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Hospitalization of rheumatoid arthritis patients at a tertiary care hospital in Saudi Arabia

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) involves a high economic burden, particularly for patients who require hospitalization, the need for which is affected by several factors including disease duration, comorbidities, medications, and socioeconomic status. *Method*: We retrospectively reviewed all adult RA patients who visited King Abdulaziz University Hospital between 2010 and 2020. *Results*: A total of 190 RA patients were identified, 176 and 141 of whom were female and seropositive, respectively. The most common comorbidity was hypertension, followed by diabetes mellitus. The most common reason for admission was sleep studies, followed by elective drug infusions, most of which were for rituximab. There were 8 admissions for infection, 4 for pneumonia; 1 for pulmonary tuberculosis; and 1 each for osteomyelitis, pyelonephritis, and urosepsis. We identified 3 and 2 cases of acute coronary syndrome and breast cancer, respectively. *Conclusion*: The most common reason for hospitalization was biological drug infusion. Patients on biological treatments had an increased hospitalization risk secondary to infection, particularly lower respiratory tract infections. A national cohort for RA patients would help better understand this disease in our region.

Keywords: Rheumatoid arthritis, hospitalization, infections, biological treatment, Saudi Arabia

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease associated with progressive joint damage and extra-articular complications that affect the patient's quality of life. The RA prevalence in Western countries ranges from 0.5% to 1%.It is ranked the 42nd disease related to disability and is considered more aggressive in women compared to men (Alamanos and Drosos, 2005; Lozano et al., 2012). There are little data on RA prevalence in Saudi Arabi. A study performed in the Qassim region estimated the prevalence at 0.22%, which is higher than that reported in Middle Eastern and North African countries (0.16%; Lozano et al., 2012; Al-Dalaan et al., 1998). A cross-sectional study that was conducted in 5 Arab countries, including Saudi Arabia, and involved 895 patients found that the majority of the patients were

women with average disease duration of 10 years. They also reported that Saudi Arabian patients had the highest usage of anti-tumor necrosis factor (TNF) and steroids (Dargham et al., 2018).

Hospitalization of RA patients creates a significant economic burden. In the last decade, as a result of the treat-to-target strategy and the introduction of biological molecular treatments, there has been a significant decrease in the overall number of patient's hospitalized (Aga et al., 2015). In England, there is a change in the hospitalization trend for RA patients. The numbers increased between 1998 and 2015 from 71 to 171.6 per 100,000 (P<0.001), including day care admissions. Contrastingly, there was a drop in the number of emergency admissions from 12.8 to 4.4 cases per 100,000. This could be related to the distribution of the new medications (Hannah et al., 2019). This was supported by a systematic review of 72 studies published between 2000 and 2019 that found that the main cost for RA patients was the medications, representing 87% of the total costs. Consequently, there was a statistically significant decrease in the hospitalization cost (P=0.004; Hsieh et al., 2020).

Hospitalizations for RA can be influenced by several factors, including disease duration, comorbidities, socioeconomic status, and corticosteroid use. This was reflected in a multicenter cross-sectional study from the Karnataka Rheumatoid Arthritis Comorbidity study involving 3247 RA patients. Of these patients, 22% were hospitalized and 2.9% had infections (Chandrashekara et al., 2019).

Here, we aimed to investigate the overall causes for hospitalization of RA patients at King Abdulaziz University Hospital (KAUH), which is a large tertiary center in the western region of Saudi Arabia. A comparison of the reasons for admission with studies that were conducted in other countries could help further our understanding of the disease behavior in our region.

2. MATERIALS AND METHODS

This was a retrospective study conducted at KAUH. Patients were selected based on the following criteria: (1) aged 18 years and above (2) fulfilled the American College of Rheumatology-European League Against Rheumatism 2010 classification criteria for RA (Aletaha et al., 2010), and (3) admission to the hospital for any reason in the past 10 years (2010–2020). Patients were excluded for the following reasons: (1) aged <18 years, (2) other coexisting connective tissue diseases such as systemic lupus erythematous and Sjogren's syndrome, and (3) new diagnosis (disease duration <6 months).

