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INVESTIGATING THE CAUSES AND INCIDENCE OF MORTALITY IN PATIENTS USING BIOLOGICAL DISEASE MODIFYING ANTIRHEUMATIC DRUG (DMARD) AND THE MORTALITY RATES THEREOF COMPARED TO THE GENERAL POPULATION

BİYOLOJİK HASTALIK MODİFİYE EDİCİ ANTİROMATİZMAL İLAÇ (BDMARD) KULLANAN HASTALARIN MORTALİTE NEDENLERİNİN, MORTALİTE İNSİDANSLARININ VE GENEL TOPLUMA ORANLA MORTALİTE ORANLARININ ARAŞTIRILMASI

Mehmet Ali BALCI[1], Lütfi AKYOL [1]

ABSTRACT

AIM: Disease-modifying antirheumatic drugs (DMARDs) are used in the treatment of most rheumatological diseases. There is a number of studies available in the literature, in which the effect of DMARDs on mortality has been investigated; however these studies were generally performed on rheumatoid arthritis (RA), and on tumor necrosis factor inhibitors (TNFi) in particular. Hence, we aimed to conduct a more comprehensive study investigating the effects of using abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, secukinumab, tofacitinib and tocilizumab on mortality in patients with RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), Behçet's disease, systemic lupus erythematosus (SLE), Takayasu's arteritis, systemic sclerosis (SSc), Sjogren's syndrome and other rheumatological diseases.

MATERIAL AND METHOD: Eight hundred forty seven patients that have used bDMARDs were included in our study. Age, gender, diagnosis and treatment information of these patients were retrospectively scanned and recorded. Death records were obtained from the National Death Notification Service, whereas the population records were obtained from the Turkish Statistical Institute. bDMARD-related incidence rates (IRs) for mortality was calculated.

RESULTS: A total of 847 patients, 464 (54.8%) of whom were female and 383 (45.2%) of whom were male, were included in the study. Mortality occurred in a total of 18 patients (2.1%) during the treatment process. Of these 18 patients, 5 patients were using rituximab, 4 patients were using infliximab, 3 patients were using adalimumab, 3 patients were using etanercept, 2 patients were using tocilizumab, and 1 patient was using golimumab. In terms of the mortalities by the type of diagnosis, 13 mortalities occurred in the group of patients diagnosed with RA, whereas 1 mortality occurred in each of the groups consisting of patients diagnosed with AS, PsA, Takayasu arteritis, granulomatosis with polyangiitis (Wegener's) or SSc. The overall mortality incidence of the patients was calculated as 5.28 cases per 1000 years. Compared to the general population, the standardized mortality ratio (SMR) of the patients using bDMARDs was found to be 3.147 ((confidence interval (CI): 1.924-4.877)).

CONCLUSION: Our study is the first mortality study conducted in Turkey on patients with rheumatologic disease that use bDMARDs. The incidence rate (IR) for mortality we have found in patients using bDMARDs was comparable to the IRs reported in the literature, however we have found a higher standart mortality ratio (SMR) in our cohort compared to the Turkish population. In this respect, it is necessary to conduct larger-scale controlled studies.

Keywords: Antirheumatic agents, mortality, rheumatic diseases

ÖZET

AMAÇ: Romatolojik hastalıkların çoğunun tedavisinde hastalık modifiye edici antiromatizmal ilaç (DMARD) kullanılmaktadır. Literatürde yapılan çalışmalarda DMARD'ların mortalite üzerine etkisi araştırılmış fakat bu çalışmalar genellikle romatoid artritte (RA) ve genellikle tümör nekroz faktör inhibitörlerinin (TNFi) üzerinde yapılmıştır. Biz ise daha kapsamlı olarak RA, ankilozan spondilit (AS), psöriatik artrit (PsA), Behçet hastalığı, sistemik lupus eritematozus (SLE), Takayasu arteriti, sistemik skleroz (SSc), Sjögren sendromu ve diğer romatolojik hastalıklarda abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliksimab, rituksimab, secukinumab, tofacitinib ve tocilizumab kullanımının mortalite üzerine etkisini araştırmayı amaçladık.

