic DMARDs and NSAIDs were 48 months in RA and 30 months in AS (p=0.106). The demographic and clinical characteristics of study population are given in Table 1.

**Table 1. Demographic and clinical characteristics of the study population**

| | Rheumatoid arthritis (n=55) | Ankylosing spondylitis (n=47) |
|---|---|---|
| **Age (year)[a]** | 54.0 (39.0−62.0) | 39.0 (31.0−48.0) |
| **Sex** | | |
| **Male[b]** | 10 (18.2) | 31 (66.0) |
| **Female[b]** | 45 (81.8) | 16 (34.0) |
| **Education (year)[a]** | 11.0 (5.0−11.0) | 11.0 (11.0−15.0) |
| **Disease duration (months)[a]** | 111.0 (60.0−180.0) | 141.0 (48.0−174.0) |
| **Using csDMARD duration (months)[a]** | 48.0 (22.0−96.0) | 30.0 (7.5−90.8) |
| **Drug administration** | | |
| **Oral[b]** | 1 (1.8) | - |
| **Subcutaneous[b]** | 37 (67.3) | 17 (36.2) |
| **Intravenous[b]** | 17 (30.9) | 30 (63.8) |
| **Mode of action*** | | |
| **TNFis[b]** | 46 (83.6) | 47 (100) |
| **Non-TNFis[b]** | 9 (16.4) | - |

**a Values are given as median (interquartile range)**
**bValues are given as n (%)**
*** This data is shown the initial biologic drug use**

Nine patients were using non-TNFi as the first bDMARD in RA patients. On the other hand, 46 patients in RA and 47 patients in AS were using TNFis as the first bDMARD. Nine patients switched another non-TNFi because of extra-articular involvement such as lung involvement. Twenty out of 46 RA patients who used to TNFis as the first bDMARD were switched to a TNFi (cycling strategy), and 25 patients received the drug

with a different mode of action (swapping strategy). The cycling and swapping ratio were 43.5% and 54.3% in RA, respectively. One RA patient switched from TNFi to TOF. All AS patients were switched from TNFi to other TNFi (cycling strategy).

When compared groups according to the duration of using first biological drug, it was longer in AS than in RA (p=0.039). First choice agent was ETN (29.1%) in RA and IFX (63.8%) in AS. According to the data, as patients were getting older, ETN choice was getting increased as the first agent in RA (p=0.023). However, there was not found any statistical significant variable clarifying the potential causes of choosing IFX as the first biological drug in patients with AS. Second choice agent was RTX (27.3%) in RA and ADA (40.4%) in AS (Table 2).

The most common cause of switching the first agent was drug inefficacy (n=88, 86.3%), which was observed 83.6% in RA and 89.4% in AS. When patients divided into primary inefficacy (lack of efficacy) and secondary inefficacy (loss of efficacy), 11 patients of 88 had lack of efficacy. Seven of 46 RA patients and 4 of 42 AS patients experienced primary inefficacy. The occurrence of new clinical condition (5.9%), adverse effects including injection/infusion reactions and skin rash (5.9%), incompatibility of drugs (drug compliance) (1.0%), and discontinuing the bDMARD because of remission (1.0%) were other reasons for switching or discontinuation of treatment. The causes of the first and second switching in patients with RA and AS are given in Table 3. While the first switching ratio of RA was 23.7% and that of AS was 21.5%, second switching ratio was 5.5% in RA, and 4.3% in AS patients. No statistically significance was found between groups (p=0.248). The median time of both first and second biological drug use was almost 2 times more in AS than in RA.

In the Kaplan-Meier analysis, drug survival rates for the first bDMARD in both groups are represented in Figure 1. Accordingly, the first biological agent use was longer in AS patients than in RA. For the first biological drug use, estimated median drug survival time was 24 months (95% CI:8.32-39.67 months) in AS patients and 12 months (95% CI:8.89-15.11 months) in RA patients (p=0.039, Log-Rank test). The second agent drug survival rates were not estimated because of the large censored data. The comparison of drug survival time of first-line TNFis between groups is shown in Figure 2 and 3. When analyzed drug survival duration of each TNFi, no statistically significance was found in RA patients (p=0.096, Log-Rank test). In contrast, ETN had higher drug survival in AS patients (p=0.036, Log-Rank test) (Table 4).

