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Use of EuroLupus Cyclophosphamide Dosing for the Treatment of Lupus Nephritis in Childhood-onset Systemic Lupus Erythematosus in North America

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ABSTRACT. ***Objective.*** Childhood-onset systemic lupus erythematosus (cSLE) has higher rates of lupus nephritis (LN) than adult-onset SLE, often requiring intensive immunosuppression. This study examined North American practices and preferences for the low-dose EuroLupus cyclophosphamide (CYC) protocol, as compared to the high-dose National Institutes of Health (NIH) CYC protocol, to treat LN in cSLE.

Methods. A 35-item Web-based survey was distributed to Childhood Arthritis and Rheumatology Research Alliance (CARRA) and Pediatric Nephrology Research Consortium (PNRC) providers. The survey assessed participant demographics, CYC prescribing practices, perceptions of EuroLupus protocol, and LN vignette treatment decisions; 1 vignette was taken from a 2009 CARRA survey and responses were compared. Multivariable logistic regression analyzed provider factors associated with use of low- vs high-dose CYC.

Results. Responses were provided by 185/421 (44%) pediatric rheumatologists (CARRA) and 40/354 (11%) pediatric nephrologists (PNRC). Among respondents who prescribed CYC for pediatric LN over the past year (n = 135), half reported using EuroLupus. When presented with the same vignette about an adolescent with class IV LN, 32% of pediatric rheumatologists chose EuroLupus dosing in 2020, vs 6% in 2009. Provider factors associated with choosing the low-dose regimen were familiarity with the protocol (OR 4.2, $P = 0.006$) and greater perceived benefit (OR 1.6, $P < 0.0001$). Pediatric nephrologists had similar responses to the pediatric rheumatology providers. Overall, 78% of respondents perceived EuroLupus protocol efficacy to be equivalent to the high-dose protocol in cSLE LN.

Conclusion. Pediatric specialists are currently more likely to use low-dose CYC to treat cSLE LN than they were a decade ago. Nevertheless, familiarity with EuroLupus dosing remains low.

Key Indexing Terms: cyclophosphamide, dosing, lupus nephritis, pediatrics, nephrology, rheumatology

An estimated 10–20% of patients with SLE develop disease during childhood (cSLE).[1] cSLE is known to have a more severe phenotype, including higher rates of lupus nephritis (LN), contributing to the higher mortality rates seen in children.[1,2] Given that there are few children included in clinical trials for LN, the treatment of LN in cSLE is largely extrapolated from adult data.[3,4] Treatment of cSLE LN may include high-risk immunosuppression with cyclophosphamide (CYC). Risk of infection and concern about cumulative toxicity are significant considerations when initiating treatment with CYC.

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a multinational research organization

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whose mission is to conduct collaborative research to prevent, treat, and cure childhood rheumatic diseases. Approximately 90% of North American pediatric rheumatologists are members of CARRA.[5] CARRA published a consensus treatment plan (CTP) for induction therapy for cSLE proliferative LN in 2012[6] shortly before a lower-dose CYC regimen known as EuroLupus[7] came into mainstream use in North America in the adult SLE population.[8]

The EuroLupus regimen consists of a fixed dose of CYC (500 mg) administered every 2 weeks for a total of 6 doses. In the adult population, EuroLupus dosing has been shown to be noninferior[7,9,10,11] to the older, higher-dose National Institutes of Health (NIH) CYC protocol, which consists of 500–1000 mg/m^2 administered monthly for 6 months. Data suggest that EuroLupus dosing results in fewer severe infections compared to the NIH protocol, with the rates of other adverse events being comparable.[7] The favorable risk-to-benefit profile has led to the replacement of the NIH protocol with EuroLupus dosing as first-line treatment in the most recent European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA)[12] and Kidney Disease Improving Global Outcomes (KDIGO) guidelines,[13] with widespread adoption across North America in adult patients.[8,9] Uptake in pediatric rheumatology, however, is less universal, given the paucity of data specific to EuroLupus dosing in cSLE. Further, the pharmacokinetics of CYC have not been studied in children with LN and there are concerns about extrapolating a fixed dose regimen to children. Concerns about potential underdosing are particularly worrisome, given that LN is known to be especially aggressive in cSLE.[14]

