

Differences in Rituximab Use Between Pediatric Rheumatologists and Nephrologists for the Treatment of Refractory Lupus Nephritis and Renal Flare in Childhood-Onset SLE

Mileka Gilbert (✉ gilbertm@musc.edu)

Medical University of South Carolina <https://orcid.org/0000-0002-3685-3764>

Beatrice Goilav

Children's Hospital at Montefiore

Joyce J. Hsu

Stanford University School of Medicine

Paul J. Nietert

Medical University of South Carolina

Esra Meidan

Harvard Medical School

Annabelle Chua

Duke University School of Medicine

Stacy P. Ardoin

Nationwide Children's Hospital

Scott E. Wenderfer

Baylor College of Medicine

Emily von Scheven

University of California San Francisco School of Medicine

Natasha M. Ruth

Medical University of South Carolina

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Abstract

Background: Consensus treatment plans have been developed for induction therapy of newly diagnosed proliferative lupus nephritis (LN) in childhood-onset systemic lupus erythematosus. However, patients who do not respond to initial therapy, or who develop renal flare after remission, warrant escalation of treatment. Our objective was to assess current practices of pediatric nephrologists and rheumatologists in North America in treatment of refractory proliferative LN and flare.

Methods: Members of Childhood Arthritis and Rheumatology Research Alliance and the American Society for Pediatric Nephrology were surveyed in November 2015 to assess therapy choices (other than modifying steroid dosing) and level of agreement between rheumatologists and nephrologists for proliferative LN patients. Two cases were presented: 1) refractory disease after induction treatment with corticosteroid and cyclophosphamide and 2) nephritis flare after initial response to treatment. Survey respondents chose treatments for three follow up scenarios for each case that varied by severity of presentation. Treatment options included cyclophosphamide, mycophenolate mofetil, rituximab, and others, alone or in combination.

Results: Treatment choices between nephrologists and rheumatologists were highly variable. A majority (>50%) consensus of either nephrologists or rheumatologists on treatment choice was only achieved in two of six total follow up scenarios for refractory LN or flare. Rheumatologists in comparison to nephrologists chose more therapy options that contained rituximab in five of six scenarios. These differences were statistically significant ($p < 0.05$).

Conclusions: Therapy choices for pediatric rheumatologists and nephrologists in the treatment of refractory LN or LN flare were highly variable with rheumatologists more often choosing rituximab. Further investigation is necessary to delineate the reasons behind this finding. This study highlights the importance of collaborative efforts in developing consensus treatment plans for pediatric LN.

Background:

Systemic lupus erythematosus (SLE) is an autoimmune-mediated disease that can cause inflammation of multiple organ systems. The involvement of the kidneys, which occurs in over half of childhood SLE, significantly alters morbidity and mortality and therefore requires more aggressive immunosuppression (1, 2). A meta-analysis showed 10%-30% higher prevalence of lupus nephritis (LN) in childhood-onset SLE compared to adult-onset SLE (3), with up to 70% of children with SLE having nephritis compared to about 50% of adults with lupus (4, 5). In the 1980s and 1990s, standard-of-care treatment with IV cyclophosphamide (CYC) was delineated by the National Institutes of Health (NIH) for adults with proliferative LN (6–9). More recently, mycophenolate mofetil (MMF) was found by the Aspreva Lupus Management Study (ALMS) investigators to be non-inferior to IV CYC (10), and both drugs are now used first-line for the treatment of proliferative LN. More black and Hispanic patients notably responded to MMF versus IV CYC (10).

While childhood-onset lupus comprises only about 15%-20% of all lupus patients (4, 5), it is difficult to perform large randomized controlled trials (RCTs) in pediatric LN given small numbers. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) has developed consensus treatment plans (CTPs) in an effort to reduce heterogeneity in treatment and better enable future comparative effectiveness studies. CTPs for the induction treatment of proliferative LN were developed in 2012, and treatment arms include both IV CYC and MMF (11). As in adults, current first-line treatment for initial diagnosis of proliferative LN encompasses CYC or MMF, along with the use of corticosteroids.

However, despite advances in the treatment of proliferative LN, a substantial number of patients never reach complete or even partial renal response after induction and are diagnosed as treatment refractory non-responders (NR). Eighteen to 69% of adult patients with LN were resistant to CYC with variable definitions of treatment response (8, 12–15), whereas 5%-48% of patients treated with MMF were described as NR (15–17). Likewise, at six and 12 months, 40%-66% and 65%-75% of children with proliferative LN achieved remission (18–22).

In the patients who do reach complete or partial renal response, unfortunately, renal flares can occur in about 50% of adult-onset SLE after long term follow up (23, 24). In children with SLE, renal flares can occur in 25%-50% of patients on therapy (25, 26). Each subsequent flare leads to more kidney injury and heightened risk for kidney failure.

Patients who do not adequately respond to the CTP regimens, or who develop disease flare after remission, warrant change in treatment. Clinical guidance is lacking for this particularly vulnerable pediatric population, as there are no RCTs or CTPs for cases of NR/refractory LN. Several case series from single centers and case reports describe the use of other medications for treating refractory LN, including biologic agents that target B cell (rituximab, ofatumumab, belimumab) and T cell activity (abatacept, calcineurin inhibitors cyclosporine and tacrolimus) (27, 28). Given the involvement of B cells in the pathogenesis of LN, rituximab (RTX) is one of the most widely employed rescue medications for patients who do not respond to standard treatment or in patients who flare (29).

