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Hypogammaglobulinemia and severe infection risk in patients with autoimmune diseases during rituximab treatment

Otoimmün hastalığı olan hastalarda rituksimab tedavisi sırasında hipogamaglobulinemi ve enfeksiyon riski

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Abstract

Objective: To assess the frequency and related factors of hypogammaglobulinemia (HGG) and severe infections in patients who received rituximab (RTX) for rheumatic diseases during routine follow-up.

Methods: Patients who were followed in Marmara University Rheumatology Clinic and received RTX are evaluated retrospectively. The immunoglobulin (Ig) G, IgM, IgA levels and clinical manifestations were obtained from patient files. The HGG frequency and related factors were assessed. Severe infections were also analysed.

Results: A total of 144 patients were included (F/M: 105/39, mean age 52.8±13.8). In the majority of the patients (67%) the diagnosis was rheumatoid arthritis (RA). At least one subgroup of HGG was observed in 30% (43/144) of the patients. During follow-up 17 (11.8%) patients had low IgG, 37 (26%) low IgM, and 7 (4%) had low IgA levels. HGG rate was similar between RA, connective tissue diseases and anti-neutrophil cytoplasmic antibody associated vasculitis patients (25%, 30%, 47%, respectively, p=0.13). HGG was more frequent in men (p=0.028), in patients with higher accumulated RTX dose (p=0.006) and with hypertension (p=0.033). Concomitant use of disease-modifying anti-rheumatic drugs, glucocorticoid use and prior cyclophosphamide was not associated with higher HGG. Methotrexate use with RTX was a protective factor for HGG (HGG rate methotrexate + vs -: 12% vs 33%, p=0.032). Two patients with HGG (5%) received intravenous immunoglobulin replacement. Twenty-seven patients (18%) had severe infections. Lower IgG levels [IgG levels odds rato (OR)

Öz

Amaç: Bu çalışmanın amacı rutin takip sırasında romatizmal hastalığı için rituksimab (RTX) alan hastalarda hipogamaglobulinemi (HGG) ve ciddi enfeksiyon sıklığı ve ilişkili faktörleri değerlendirmektir.

Yöntem: Marmara Üniversitesi Romatoloji Kliniği'nde takip edilen ve RTX tedavisi alan hastalar retrospektif olarak değerlendirildi. İmmünoglobulin (Ig) G, IgM, IgA seviyeleri ve klinik bulgular hasta dosyalarından elde edildi. HGG sıklığı ve ilişkili faktörler değerlendirildi. Ciddi enfeksiyonlar da ayrıca analiz edildi.

Bulgular: Çalışmaya toplam 144 hasta dahil edildi (K/E: 105/39, ortalama yaş 52,8±13,8). Hastaların çoğunluğunda (%67) tanı romatoid artrit (RA) idi. Herhangi bir subgrup HGG %30 (43/144) hastada gözlendi. İzlem sırasında 17 (%11,8) hasta düşük IgG, 37 (%26) hasta düşük IgM, 7 (%4) hasta ise düşük IgA seviyelerine sahipti. RA, bağ doku hastalıkları ve anti-nötrofil sitoplazmik antikor ilişkili vaskülitlerde HGG oranı benzerdi (sırasıyla %25, %30, %47, p=0,13). HGG erkeklerde (p=0,028), kümülatif RTX dozu yüksek olan hastalarda (p=0,006) ve hipertansiyonu olan hastalarda (p=0,033) daha sık idi. Eşlik eden hastalık modifiye edici anti-romatizmal ilaç kullanımı, glukokortikoid ve siklofosfamid kullanım öyküsü HGG ile ilişkili değildi. RTX ile metotreksat kullanımı HGG gelişimi için koruyucu bir faktördü (HGG oranı metotreksat +vs -: %12 vs %33, p=0,032). HGG gelişen 2 (%5) hastaya intravenöz immünoglobulin verildi. Yirmi yedi (%18) hastada ciddi enfeksiyon geliştiği görüldü. Çok değişkenli analizde düşük IgG seviyeleri [IgG düzeyi risk oranı (RO) (%95 güven aralığı [GA]) 0,82 (0,70-0,96), p=0,018] ve kronik akciğer hastalığı (KAH)

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(95% confidence interval [CI]) 0.82 (0.70-0.96), p=0.018] and chronic lung disease (CLD) [CLD present OR (95% CI) 3.7 (1.2-10.8), p=0.017] were associated with severe infections in multivariate analysis. A total of 38 patients died during follow-up. Mortality was more frequent in patients with HGG [mortality rate HGG+ vs HGG -: 40% (17/43) vs 21% (20/101), p=0.02].

