Safety and Efficacy of Rituximab in Childhood-onset Systemic Lupus Erythematosus and Other Rheumatic Diseases

Ajay Tambralli, Timothy Beukelman, Randy Quentin Cron, and Matthew Laurence Stoll

ABSTRACT. ***Objective.*** Rituximab (RTX) has been used to treat many pediatric autoimmune conditions. We investigated the safety and efficacy of RTX in a variety of pediatric autoimmune diseases, especially systemic lupus erythematosus (SLE).

Methods. Retrospective study of children treated with RTX. Effectiveness data was recorded for patients with at least 12 months of followup; safety data was recorded for all subjects.

Results. The study included 104 children; 50 had SLE. Improvements in corticosteroid dosage, physician's global assessment of disease activity, and SLE-associated markers of disease activity were seen. The incidence of hospitalized infections was similar to previous studies of patients with childhood-onset SLE.

Conclusion. RTX can be safely administered to children and appears to contribute to decreased disease activity and steroid burden. (J Rheumatol First Release Jan 15 2015; doi:10.3899/jrheum.140863)

Key Indexing Terms:
PEDIATRICS RITUXIMAB SYSTEMIC LUPUS ERYTHEMATOSUS TREATMENT

Rituximab (RTX) is a chimeric monoclonal antibody that specifically targets CD20-positive B cells. Although it lacks any pediatric indications, RTX has been widely studied for various pediatric rheumatologic conditions, including autoimmune hemolytic anemia, immune thrombocytopenic purpura, systemic lupus erythematosus (SLE), vasculitis, and juvenile dermatomyositis[1,2,3,4]. The use of RTX to treat pediatric autoimmune disease has particularly focused on SLE[5,6]. Although only 15–20% of cases are diagnosed in childhood, SLE has a more severe phenotype in children compared to adults, particularly in those with nonwhite ethnicity[7,8,9]. Several open-label studies of RTX in pediatric subjects have demonstrated benefit in life-threatening or organ-threatening SLE[5,10,11,12,13,14,15]. However, limitations of these studies include low patient numbers and demographic cohorts not representative of many patients with SLE in the United States. Herein, we report on the safety and effectiveness of RTX in 104 subjects with a variety of pediatric autoimmune diseases, with a focus on SLE.

From the University of Alabama at Birmingham, Department of Pediatrics, Division of Rheumatology, Birmingham, Alabama; University of Rochester Medical Center, Department of Medicine, Rochester, New York, USA.

A. Tambralli, MD, University of Rochester Medical Center, Department of Medicine; T. Beukelman, MD, MSCE; R.Q. Cron, MD, PhD; M.L. Stoll, MD, PhD, MSCS, University of Alabama at Birmingham, Department of Pediatrics, Division of Rheumatology.

Address correspondence to Dr. M.L. Stoll, Children's Hospital of Alabama, CPP N 210M, 1600 7th Ave. South, Birmingham, Alabama 35226, USA. E-mail: mstoll@peds.uab.edu

Accepted for publication November 24, 2014.

MATERIALS AND METHODS

Patients. This was a retrospective study of children treated by 1 or more pediatric rheumatologists at Children's Hospital of Alabama (CoA) with at least 1 course of RTX between August 1, 2007, and April 1, 2014. Patients were identified in the electronic medical record using medication codes for RTX, limited to those evaluated by a rheumatologist[16]. Institutional Review Board approval at the University of Alabama at Birmingham was obtained.

RTX administration. RTX was typically administered at a dose of 750 mg/m^2 × 2 doses (max 1 g/dose) 2 weeks apart[17]. Subjects were premedicated with methylprednisolone at doses ranging from 2 mg/kg to 30 mg/kg, depending on the underlying diagnosis and disease severity, maximum of 1 g; additional premedications included standard doses of acetaminophen and diphenhydramine. The RTX was diluted in normal saline at a concentration of 4 mg/ml and administered at a starting rate of 0.25 ml/kg/h (max 25 ml/h) for the first hour, then increased by increments of 0.25 mg/kg/h every 20 min up to a maximal rate of 100 ml/h. Vital signs were obtained every 15 min for the first hour, then hourly. RTX was administered in our outpatient infusion department or on an inpatient basis.

