Original Article

The Incidence of Electrocardiogram Changes Following Rituximab Infusion in Rheumatic Patients

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ABSTRACT

Background: Rheumatism is one of the most common chronic diseases of the musculoskeletal system and connective tissue, which affects different age groups.

Objectives: To investigate the incidence of electrocardiogram (ECG) changes following rituximab infusion in rheumatic patients.

Methods: This cross-sectional study was conducted on 60 patients with a definite diagnosis of rheumatic diseases with the indication of receiving rituximab. Before the infusion of rituximab (500 mg or 1000 mg), the patients with abnormal ECG changes were excluded from the study. Then, all patients were subjected to complete cardiopulmonary monitoring (including data on heart rate, respiratory rate, blood pressure, and pulse oximetry) during infusion up to 2 hours after receiving rituximab, and the occurrence of changes in ECG was evaluated.

Results: Their Mean±SD age was 43.40±9.43 years, and their mean heart rate before rituximab infusion was 79.26±10.83 per minute. Fifty-seven patients (95%) were women. Rheumatoid arthritis (RA), dermatomyositis, and systemic lupus erythematosus (SLE) were the most common rheumatoid disorders, with 43.3%, 23.3%, and 16.7%, respectively. Prednisolone, methotrexate, and hydroxychloroquine were the most commonly used drugs, with 90%, 60%, and 33.3%, respectively. The incidence of ECG abnormalities was 70%. The incidences of premature atrial contractions and sinus tachycardia were 43.3% and 31.3%, respectively. The incidence of premature ventricular contractions (PVCs) was 13.3%. The incidences of sinus bradycardia and ST-T abnormality were 8.3% and 3.3%, respectively. No statistically significant relationship was observed between the incidence of ECG abnormalities with age, sex, heart rate, type of rheumatic disorder, cardiovascular disease risk factors, rituximab dosage, and drug use (P>0.05).

Conclusion: The incidence of ECG abnormalities following rituximab infusion in rheumatic patients was 70%, which is high. Therefore, complete cardiopulmonary monitoring of these patients following receiving rituximab seems essential.

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Introduction

Rheumatism is one of the most common chronic diseases of the musculoskeletal system and connective tissue, which affects different age groups [1]. This chronic autoimmune disease affects the bones, joints, and other skeletal system parts, causing disability and high health costs [2]. Rheumatic diseases include various types of diseases, including systemic lupus erythematosus (SLE), gout, fibromyalgia, rheumatoid arthritis (RA), back pain, osteoarthritis, Sjögren's syndrome (SS), vasculitis, and non-articular rheumatism [3, 4]. Osteoarthritis, back pain, fibromyalgia, and RA are more prevalent among musculoskeletal diseases, so one-sixth of the visits to medical specialists are due to musculoskeletal problems [4]. Rheumatism, as a chronic systemic autoimmune disease, usually has a higher prevalence in women and older people. Studies have estimated the global prevalence of rheumatism to be 0.46% (95% CI, 0.39%, 0.54%) with a 95% prediction interval (0.06-1.27) [5]. The global prevalence of RA as one of the most common rheumatic diseases is reported to be about 460 per 100000 population in 2019. Also, this year, about 528 million people suffered from osteoarthritis worldwide, which shows an increase of 113% compared to 1990. About 73% of the patients were over 55 years old and 60% were women [6-8].

Despite the ever-increasing advances in the pharmaceutical treatment of rheumatic diseases, none of the drug treatments cure this disease definitively. They are used only to relieve symptoms and control attacks [9]. Since the immune mechanism plays a fundamental role in the pathogenesis of these diseases, drugs that weaken the immune system are more effective in cases where other rheumatic drugs are not responsive [10]. Rituximab is one of the immunosuppressive drugs used in treating this disease. This chimeric monoclonal IgG1 antibody was developed as a new therapeutic agent in treating human lymphoma 1994 [11, 12]. Rituximab binds to the CD20 antigen on B lymphocytes and causes their death. Recent evidence suggests that B-cell depletion is a safe and highly effective therapeutic option in treating autoimmune diseases [13, 14].