A total of 190 patients fulfilled the inclusion criteria and were selected for this study. The charts from KAUH were reviewed from 2010 and 2020 using the Phoenix system (E*Health Line, Sacramento, CA, United States). The study was approved by the university's Department of Bioethics (Reference No. 531–19).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY, United States). Categorical variables were presented as numbers and percentages and compared using the Chi-square test. Continuous variables were non-normally distributed; thus, they were presented as the median and range (minimum-maximum) and compared using the Mann-Whitney *U* test. All tests were 2-tailed, and a P-value<0.05 was considered statistically significant.

3. RESULTS

Of the 190 RA patients, 98(51.6%) were aged 50 years or older. The majority (176 patients, 92.6%) were women, and 125 (65.8%) were Saudi. Almost all were nonsmokers, with only 3 smokers. Most of the patients were overweight or moderately obese (28.9% and 27.4%, respectively). There were 37 patients (19.5%) with normal body mass indices (BMIs), while the rest were severely and morbidly obese (10.5% and 13.7%, respectively; Table 1).

Table 1 Demographic data.

Variable	N	%
Age*		
20–50 years	92	48.4
≥50 years	98	51.6
Sex*		
Male	14	7.4
Female	176	92.6
Nationality*		
Saudi	125	65.8

Non-Saudi	65	34.2
Smoking *		
Yes	3	1.6
No	187	98.4
BMI*		
Normal	37	19.5
Overweight	55	28.9
Moderate obese	52	27.4
Severe obese	20	10.5
Morbid obese	26	13.7
Variable	Median	Range (min-max)
Weight in Kg**	74	37–185

*Note. * variables are summarized as number and percentage.*

*** variables are summarized as median and range.*

Abbreviations: N, number; BMI, body mass index.

The most common comorbidity was hypertension (43 patients, 22.6%), followed by diabetes mellitus, osteopenia, osteoporosis, gastroesophageal reflux disease, and chronic obstructive pulmonary disease (40, 11, 9, and 1 patient; 21.1%, 5.8%, 4.7%, and 0.5% respectively; Figure 1). Most of the patients (141, 74%) had seropositive disease (either rheumatoid factor or anti-cyclic citrullinated peptide positive). Regarding the disease activity assessment using the Disease Activity Score 28 with C-reactive protein (DAS-28 CRP), we identified 99 patients (52%) who were in remission and had low disease activity. The median RA disease duration was 75 months and the median total number of admissions was 1 (Table 2).

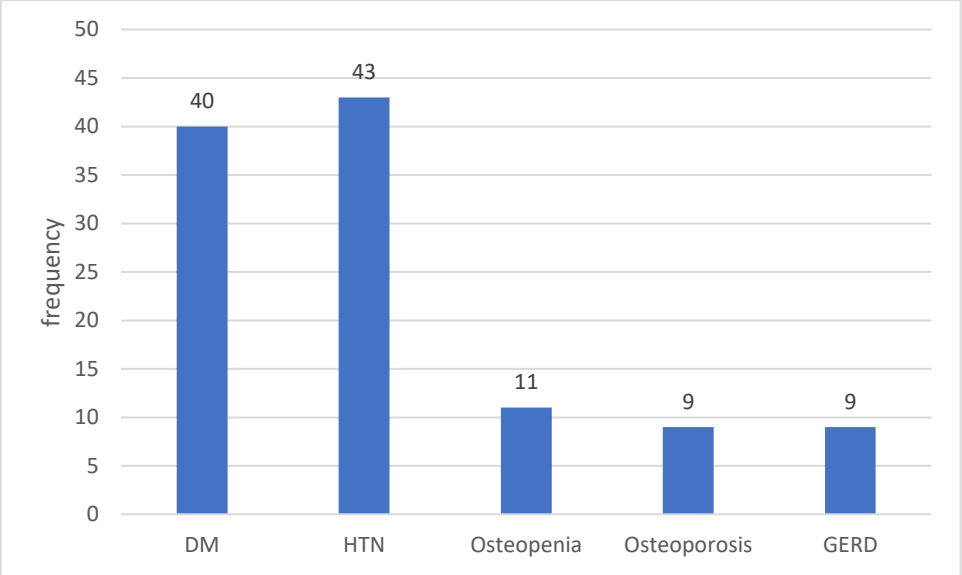

Figure 1 Patient comorbidities includes: hypertension (HTN), diabetes mellitus (DM), osteopenia, osteoporosis and gastroesophageal reflux disease (GERD).