Data collection. Effectiveness data were collected for all patient visits 12 months following the first RTX infusion and entered into a Microsoft Excel database, while safety data were recorded from the time of the first infusion until the final visit that occurred at or before April 1, 2014. Safety events were identified through review of all visit notes, emergency department visits, hospitalization records, and phone notes.

Outcomes. For effectiveness, the physician's global assessment (PGA) of disease activity[18] and oral corticosteroid (CS) dosage at baseline (just prior to RTX) and at 12 months of followup were documented on all patients. Additional documentation on patients with SLE included complement levels, erythrocyte sedimentation rate, complete blood count, creatinine, albumin, urine protein, and anti-DNA levels[6]. SLE Disease Activity Index scores are not routinely obtained at this center, so they were not available for this retrospective study. Safety was evaluated in all patients. The primary safety outcomes evaluated included (1) all serious adverse events (SAE) according to the US Food and Drug Administration definition (any events resulting in death, hospitalization, or prolongation of existing hospitalization, significant loss of function, or congenital anomaly); (2) all

medically important infections defined as those requiring intravenous antimicrobial therapy or hospitalization; and (3) all infusion reactions.

Statistical analysis. Continuous data were reported as medians and ranges, and categorical data were reported as percentages. Comparisons of effectiveness data at baseline and 12 months were performed with the paired Student t test. Analyses were performed using SPSS software, version 22.

RESULTS

Patient population. The study included 104 children, 50 of whom had SLE. Their demographic information and diagnoses are shown in Table 1. Sixty-four percent of the entire cohort and 76% of the patients with SLE were African American, and most of the remainder were white. Twenty of the 50 patients with SLE and 11 of the 54 additional subjects were treated with RTX as part of their initial therapy, while the remainder had previously failed 1 or more additional agents. A summary of previous as well as concurrent therapies is shown in Table 2. Among those who had previously failed conventional therapy, the mean (± SD) disease duration was 1.6 ± 1.3 years for the patients with SLE and 1.8 ± 1.8 years for the others. All of the subjects received at least 1 course of RTX, with a course consisting of 2 doses at 750 mg/ m^2 (max 1 g), administered 2 weeks apart. Median number of courses received was 2 (range 1–11). In total, 466 infusions were administered. Ninety-nine patients had at least 12 months of followup (range 1 month–6.4 yrs). A total of 253.3 person-years of followup was available.

Effectiveness of depletion. Post-RTX CD19 counts were available on 100 of 104 subjects, of whom 78 also had pre-RTX CD19 counts available. At least partial depletion was observed in all cases (mean CD19 counts decreased from 422 to 2.9 cells/μl, $p < 0.0001$), with B cell counts dropping to fewer than 5 cells/μl in 82 subjects, with the highest post-RTX B cell count of 37 cells/μl.

Clinical effectiveness. Of the 99 subjects with at least 12 months of followup, 12-month data are available on 98. Mean daily oral CS (prednisone) dose decreased from 29.8 ± 25.7 mg to 8.7 ± 13.1 mg ($p < 0.001$), and among the 88 subjects on whom data were available, mean PGA of disease

Table 1. Subjects included in this study. Data are n (%) unless otherwise indicated.

