ORIGINAL RESEARCH

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The frequency and associated factors of infusion-related reactions to rituximab for patients with rheumatoid arthritis

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Abstract

Objectives: Rituximab is an effective biological agent for treating patients with rheumatoid arthritis (RA). Rheumatologists can avoid rituximab therapy because of infusion-related reactions (IRR). There is a lack of data about rituximab-related IRR, especially in rituximab-naïve patients with RA; therefore, we aimed to determine the frequency and associated factors of rituximab-related IRR in these patients.

Methods: Baseline demographic, laboratory, and treatment data were noted. One course of rituximab was used in two infusions to 95 rituximab-naïve patients with RA. Standardized premedication was administered before infusions. Rates, severity, and management of IRR were recorded. Efficacy and infections were also noted if there were.

Results: Ninety-four of 95 patients completed the rituximab course successfully. We observed a total of 23 IRRs in 20 patients. The frequency of IRR was 12.1%, and serious IRR was 0.52%. Grade 1-2-3 IRRs had a rate of 52.2%, 30.4%, and 17.4%, respectively; grade 4 or 5 IRR wasn't detected. Age <60 years, anti-CCP <200U/ml and absence of biologic agent use before rituximab was significantly higher in patients with IRR than without IRR (p=0.01, p=0.002, p=0.01 respectively). We found out that if only the disease age is above 60 months, it is protective against IRR as per the results of multivariate model analysis.

Conclusion: Results supported that rituximab is a safe biological agent option for patients with RA at secondary central hospitals. Identified risk factors of IRR need to be corroborated in larger studies for safer rituximab therapy.

Keywords: Rituximab, Infusion-Related Reactions, Rheumatoid Arthritis, Risk Factors

INTRODUCTION

Rituximab is an IgG1 kappa chimeric monoclonal anti-CD20 antibody, which consists of a variable region of mouse origin (against human CD20) and a constant region of human origin (including the Fc portion). CD20 is a probable calcium ion channel and plays an essential role in B-cell differentiation. Rituximab binds with high affinity to cells expressing the CD20 antigen on the surface of malignant and normal pre-B/mature B lymphocytes, so these immune cells are targeted for lysis with different mechanisms. Rituximab was approved by the US Food and Drug Administration (FDA) for the indication of relapsed or refractory, CD20 positive B-cell, low-grade or follicular non-Hodgkin's lymphoma in November 1997; thus, rituximab was the firstly approved monoclonal antibody (Mab) for cancer therapy (1).

Recently, the role of B lymphocytes in the pathogenesis of rheumatic diseases is better understood (2), and rituximab was approved by FDA for rheumatoid arthritis (RA) in 2006 (3), for microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis) in 2011 (4). Currently, rituximab is not licensed for autoimmune connective tissue diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome, systemic sclerosis, and idiopathic

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inflammatory myopathies, but uncontrolled studies and case reports described the efficacy of rituximab for these diseases (5). Therefore, rituximab is used worldwide as labeled and off-labeled for the treatment of many rheumatic diseases by rheumatologists.

Biological drugs (Mabs, fusion proteins, and cytokines) are produced using biotechnological techniques; act on the immune system and inflammation. In contrast to chemical drugs, biological drugs are highly immunogenic proteins, administered parenterally, and are not metabolized (6). Distinctive side effects of Mabs are non-allergic infusion reactions caused mainly by cytokine release, and they are not mediated by immunoglobulin E (IgE). Allergic infusion reactions like anaphylactic type 1 hypersensitivity, mediated by IgE, are rarely seen in Mab therapy. The cytokine release syndrome (CRS) is clinically similar to hypersensitivity and may be indistinguishable during Mab infusion therapy. Releasing cytokines from targeted and immune effector cells is the mechanism of CRS, which usually occurs in the first infusion within 30 minutes to two hours. Symptoms are generally mild to moderate, resolved by slowing or short-term cessation of infusion and restarting the infusion at a slower rate (7).

Despite the efficacy and safety of rituximab in RA treatment (3,8), rheumatologists can avoid rituximab therapy (especially in secondary central hospitals) because of infusion-related reactions (IRRs). What are the risk factors or the clinical features of rituximab-related IRR in rituximab-naïve patients with RA? The answers to these questions are still uncertain; current data is insufficient about risk factors and clinical courses of IRR in rituximab-naïve patients with RA. The primary aim of this study was to answer the above questions. We hope that our research will be helpful for rituximab therapy in daily rheumatologic practice.