Table 2 Medical characteristics of the patients with rheumatoid arthritis

Variable	N	%
Comorbidity		
DM*	40	21.1
HTN*	43	22.6
Osteopenia*	11	5.8
Osteoporosis*	9	4.7
GERD*	9	4.7

Seropositive disease (either RF or anti-CCP positive)	141	74.2
Disease activity (DAS28)		
Remission	24	12.6
Low	75	39.5
Moderate	17	8.9
High	0	0
Unknown	74	38.9
Variable	Median	Range (min-max)
RA duration in months**	75	9–336
Total number of admissions**	1	0–34

*Note. * variables are summarized as number and percentage.*

*** variables are summarized as median and range.*

Abbreviations: N, number; DM, diabetes mellitus; HTN, hypertension; GERD, gastroesophageal reflux disease; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptides; DAS28, Disease Activity Score 28; RA, rheumatoid arthritis.

Regarding the medications used in our study population (Table 3), the most common drugs were conventional disease-modifying anti-rheumatic drugs (cDMARDs; methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, and chloroquine) which 90.5% of the patients used, followed by biological DMARDs (adalimumab, etanercept, rituximab, and tocilizumab) at 28.3%. Moreover, 20% and 21% of the patients used corticosteroids (prednisolone) and combined therapy (biological and conventional DMARDs), respectively.

Table 3 Medications of the patients with rheumatoid arthritis (n=190)

Drug	N	%
Conventional DMARDs	172	90.5
Methotrexate	137	73.3
Leflunomide	14	7.5
Sulfasalazine	10	5.3
Hydroxy chloroquine	58	31
Azathioprine	4	2.1
Chloroquine	3	1.6
Prednisolone	38	20
Biological DMARDs	53	28.3
Adalimumab	24	12.6
Etanercept	10	5.3
Rituximab	10	5.3
Tocilizumab	4	2.1
Biological monotherapy	13	6.8
DMARD monotherapy	132	69.5
Combined biological and DMARD	40	21.1

Note. All variables are summarized as the number and percentage.

DMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine and chloroquine.

Corticosteroid: prednisolone. Biological: adalimumab, etanercept, rituximab and tocilizumab (Combined therapy was administered to our patients)

Abbreviations: N, number; DMARDS, disease-modifying anti-rheumatic drugs.

In the analysis of the reasons for hospitalization (Table 4 and Figure 2), the most common reason for admission in RA patients was sleep studies, followed by elective drug infusions (59 and 51 patients, 31.1% and 26.8%, respectively), most of which were for rituximab infusions (17.1%). Moreover, 20 patients (10.5%) were admitted for endoscopy, followed by gynecological admissions; day procedures, 6 of which were for cataracts; and obstetrics or deliveries, 7 of which were deliveries; (15, 11, and 9; 7.9%, 5.8%, and 4.7%, respectively). There were 8 hospitalizations due to infection (4.7%), 4 for pneumonia; 1 for pulmonary tuberculosis (TB); and 1 each for osteomyelitis, pyelonephritis, and urosepsis (Table 5). Other reasons for admission included disease flares, acute coronary syndrome (ACS), orthopedic surgeries, fractures not requiring surgery, cerebrovascular accidents (CVAs), malignancy, and pulmonary embolism.

Table 4 Reasons for admissions in the patients with rheumatoid arthritis (n=190)

Reasons	N	Percentage (%)
Elective drug infusion	51	26.8%
Endoscopy	20	10.5%
Sleep study	59	31.1%
Acute coronary syndrome	3	1.6%
Cerebrovascular accidents	2	1.1%
Pulmonary embolism	1	0.5%
Disease flare	5	2.6%
Day procedure	11	5.8%
Orthopedic surgeries	3	1.6%
Other surgeries	10	5.3%
Fracture not requiring surgery	3	1.6%
Obstetrics or delivery	9	4.7%
Gynecological admission	15	7.9%
Infection	8	4.2%
Malignancy	2	1.1%
Other causes	9	4.7%

Note. Variables are summarized as the number and percentage.