Characteristic	Patients with SLE, n = 50	Entire Cohort, n = 104
Male:female	9:41	23:81
Diagnosis		
SLE	50	50 (48)
Dermatomyositis		11 (10.6)
Mixed connective tissue disease/overlap		10 (9.6)
Sjögren syndrome		8 (7.7)
Henoch-Schönlein purpura		7 (6.7)
ANCA-associated vasculitis		5 (4.8)
Juvenile idiopathic arthritis*		4 (3.8)
Idiopathic pulmonary hemosiderosis		3 (2.9)
CNS vasculitis		2 (1.9)
Miscellaneous*		4 (3.8)
Race		
White	9 (18)	31 (30)
African American	38 (76)	67 (64)
Hispanic or Latino	2 (4)	5 (4.8)
Asian	1 (2)	1 (1.0)
Age at initiation of RTX, yrs (mean ± SD)	13.6 ± 3.5	12.3 ± 4.8
No. RTX courses, median (range)	2 (1–11)	2 (1–5)
Duration of followup, yrs (mean ± SD)	2.6 ± 1.5	2.2 ± 1.3
Initial concurrent cyclophosphamide use	28 (56)	50 (48)
Patients with SLE who had nephritis, according to WHO stages		
None suspected and not biopsied	28 (56)	
II	3 (6)	
III	4 (8)	
IV	7 (14)	
V	3 (6)	
III/V	5 (10)	

*Of the 4 patients with JIA, 1 had polyarticular JIA, 2 had systemic JIA, and 1 had enthesitis-related arthritis/inflammatory bowel disease. Of the 4 miscellaneous patients, 1 had CREST, 1 had Castleman disease, 1 had ITP, and 1 had ARRON syndrome. JIA: juvenile idiopathic arthritis; CREST: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias; ITP: idiopathic thrombocytopenic purpura; ARRON: autoimmune-related retinopathy and optic neuropathy; SLE: systemic lupus erythematosus; ANCA: antineutrophil cytoplasmic antibodies; CNS: central nervous system; WHO: World Health Organization; RTX: rituximab.

Table 2. Prior and concurrent medications of subjects included in the current study.

Diagnosis	Prior Therapy			Concurrent Therapy (first course)		
	Biologics	CNV DMARD	CYC	Biologics	CNV DMARD	CYC
SLE, n = 50	3	32	4	1	46	23
JDM, n = 11	2	11	0	0	10	0
MCTD, n = 10	2	10	0	0	9	2
Sjögren, n = 8	0	7	0	0	5	2
HSP, n = 7	1	5	0	0	5	2
AAV, n = 5	0	3	1	0	1	3
JIA, n = 4	4	4	1	2	1	1
IPH, n = 3	0	2	0	0	1	2
PACNS, n = 2	0	2	2	0	0	2
Other, n = 4	0	1	0	0	1	2

AAV: ANCA-associated vasculitis; CNV DMARD: conventional disease-modifying antirheumatic drugs (azathioprine, hydroxychloroquine, methotrexate, mycophenolate mofetil); CYC: cyclophosphamide; HSP: Henoch-Schönlein purpura; IPH: idiopathic pulmonary hemosiderosis; JIA: juvenile idiopathic arthritis; JDM: juvenile dermatomyositis; MCTD: mixed connective tissue disease; PACNS: primary angiitis of the central nervous system; SLE: systemic lupus erythematosus.

activity decreased from 34.4 ± 19.2 to 15.7 ± 12.3 ($p < 0.001$). Data for the 48 patients with SLE who had at least 12 months of followup is shown in Table 3. Consistent with the cohort as a whole, significant improvement was observed in CS dosage and PGA of disease activity, as well as in multiple SLE-associated markers of disease activity. Similar improvements were observed among the 22 patients with SLE who had nephritis and at least 12 months of followup (Figure 1).

Safety. Overall, RTX was well tolerated. Twenty-six infusion reactions (5.6% of infusions, none of which required intervention with epinephrine or urgent admission), were reported in 18 patients. All of those patients were able to successfully complete the infusion or tolerated subsequent infusions. Most of the time, slowing the rate of the infusion appeared to be of benefit.