Depending on the geographic location of a patient and availability of subspecialists in close proximity, pediatric nephrologists may be the primary subspecialists caring for patients with LN. Conversely, pediatric rheumatologists may be treating patients with LN as the leading organ system involvement in a SLE patient. Given this difficult-to-treat disease, treatment practices may vary by type of subspecialist, treating center, and even within practices.

In this study, members from both CARRA and the American Society for Pediatric Nephrology (ASPN) were surveyed to determine the current opinions and practices in the treatment of proliferative LN refractory to induction therapy and in patients who have a renal flare after achieving renal response in childhood-onset SLE.

Methods:

A web-based survey to assess immunosuppression treatment choices and level of agreement between pediatric rheumatologists and nephrologists for pediatric patients with proliferative LN was developed by the Pediatric Nephrology and Rheumatology Collaborative Group (PNR-CG) comprised of members of CARRA and the ASPN. Internal Review Board exemption for the study was obtained through Nationwide Children's Hospital. The survey was sent to the membership of CARRA and the ASPN via Survey Monkey in November 2015.

Two cases were presented in the survey: 1. Pediatric patient with proliferative LN refractory to six months of induction therapy with CYC (See Additional File 1) and 2. Pediatric patient with renal flare three months after achieving remission in response to induction therapy for proliferative LN (See Additional File 2).

Renal response and flare definitions defined in CARRA proliferative LN CTPs (11) were used in the cases. In summary, the core renal parameters were proteinuria, renal function, and urine sediment. Substantial response (complete remission) was defined as normalization of renal function, inactive urine sediment, plus spot protein/creatinine ratio < 0.2. Moderate and mild renal responses were defined as at least 50% improvement (moderate) or 30–50% improvement (mild) in two core renal parameters without clinically relevant worsening of the remaining core parameter. NR included any patient who did not qualify for mild, moderate, or substantial response. Proteinuric/nephrotic renal flare was defined as a persistent increase in urine protein/creatinine ratios to values > 0.5 after achieving complete response, or a doubling of proteinuria with values > 1.0 after achieving a partial response. Non-proteinuric/nephritic renal flare was defined as increase or recurrence of active urinary sediment with or without increase in proteinuria.

Physicians were surveyed on treatment choices for three fictional follow up scenarios for each case. The treatment choices included IV CYC, MMF, calcineurin inhibitors, RTX, belimumab, RTX in combination with IV CYC, and RTX in combination with MMF. Statistical analyses of differences between responses of pediatric nephrologists and rheumatologists were determined using Fisher's Exact Test with p value < 0.05 considered statistically significant.

Results:

The survey was distributed to members of the ASPN and CARRA who completed fellowship programs in pediatric nephrology and pediatric rheumatology. The 76 respondents from ASPN and 41 respondents from CARRA represented approximately 15% of the eligible members from each organization. All respondents were board-eligible or board-certified in their subspecialty with the vast majority having at least two years of post-fellowship experience, and 45% of pediatric nephrologists and 60% of pediatric rheumatologists having greater than 10 years of experience. Fifty-two percent of pediatric nephrologists reported managing less than 25 patients with SLE, and half of pediatric rheumatologists reported managing 25 to 100 patients with SLE (Table 1). Only 51% of the pediatric nephrologists and 24% of the pediatric rheumatologists surveyed in this study follow a standard protocol for treatment of LN (Table 1) reflecting the lack of guidance from RCTs for pediatric LN.

For the case of refractory class IV LN (See Additional File 1), a 16-year-old female failed induction therapy with seven monthly doses of CYC 500–1000 mg/m² IV in addition to steroids. Although fever, rash, and arthritis improved, a repeat renal biopsy showed persistent activity, little chronicity, and no evidence of membranous LN. In the first follow-up scenario (See Additional File 1), patient was found to have no renal response to induction therapy with hypertension, peripheral edema, hypocomplementemia, hypoalbuminemia, positive dsDNA antibody, persistent proteinuria, and active urine sediment, as well as a significant increase in serum creatinine. Survey respondents were asked to consider their next choice in immunosuppressive agent. Pediatric nephrologists and rheumatologists agreed with the top choice of MMF in combination with RTX (42% vs. 44%, Fig. 1). CYC in combination with RTX (16% vs. 27%, Fig. 1) and MMF alone (20% vs. 20%, Fig. 1) were the next most common choices for therapy. Overall, while the choices varied within groups, there was no statistically significant difference between nephrologist and rheumatologist responses ($p = 0.40$).

In the second follow-up scenario of refractory class IV LN after CYC induction therapy (See Additional File 1), the patient was found to have mild renal response with hypertension, peripheral edema, hypocomplementemia, hypoalbuminemia, positive dsDNA antibody, and persistent proteinuria, but improvement in serum creatinine and only mild hematuria. Pediatric nephrologists and rheumatologists chose MMF alone (41% vs. 37%, Fig. 2) and MMF in combination with RTX (15% vs. 34%, Fig. 2) as their top choices for next step in immunosuppressive therapy in this scenario. Overall, there was no statistically significant difference between nephrologist and rheumatologist responses ($p = 0.10$). However, the majority of rheumatologists (53%) chose therapies that involved RTX alone or in combination, compared to only 31% of nephrologists that chose RTX therapies (Fig. 2). There was a statistically significant difference between the groups of nephrologist and rheumatologist responses in choices of RTX-containing regimens versus choices without RTX ($p = 0.03$).