Conclusion: While male gender, increased number of RTX courses and hypertension were found to be risk factors for HGG, CLD and lower IgG levels were associated with severe infections. Therefore, measuring Ig levels and assessing risk factors for HGG and severe infections during RTX treatment may provide information to prevent both conditions.

Keywords: Rituximab, hypogammaglobulinemia, severe infection, rheumatic diseases

[KAHv arlığı RO (%95 GA) 3,7 (1,2-10,8), p=0,017] ciddi enfeksiyonda artış ile ilişkili idi. İzlem sırasında 38 hastada ölüm görüldü. Mortalite HGG gelişen hastalarda daha sık idi [mortalite oranı HGG+ vs HGG -: %40 (17/43) vs %21 (20/101), p=0,02].

Sonuç: Erkek cinsiyet, RTX doz artışı ve hipertansiyon HGG için risk faktörü iken, kronik akciğer hastalığı ve düşük IgG düzeyi ciddi enfeksiyon ile ilişkiliydi. Bu nedenle RTX tedavisi sırasında Ig düzeylerinin ölçümü ve HGG ve ciddi enfeksiyon için risk faktörlerinin değerlendirilmesi her iki durumun önlenmesinde yarar sağlayabilir.

Anahtar Kelimeler: Rituksimab, hipogamaglobulinemi, ciddi enfeksiyon, romatolojik hastalıklar

Introduction

Rituximab (RTX) which targets CD20 expressing B-cells, is indicated in a wide spectrum of diseases such as rheumatoid arthritis (RA) and anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). In addition, RTX is used in the treatment of other rheumatic diseases including systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) which are resistant to multiple other treatment options.[1-5]

The development of hypogammaglobulinemia (HGG) has been reported after repeated doses of RTX and being explored increasingly.[6] However, this effect is expected to be temporary since stem cells are not targeted.[7] Although B cell depletion is expected to last for 6-9 months after RTX infusion, it has been reported that this period may be longer in some of the patients.[8] HGG duration was prolonged to 18-24 months in patients receiving additional chemotherapy due to malignancy.[9] In a review evaluating HGG and infection risk in patients receiving RTX, malignancy, pre-treatment low immunoglobulin (Ig) levels, cumulative RTX dose, baseline Ig levels and concomitant use of immunosuppressives such as mycophenolate mofetil (MMF) or purine analogues were found to increase the risk of HGG.[10]

There are conflicting data in the literature regarding the development of serious infections due to RTX treatment and RTX related HGG.[3,8,11,12] Although RTX seems safe in initial studies, subsequent studies have shown that RTX may increase the risk of severe infections.[8] Especially low IgG levels were reported to be associated with increased serious infections.[4,13] Older age, the number of RTX courses, prolonged low IgG levels, granulocyte colony-stimulating factor use, chronic lung disease (CLD), cardiac insufficiency and extra-articular involvement in RA patients were other risk factors for infections in patients under treatment with RTX.[10]

In this study we aimed to assess HGG, severe infection rates and related factors in patients receiving RTX treatment.

Materials and Methods

Consecutive patients who were followed in Marmara University Rheumatology Clinic and received RTX therapy between October 2016 and January 2019 were involved in this retrospective cohort study. The study was approved by the local Ethics Committee (no: 09.2023.1332). All patients received at least one course of RTX. Patients who did not complete at least 1 course of RTX treatment were excluded from the study. In routine practice, RTX was administered as 1.000 mg on 1st and 14th days every 6 months, unless lower doses deemed appropriate.

IgG, IgA, and IgM levels which were tested during routine follow-up. Ig levels were measured 6 months after the previous RTX dose and before the next infusion. Normal ranges were 6.5-16 g/L for IgG, 0.4-3.5 g/L for IgA and 0.5-3 g/L for IgM g/L based on our local laboratory cut-off values. In addition, IgG levels between 5-6.5 g/L was defined as mild, 3-5 g/L as moderate, <3 g/L as severe HGG.[14] Severe infection was defined as infection requiring parenteral antibiotic therapy or hospitalization.[3]

Additional data including age, gender, disease duration, comorbidities, previous cyclophosphamide (CyC) and concomitant immunosuppressive use, concomitant glucocorticoid (GC) use and cumulative RTX dose were recorded from patient files.

