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ORIGINAL ARTICLE PEDIATRICS

The effect of Rituximab on B cells in pediatric autoimmune rheumatic diseases

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ABSTRACT

OBJECTIVE: This study examines how demographic factors and disease conditions affect B-cell depletion and regeneration after Rituximab (RTX) infusion in pediatric patients with rheumatic conditions.

METHODS: We retrospectively reviewed 27 patients approved by the Institutional Review Board, all of whom received at least one RTX infusion, analyzing 99 lymphocyte subunits. Inclusion: patients under 18 at their first RTX infusion, diagnosed with pediatric rheumatologist-confirmed autoimmune diseases. B-cell depletion was defined as a CD19 positive B Cells (CD19+) count below 10 cells/μL, assessed at 6- and 12-months post-RTX infusion. Complete regeneration was defined as CD19+ ≥170 cells/μL using adolescent norms.

RESULTS: Most patients had connective tissue disorders (CTD); Systemic Lupus Erythematosus, Sjögren's Disease, Systemic Sclerosis; n=17; 63%), followed by vasculitis (n=5; 18.5%), juvenile dermatomyositis (n=4; 14.8%), and miscellaneous conditions (n=1; 3.7%). Among patients with CTD, 4 out of 12 (33%) had B-cell depletion at 6 months. At 12 months, 3 out of 6 (50%) achieved CD19+ counts ≥10 cells/μL, while 5 out of 6 (83%) did not reach normal levels of CD19+ (≥170 cells/μL). No significant correlation existed between immunosuppressants (mycophenolate mofetil, methotrexate, azathioprine, cyclosporine, cyclophosphamide) and CD19+≥10 cells/μL at 6 or 12 months. However, hydroxychloroquine significantly differed for persistent depletion at 12 months.

CONCLUSION: This study demonstrates that demographic factors and disease conditions influence B-cell depletion and regeneration in pediatric patients treated with RTX for rheumatic conditions. The findings highlight the variability in response to RTX and suggest that factors such as hydroxychloroquine use may impact long-term B-cell levels.

Keywords: Autoimmune diseases in children; B cell depletion; pediatric rheumatology; rituximab treatment.

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Rituximab (RTX) is a human chimeric anti-CD20 monoclonal antibody, a licensed B-cell depleting agent. CD 20 is a B lymphocyte transmembrane protein, is expressed on peripheral and malignant B cells [1]. RTX, widely used for lymphomas and posttransplant lymphoproliferative disorders in adults and children, it is approved in the United States for B cell malignancies, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris [2–4]. In off-label use, it benefits children with the mentioned conditions and antibody-mediated autoimmune diseases such as systemic lupus erythematosus (SLE), multiple sclerosis, immune thrombocytopenic purpura, and IgG4-related disease [5, 6]. Autoimmune diseases exhibit diverse clinical presentations, often involving intricate pathophysiology. Recent immunology insights identi-

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fy cellular and molecular targets with potential impact on the pathogenesis of various autoimmune diseases. Notably, recognizing the central role of B lymphocytes in pathogenesis suggests their elimination as a valuable therapeutic goal [7]. Following the RTX treatment, there is an immediate rapid decrease of circulating CD20+ B cells [8]. Most patients experience this dose-dependent effect for 2–3 months; however, in some cases, it lasts for 6 months before slowly reversing [9].

Some disorders like SLE show less pronounced depletion due to differences in drug effects [10, 11]. Detectable RTX in circulation for months suggests a potential lasting effect roll p [12]. Long-lived plasma cells, responsible for antibody production, are minimally affected by RTX [13–15]. RTX-induced B cell depletion is variable in the many autoimmune and lymphoproliferative disorders, reflecting the various phenotypic and functional variability of human B cell populations involved in diverse pathogenetic functions in inflammatory and malignant disorders [16, 17].