In a third follow-up scenario of the refractory class IV LN case (See Additional File 1), the patient was found to have moderate renal response with persistent hypertension, resolution of peripheral edema, hypocomplementemia, hypoalbuminemia, positive dsDNA antibody, active urine sediment, but greater than 50% improvement in serum creatinine and proteinuria. Whereas a majority of pediatric nephrologists chose MMF alone (59%, Fig. 3), rheumatologists were split over use of MMF alone (38%) or in combination with RTX (35%) as their top choices for next step in immunosuppressive therapy. Overall, there was a statistically significant difference between nephrologist and rheumatologist responses ($p < 0.01$), unlike in the prior follow-up scenarios. Additionally, rheumatologists again chose more therapies that involved RTX compared to nephrologists (59% vs 21%, $p < 0.01$, Fig. 3). Thus, pediatric rheumatologists were more likely to use RTX in this scenario of active urine sediment but improvement in other renal parameters, and thus may be more aggressive with use of RTX. In all follow-up scenarios, there was no difference between groups of nephrologist and rheumatologist choices in therapies when considering additional CYC versus MMF or other options.

The second clinical vignette presented a case of a 12-year-old patient with SLE and class IV LN who achieved complete renal remission after induction therapy with CYC in addition to steroids for

proliferative LN according to published CTP (11) (See Additional File 2). She was transitioned to MMF 1000 mg twice daily for maintenance therapy and tapering prednisone dose. Three months later, she developed nephrotic syndrome, hematuria with active urine sediment, hypocomplementemia, and high titer dsDNA antibody, without change in serum creatinine. She was diagnosed with renal flare, and repeat renal biopsy showed class IV LN with high activity and low chronicity scores. Pediatric nephrologists chose CYC alone (22%) or increased dose of MMF to 1500 mg twice daily (22%), whereas pediatric rheumatologists chose CYC in combination with RTX (36%) or CYC alone (21%) as their top choices for therapy (Fig. 4).

If the second case used MMF as the induction agent instead of CYC at diagnosis (See Additional File 2), nephrologists chose increased dose of MMF to 1500 mg twice daily (39%) or CYC alone (25%) to treat renal flare (Fig. 5). Rheumatologists chose CYC alone (27%) or MMF in combination with RTX (24%) as their top choices for treatment of renal flare (Fig. 5).

In the third follow up scenario of renal flare after complete renal remission was achieved with CYC and steroids followed by maintenance MMF therapy, the patient was also found to have elevated serum creatinine, rapidly progressive glomerulonephritis, and class IV LN on repeat renal biopsy (See Additional File 2). Nephrologists and rheumatologists (81% vs. 82%, Fig. 6) agreed that CYC with or without RTX were the best therapeutic choices for renal flare in this scenario, although more rheumatologists compared to nephrologists (52% vs. 22%, Fig. 6) would use CYC in combination with RTX.

In all three follow up scenarios involving case of renal flare after achieving remission with induction therapy, there was a statistically significant difference between the groups of nephrologist and rheumatologist responses ($p = 0.02, 0.02, 0.04$ respectively; Figs. 4–6). Additionally, rheumatologists chose more therapies that involved RTX than nephrologists in all scenarios ($p = 0.03, 0.02, < 0.01$ respectively; Figs. 4–6). There was no difference between groups of nephrologist and rheumatologist choices in therapies when considering additional CYC versus MMF or other options. Thus, pediatric rheumatologists chose RTX in more situations of renal flare than pediatric nephrologists, similar to the first case of proliferative LN refractory to induction therapy. Belimumab was included as a treatment option in both cases, however was rarely chosen.

Discussion:

The approach to refractory proliferative LN after initial therapy with CYC or MMF is limited by the absence of evidence-based studies. This is particularly true in the case of pediatric LN where there is a lack of clinical trials. Thus, pediatric rheumatologists and nephrologists must make decisions on treatment of refractory LN based on retrospective cohort studies. CTPs are a useful tool to compare effectiveness of currently practiced treatments in the clinical setting. The first step in developing CTPs for refractory proliferative LN in pediatric patients is to understand the clinical practices of pediatric rheumatologists and nephrologists.

This survey assessed the choices of immunosuppressive agents in clinical scenarios of refractory and relapsing childhood-onset proliferative LN. Treatment choices between nephrologists and rheumatologists were highly variable and received greater than 50% agreement for an individual treatment choice in only two scenarios. Of note, pediatric rheumatologists and nephrologists did agree on the treatment of the most severe case of proliferative LN that was refractory to induction therapy, and both groups tended to choose more aggressive treatment options. However, there were differences in choice of therapies in the more moderate cases of refractory proliferative LN and in all cases of renal flare, particularly in the use of RTX.

