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Assessment of the effect of DMARD use on the mortality of patients with rheumatoid arthritis

Romatoid artrit hastalarında DMARD kullanımının mortalite üzerine etkisinin araştırılması

Mehmet Ali Balcı, Lütfi Akyol

University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Diyarbakır, Turkey

Abstract

Objective: The aim of this study was to investigate the causes of mortality in patients diagnosed with rheumatoid arthritis (RA) and the effects of disease-modifying antirheumatic drugs (DMARDs) to be used for treating RA on mortality.

Methods: A total of 743 patients with RA over the age of 18 who attended between 2010 and 2020 in the hospital where this study was conducted, were included in the study. The patients' clinical and laboratory information were obtained from the hospital database, whereas the relevant mortality and population data were obtained from the Turkish Ministry of Health system and the Turkish Statistical Institute, respectively. The standardized mortality ratio (SMR) was calculated by dividing the number of mortality observed in the cohort by the number of mortality in the Turkish population of the same age and gender. Patients were divided into two groups: Those who used only conventional (cDMARDs) and those who took cDMARDs plus biological (bDMARDs).

Results: Mortality occurred in 61 patients from the 743 patients with RA. SMR of the patients with RA was found to be 1.42 [confidence interval (CI) 1.09-1.81)] in the Turkish population. SMR was determined to be higher in the cDMARD cohort than in the bDMARD cohort [2.05 (CI 1.53-2.69) and 0.66 (CI 0.37-1.11), respectively]. The most common causes of mortality in patients with RA were determined as cardiovascular diseases 18 (29.5%), infectious diseases 13 (21.3%) and respiratory system diseases 12 (19.7%).

Conclusion: This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. Generally, there is an increased mortality in patients with RA compared with the Turkish population. Therefore, to reduce mortality in patients with RA, patients with RA should be followed more carefully, and treated more effectively in terms of both RA and any comorbid diseases they might have.

Keywords: Rheumatoid arthritis, mortality, antirheumatic agents

Öz

Amaç: Çalışmamızın amacı romatoid artrit (RA) tanılı hastaların mortalite nedenlerinin ve tedavide tercih edilen ilaçların mortalite üzerine etkisinin araştırılmasıdır.

Yöntem: Hastanemizde 2010-2020 yılları arasında takip edilmiş RA tanılı 18 yaşından büyük 743 hasta çalışmaya alındı. Hastaların klinik ve laboratuvar verileri hastane veritabanından, mortalite verileri Türkiye Sağlık Bakanlığı sisteminden ve nüfus verileri Türkiye İstatistik Kurumu'ndan alındı. Standartlaştırılmış ölüm oranı (SMR) kohortta gözlemlenen ölüm sayısının aynı yaş ve cinsiyetteki Türk toplumunda görülen ölüm sayısına bölünmesiyle hesaplandı. Hastalar sadece konvansiyonel hastalık modifiye edici antiromatizmal ilaç (cDMARD) kullanan hastalar ve cDMARD ile birlikte biyolojik (bDMARD) kullanan hastalar olmak üzere iki gruba ayrıldı.

Bulgular: Takip süreci boyunca 61 hastada mortalite gerçekleşti. RA hastalarının SMR'si 1,42 [güven aralığı (GA) 1,09-1,81] olarak Türk toplumuna göre daha yüksek tespit edildi. cDMARD kohortunda SMR, bDMARD kohortuna göre daha yüksek tespit edildi [sırasıyla; 2,05 (GA 1,53-2,69) ve 0,66 (GA 0,37-1,11)]. RA hastalarında genel olarak en sık ölüm nedeni kardiyovasküler hastalıklar 18 (%29,5), enfeksiyon hastalıkları 13 (%21,3) ve solunum sistemi hastalıkları 12 (%19,7) tespit edildi.

Sonuç: Çalışmamız RA tanılı hastalarda Türkiye'den bildirilen ilk mortalite çalışmasıdır. RA tanılı hastalarda genel olarak Türk toplumuna göre artmış bir mortalite mevcuttur. RA tanılı hastalarda mortaliteyi azaltmak için hem RA'nın kendisi hem de komorbidit hastalıklar daha dikkatli ve etkin bir şekilde takip ve tedavi edilmelidir.