Excluding admissions for disease flares, 26 patients underwent 29 admissions over 253.3 person-years of followup (114/1000 person-yrs). Of those, 20 subjects underwent 22 admissions for possible or definite infections (86.9/1000 person-yrs; Table 4), with the remainder consisting of 1 DVT, 2 admissions in 1 subject for poor weight gain thought to be attributed to depression, 2 admissions for psychiatric issues, 1 for appendicitis, and 1 for vomiting attributed to mycophenolate mofetil (MMF). Additionally, an 18-year-old female with Ro-positive Sjögren syndrome gave birth to a child with fetal heart block. There was also a case of herpes zoster that did not result in admission, but was considered an opportunistic infection. Among the 50 patients with SLE, there were 12 infections requiring hospitalization out of a total of 132.2 person-years (90.8/1000). One subject with progressive interstitial lung disease died after transition to adult rheumatology care. There was no obvious association between race and incidence of infection. Intravenous immunoglobulin (IVIG) was administered to 26 patients, 13 of whom received IVIG therapy as treatment for their underlying disorder (e.g., dermatomyositis, idiopathic thrombocytopenic purpura). Of the 13 subjects who received IVIG for replacement secondary to hypogammaglobulinemia, the median IgG level was 386 mg/dl, with a range of 160–798 mg/dl. Baseline IgG levels were available on 7 of those patients, 3 of whom had low levels (250–706 mg/dl) prior to RTX. Two of those 13 subjects were found to have hypogammaglobulinemia within weeks of the initial infusion, while most others did not develop hypogammaglobulinemia for months to years after the initial infusion (mean 8 mos).

Table 3. Effectiveness data among patients with SLE who had at least 12 months of followup. Data are median ± SD.

Variable	Baseline	12 Mos	p
Corticosteroid dose, n = 48	31.7 ± 23.4	8.8 ± 12.1	< 0.001
C3, n = 29	70.4 ± 39.8	115 ± 41.8	< 0.001
C4, n = 29	11.6 ± 11.5	25.6 ± 15.9	< 0.001
ESR, n = 47	57.4 ± 37.7	37.2 ± 28.4	0.005
Hemoglobin, n = 48	10.9 ± 1.6	12.0 ± 1.4	< 0.001
Creatinine, n = 48	1.0 ± 2.0	0.84 ± 1.1	0.143
Albumin, n = 48	3.7 ± 0.76	4.2 ± 0.51	< 0.001
Urine pr:cr, n = 40	0.96 ± 2.0	0.75 ± 1.8	0.548
dsDNA, n = 37	860 ± 3300	85 ± 301	0.128
PGA, n = 41	35.2 ± 19.2	14.3 ± 12.1	< 0.001

P value calculated with paired Mann-Whitney U test. SLE: systemic lupus erythematosus; ESR: erythrocyte sedimentation rate; PGA: physician's global assessment; pr:cr: protein-to-creatinine ratio.

DISCUSSION

To our knowledge, this work represents the largest single-center collection of pediatric patients treated with