While RTX in combination with MMF and corticosteroids did not meet primary endpoint of renal response in LN in patients 16–75 years of age after one year of treatment in the randomized, double-blind, placebo-controlled LUNAR clinical trial (30), small prospective studies of use of RTX alone or in combination with MMF for induction therapy of childhood LN have shown some efficacy and steroid-sparing effect (31, 32). The degree of circulating B cell depletion by RTX appears to be critical for clinical effect and may explain the LUNAR trial results (33). Meta-analyses of RTX treatment in refractory LN support an additional benefit (34, 35). Moreover, several case series in childhood-onset LN report complete and partial remission at varying rates and steroid-sparing effect of RTX in refractory cases (29). EULAR (36), ACR (37), and KDIGO (38, 39) guidelines support the use of RTX as one of the treatment options in patients with refractory LN.

Pediatric rheumatologists may treat more aggressively as compared to nephrologists, given the increased choice of RTX in more moderate case scenarios of refractory and relapsing LN in this survey. Pediatric rheumatologists may also be more comfortable with using RTX as this medication is also used for other rheumatologic indications with renal and non-renal manifestations. This study highlights the importance of collaborative effort in developing CTPs for pediatric LN, as there are significant differences in the management of LN between pediatric rheumatologists and nephrologists.

Given the limited number of FDA approved therapies for LN and lack of guidelines for refractory LN, there are several biases and limitations of this case-based survey. Familiarity with treatment options with use for other indications may affect choice of therapy. Access to certain medications may be limited by insurance and thus affect physician experience with certain medications like belimumab. Belimumab was FDA approved for pediatric SLE in 2019, and has been recently shown as an effective add-on therapy for induction therapy for proliferative LN (40–42), but was not in widespread use at the time of this survey in 2015. The approach for nephrologists and rheumatologists is likely evolving now that the results of the BLISS-LN trial have been published (40). Fifteen percent of pediatric nephrologists and rheumatologists in the ASPN and CARRA responded to the cases in the survey likely reflecting a selection bias for those physicians who take care of more lupus patients; although the majority of nephrologists surveyed manage less than 25 pediatric patients with LN. The low response rate to the survey is certainly a limitation of this study; however, the vast majority of pediatric rheumatologists and 49% of pediatric nephrologists surveyed do not follow a standard protocol for treatment of LN and are not following

CARRA CTPs. Thus, even with higher response rates, we would likely still see highly variable responses to the clinical scenarios presented.

Conclusions:

Therapy choices for pediatric rheumatologists and nephrologists in the treatment of proliferative LN refractory to induction therapy or LN flare after remission were highly variable. In addition, there were differences between rheumatologists and nephrologists particularly in the use of RTX for the majority of scenarios presented in these cases. This provides an opportunity to work towards consensus to reduce heterogeneity in the treatment of refractory pediatric LN so that we can perform comparative effectiveness trials. This study highlights the importance of collaborative effort in developing CTPs for pediatric LN.

Abbreviations

ACR – American College of Rheumatology

ALMS – Aspreva Lupus Management Study

ASPN – American Society of Pediatric Nephrology

CARRA – Childhood Arthritis and Rheumatology Research Alliance

CTP – Consensus Treatment Plan

CYC – cyclophosphamide

DNA – deoxyribonucleic acid

EULAR – European League Against Rheumatism

FDA – Food and Drug Administration

ISN/RPS – International Society of Nephrology and the Renal Pathology Society

KDIGO – Kidney Disease Improving Global Outcomes

LN – lupus nephritis

LUNAR – Lupus Nephritis Assessment with Rituximab study

MMF – mycophenolate mofetil

NIH – National Institutes of Health

NR – non-responders

PNR-CG – Pediatric Nephrology and Rheumatology Collaborative Group

RCT – randomized controlled trial

RTX – rituximab

SLE – systemic lupus erythematosus

Declarations

Ethics approval and consent to participate – Internal Review Board exemption for study was obtained at Nationwide Children’s Hospital, IRB # IRB15-00843.

Consent for publication – Not applicable

Availability of data and materials -All data generated or analyzed during this study are included in this manuscript.

Competing interests – The authors have no financial competing interests.

