Acta Dermatovenerol Croat 2020;28(2):63-69 ORIGINAL ARTICLE

Rituximab in Treatment of Children with Refractory Vasculitis and Systemic Lupus Erythematosus – Single Center Experience in Croatia

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ABSTRACT The aim of this study was to present our experience in rituximab therapy in patients with childhood-onset systemic lupus erythematosus, lupus nephritis, and ANCA-associated vasculitis. We conducted a retrospective clinical chart review of all patients treated with rituximab in the time period from January 2009 to December 2015. Eight patients (3 boys and 5 girls) aged 8 to 15 at the onset of disease were treated with rituximab. Remission of disease was accomplished in 4 patients with childhood-onset systemic lupus erythematosus and lupus nephritis, a partial improvement was achieved in 1 patient with childhood-onset systemic lupus erythematosus and lupus nephritis as well as in 2 patients with vasculitis, while in one patient with vasculitis treatment with rituximab showed no effect and the patient died due to *Candida* sepsis. Reduction of corticosteroid doses was enabled by rituximab treatment. Rituximab appeared to be a safe and efficient therapeutic option in severe cases of childhood-onset systemic lupus erythematosus or ANCA-associated vasculitis that failed to respond to conventional therapy or as a rescue therapy in life-threatening conditions.

KEY WORDS: systemic lupus erythematosus, vasculitis, child, adolescent

INTRODUCTION

Systemic autoimmune diseases such as systemic lupus erythematosus (SLE), different forms of vasculitis, antiphospholipid syndrome, and others often involve multiple organs. The skin is often affected in these patients, and rash can be the first symptom of disease. Such cases can be a real therapeutic challenge if patients are refractory to conventional treatment or develop severe vital organ involvement and life-threatening conditions. There are only a few treatment options that can achieve a rapid effect in these situations: high dose corticosteroids, cyclophosphamide, intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab (RTX) (1).

Rituximab is a chimeric monoclonal mouse-human antibody that reacts with the B-cell CD20 receptor present on pre-B and mature B-cells, but not on

Acta Dermatovenerol Croat
2020;28(2):63-69

stem cells or plasma cells, causing B-cell depletion (2). It was originally used in Hodgkin B-cell lymphoma treatment and was later approved for rheumatoid arthritis and ANCA-associated vasculitis (AAV) and used off-label in many other autoimmune diseases, especially SLE (3).

There are not many reports of RTX efficacy in children with autoimmune diseases refractory to conventional therapy protocols and there are no clear treatment guidelines (1,4-9). The aim of this study was to present our experience in RTX treatment of children with refractory autoimmune diseases.

PATIENTS AND METHODS

We conducted a retrospective clinical chart review of all patients treated with RTX at the Department of Pediatrics, Division of Rheumatology and Immunology, University Hospital Centre Zagreb in the time period from January 2009 to December 2015. Patients with failure of conventional treatment with high doses of corticosteroids, cyclophosphamide, and other cytotoxic and antimetabolic agents as well as plasmapheresis were defined as treatment refractory. We collected general demographic, epidemiological, laboratory, and clinical data, observed and followed RTX-related as well as disease- and other medication-related complications during the post-RTX application follow-up and response to treatment. In patients with childhood-onset SLE (cSLE), response was defined as remission if the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score after 6 months was 2 or less, as partial improvement if SLEDAI score was 3 or higher after 6 months but at least 50% lower than before treatment with RTX, and as no effect for patients who did not meet those criteria (10,11). We assessed patients with vasculitis with the Paediatric Vasculitis Activity Score (PVAS) and defined remission as PVAS score 0 and no signs of disease damage, partial improvement as PVAS score reduction of at least 50% or presence of disease damage while the score was 0, and no effect for patients who do not meet those criteria (12). Failed conventional treatment was defined as the inability of achieving remission of disease or severe deterioration of disease that was previously in remission.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median with interquartile range (IQR). Analyses were performed using Microsoft Excel 2016.