Although several methods have been used to investigate the impact of RTX therapy on biochemical biomarkers, no comprehensive, precise cytofluorimetry regimen to use before and after RTX treatment has yet to be devised [18]. There are conflicting reports in the literature on whether RTX-induced B cell depletion assessment could be a prognostic marker of disease relapses [11, 19–21]. Antibody levels might decrease, but clinical improvement in many patients correlates with lower autoantibody levels [10, 11, 19, 22].

The aim of this investigation is to examine the factors impacting the timing of B cell depletion and regeneration after RTX infusion in pediatric rheumatologic patients.

MATERIALS AND METHODS

Study Design

This study was designed to examine the CD-19 levels in patients treated with RTX.

Participants

Inclusion Criteria

In our study, a total of 27 patients have been examined for their CD-19 levels. Individuals aged 18 or below at their initial RTX infusion, diagnosed and being followed with an autoimmune disorder at Umraniye Research and Training Hospital between December 2016 and July 2023, were enrolled.

Highlight key points

- Demographic factors and specific disease conditions significantly affect B-cell depletion and regeneration in pediatric patients treated with Rituximab for rheumatic diseases.
- A considerable number of patients with connective tissue disorders show incomplete B-cell regeneration within 12 months post-Rituximab treatment.
- Hydroxychloroquine use is linked to sustained B-cell depletion at 12 months, suggesting its influence on long-term B-cell recovery.
- Rituximab treatment in pediatric rheumatic diseases is associated with a low incidence of infection-related hospitalizations, indicating its safety.
- Other immunosuppressive medications, except hydroxychloroquine, do not show a significant correlation with B-cell regeneration, highlighting the need for individualized treatment strategies.

Exclusion Criteria

Patients who did not receive at least 1 round and were diagnosed over the age of 18 were not included in this study.

Limits of the Study

The relatively small sample size of 27 patients, and even smaller subgroups based on disease diagnosis, may limit the generalizability of the findings. CD-19 values of each patient, which were analyzed at certain periods, were not available.

Ethics Approval

Ethical considerations were strictly adhered to in accordance with the principles of the Declaration of Helsinki (2013 revision).

The study has the ethics committee approval from the Umraniye Training and Research Hospital with the number of: B.10.1.TKH.4.34.H.GP.0.01/369 on 28/11/2022.

Interventions

The administration of RTX adhered to institutional protocols: two infusions separated by two weeks, 750 mg/m^2 (max 1 g) each. Premedication included iv methylprednisolone (2 mg/kg; max 100mg) to reduce RTX infusion reaction risk and as disease treatment. RTX was administered to inpatients at our clinic. Repeat RTX dosing depended on clinical disease activity, often redosed if B cell repletion occurred during a flare.

Outcome Measures

Depletion of B cells was defined as a CD19+ count that is lower than 10 cells/μL in the study of Mitchell et al [23]. Levels were evaluated at 6- and 12-months post-RTX infusion. Complete regeneration of B cells to normal levels was characterized by a CD19+ level of ≥170 cells/μL using adolescent norms [24]. Patients exhibiting <170 cells/μL at 12 months or beyond after the last RTX infusion fulfilled the criteria for persistent B cell depletion. CD19+ levels were determined at the discretion of the provider, with data missing for 11 patients at 6 months and 17 patients at 12 months. Eight patients underwent CD19+ level assessments just before the culmination of 12 months, with counts exceeding 10 but falling short of 170 cells/μL, designated as repleted at ≥10 cells/μL but lacking complete regeneration at ≥170 cells/μL.

Statistical Analysis

Data was extracted, compiled, and analyzed using SPSS v22.0 statistical software. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) statistical software. Continuous variables were presented with observation count, mean and standard deviation, or median and range. Qualitative values were expressed as patient count and percentage for relevant variables. Analysis of variance (ANOVA), Kruskal-Wallis and chi-squared tests were applied to continuous (age, rounds) and nominal variables (gender, B cell response, concurrent immunosuppression), respectively, utilizing the significance of $p<0.05$. For data following a normal distribution, the mean (standard deviation) is reported, while for non-normally distributed data, the median (range) is presented.