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Authors’ contributions – MG, BG, and JJH participated in development of survey, interpretation of results, and were major contributors in writing the manuscript. PJN performed statistical analysis and participated in interpretation of results. EM, AC, and SPA participated in development of survey. SW and EVS participated in development of survey and interpretation of results. NMR participated in interpretation of results and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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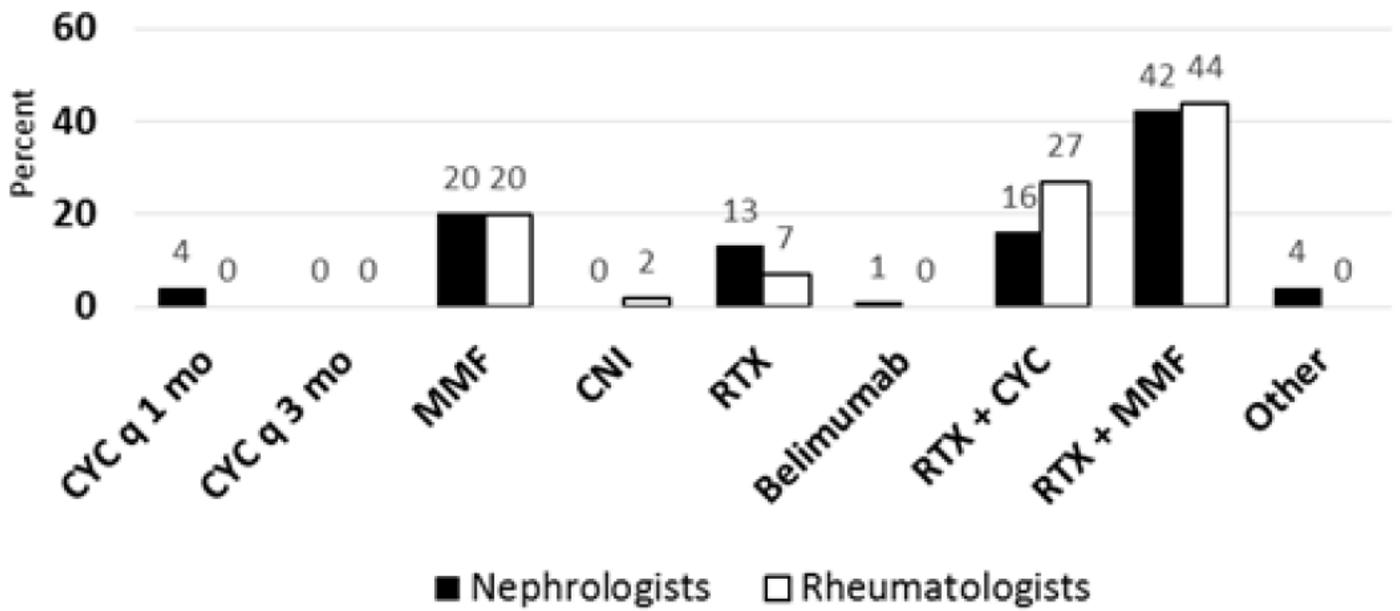
Tables

Table 1. Demographics of Survey Respondents

	Pediatric Nephrologists	Pediatric Rheumatologists
Total Respondents	N = 76*	N = 41*
Medical Centers	N = 56	N = 15
Peds Neph Board-Eligible	100%	0%
Peds Rheum Board-Eligible	0%	100%
Years in Practice		
< 2	2%	7%
2-5	29%	17%
6-10	25%	17%
> 10	45%	60%
# of Pediatric SLE Patients		
0-25	52%	37%
25-50	14%	20%
50-100	19%	30%
> 100	6%	13%
LN Standard Protocol	51%	24%

*Approximately 15% of ASPN and CARRA membership

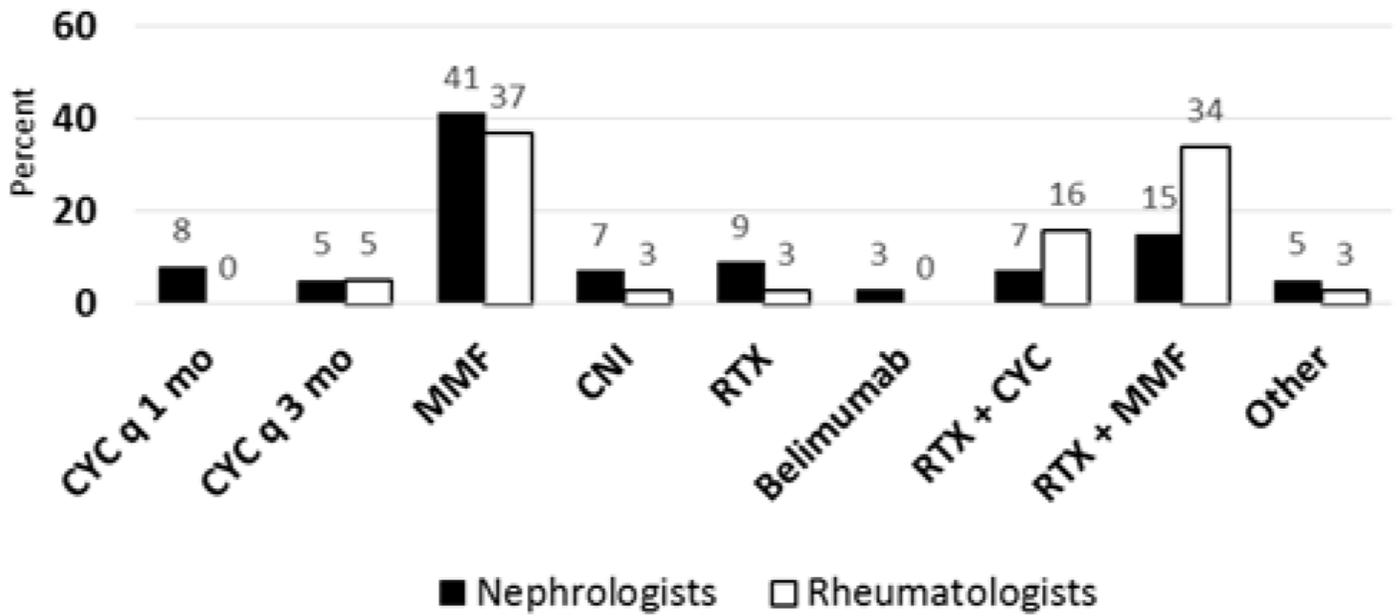
Figures



	Nephrologists	Rheumatologists	<i>p</i> value
All choices			0.40
RTX vs. Non-RTX	71% vs. 29%	78% vs. 22%	0.51
CYC vs. MMF vs. Other	20% vs. 62% vs. 18%	27% vs. 63% vs. 10%	0.41