Anahtar Kelimeler: Romatoid artrit, mortalite, antiromatizmal ajanlar

Correspondence / İletişim:
Mehmet Ali Balcı MD, University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Diyarbakır, Turkey
Phone: +90 212 496 50 00 **E-mail:** abalci13@gmail.com **ORCID ID:** orcid.org/0000-0003-0597-7788
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Introduction

Rheumatoid arthritis (RA) is a symmetrical, inflammatory and peripheral polyarthritis of unknown etiology. Studies conducted with patients with RA revealed that the mortality rates in patients with RA are higher than the mortality rates in the general population.[1-3] In the literature, cardiovascular diseases, malignant diseases, respiratory and infectious diseases have been cited as the main causes of mortality in patients with RA.[1,4,5] Chronic inflammation, disability, comorbidities and drugs used in treatment can be listed as causes of increased mortality. Recently, biological disease-modifying antirheumatic drugs (bDMARDs) have been used in addition to conventional (cDMARDs) for the treatment of RA. Although the effects of bDMARDs used in addition to cDMARDs on mortality have been studied in different societies, no study has been conducted on this subject in Turkish society.[3,4,6] Therefore, is aimed this study to investigate the causes and incidences of mortality, the mortality rates in patients with RA compared to the general population, and the effects of the medications preferred according to local and international guidelines to be used for treating RA on mortality.

Materials and Methods

The sample of this study consisted of 743 patients with RA who were older than 18 years and followed up in the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital between 2010 and 2020. RA diagnoses of all 743 patients conformed to the American College of Rheumatology Criteria.[7] Records of these patients, i.e. their demographic, clinical and laboratory data, the treatments they received, their follow-up periods, disease courses, disease outcomes and related complications, were obtained from the hospital database, and analyzed retrospectively. Treatment durations of the patients were checked from the hospital database. The compliance of the patients with the treatment was checked from the hospital database. The patient who did not attend regular follow-ups was excluded from the study. Diagnoses of RA and comorbid diseases were obtained from the hospital database, in accordance with the International Statistical Classification of Diseases and Related Health Problems Tenth Revision [ICD-10 (B16-B18), (J45), (I10), (I24-I25), (E13-E14), (E78), (M05-M06), (M80-M81), (N18)]. Death records were obtained from the National Death Reporting System of the Ministry of Health of the Republic of Turkey (NDRS).[8] NDRS is an institutional web-based application that allows data exchange among the relevant units of the Ministry of Health, the General Directorate of Population and Citizenship Affairs and the Turkish Statistical Institute in order for the compilation of the death statistics established by the Government of the Republic of Turkey. Additionally, national population records were obtained from the Turkish Statistical Institute (TSI).[9] TSI is the national institution established to compile, evaluate, analyze and publish statistics in the respect of the economy, society, demographics, culture, environment, science and technology and other fields deemed necessary. The incidence-based mortality (IBM) was calculated by dividing the total number of mortality by the aggregate value of patient-time in the cohort. The 95% confidence intervals (CIs) for IBMs were calculated using Byar's formula.[10] The treatment of patients with RA was started with cDMARDs and bDMARDs were added to the treatment if the target remission was not achieved in line with the recommendations of the "EULAR recommendations for managing RA with synthetic and bDMARDs".[11] Patients were divided into two groups: those who only used cDMARDs and those who took cDMARDs plus bDMARDs. That is, the bDMARDs group uses both cDMARDs and bDMARDs together. Head-to-head comparisons were made between with a new mechanism of action (rituximab, tocilizumab) versus cycling to tumour necrosis factor inhibitors (TNFi) (adalimumab, etanercept, golimumab, infliximab) among patients with RA in which mortality occurred, within the bDMARD cohort. The standardized mortality ratio (SMR) was calculated by dividing the number of mortality observed in the cohort by the number of mortality in the Turkish population of the same age and gender. The number of mortality observed in the Turkish population of the same age and gender was obtained from the TSI's database.[9]

Statistical Analysis

Statistical analysis were performed using the SPSS 21.0 (Statistical Package for the Social Sciences, Version 21.0, IBM, Armonk, NY) software package. Cumulative survival curves were created using the Kaplan-Meier method. All-cause mortality risk factors such as gender, age, disease activity score of 28 joints (DAS28) score, RF, anti-CCP positivity, comorbidities, bDMARD and cDMARD use analyses were performed using the Cox regression analysis. Probability (p) values of <0.05 were considered to indicate statistical significance.