Throughout this study, there have not been any sections partially or entirely supported, sourced or scripted by the use of a Large Language Model (LLM).

RESULTS

We conducted a retrospective review approved by the Institutional Review Board involving 27 patients who underwent at least one RTX infusion. The analysis covered 99 lymphocyte subunits. Among the 27 eligible patients, the majority were females (n=22; 81%) and males (n=5; 19%). The median age at diagnosis was 13.00 (min-max=1-17.8 years), while the median age at initial RTX infusion was 17 years (min-max=5-17.9 years). The median number of RTX rounds was 1.5 (min-max=1-5.5).

Patients were primarily diagnosed with connective tissue disorders (CTD; SLE, Sjögren diseases, Systemic sclerosis; n=17; 63%), followed by vasculitis (n=5; 18.5%), juvenile dermatomyositis (n=4; 14.8%), and miscellaneous conditions (n=1; 3.7%). A significant difference for age at diagnosis versus diagnostic categories have been observed (p=0.026) (Table 1). The median age of vasculitis patients was 17.8, while for JDM patients it was 6.2. Mean CD19+ levels before RTX were 271 cells/μL (min–max=57-359 cells/μL). The number of RTX rounds used in each group did not differ significantly (p=0.376) (Table 1).

Following the administration of RTX, we observed distinct patterns in B cell repletion among our patient cohort. At the 6-month mark post-RTX infusion, exactly 50% of the patients (8 out of 16) exhibited sustained depletion, characterized by CD19+ levels below 10 cells/μL. Conversely, the remaining half of the cohort (n=8, 50%) demonstrated CD19+ levels of 10 cells/μL or higher. It is noteworthy that a significant proportion of those with persistent depletion at the 6-month milestone presented with connective tissue diseases (CTD), constituting 50% of the affected subgroup (n=4 out of 8).

As we extended our observation to the 12-month interval post-infusion, we noted a notable shift in the dynamics of CD19+ levels. At this juncture, 50% of the patients (5 out of 10) had successfully replenished their CD19+ levels to 10 cells/μL or more. However, most patients, precisely 80% (8 out of 10), still grappled with depletion below the threshold of 170 cells/μL. These findings are succinctly summarized in Table 1.

Within the CTD group, 4 out of 12 (33%) patients continued to have low CD19+ levels at 6 months. By the 12-month mark, 3 out of 6 (50%) patients showed CD19+ regeneration to 10 cells/μL or more, while 5 out of 6 (83%) did not achieve normal levels (170 cells/μL) of CD19+. While both vasculitis patients (n=2) exhibited depletion at 6 months, they regained normal CD19+ levels by 12 months, highlighting a faster recovery compared to other disease categories. Despite this observation, no significant differences in depletion or regeneration rates were detected between diagnostic groups at 6 or 12 months. No statistical significance was observed for depletion at 6 months (p=0.082), 12 months (p=0.549), or failure to regenerate by 12 months (p=0.116) in relation to diagnosis.

Table 1. Demographic data by diagnosis

Variable	Diagnostic Category, n (%)					p
	Total (n=27)	CTD (n=17)	JDM (n=4)	Vasculitis (n=5)	Miscellaneous (n=1)	
Sex						0.497
Female	22	15	3	3	1	
Male	5	2	1	2	0	
Age at initial Rituximab infusion (years)						**0.026**
Mean±SD	14.66±1.25	15.2±3.33	8.1±4.73	17.6±0.67	17±0	
Median	17.00	17.20	6.20	17.80	17.00	
CD19+<10 cells at 6 months following RTX	8 (50)	4 (33.3)	2 (100)	2 (100)	0	0.069
CD19+<10 cells at 12 months following RTX	5 (50)	3 (50)	2 (66.7)	0 (0)	0	0.513
CD19+<170 cells at 12 months following RTX	8 (80)	5 (83.3)	3 (100)	0 (0)	0	0.091
Rounds (n)						0.376
Mean±SD	1.93±0.43	2.17±1.48	1.875±0.63	1.3±0.45	1±0	
Median	1.50	1.5	2	1	1	

SD: Standard deviation; CTD: Connective tissue disorders; JDM: Juvenile dermatomyositis.