METHODS

Patient selection

A retrospective analysis of rituximab-naïve patients with RA, diagnosed according to The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria (9) and aged ≥18 years, was performed in a secondary central state hospital in the East of Turkey. Patients who received rituximab therapy between October 2018 and June 2020 during the follow-up period as a rheumatologist were included in the study. Patients who have a malign disorder or immune-mediated inflammatory diseases (such as Crohn's disease, multiple sclerosis) history or immunosuppressive drug use (such as cyclosporine, azathioprine, or mycophenolate mofetil) were excluded from the study. Patients' electronic files were evaluated for clinical features, demographic data, and laboratory findings, which also included baseline complete hematologic and biochemical profile, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), autoantibodies including rheumatoid factor: RF (determined by nephelometric assay, samples with results ≥14 IU/ml were defined as positive), anti-cyclic citrullinated peptide: anti-CCP (determined by enzyme-linked immunosorbent assay: ELISA, samples with results ≥20 U/ml were defined as positive) and anti-nuclear antibody: ANA (determined by ELISA), serologic tests for hepatitis B virus and hepatitis C virus. Regarding treatment, daily steroid doses, concomitantly conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) use, and biological agent use before rituximab were noted.

Treatment Protocol

Rituximab was administered in the outpatient clinic of the hospital. Premedication with paracetamol 1g orally, methylprednisolone 80-120 mg I.V., and an anti-histamine agent I.V. were administered to every patient before infusion; premedication protocol was applied according to van Vollenhoven RF et al.'s study (8). Patients received infusions in two steps. The first infusion was 1000 mg on day 1(D1), and the second infusion was 1000 mg on day 15 (D15); a total of 2000 mg rituximab was administered. Only six patients received therapy with half doses (two 500 mg infusions; a total of 1000 mg), preventing infections because of advanced age. The initial infusion rate was 50 mg/hour according to the administration protocol. If IRR wasn't observed and the vital findings were normal, the infusion rate would increase by 50 mg/hour every 30 minutes to a maximum 400 mg/hour rate. If any IRR were detected, the infusion rate would decrease or stop; treatment was resumed with half of the initial rate after resolving IRR.

Assessments

The infusion-related reaction occurred during or within 24 hours after an infusion (10). A serious infusion-related reaction (SIRR) was defined as discontinuing treatment, requiring hospitalization, persistent disability, or death. Signs, symptoms, duration, management (either reducing or stopping the rate), and additional premedications were recorded. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade IRR severity (11). Rheumatoid arthritis disease activity was classified according to DAS-28 categories (12). The clinical efficacy of rituximab was evaluated within 4.5 to 8 months after the first course. In addition to disease activity, serum globulin level was assessed after the rituximab course. Hypogammaglobulinemia was defined if the serum globulin level was <2.5g/dl. In case of infection, this was noted.

Statistical analysis

SPSS 21.0 software package was used for data analysis. The results were described as a number, frequency, and

percentage. The chi-square test was used to assess differences between qualitative variables. A p-value smaller than 0.05 and a 95% confidence interval were considered statistically significant. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-1 error level was used to infer statistical significance. Results were expressed as odds ratios and 95% confidence intervals for logistic regression. The study was approved by the Ethics Committee of the University where the study was conducted.

RESULTS

Of the 95 patients included, 77 (81%) were female, and the mean age was 58 years. The female-to-male ratio was 4.3/1, and the mean disease duration was 108 months. Concomitantly used csDMARDs included leflunomide (LEF), hydroxychloroquine (HQ), methotrexate (MTX), and sulphasalazine (SSZ); MTX use had a low rate because of drug incompatibility, gastrointestinal problems, and insufficient effectiveness. The rarest used csDMARD was sulphasalazine because most patients were seropositive, and sulphasalazine had insufficient effectivity. Glucocorticoid (prednisolone: P or methylprednisolone: MP) use was 88.4%, and the mean MP dose was 3.6 mg/day orally. A total of 23 biological agents were used in 18 patients before rituximab therapy. Table 1 shows demographic, laboratory, and treatment characteristics.

At the baseline, the DAS-28 scores of all patients were greater than 5.1. The mean evaluation time of rituximab efficacy on disease activity was at the sixth month. Rituximab treatment was effective in all patients who completed the cycle (n=94); 86% had remission, 12% had low disease activity, and 2% had moderate disease activity.

Ninety-four of 95 patients completed the first course successfully. Only one (40-year-old male) patient experienced grade 3 IRR in D1 infusion, and rituximab was discontinued; symptoms were fully resolved in two hours, and prolonged hospitalization wasn't required. 188 of 189 infusions were completed; the total number of IRR was 23 (12%), and the SIRR number was only one (0.5%). Rates of grade 1,2 and 3 IRR were 52% (n=12), 31% (n=7), and 17% (n=4), respectively; grade 4 or 5 IRR didn't occur. Generally, IRR developed in D1 infusion; only; only three patients developed IRR during both D1 and D15 infusions. All IRRs that occurred in the D15 infusion were grade 3. Still, we didn't consider a type 1 hypersensitivity reaction because IRRs occurred 30 minutes after starting the infusion, and infusion was completed successfully by short-term cessation of infusion and restarting the infusion at a slower rate.

