

Safety and Effectiveness of Combination Rituximab and Cyclophosphamide Therapy for Treating Pediatric Patients With Severe Manifestations of Rheumatic Disease

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Objective. Current practice guidelines recommend the use of either rituximab (RTX) or cyclophosphamide (CYC) for the treatment of severe manifestations of systemic vasculitis or connective tissue disease. Few studies have evaluated safety and efficacy outcomes of combination therapy with RTX and CYC. We undertook this study to evaluate outcomes in the first 12 months of RTX/CYC combination therapy in pediatric patients with rheumatic disease.

Methods. Patients who received combination RTX/CYC therapy for a rheumatic disease between January 2020 and February 2023 at a single center were included. The primary outcomes of interest were death and infection requiring hospitalization within 12 months of combination therapy. Secondary outcomes included change in serologic lupus disease activity markers and glucocorticoid (GC) dose, flare in disease activity, infusion reactions, and incident hypogammaglobulinemia.

Results. Eighty-nine pediatric patients received combination RTX/CYC therapy for a rheumatic disease. There were no reported deaths; eight patients (8.9%) were hospitalized for infection. The mean prednisone-equivalent daily dose significantly decreased by the end of the follow-up period ($P < 0.0001$), and 54 patients (62%) were able to discontinue GCs. Patients with systemic lupus erythematosus demonstrated improvements across all serologic disease activity markers ($P < 0.0001$). Six patients (6.7%) experienced flare of disease, 11 patients (12%) experienced infusion reactions, and 26 patients (31%) experienced incident hypogammaglobulinemia.

Conclusion. Combination therapy with RTX and CYC can be safely administered to children with rheumatic diseases. Risk of serious adverse events and disease flare is uncommon, allowing for effective treatment with decreased GC burden. Prospective controlled trials comparing combination therapy to standard therapy are needed.

INTRODUCTION

Current practice guidelines recommend the use of either rituximab (RTX) or cyclophosphamide (CYC) for the treatment of severe, organ-threatening manifestations of systemic vasculitis or connective tissue disease (eg, diffuse alveolar hemorrhage, active class III, IV, or V lupus nephritis).^{1,2} These diseases are associated with high morbidity and mortality and are often refractory to standard therapy options. Both RTX and CYC have significant risk profiles as monotherapy, particularly when paired with concurrent glucocorticoids (GCs). The rationale for combination

RTX/CYC therapy is based on the differential effect these medications have across the B cell lineage.³ Rituximab is an anti-CD20 monoclonal antibody that targets precursors of autoantibody-producing cells in circulation but has little direct effect on plasmablasts and plasma cells.⁴ CYC, an alkylating agent, targets autoantibody-producing plasmablasts, plasma cells, and T cells, thus presumably achieving more rapid and broad disease control.^{5,6}

Studies evaluating combined therapy for refractory rheumatic disease in children are lacking. The few prospective studies in adult patients evaluating efficacy and safety in systemic lupus

Dr Rife's work was supported by the Rheumatic and Musculoskeletal Disease T32 AR 069516 NIH Ruth L. Kirschstein National Research Service Award and an Arthritis Foundation grant. Drs Cron, Smitherman, and Mannion's work was supported by the Rheumatology Research Foundation. Dr Mannion's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K23-AR-081410).

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.2.70095>.

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Submitted for publication March 25, 2025; accepted in revised form June 23, 2025.

SIGNIFICANCE & INNOVATIONS

- In this single-center study of children with severe life-threatening manifestations of rheumatic diseases, combination therapy with rituximab (RTX) and cyclophosphamide (CYC) was safe and well tolerated.
- Hospitalized infections, disease flares requiring admission, and medication-related adverse events leading to treatment discontinuation were uncommon.
- Combination therapy with RTX and CYC effectively treated severe life-threatening manifestations of a diverse group of rheumatic diseases, leading to improvements in serologic disease activity markers and successful reduction in glucocorticoid exposure.

erythematosus (SLE) were small, with a wide array of dosing regimens and mixed results regarding efficacy.^{7–9} Several retrospective studies of adult patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and SLE who received combined therapy were also limited by the small number of patients included and variation in dosing regimens.^{3,10,11} Nevertheless, the limited data available for combination therapy in patients with rheumatic diseases are promising, indicating efficacy, safety, improved ability to taper GCs, and decreased relapse rates, but many questions remain unanswered.^{3,7,10,12,13} Combination RTX/CYC therapy is common practice at our center for pediatric patients with severe, organ-threatening rheumatic disease. The goal of this study was to evaluate efficacy and safety outcomes of combined RTX/CYC in pediatric patients with rheumatic disease.