GEREÇ VE YÖNTEM: Çalışmamıza bDMARD kullanan 847 hasta alındı. Hastaların yaş, cinsiyet, tanı, tedavi verileri retrospektif olarak taranıp kayıt edildi. Ölüm kayıtları Ulusal Ölüm Bildirim Sistemi'nden nüfus kayıtları Türkiye İstatistik Kurumu'ndan alındı. bDMARD ilişkili mortalite insidans oranları hesaplandı.

BULGULAR: Çalışmaya 464 (54,8%) kadın, 383 (45,2%) erkek olmak üzere toplam 847 hasta alındı. Tedavi sürecinde rituksimab, infliksimab, adalimumab, etanercept, golimumab ve tocilizumab kullanan hastalarda (sırasıyla; 5, 4, 3, 3, 1, 2) olmak üzere toplam 18 hastada (%2,1) mortalite gerçekleşti. Tanıya göre bakıldığında RA, AS, PsA, Takayasu arteriti, granülomatozisli polianjitis (Wegener granülomatozis), SSc tanılı hastalarda mortalite gerçekleşti (sırasıyla; 13, 1, 1, 1, 1, 1). Hastaların genel mortalite insidansı 1000 hasta yılında 5,28 vaka olarak tespit edildi. Genel nüfusa oranla bDMARD kullanan hastaların standart ölüm oranı (SMR) 3,147 (CI: 1,924-4,877) olarak saptandı.

SONUÇ: Çalışmamız Türkiye'deki bDMARD kullanıp romatolojik hastalığı olan hastalarda yapılan ilk mortalite çalışmasıdır. Çalışmamızda genel olarak bDMARD kullanan hastalarda literatüre benzer bir mortalite insidans oranı tespit ettik; fakat kohortumuzda Türk toplumuna göre yüksek bir SMR saptadık. Bu açıdan daha geniş ölçekli, kontrol gruplu çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: Antiromatizmal ajanlar, mortalite, romatizmal hastalıklar

[1] Department of Internal Medicine, Division of Rheumatology, Health Sciences University, Gazi Yaşargil Training and Research Hospital, Diyarbakır,Turkey

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Sorumlu Yazar / Corresponding Author:
Mehmet Ali BALCI
Department of Internal Medicine, Division of Rheumatology, Health Sciences University, Gazi Yaşargil Training and Research Hospital, Diyarbakır,Turkey
Gsm: +90 530 346 22 98 **Fax:** +90 (412) 258 00 60
E-mail: abalci13@gmail.com

Yazar Bilgileri /Author Information:
Mehmet Ali BALCI (ORCID: 0000-0003-0597-7788),
Lütfi AKYOL (ORCID: 0000-0001-6652-4008) E-mail: drakyol19@gmail.com

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INTRODUCTION

Immunosuppressive agents are used in the treatment of rheumatological diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and systemic lupus erythematosus (SLE). These immunosuppressive agents are generally called disease-modifying antirheumatic drugs (DMARDs). DMARDs are divided into 3 subgroups as conventional synthetic (cs) DMARDs (methotrexate, leflunomide, sulfasalazine), biological (b) DMARDs (tumor necrosis factor inhibitors [adalimumab, certolizumab pegol, etanercept, golimumab, infliximab], abatacept, rituximab, tocilizumab, secukinumab, sarilumab and biosimilar DMARDs), and targeted synthetic (ts) DMARDs (the Janus kinase inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib) (1). There is a number of meta-analyses available in the literature, in which the effect of biological treatments on mortality has been investigated; however these studies were generally conducted on rheumatoid arthritis and on tumor necrosis factor inhibitors (TNFi) in particular (2-5). Additionally, a review of the relevant literature did not reveal any mortality studies conducted in Turkey on the patients with rheumatic disease that use bDMARDs. Hence, we aimed to conduct a more comprehensive study investigating in general the causes and incidence of mortality in patients using bDMARDs and the mortality rates thereof compared to the general population, and in particular the effects of using abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, secukinumab, tofacitinib and tocilizumab on mortality in patients with RA, AS, Psoriatic Arthritis (PsA), Behçet's disease, SLE, Takayasu's arteritis, systemic sclerosis (SSc), Sjogren's syndrome and other rheumatological diseases.