Table 1. Demographic, laboratory, and treatment characteristics

Age, mean (range), years	58 (21-86)	
Female sex, n, %	77	81
Male sex, n,%	18	19
Disease duration, mean (range), months	108 (12-482)	
RF positivity, n, %	78	82
RF mean titer, IU/ml	217	
Anti-CCP positivity, n, %	70	74
Anti-CCP mean titer, U/ml	2 53 (available data from 62 /70 patients)	
RF or anti-CCP or both positive, n, %	81	85
ANA positivity, n, %	4	4
Serum globulin levels at baseline, mean (range), g/dl	2.9 (2.1-4.2)	
Serum globulin levels after RTX course, mean (range), g/dl	2.7 (1.8-3.5)	
Globulin decline after RTX therapy, n, %	52	57
Hypogammaglobulinemia after RTX course, n, %	14	15
Concomitantly used drugs, n, (%)		
-Hydroxychloroquine (HQ)	49	52
-Sulphasalazine (SSZ)	9	10
-Methotrexate (MTX)	32	34
-Leflunomide (LEF)	71	75
-Glucocorticoids (GC) (prednisolone: P or methylprednisolone: MP), n, %	84	89
Daily methylprednisolone dose, mean (range), mg	3.6 (2-16)	
Patients who received biological agent before the RTX course, n (%)	18	19
Number of biological agents before the RTX course	23	
Biological agents before RTX, n		
-Adalimumab	8	
-Etanercept	6	
-Tocilizumab	3	
-Certolizumab pegol	2	
-Abatacept	2	
-Infliximab	1	
-Tofacitinib	1	

Table 2. Adverse events of rituximab therapy

Patient with IRR, n, %	20	21
Number of total IRR	23	
Number of total SIRR	1	
The severity of IRR, n, %		
-Grade 1	12	52
-Grade 2	7	31
-Grade 3	4	17
-Grade 4 or 5	0	0
Infections, n (%)	3	3.1

Abbreviations: IRR, infusion-related reaction; SIRR, serious infusion-related reaction

Twenty-one of 23 IRR (91%) developed during infusion; two developed within 24 hours after infusion. We decreased the infusion rate in 18 IRRs and stopped in five IRRs. Thirteen of 23 IRR were persistent and not tolerated by patients; therefore, additional methylprednisolone (40 mg I.V.) was used to resolve IRR. We managed all of the stopped IRRs with additional steroid doses and restarted the infusion at a slower rate when symptoms resolved and infusions completed successfully. Signs/symptoms of IRRs were pruritus (n=13), erythema (n=12), sore throat (n=6), dyspnea (n=4), nausea/vomiting (n=2), hypotension (n=2), tinnitus (n=1), and headache (n=1). Infections developed in three (3%) patients after rituximab therapy; one patient had pneumonia and needed hospitalization, and intravenous antibiotic therapy, one had cellulitis, and one had cutaneous herpes zoster infection.

In univariate analysis, we found that age <60 years (p=0.01), anti-CCP titer <200 U/ml (p=0.002), and absence of biological agent used before rituximab therapy (p=0.01) were significantly higher in patients with IRR than without IRR (table 3). Age, sex, disease duration time, RF, anti-CCP, and biologic agent history were included in the multivariate model; increasing disease age was the only independent predictor of IRR and being protective against IRR.

Table 3. Univariate analysis of variables

Variable	IRR(+) group	IRR (-) group	p-value
Age <60 years	16/20	36/75	**0.01**
Female sex	18/20	59/75	0.25
Disease duration time ≥60 months	11/20	56/75	0.08
Serum baseline globuline ≥3g/dl	11/20	34/75	0.4
RF positivity	17/20	61/75	0.70
RF titer ≥100 IU/ml	11/17	35/61	0.58
Anti-CCP positivity	13/20	57/75	0.32
Anti-CCP titer <200 U/ml	12/23	26/57	**0.002**
Hydroxychloroquine use, n	11/20	38/75	0.73
Methotrexate use, n	10/20	24/75	0.13
Leflunomide use, n	14/20	59/75	0.41
Biologic naïve history, n	20/20	57/75	**0.01**

Abbreviations: IRR, infusion-related reaction; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; RTX, rituximab

DISCUSSION

The primary aim of this study was to identify the frequency and associated factors of rituximab-related IRR in rituximab-naïve patients with RA, and we found that age <60 years, anti-CCP titer <200 U/ml, and having biologic-naïve history were the associated with IRR. In medical literature, we defined that increasing disease age was the only independent predictor of IRR and protective against IRR. Totally, 21% of patients experienced IRR, and the rate of IRR was 12% in 189 infusions; 83% of patients had grade 1 and 2 IRRs, prolonged hospitalization or death was absent; 98% of patients completed the first rituximab course successfully.