Regarding additional factors, there were no significant correlations detected between age (p=0.478), gender (p=0.209), or the quantity of rounds of RTX treatment (p=0.359) and CD19+ levels falling below the established threshold of 170 cells/μL at 12 months post-administration of RTX. Similarly, no associations were noted between age, gender, or the frequency of RTX treatments and B cell depletion below 10 cells/μL either at 6 months or 12 months following the treatment.

The frequency of administrations of RTX exhibited similarity in both genders. A paired comparison of patients with available CD19+ levels at both 6 and 12 months demonstrated no statistically significant concordance (p>0.05), particularly concerning the absence of replenishment at 6 months and enduring depletion below standard levels at 12 months. Patients who sustained low CD19+ levels at 6 months (CD19+ levels less than 10 cells/μL) typically did not reach CD19+ counts surpassing 170 cells/μL by 12 months post-RTX, with four out of five falling into this category. Conversely, among the patients who achieved repletion (10 cells/μL or higher) at 6 months, three did not revert to standard levels by 12 months following the administration of RTX.

Among the 27 patients, 20 (74%) received concurrent immunosuppression (IS). Specifically, 18 (67%) were treated with mycophenolate mofetil (MMF), 2 (35%) with methotrexate (MTX), and 1 with cyclophosphamide (CYC). Out of the patients administered CYC, 2 out of 8 (25%) remained depleted at 6 months (p=0.131). Similarly, among the five patients who did not replenish (CD19+ count <10 cells/μL) at 12 months, two had been treated with CYC (p=0.114). No significance was found between simultaneous CYC use and restoration to standard levels by 12 months post-RTX (p=0.429). Additionally, there was no substantial correlation between simultaneous use of MMF, MTX, CYC, cyclosporin, azathioprine or tacrolimus and CD19+ levels ≥10 cells/μL at 6 or 12 months. However, a statistically significant difference was observed with hydroxychloroquine and enduring depletion at 12 months (Table 2).

A statistically significant difference was observed in the reduction of CD19+ levels during the 1st and 2nd months following RTX between autoimmune diseases and vasculitis (Polyarteritis Nodosa, Granulomatosis with polyangiitis, Henoch Schoenlein Purpura). The decline during these months was more pronounced in autoimmune diseases (Table 3).

Safety Assessment

Out of the 27 patients, 14 (52%) were admitted to the hospital due to non-life-threatening infections. Among these, three patients were hospitalized twice, and one pa-