MATERIAL AND METHOD

Eight hundred forty seven patients who applied to the University of Health Sciences, Gazi Yaşargil Training and Research Hospital Rheumatology Outpatient Clinic and used bDMARDs between 2010 and 2020 were included in the study. Age, gender, diagnosis and treatment information of these patients were retrospectively scanned and recorded. The study was conducted in accordance with the Helsinki Declaration and ethical permission was obtained from ethical review board of University of Health Sciences, Gazi Yaşargil Training and Research Hospital (29.01.2021, No: 660). The diagnosis information were taken from the database of our hospital based on the coding set forth in the 9th revision of the International Classification of Diseases (ICD-9). All patients with rheumatic diseases over the age of 18 who used bDMARD were included in the study. Death records were obtained from the National Death Notification Service (6). The data regarding the number of deaths that occurred in the Turkish population of the same age and sex were taken from the data base of the Turkish Statistical Institute (7). Incidence rate (IR) for mortality was calculated by dividing the number of mortalities by the total amount of person-time in the cohort. 95% confidence intervals (CIs) were calculated for IRs using the Byar's formula (8). Head-to-head comparisons were made among the biological agents in terms of mortality rates. The standardized mortality ratio (SMR) was calculated by dividing the number of mortalities observed in the cohort by the number of deaths occurred in the Turkish population of the same age and gender. Statistical analyses were carried out using the SPSS V22.0 (IBM, Armonk, NY) software. Chi-square test was used to compare the categorical data. Cumulative survival curves were created using the Kaplan-Meier method. Cox regression analysis was carried out to determine the risk factors affecting survival. Values of $p<0.05$ were considered to be statistically significant.

RESULTS

A total of 847 patients, 464 (54.8%) of whom were female and 383 (45.2%) of whom were male, were included in the study. The mean age of the patients was calculated as 42.3 ± 13.9 years, whereas the mean duration of medication use of the patients was calculated as 44.8 ± 36.4 months. Mortality occurred in a total of 18 patients (2.1%) during the treatment process. Of these 18 patients, 5 patients were using rituximab, 4 patients were using infliximab, 3 patients were using adalimumab, 3 patients were using etanercept, 2 patients were using tocilizumab, and 1 patient was using golimumab. No mortalities were observed in patients using abatacept, secukinumab, certolizumab pegol or tofacitinib. The overall survival analysis of the patients who have been using bDMARDs is shown in **Figure 1,** whereas the individual survival analysis of the patients based on the type of bDMARD they have been using is shown in **Figure 2.**