Results

A total of 743 patients, of whom 338 (261 women, 77 men) were using bDMARDs and 405 (325 women, 80 men) were using cDMARDs, were included in the study. The mean age at diagnosis of the cDMARD cohort was found to be higher than the mean age of the bDMARD cohort (56.8

years and 49.2 years, respectively; p=0.00). The mean follow-up period of the patients using cDMARDs was found to be longer than the mean follow-up period of the patients using bDMARDs (56.8 months and 49.9 months, respectively; p=0.00). DAS28 scores of the patients using bDMARDs and cDMARDs were found to be similar (3.29 and 3.28, respectively; p>0.05). At least one comorbidity such as diabetes, hypertension, and coronary disease, was detected in 26% of the patients included in the study. Hypertension (23.1% and 15.3%, respectively; p=0.06) and hyperlipidemia (10.9 and 5.3, respectively; p=0.07) were found to be more frequent in the cDMARD cohort than in the bDMARD cohort. There was no significant difference between the cohorts in terms of other comorbidities.

The risk of mortality was found to be higher in patients with comorbidities [hazard ratio (HR) was 2.20 (1.04-4.65), p=0.039 in the presence of one comorbidity, whereas HR was 17.67 (5.31-58.82), p=0.00 in the presence of five comorbidities]. The clinical and laboratory characteristics of the patients who use cDMARDs and bDMARDs as well as the treatment modalities administered to these patients are summarized in Table 1.

Out of the 743 patients, mortality occurred in 61 patients. Thirteen of these patients were using bDMARDs whereas 48 patients of them were using cDMARDs, during the treatment period. Cardiovascular disease was found to be the most common cause of death in both the bDMARD cohort and the cDMARD cohort (23.1% and 31.3%, respectively). The mortality rate due to infectious diseases was determined to be higher in the bDMARD cohort compared to that the cDMARD cohort (30.8% and 18.8%, respectively; p>0.05), whereas the mortality rate due to cardiovascular causes was determined to be higher in the cDMARD cohort compared to the bDMARD cohort (31.3% and 23.1%, respectively; p>0.05), albeit not statistically significantly in either of the cases. Data on the underlying causes of the mortality are shown in Table 2. Kaplan-Meier survival curves of patients who have been using bDMARDs and cDMARDs are shown in Figure 1A.

The retrospective analysis of the follow-up periods of the patients with RA included in this study revealed that they were followed up for a total of 3.690 patient-years. Of the patients with RA, the patients who have been using cDMARDs were followed up for 2.240 patient-years and the patients who have been using bDMARDs were followed up for 1.450 patient-years. Additionally, IBM was found as 16.53 per 1000 person-years in patients with RA in general. IBM of the patients who have been using cDMARDs was found as 21.34 per 1000 person-years, whereas IBM of the patients who have been using bDMARDs was found as 8.96 per 1000 person-years. It was determined that 52 patients (15.4%) in the cDMARD cohort had switched from one biological to another. It was mostly the patients who had been using infliximab (34.5%) who switched to another biological. Diagnosis, clinical characteristics,

Table 1. The clinical and laboratory characteristics of, and the treatment modalities administered to, the patients that use cDMARDs and bDMARDs

	bDMARD	cDMARD	p
Number of patients (t/f/m)	338/261/77	405/325/80	>0.05
Age (years), mean	49.2±15.3	56.8±15.1	0.00
Disease duration (months), mean	49.9±39.3	76.7±41.9	0.00
Disease activity score, mean	3.29±1.23	3.28±1.33	>0.05
Gender (female), (%)	77.2	80.2	>0.05
RF positivity, (%)	69.2	66.2	>0.05
Anti CCP positivity, (%)	62.7	54.8	0.03
Diabetes, (%)	8.0	8.2	>0.05
Hypertension, (%)	15.3	23.1	0.09
Hyperlipidemia, (%)	5.3	10.9	0.07
Coronary artery disease, (%)	8.9	12.3	>0.05
Chronic renal failure, (%)	1.5	2.7	>0.05
Osteoporosis, (%)	4.7	4.2	>0.05
Asthma, (%)	2.7	2.5	>0.05
Hepatitis B, (%)	2.1	1.2	>0.05
Steroid use, (%)	71.9	51.9	0.00
Methotrexate use, (%)	47.9	72.1	0.00
Leflunomide use, (%)	37.6	25.7	0.01
Sulfasalazine use, (%)	20.1	38.0	0.00
Hydroxychloroquine use, (%)	47.6	60.5	0.00

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, t/f/m: Total/female/male

incidence-based mortality rates of, and the treatment modalities administered to, the patients who have been using bDMARDs are given in Table 3.