As a first step toward studying EuroLupus dosing in cSLE LN, we conducted a cross-sectional survey of North American pediatric rheumatologists and pediatric nephrologists regarding CYC prescribing practices. We sought to better characterize how North American pediatric lupus specialists are using CYC for LN induction therapy in cSLE. We also sought to understand providers' perceptions regarding the advantages and disadvantages of EuroLupus dosing compared to NIH dosing.

METHODS

Ethics approval. The study was considered exempt from the institutional review board (IRB) by the Duke University Hospital System IRB.

Survey design. A 35-item online survey (Supplementary Figure 1, available with the online version of this article) was developed by a subset of the authors and then piloted by members of CARRA's LN Work Group to determine clarity of questions. The survey, built in Survey Monkey (www.surveymonkey.com), included questions about provider demographics, provider CYC prescribing practices (including experience with the EuroLupus protocol, and EuroLupus administration practices), and beliefs about EuroLupus dosing advantages and disadvantages compared to the NIH protocol. In addition, providers were asked to select perceived advantages and disadvantages of EuroLupus dosing compared to NIH dosing, using a predefined list from which they could select multiple options. Similarly, providers were asked about patient factors that would influence their choice of CYC dosing, using a predefined list from which they could select multiple patient factors.

The survey also included 2 specific clinical vignettes wherein providers were asked to choose a specific treatment based on a clinical scenario. The survey's first clinical vignette described a 70-kg, 16-year-old female with first onset of LN. Respondents were asked to choose a CYC dosing regimen (EuroLupus vs NIH) based on class of LN and glomerular filtration rate (GFR). The second clinical vignette described a 14-year-old female with LN class IV; this vignette was repeated verbatim from a 2009 CARRA member survey that was administered prior to development of the CARRA CTP for induction therapy in cSLE LN.

Survey logic was utilized so that only providers who had used EuroLupus for cSLE LN were asked follow-up questions regarding their administration practices and experiences with the EuroLupus protocol. All respondents who had prescribed CYC, however, were asked about their beliefs regarding the advantages and disadvantages of EuroLupus dosing compared to NIH dosing, and all respondents were asked to answer the clinical vignettes.

Outcomes. The primary study outcome was the use of EuroLupus dosing for induction treatment of LN in cSLE. To assess this outcome, providers were asked to report the following: (1) if they had ever administered CYC for cSLE LN (yes/no); (2) how many times they had administered CYC (any protocol) for cSLE LN in the last year (integer value); and (3) how many times they used EuroLupus CYC dosing for cSLE LN in the past year (integer value). Two clinical vignettes were used to assess if and when respondents would choose to use EuroLupus over NIH CYC dosing.

Secondary outcomes included the following: (1) factors that influenced providers' treatment decisions for LN in cSLE; (2) perceived advantages and disadvantages to EuroLupus CYC dosing over NIH CYC dosing; (3) EuroLupus administration protocols (dosing, frequency, hydration) and provider familiarity with the logistics of EuroLupus administration; and (4) provider satisfaction with EuroLupus dosing in cSLE LN.

Recruitment. The survey was distributed by email to provider members of CARRA (n = 421) and to members of the Pediatric Nephrology Research Consortium (PNRC, n = 354) from March to April of 2020. Members were informed that the survey was both anonymous and voluntary and that survey completion implied consent for deidentified answers to be studied in aggregate. Reminders to complete the survey were sent at regular intervals to each of the groups over the course of 2 months.