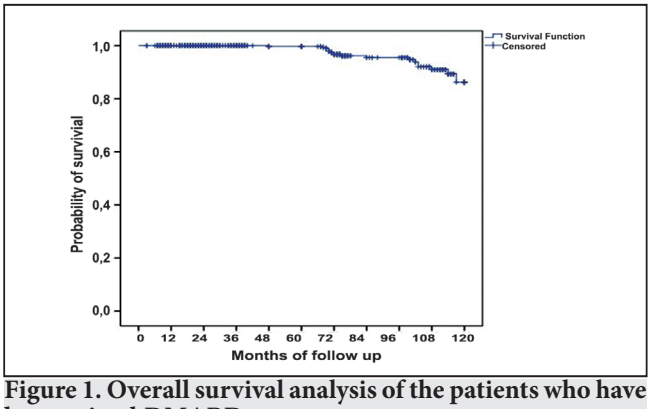

Figure 1. Overall survival analysis of the patients who have been using bDMARDs

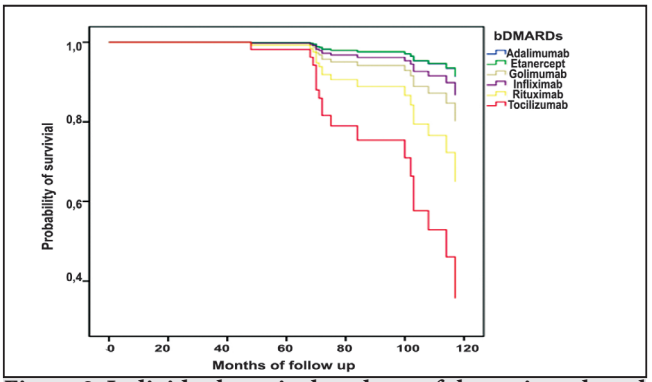

Figure 2. Individual survival analyses of the patients based on the type of the bDMARD they have been using

In terms of the mortalities by the type of diagnosis, 13 mortalities occurred in the group of patients diagnosed with RA, whereas 1 mortality occurred in each of the groups consisting of patients diagnosed with AS, PsA, Takayasu arteritis, granulomatosis with polyangiitis or SSc. The patients were followed up for a total of 3,410 patient-years. Breakdown of the patients years in descending order by the types of the bDMARDs revealed that the patients who have been using etanercept, adalimumab, infliximab, golimumab, rituximab, tocilizumab, certolizumab pegol, tofacitinib, abatacept and secukinumab were followed up for 855, 845, 522, 438, 322, 152, 125, 62, 58, and 26 patient-years, respectively.

The overall mortality incidence of the patients was calculated as 5.28 cases per 1000 years. Breakdown of the mortality incidences in ascending order by the types of the bDMARDs revealed that mortality incidence of the patients who have been using etanercept, adalimumab, infliximab, golimumab, rituximab, and tocilizumab were 3.51, 3.55, 7.66, 2.29, 15.52, 13.15, respectively. Of the 847 patients, 100 patients (11.8%) were determined to have switched from one biological to another. The highest rate (25%) of switching to another biological was observed in the patients who have been using abatacept. The diagnoses, treatment data, clinical features and mortality incidences of the patients are shown in **Table 1.**

Compared to the general population, the SMR of patients using bDMARDs was found to be 3.147 (CI: 1.924-4.877). Breakdown of the SMRs of patients by the age groups revealed that the patients between the ages of 55-64 had the highest SMR, which is 7.252 (CI: 2.939-15.080). The SMR value of the patients included in the 15-44 age group compared to the general population could not be calculated, since no mortality had occurred in the said age group in our cohort. In conclusion, it was determined that the mortality rates in patients using bDMARDs were higher compared to the general population. The related data are given in **Table 2** in detail.

Head-to-head comparisons of the patient groups using different bDMARDs in terms of the increases observed in mortality risks revealed that the highest increase was observed in the group of patients who have been using tocilizumab, in comparison with the group of patients who have been using etanercept (HR: 21.701, CI: 1.931-243.893, p: 0.013). The related data are given in **Table 3** in detail.

Table 1. Clinical features and mortality rates of patients by the types of biological treatment