RESULTS

During the time period investigated in this study, 8 patients were treated with rituximab, of which 3 boys and 5 girls. Average age at disease onset was 11.75 years (SD 2.49). Four patients were treated due to cSLE and LN, 1 had cSLE and autoimmune hepatitis (AH), and 3 were suffering from different forms of vasculitis (2 had AAV and 1 had Takayasu arteritis) (Table 1). Patients had renal, cardiovascular, respiratory, and central nervous system involvement. Six patients had renal involvement, four of them lupus nephritis, and two had renal complications of vasculitis (Table 1). The average time between the beginning of conventional therapy and RTX introduction was 16.88 months (SD 25.15 months), with a median of 4 months (IQR 1-22 months). One of the patients with cSLE was treated with conventional therapy for 6 years and was in remission, and had a severe flare of disease after 6 years that was refractory to conventional treatment when we decided to treat him with RTX.

Failed conventional treatment included corticosteroids, non-steroid anti-inflammatory drugs, hydroxychloroquine, methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, and plasmapheresis (Table 2). In all cases, rituximab was introduced due to the ineffectiveness of conventional therapy in inducing remission of the disease or deterioration of previously well-controlled disease. In 7 patients, rituximab was administered in a dose 2×750 mg/m^2, (max. 1 g), that was combined with cyclophosphamide "mini pulses" (350 mg/m^2), and in 1 patient it was administered in 4 doses of 375 mg/m^2 (Table 2). Due to the flare of disease in one patient with cSLE and LN, rituximab treatment was repeated after 3 years (4×375 mg/m^2) with complete remission of the disease achieved once again. The treatment effect was measured with SLEDAI and PVAS scores (Table 1). Remission was induced in 4 out of 8 patients, all of them with cSLE and LN, and partial improvement was achieved in another 3, 1 with cSLE and LN, and 2 with vasculitis. One patient with AAV, whose condition was extremely severe when she was admitted to our Department, died due to *Candida* sepsis within 2 months of rituximab administration. Corticosteroid doses were reduced or discontinued in all of the patients after RTX treatment (Table 2). The CD20 level was unmeasurable in most of the patients 6 months after treatment with RTX, showing the prolonged immunosuppression effect of RTX. Average follow-up period after RTX was 49.1 months (SD 26.0), during which time 3 patients sustained remission, one had a flare of disease after 3 years of remission, which was induced again after repeated RTX treatment. Three

Table 1. Overview of demographic and clinical data of patients treated with rituximab, including response to rituximab therapy

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Sex	F	M	M	M	F	F	F	F
Ethnicity	Caucasian (Albanian)	Caucasian (Croatian)	Caucasian (Croatian)	Caucasian (Croatian)	Caucasian (Croatian)	Caucasian (Croatian)	Caucasian (Croatian)	Caucasian (Croatian)
Diagnosis	cSLE	cSLE	cSLE	cSLE	cSLE, AH	Takayasu arteritis	AAV	AAV
Age at time of diagnosis (years)	10	12	15	8	10	13	11	15
Affected organs and organic systems	Kidney, CNS, skin	Kidney, skin	Kidney, skin	Kidney, heart, skin	Liver, CNS, skin	Cardiovascular system	Kidney, CNS	Kidney, lung
Nephritis (class)	Yes (IV – S (A/C))	Yes (V)	Yes (IV – S (A/C))	Yes (V)	No	No	Yes (V)	Yes
Time period from disease onset until beginning of RTX treatment (months)	1	8	5	72	34	18	1	1
Disease activity index (SLEDAI) before / 6 months after RTX	38 / 2	10 / 0	20 / 10	16 / 2	12 / 2	-	-	-
Disease activity index (PVAS) before / 6 months after RTX	-	-	-	-	-	PVAS 12 / 5	PVAS 40 / 0	Died within 6 months
Effect of RTX	remission	remission	partial improvement	remission	remission	partial improvement	partial improvement	no effect
Follow-up period (months)	52	84	24	78	48	57	30	2

