Approach to Membranous Lupus Nephritis: A Survey of Pediatric Nephrologists and Pediatric Rheumatologists

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ABSTRACT. ***Objective.*** To describe treatment practices for childhood pure membranous lupus nephritis (MLN).
Methods. Survey study of Childhood Arthritis and Rheumatology Research Alliance and American Society of Pediatric Nephrology members.
Results. There were 117 respondents who completed the survey (60 pediatric nephrologists, 57 pediatric rheumatologists). Steroids and nonsteroid immunosuppression (NSI) were routinely used by the majority for MLN. Mycophenolate mofetil was the favored initial NSI. Nephrologists used steroids (60% vs 93%) and NSI (53% vs 87%) less often than did rheumatologists for MLN without nephrotic syndrome (NS).
Conclusion. Pediatric rheumatologists and nephrologists both recommend steroids and NSI for children with MLN, with or without NS. (First Release September 15 2017; J Rheumatol 2017;44:1619–23; doi:10.3899/jrheum.170502)

Key Indexing Terms:
LUPUS NEPHRITIS PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS
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Membranous lupus nephritis (MLN), defined as Class V LN in the International Society of Nephrology/Renal Pathology Society classification, is found in 8–30% of patients with pediatric LN[1,2,3,4,5,6,7]. MLN can manifest in isolation (pure MLN) or in combination with proliferative glomerulonephritis (mixed MLN). In a recent large, multicenter childhood-onset systemic lupus erythematosus (SLE) cohort, 56% of patients with MLN had pure MLN (74 patients with pure MLN out of 132 patients with MLN)[7].

LN treatment guidelines have been issued by the American College of Rheumatology (ACR), Asian Lupus Nephritis Network (ALNN), European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA), Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group (KDIGO), and Systemic Autoimmune Disease Group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology (GEAS)[8,9,10,11,12]. These

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guidelines are not consistent in their recommendations for pure MLN (Table 1)[8,9,10,11,12]. All but the GEAS guidelines distinguish between patients with nephrotic versus non-nephrotic proteinuria. The ACR and EULAR/ERA-EDTA do not specifically address immunosuppressive treatment of patients with non-nephrotic proteinuria, while the KDIGO guidelines suggest prednisone and/or nonsteroid immunosuppressive (NSI) therapy only for those patients with nephrotic-range proteinuria. Choice of NSI also varies among the guidelines, with the ACR and EULAR/ERA-EDTA preferring mycophenolate (either mycophenolate mofetil or mycophenolic acid), while the ALNN, KDIGO, and GEAS do not express a preference among their recommendations for mycophenolate, azathioprine, cyclophosphamide, or calcineurin inhibitors.

Recent data from childhood-onset SLE patients with pure MLN in a large North American registry revealed a high percentage of patients who were exposed to systemic steroids (96%) and NSI (95%)[7]. This suggests that pediatric rheumatologists and nephrologists may be recommending steroids and additional immunosuppressive medications for the majority of patients with pure MLN, regardless of whether nephrotic-range proteinuria is present. The objective of our study was to describe treatment practices for pediatric rheumatologists and pediatric nephrologists who care for patients with pure MLN. We used physician surveys with hypothetical patient scenarios to assess respondents' approach to immunosuppression and renin-angiotensin-aldosterone system (RAAS) inhibition.

MATERIALS AND METHODS

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the American Society of Pediatric Nephrology (ASPN). CARRA is an organization composed of pediatric rheumatologists and researchers in North America that conducts collaborative basic science, clinical and translational research to prevent, treat, and cure pediatric rheumatic diseases. The ASPN is a society of pediatric nephrologists that promotes optimal care for children with kidney disease through advocacy, education, and research.

Survey. We sent an online survey to 272 members of CARRA and 507 members of ASPN through SurveyMonkey in November 2015. The survey included questions relating to use of steroids, NSI, and RAAS-blocking medications. Two hypothetical cases were used to frame questions: one case was a patient with pure MLN with nephrotic syndrome (NS), and the other was a patient with pure MLN without NS where proteinuria was described as < 1 g/day. The patient with NS was described as having "hypoalbuminemia, hyperlipidemia, and an abnormal urinalysis (5 g/day of protein, 5–10 red blood cells/high power field)." No significant extrarenal disease was present in these cases. Maintenance therapy was defined as starting 4 to 6 months after start of initial treatment. This survey and the data analysis plan for this study were approved by the Institutional Review Board of Nationwide Children's Hospital (IRB15-00843). Descriptive statistics (percentages) were used to summarize categorical survey responses.