	Abatacept	Adalimumab	Etanercept	Golimumab	Infliximab	Rituximab	Secukinumab	Certolizumab pegol	Tofacitinib	Tocilizumab	Total
Gender (F/M/T)	7/5/12	80/102/182	71/89/147	78/69/147	46/45/91	76/17/93	7/8/15	37/23/60	29/3/32	42/13/55	464/383/847
Age (year), mean±sd	52,3±17,9	38,3± 13,5	40,2±11,5	40,2±11,0	40,1±14,0	51,4±15,2	39,2±9,6	38,1±11,1	54,5±12,5	50,8±14,8	42,3±13,9
Duration of treatment (month), mean±sd	53,0±27,3	51,6±39,0	60,3±37,8	30,9±22,0	67,5±42,2	40,9±37,1	15,5±4,3	20,0±10,9	21,2±15,2	29,9±24,1	44,8± 36,4
Follow-up/ patient-years	58	845	855	438	522	322	26	125	62	152	3.410
incidence of mortality/ per 1.000 years	NA	3.55	3.51	2.29	7.66	15.52	NA	NA	NA	13.15	5.28
Switch, %	25	14.2	12.2	12.9	18.6	3.2	6.6	10	6.2	9.1	11.8
Death, n	0	3	3	1	4	5	0	0	0	2	18
RA, n/d	12/0	60/3	60/2	38/0	30/3	56/3	0/0	14/0	32/0	47/2	349/13
AS, n/d	0/0	104/0	98/1	103/0	40/0	0/0	10/0	44/0	0/0	0/0	399/1
PsA, n/d	0/0	11/0	2/0	6/1	2/0	0/0	5/0	2/0	0/0	0/0	28/1
Behçet, n/d	0/0	7/0	0/0	0/0	15/0	0/0	0/0	0/0	0/0	0/0	22/0
SLE, n/d	0/0	0/0	0/0	0/0	0/0	12/0	0/0	0/0	0/0	0/0	12/0
Takayasu, n/d	0/0	0/0	0/0	0/0	4/1	0/0	0/0	0/0	0/0	7/0	11/1
SSc, n/d	0/0	0/0	0/0	0/0	0/0	9/1	0/0	0/0	0/0	0/0	9/1
Wegener, n/d	0/0	0/0	0/0	0/0	0/0	8/1	0/0	0/0	0/0	0/0	8/1
Sjogren, n/d	0/0	0/0	0/0	0/0	0/0	6/0	0/0	0/0	0/0	0/0	6/0
Others*, n/d	0/0	0/0	0/0	0/0	0/0	2/0	0/0	0/0	0/0	1/0	3/0

F: female, M: male, T: total, sd: standard deviation, RA: rheumatoid arthiritis, AS: ankylosing spondylitis, PsA: psoriatic arthritis, SLE: systemic lupus erythematosus, SSc: systemic sclerosis, NA: not available, n: number, d: death, Others*: polymyalgia rheumatica, familial mediterranean fever, dermatomyositis, adult-onset Still disease, polyarteritis nodosa

Table 2. SMRs by age groups

Age bracket	Number of deaths	Number of patients	SMR (CI)
18-24	0	71	NA
25-34	0	202	NA
35-44	0	241	NA
45-54	5	164	11.54 (4.229-25.58)
55-64	6	103	7.252 (2.939-15.08)
65-74	3	53	2.667 (0.6785-7.259)
75-84	4	13	2.824 (0.8973-6.812)
Total	18	847	3.147 (1.924-4.877)

SMR: Standardized mortality ratio, CI: Confidence interval, NA: not available

Table 3. Head-to-head comparisons of various bDMARD treatments by mortality risks

bDMARDs	HR	CI	p
Adalimumab vs Etanercept	1.070	0.215-5.318	0.934
Golimumab vs Adalimumab	1.630	0.147-18.012	0.690
Golimumab vs Etanercept	3.652	0.228-58.389	0.326
Golimumab vs İnfliximab	4.118	0.227-74.636	0.306
İnfliximab vs Adalimumab	1.462	0.325-6.566	0.620
İnfliximab vs Etanercept	1.351	0.299-6.105	0.695
Rituximab vs Adalimumab	4.525	1.081-18.944	**0.038**
Rituximab vs Etanercept	4.841	1.53-20.329	**0.017**
Rituximab vs Golimumab	3.305	0.369-29.592	0.257
Rituximab vs İnfliximab	2.906	0.769-10.989	0.100
Tocilizumab vs Adalimumab	8.972	1.236-65.141	**0.030**
Tocilizumab vs Etanercept	21.701	1.931-243.893	**0.013**
Tocilizumab vs Golimumab	3.188	0.243-41.778	0.361
Tocilizumab vs İnfliximab	16.623	1.435-192.636	**0.025**
Tocilizumab vs Rituximab	1.649	0.301-9046	0.561

HR: Hazard Ratio, CI: 95% Confidence Intervals, bDMARD: biological disease modifying antirheumatic drug

Table 4. The clinical features, laboratory results and causes of death of the patients who had died during the follow-up period