Abbreviations: M – male; F – female; RTX – rituximab; cSLE – childhood-onset systemic lupus erythematosus; AH – autoimmune hepatitis; AAV – ANCA-associated vasculitis; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; PVAS – Pediatric Vasculitis Activity Score; CNS – central nervous system

Acta Dermatovenerol Croat
2020;28(2):63-69

patients showed partial improvement and 1 patient showed no response to therapy and died (Table 1).

Three patients developed herpes zoster infection after therapy with RTX that was successfully treated with acyclovir, and 1 developed cellulitis and thrombophlebitis. One patient died because of *Candida* sepsis that developed 1 month after RTX treatment.

There were several disease complications or side-effects of therapy with other medications (such as corticosteroids, etc.): 1 patient had end-stage renal disease followed by a kidney transplant. Two patients sustained pathological bone fractures, 2 had neurological complications (posterior reversible encephalopathy, CNS vasculitis). One patient had a Cushingoid appearance, and 1 had total obstruction of the left subclavian artery as well as stenosis of the left carotid artery and thoracic aorta combined with hypertension. The patient who died had renal failure and pulmonary hemorrhage.

Two patients did not have any complications or side-effects during the follow-up period (Table 2).

DISCUSSION

RTX is used in the treatment of many autoimmune diseases, either as an alternative therapy regimen in patients with poorly controlled diseases or as a steroid-sparing agent in patients with steroid-dependent diseases. It is also used as a rescue therapy in life-threatening conditions (1,13-16). Although there are numerous reports of the safety and efficiency of RTX in those diseases, some well-known controlled trials failed to show the superiority of RTX as an add-on therapy to standard protocol (1,7,9,15-23).

In our study, 4 out of 8 patients achieved remission following RTX treatment, and 3 patients showed partial improvement, while 1 patient showed no effect of RTX therapy and eventually died. One of 4 patients with remission experienced a flare of disease during the follow-up period, which was successfully treated with repeated RTX treatment. All of our patients were treated with RTX after a failure of conventional treatment protocols. Side-effects that occurred in our patients (sepsis, herpes zoster, cellulitis, thrombophlebitis) resemble those most often described in the literature (6).

Although controlled trials such as Lupus Nephritis with Rituximab (LUNAR) and Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) failed to show the expected effectiveness of RTX in patients with SLE for reasons that are beyond the scope of this study, use of RTX in treatment protocols based on induction of remission with RTX and avoiding prolonged use of corticosteroids such as in the Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis (RITUXILUP) showed RTX was effective and safe choice (3,8,9,17-19,24). A recent systemic review showed improvements in renal, neuropsychiatric, and hematological manifestations, disease activity, and complement and anti-double-stranded Desoxy-Nucleo-Adenosine antibodies level, with a steroid-sparing effect in patients with cSLE treated with RTX (5). Our results showed the effectiveness of RTX in the treatment of severely ill patients recalcitrant to conventional treatment, confirming results of similar studies, although no definite conclusions about effectiveness can be drawn because of the small number of patients (1,7,13-16,20,21). We achieved better results in patients treated due to cSLE and LN, where we induced remission in 4 patients, whereas in patients with AAV we only accomplished partial improvement. One patient with vasculitis had a PVAS score of 0 after treatment with RTX, but due to substantial damage caused by the disease we considered her as just a partial improvement.