Respondents. Respondents were categorized as medical doctor/doctor of osteopathic medicine (MD/DO) or nurse practitioner/physician assistant (NP/PA). Due to the small numbers of NP/PA respondents (n = 2) from the CARRA survey, only MD/DO responses were included in the analysis. An additional 7 respondents were excluded because they were no longer actively involved in the treatment of patients with LN. Four respondents practicing outside of North America were also excluded from the analysis.

Respondents were categorized as pediatric rheumatologists or nephrologists. Due to the small numbers of pediatric nephrologists who responded to the CARRA survey (n = 3), only pediatric rheumatologists were included in the CARRA analysis. The 3 pediatric nephrologists responding to the CARRA survey email were analyzed along with the 37 PNRC respondents (100% pediatric nephrology MD/DO, from a member population of 354) for a total of 40 nephrology respondents.

Analysis. Data were analyzed using SAS 9.4 (SAS Institute). Descriptive statistics were used to summarize primary and secondary outcomes. Logistic regression models were constructed to examine the relationship between the binary outcome use of EuroLupus dosing (yes/no) and provider factors that included the following: (1) years in practice (continuous variable); (2) training background (pediatric residency vs combined internal medicine and pediatric residencies); (3) familiarity with the EuroLupus protocol (strongly agree/agree vs strongly disagree/disagree); and (4) an advantages-to-disadvantages composite score of EuroLupus vs NIH dosing, which was calculated for each individual as the number of identified advantages to EuroLupus dosing minus the number of identified disadvantages to EuroLupus dosing.

Bivariate analyses to examine differences in survey responses between provider types (pediatric nephrologist vs pediatric rheumatologist) included

chi-square tests for categorical responses and Wilcoxon rank-sum tests for continuous responses.

RESULTS

Pediatric rheumatology and nephrology providers. There were 185/421 (44%) CARRA member responses included in the analysis (Table 1). Ninety-two percent of the pediatric rheumatology respondents practiced in the US (representing 35 states and the District of Columbia) and 8% of respondents practiced in Canada (representing 5 provinces). The majority of pediatric rheumatology respondents were trained in pediatrics (90%), whereas 10% were trained in internal medicine/pediatrics. Nineteen percent were fellows, compared to 29% faculty in practice for 1–5 years, 27% 6–15 years, and 25% 16+ years. A little over one-third of respondents reported that their colleagues would consider them to be a cSLE expert. Demographics of the 40 pediatric nephrology participants from the PNRC were largely comparable to the pediatric rheumatology respondents (Table 1), with representation from all stages of training, and a slight shift toward midcareer as opposed to late-career faculty in comparison to pediatric rheumatology respondents.

When asked about institutional care models for cSLE patients with LN, 92% of respondents indicated that patients with LN are seen by any of the pediatric rheumatologists within their division, vs 8% who are seen by a subset of pediatric rheumatologists who serve as institutional "lupus experts" (Table 1). Slightly over one-third of institutions indicated that they have a combined "lupus clinic" where patients with cSLE LN are evaluated by both rheumatology and nephrology at the same clinic visit. When asked whether cSLE LN is treated primarily by rheumatology, primarily by nephrology, or comanaged by pediatric rheumatology and pediatric nephrology, the vast majority (77%) indicated that their patients with LN are comanaged, whereas at 17% of institutions pediatric LN is treated primarily by

Table 1. Demographics of survey respondents.