Despite the promising effects of rituximab in reducing symptoms, complications such as respiratory and urinary infections, varicella zoster, herpes simplex, and malignancies may occur in the long term. Also, side effects such as fatigue, headache, chills, vomiting, and muscle spasms can occur after taking rituximab, which is related to the infusion in the initial phase [15]. In addition, some studies have shown complications such as cardiac arrhythmias, polymorphic ventricular tachycardia, increased QT interval, increased atrial and ventricular premature beats, and decreased ejection fraction after infusion in patients with autoimmune diseases such as lymphoma, pemphigus, and multiple sclerosis [16-19]. However, based on our knowledge, the studies conducted regarding cardiac complications and disorders following rituximab infusion in rheumatic patients are limited. Therefore, this study was designed to investigate the incidence of electrocardiogram (ECG) changes following rituximab infusion in rheumatic patients.

Materials and Methods

Study design and subjects

This cross-sectional study investigated the incidence of ECG following rituximab infusion on 60 rheumatic patients referred to Loqman Hakim Hospital in Tehran City, Iran, from February to July 2023. Sampling was done using convenience sampling, and patients were selected consecutively. Inclusion criteria were: 1) Age ≥18 years, 2) Definitive diagnosis of any rheumatic disease with indications for receiving rituximab based on guidelines, 3) Normal echocardiography, and 4) Patient's informed consent to participate in the study. The exclusion criteria were: 1) Any known cardiovascular disease, 2) Diabetes, and 3) Kidney failure.

Conducting the study

Before the study began, the research objectives were explained to the patients, and informed consent was obtained. Then, 60 patients with a definite diagnosis of rheumatic diseases with the indication of receiving rituximab based on the guidelines were examined. It should be noted that before the infusion of rituximab, ECG was taken from all participants, and patients with any abnormal ECG changes were excluded from the study. All patients were subjected to complete cardiopulmonary monitoring (including data on heart rate, respiratory rate, blood pressure, and pulse oximetry) during infusion up to 2 hours after receiving rituximab, and the occurrence of changes in ECG was evaluated. The data collection tool was a checklist including age, gender, type of rheumatic disorder (RA, dermatomyositis, SLE, polymyositis, SS and granulomatosis with polyangiitis [GPA]), risk factors of cardiovascular disease, type of drugs used by patients, rituximab dosage (500 or 1000 mg), heart rate and ECG changes (sinus bradycardia, sinus tachycardia, premature ventricular contractions [PVCs], premature atrial contractions [PACs] and ST-T abnormality). Part

of this data was from the patient's medical record, which was collected through ECG tests and interviews with the patient.

Statistical analysis

Data were analyzed using Stata software, version, 14.0 (Stata Corp, College Station, TX, USA). The Mean±SD, and number (%) were used for descriptive analyses. In the analytical study, the Mann–Whitney U and chi-square tests, or Fisher exact test, were used to investigate the relationship between ECG changes and demographic and clinical variables. P<0.05 was considered a significant level.

Results

A total of 60 patients with rheumatic diseases referred to Loqman Hakim Hospital in Tehran City were investigated. The Mean±SD age and heart rate before rituximab infusion were 43.40±9.43 years and 79.26±10.83 per minute, respectively. RA, dermatomyositis, and SLE were the most common rheumatoid disorders, with 43.3%, 23.3%, and 16.7%, respectively. Hypertension was also the most common risk factor for cardiovascular disease in the patients (13.3%). Prednisolone, methotrexate, and hydroxychloroquine were the most commonly used drugs in these patients, with 90%, 60%, and 33.3%, respectively. In addition, 53.3% of patients had received a dose of 1000 mg of rituximab (Table 1).

The incidence of ECG abnormalities following rituximab infusion was 70%. Also, the incidence rates of PACs, sinus tachycardia, PVCs, sinus bradycardia, and ST-T abnormality were 43.3%, 31.3%, 13.3%, 8.3%, and 3.3% respectively (Table 2).

There was no statistically significant relationship between age and heart rate with the incidence of ECG changes (P>0.05) (Table 3).

There was no statistically significant relationship between cardiovascular disease risk factors, rituximab dose, and the type of rheumatic disorder with the incidence of ECG changes (P>0.05). Since 95% of patients were women, the relationship between ECG changes and gender did not occur (Table 4).