Statistical Analysis

SPSS statistics 22 was used for the statistical analysis. Dichotomous variables were expressed as number and frequencies. The continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution. In non-normal distribution median (25-75

percentile) was presented. Chi-square, Mann-Whitney U and Kruskal-Wallis tests were used to compare the data. A p-value <0.05 was considered statistically significant. Binary logistic regression was performed to assess the predictive factors for HGG and severe infections. HGG and severe infection were dependent variables for separate logistic regression analysis. Age, gender, disease duration, cumulative RTX dose, comorbidities, concomitant DMARDs, GC were used as covariates. Low IgG, IgM, IgA levels were additional covariates for the logistic regression analysis of severe infections. Variables with a p-value of <0.2 in univariable analysis were involved in multivariable analysis.

Results

One hundred and forty-four (105 female, 39 male) patients were included in the study. Mean (± SD) follow-up duration under RTX treatment was 3.4 (2.3) years. The diagnosis was RA in 96 (67%), AAV in 21 (15%), SLE in 15 (10%), scleroderma (SSc) in 6 (4%), primary SS in 3 (2%) and polyarteritis nodosa in 2 (1%) patients. Two patients with RA had secondary SS and 2 SLE patients had secondary antiphospholipid syndrome. Table 1 shows demographic and clinical characteristics of the patients.

A total of 198 visits (number of the patients with one visit 144, two visits 43, three visits 11) were evaluated. During the follow-up, 43 (30%) patients had any subgroup of HGG. Thirteen (9%) patients had at least two subgroups of low Ig and 4 (2.8%) patients had HGG in all three subgroups. Low IgG levels were observed in 17 (11.8%), low IgM in 37 (26%), low IgA in 7 (4%) patients at any time of the follow-up. In most of the patients with low IgG the HGG was mild (13/17, 77%) (Table 2). Between RA, connective tissue diseases (CTD) (SLE, SSc and PSS were included in this group) and AAV groups, there were no difference in terms of HGG frequency (25%, 30%, 47%, respectively, p=0.13) and severe infections (16%, 18%, 29% respectively, p=0.42).

Among the 43 patients who had recurrent Ig measurements, low levels of IgG persisted in 67% (4/6) patients. The remaining 2 patients had IgG levels <7 g/L but in the normal range. In 70% (12/17) of the patients with low IgM and 33% (1/3) patients with low IgA, the HGG persisted during follow-up. The follow-up IgM levels were median 0.53 (0.42-0.56) g/L and the IgA levels were 0.62 and 1.11 g/L in the patients who had HGG in one visit and did not persist in the follow-up visits.

HGG was more frequent in male patients (M vs F: 44% vs 25%, p=0.028). Similar HGG rates were found between patients with and without concomitant azathioprine (p=0.08), leflunomide (p=0.74), MMF (p=0.25), hydroxychloroquine

Table 1. Demographic and clinical characteristics of the patients who received rituximab treatment

Diagnosis, n (%)	
Rheumatoid arthritis	96 (67)
ANCA associated vasculitis	21 (15)
Systemic lupus erythematosus	15 (10)
Scleroderma	6 (4)
Primary Sjögren syndrome	3 (2)
Poliarteritis nodosa	2 (1)
Age, years, mean ± SD	52.8±13.8
Gender, female, n (%)	105 (71)
Comorbidities, n (%)	
Diabetes	24 (17)
Hypertension	45 (32)
Chronic kidney disease	13 (9)
Chronic obstructive lung disease	12 (9)
Coronary artery disease	20 (15)
Asthma	9 (7)
Lung involvement of the rheumatological disease	3 (2)
Disease duration, years, mean ± SD	
Rheumatoid arthritis	15.9±8.7
ANCA associated vasculitis	3.9±4.4
Systemic lupus erythematosus	5.3±3.4
Scleroderma	8.1±5.6
Primary Sjögren syndrome	7.5±0.7
Poliarteritis nodosa	*
Prior cyclophosphamide, n (%)	10 (7)
Concomitant hydroxychloroquine use, n (%)	17 (12)
Concomitant csDMARD use, n (%)	
Azathioprine	14 (10)
Leflunamide	54 (38)
Methotrexate	25 (17)
Mycophenolate mofetil	3 (2)
Concomitant GC use, present, n (%)	71 (50)
Cumulative rituximab dose, g, mean ± SD	11.5±7.6
Ig levels, mean ± SD, g/L	
IgG	10.53±3.99
IgM	0.79±0.62
IgA	2.06±1.24
Severe infection, present, n (%)	27 (18%)