RESULTS

A total of 117 physicians responded to the survey, with 57 pediatric rheumatologists and 60 pediatric nephrologists. Response rates were 21% for pediatric rheumatologists and 12% for pediatric nephrologists, with a combined response rate of 15%. Respondents were evenly distributed across the range of years in practice, number of pediatric SLE patients at their center, and number of new patients with LN per year at their center (data not shown).

Table 1. Guidelines for immunosuppressive treatment of pure membranous lupus nephritis in adults.

Guideline Organization	Publication Yr	Location	Induction	Treat Non-nephrotic Proteinuria	Maintenance
ACR[9]	2012	USA	MMF + oral GC. Alt: CYC + GC pulse followed by oral GC	Not addressed	MMF or AZA
ALNN[12]	2013	Asia	GC + MMF, AZA, MMF, or CNI	Yes, if deteriorating renal function or "active serology"	Not addressed
EULAR/ERA-EDTA[8]	2012	Europe	MMF + oral GC. Alt: CYC, CNI, RTX	Not addressed	MMF + oral GC. Alt: AZA, CNI
GEAS[11]	2012	Spain	Oral GC + CYC, CNI, MMF, or AZA	No distinction for non-nephrotic range proteinuria	Oral GC + MMF, CNI, or AZA
KDIGO[10]	2012	International	GC + CYC, CNI, MMF, or AZA	As dictated by extrarenal manifestation	Not addressed

ACR: American College of Rheumatology; ALNN: Asian Lupus Nephritis Network; EULAR/ERA-EDTA: European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association; GEAS: Systemic Autoimmune Disease Working Group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology; KDIGO: Kidney Disease: Improving Global Outcomes; MMF: mycophenolate; GC: glucocorticoid (oral, prednisone; pulse, methylprednisolone); Alt: alternative; CYC: cyclophosphamide; AZA: azathioprine; CNI: calcineurin inhibitors; RTX: rituximab.

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Use of steroids for treatment of pure MLN. Most pediatric rheumatologists (98%) and pediatric nephrologists (91%) agreed that the initial treatment of pure MLN with NS should include systemic steroids (Table 2). More rheumatologists (93%) than nephrologists (60%) recommended steroids for first-line treatment of pure MLN without NS. For patients with pure MLN with NS who responded to initial therapy, similar proportions of rheumatologists (53%) and nephrologists (49%) would continue oral low-dose maintenance steroids. Somewhat fewer respondents (rheumatologists 30%, nephrologists 33%) would continue oral low-dose maintenance steroids for patients with pure MLN without NS who responded to initial therapy.

Use of NSI. For patients with pure MLN with NS, 98% of pediatric rheumatologists and 83% of pediatric nephrologists recommended NSI (Table 2). For patients with pure MLN without NS, 87% of rheumatologists and 53% of nephrologists recommended NSI. Mycophenolate was the most frequently chosen first-line NSI for both respondent groups and both cases, with some respondents choosing more than 1 agent as a first-line choice. For patients with pure MLN with NS who are nonresponsive to initial first-line therapy, 98% of rheumatologists and 96% of nephrologists recommended a range of other agents for NSI, without a clear preference (Table 3). For patients with pure MLN without NS who are nonresponsive to first-line therapy, 92% of rheumatologists and 91% of nephrologists recommended NSI, again without a clear preference among the alternative agents.

Use of renin-angiotensin-aldosterone system inhibition. Most pediatric nephrologists (93%) would use either angiotensin-converting enzyme inhibitor therapy or angiotensin-receptor blockers for pure MLN. Of pediatric rheumatologists, 54% defer to nephrology for decisions regarding RAAS blockers.

DISCUSSION

Our study provides new insight into the treatment practices of pediatric subspecialists who care for patients with pure MLN. Previously reported rates of steroid treatment for pediatric pure MLN have been > 90% for patients with and without NS[4,7]. Our survey data provide additional support for this observation, with most pediatric rheumatologists and pediatric nephrologists reporting systemic steroid treatment for MLN, regardless of the degree of proteinuria. Recent surveys have documented high levels of collaboration between pediatric nephrologists and rheumatologists when caring for patients with LN, and it may be that co-management of these patients increases the likelihood that at least 1 specialist will opt for steroid treatment[13].