MATERIALS AND METHODS

Patients. The University of Alabama at Birmingham Institutional Review Board approved this study via decision number 300008468. This was a retrospective, single-center study of children treated by pediatric rheumatologists at the University of Alabama at Birmingham/Children's of Alabama (CoA) who received both RTX and CYC between January 2010 and February 2023 for an organ- or life-threatening manifestation of a rheumatic disease. Patients were identified in the electronic medical record (EMR) using medication and infusion codes for RTX and CYC for both inpatient and outpatient encounters. Patients were considered to have received combination therapy if they had infusions for both medications with less than 30 days between infusion start dates. The index date was the date of receipt of the second medication regardless of order, and data were collected for 12 months following the index date, referred to herein as the follow-up period. Patients who did not receive both medications within the outlined time frame were excluded. Patients were also excluded

if combination RTX/CYC therapy was prescribed by another specialty for nonrheumatic disease diagnoses, including malignancy.

Medication administration. All infusions were administered at CoA. CYC dosing was in accordance with the National Institutes of Health protocol, typically 500 to 750 mg/m² intravenously once a month for six months. Extended-dosing regimens were used depending on practitioner preference, disease activity, and severity. Premedication for CYC included rehydration fluids, mesna, and standard doses of diphenhydramine, acetaminophen, and antiemetics as needed. RTX was typically administered at a dose of 750 mg/m² (with a maximum of 1 g per dose) intravenously, with two doses administered two weeks apart every six months or when peripheral blood CD19/20 counts repopulated above five cells per microliter.¹⁴ Patients were premedicated with methylprednisolone at varying doses depending on practitioner preference, underlying diagnosis, and disease severity, with a maximum of 1 g per dose administered. Additional premedication for RTX included standard doses of diphenhydramine and acetaminophen. Patients were not routinely vaccinated before (or during) combination therapy.

Data collection. Patient demographic information was reported from the index visit. Outpatient medications, relevant laboratory markers, and admission data were collected for all patient encounters for 12 months following the index date.

Primary outcomes. Primary outcomes were as follows:

1. Death: records were reviewed for death certificates, coroner notes, cessation of follow-up, and EMR notifications during the follow-up period.
2. Severe infection: defined as requiring hospitalization with a discharge diagnosis code indicating infection within 12 months of the index date. The EMR was queried and reviewed for admission dates and discharge diagnosis codes. Progress notes, media uploads, and telephone encounters were abstracted to identify admissions at other hospitals.

Secondary outcomes. Secondary outcomes were as follows:

1. Effectiveness data: serum complement (C3, C4) and double-stranded DNA (dsDNA) values were collected for all patients with SLE at index (± 30 days) and at 12 months' follow-up (± 30 days). Daily oral GC doses were abstracted from the EMR on all patients at index and at 12 months' follow-up (± 30 days).
2. Flare in disease activity: the EMR was queried and reviewed for inpatient admission dates and discharge diagnosis codes. History and physical notes, progress

notes, medication administration records, laboratory data, and discharge summaries were abstracted and reviewed to discern underlying admission indication. In cases in which multiple factors may have contributed to admission, patients were classified as experiencing a flare if they received additional treatments for their underlying rheumatic disease (e.g., pulse GC).

3. Adverse medication reactions: any documented reaction or adverse event during RTX or CYC infusions. All infusion notes, nursing notes, progress notes, and allergies were reviewed for documented reactions.
4. Incident hypogammaglobulinemia: defined as an IgG level <600 mg/dL during the follow-up period after a documented normal IgG level before the index date or RTX infusion if it was the first infusion.
5. Long-term survival data: all available patient records were reviewed to assess current disease status after the 12-month follow-up period.

Statistical analysis. Continuous data were reported as medians and interquartile ranges; categorical data were reported as percentages. Evaluation of effectiveness data at 12 months compared to index was performed with Student's *t*-test using GraphPad Prism software.

RESULTS

Patient population. Eighty-nine patients received combination RTX/CYC and had 12 months of clinical observation following the index date. Demographic information and diagnoses are shown in Table 1. The median age at the time of combined therapy was 14 years. Seventy-eight percent of patients were female ($n = 69$), and 67% ($n = 60$) identified as Black. Most patients ($n = 85$, 96%) received combination therapy at diagnosis. The most common rheumatic diagnosis was SLE, which accounted for 66% ($n = 59$) of the cohort. The second most frequent diagnosis was ANCA-associated vasculitis, affecting 6.7% ($n = 6$) of patients.