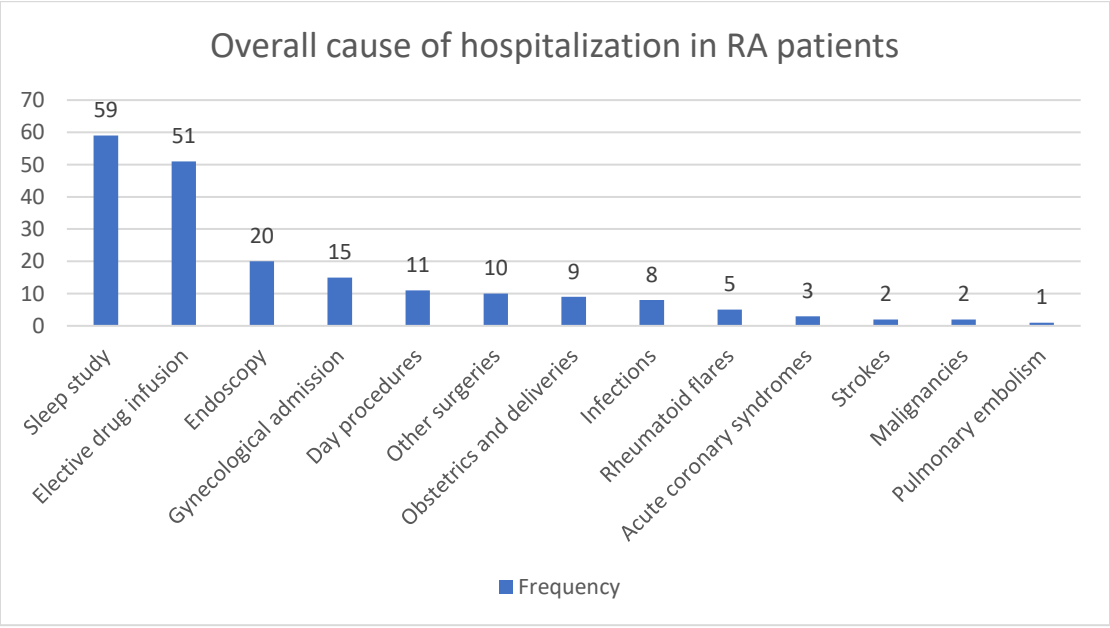

Figure 2 Reasons for patient admissions in descending order.

Table 5 Types of infections that required hospitalization

Type of infection	N	Medication
Pneumonia	2	Adalimumab
Osteomyelitis	1	Adalimumab
Pulmonary tuberculosis	1	Adalimumab
Pyelonephritis	1	Adalimumab
Pneumonia	1	Tocilizumab
Pneumonia	1	Methotrexate
Urosepsis	1	Methotrexate

Abbreviations: N, number.

All 3 patients that were admitted to the cardiac unit secondary to ACS were on cDMARDs, and 2 of them were on combination therapy. Regarding the CVAs, both cases were on cDMARD monotherapy. The patients admitted for infection were on combined therapy and those admitted for malignancy were on cDMARDs (Supplementary table 1). Regarding the relationship between the reason for admission and cDMARD type, 35 and 9 patients (79.5%and 20.5%, respectively) that were admitted for elective drug infusions were on methotrexate and hydroxychloroquine, respectively. Of the patients admitted for ACS, 2 of the 3 were on methotrexate and 1 was on sulfasalazine. All cases admitted for infection and malignancy were on methotrexate (Supplementary table 2).

In our patients, the most common medication used for drug infusion was rituximab (followed by tocilizumab (17.6% and 7.8%, respectively). One patient in the rituximab and adalimumab groups each was admitted for ACS. The risk of infection was higher in the adalimumab group, followed by the rituximab group (50% and 12.5% of the admitted patients, respectively; Supplementary table 3).