Figure 1

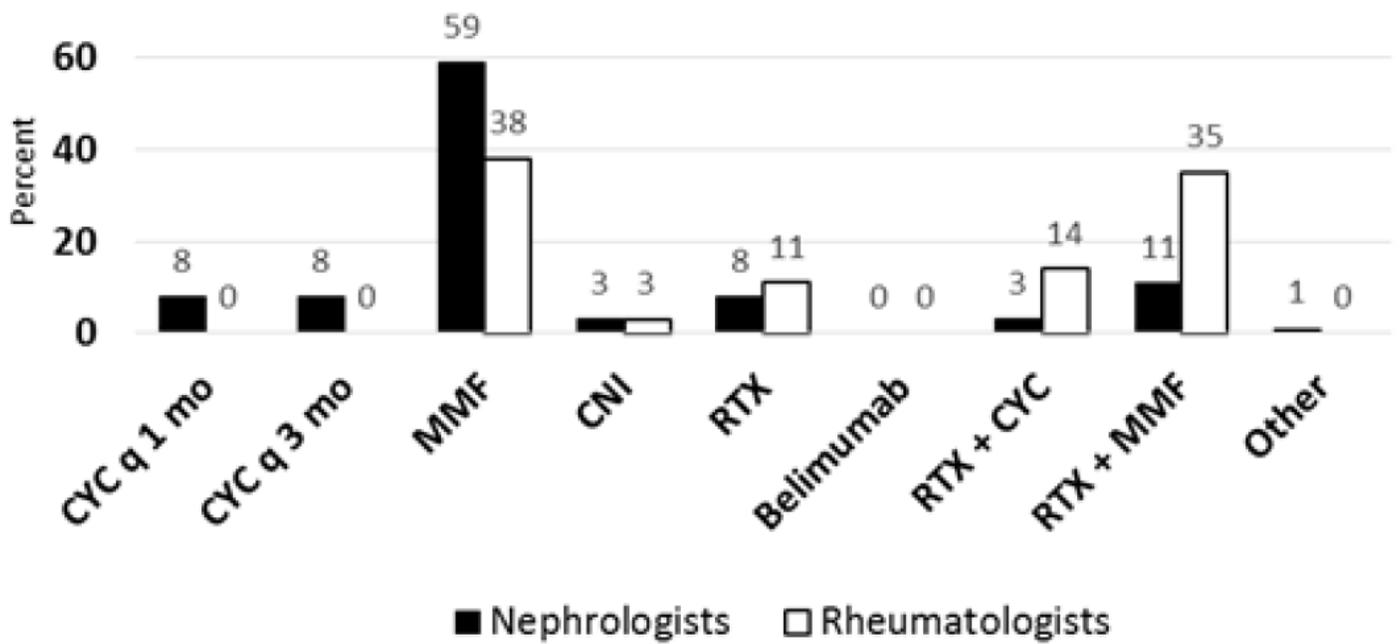
Treatment choices for LN refractory to induction therapy with renal insufficiency, nephrotic syndrome, and hematuria. 76 nephrologists and 41 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in chart. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)



	Nephrologists	Rheumatologists	<i>p</i> value
All choices			0.10
RTX vs. Non-RTX	31% vs. 69%	53% vs. 47%	0.03
CYC vs. MMF vs. Other	20% vs. 56% vs. 24%	21% vs. 71% vs. 8%	0.10