**Disease duration for the patients diagnosed with PAN was 4 and 6 years, ANCA: Anti-neutrophil cytoplasmic antibody, csDMARD: Conventional synthetic disease-modifying antirheumatic drug, GC: Glucocorticoid, Ig: Immunoglobulin, PAN: Polyarteritis nodosa, SD: Standard deviation*

Table 2. The frequency of hypogammaglobulinemia during follow-up

Any subgroup of hypogammaglobulinemia, n (%)	43 (30)
Low IgG, n (%)	17 (12)
Mild	13 (77)
Moderate	3 (18)
Severe	1 (6)
Low IgM, n (%)	37 (26)
Low IgA, n (%)	7 (4)

Ig: Immunoglobulin

(p=0.52) and GC (p=0.37) use and prior CyC (p=0.46) treatment. HGG was less frequent in patients who were using concomitant methotrexate (MTX) (HGG rate MTX +vs -: 12% vs 33%, p=0.032). Age (p=0.20) and disease duration (0.37) were similar between patients with and without HGG. Higher RTX dose (RTX dose HGG + vs - : 13.6±8.3 vs 9.6±6.8 g, p=0.006) and presence of hypertension (HT) (HT present in HGG+ vs-: 44% vs 26%, p=0.033) were associated with HGG (Table 3). In multivariate logistic reression analysis, male gender [odds ratio (OR) (95% confidence interval [CI]) 2.39 (1.01-5.68), p=0.047], HT [OR (95% CI) 2.68 (1.15-6.22), p=0.021], higher cumulative RTX dose [OR (95% CI): 1.08 (1.02-1.14), p=0.005] and not using MTX [MTX use OR (95% CI) 0.18 (0.04-0.73), p=0.016] were related to more frequent HGG (Table 4). RTX treatment was discontinued in 2 of the patients with HGG and intravenous Ig (IVIG) replacement was used. In one patient with SLE, IVIG was given for autoimmune hemolytic anemia in addition to RTX treatment. A total of 38 patients died during follow-up. Mortality was more frequent in patients with HGG [mortality rate HGG+ vs HGG -: 40% (17/43) vs 21% (20/101), p=0.02].

Twenty-seven (18%) patients had severe infections during follow-up. In most of the severe infections (19/27 patients, 70%) the source of the infection was respiratory tract. Three (11%) of the patients had urinary tract infections, 3 (11%) patients had an infection related to joint prothesis, 1 (4%) patient had cholecystitis and 1 (4%) patient had dental abscess. The increased cumulative RTX doses (p=0.04), presence of CLD (p=0.03) and lower IgG levels (p=0.03) were related to severe infections in univariate analysis. Age (p=0.73), disease duration (p=0.41), IgM (p=0.46) and IgA

Table 3. The features of patients who had and did not have hypogammaglobulinemia

	HGG present n=43	HGG absent n=101	p
Age, years, mean ± SD	55.2±12.7	51.2±14.4	0.20
Male gender, n (%)	17 (44)	22 (25)	**0.028**
Disease duration, years, mean ± SD	11.2±8.5	12.7±9.1	0.37
RTX cumulative dose, g, mean ± SD	13.6±8.3	9.6±6.8	**0.006**
Comorbidities, n (%)			
Diabetes	6 (14)	18 (18)	0.54
Hypertension	19 (44)	26 (26)	**0.033**
Coronary artery disease	4 (9)	15 (15)	0.34
Chronic lung disease	10 (23)	13 (13)	0.12
Renal disease	3 (7)	12 (12)	0.36
Prior CyC, n (%)	4 (9)	6 (6)	0.46
Concomitant DMARDs, n (%)			
Azathioprine	7 (16)	7 (7)	0.08
Leflunomide	17 (39)	37 (37)	0.74
Methotrexate	3 (7)	22 (22)	**0.032**
Mycophenolate mofetil	0 (0)	3 (3)	0.25
Hydroxychloroquine	4 (9)	13 (13)	0.52
Concomitant GC use, present, n (%)	16 (37)	46 (46)	0.37