The main indications for combination RTX/CYC therapy are shown in Table 2. The most common indication for combination therapy was nephritis, accounting for 61% ($n = 54$) of cases. Most nephritis cases were categorized on biopsy as lupus nephritis (LN) class IV ($n = 21$, 39%). Neurologic indications, including cerebritis, encephalitis, and central nervous system vasculitis, accounted for a combined 20% ($n = 18$) of cases. Of the seven patients with a renal indication listed as "other nephritis," four had ANCA-associated vasculitis with pauci-immune glomerulonephritis by biopsy, two had IgA vasculitis with nephritis by biopsy, and one had SLE with presumed LN, but the family had declined the biopsy. Other indications for combination therapy included various pulmonary, ophthalmologic, cardiovascular, and gastrointestinal indications, as listed in Table 2.

Table 1. Demographics and disease, $N = 89^*$

	Value
Age at start of dual therapy, y	
Median (IQR)	14 (12–15)
Sex, no. (%)	
Female	69 (77.5)
Race, no. (%)	
White	27 (30.3)
Black	60 (67.4)
Other	2 (2.2)
Ethnicity, no. (%)	
Hispanic	8 (9.0)
Non-Hispanic	81 (91.0)
Primary diagnosis, no. (%)	89
Systemic lupus erythematosus	59 (66.3)
ANCA-associated vasculitis	6 (6.7)
Sjögren disease	5 (5.6)
Retinal vasculitis	3 (3.4)
Idiopathic pulmonary hemosiderosis	2 (2.2)
IgA vasculitis	2 (2.2)
Systemic sclerosis	2 (2.2)
Vasculitis/arteritis, unspecified	2 (2.2)
Castleman disease	1 (1.1)
Mixed connective tissue disease	1 (1.1)
Nephritic syndrome, unspecified	1 (1.1)
NMDA encephalitis	1 (1.1)
Polyarteritis nodosa	1 (1.1)
Relapsing polychondritis	1 (1.1)
SAVI	1 (1.1)
Takayasu arteritis	1 (1.1)

*ANCA, antineutrophil cytoplasmic antibody; IQR, interquartile range; NMDA, N-methyl-D-aspartate; SAVI, stimulator of interferon genes-associated vasculopathy with onset in infancy.

A summary of the RTX and CYC infusions, infection prophylaxis, GC dosing, and infusion reactions is shown in Table 3. All patients received at least one dose of RTX and CYC. The median number of RTX doses received was 4 (range 1–6) within the 12-month follow-up period (including the index date infusion); 52 patients (58%) received more than 1 cycle (or 2 doses). The median (and maximum) RTX dose administered was 1,000 mg (which yielded a median of 585 mg/m²). In total, 282 RTX infusions were administered to all included patients during the 12-month study period. The median number of CYC doses received was 6 (range 1–12), with 42 (47%) patients receiving more than 6 doses. The median CYC dose administered was 750 mg/m² and 1,000 mg. In total, 539 CYC infusions were administered to all included patients during the follow-up period, and the average cumulative exposure for all patients during the one-year study period was 6,338 mg. Ninety-nine percent of patients received intravenous methylprednisolone at a median dose of 1,000 mg with at least one infusion. Ninety-eight percent of patients subsequently started oral GCs after the infusion, with a median dose of 60 prednisone-equivalent mg/day. Most patients (93%) were prescribed *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, with 81% prescribed trimethoprim/sulfamethoxazole (TMP/SMX).

Table 2. Primary indication for rituximab and cyclophosphamide therapy, N = 89*

	Value
Total	89
Renal	54 (60.7%)
LN class II	2
LN class III	8
LN class IV	21
LN class V	3
LN class II/V	1
LN class III/V	5
LN class IV/V	7
Other nephritis	7
Neurologic	18 (20.2%)
Cerebritis	9
CNS vasculitis	4
Encephalitis	3
MCA stroke	1
Subdural hematoma	1
Pulmonary	9 (10.1%)
Interstitial lung disease	4
Pulmonary hemorrhage	2
Airway compromise	1
Diffuse alveolar hemorrhage	1
Idiopathic pulmonary hemosiderosis	1
Ophthalmologic	6 (6.7%)
Retinal vasculitis	5
Scleritis	1
Cardiovascular	1 (1.1%)
Aortitis	1
Gastrointestinal	1 (1.1%)
Gastrointestinal vasculitis	1

*CNS, central nervous system; LN, lupus nephritis; MCA, middle cerebral artery.