SMR of the patients with RA was found to be 1.42 (CI 1.09-1.81) in the general Turkish population. However, SMR was determined to be higher in the cDMARD cohort than in the bDMARD cohort [2.05 (CI 1.53-2.69) and 0.66 (CI 0.37-1.11), respectively]. The age group with the highest SMR was the 35-44 age group with an SMR of 3.31 (0.55-10.97). The 35-44 age group was also the age group with the highest SMR in the bDMARD cohort with a SMR of 3.26 (0.16-16.11) and in the cDMARD cohort with a SMR of 3.37 (0.16-16.63). SMR of the 18-34 age group compared to the general population could not be calculated as no mortality was observed in this age group in the respective cohorts. Detailed data on the SMRs are given in Table 4. The mortality risk was found to be higher in the cDMARD cohort compared to the bDMARD cohort, albeit not statistically significantly [HR 1.59 (0.85-2.97), p=0.1].

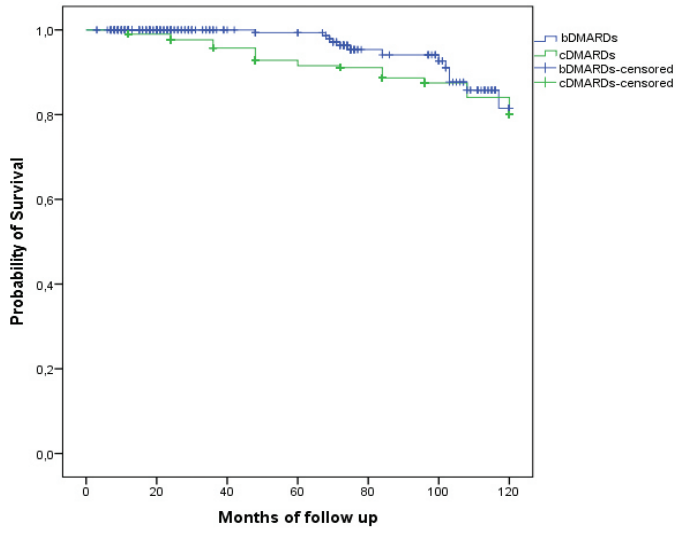

Figure 1A. Kaplan-Meier survival curves of patients who have been using bDMARDs and cDMARDs

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs

Table 2. Data on underlying causes of death in patients with rheumatoid arthritis

Cause of death	Death in the cDMARD cohort (n=48)	Death in the bDMARD cohort (n=13)	Death in all patients with RA (n=61)
Cardiovascular diseases, n (%)	15 (31.3)	3 (23.1)	18 (29.5)
Infectious diseases, n (%)	9 (18.8)	4 (30.8)	13 (21.3)
Respiratory system diseases, n (%)	3 (23.1)	9 (18.8)	12 (19.7)
Malignant diseases, n (%)	7 (14.6)	2 (15.4)	9 (14.8)
Renal diseases, n (%)	4 (8.3)	0 (0)	4 (6.6)
Neurological diseases, n (%)	2 (4.2)	0 (0)	2 (3.3)
Other causes, n (%)	2 (4.2)	1 (7.7)	3 (4.9)

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, RA: Rheumatoid arthritis

Table 3. Clinical characteristics and incidence-based mortality rates of the patients with RA in general, and the patients with RA who have been using bDMARDs or cDMARDS