CyC: Cyclophosphamide, DMARD: Disease modifying anti-rheumatic drugs, GC: Glucocorticoid, HGG: Hypogammaglobulinemia, RTX: Rituximab, SD: Standard deviation

Table 4. The multivariate analysis for the risk factors of hypogammaglobulinemia and severe infection

Variable	OR (95% CI)	p
Hypogammaglobulinemia		
RTX dose, g	1.08 (1.02-1.14)	**0.005**
Hypertension	2.68 (1.15-6.22)	**0.021**
Male gender	2.39 (1.01-5.68)	**0.047**
MTX use	0.18 (0.04-073)	**0.016**
Severe infections		
RTX dose, g	1.03 (0.98-1.09)	0.20
IgG levels, g/L	0.82 (0.70-0.96)	**0.018**
Lung disease	3.70 (1.27-10.82)	**0.017**

CI: Confidence interval, Ig: Immunoglobulin, MTX: Methotrexate, OR: Odds ratio, RTX: Rituximab

(p=0.52) levels were not associated with severe infections (Table 5). Multivariate logistic regression analysis showed that lower IgG levels [IgG levels OR (95% CI) 0.82 (0.70-0.96), p=0.018] and CLD [CLD present OR (95% CI) 3.7 (1.2-10.8), p=0.017] were associated with increased severe infections. The cumulative RTX dose did not differ significantly between the patients with and without severe infections in multivariate analysis [OR (95% CI) 1.03 (0.98-1.09), p=0.20] (Table 4).

Discussion

In the current study any subgroup of HGG occurred in 30% of the patients with systemic autoimmune diseases receiving RTX in routine follow-up. Low IgG, IgM and IgA levels were found in 12%, 26% and 4% patients respectively. Higher RTX cumulative doses, male gender, HT and absence of concomitant MTX treatment were predictive factors for more frequent HGG. Severe infections were observed in 18% of the patients which was associated with low IgG levels and CLD.

HGG was reported in 10-56% of the patients with autoimmune diseases.[1,14-18] Factors such as the cumulative RTX dose, RTX dose regimens, the timing of the Ig measurement after RTX and cut-off values for HGG may have affected the variability of the HGG frequency in the literature. In AAV, patients who received 500 mg as maintenance dose developed HGG less frequently compared to patients who received 1000 mg.[19] In different studies the cut-off for HGG was considered as 565 mg/dL,[12] 600 mg/dL[3] or 700 mg/dL[14] for IgG. The values <55 mg/dL, <50 mg/dL, <40 mg/dL for IgM and <80 mg/dL, <70 mg/dL for IgA were evaluated as HGG in different studies.[3,12,14] In our cohort, almost one third of the patients had HGG in any subgroup of Ig during follow-up in line with the literature.

Data about the predictive factors of HGG is contradictory. Age was identified as a risk factor for RTX-related HGG and serious infections in several studies.[15,20] HGG was more frequent in female patients in a study which reported RTX associated HGG in autoimmune diseases.[21] In contrast, Besada et al.[19] found that male gender was a risk factor for severe HGG and withdrawal of RTX due to HGG.

Table 5. The comparison of the characteristics of the patients with and without severe infections