Table 2. Concurrent treatment and CD19+ levels

	CD19+<10 cells/μL n (%) at 6th month			CD19+<10 cells/μL n (%) at 12th month			CD19+<170 cells/μL n (%) at 12th month		
	Yes	No	p	Yes	No	p	Yes	No	p
Mycophenolate mofetil			0.248			1			0.429
No (n=9)	1 (25)	3 (75)		1 (50)	1 (50)		2 (100)	0 (0)	
Yes (n=18)	7 (58.3)	5 (41.7)		4 (50)	4 (50)		6 (75)	2 (25)	
Methotrexate			1			0.292			0.598
No (n=25)	7 (50)	7 (50)		4 (44.4)	5 (55.6)		7 (77.8)	2 (22.2)	
Yes (n=2)	1 (50)	1 (50)		1 (100)	0 (0)		1 (100)	0 (0)	
Azathioprine			0.055			0.114			0.429
No (n=22)	5 (38.5)	8 (61.5)		3 (37.5)	5 (62.5)		6 (75)	2 (25)	
Yes (n=5)	3 (100)	0 (0)		2 (100)	0 (0)		2 (100)	0 (0)	
Cyclosporine			0.131			0.114			0.429
No (n=25)	6 (42.9)	8 (57.1)		3 (37.5)	5 (62.5)		6 (75)	2 (25)	
Yes (n=2)	2 (100)	0 (0)		2 (100)	0 (0)		2 (100)	0(0)	
Methylprednisolone			0.522			0.114			0.236
No (n=7)	2 (66.7)	1 (33.3)		0 (0)	2 (100)		1 (50)	1 (50)	
Yes (n=20)	6 (46.2)	7 (53.8)		5 (62.5)	3 (37.5)		7 (87.5)	1 (12.5)	
Hydroxychloroquine			0.248			0.292			**0.035**
No (n=7)	3 (75)	1 (25)		0 (0)	1 (100)		0 (0)	1 (100)	
Yes (n=20)	5 (41.7)	7 (58.3)		5 (55.6)	4 (44.4)		8 (88.9)	1 (11.1)	
Cyclophosphamide			–			–			–
No (n=26)	8 (50)	8 (50)		5 (50)	5 (50)		8 (80)	2 (20)	
Yes (n=1)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Tacrolimus			0.302			–			–
No (n=25)	7 (46.7)	8 (53.3)		5 (50)	5 (50)		8 (80)	2 (20)	
Yes (n=2)	1 (100)	0 (0)		0 (0)	0(0)		0 (0)	0 (0)	

Table 3. CD 19 levels for disease categories

Diseases	CD19+ levels at 1–2 months after RTX treatment (Mean)	SD	p
Autoimmune diseases (n=18)	6.46	20.71	**0.014**
Vasculitis (n=3)	153.0	261.5	

SD: Standard deviation; RTX: Rituximab.

tient experienced three hospitalizations. Among the 13 infection-related hospitalizations, one (44%) was due to syncope. An allergic reaction to RTX infusion was reported in one patient. No other adverse events linked to RTX infusion or CD19+ levels were noted. Independent of CD19+ counts, 20 patients out of 27 (74%) received intravenous immunoglobulin (IVIg) for reasons unrelated to disease management. In five patients, hypogammaglobulinemia was confirmed. Among the remaining 22 patients, IgG levels were checked and found to be within the normal range. Prior to RTX infusion, the mean B cell count was 271 cells/μL (range=57–359). Following RTX, at the six-month mark, B cell counts below 10 cells/μL were observed in 46.6% of patients. Within our

Table 4. CD19+ levels after RTX treatment by changes the months

Months (after RTX treatment)	CD19+ (mean diff. µl)	p
CD19+ levels at 1-2 months after RTX treatment	**236.8**	**0.003**
CD19+ levels at 3-4-5 months after RTX treatment	**275.3**	**0.009**
CD19+ levels at 6-7-8 months after RTX treatment	**223.7**	**0.004**
CD19+ levels at9-10-11 months after RTX treatment	-65.9	0.970

RTX: Rituximab.

study, we conducted a thorough examination of CD19+ levels depletion over distinct monthly intervals. This analysis resulted in the categorization of our observations into four distinct groups: the initial 2 months, the subsequent 3 months, the subsequent 3 months, and the final 3 months following the administration of RTX infusion. Our rigorous evaluation of these categories revealed a statistically significant difference in CD19+ depletion between the first three categories, as indicated in Table 4.

DISCUSSION

This study represents a comprehensive investigation into the dynamics of B cell repletion following RTX treatment among pediatric rheumatologic patients, shedding light on the influence of demographic factors on this process. While existing literature documents variable timelines for B cell repletion post-RTX treatment, our study explores the effect of the demographic factors on the frequency of B cell depletion and full regeneration in this patient cohort [5–7, 20, 22].