There was no statistically significant relationship between the type of drug used and the incidence of ECG changes (P>0.05) (Table 5).

Discussion

Among the immunosuppressive drugs, rituximab is a common drug for rheumatic diseases. This drug, a chimeric monoclonal anti-CD20 antibody, is currently approved by the Food and Drug Administration (FDA) for the treatment of different diseases such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, RA, antineutrophil cytoplasmic antibody-associated vasculitis including GPA, and microscopic polyangiitis [20, 21]. Rheumatic diseases can lead to tissue damage, disability, reduced quality of life, and increased mortality. Despite its relative safety profile, the most common reason for discontinuation of rituximab treatment in rheumatic diseases is drug side effects [22]. Hence, we conducted this study to investigate the incidence of ECG changes following rituximab infusion in rheumatic patients.

Our study shows that RA, dermatomyositis, and SLE are the most common rheumatoid disorders, with 43.3%, 23.3%, and 16.7%, respectively. Hypertension was also the most common risk factor for cardiovascular disease in the patients (13.3%). Prednisolone, methotrexate, and hydroxychloroquine were the most commonly used drugs, with 90%, 60%, and 33.3%, respectively. The incidence of ECG abnormalities was 70%. Also, the incidences of PACs, sinus tachycardia, PVCs, sinus bradycardia, and ST-T abnormality were 43.3%, 31.3%, 13.3%, 8.3%, and 3.3%, respectively. No statistically significant relationship was observed between the incidence of ECG abnormalities with age, sex, heart rate, type of rheumatic disorder, cardiovascular disease risk factors, rituximab dosage, and drug use (P>0.05).

Due to the lack of similar studies regarding the effect of rituximab infusion on ECG changes in rheumatic patients, we inevitably focused on studies conducted in patients with other autoimmune diseases. For example, in a study done by Aidi et al. to investigate adverse electrocardiographic effects of rituximab infusion in pemphigus patients in Iran, the mean number of heart rate, QT interval, the number of PACs, and PVCs increased significantly after rituximab infusion (P<0.05). This study concluded that although rituximab may have arrhythmogenic side effects (increased heart rate, QT interval, the number of PACs, and PVCs), eligible patients should not be excluded from receiving rituximab infusion due to these side effects [17].

Evidence has shown that rituximab can cause side effects such as fever and convulsions, especially in the early hours after injection, by releasing cytokines (especially interleukin 6). In addition, in 10% of cases,

Table 1. Demographic and clinical characteristics of rheumatic patients

Qualitative Variables		No. (%)
Sex	Male	3(5)
	Female	57(95)
	Total	60(100)
Type of rheumatic disorder	SLE	10(16.7)
	RA	26(43.3)
	GPA	6(10)
	Dermatomyositis	14(23.3)
	Polymyositis	3(5)
	SS + SLE	1(1.7)
	Total	60(100)
Risk factors of cardiovascular disease	No.	46(76.7)
	Ischemic heart disease	0
	Congestive heart failure	0
	Arrhythmia	0
	Valvular heart disease	0
	Hypertension	8(13.3)
	Diabetes mellitus	2(3.3)
	Hyperlipidemia	4(6.6)
	Total	60(100)
Type of drugs used by patients	Prednisolone	54(90)
	Mycophenolate	1(1.7)
	Methotrexate	36(60)
	Azathioprine	11(18.3)
	Tacrolimus	5(8.3)
	Hydroxychloroquine	20(33.3)
	Leflunomide	0
Rituximab dosage (mg/patient)	500	28(46.7)
	1000	32(53.3)
	Total	60(100)

Quantitative Variables	Mean±SD	Min-Max
Age (y)	43.40±9.43	24-63
Heart rate (per minute)	79.26±10.83	55-99

Abbreviations: SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; GPA: Granulomatosis with polyangiitis.