Primary outcomes. There were no patient deaths during the study period. Eight patients (8.9%) were admitted for possible or definite infection, with hospitalization data noted on Table 4. These eight patients were hospitalized with a median length of stay of 4.5 days and a mean of 7 days. Two patients were admitted for longer than 5 days; one required a critical care admission 34 days after the index date for *Serratia marcescens* bacteremia. That patient made a full recovery and was discharged home after 25 days as an inpatient. One patient had herpes simplex II and *Chlamydia trachomatis* with pelvic inflammatory disease. Three patients were diagnosed with respiratory infections. Seven of the eight (87.5%) patients admitted for infection had nephritis as their RTX/CYC indication. Four patients had infection diagnosis codes listed, but no infectious agents were identified on various testing. One patient with a peritoneal dialysis catheter underwent paracentesis with no organism identified but was administered intravenous antibiotics empirically for peritonitis.

Secondary outcomes. The mean $\pm$ SD dsDNA antibody level for the 59 patients with SLE was 2,645 $\pm$ 4,345 IU/mL before combination therapy and 85 $\pm$ 347 IU/mL at the end of the follow-up period ($P < 0.0001$) (Figure 1). The mean $\pm$ SD C3 level was 47 $\pm$ 29 mg/dL before index and 115 $\pm$ 34 mg/dL at the end of

Table 3. Medications and reactions*

	Value
Rituximab, median (IQR)	
Doses during follow-up period (12 mo)	4 (2–4)
Dose, mg	1,000.0 (1,000–1,000)
Dose, mg/m ²	585.0 (500–682)
Cyclophosphamide, median (IQR)	
Doses during follow-up period	6 (6–7)
Dose, mg	1,000.0 (925–1,178)
Dose, mg/m ²	750.0 (500–750)
GCS	
Patients taking oral GCS during follow-up period, no. (%)	87 (97.8)
Prednisone dose equivalent per day start of follow-up period, median (IQR), mg	60 (40–60)
Patients receiving IV GCS at index, no. (%)	88 (98.9)
Methylprednisolone dose equivalent, median (IQR), mg	1,000.0 (1,000–1,000)
Infection prophylaxis, no. (%)	
Any	83 (93.3)
Dapsone	1
Pentamidine	10
TMP/SMX	72
None	6 (6.7)
Patients with infusion reactions, no. (%)	11 (12.4)
Rituximab reactions, total no.	8
Cyclophosphamide reactions, total no.	4
Methylprednisolone reactions, total no.	1
Patients stopping medications due to reaction, total no.	1

*GC, glucocorticoid; IQR, interquartile range; IV, intravenous; TMP/SMX, trimethoprim/sulfamethoxazole.

follow-up ($P < 0.0001$). The mean $\pm$ SD C4 level was 8 $\pm$ 10 mg/dL before index and 29 $\pm$ 13 mg/dL at the end of the follow-up period ($P < 0.0001$). Eighty-seven patients (98%) required daily oral GCS during at least a portion of the follow-up period. Of those, 54 patients (62%) were able to discontinue GCS at a mean of 212 days after the index date. Twenty-eight of the 32 patients (88%) who were not able to wean off GCS had a primary diagnosis of SLE, and 25 (78%) carried a primary diagnosis of LN. The mean $\pm$ SD prednisone-equivalent daily dose decreased from 54 $\pm$ 23.56 mg to 11 $\pm$ 9.3 mg ($P < 0.0001$) during the follow-up period.

Six patients (6.7%) were hospitalized for a presumed disease flare: four with diagnosis codes for SLE with nephrotic syndrome, edema, or fluid overload; one for hypoxic respiratory failure; and one for macrophage activation syndrome. Of the patients admitted with presumed SLE flare, all had marked improvements in dsDNA antibody levels from the index visit to the date of admission. At the time of flare admission, the mean $\pm$ SD dsDNA antibody level of the four patients with SLE was 325 $\pm$ 775 IU/mL, down from 2,208 $\pm$ 2,249 IU/mL at index. Similarly, these four patients demonstrated clinical improvement in complement levels from diagnosis to time of flare admission. The mean $\pm$ SD value for C3 increased from 33 $\pm$ 10 mg/dL to 81 $\pm$ 42 mg/dL, and the mean $\pm$ SD value for C4 increased from 4 $\pm$ 2 mg/dL to 21 $\pm$ 8 mg/dL.