	Pediatric Rheumatologists, CARRA, n = 185	Pediatric Nephrologists, PNRC, n = 40
Years in practice		
Fellow	35 (19)	8 (20)
Faculty		
1–5	53 (29)	9 (23)
6–15	51 (27)	16 (40)
> 16	46 (25)	7 (17)
Training pathway		
Pediatric rheumatology	166 (90)	39 (98)
Internal medicine/pediatrics rheumatology	19 (10)	1 (2)
Practicing both	14 (74)	1 (2)
Practicing pediatrics	4 (21)	0 (0)
Practicing adult	1 (5)	0 (0)
Practice location		
North America		
US	171 (92)	36 (90)
Canada	14 (8)	1 (3)
Other	0 (0)	1 (3)
Did not respond	0 (0)	2 (5)
Perceived as a cSLE expert		
Yes	64 (35)	15 (38)
No	121 (65)	25 (63)
Ever initiated IV CYC		
Yes	172 (93)	34 (85)
No	7 (4)	3 (8)
Did not respond	6 (3)	3 (8)
Structure for seeing LN patients		
Comanagement in a combined clinic	68 (37)	17 (43)
Comanagement, no combined clinic	75 (40)	14 (35)
Rheumatology is primary	32 (17)	1 (2)
Nephrology is primary	9 (5)	8 (20)
Did not respond	1 (1)	0 (0)
Funneling LN to "lupus expert"		
Yes	15 (8)	10 (25)
No	170 (92)	30 (75)

Values are expressed as n (%). CARRA: Childhood Arthritis and Rheumatology Research Alliance; cSLE: childhood-onset systemic lupus erythematosus; CYC: cyclophosphamide; IV; intravenous; LN: lupus nephritis; PNRC: Pediatric Nephrology Research Consortium.

rheumatology and at 5% of institutions pediatric LN is treated primarily by nephrology.

Use of EuroLupus CYC dosing. The majority of CARRA respondents (93%) reported having initiated CYC for pediatric LN. Of those who had prescribed CYC for pediatric LN over the past 12 months (n = 135), half reported having ever used EuroLupus dosing. There was no association between use of the EuroLupus protocol and years in practice, identification as a lupus expert, or training in medicine/pediatrics. There was also no association with having a combined lupus clinic in which patients are seen by both rheumatology and nephrology. There was, however, a strong association between providers who had used EuroLupus dosing in the past and those who indicated familiarity with how to prescribe the EuroLupus protocol (OR 5.2, 95% CI 2.2–12.3, $P = 0.0001$), compared to providers who disagreed or strongly disagreed with being familiar with EuroLupus protocol (Table 2). Seventy-one percent of respondents who indicated familiarity with EuroLupus dosing and administration reported using EuroLupus protocol.

The 40 pediatric nephrologists' responses regarding use of EuroLupus dosing to treat pediatric LN were similar to the pediatric rheumatologists' responses. Although a smaller percentage of nephrologists reported having ever prescribed the EuroLupus regimen (36% vs 50%), this difference was not statistically significant. For nephrology EuroLupus CYC prescribers, there was higher utilization (median 2.4 patients per nephrologist over the last 12 months) compared to pediatric rheumatologists (1.3 patients over the last 12 months); this difference, however, did not reach statistical significance. Overall, pediatric nephrologists indicated less familiarity with EuroLupus dosing: pediatric nephrologists were half as likely to strongly agree, and were 4 times as likely to strongly disagree with familiarity with EuroLupus protocol ($P = 0.01$).

Use of CYC in clinical vignettes. In the survey's first clinical vignette, 60% of respondents chose EuroLupus dosing over NIH dosing for induction treatment of a 16-year-old adolescent with LN class III. When the case specified mild/moderate LN class IV (with normal GFR), 45% of respondents chose EuroLupus dosing over NIH dosing; in contrast, when the case specified severe LN class IV, only 23% chose EuroLupus dosing. Multivariable logistic regression analysis revealed 2 factors associated with choosing EuroLupus dosing over NIH dosing in this vignette: familiarity with the EuroLupus protocol (OR 3.9, 95% CI 1.6–9.4, $P < 0.003$) and a greater advantages-to-disadvantages composite score (OR 1.6, 95% CI 1.3–2.1, $P < 0.0001$).