4. DISCUSSION

The age distribution of RA patients in our study was consistent with those of other studies in which most of the patients were more than 50 years old, women, and seropositive (Bawazir, 2020; Kiadaliri and Englund, 2018; Almoallim et al., 2020). Here, the most common reason for hospitalization was sleep studies (31.1%), which peaked between 2018 and 2020 due to an ongoing study at the center. Approximately 17% of the recruited patients had moderate to high disease activity. Treatment in such patients with active disease includes, but is not limited to, biological infusions, as recommended by the American College of Rheumatology treatment guidelines for RA (Singh et al., 2016). Here, the second most common reason for hospitalization was medication infusions (26.8%). The medications available at our center were rituximab and tocilizumab, which were used in 5.3% and 2.1% of the patients, respectively. Moreover, 28.3% of our patients received biological treatments, which is low when compared to cohorts from the same region that reported up to 60% biological treatment use. This could be explained by the fact that 35% of the patients were non-Saudis and were not eligible to undergo biologic treatment at a government hospital (Almoallim et al., 2020). A study of the impact of the biological treatment infusion cost on a health care system in the United States found that it represents the greatest proportion of the overall costs. The estimated cost of a rituximab infusion per patient per year is 36,663 United States dollars (USD), while for tocilizumab it is 36,821 USD (Schmier et al., 2017). To the best of our knowledge, these numbers are similar to the costs in Saudi Arabia. This gives insight into the burden that this places on our health care system, and further exploratory studies in this regard are required.

RA treatment with anti-rheumatoid drugs is associated with increased frequency of gastrointestinal (GI) manifestations, regardless of non-steroidal anti-inflammatory drug (NSAID) use (Sugimori et al., 2008). Endoscopy admissions represented 10.5% of the reasons for hospitalization. Two patients were osteoporotic on oral bisphosphonates and 1 was on methotrexate and developed candida esophagitis. The endoscopic findings in the remaining patients included esophagitis, gastritis, peptic and duodenal ulcers, and upper and lower GI bleeding. There were no bowel perforation cases in the tocilizumab group. Unfortunately, we did not include proton pump inhibitor use and other gastric protective medications in our analysis due to missing data. RA patients are susceptible to infections that may require hospitalization. Several risk factors are known to increase this risk, including: seropositive disease, leukopenia, increasing age, extraarticular disease, corticosteroid use, chronic lung disease, alcoholism, diabetes, and organic brain syndrome (Doran et al., 2002b). Doran et al. (2002a) reported increased infection risk in RA patients compared with healthy age- and sex-matched controls. The most common infections that require hospitalization were septic

arthritis, osteomyelitis, and skin and soft tissue infections. Moreover, patients on anti-TNF-alpha therapies were at a higher infection risk compared with biologic naïve patients. Those on anti-TNF-alpha therapies also tended to develop a higher rate of lower respiratory tract, skin, and bone infections compared with anti-TNF naïve patients (Dixon et al., 2006). These data are consistent with our results, as most patients developed lower respiratory infections and most were on anti-TNF-alpha therapy; however, we did not identify cases with soft tissue infections that required hospitalization nor were there septic arthritis cases.

We encountered 1 case of pulmonary TB reactivation after exposure to anti-TNF medications. This case was screened using the purified protein derivative skin test, which was negative. TB can occur in patients on anti-TNF medications due to infection reactivation or new exposure to *Mycobacterium tuberculosis*. Two-thirds of the reactivation cases presented as disseminated extrapulmonary TB, while pulmonary involvement was evident in one-third of the cases (Rodríguez-Jiménez et al., 2018). There is still controversy around the best screening method for latent TB, with some studies suggesting that the Quanti FERON TB screening test (Qiagen, Hilden, Germany) is superior (Diel et al., 2012).

RA patients are at increased risk of malignancy compared with the general population. The most common are lymphoproliferative hematological malignancies, including leukemia and lymphoma (Cibere et al., 1997). Simon et al. conducted a meta-analysis to study this relationship and found an increased lymphoma and lung cancer risk and decreased colorectal and breast cancer risk compared with the general population (Simon et al., 2015). Here, we identified 2 patients with long-standing RA who developed invasive ductal carcinoma of the breast, both of whom were on methotrexate monotherapy with no previous exposure to biological treatments.