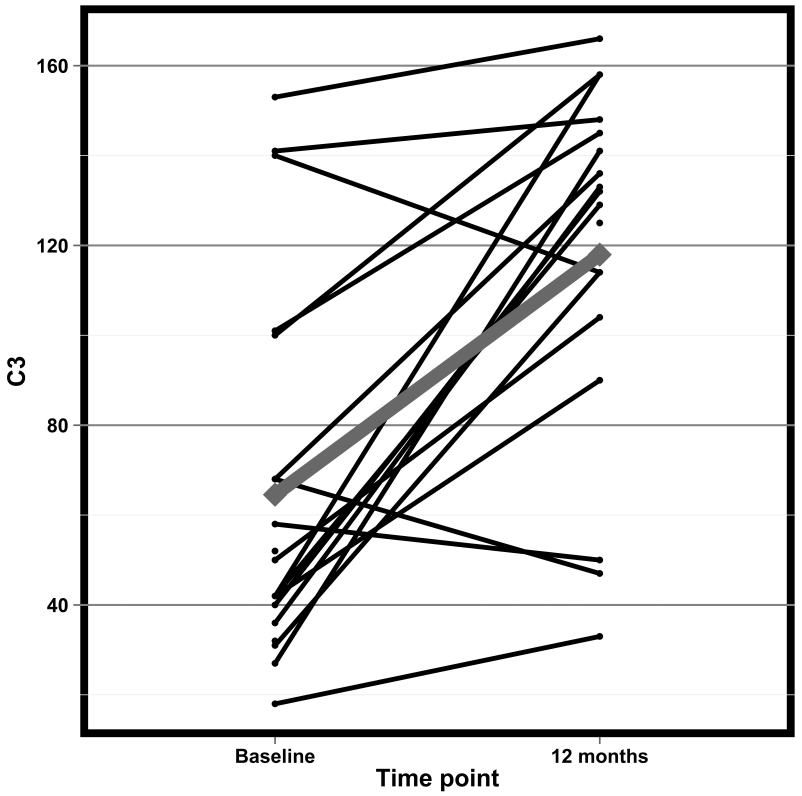

Figure 1. Changes in C3 before and after rituximab (RTX) therapy among subjects with lupus nephritis. The wider grey line represents the regression line. This improvement was significant at $p < 0.001$, paired Mann-Whitney U test.

RTX for autoimmune/rheumatic indications. In this ethnically diverse population with a variety of rheumatologic conditions, we demonstrated that treatment regimens that included RTX are safe and generally appear to be effective. Although there was a rate of hospitalized infections of 86.9/1000 person-years among the cohort as a whole, and 90.8/1000 among the patients with SLE, the safety profile compares favorably with several previous studies. For example, Costa-Reis, *et al* reported a rate of 169 "serious infections"/1000 person-years; however, their definition included those requiring oral antibiotics for 7 or more days and is thus not directly comparable to ours[19]. Opastirakul and Chartapisak reported a rate of infections requiring hospitalization for IV antibiotics of 176/1000 among subjects receiving IV cyclophosphamide (CYC; calculated from text)[20]. Vachvanichsanong, *et al* reported 23 deaths out of 108 childhood-onset subjects with SLE followed for 3 years[21], although this study as well as the one by Opastirakul and Chartapisak were both published from Thailand, where there may be higher risk of infections and less-advanced medical care. Two smaller studies did show more favorable safety profiles of CYC usage in childhood-onset SLE: Lehman and Onel reported no serious infections among 16 CYC-treated patients followed 3 years each[22], nor did Barbano, *et al* among 14 subjects followed for a mean of 9.2 years each[23].

The nature of our study did not permit direct effectiveness comparisons with regimens containing CYC or MMF, accompanied by CS, although a recent open-label study showed RTX to be comparable to both agents over a 12-month period in the management of lupus nephritis[24]. The reduction of the CS dose from 31 mg at baseline to 8.8 mg at 12 months among the 50 patients with SLE appears to compare favorably with the reduction reported by Lehman and Onel in the pre-RTX era[22], and is similar to that reported by Lehman, *et al* following use of RTX[5]. Because major risk factors for SAE, including mortality, in patients with SLE are active disease and high doses of CS[25], any medicine that can help minimize CS use and help attain disease control is likely to be of substantial benefit.

Limitations of our study include its retrospective design, the absence of a standardized approach to treatment and monitoring, and lack of a comparator group that was not treated with RTX. In addition, this was a heterogeneous population; even among the patients with SLE, only 22 of them had nephritis. Further, while all the infusions were administered at CoA, it is possible that not all safety events were identified, because many of our patients live a consid-

Table 4. Infectious SAE and opportunistic infections among patients taking RTX.