The second clinical vignette asked respondents to choose between mycophenolate mofetil (MMF) and CYC to be given alongside corticosteroids for induction therapy in a 14-year-old girl with LN class IV. Fifty-three percent of respondents chose CYC vs 39% who selected MMF. The remaining respondents indicated "other" and requested more information before making a treatment decision, while 2 respondents in this group indicated they would choose rituximab (RTX) for treatment (Figure 1). Regardless of initial choice of treatment, respondents were next asked to choose a CYC regimen for this patient; 63% of providers chose NIH dosing, 32% chose EuroLupus dosing, and 5% selected other. Multivariable logistic regression analysis revealed the same 2 factors associated with choosing EuroLupus dosing over NIH dosing in this vignette: familiarity with EuroLupus protocol (OR 4.2, 95% CI 1.5–11.8, $P = 0.006$) and a greater advantages-to-disadvantages composite score (OR 1.6, 95% CI 1.3–2.0, $P < 0.0001$).

The same clinical scenario had been used in a survey that was administered to CARRA providers in 2009. At that time, 79% of respondents chose to initiate therapy with CYC and only 17% had selected MMF. The remaining 4% indicated "other"; of these, 1% chose RTX (Figure 1). When asked about the dosing regimen of CYC, 87% chose the NIH protocol vs 6% who chose EuroLupus dosing. The remaining 7% indicated "other" for dosing regimen.

Perceived advantages, disadvantages, and efficacy of EuroLupus dosing. When asked about advantages of EuroLupus dosing over NIH CYC dosing, the most commonly cited was decreased risk of infertility (63%), followed by decreased infection risk (50%; Table 3). Only 9% of respondents felt there were no advantages of EuroLupus dosing compared to NIH CYC dosing. When asked about the disadvantages of EuroLupus dosing compared to NIH CYC dosing, 61% of respondents pointed to insufficient EuroLupus dosing efficacy data in pediatrics, followed by 54% of respondents who had reservations about fixed dosing in pediatrics, and 43% of respondents who felt there was insufficient data about the efficacy of EuroLupus dosing in Black and Hispanic patients. Only 3% of providers felt there were no disadvantages to EuroLupus dosing as compared to NIH CYC dosing; 41% of respondents identified more advantages than disadvantages. Of pediatric rheumatologists with experience using EuroLupus dosing, 53/68 respondents (78%) perceived the efficacy of EuroLupus and NIH CYC dosing to be equivalent in cSLE LN, with 1 individual (1%) rating EuroLupus dosing as superior and 14 (21%) rating EuroLupus dosing as inferior to NIH dosing.

Table 2. Provider factors associated with use of EuroLupus CYC dosing based on results of logistic regression models.

	OR	95% CI	*P*
Training, pediatrics vs medicine and pediatrics	1.19	0.31–4.62	0.81
Familiarity with EuroLupus dosing	5.24	2.24–12.26	0.0001
Years in practice	1.00	0.96–1.04	0.92
Proportion of benefits vs disadvantages	1.52	1.23–1.87	0.0001

Results from a logistic regression model comparing provider factors for those selecting EuroLupus dosing vs NIH dosing who had prescribed CYC for pediatric lupus nephritis over the past 12 months (n = 135). CYC: cyclophosphamide; NIH: National Institutes of Health.