Table 4. Infections*

Age, sex	Race and ethnicity	Diagnosis	RTX/CYC indication	Infection	Infectious agent	Level of care	Days since index	Length of stay, days	IgG at admission, mg/dL	Additional medications	Prednisone equivalent at infection, mg
5 y, F	Black	AAV	Nephritis	Peritonitis	NI	AC	16	5	-	Oral GC	20
10 y, F	White	AAV	Nephritis	Gastroenteritis	NI	AC	89	4	-	Oral GC	20
14 y, F	White	AAV	Nephritis	Meningitis	NI	AC	160	5	-	Oral GC, TMP/SMX	60
12 y, M	Black	SAVI	ILD	URI	Parainfluenza	AC	200	2	1,042	Oral GC	10
6 y, F	Black	SLE	Nephritis	URI	Influenza B	AC	209	1	715	Oral GC, MMF	3
13 y, F	Hispanic	SLE	Nephritis	URI	NI	AC	101	3	-	Oral GC	3
13 y, F	Black	SLE	Nephritis	Pelvic inflammatory disease	HSV II, <i>Chlamydia</i>	AC	261	14	1,513	Oral GC	60
14 y, F	White	SLE	Nephritis	Bacteremia	<i>Serratia marcescens</i>	ICU	34	25	<109	Oral GC, HCQ, IVIg	40

*AAV, antineutrophil cytoplasmic antibody-associated vasculitis; AC, acute care; CYC, cyclophosphamide; F, female; GC, glucocorticoids; HCQ, hydroxychloroquine; HSV, herpes simplex virus; ICU, intensive care unit; ILD, interstitial lung disease; IVIg, intravenous Ig; M, male; MMF, mycophenolate mofetil; NI, none identified; RTX, rituximab; SAVI, stimulator of interferon genes-associated vasculopathy with onset in infancy; SLE, systemic lupus erythematosus; TMP/SMX, trimethoprim/sulfamethoxazole; URI, upper respiratory infection.