Figure 2

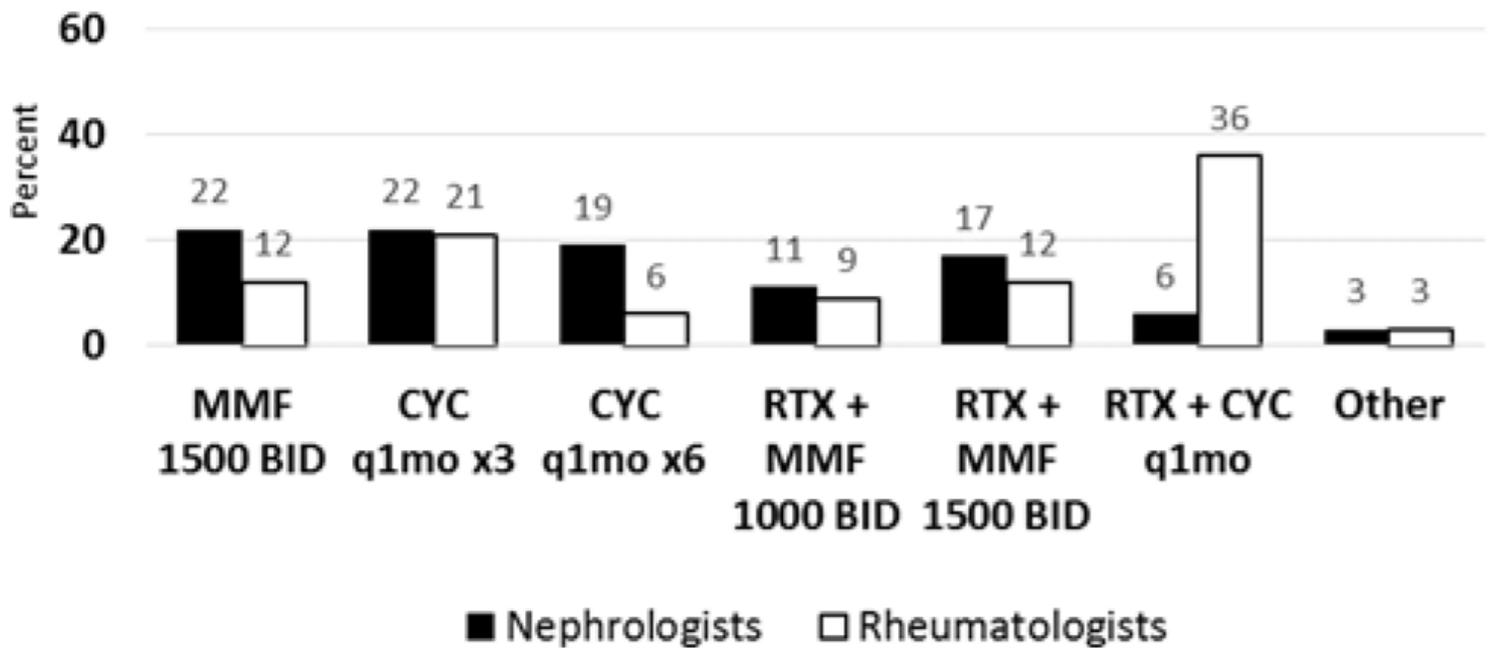
Treatment choices for LN refractory to induction therapy with nephrotic syndrome, improved hematuria and creatinine. 75 nephrologists and 38 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in chart. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)



	Nephrologists	Rheumatologists	<i>p</i> value
All choices			<0.01
RTX vs. Non-RTX	21% vs. 79%	59% vs. 41%	<0.01
CYC vs. MMF vs. Other	19% vs. 69% vs. 12%	14% vs. 73% vs. 14%	0.81

Figure 3

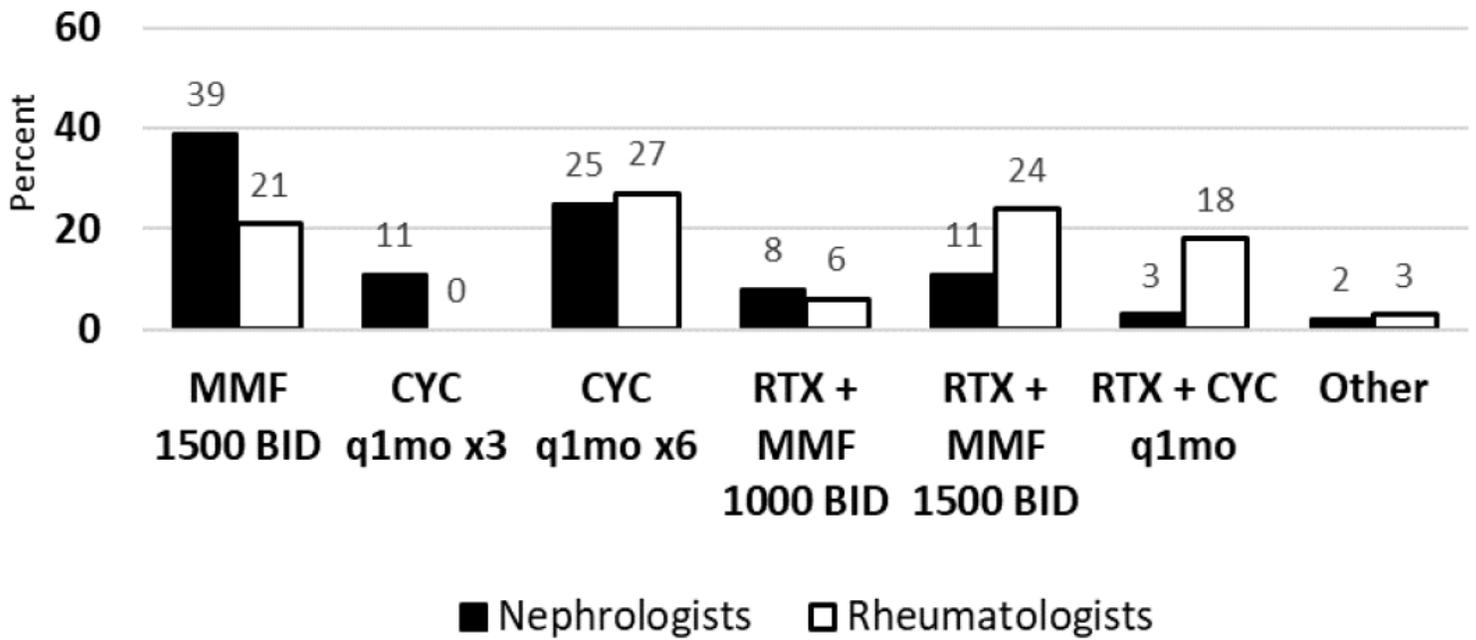
Treatment choices for LN refractory to induction therapy with hematuria, improved creatinine and proteinuria. 75 nephrologists and 37 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in table. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)