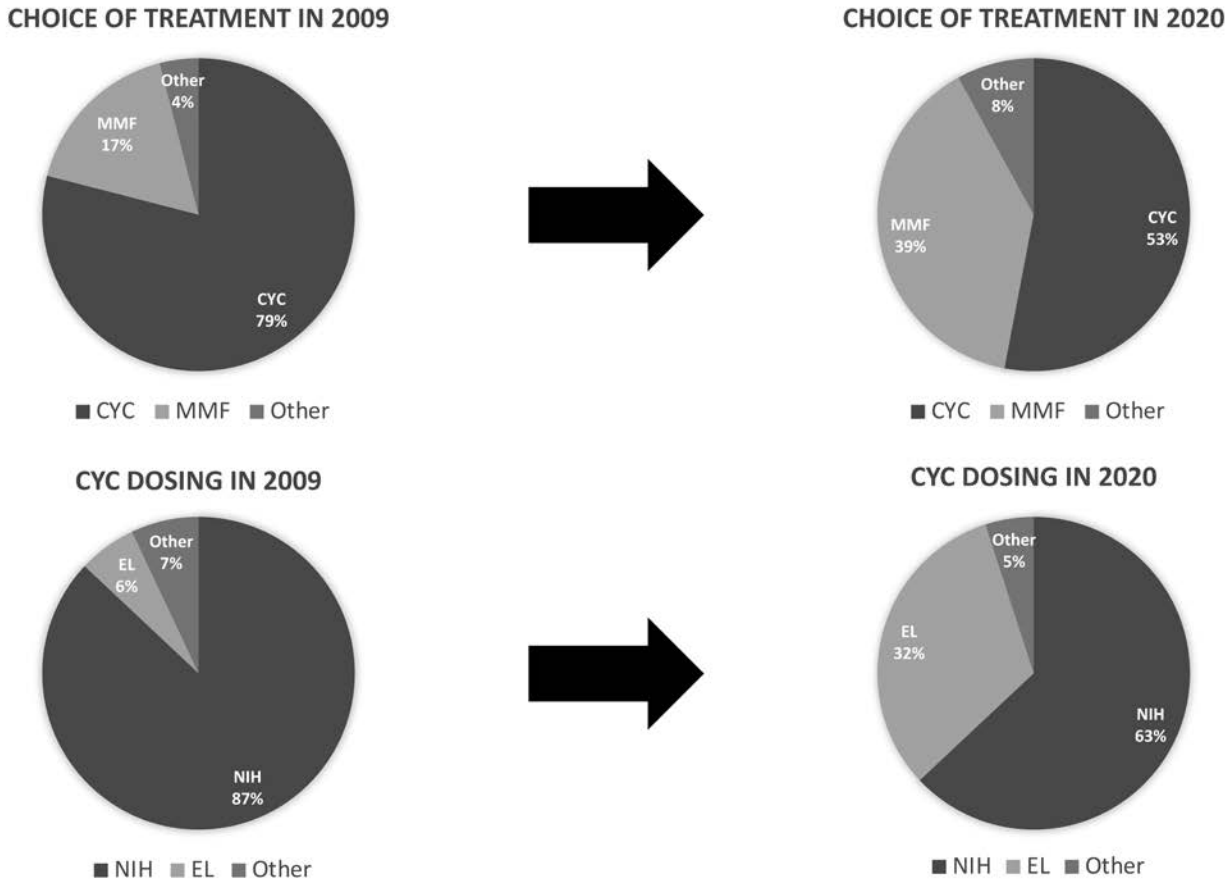

Figure 1. Survey respondents from the CARRA membership (n = 134) were presented with the same clinical vignette that had been posed in 2009 (n = 71) regarding first-line therapy for newly diagnosed systemic lupus erythematosus with class IV lupus nephritis in a 14-year-old girl. CARRA: Childhood Arthritis and Rheumatology Research Alliance; CYC: cyclophosphamide; EL: EuroLupus; MMF: mycophenolate mofetil; NIH: National Institutes of Health.

Similar to pediatric rheumatologists, the majority of pediatric nephrologist respondents (80%) perceived the efficacy of EuroLupus and NIH CYC dosing to be equivalent.

Rationale for choosing NIH over EuroLupus CYC dosing. Providers were asked about patient factors that would influence them to choose NIH over EuroLupus dosing. Fifty percent responded that high-risk renal biopsy features (eg, crescents or tuft necrosis) would lead to the choice of NIH dosing over EuroLupus dosing, and 33% said that impaired renal function would influence them to choose NIH dosing. Twenty-four percent of respondents said they would use NIH dosing over EuroLupus dosing if the patient was non-White. Approximately 20% of respondents indicated they would use NIH dosing for patients who weigh > 120 kg, or < 50 kg. Five percent of respondents would never choose NIH dosing over EuroLupus dosing.