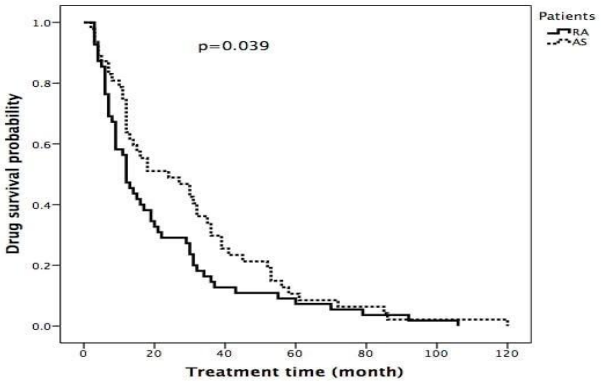


**Figure 1. First-line bDMARDs survival rates in RA and AS. Differences between RA and AS were analyzed using Log-Rank tests (p=0.039).**

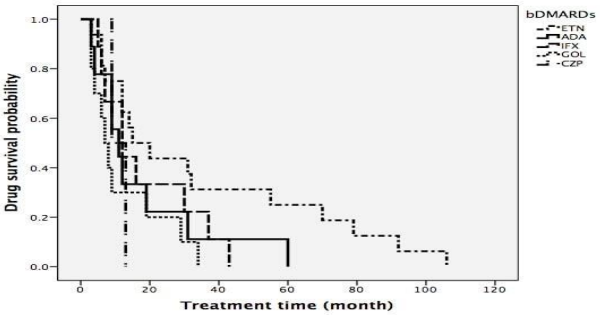


**Figure 2. First-line TNFi survival rates in RA**

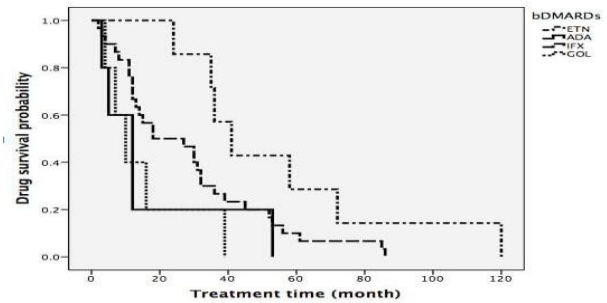


**Figure 3. First-line TNFi survival rates in AS**

**Table 2. Distribution of biological DMARDs as first and second choice in patients with Rheumatoid Arthritis and Ankylosing Spondylitis**

| | ETN | ADA | IFX | GOL | CZP | ABA | RTX | TOC | TOF |
|---|---|---|---|---|---|---|---|---|---|
| | **Rheumatoid arthritis** | | | | | | | | |
| **1st bDMARD** | 16 (29.1) | 9 (16.4) | 9 (16.4) | 10 (18.2) | 2 (3.6) | 5 (9.1) | 3 (5.5) | N/A | 1 (1.8) |
| **2nd bDMARD** | 9 (16.4) | 4 (7.3) | 2 (3.6) | 3 (5.5) | 6 (10.9) | 10 (18.2) | 15 (27.3) | 5 (9.1) | 1 (1.8) |
| | **Ankylosing spondylitis** | | | | | | | | |
| **1st bDMARD** | 7 (14.9) | 5 (10.6) | 30 (63.8) | 5 (10.6) | N/A | N/A | N/A | N/A | N/A |
| **2nd bDMARD** | 9 (19.1) | 19 (40.4) | 9 (19.1) | 5 (10.6) | 5 (10.6) | N/A | N/A | N/A | N/A |