	Gender (f/m/t)	Age (year) at diagnosis mean ± SD	Duration of treatment (mounth), mean ± SD	Follow-up patient-years,	Incidence of mortality/per 1.000 years	Switch, n (%)	≥1 Comorbidity, n (%)	Death, n
Abatacept	5/5/10	55.5±17.1	56.5±26.6	52	NA	3 (30)	2 (20)	0
Adalimumab	43/15/58	43.7±15.7	63.1±42.9	312.5	9.6	13 (22.4)	3 (5.2)	3
Etanercept	42/15/57	43.4±13.6	63.6±40.8	312	6.41	8 (14.0)	15 (26.3)	2
Golimumab	32/6/38	46±14.6	36.9±26.4	132	NA	9 (23.7)	5 (13.2)	0
Infliximab	22/7/29	49.9±14.8	98.4±26.9	225.5	13.3	10 (34.5)	9 (31)	3
Rituximab	45/11/59	56.7±13.8	42.6±38.1	200.5	14.6	3 (5.1)	15 (26.8)	3
Certolizumab	11/2/13	43.7±16.8	16.4±8.6	22	NA	1 (7.7)	0 (0.0)	0
Tofacitinib*	29/3/32	55.1±11.5	21.3±15.2	63	NA	0 (0.0)	6 (18.7)	0
Tocilizumab	32/13/45	52.5±15.2	32.6±25.4	132	15.15	5 (11.1)	19 (46.2)	2
All bDMARD patients	261/77/338	49.2±15.3	49.9±39.3	1.450 (total)	8.96	52 (15.4)	74 (21.8)	13
All cDMARD patients	325/80/405	56.8±15.1	76.7±41.9	2.240 (total)	21,34	NA	119 (29.4)	48
All patients with RA	586/157/743	53.36±15.57	64.51±42.87	3.690 (total)	16.53	NA	193 (26)	61

*bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, , F: Female, M: Male, n: Number, RA: Rheumatoid arthritis, SD: Standard deviation, T: Total, *Tofacitinib: b/tsDMARD*

Head-to-head comparisons of the treatment groups within the group of patients who have been using bDMARDs revealed that the patients who have been using tocilizumab had the highest increase in the mortality risk increase compared with the patients who have been using etanercept (HR 21.701, CI 1.931-243.893, p=0.013). Detailed data on the head-to-head comparisons of various bDMARD treatments indicated for RA in terms of the associated mortality risks are given in Table 5.

Additionally, individual survival analyses based on the type of bDMARD the patients have been using are shown in Figure 1B.

Discussion

The mortality data were analyzed according to the treatment modalities administered to the patients with RA during the 10-year follow-up period. This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. Mortality occurred in 61 patients with RA during the follow-up period. SMR of the patients with RA included in this study was found to be 1.42 (CI 1.09-1.81) in the general Turkish population. However, SMR of the patients with RA who have been using bDMARDs was found to be 0.66 (CI 0.37-1.11) and lower than the SMR of the general Turkish population. In comparison, SMR in patients with RA was reported as 1.65 (95% CI 1.44-1.87) in a study conducted in South Korea, [1] as 1.49 (95% CI 1.36-1.63) in a study conducted in Germany[12] and as 1.54 (95% CI 1.41-1.67) in a study conducted in the Netherlands.

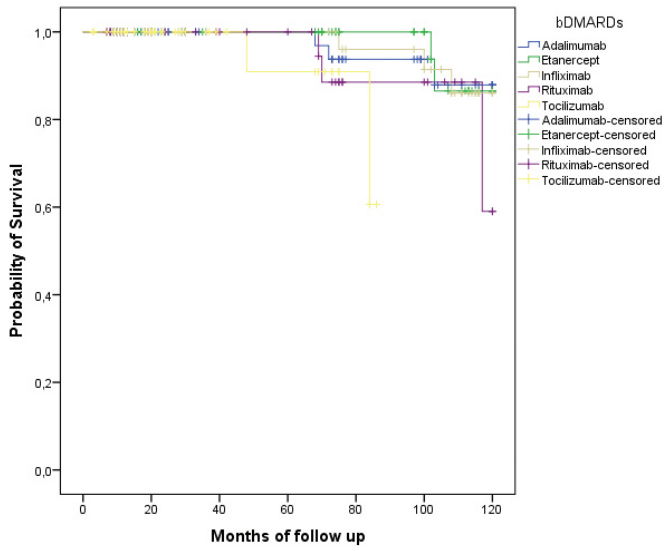

Figure 1B. Individual survival analyses of the patients based on the type of bDMARD they have been using