Data from a global RA clinical trial with 2578 patients with RA, the first infusion was the most IRR occurring infusion with a rate of 25%, and the IRR rate decreased with subsequent infusions. Overall, 36% of patients experienced IRR, and <1% withdrew because of IRR; IRR rate, severity, and drug discontinuation were similar to our study (8). The most common adverse event of rituximab treatment in patients with RA is IRR, which has a lower incidence if the intravenous steroid is given as a part of premedication (13). Faster rituximab administration in patients with RA at the second and subsequent infusions doesn't cause an increasing rate or severity of IRR (14); nevertheless, our patients received therapy with the same protocol in D1 and D15 infusions.

There are many biological agent options for the treatment of RA which act with different mechanisms on disease pathogenesis, and IRR can be a reason for biological agent choice by rheumatologists. In a prospective study (n=4145), rituximab had a higher SIRR incidence than abatacept and tocilizumab in patients with RA; absence of concomitantly csDMARDs use, and anti-CCP positivity were the risk factors for SIRR, and patients with SIRR had more often previous anti-tumor necrosis factor (anti-TNF) use (15). Previous biological agent history could be a risk factor for IRR because anti-TNF agents lead to B-cell hyperactivity, as an immunologic side effect. Still, our results were controversial regarding this phenomenon (16).

Rituximab-related IRR rates are lower in patients with SLE than in those with RA, which may result from higher glucocorticoid doses in SLE. Indeed our patients had a low dose of glucocorticoid treatment (17). In patients with SLE, the first infusion is the most frequently rituximab-related IRR occurring infusion, and decreasing rates in subsequent infusions are similar to the RA studies. Still, risk factors are unknown (18). Rituximab-related IRR rates for lymphoproliferative disorders are higher than for autoimmune diseases (19), probably due to tumor burden. Rituximab-related IRR occurs in 84% of patients who have relapsed low-grade or follicular lymphoma, and the majority of IRRs are grade 1 or 2 and occur during the first infusion; fever and chills which were not observed in our patients are the most common symptoms (20). On the other hand, patients with multiple sclerosis (MS) treated with rituximab have similar IRR rates and severity to RA (21). If steroid treatment is not given before rituximab infusion in patients with MS, IRR increases dramatically (22). Regardless of the disease type (RA, SLE, MS, or lymphoproliferative diseases), steroid use decreases rituximab-related IRR.

Usually, Mabs are better tolerated and have lower toxicity than conventional cytotoxic drugs. However, IRR is a problem for all the Mabs (it is not specific to rituximab). Although the IRR varies among Mabs, it is most common in rituximab and generally occurs at the first infusion (23). Levels of inflammatory cytokines increase significantly during rituximab infusion compared with baseline measurements (24). IRR generally depends on CRS, which was caused by massive B cell lysis, and levels of inflammatory cytokines (TNF-a and IL-6) are correlated with IRR severity (25). The negative effects of aging on B-cells may explain the protective feature of increasing age against IRR (26).

Retrospective design, small sample size, absence of analysis for comorbidities such as diabetes mellitus or hypertension, and lack of allergy-immunology department consultation in IRR-developing patients (especially in D15 infusions) were the study's limitations.

CONCLUSION

In conclusion, 98% of rituximab-naive patients with RA successfully completed the first rituximab course in a secondary central hospital; IRR occurred in 21% of patients and 12% of total infusions. Drug discontinuation was very rare. Age <60 years, anti-CCP titers <200 U/ml and bio-naïve history were significantly higher in IRR developing group. Only the independent predictor of IRR was disease age; increasing disease age was protective against it. The unique results of our study will contribute to the safety of rituximab therapy in daily rheumatologic practice if patient-based risk factors are evaluated before infusion. Current knowledge about identified risk factors, rates, and severity of rituximab-related IRRs was generally obtained from non-RA patients. The identified factors of our study need to be corroborated in larger studies for safer rituximab treatment. Safety data of Mab infusion therapy is needed for other rheumatic diseases and drugs so that further studies can be focused on this subject.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical approval was obtained from Mus Alparslan University Clinical Research Ethical Committee with date 29.10.202 and number E-79236777-605.99-2541, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MP, Design:MP, Supervising: MP, Financing and equipment:MP, Data collection and entry: MP, Analysis and interpretation MP, Literature search: MP, Writing: MP, Critical review: MP.

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