Previous knowledge regarding RTX for the depletion of B cells primarily stems from studies involving adult patients, which predominantly focus on effects in closer periods. For instance, Popa et al. [24] reported persistent B cell depletion 12 months post-RTX treatment in adults with rheumatoid arthritis (RA). Similarly, Thiel et al. [25] reported prolonged B cell depletion in adult cohorts encompassing connective tissue diseases (CTD), RA, and vasculitis, spanning a duration of more than 12 months. They defined full regeneration of B cells, which appear to be in absolute form, surpassing 70 cells/µL. Notably, patients with vasculitis exhibited a significantly higher failure rate in achieving total regeneration, exceeding 90%, compared to 7% in RA. Additionally, CTD levels which tend to be at 12% are in this scope. When the exact time of depletion after RTX infusion was examined, it was observed that this condition occurred most often in the ninth month in patients diagnosed with CTD and RA, and this period extended to the 26th month in patients diagnosed with vasculitis [24–26].

In our study, we present data from a clinically noteworthy group of 27 pediatric individuals subjected to RTX such as, vasculitis, juvenile dermatomyositis, SLE, and juvenile idiopathic arthritis (JIA). This investigation primarily delves into the enduring impacts of RTX treatment on B cell depletion and regeneration. About half sustained depletion with counts below 10 cells/µL at 6 months, while roughly 50% achieved regeneration to levels surpassing 10 cells/µL at 12 months. Eighty percent of the patients did not reach standard CD19+ levels (above 170 cells/µL) within one year following the final dose of RTX treatment. Despite the majority of the patients in our study being diagnosed with SLE, no statistically significant difference was observed between diagnostic groups in terms of sustained depletion from 6 to 12 months. Interestingly, our data indicates that patients who fail to achieve CD19+ levels of 10 cells/µL or higher within 6 months have an 80% likelihood of persistent depletion at 12 months. This finding closely aligns with the results of Mitchell et al. [23].

Age and gender were examined as demographic factors influencing the variability in B-cell depletion and regeneration. In according to our data did not uncover any statistically significant correlation between age and B cell regeneration, nor did it detect variances in the frequency of RTX treatments administered across distinct disease categories. Moreover, no statistically significant difference was found between the mean number of treatments and CD19+ depletion at 6 and 12 months or remaining below normal levels at 12 months. These findings suggest that B cell normalization may be influenced by patient-specific factors, potentially involving genetic predispositions or unique disease manifestations that regulate CD19+ levels post-RTX treatment. This suggests that

additional therapeutic interventions may have an impact on B cell regeneration.

Despite the well-established B cell reducing effects of cyclophosphamide (CYC), Thiel et al. [25] demonstrated an independent relationship between CD19+ proliferation and cumulative CYC dose [21–24, 26]. They showed that in our pediatric cohort, patients mostly increased their CD19+ levels to 10 cells/μL or more within the first 12 months, regardless of their primary disease. Notably, approximately 55% of Mitchell et al.'s [23] study underwent combined RTX and CYC treatments. Although we observed a trend hinting at potential statistical significance in persistent B cell depletion at both 6 and 12 months when CYC was involved, there was no correlation between CYC usage and the incidence of complete regeneration to normal CD19+ levels. These findings strongly suggest a potential synergistic effect of RTX and CYC, suppressing B cell numbers and extending the duration of B cell depletion in tandem.

In our study, we identified a significant difference between age groups and disease categories. Half of the patients (50%) continued to experience depletion at both 6 and 12 months. By the 12-month mark, 80% of patients achieved CD19+ regeneration levels of 170 cells/μL or lower but did not reach normal CD19+ levels. Notably, we did not observe any severe adverse events linked to RTX infusion or CD19+ levels. Irrespective of CD19+ counts, 74% of our patients received intravenous immunoglobulin (IVIG) for reasons unrelated to disease management. Out of the 27 patients, 52% were admitted to the hospital due to non-life-threatening infections, including acute gastroenteritis and upper respiratory infections.