bDMARDs: Biologic disease-modifying antirheumatic drugs

Table 4. SMRs by the age group

Age bracket	bDMARD (number of deaths/patients)	SMR (CI)	cDMARD (number of deaths/patients)	SMR (CI)	All patients (number of deaths/patients)	SMR (CI)
18-24	0/20	NC	0/4	NC	0/24	NC
25-34	0/45	NC	0/23	NC	0/68	NC
35-44	1/64	3.26 (0.16-16.11)	1/62	3.37 (0.16-16.63)	2/126	3.31 (0.55-10.97)
45-54	3/78	1.87 (0.47-5.11)	3/86	1.70 (0.43-4.63)	6/164	1.78 (0.72-3.71)
55-64	2/74	0.62 (0.10-2.05)	10/101	2.28 (1.15-4.06)	12/175	1.58 (0.85-2.68)
65-74	6/47	0.96 (0.39-2.01)	13/79	1.24 (0.69-2.07)	19/126	1.14 (0.70-1.74)
75+	1/10	0.41 (0.02-2.05)	21/50	1.74 (1.11-2.62)	22/60	1.52 (0.98-2.27)
Total	13/338	0.66 (0.37-1.11)	48/405	2.05 (1.53-2.69)	61/743	1.42 (1.09-1.81)

bDMARDs: Biologic disease-modifying antirheumatic drugs, cDMARDs: Conventional disease-modifying antirheumatic drugs, CI: Confidence interval, NC: Not calculated, SMR: Standardized mortality ratio

Table 5. Head-to-head comparisons of various bDMARD treatments indicated for RA in terms of the associated mortality risks

bDMARDs	HR	CI	p
Adalimumab vs Etanercept	1.379	0.230-8.277	0.724
Adalimumab vs Infliximab	1.050	0.210-5.239	0.952
Infliximab vs Etanercept	1.178	0.196-7.072	0.858
Rituximab vs Adalimumab	2.091	0.419-10.436	0.368
Rituximab vs Etanercept	2.760	0.458-16.629	0.268
Rituximab vs Infliximab	1.870	0.373-9.388	0.440
Tocilizumab vs Adalimumab	4.159	0.567-30.476	0.161
Tocilizumab vs Etanercept	21.701	1.931-243.893	0.013
Tocilizumab vs Infliximab	9.291	0.801-107.800	0.034
Tocilizumab vs Rituximab	2.186	0.305-15.650	0.436

bDMARD: Biological disease modifying antirheumatic drug, CI: Confidence interval, HR: Hazard ratio, RA: Rheumatoid arthritis

[5] In a study conducted in Sweden, [13] the mortality rates of patients with RA were investigated on the basis of their use of TNFi and compared with the mortality rates of the general population. Consequentially, SMRs in both groups were found to be similar, as the SMR in patients with RA who had been using TNFi was 1.50 (95% CI 1.03-1.96) and SMR in patients with RA who had not been using TNFi was found as 1.50 (95% CI 1.14-1.86). However, in a study conducted in the United States, SMR in patients with RA using TNFi was found to be 0.95 (95% CI 0.73-1.17) and lower than the SMR of the general population,[14] similar to the findings of this study. Considering the age group, the greatest SMR in patients with RA was reported to be 2.56 (95 percent CI 0.00-7.59) in the 30-34 age range in a study conducted in South Korea.[1] This result is different from the respective results of this study, in that the age group with the highest SMR in this study was found to be the 35-44 age group with an SMR of 3.31 (95% CI 0.55-10.97).

In this study, IBM was found as 16.53 per 1000 person-years in patients with RA in general. Additionally, IBM of the patients who have been using cDMARDs was found as 21.34 per 1000 person-years, whereas the IBM of the patients who have been using bDMARDs was found as 8.96 per 1000 person-years. In a study conducted in Canada, all-cause IBM in patients with RA was reported to be between 17.10 per 1000 person-years (95% CI 14.77-19.44) and 21.04 per 1000 person-years (95% CI 18.03-24.05)[2] and in another study conducted in a Sweden, the IBM of patients with RA was found to be 19 (17 to 21) per 1000 person-years.[3] Thus, the overall IBM in patients with RA found in this study is a comparable finding to the respective findings reported in the literature.

In another study, which has been conducted in the United States on patients with RA who use anti-TNF, i.e. infliximab, etanercept, and adalimumab, IBM was found as 5.34 per 1000 person years in the said patient groups (95% CI 4.20-6.69).[14] In comparison, the respective findings in this study, that is IBM in the bDMARD cohort, was found as 8.96 per 1000 person-years, and is thus a comparable finding.