Rheumatologists and nephrologists responded similarly regarding the use of NIH dosing over EuroLupus dosing in patients with high-risk findings on renal pathology: 50% of rheumatologists and 45% of nephrologists indicated that this would be a factor that would influence them to choose NIH dosing. They differed, however, on the use of NIH dosing over EuroLupus dosing in patients with impaired renal function, with fewer nephrologists (3%) compared to rheumatologists (33%) determining this to be a factor leading to the choice of NIH dosing over EuroLupus dosing.

DISCUSSION

Our results demonstrate that pediatric rheumatologists are considerably more likely to use EuroLupus dosing over NIH CYC dosing now as compared to a decade ago. For a vignette about a 14-year-old girl with LN class IV, our survey found that 32% of pediatric rheumatologists would opt for EuroLupus dosing of CYC, vs only 6% of pediatric rheumatologists who were posed the same vignette in 2009. This change over time may be reflective of many factors, including more widespread adoption of EuroLupus dosing outside of Europe for the treatment of adult patients[8,10,11,15,16] as well as the encouraging follow-up outcomes from the Euro-Lupus Nephritis Trial (ELNT), which demonstrated similar renal outcomes between EuroLupus and NIH CYC dosing at 10 years.[17,18] These findings, in addition to pediatric providers acquiring positive experiences with the use of EuroLupus dosing for the treatment of LN in children and adolescents, have likely influenced practice. Indeed, approximately 80% of pediatric providers using EuroLupus dosing, including both pediatric rheumatologists and pediatric nephrologists, consider the effects of EuroLupus

Table 3. Perceived advantages and disadvantages of EuroLupus.

	Pediatric Rheumatologists, n = 185	Pediatric Nephrologists, n = 40
Perceived advantages		
Ease of administration		
Decreased IVF requirements	41 (22)	4 (10)
No need for mesna/leuprolide	31 (17)	6 (15)
No need for nadir labs	43 (23)	6 (15)
Reduced toxicity		
Decreased risk for infection	93 (50)	21 (53)
Decreased risk for malignancy	71 (38)	18 (45)
Decreased risk for infertility	118 (63)	26 (65)
More acceptable to patients		
Decreased nausea/fatigue/alopecia	82 (44)	15 (38)
Less time to complete	36 (19)	8 (20)
More acceptable risk profile	64 (34)	9 (23)
No advantages	16 (9)	2 (5)
Perceived disadvantages		
Insufficient data		
In pediatrics	113 (61)	25 (63)
In Black and Hispanic patients	80 (43)	19 (48)
In comparison to NIH	61 (33)	12 (30)
Increased risk		
Risk of cytopenias/infection	10 (5)	2 (5)
Fixed-dose problematic in pediatrics	105 (54)	19 (48)
Provider knowledge		
Insufficient familiarity with protocol	26 (14)	10 (25)
No disadvantages	6 (3)	0 (0)

Values are expressed as n (%). IVF: intravenous fluid; NIH: National Institutes of Health.

dosing to be comparable to NIH dosing in their personal experiences.

In addition to efficacy, increased adoption of EuroLupus may also be related to other benefits over NIH dosing, including shorter infusion time, the need for less intravenous fluid with administration, and no need for nadir blood counts.[19] EuroLupus CYC dosing is thought to have less effect on ovarian reserve, which is an important consideration for young patients who may require multiple courses of CYC during their lifetime.[20] Respondents most commonly cited decreased risk of infertility and infection as advantages of EuroLupus over NIH-dosed CYC, both of which have been described in the literature as advantages of the EuroLupus regimen.[7,19,21] Patients also experience less nausea when treated with the low-dose EuroLupus protocol, rather than high-dose NIH protocol.[22]