	Nephrologists	Rheumatologists	<i>p</i> value
All choices			0.02
RTX vs. Non-RTX	34% vs. 66%	58% vs. 42%	0.03
CYC vs. MMF vs. Other	47% vs. 50% vs. 3%	64% vs. 33% vs. 3%	0.24

Figure 4

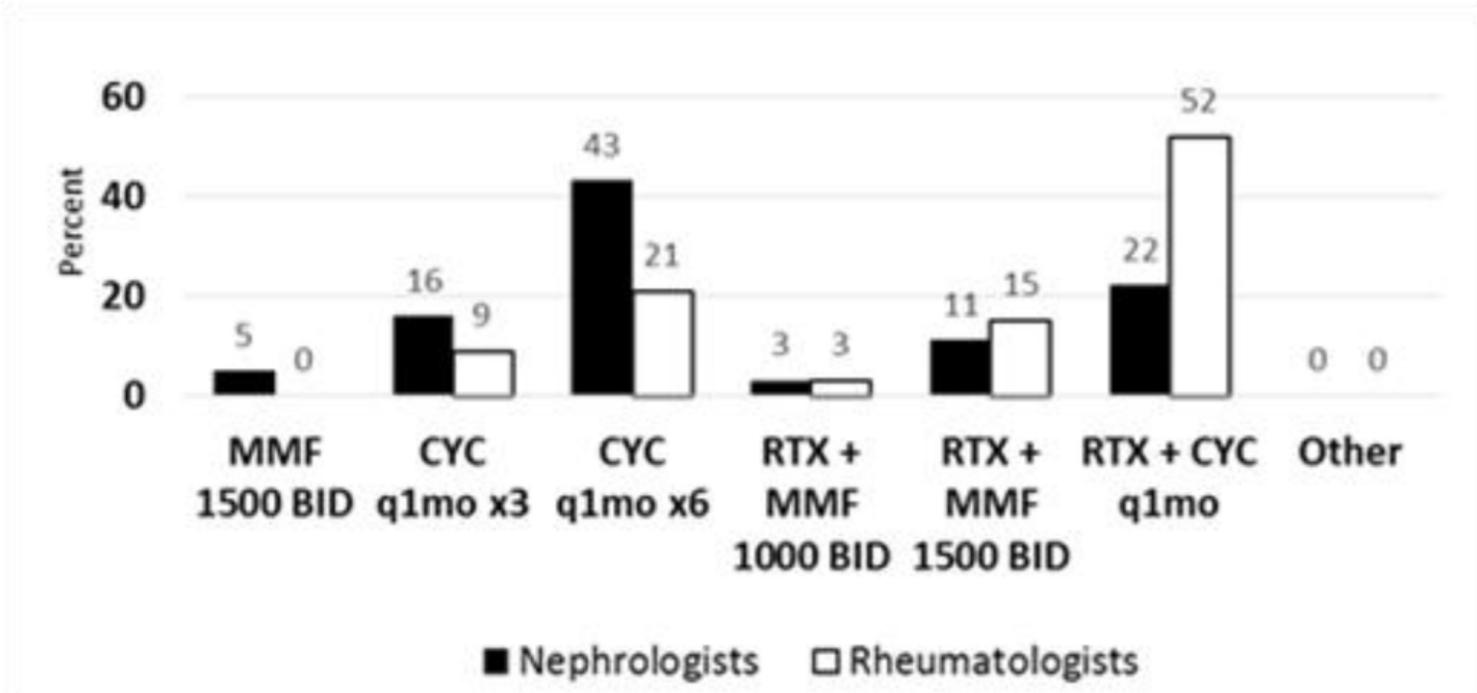
Treatment choices for renal flare in proliferative LN after achieving remission with CYC induction therapy. 64 nephrologists and 33 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in chart. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)



	Nephrologists	Rheumatologists	<i>p</i> value
All choices			0.02
RTX vs. Non-RTX	23% vs. 77%	48% vs. 52%	0.02
CYC vs. MMF vs. Other	39% vs. 59% vs. 2%	45% vs. 52% vs. 3%	0.70

Figure 5

Treatment choices for renal flare in proliferative LN after achieving remission with MMF induction therapy. 61 nephrologists and 33 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in table. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)



	Nephrologists	Rheumatologists	p value
All choices			0.04
RTX vs. Non-RTX	37% vs. 63%	70% vs. 30%	<0.01
CYC vs. MMF vs. Other	81% vs. 19% vs. 0%	82% vs. 18% vs. 0%	1.00

Figure 6

Treatment choices for renal flare after induction with renal insufficiency and rapidly progressive glomerulonephritis. 63 nephrologists and 33 rheumatologists responded to survey question. Treatment choices are depicted in graph. Statistical analysis of differences in responses between groups is depicted in table. P value < 0.05 is considered statistically significant. (RTX=Rituximab, CNI=Calcineurin Inhibitor, MMF=Mycophenolate mofetil, CYC=Cyclophosphamide)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalFile1.pdf](#)
- [AdditionalFile2.pdf](#)