Table 2. Incidences of ECG changes following rituximab infusion in rheumatic patients

Qualitative Variables		No. (%)
Sinus bradycardia	No	55(91.7)
	Yes	5(8.3)
	Total	60(100)
Sinus tachycardia	No	41(68.7)
	Yes	19(31.3)
	Total	60(100)
PVCs	No	52(86.7)
	Yes	8(13.3)
	Total	60(100)
PACs	No	34(56.7)
	Yes	26(43.3)
	Total	60(100)
ST-T abnormality	No	58(96.7)
	Yes	2(3.3)
	Total	60(100)
ECG abnormalities	No	18(30)
	Yes	42(70)
	Total	60(100)

Abbreviations: ECG: Electrocardiogram; PVCs: Premature atrial contractions; PACs: Premature ventricular contractions.

Table 3. The relationship between demographic and clinical variables with ECG changes following rituximab infusion

Variables		No.	Mean±SD	P*
Age (Y)				
Sinus tachycardia	No	41	42.32±9.47	0.194
	Yes	19	45.73±9.13	
PACs	No	34	44.12±9.47	0.505
	Yes	26	42.46±9.45	
ECG abnormalities	No	18	41.88±9.37	0.421
	Yes	42	44.05±9.49	
Heart rate				
Sinus tachycardia	No	41	77.49±10.64	0.061
	Yes	19	83.1±10.49	
PACs	No	34	77.35±10.43	0.119
	Yes	26	81.77±11.04	
ECG abnormalities	No	18	75.88±8.94	0.115
	Yes	42	80.71±11.34	

Abbreviations: ECG: Electrocardiogram; PVCs: Premature atrial contractions; PACs: Premature ventricular contractions.
*Mann–Whitney U test.

Table 4. The relationship between demographic and clinical variables with ECG changes following rituximab infusion

Variables		No. (%)		P*
		Gender		
		Male	Female	
Sinus tachycardia	No	2(66.7)	39(68.4)	-
	Yes	1(33.3)	18(31.6)	
PACs	No	2(66.7)	33(57.9)	-
	Yes	1(33.3)	24(42.1)	
ECG abnormalities	No	2(66.7)	17(29.8)	-
	Yes	1(33.3)	40(70.2)	

Variables		Risk Factors of Cardiovascular Disease		P*
		No	Yes	
Sinus tachycardia	No	34(73.9)	7(50)	0.111
	Yes	12(26.1)	7(50)	
PACs	No	25(54.3)	9(64.3)	0.551
	Yes	21(45.7)	5(35.7)	
ECG abnormalities	No	16(34.8)	2(14.3)	0.192
	Yes	30(65.2)	12(85.7)	

Variables		Rituximab Dosage (mg)		P*
		500 mg	1000 mg	
Sinus tachycardia	No	19(67.9)	22(68.8)	0.941
	Yes	9(32.1)	10(31.3)	
PACs	No	13(46.4)	21(65.6)	0.134
	Yes	15(53.6)	11(34.4)	
ECG abnormalities	No	7(25)	11(34.4)	0.429
	Yes	21(75)	21(65.6)	

Variables		Type of Rheumatic Disorder		P*
		RA	Other	
Sinus tachycardia	No	24(70.6)	17(65.4)	0.668
	Yes	10(29.4)	9(34.6)	
PACs	No	17(50)	17(65.4)	0.233
	Yes	17(50)	9(34.6)	
ECG abnormalities	No	9(26.5)	9(34.6)	0.495
	Yes	25(73.5)	17(65.4)	

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*Chi-squared test.

Abbreviations: ECG: Electrocardiogram; PVCs: Premature atrial contractions; PACs: Premature ventricular contractions; RA: rheumatoid arthritis.

Table 5. The relationship between history of drug use with ECG changes following rituximab infusion

Variables		No. (%)		P*
		Prednisolone		
		No	Yes	
Sinus tachycardia	No	4(66.7)	37(68.5)	0.626
	Yes	2(33.3)	31(31.5)	
PACs	No	4(66.7)	30(55.6)	0.472
	Yes	2(33.3)	24(44.4)	
ECG abnormalities	No	4(66.7)	16(29.6)	0.589
	Yes	2(33.3)	38(70.4)	

Variables		Methotrexate		P*
		No	Yes	
Sinus tachycardia	No	18(75)	23(63.9)	0.365
	Yes	6(25)	13(36.1)	
PACs	No	13(54.2)	21(58.3)	0.750
	Yes	11(45.8)	15(41.7)	
ECG abnormalities	No	7(29.2)	11(30.6)	0.908
	Yes	17(70.8)	25(69.4)	