Generally, there are not as many evidence-based studies considering AAV treatment with rituximab in the pediatric population as in adults, and many pediatric rheumatologists use adult treatment guidelines for treating their patients. There is both need and interest for creating consensus treatment guidelines for the pediatric population with AAV (25). Recently, the European League Against Rheumatism/European Renal Association – European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of AAV recommended treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab for remission-induction of new-onset organ-threatening or life-threatening AAV as well as for a major relapse of organ-threatening or life-threatening diseases (26). Studies like Rituximab for ANCA – associated vasculitis (RAVE) and Rituximab versus cyclophosphamide in ANCA – associated vasculitis (RITUXVAS) found an important role of RTX in the induction of remission, and the Rituximab vasculitis maintenance study (RITAZAREM) and Maintenance using rituximab in remission after vasculitis (MAINRISTAN) studies showed RTX was effective in maintenance of remission in AAV (27-29).

One of the possible benefits of RTX treatment is a reduction in doses of other medications and their subsequent side-effects. In our study, RTX treatment enabled us to reduce doses of corticosteroids or even completely discontinue its use. Similar experiences were also reported in other studies, while some novel treatment protocols such as RITUXILUP completely avoid oral steroids in maintenance treatment (3,7,24).

Table 2. Dosing schemes applied in our patients treated with rituximab, corticosteroid doses, and complications that occurred during follow-up

Patient	1	2	3	4	5	6	7	8
Treatment before rituximab	CS, HCQ, CYC	CS, HCQ, CYC, MMF	CS, HCQ, CYC	CS, CsA, AZA, CYC	CS, MTX, CYC AZA	CS, CYC, MTX	CS, CYC, PPh	CS, CsA, CYC, PPh
Rituximab dose (max. 1 g/dose)	2x750 mg/m^2	2x750 mg/m^2	2x750 mg/m^2	4x375 mg/m^2, relapse after 3 years – 4x375 mg/m^2 repeated	2x750 mg/m^2	2x750 mg/m^2	2x750 mg/m^2	2x750 mg/m^2
Cyclophosphamide pulses with RTX	2 mini pulses (350 mg/m^2)	no	yes	no	2 mini pulses (350 mg/m^2)	no	yes	2 mini pulses (350 mg/m^2)
Corticosteroid (prednisone or methylprednisolone) dose at beginning of treatment with rituximab	3 pulses (1 g) followed by 1.2 mg/kg	3 pulses (1 g) followed by 0.25 mg/kg	3 pulses (1 g) followed by 0.85 mg/kg	0.2	0.45	0.7	3 pulses (1 g) followed by 1.2 mg/kg	3 pulses (1 g) followed by 1.2 mg/kg
Corticosteroid dose 6 months after treatment with RTX (mg/kg)	0.15	0.05	0.35	0.15	0.25	0.1	0.15	died
Complications of RTX	herpes zoster	herpes zoster	none	none	cellulitis, thrombophlebitis	none	herpes zoster	death due to *Candida* sepsis
Complications of the disease and other therapies	seizures, PRES, CNS vasculitis, fracture of sacrum bone	pathological bone fractures, osteoporosis	Cushingoid appearance	none	none	total obstruction of the left subclavian artery, stenosis of the left carotid artery and thoracic aorta, hypertension	ESRD followed by a kidney transplant, PRES, hypertension	renal failure, pulmonary hemorrhage

Abbreviations: AZA – azathioprine; CS – corticosteroids; HCQ – hydroxychloroquine; CYC – cyclophosphamide; CsA – cyclosporine A; MMF – mycophenolate mofetil; MTX – methotrexate; Pph – plasmapheresis; RTX – rituximab; PRES - posterior reversible encephalopathy syndrome; CNS – central nervous system; ESRD – end-stage renal disease

CONCLUSION

There are numerous case reports and open-label studies showing the effectiveness and safety of RTX in severely ill patients suffering from different types of autoimmune diseases which are refractory to conventional therapy. Even though large controlled studies failed to show the superiority of RTX over placebo, we believe that RTX has an important place as a safe and efficient treatment option in pediatric patients with severe cases of childhood-onset SLE or AAV refractory to conventional therapy, as a rescue therapy in a life-threatening conditions, or as an alternative to highly toxic agents such as cyclophosphamide in young patients.

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