Age/Gender	Follow-up period (months)	Diagnosis	bDMARD	Causes of death
62/M	72	RA	Adalimumab	Cardiac arrest
66/M	68	RA	Adalimumab	Pneumonia, sepsis
67/F	103	RA	Adalimumab	Cardiac arrest
50/F	103	RA	Etanercept	Metastatic breast cancer, arf
57/F	70	AS	Etanercept	Cardiac arrest, crf, amyloidosis
64/F	102	RA	Etanercept	Unknown
49/F	70	PsA	Golimumab	Murder
47/F	114	Takayasu	İnfliximab	Unknown
55/F	108	RA	İnfliximab	Lumbar abscess, sepsis
77/F	75	RA	İnfliximab	Pneumonia, sepsis
73/F	100	RA	İnfliximab	Cardiac arrest
48/M	117	RA	Rituximab	Lung adenocarcinoma, pneumosepsis
50/F	71	Wegener	Rituximab	Cardiac arrest
62/F	72	SSc	Rituximab	Cardiac arrest
75/M	70	RA	Rituximab	Sepsis
75/M	69	RA	Rituximab	Cardiac arrest
55/F	48	RA	Tocilizumab	Sepsis
83/M	84	RA	Tocilizumab	CVA

arf: acute renal failure, crf: chronic renal failure, bDMARD: biological disease modifying antirheumatic drug, RA: rheumatoid arthiritis, AS: ankylosing spondylitis, PsA: psoriatic arthritis, SSc: systemic sclerosis, CVA: cerebrovascular accident.

Causes of deaths in our cohort were determined as cardiovascular diseases (7 deaths), infectious diseases (5 deaths), malignancies (2 deaths), cerebrovascular disease (1 death), murder (1 death), and unknown causes (2 deaths). The clinical features, laboratory results and causes of death of the patients who had died during the follow-up period are summarized in **Table 4.**

DISCUSSION

In this study, we evaluated the relationship between bDMARD use and mortality in a cohort of rheumatic diseases. Our study is the most comprehensive study available in the literature investigating the effects of biological treatments on mortality taking different types of rheumatological diseases and bDMARDs into consideration. Our findings revealed an increase in general in the mortality rates in patients using bDMARDs compared to the general population (SMR: 3.147 [CI:1.924-4.877]) (5). In a study conducted in Sweden, SMR was found as 1.50 in both groups of RA patients that have (SMR: 1.03 to 1.96) and have not (SMR: 1.14 to 1.86) been using TNFis compared to the general population. In other words, although an increase was observed in the SMRs of patients with RA compared to the general population, TNFi use did not play a part in this increase (4). In two other studies, SMRs in RA patients using TNFis were found as 1.49 (95% CI 1.36 to 1.63) (5) and 0.82 (0.47-1.19) (9) , whereas the SMR we have found was higher than the SMRs reported in the literature.

In some studies (5, 10) it was reported that the TNFi use reduced the mortality risk in patients with RA in general, despite the fact that the breakdown of the relationship between the TNFi use and the mortality risk by the types of TNFis was not laid out in these studies; whereas in other studies (2, 11-13), it was reported that the TNFi use did not increase the risk of mortality in patients with RA. In another study, it was reported that TNFi use reduced the risk of mortality in female RA patients, but it did not have any effect on male RA patients (4). Yet in another study, TNFi use was found to have reduced mortality in RA patients with more than two comorbidities (3).

The overall mortality incidence of the patients was calculated as 5.28 cases per 1000 years, which is comparable to the results reported in the literature. To give an example, in a study conducted on patients with RA using infliximab, etanercept and adalimumab, the overall mortality incidence was found as 5.34 per 1000 person years (95% CI 4.20 to 6.69) (9).

The breakdown of the mortality incidences by the type of treatment revealed the following results: Mortality incidence in patients using adalimumab was found as 3.55 per 1.000 years, which is comparable to the results reported in several studies available in the literature. To cite a few of these articles; the mortality incidence of RA patients using adalimumab was found as 3.3/1000 per years in a study conducted in the United States of America (14) , and as 13 per 1000 person - years in another study conducted in Sweden (15).