When asked to identify disadvantages of EuroLupus dosing compared to NIH dosing, 43% of pediatric rheumatologists indicated concern that there is insufficient data regarding the efficacy of EuroLupus dosing in Black and Hispanic patients. Although there were limited numbers of Black and Hispanic patients in the ELNT study, and there is evidence suggesting more severe LN in these populations,[23] the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS) addressed this concern. In the control group for ACCESS, the EuroLupus protocol was shown to be as effective in Black (39% of trial participants) and Hispanic (40% of trial participants) adult patients with LN as in the largely non-Hispanic White patients in the historical ELNT cohort,[9] suggesting that high-risk racial and ethnic groups respond equally well to EuroLupus dosing. Our survey data suggests that the implications of ACCESS findings related to EuroLupus dosing's efficacy in Black and Hispanic patients with LN may not be widely known by pediatric rheumatologists.

The major caveat to the mentioned studies, however, is that all were performed on lupus populations consisting almost entirely of adult patients. The treatment of patients with cSLE is unique because the average patient with cSLE LN has more aggressive disease[14] and children have lower body surface area. Drug metabolism is also faster for many medications in young children compared to adult patients, which has been observed in CYC,[24,25] though pharmacokinetic data specifically in adolescents are scarce. These characteristics may interfere with extrapolation of adult EuroLupus dosing outcomes to the cSLE LN population. Children and younger adolescents may also display different risk–benefit profiles with less sensitivity to the reproductive risks of high-dose CYC. Nevertheless, there exists strong rationale for preferring low-dose CYC in cSLE LN, including the potential need for additional courses of CYC over many years of disease and established cumulative toxicities.

Results from our survey indicate that CYC use has declined in popularity as first-line therapy for proliferative LN in cSLE in favor of MMF, with CYC dropping from 79% in 2009 to 53% in 2020. Although MMF was shown to be noninferior to CYC

for induction therapy for LN in the adult population,[26] roughly half of providers continue to use CYC for first-line therapy for proliferative LN. Awareness of the EuroLupus protocol is important to potentially reduce toxicity for patients with cSLE. Given that many providers were not familiar with EuroLupus dosing's clinical benefits or prescribing logistics, education of pediatric rheumatologists and nephrologists could further increase the utilization of EuroLupus dosing and should include both the patient-centered advantages (eg, decreased infection rates, decreased effect on fertility, decreased nausea) and the advantages related to ease of administration (eg, nadir labs not required, less fluids required, mesna not required, less need for GnRH agonists). Some providers have been averse to trying the EuroLupus protocol for fear that the dosing every 2 weeks would be burdensome for families, but those with experience in EuroLupus dosing often find adherence is greater soonest after the diagnosis, such that completing the CYC course in 3 months rather than 6 months confers advantages. While some providers have felt that higher doses of CYC would be beneficial for more severe disease, there is rationale for lower-dose CYC potentially being more effective. Data suggest that profound B cell depletion as seen with higher doses of CYC can result in increased B cell activating factor, which is thought to preferentially drive reemergence of autoreactive B cells during reconstitution of the B cell repertoire.[27,28,29]

There are potential limitations to our study. First, the survey data are self-reported; as such, the data are subject to recall bias. In addition, given the response rate of 44%, it is possible that a higher percentage of members with more expertise and interest in cSLE responded, compared to physicians who are less experienced or less comfortable treating LN, leading to selection bias. The similarity of responses between the pediatric nephrologists and the larger sample of pediatric rheumatologists supports our sampling as being representative. Finally, while the survey is able to describe factors that are associated with provider prescribing patterns, it cannot establish causation.

Despite these limitations, this study included respondents from 35 states and 5 Canadian provinces, and represents the largest published survey of pediatric rheumatologists on the treatment of LN. Further, respondents from small, medium, and large centers across North America with varying practice models and patient populations participated. Survey responses demonstrated a clear change in CYC prescribing practices over the last 10 years, including increased adoption of EuroLupus CYC dosing for cSLE LN. This highlights the need for studies regarding safety, efficacy, and pharmacokinetics of EuroLupus CYC dosing for pediatric patients with proliferative LN.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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