	Severe infections (+) n=27	Severe infections (-) n=117	p
Age, years, mean ± SD	57.3±10.3	50.9±14.6	0.73
Gender, female, n (%)	20 (74)	84 (72)	0.86
Disease duration, years, mean ± SD	14.8±12.6	11.5±8.1	0.41
Cumulative rituximab dose, g, mean ± SD	14.5±7.2	10.3±8.1	**0.04**
Prior CyC use, n (%)	2 (7)	8 (7)	0.92
Concomitant csDMARD use, n (%)			
Azathioprine	1 (4)	13 (11)	0.23
Leflunomide	8 (30)	46 (39)	0.33
Methotrexate	7 (26)	18 (15)	0.20
Mycophenolate mofetil	0 (0)	3 (3)	0.39
Hydroxychloroquine use, n (%)	3 (11)	14 (12)	0.90
Concomitant GC use, n (%)	10 (37)	52 (44)	0.87
Comorbidities, n (%)			
Diabetes	5 (19)	19 (16)	0.76
Hypertension	10 (37)	35 (30)	0.46
Coronary artery disease	2 (11)	17 (14)	0.32
Chronic lung disease	8 (30)	15 (13)	**0.03**
Renal disease	5 (19)	10 (8)	0.12
Hypogammaglobulinemia, n (%)			
Low IgG	6 (22)	11 (9)	0.06
Low IgM	10 (37)	27 (23)	0.11
Low IgA	2 (7)	5 (4)	0.47
Ig levels, g/L, mean ± SD			
IgG	9.9±9.6	11.5±4.6	**0.03**
IgM	1.0±0.9	0.8±0.6	0.46
IgA	1.9±0.6	2.2±1.3	0.52

csDMARD: Conventional synthetic disease-modifying antirheumatic drug, CyC: Cyclophosphamide, GC: Glucocorticoid, Ig: Immunoglobulin, SD: Standard deviation

Association of male gender with HGG in our study is consistent with the second study. Age was similar in patients with and without HGG. Stabler et al.[22] reported that diabetes and malignancy were risk factors for HGG in terms of comorbidities. Diabetes was not a predictive factor for HGG in our study, whereas HT was related. It has been shown that there is an immune activation, including B-cells, in the pathogenesis of HT.[23] However, HT has not been linked to RTX-related HGG in the studies. HT may be a result of higher cumulative GC doses which may be related to HGG development in our study. In addition, HT, which occurred because of renal involvement, may have affected the frequency of HGG.

Concomitant medications such as CyC, MMF and GC use were found to be predictors of HGG in previous studies.[15,17,24,25] Also, prior CyC was shown to increase the HGG rate.[21] In contrast, HGG was not associated with conventional disease-modifying anti-rheumatic drugs (cDMARD) or CS use in a retrospective study including 83 RA patients.[14] In our study the use of additional cDMARDs and GC did not seem to affect the HGG rate other than MTX. Interestingly, concomitant MTX therapy was associated with a reduced risk of HGG in patients who were mostly diagnosed with RA (23/25). In the literature the data about the effect of MTX on Ig levels are scarce. In a study, juvenile RA patients, who were treated with MTX, had lower Ig levels compared to patients without treatment.[26] In another study MTX was not associated with HGG in inflammatory bowel disease patients.[27] Boleto et al.[11] studied predictive factors for HGG in RA patients and reported MTX had a protective role for HGG.[28] Not using concomitant MTX was a risk factor[14] for HGG in another trial similar to our results. This may be related to the characteristics of patients receiving concomitant MTX treatment. However, this result was not well explained and this protective effect of MTX on HGG remains to be confirmed in other studies.

The diagnosis of the patient is one of the factors that may influence the development of HGG in the literature. In a study which compared HGG between AAV and SLE patients after 3-6 months after RTX administration, HGG was found more frequently in AAV patients.[15] Similarly, Thiel et al.[29] reported more frequent and long-lasting HGG in AAV patients compared to RA and CTD. Although HGG was numerically higher in the AAV group compared to RA and CTD patients, the difference was not statistically significant in our study.

HGG is not an absolute contraindication for continuing RTX therapy and may be transient in some of the patients. In a longitudinal observational study HGG was temporary in 73% of the AAV cases.[15] In contrast to this study Evangelatos et al.[14] found that HGG was persistent in all of the 37 patients with RA who developed HGG at any time of the follow-up. Consistent with the results of the latter, HGG was 65% persistent in our patients during follow-up.

In several studies higher cumulative RTX dose was shown not to increase the HGG and severe infection frequencies in RA patients.[28,30] According to our results higher cumulative RTX dose was associated with increased HGG rate but did not have a significant effect on severe infections.

The effect of HGG on severe infection rate is controversial in the literature. Although there are reports about an increase of severe infections in patients with HGG,[3,11,12] in some of the previous studies severe infection rate was similar between patients with and without HGG.[14,31-33] The risk of infection is also reported to be associated with the deficient Ig subgroup. IgG deficiency is considered to be more important in terms of infection risk compared to IgA and IgM.[34] Md Yusof et al.[3] reported that serious infection risk was increased in patients with IgG <6 g/L. In our study lower IgG levels were associated with severe infections.