Variables		Azathioprine		P*
		No	Yes	
Sinus tachycardia	No	31(63.3)	10(90.9)	0.148
	Yes	18(36.7)	1(9.1)	
PACs	No	30(61.2)	4(36.4)	0.182
	Yes	19(38.8)	7(63.6)	
ECG abnormalities	No	16(32.7)	2(18.2)	0.478
	Yes	33(67.3)	9(81.8)	

Variables		Hydroxychloroquine		P*
		No	Yes	
Sinus tachycardia	No	26(65)	15(75)	0.432
	Yes	14(35)	5(25)	
PACs	No	25(62.5)	9(45)	0.197
	Yes	15(37.5)	11(55)	
ECG abnormalities	No	13(32.5)	5(25)	0.550
	Yes	27(67.5)	15(75)	

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Abbreviations: ECG: Electrocardiogram; PVCs: Premature atrial contractions; PACs: Premature ventricular contractions.
*Fisher exact test; **Chi-squared test.

complications such as hypotension, angioedema, hypoxia, and bronchospasm have been reported following rituximab infusion [23-25]. Cardiotoxicity in the form of cardiac arrhythmia (including monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, supraventricular tachycardia, trigeminy, bradycardia, atrial fibrillation, and nonspecific dysrhythmias or tachycardia) has occurred in 8% of patients after rituximab infusion [20, 26]. Studies have suggested that CD-20 antigen may affect the calcium channel. The therapeutic mechanism of rituximab may be through cell lysis through complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and apoptosis. The CD20 antigen is on immune-effector cells and, after cytotoxic-mediated lysis, may sequester itself in normal body tissues, including cardiac myocytes. Therefore, rituximab may affect conduction by inhibiting the calcium channel properties of CD20 antigen. Finally, inhibition of calcium ion channels in cardiac myocytes may lead to premature formation after depolarization [27, 28].

Also, amounts of reticulin fiber have been observed with increased serum levels transforming growth factor-β following rituximab infusion in cardiac myocytes of patients. The transforming growth factor-β levels may increase the formation of reticulin fiber, followed by a decrease in myocardial contractility and, finally, non-ischemic cardiomyopathy [29, 30]. In addition, complications such as arrhythmia, rituximab-induced cardiogenic shock, delayed reduction in left ventricular ejection fraction, Takotsubo cardiomyopathy, and non-ischemic cardiomyopathies have been reported following rituximab infusion [25, 31-33].

Generally, studies conducted on other autoimmune diseases, except for rheumatism, have reported the inci-

dence of angina pectoris, acute coronary syndrome, and cardiac arrhythmias following rituximab infusion. Even in some cases, they have shown fatal complications such as hypotension, hypoxia, acute myocardial infarction, arrhythmia, and shock. Therefore, the FDA emphasizes that rituximab infusion should be done cautiously in patients with cardiovascular risk factors [23, 34, 35].

Conclusion

The results of the present study showed the incidence of ECG abnormalities following rituximab infusion in rheumatic patients was relatively high. Therefore, complete cardiopulmonary monitoring of these patients following receiving rituximab seems essential.

Study limitations

This study has some limitations. Perhaps the most crucial limitation of this study is the cross-sectional nature of the study because these studies measure exposure and outcome simultaneously, and a detailed investigation of cause and effect relationships is not possible due to the lack of temporal relationship between exposure and outcome. The second limitation of the current study is the single-center study and its small sample size, which makes the need for multi-center prospective cohort studies with a high sample size and a long-term follow-up necessary in future research. The third limitation was the lack of similar studies conducted in this field to compare the study findings.

Ethical Considerations

Compliance with ethical guidelines

Before data collection, the research aims were explained to the patients, and informed consent was obtained. In addition, this study was performed according to the principles expressed in the Declaration of Helsinki. It was approved by the Deputy of the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Code: IR.SBMU.MSP.REC.1402.380).

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Authors' contributions

Conceptualization, study design, data collection, statistical analysis, and writing: Shilan Haseli, and Faraneh Farsad; Final approval: All authors.

Conflict of interest

The authors declared no conflict interests.

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