Event	Duration Since Last RTX Infusion	Concurrent Medications	B Cells	IgG
DVT + cellulitis	22 days	HCQ, MTX, CYC, P[1]	1	NA
MRSA abscess	6 mos	MMF, P 10 mg/day	NA	901
GNR peritonitis	5 days	MMF, HCQ, P 40 mg/day	0	NA
Staphylococcus epidermidis bacteremia	36 mos	None (self-discontinued)	302	1510
Necrotizing fasciitis	2 mos	AZT, P 10 mg/day	0	522
PCP	3 mos	MTX, P 21 mg/day	2	NA
MSSA bacteremia	3 mos	P 15 mg/day	0	1030
Pyelonephritis	8 mos	HCQ, CYC, P 10 mg/day	7	1043
Febrile neutropenia	5 mos	HCQ, CYC	0	291
Streptococcus pneumonia bacteremia[2]	8 mos	CYC, P 10 mg/day	8	NA
Pneumonia[2]	38 mos	MTX, IFX	NA	NA
Febrile neutropenia	5 mos	MTX, ETN, P 32 mg/day	2	NA
Escherichia coli bacteremia	2 mos	HCQ, P 60 mg/day	NA	972
MRSA pneumonia and bacteremia	14 days	HCQ, CYC, P 80 mg/day	28	1313
Febrile neutropenia	3 mos	HCQ, CYC, P 30 mg/day	0	483
Pulmonary aspergillosis	2 mos	CYC, P 60 mg/day	0	NA
Zoster	3 weeks	CYC, P 50 mg/day	0	1414
Cellulitis[3]	11 days	MMF, HCQ, P 15 mg/day	55	NA
Zoster ophthalmicus[3]	12 mos	MMF, HCQ, P 15 mg/day	66[4]	NA
HSV mucositis, bacillus bacteremia	6 mos	None	30	NA
Possible pneumonia	3 mos	CYC, P 40 mg/day	0	NA
Klebsiella oxytoca bacteremia	5 mos	MTX	17	NA
Fever, possible pneumonia	1 month	HCQ, P 40 mg/day	211	NA

[1]Dose of prednisone unclear from medical records. [2]*Streptococcus pneumonia* bacteremia and pneumonia were in the same subject. [3]Cellulitis and zoster ophthalmicus were in the same subject. [4]B cell count obtained 4 mos prior to infection. SAE: serious adverse events; AZT: azathioprine; CYC: cyclophosphamide; DVT: deep vein thrombosis; ETN: etanercept; GNR: gram-negative rods; HCQ: hydroxychloroquine; HSV: herpes simplex virus; IFX: infliximab; MMF: mycophenolate mofetil; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *S. aureus*: MTX: methotrexate; P: prednisone; PCP: pneumocystis pneumonia; RTX: rituximab; NA: not available.

erable distance from our center. However, in this critically ill population, it is unlikely that any significant illness, including hospitalizations, would not have been reported to us or noted in a subsequent visit.

In a diverse population of pediatric patients with autoimmune diseases, RTX therapy when combined with standard immunosuppressive therapy appears to be safe and to permit reductions in CS dosage, among other beneficial effects. Clearly, future prospective studies are warranted in the pediatric population.