In a recent large cohort study, NSI treatment was reported for 95% of pediatric patients who had pure MLN, again suggesting that decisions to treat with these medications may not be dependent on degree of proteinuria[7]. Our data suggest that physicians frequently recommend NSI treatment for MLN without nephrotic-range proteinuria, with 87% of pediatric rheumatologists and 53% of pediatric nephrologists supporting such treatment. Notably, the hypothetical cases did not have any extrarenal disease that would warrant such

Table 2. First-line initial immunosuppression for pure MLN. Values are n (%).

Variables	Steroids	MMF	CNI	CYC	RTX	AZA	None
MLN with NS							
Pediatric rheumatologists, n = 57	56 (98)	44 (77)	15 (26)	4 (7)	4 (7)	1 (2)	1 (2)
Pediatric nephrologists, n = 60	55 (91)	30 (50)	9 (15)	9 (15)	6 (10)	1 (2)	10 (17)
MLN without NS							
Pediatric rheumatologists, n = 52	52 (93)	39 (75)	10 (19)	2 (4)	1 (2)	2 (4)	7 (13)
Pediatric nephrologists, n = 55	34 (60)	21 (38)	5 (9)	2 (4)	3 (5)	1 (2)	26 (47)

MLN: membranous lupus nephritis; NS: nephrotic syndrome; MMF: mycophenolate; CNI: calcineurin inhibitors; CYC: cyclophosphamide; RTX: rituximab; AZA: azathioprine.

Table 3. Immunosuppression for patients with MLN nonresponsive to first-line treatment. Values are n (%).

Variables	CYC	MMF	AZA	CNI	RTX	None
MLN with NS						
Pediatric rheumatologists, n = 56	18 (32)	14 (25)	6 (11)	17 (30)	17 (30)	1 (2)
Pediatric nephrologists, n = 56	9 (16)	16 (29)	0 (0)	15 (27)	18 (32)	2 (4)
MLN without NS						
Pediatric rheumatologists, n = 52	10 (22)	22 (45)	7 (12)	16 (31)	13 (25)	2 (8)
Pediatric nephrologists, n = 55	6 (11)	26 (47)	1 (2)	11 (20)	9 (16)	5 (9)

MLN: membranous lupus nephritis; NS: nephrotic syndrome; CYC: cyclophosphamide; MMF: mycophenolate; AZA: azathioprine; CNI: calcineurin inhibitors; RTX: rituximab.

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treatment, supporting the idea that physicians are recommending immunosuppression solely for MLN treatment. Whether degree of proteinuria should guide treatment decisions for MLN is unknown. Several investigators have reported that degree of proteinuria at baseline is not a significant predictor of renal function deterioration in adults, although nephrotic syndrome has been linked to increased risk for renal failure[14,15,16]. In pure adult-onset MLN, 1 randomized controlled trial has been done and 2 other trials have included pure class V nephritis, and these patients have been analyzed separately[17,18]. The patients included with pure MLN in these studies mostly had ≥ 2 g/day of proteinuria. Further study is needed to assess outcomes for pediatric patients with pure MLN.

Limitations of our study include the possibility of selection bias or reporting bias. Our response rates were low, but not unexpectedly so for a survey distributed through e-mail and without a paid incentive for participating subspecialist physicians[19]. By surveying providers participating in either CARRA or ASPN, we may have biased the results toward particular types of respondents. Another possible limitation of our study, which arises from its design as a case-based survey, is the risk of sentinel effect, when respondents' knowledge that they are being evaluated creates bias in their responses. Despite these possible limitations, the frequent use of steroids and NSI medications reported by respondents is consistent with recently reported retrospective data from the CARRA Registry, suggesting that the respondents in our study are representative of the larger population of North American pediatric rheumatologists[7].

Our study was not designed with the goal of comparing pediatric rheumatologists to pediatric nephrologists. However, it is notable that nephrologists tend to choose NSI and steroids less frequently than do rheumatologists, and they seem willing to wait longer, on average, before determining a patient to be nonresponsive to initial therapy (data not shown). Our data raise the possibility that rheumatologists and nephrologists may differ in their approach to patients with pediatric LN. Given the fact that nephrologists and rheumatologists frequently cooperate in caring for these patients, it is not clear that differences between providers will ultimately lead to substantial differences in treatment. Further descriptive study will be required to elucidate these trends.

The results of our study highlight the empirical character of treatment decisions for pediatric MLN. Future observational studies are needed to better describe treatment practices and renal outcomes for patients with MLN. Collaboration between pediatric rheumatologists and pediatric nephrologists will be important in formulating standardized approaches to treatment that will allow for comparative effectiveness and longterm outcome studies.

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