Furthermore, RA patients have an increased risk of cardiovascular disease. This relationship cannot be explained by the ordinary cardiovascular risk factors; however, it could be related to the inflammatory changes secondary to RA (Crowson et al., 2013). Several local studies showed a strong relationship between cardiovascular disease in RA and high disease activity (Bawazir, 2020; Almoallim et al., 2020). We identified 3 cases with acute coronary syndrome (ACS), 2 of which were on rituximab, while 1 was on more than 10mg of prednisone and another was on methotrexate and adalimumab.

Limitations

This study had several limitations. Low patient numbers; missing data, particularly regarding disease activity; a lack of detailed data on the corticosteroid doses; and information on whether the patients were using NSAIDs were the major limitations in this study. This type of bias is generally expected in retrospective studies. We propose that a national cohort for RA patients must be developed, that will help us to better understand this disease in our region.

5. CONCLUSION

This was a descriptive study that analyzed the reasons for hospitalization of RA patients at a tertiary center in Saudi Arabia. The most common reason was medication infusions, including rituximab and tocilizumab. There was an increased hospitalization risk secondary to infection for patients on biological treatments, particularly regarding lower respiratory tract infections, which was a similar finding to that of international data. Contrastingly, we found a lower rate of soft tissue infections that required hospitalization.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dr. Maram and Dr. Lujain. The first draft of the manuscript was written by Dr. Yasser, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

Conflict of interest statement

The authors declare that they did not have any conflict of interest.

Funding information

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Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for study protocol /study design /Methodology

The study was approved by the Biomedical Ethics research Committee of King Abdulaziz University (Reference No 531-19) Retrospective study.

Data and materials availability

All data associated with this study are present in the paper.

Supplementary table 1 Reasons for admissions in the patients with rheumatoid arthritis according to treatment type (n=190)

Reason	Conventional DMARDS		Prednisolone		Biological DMARDs	
	N	%	N	%	N	%
Elective drug infusion	44	86.3%	15	29.4%	20	39.2%
Acute coronary syndrome	3	100.0%	2	66.7%	2	66.7%
CVA	2	100.0%	1	50.0%	0	0.0%
Infection	5	62.5%	2	25.0%	5	62.5%
RA flare	4	80.0%	1	20.0%	1	20.0%
Malignancy	2	100.0%	1	50.0%	0	0.0%

Note. Variables are summarized as the number and percentage.

Abbreviations: N, number; DMARDS, disease-modifying anti-rheumatic drugs; CVA, cerebrovascular accident; RA, rheumatoid arthritis.

Supplementary table 2 Reasons for admissions in the patients with rheumatoid arthritis according to the cDMARD prescribed (n=190)

	Methotrexate		Chloroquine		Hydroxy chloroquine		Sulfasalazine		Leflunomide	
	N	%	N	%	N	%	N	%	N	%
Elective drug infusion	35	79.5%	1	2.3%	9	20.5%	3	6.8%	3	6.8%
Acute coronary syndrome	2	66.7%	0	0.0%	0	0.0%	1	33.3%	0	0.0%
CVA	1	50.0%	0	0.0%	1	50.0%	0	0.0%	0	0.0%
Infection	5	100.0%	0	0.0%	1	20.0%	0	0.0%	0	0.0%
RA flare	3	75.0%	0	0.0%	2	50.0%	0	0.0%	0	0.0%
Malignancy	2	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Note. Variables are summarized as the number and percentage.

Abbreviations: N, number; DMARDS, disease-modifying anti-rheumatic drugs; CVA, cerebrovascular accident; RA, rheumatoid arthritis.

Supplementary table 3 Reasons for admissions in the patients with rheumatoid arthritis according to the biological treatment prescribed (n=190)

	Etanercept		Adalimumab		Rituximab		Tocilizumab	
	N	%	N	%	N	%	N	%
Elective drug infusion	0	0.0%	3	5.9%	9	17.6%	4	7.8%
Acute coronary syndrome	0	0.0%	1	33.3%	1	33.3%	0	0.0%
CVA	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Infection	0	0.0%	5	62.5%	0	0.0%	1	12.5%
RA flare	0	0.0%	1	20.0%	0	0.0%	0	0.0%
Malignancy	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Note. Variables are summarized as the number and percentage.

Abbreviations: N, number; DMARDS, disease-modifying anti-rheumatic drugs; CVA, cerebrovascular accident; RA, rheumatoid arthritis.

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