When we performed subgroup analysis in the bDMARD cohort, the IBM in patients using adalimumab was found to be 9.6 per 1000 years in our study. In comparison, in the studies conducted in Sweden,[15] and United States,[16] IBMs in patients with RA who use adalimumab were reported as 13 per 1000 person-years and 3.3 per 1000 person-years, respectively, which are similar to our study. IBM in RA patients who use etanercept was reported as 9 per 1000 person-years (95% CI 7-12), which is higher than the respective findings of this study mentioned above; in another study conducted in Sweden.[15] IBM in RA patients who use infliximab was reported as 12 per 1000 person-years (95% CI 9-15), which is comparable to the respective findings of this study mentioned above; and in the study conducted in England.[17] IBM in RA patients who use rituximab was reported as 53 per 1000 person-years (95% CI 22.9-104.6), which is higher than the respective findings of this study mentioned above. Furthermore, in this study, IBM in patients with RA who have been using tocilizumab was found to be 15.15 per 1.000 person-years. However, a thorough literature review did not reveal any other study with a result on IBM of RA patients who have been using tocilizumab, therefore no comparison could be made in that regard.

As for the patient groups that have been abatacept, golimumab, certolizumab pegol, or tofacitinib, IBMs in these patient groups could not be calculated since no mortalities occurred in any of these groups.

However, head-to-head comparisons of the patient groups within the bDMARD cohort included in this study in terms of different types of bDMARDs the patients have been using revealed a significant increase in the risk of mortality in patients using tocilizumab compared to with patients using etanercept (HR 21.701, CI 1.931-243.893, p=0.013) and infliximab (HR 9.291, CI 0.801-107.800, p=0.034). This result may be attributed to the fact that the number of patients who have been using tocilizumab and the follow-up durations of these patients was lower than other patient groups included in the bDMARD cohort. Another reason is; it may be that comorbidity is higher in the tocilizumab group than in the other groups (46.2%). In head-to-head comparisons, no significant difference in mortality was detected between the other therapies. In head-to-head comparisons with infliximab, etanercept, and adalimumab in the literature, no significant difference in mortality was detected.[18]

As for the patients who have changed from one treatment modality to another, it was determined that 52 patients (15.4%) had switched from one biological to another. A detailed analysis of these patients revealed that 34.5% of the 52 patients have been using infliximab in the first place before switching to another treatment modality, whereas 22.4% of them have been using adalimumab, and 14.0% of them have been using etanercept. According to the literature, 19% of patients on etanercept, 35% of patients taking infliximab, and 25% of patients taking adalimumab experienced a switch from one biological to another.[15] These findings are comparable to the respective findings of this study.

Last but not least, analysis of the mortality in patients with RA included in this study by the causes of mortality revealed that the most common cause of mortality was cardiovascular diseases, which caused mortality in 29.5% of the fatalities, followed by infectious diseases, which caused mortality in 21.3% of the fatalities, and respiratory system diseases, which caused mortality in 19.7% of the fatalities. In comparison, in the study conducted in South Korea, the most common cause of mortality in patients with RA was reported as the malignant diseases, which caused mortality in 17.8% of the fatalities, followed by respiratory system diseases that caused mortality in 16.9% of the fatalities and cardiovascular diseases that caused mortality in 14.2% of the fatalities;[1] whereas in the study conducted in the Netherlands, the most common cause of mortality in patients with RA was reported as the cardiovascular diseases (n=172), followed by malignancies (n=112), and respiratory system diseases (n=62).[5] These findings are comparable to the respective findings of this study.

Study Limitations

The study strength is that it is the first mortality study reported from Turkey in patients with RA. However, the limitations of this study are that first, it was a retrospective study and secondly, the total number per 1000 person-years was low due to the relatively small number of patients despite a 10-year follow-up period.

Conclusion

This study is the first mortality study reported from Turkey in patients with a diagnosis of RA. The results of this study indicated that the SMR and IBM of patients with RA were higher than the SMR and IBM observed in the general Turkish population, yet were comparable to the respective findings reported in the literature. Additionally, SMRs in the cDMARD and bDMARD cohorts were found to be higher and lower, respectively, as compared to the SMR observed in the general Turkish population. In conclusion, to reduce mortality in patients with RA, they be followed more carefully and treated more effectively in terms of both RA and any comorbid diseases they might have.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 837, date: 09.07.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A.B., Design: M.A.B., Data Collection or Processing: M.A.B., L.A., Analysis or Interpretation M.A.B., L.A., Literature Search: M.A.B., L.A., Writing: M.A.B.

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