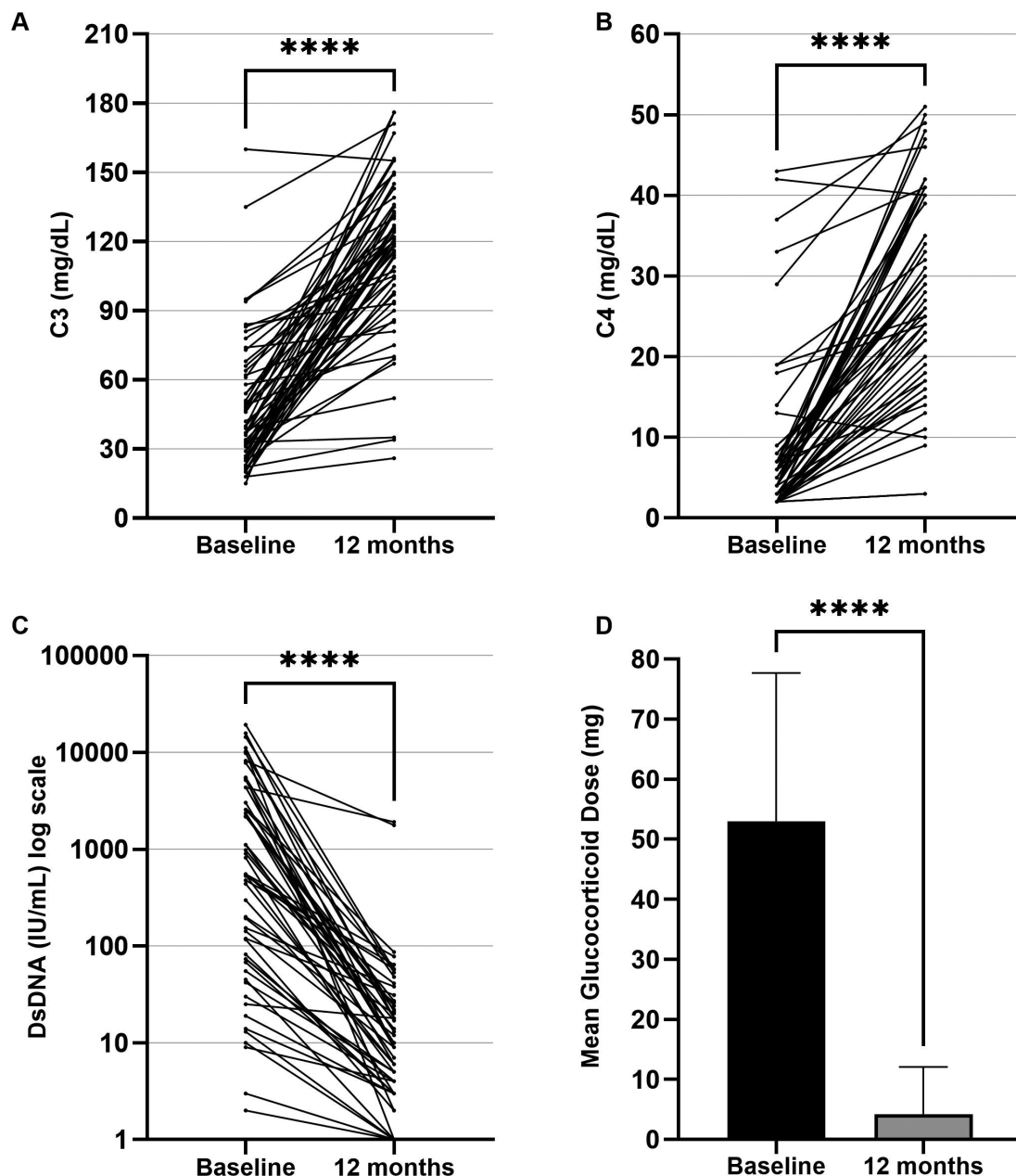


Figure 1. Change in complement levels, dsDNA levels, and mean glucocorticoid daily dose with RTX/CYC therapy. (A) Change in C3 levels: mean $\pm$ SD 47 ± 29 mg/dL before RTX/CYC and 115 ± 34 mg/dL at 12 months. (B) Change in C4 levels: mean $\pm$ SD 8 ± 10 mg/dL before RTX/CYC and 29 ± 13 mg/dL at 12 months. (C) Change in dsDNA levels: mean $\pm$ SD $2,645 \pm 4,345$ IU/mL before RTX/CYC and 85 ± 347 IU/mL at 12 months. (D) The mean $\pm$ SD daily prednisone-equivalent dose decreased from 54 ± 23.6 mg to 11 ± 9.3 mg by 12 months. **** $P < 0.0001$. CYC, cyclophosphamide; dsDNA, double-stranded DNA; RTX, rituximab.

There were several hospital admissions listed during the follow-up period that were not for infection or flare of disease. Five patients were admitted for behavioral health concerns: suicidal ideation, psychosis, depression, and psychogenic nonepileptic seizure (two patients). These patients all symptomatically improved during admission with behavioral health interventions and did not require immunomodulatory therapy changes. Three patients were admitted for hyperglycemia in the setting of poorly controlled diabetes, two were admitted for scheduled renal

biopsies, two were admitted for other procedures (gastrostomy tube, peritoneal catheter), one was admitted for deep vein thrombosis, and one was admitted for missed hemodialysis.

Eleven patients (12%) experienced at least one medication reaction during infusion of RTX, CYC, or premedication; the majority occurred with RTX infusions. There was a wide range of reactions, including rash, hypertension, pruritus, nausea, agitation, body aches, chills, intravenous infiltration, and bradycardia. Therapy was continued in these cases, although most required a

reduction in infusion rate. One patient had a documented anaphylactic reaction with the second dose of RTX, necessitating discontinuation of therapy, but did not require epinephrine or hospital admission. The patient was managed with intravenous fluids, antihistamines, and close monitoring in the outpatient infusion center.

Data on incident hypogammaglobulinemia are shown in Table 5. Five patients (5.6%) were hypogammaglobulinemic before the index date, defined as IgG levels less than 600 mg/dL (cutoff value used by our laboratory). Twenty-six of 85 patients (31%) experienced incident hypogammaglobulinemia during the follow-up period, with normal levels recorded before infusions. Nine of the incident patients (35%) recovered IgG counts within 12 months without intervention. Seven of the incident patients (27%) required IgG replacement during the follow-up period, six for low IgG levels, which were measured as part of routine care, and one for possible peritonitis with concomitant IgG levels <600 mg/dL. Of those who received IgG replacement, four recovered IgG counts and were able to stop intravenous Ig (IVIg), and three required long-term IgG replacement through transition to adult care or until they were lost to follow-up.

Two of the incident patients (8%) started IgG replacement outside of the 12-month follow-up period; they recovered counts and were able to discontinue replacement therapy. Four of the incident patients (15%) remained hypogammaglobulinemic past 12 months but did not receive IgG replacement therapy due to either provider preference or parental refusal: three of these patients recovered counts without replacement therapy, whereas one remained hypogammaglobulinemic through transition to adult care. The other four incident patients (15%) did not have repeat IgG levels available. At our institution, IVIg is administered

at a dose of 0.4 to 0.5 g/kg for Ig replacement and 2 g/kg for therapeutic treatment. The maximum total IVIg dose administered is capped at 100 g. The number of IVIg infusions and doses given to each patient is summarized in Table 5.

Data were available on all 89 patients for the duration of their management by the University of Alabama at Birmingham Division of Pediatric Rheumatology at CoA. Patients were observed for a range of 12 to 132 months. At the time of manuscript submission, 17 patients (19%) were still actively being observed in our clinic, with 298.8 total person-years of follow-up data available. There was one patient death in the cohort, which occurred 28 months after the end of the study period. The patient's underlying diagnosis was SLE with class III/IV LN. The patient received six total doses of RTX and two doses of CYC during the follow-up period. She was hypogammaglobulinemic and receiving long-term IVIg therapy, and the final discharge summary listed sepsis of a pulmonary source as the underlying cause of death. Nine patients were lost to follow-up after the study period but have 19 to 25 months of data available. Most patients (n = 62, 70%) successfully transitioned to an adult provider or subspecialty service.