Severe infection rate was reported 20-40% of the patients on RTX treatment.[22,35-37] Focus of the infection was mostly sino-pulmonary infections.[15,16]. CLD, diabetes and heart failure were predictors for severe infections in musculoskeletal diseases during RTX treatment.[3] CLD (including lung involvement of the primary rheumatic disease) was also a risk factor for severe infections in our results. In a study including RTX-treated patients with rheumatic diseases, MTX was found a protective factor for severe infections.[38] We observed that MTX was not related with a decrease in serious infections, unlike HGG.

IVIG replacement was found to decrease the annual infection rate but not severe infections in a study in which 20% of the patients with HGG received IVIG.[21] In our cohort, fewer patients with HGG received IVIG (5%) replacement. According to recommendations which were created specifically for RTX-related HGG, it has been suggested that the decision for IVIG replacement should be made according to the severity of HGG, presence of severe, recurrent, or unusual infections, or lack of response to vaccines. In addition, it is recommended that the Ig levels should be checked every 6-12 months in patients with autoimmune rheumatic disease receiving RTX.[34] However, there is not a global consensus on the frequency of Ig measurement and the indications for IVIG replacement.

Mortality is another outcome that has been associated with HGG. Bartmettler et al.[8] showed increased risk of mortality in RTX-related HGG. Similarly, in our results mortality rate was higher in patients with HGG.

Study Limitations

Our study has some limitations. The main limitation was the retrospective design of the study. The baseline Ig levels was shown to be related with an increase in HGG risk in the literature.[17,19,39,40] As a second limitation, since a small number of our patients had baseline Ig measurement, baseline IgG levels were not included in the analysis. However, presence of follow-up Ig measurements allowed the assessment of whether HGG was persistent or transient.

Conclusion

In the current study we observed HGG almost in one-third of the patients which was associated with higher cumulative RTX doses, male gender and HT. Although low IgG levels were associated with severe infection, the risk of serious infections was similar in patients with and without low IgG type HGG. CLD was a risk factor for severe infections. Since RTX can improve CLD in rheumatic diseases, the risk of infection may be affected, especially in fibrotic type CLD. There are no globally accepted algorithms for IVIG treatment and monitoring Ig levels during RTX treatment. Therefore, determining risk factors for HGG and serious infections, which is a major concern for HGG, is important in the follow-up of the patients and making clinical decisions.

Ethics

Ethics Committee Approval: The study was approved by the local Ethics Committee (no: 09.2023.1332).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.K.T., F.A.Ö., E.A., Z.S.T., H.D., Design: S.K.T., F.A.Ö., H.D., Data Collection or Processing: S.K.T., F.A.Ö., T.K., Y.Y., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D., Analysis or Interpretation: S.K.T., F.A.Ö., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D., Literature Search: S.K.T., F.A.Ö., T.K., Y.Y., H.D., Writing: S.K.T., F.A.Ö., T.K., Y.Y., N.İ., M.P.A., D.B.A., E.A., Z.S.T., H.D.

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References

1. Aguiar R, Araújo C, Martins-Coelho G, Isenberg D. Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience Over 14 Years. Arthritis Care Res (Hoboken) 2017;69:257-62.
2. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4.
3. Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, Rawstron AC, Buch MH, Emery P, Savic S. Predicting Severe Infection and Effects of Hypogammaglobulinemia During Therapy With Rituximab in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol 2019;71:1812-23.
4. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909-20.
5. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73:1366-83.
6. Brinkman IH, van de Laar MA, Jansen TL, van Roon EN. The potential risk of infections during (prolonged) rituximab therapy in rheumatoid arthritis. Expert Opin Drug Saf 2011;10:715-26.
7. Rehnberg M, Amu S, Tarkowski A, Bokarewa MI, Brisslert M. Short- and long-term effects of anti-CD20 treatment on B cell ontogeny in bone marrow of patients with rheumatoid arthritis. Arthritis Res Ther 2009;11:R123.
8. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia. JAMA Netw Open 2018;1:e184169.
9. Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456-73.
10. Christou EAA, Giardino G, Worth A, Ladomenou F. Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab. Int Rev Immunol 2017;36:352-9.
11. Boleto G, Avouac J, Wipff J, et al. Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: A 12-year longitudinal multi-center study. Semin Arthritis Rheum 2018;48:149-54.
12. van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. J Rheumatol 2015;42:1761-6.
13. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010;62:2625-32.
14. Evangelatos G, Fragoulis GE, Klavdianou K, Moschopoulou M, Vassilopoulos D, Iliopoulos A. Hypogammaglobulinemia after rituximab for rheumatoid arthritis is not rare and is related with good response: 13 years real-life experience. Rheumatology (Oxford) 2021;60:2375-82.
15. Padoan R, Felicetti M, Gatto M, Polito P, Doria A, Schiavon F. Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: a longitudinal observational study. Clin Exp Rheumatol 2020;38(Suppl 124):188-94.
16. De La Torre I, Leandro MJ, Valor L, Becerra E, Edwards JC, Cambridge G. Total serum immunoglobulin levels in patients with RA after multiple B-cell depletion cycles based on rituximab: relationship with B-cell kinetics. Rheumatology (Oxford) 2012;51:833-40.

17. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60-5.

18. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-400.

19. Besada E, Koldingsnes W, Nossent JC. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2014;53:1818-24.

20. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583-94.

21. Tieu J, Smith RM, Gopaluni S, et al. Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease. Front Immunol 2021;12:671503.

22. Stabler S, Giovannelli J, Launay D, et al. Serious Infectious Events and Immunoglobulin Replacement Therapy in Patients With Autoimmune Disease Receiving Rituximab: A Retrospective Cohort Study. Clin Infect Dis 2021;72:727-37.

23. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. Nat Rev Immunol 2019;19:517-32.

24. Marco H, Smith RM, Jones RB, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord 2014;15:178.

25. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:334-6.

26. Bingham CO 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62:64-74.

27. Looney RJ, Srinivasan R, Calabrese LH. The effects of rituximab on immunocompetency in patients with autoimmune disease. Arthritis Rheum 2008;58:5-14.

28. Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2015;74:1799-807.

29. Thiel J, Rizzi M, Engesser M, et al. B cell repopulation kinetics after rituximab treatment in ANCA-associated vasculitides compared to rheumatoid arthritis, and connective tissue diseases: a longitudinal observational study on 120 patients. Arthritis Res Ther 2017;19:101.

30. Sciascia S, Cuadrado MJ, Karim MY. Management of infection in systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2013;27:377-89.

31. van Vollenhoven RF, Emery P, Bingham CO 3rd, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 2010;37:558-67.

32. Vassilopoulos D, Delicha EM, Settas L, et al. Safety profile of repeated rituximab cycles in unselected rheumatoid arthritis patients: a long-term, prospective real-life study. Clin Exp Rheumatol 2016;34:893-900.

33. Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 2007;56:3896-908.

34. Wijetilleka S, Jayne DR, Mukhtyar C, et al. Recommendations for the management of secondary hypogammaglobulinaemia due to B cell targeted therapies in autoimmune rheumatic diseases. Rheumatology (Oxford) 2019;58:889-96.

35. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417-27.

36. Reddy V, Martinez L, Isenberg DA, Leandro MJ, Cambridge G. Pragmatic Treatment of Patients With Systemic Lupus Erythematosus With Rituximab: Long-Term Effects on Serum Immunoglobulins. Arthritis Care Res (Hoboken) 2017;69:857-66.

37. Cassia MA, Alberici F, Jones RB, et al. Rituximab as Maintenance Treatment for Systemic Lupus Erythematosus: A Multicenter Observational Study of 147 Patients. Arthritis Rheumatol 2019;71:1670-80.

38. Cobo-Ibáñez T, Descalzo MÁ, Loza-Santamaría E, Carmona L, Muñoz-Fernández S. Serious infections in patients with rheumatoid arthritis and other immune-mediated connective tissue diseases exposed to anti-TNF or rituximab: data from the Spanish registry BIOBADASER 2.0. Rheumatol Int 2014;34:953-61.

39. Roberts DM, Jones RB, Smith RM, et al. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. J Autoimmun 2015;57:24-9.

40. Cortazar FB, Pendergraft WF 3rd, Wenger J, Owens CT, Laliberte K, Niles JL. Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2017;69:1045-53.