REFERENCES

1. Alexeeva EI, Valieva SI, Bzarova TM, Semikina EL, Isaeva KB, Lisitsyn AO, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. Clin Rheumatol 2011;30:1163-72.
2. Cooper MA, Willingham DL, Brown DE, French AR, Shih FF, White AJ. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. Arthritis Rheum 2007;56:3107-11.
3. Jansson AF, Sengler C, Kuemmerle-Deschner J, Gruhn B, Kranz AB, Lehmann H, et al. B cell depletion for autoimmune diseases in paediatric patients. Clin Rheumatol 2011;30:87-97.
4. Kavcic M, Fisher BT, Seif AE, Li Y, Huang YS, Walker D, et al. Leveraging administrative data to monitor rituximab use in 2875 patients at 42 freestanding children's hospitals across the United States. J Pediatr 2013;162:1252-8, 1258 e1.
5. Lehman TJ, Singh C, Ramanathan A, Alperin R, Adams A, Barinstein L, et al. Prolonged improvement of childhood onset systemic lupus erythematosus following systematic administration of rituximab and cyclophosphamide. Pediatr Rheumatol Online J 2014;12:3.
6. Watson L, Beresford MW, Maynes C, Pilkington C, Marks SD, Glackin Y, et al. The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE. Lupus 2015;24:10-7.
7. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010;6:538-46.
8. McCurdy DK, Lehman TJ, Bernstein B, Hanson V, King KK, Nadorra R, et al. Lupus nephritis: prognostic factors in children. Pediatrics 1992;89:240-6.
9. Contreras G, Lenz O, Pardo V, Borja E, Cely C, Iqbal K, et al. Outcomes in African Americans and Hispanics with lupus nephritis. Kidney Int 2006;69:1846-51.
10. Nwobi O, Abitbol CL, Chandar J, Seeherunvong W, Zilleruelo G. Rituximab therapy for juvenile-onset systemic lupus erythematosus. Pediatr Nephrol 2008;23:413-9.
11. Willems M, Haddad E, Niaudet P, Kone-Paut I, Bensman A, Cochat P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. J Pediatr 2006;148:623-7.
12. Marks SD, Patey S, Brogan PA, Hasson N, Pilkington C, Woo P, et al. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. Arthritis Rheum 2005;52:3168-74.
13. Kumar S, Benseler SM, Kirby-Allen M, Silverman ED. B-cell depletion for autoimmune thrombocytopenia and autoimmune

hemolytic anemia in pediatric systemic lupus erythematosus. Pediatrics 2009;123:e159-63.
14. Trachana M, Koutsonikoli A, Farmaki E, Printza N, Tzimouli V, Papachristou F. Safety and efficacy of rituximab in refractory pediatric systemic lupus erythematosus nephritis: a single-center experience of Northern Greece. Rheumatol Int 2013;33:809-13.
15. Ale'ed A, Alsonbul A, Al-Mayouf SM. Safety and efficacy of combined cyclophosphamide and rituximab treatment in recalcitrant childhood lupus. Rheumatol Int 2014;34:529-33.
16. Record JL, Beukelman T, Cron RQ. High prevalence of myositis in a southeastern United States pediatric systemic lupus erythematosus cohort. Pediatr Rheumatol Online J 2011;9:20.
17. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology 2005;44:1542-5.
18. FitzGerald JD, Grossman JM. Validity and reliability of retrospective assessment of disease activity and flare in observational cohorts of lupus patients. Lupus 1999;8:638-44.
19. Costa-Reis P, Nativ S, Isgro J, Rodrigues T, Yildirim-Toruner C, Starr A, et al. Major infections in a cohort of 120 patients with juvenile-onset systemic lupus erythematosus. Clin Immunol 2013;149:442-9.
20. Opastirakul S, Chartapisak W. Infection in children with lupus nephritis receiving pulse and oral cyclophosphamide therapy. Pediatr Nephrol 2005;20:1750-5.
21. Vachvanichsanong P, Dissaneewate P, McNeil E. Intravenous cyclophosphamide combined with steroids in pediatric onset severe lupus nephritis. Int Urol Nephrol 2013;45:1301-8.
22. Lehman TJ, Onel K. Intermittent intravenous cyclophosphamide arrests progression of the renal chronicity index in childhood systemic lupus erythematosus. J Pediatr 2000;136:243-7.
23. Barbano G, Gusmano R, Damasio B, Alpigiani MG, Buoncompagni A, Gattorno M, et al. Childhood-onset lupus nephritis: a single-center experience of pulse intravenous cyclophosphamide therapy. J Nephrol 2002;15:123-9.
24. Moroni G, Raffiotta F, Trezzi B, Giglio E, Mezzina N, Del Papa N, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. Rheumatology 2014;53:1570-7.
25. Kang KY, Kwok SK, Ju JH, Park KS, Cho CS, Kim HY, et al. The causes of death in Korean patients with systemic lupus erythematosus over 11 years. Lupus 2011;20:989-97.