DISCUSSION

To our knowledge, this article represents the largest single-center collection of pediatric patients treated with combination RTX/CYC therapy for severe organ-threatening manifestations of rheumatic disease. This is a diverse patient population with a variety of disease processes, and nearly all were treated with combination therapy at diagnosis (n = 85, 95.5%). We demonstrate that a combination therapy regimen is generally safe, effective, and well tolerated. There were no deaths during our study period, but there is scant literature on combination therapy in pediatric rheumatology patients for comparison. Cortazar et al reported 4 of 129 deaths (3.1%) in a retrospective study of combination therapy in adults with ANCA vasculitis.³ Jónsdóttir et al reported zero deaths in a small clinical trial of 16 adult patients with refractory SLE receiving combination therapy.⁹ Roberts et al reported 7 of 1,567 deaths (0.44%) in a large study of patients with childhood-onset SLE receiving RTX therapy.¹⁵ Interestingly, 608 of 1,567 patients (39%) in their cohort were also receiving concomitant CYC therapy.¹⁵ Opastirakul et al reported 2 of 61 deaths (3%) in their pediatric cohort receiving CYC monotherapy, both of which were infection related.¹⁶ Vachvanichsanong et al reported a much higher proportion of deaths (23 of 108 [21%]) in a three-year Thai study of pediatric patients with SLE and refractory LN receiving CYC monotherapy.¹⁷ Lupus Nephritis Assessment with Rituximab (LUNAR) randomized placebo-controlled trial¹⁸ of RTX therapy in adult patients with SLE and LN reported deaths in 73 patients (2.7%). In comparison, our report using combination RTX/CYC at onset of disease has favorable mortality outcomes.

Table 5. Hypogammaglobulinemia and IgG replacement*

Onset before Index, n/N (%)	5/89	(6)
Onset during follow-up period, n/N (%)	26/84	(31)
Days to hypogammaglobulinemia, median (IQR)	116	(57–191)
Decrease in IgG, median percent (IQR)	68.3	(60.4–78.4)
IgG count recovery within 12 mo without replacement, n/N (%)	9/26	(35)
Received IVIg during follow-up period for IgG <600mg/dL, n/N (%)	7/26	(27)
IgG counts recovered after IgG replacement	4/7	(57)
Prolonged IgG replacement	3/7	(43)
Received IVIg after 12 mo follow-up period, n/N (%)	2/26	(8)
Recovered counts and discontinued IgG replacement	2/2	
Hypogammaglobulinemia after 12 mo follow-up period, no IgG replacement ^a	4/26	(15)
IgG count recovery without replacement, n/N (%)	3/4	(75)
Repeat IgG counts unavailable	4/26	(15)

*IQR, interquartile range; IVIg, intravenous Ig.

^aPatient 1 received 2 monthly IVIg infusions at 0.5g/kg. Patient 2 received 7 monthly IVIg infusions at 0.4 g/kg. Patient 3 received 1 IVIg infusion at 0.5g/kg. Patient 4 received 10 monthly IVIg infusions at 0.5 g/kg.

The rate of hospitalization for presumed or definite infection in our study was 8.9 per 100 person-years; this safety profile is comparable to previous studies. Roberts et al reported a serious infection rate of 14 per 100 patient-years in pediatric patients taking RTX, many of whom were also taking CYC.¹⁵ In their study,¹⁵ combination therapy was not associated with higher infection risk than RTX monotherapy, with a hazard ratio of 1.05 (95% confidence interval 0.79–1.39). Tambralli et al¹³ reported a serious infection rate of 8.69 per 100 person-years in children taking RTX; it should be noted that there may be some overlapping patients between our study and this study, which was performed at the same center in 2015. One small adult SLE LN study reported 27% (6 of 22) of patients with incident infections while receiving combination therapy.⁸ Two other studies reported no serious infections among CYC-treated patients with childhood-onset SLE receiving long-term therapy.^{19,20} Rovin et al reported a serious infection rate of 16.6 per 100 patient-years in the LUNAR trial.¹⁸ Of those, 15% were diagnosed with herpes zoster, 23.3% were diagnosed with urinary tract infections, and 28.8% were diagnosed with upper respiratory infections.¹⁸ Rates of serious infections were similar in the RTX group and the control group in this study,¹⁸ as well as in the study by Stone et al.²¹ Herpes viral infections and PJP are well documented in association with RTX, CYC, and prednisone literature.^{15,16,18} There was one case of herpes simplex in our study group and no PJP (93% of our study group were receiving PJP prophylaxis). Similar to in our study, patients with end stage kidney disease (ESKD) or patients with severe renal insufficiency were overrepresented among those with infection.¹⁵