**Values are given n (%); N/A, not available**

**ETN, Etanercept; ADA, Adalimumab; IFX, Infliximab; GOL, Golimumab; CZP, Certalizumab pegol; ABA, Abatacept; RTX, Rituximab; TOC, Tocilizumab; TOF, Tofasitinib; 1st bDMARD, first-line biological disease modifying antirheumatic drugs; 2nd bDMARD, second-line biological disease modifying antirheumatic drugs**

**Table 3. The frequencies of first and second switching causes in patients with Rheumatoid arthritis and Ankylosing spondylitis**

| | **First switching** | | **Second switching** | |
|---|---|---|---|---|
| | Rheumatoid arthritis | Ankylosing spondylitis | Rheumatoid arthritis | Ankylosing spondylitis |
| **Inefficacy** | 46 (83.6) | 42 (89.4) | 16 (29.1) | 8 (17.0) |
| **Occurrence of new clinical condition** | 5 (9.1) | 1 (2.1) | 2 (3.6) | N/A |
| **Adverse effect** | 2 (3.6) | 4 (8.5) | N/A | 2 (4.3) |
| **Drug incompatibility** | 1 (1.8) | N/A | N/A | N/A |
| **Discontinuation** | 1 (1.8) | N/A | 2 (3.6) | N/A |

**Values are given n (%); N/A, not available**

**Table 4. The comparison of drug survival rates for each TNFi using as the first-line treatment between rheumatoid arthritis and ankylosing spondylitis**

| | **Rheumatoid arthritis** | | | | **Ankylosing spondylitis** | | | |
|---|---|---|---|---|---|---|---|---|
| | Median survival time (month) | Std. Error | 95% Confidence Interval | p | Median survival time | Std. Error | 95% Confidence Interval | p |
| **ETN** | 15.0 | 6.0 | 3.24−26.76 | | 41.0 | 6.54 | 28.16−53.83 | |
| **ADA** | 11.0 | 2.98 | 5.15−16.84 | | 12.0 | 3.13 | 5.86−18.13 | |
| **IFX** | 12.0 | 3.72 | 4.96−19.30 | 0.096 | 18.0 | 8.21 | 1.89−34.10 | **0.036*** |
| **GOL** | 7.0 | 1.58 | 3.90−10.09 | | 10.0 | 3.28 | 3.55−16.44 | |
| **CZP** | 9.0 | - | - | | - | - | - | |

***p <0.05, p values represent Log-Rank tests**

**ETN, Etanercept; ADA, Adalimumab; IFX, Infliximab; GOL, Golimumab; CZP, Certalizumab pegol**

**DISCUSSION**

In the present study, we investigated the switching patterns of bDMARDs, drug survival rates, and causes of switching in RA and AS patients based on Real-World data. Several papers and drug retention studies based on different registries have studied these parameters in each disease (12,13,18,24-26), but the articles comparing of them between RA and AS are scarce in the literature.

When compared groups, no differences were found in respect to the rates of first and second switching. The first and second switching ratios in RA patients were found as 23.7% and 5.5%, respectively. The study conducted by Rashid et al. was observed that the first switching ratio was 12% in patients with RA. According to the literature, the rates could be different range from 7.8% to 30-40% (14,27). On the other hand, no certain data that show the second switching rates in RA have been published. A study from Korea investigating the switching medicine in RA patients suggested that 32.3% of patients were at least one-time switchers (28). In the present study, 21.5% and 4.3% were found as the first and second switching ratios in AS patients. Gulyas et al. showed that the almost half of patients switched to second TNFis and 14.3% of patients altered to the third TNFis (29). The lower rate was observed in the data from five Norwegian rheumatology departments (NOR-DMARD registry) (30).

In the current study, the cycling rate was 43.5% whilst swapping rate was 54.3% in RA patient. Besides that, the cycling rate was 100% in AS patients. Even though we preferred TNFi cycling for patients with AS, two types of switching strategy (cycling and swapping) can be chosen to change the treatment. Cycling strategy has been remained as a controversial treatment choice for both diseases. Because cycling strategy targets the same mode of action with the previous drug that not inhibit the disease activity (11). According to the EULAR recommendations for the management of RA and AS, TNFis might be selected as the second-line biologic drug (5,6). Some papers have supported the cycling strategy (31,32), whereas some studies have claimed that the swapping strategy is more useful and cost-effective treatment approach than the cycling. Additionally, after choosing TNFis as second or third-line treatment, the achievement of decreased disease activity via these agents is less observed in comparison with non-TNF biologics (16,17,27,33) Cycling strategy was frequently selected in the past because of the lack of alternative options for the treatment, but nowadays, swapping strategy seems to have a promising future (11,16).