Mortality incidence in patients using etanercept was found as 3.51 per 1.000 years, which is lower than the results reported in another study (15), in which the mortality incidence of RA patients using etanercept was found as 9 death per 1000 person-years (95% CI 7–12). Mortality incidence in patients using infliximab was found as 7.66 per 1.000 years, which is lower than the results reported in another study (15), in which the mortality incidence of RA patients using infliximab was found as 12 deaths per 1000 person-years (95% CI 9–15).

Mortality incidence in patients using rituximab was found as 15.52 per 1.000 years, which is lower than the incidence of mortality reported in another study (16) available in the literature. In the said study, the patients with RA and interstitial lung disease were compared in terms of mortality on the basis of using either rituximab or TNFi, and the mortality in those using rituximab was found to be 53.0 per 1000 person years, which is lower than the mortality in those using TNFi, which was found to be 94.8 per 1000 person years (95% CI: 74.4 to 118.7).

Lastly, mortality incidences in patients using golimumab and tocilizumab were found as 2.29 per 1.000 years and 13.15 per 1.000 years, respectively. However, we could not compare our results with the results of other studies as we could not find any other publications in the literature with mortality data in patients with rheumatologic disease using golimumab or tocilizumab.

Since tocilizumab and rituximab are also used in diseases with higher mortality such as vasculitis, it may have caused a higher mortality rate in patients using this drug compared to other drug groups.

Head-to-head comparison of biological treatments revealed that the highest increase in the risk of mortality was between the patients using tocilizumab and patients using etanercept (HR: 21.701, CI: 1.931-243.893, p: 0.013); whereas no significant difference was found between the patients that use infliximab, etanercept or adalimumab. This is a comparable result to the results available in the literature, where no significant difference was reported in terms of mortality between the patients that use infliximab, etanercept or adalimumab (3).

Of the 847 patients, 100 patients (11.8%) were determined to have switched from one biological to another. The breakdown of the number of patients switched from one biological to another based on the type of treatment revealed that 14.2% of patients using adalimumab, 12.2% of patients using etanercept, and 18.6% of patients using infliximab have switched to another biological, whereas in another study, it was found that 25% of patients using

adalimumab, 19% of patients using etanercept, and 35% of patients using infliximab have switched to another biological (15). The reason we have found lower results in our study may be due to the fact that the total follow-up time (3,410 patient-years) in our study was lower than the total follow-up time (19,118 person-years) in the said study (15).

Causes of deaths in our cohort were determined as cardiovascular diseases, infectious diseases, malignancies, cerebrovascular disease, murder and other diseases, which are comparable to the results reported in the literature (11).

The limitations of our study were that it was a retrospective study, that 1000 person-years was relatively a low value due to the low number of patients included in the study in spite of the 10-year follow-up period, that the fatal infection rate and the fatal malignancy incidence rate could not be calculated separately due to the low number of mortality, that separate mortality analyses based on the diagnoses could not be performed since mortalities by the types of rheumatological diseases were not homogeneously distributed, heterogeneity of disease groups and that no comparison can be made in terms of mortality with the patients that did not use TNFi as we did not have a control group that did not use TNFi. Mortality rates of diseases such as Wegener's, SSc and SLE will be different from AS, PsA and RA. On the other hand, the strengths of our study were that it included a wide range of rheumatological diseases and bDMARDs, and that it was the first mortality study on this subject conducted in Turkey.

CONCLUSIONS

Our study is the first mortality study conducted in Turkey on patients with rheumatologic disease that use bDMARDs. The incidence rate (IR) for mortality we have found in patients using bDMARDs in general was higher compared to the Turkish population and comparable to the IRs reported in the literature. However it was not possible to conclude that it was in fact the bDMARDs that have caused an increase in the mortality rate, as we could not compare our cohort with the group of rheumatologic patients who did not use bDMARDs, which is why larger-scale controlled studies are needed.

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