The cohort of pediatric patients in Mitchell et al.'s investigation exhibited a remarkable resilience to RTX treatment, with a mere 14% necessitating hospitalization due to non-life-threatening infections while undergoing RTX. However, there are also studies showing a 30% infection rate during the treatment process in patients using only RTX. [23, 27]. Importantly, about 44% of those hospitalized had CD19+ levels below 10 cells/μL. Studies have shown that different CD19+ levels affect the hospitalization rate. Nevertheless, these findings are limited by their concentration on a single time point, as CD19+ levels were not consistently monitored in their cohort. The timing of CD19+ level assessments concerning infection episodes remained unclear, and prolonged B cell depletion might indeed increase the vulnerability to infections. Notably, Mitchell et al. [23] study experienced infrequent hypogammaglobulinemia necessitating IVIG replacement therapy, although immunoglobulin levels were not consistently measured, and prophylactic IVIG was administered in some cases prior to confirmed hypogammaglobulinemia. Patients with prolonged B cell depletion were at very high risk of severe infections, emphasizing the importance of monitoring immunoglobulin levels and B cell in RTX-treated patients. Some individuals might require IVIg replacement therapy, especially when confronted with B cell depletion.

Mitchell et al. [23] similarly emphasize the variability in the timing of proliferation and B-cell regeneration, aligning with our study's findings. Considering the cytotoxic effects of CYC on lymphocytes, normalization of B cell numbers is delayed when RTX and CYC are administered together. Our study makes an important contribution to the literature by examining the relationship between demographic factors and B cell regeneration responses. Our results show that other demographic variables, including primary disease diagnosis, do not significantly influence B cell depletion and full regeneration. However, larger studies are needed to further investigate the complex interplay between demographic factors and B cell regeneration.

It's crucial to acknowledge the limitations of our retrospective study, marked by the absence of a universally agreed-upon definition for depletion and regeneration in the existing literature. In our investigation, the cutoff definitions for CD19+ were established based on specific literature [8, 23, 28, 29]. Thiel et al. [25] adopted a lower regeneration threshold, set at CD19+ counts of 70 cells/μL or higher, and defined depletion as fewer than 1 cell/μL [23]. While reducing the CD19+ threshold could potentially heighten sensitivity, the clinical significance of such adjustments remains uncertain. Moreover, CD19+ were not consistently monitored in our cohort, usually occurring before subsequent RTX treatments. Consequently, the absence of B cells might refer to disease remission. Importantly, Charles et al. [30] found no difference in disease relapse rates among adult ANCA-associated vasculitis patients, regardless of whether they received RTX treatment on a fixed schedule or based on CD19+ levels [23]. Although regular monitoring of B cells may hold potential benefits, the clinical relevance concerning absolute values and disease activity remains unclear. The response of B cells to RTX is multifaceted, with the underlying pathophysiology of B cell elimination and reconstitution yet to be fully elucidated. Consequently, a larger study population is needed to fully assess the potential risk factors contributing to persistent B cell depletion.

Conclusion

Extensive investigation is needed to unravel the intricate interplay between demographic variables and the regeneration of B cells. Our study sheds light on the tolerability of RTX therapy among pediatric rheumatic disease patients and accentuates the variations in B cell repletion and normalization at 6 and 12 months. The resurgence of B cells appears predominantly unaffected by the number of RTX treatments and the underlying disease, while the utilization of other immunosuppressive therapies, particularly CYC, might extend the duration of B cell depletion. Our study adds significant insights by exploring the influence of demographic variables on responses to B cell regeneration. Notably, we observed no substantial correlation between demographic factors and the decline and subsequent full recovery of B cells. Nonetheless, a more comprehensive examination is imperative to unravel the intricate dynamics between demographic factors and the regeneration of B cells.

Ethics Committee Approval: The Umraniye Research and Training Hospital Ethics Committee granted approval for this study (date: 28.11.2022, number: B.10.1.TKH.4.34.H.GP.0.01/369).

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