In the present study, when compared the drug survival of first agent between groups, the treatment duration was longer in AS patients than in RA patients. Heinonen et al. showed that drug survival rates was 75% at 2 years for first TNFi in AS (34). In a different study, the authors found that drug survival of first TNFi and non-TNFi was almost one year in RA patients (12). The comparison of drug (TNFi) survival between RA and AS was studied using the data from Spanish registry for adverse events of biological therapy in rheumatic diseases (BIOBADASER). Accordingly, they showed that treatment persistence was greater in AS than in RA (13).

Common causes of switching bDMARDs in RA are the lack of efficacy, the loss of efficacy and adverse events including injection/infusion reactions, infections, and malignancies (11,25,26). Patients' preference, drug compliance and new clinical conditions such as interstitial lung disease are the other reasons for changing the therapy (27). Similar reasons are observed in AS (24,29). In the present study, drug inefficacy (the lack of efficacy and the loss of efficacy), adverse events (injection/infusion reactions and skin rash), and existence of new clinical conditions accepted as the extra-articular manifestations (uveitis, lung involvement) were defined as causes of the drug switching in both groups. However, the drug inefficacy, especially loss of efficacy, was the most recorded reason. Neither infection, nor malignancy was identified in our study population.

In current study, the initial drug choice was different between both diseases. Accordingly, whereas ETN was preferred in RA, IFX was selected in AS. In some registries, ETN and IFX were found the most two biologic drugs as the first choice of the treatment in RA (25,35). We found that ETN selection tended to be higher in older RA patients. On the other hand, any obvious reason could not be shown to clarify why IFX choice was

plentiful. The preference might depend on the patient's choice, patient's clinical conditions (e.g. lung involvement), and/or the country's health care insurance. Also, cost-effectiveness is the other factor in order to select these agents. According to the multidisciplinary expert panel (the Italian board for the Tailored BIOlogic therapy (ITABIO), they agreed with that ETN and biosimilar IFX had a better cost-effective profile in RA (35). Similar to RA, IFX and ETN were chosen as the first-line bDMARD in patients with AS. Two studies conducted by Rudwaleit et al. and Gulyas et al. showed that IFX was the first choice biological drug in AS (29,36). According to a few studies, ETN was used as the first treatment (24,34). Although ETN and the other TNFis are as effective as IFX in the treatment of AS, there is a tendency to choose IFX or biosimilar IFX, particularly, as the first-line therapy (35).

**Limitations of the Study**

The current study has some limitations. Initially, the retrospective nature of the study may be prone the treatment selection bias. Secondly, the study population is small to interpret results precisely. Finally, laboratory outcomes that were obtained distinct laboratories, were not analyzed not to make the results complicated, thus, the important laboratory outcomes including ACPA, rheumatoid factor and HLA-B27 could not be involved in the study. We also did not calculate disease activities due to the lack of data. The strength of the study may be that comparing Real-World switching patterns of bDMARDs between RA and AS. As far as we know, there are not enough papers that compare the switching rates and reasons between both diseases in the literature.

**Conclusion**

In conclusion, when we interpreted the comparison of switching ratio of biological DMARDs, the drug survival rates and the reasons for switching between RA and AS patients, we found the similar first and second switching ratios, and similar switching causes in both groups. Accordingly, the most detected reason for switching was the lost of drug efficacy. This result suggests that drug discontinuation in both diseases is frequently related to the secondary inefficacy. Additionally, we found that the drug survival rate was longer in AS than in RA. This result is compatible with good treatment persistence and suitable costs.

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