In addition to the beneficial safety profile, combination RTX/CYC therapy was effective treatment for a wide variety of rheumatic diseases. In patients with identifiable disease activity markers, RTX/CYC combination therapy elicited drastic improvement, as typified by the trends in dsDNA, C3, and C4 levels. The primary driver of disease flare in 67% (4 of 6) of our patients who required admission was refractory edema, proteinuria, or anasarca related to underlying renal insufficiency or ESKD. Interestingly, of the four patients admitted with SLE and flare, all had marked improvements in dsDNA, C3, and C4 levels from index to the time of flare admission. These findings call into question the diagnosis of true disease flare versus persistent renal damage and/or podocytopathy early in the treatment course.

Regarding hypogammaglobulinemia, we used 600 mg/dL as a cutoff IgG level because this level is used by our in-house laboratory. The American Academy of Allergy, Asthma, and Immunology defines hypogammaglobulinemia as <700 mg/dL in adults; however, there is a lack of consensus on cutoff points in children.²² Secondary hypogammaglobulinemia (SHG) from RTX administration and subsequent treatment with replacement IgG is well described in the adult literature.^{22–25} The literature in pediatric patients is less robust particularly in pediatric rheumatic disease. Lim et al observed hypogammaglobulinemia in 7% (6 of

86) of their childhood-onset SLE cohort.²⁶ They found significant associations with White race, male sex, and presence of SLE LN at diagnosis but not with use of immunosuppressive therapies.²⁶ McAtee et al reported 23.2% (67 of 289) of patients had hypogammaglobulinemia in a diverse pediatric cohort, with 13.7% persisting past 12 months.²⁷ Khojah et al reported 44% (28 of 63) of patients had SHG after RTX therapy in a pediatric autoimmune disease cohort.²³ Most SHG cases developed within 6 months following RTX therapy and resolved by 24 months.^{23,27,28} These data are similar to our study group, with 29.2% (26 of 89) developing SHG, with a median onset of around four months, and a majority recovering counts within two years. Tieu et al reported that 20% (29 of 142) required IgG replacement,¹¹ which is similar to our study at 27% (7 of 26). Our long-term data indicated that 82% (18 of 22) of patients with SHG eventually recovered counts without the requirement of long-term IgG replacement.

Risk factors for persistent SHG include nephrotic-range proteinuria, immunosuppressive therapy, and longer duration of renal disease.^{28,29} In our study group, 5.6% (5 of 89) of patients were hypogammaglobulinemic before the index date and were primarily patients with nephrotic-range proteinuria. Smilek et al reported 15.7% (16 of 102) of patients with SLE were hypogammaglobulinemic before induction therapy.²⁸ There are many reports of patients with hypogammaglobulinemia who are ultimately diagnosed with primary immunodeficiency both before and after RTX therapy.^{28,30} Suspicion should increase if there is persistent hypogammaglobulinemia after discontinuing RTX therapy, and ideally levels should be checked at baseline before therapy.^{22,30} In children, risks for persistent hypogammaglobulinemia include younger age at onset, autoimmune disease, lower pre-RTX levels and impaired post-RTX recovery.^{22,25,30} Some articles report association with infection, whereas others did not find any association.^{22,25,27,28} There was no significant increase in infection risk between our patients who were hypogammaglobulinemic compared to those who were not.

Limitations of our study include its retrospective design, the nonstandardized treatment approaches (including indications and dosing regimens) used by different providers at a single center, and the absence of comparator groups. Given the nature of using EMR data, we may have missed hospitalizations at external facilities that were not documented in the chart or referenced in provider notes. This is, however, mitigated by the fact that we are the only pediatric rheumatology group in the state. Patients with known rheumatic disease are almost uniformly transferred to our hospital or are discussed with the on-call pediatric rheumatology provider here at CoA for recommendations. Calls are documented in the EMR and thus would have been abstracted from EMR review. This study did have considerable long-term follow-up safety data, which is remarkable considering the severity of the manifestations and diseases included.

Combination RTX and CYC can be safely administered to children with severe life-threatening rheumatic disease.

Hospitalized infections, disease flares requiring admission, and medication reactions requiring cessation of treatment are uncommon. This regimen allows for effective treatment of rheumatic disease and successful reduction of GC exposure. Additional prospective studies evaluating this treatment strategy are warranted.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Rife confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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