Editorial

Treatment of Childhood-onset Proliferative Lupus Nephritis in the 21st Century: A Call to Catch Up With the Evidence

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Proliferative lupus nephritis (PLN) is associated with significant morbidity, mortality, and kidney failure, especially in childhood-onset PLN (cPLN). Therefore, it is important to treat it promptly and aggressively, while being cognizant of the risk-benefit ratio and side effects of therapies. In 1986, a study that dramatically changed the treatment of PLN was the “National Institutes of Health (NIH) protocol,” which used intravenous (IV) cyclophosphamide (CYC) pulse therapy and became the standard of care for patients with adult-onset (aPLN) and cPLN (none of the patients had cPLN).1 The major limitation to the use of CYC is its side effects, particularly infections, leukopenia, malignancy, and premature ovarian failure; this led to the advent of the lower cumulative dose EuroLupus protocol.2 Subsequently, multiple large randomized controlled trials (RCTs) showed that mycophenolate mofetil (MMF) was as efficacious as IV CYC, with a better safety profile.3,4,5,6

In this issue of The Journal of Rheumatology, Cannon et al7 conducted a Web-based, cross-sectional survey of North American physicians on their prescribing practices for the treatment of cPLN, in the spring of 2020. Preferences for and perceptions of the 2 commonly used IV CYC protocols to treat LN was the primary aim of the study. One must wonder why this was the aim, rather than focusing on the use of IV CYC vs MMF, with the choice of IV CYC protocol as a secondary aim. The survey was distributed through Childhood Arthritis and Rheumatology Research Alliance (CARRA), an international research organization where 90% of North American pediatric rheumatologists are members (185 respondents), and the Pediatric Nephrology Research Consortium (40 respondents) to capture both pediatric rheumatologists and nephrologists who might look after patients with cPLN. This was a follow-up article to the CARRA initial consensus treatment plan (CTP) for induction therapy for cPLN published in 2012, in which 79% of respondents stated the NIH protocol was their chosen first-line treatment for the initial 6-month treatment phase of cPLN, whereas 17% preferred MMF.8

Although limited by multiple biases that come with a survey study, including sampling, nonresponse, acquiescence, recall, and selection,9,10 this study highlights some important points about the care of cPLN in North America. First, there seems to be significant practice variation despite attempts to harmonize treatment strategies.8 There are institutional care models that provide care to children with systemic lupus erythematosus (SLE), including general pediatric rheumatologists and SLE experts/specialists, to multidisciplinary specialized clinics where pediatric rheumatologists and nephrologists cohabit the clinic. Second, there are certain key knowledge gaps in the current literature. Last, there is a surprisingly high use of IV CYC as an induction agent rather than MMF. Multiple RCTs and meta-analyses comparing IV CYC to MMF confirmed that MMF was as efficacious as IV CYC across ethnicities and in patients with low glomerular filtrate rate (GFR); MMF also had a superior safety profile to IV CYC.3,5,6,11,12,13

In a case vignette, the investigators examined practices and changes in practice over the past decade.7 This vignette examined how increasing severity of the renal lesion influenced the choice of IV CYC protocol. When the case was Class III LN, 60% chose EuroLupus, and 45% chose EuroLupus when it was Class IV LN with normal GFR; however, when it was severe Class IV LN, only 23% chose EuroLupus. MMF was not a choice despite...
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7 has highlighted some important considerations and can be adjusted downward using AUC or trough levels to under the concentration-time curve (AUC) and trough levels21,22 therapeutic drug–monitoring laboratories with known target area headaches. MMF concentrations can be measured in many ther-

particularly gastrointestinal complications, or, less commonly, with more “aggressive” disease (rapidly progressive glomeru- lonephritis or having more crescents on biopsy), despite the lack of data to support this as these patients are often excluded from studies. It seems, however, that the adage that “bad disease requires bad medicine” was the motto.

The second vignette examined IV CYC vs MMF. Although there was a decline in the popularity of CYC over MMF the past decade as induction therapy for cPLN, down from 79%8 to 53%, more than half of respondents still chose IV CYC over MMF and 63% chose NIH over EuroLupus protocol, which was an improvement from 94% in 2009.

Provider perceptions of the EuroLupus protocol were assessed in the study. A common misconception regarding EuroLupus dosing is that there are no data regarding efficacy in Black and Hispanic patients, although the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study demonstrated that the EuroLupus protocol was as effective in these patients.15 The current Kidney Disease Improving Global Outcomes (KDIGO) guidelines pointed out that MMF has mostly replaced CYC as first-line treatment of PLN and emphasized that MMF is generally the preferred agent for PLN, including those of Asian, Hispanic, or African ancestry.16 MMF was associated with better renal response as compared to CYC for patients of Black and Hispanic ancestry in a subanalysis of the Aspreva Lupus Management Study.3

Considering 53% of respondents still used CYC,7 there now is a responsibility to increase the use of MMF as first-line induction therapy for LN considering the data from multiple RCTs and metaanalyses showing that MMF is noninferior to IV CYC for induction therapy in adults16,17,18 and keeping in line with current guidelines.16,19 However, if CYC is deemed necessary for reasons of nonadherence or MMF failure, we should encourage use of the EuroLupus dosing over the NIH protocol to reduce toxicities in patients. This recommendation is in keeping with the recently published KDIGO and European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association guidelines that recommend the EuroLupus protocol be the preferred first choice for those treated with CYC, as there is a similar 10-year renal outcome with a better side effect profile.16,19,20 MMF also has side effects, particularly gastrointestinal complications, or, less commonly, headaches. MMF concentrations can be measured in many ther-

apeutic drug–monitoring laboratories with known target area under the concentration-time curve (AUC) and trough levels22,23 and can be adjusted downward using AUC or trough levels to abrogate toxicities.24

The initial CARRA CTP was published in 2012, prior to the more widespread adaptation of the EuroLupus protocol in North America, which may be part of the reason why so many North American centers continued to use the NIH protocol.24 However, could the models of care be a contributing factor to the slow adoption of newer and potentially safer practices, or is the reticence to change reflected in this study? Over 90% of respondents disclosed that patients with cPLN were seen by multiple pediatric rheumatologists within their practice, as opposed to local “lupus experts,” and only approximately one-third of patients with cPLN were seen in a combined SLE clinic with both a pediatric nephrologist and rheumatologist, although 80% were seen by both.27 Could quality of care be enhanced in multidisciplinary specialty SLE clinics as opposed to general rheumatology clinics?25,26 In 2021, a study proposed the use of a 13-point pediatric-specific SLE care metric to drive better quality as well as consistent and consensus-driven care for all children with cSLE.27 In that study, again from a large North American center, only approximately 50% of the patients with cSLE were managed in a dedicated multidisciplinary clinic by specialists.27

So, beyond moving away from CYC to more MMF as initial therapy of cPLN, what is next? Belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator protein in addition to standard therapy of steroids and immunosuppression, was shown to be superior to placebo in patients with active LN28 and has been approved for the treatment of active LN in adult patients in North America and Europe. A study from 2015 suggested that triple immunosuppressive therapy including a calcineurin inhibitor, steroids, and MMF showed a superior renal response after 2 years as compared to the NIH protocol.29 Subsequently, voclosporin (a cyclosporine A analog), following an initial dose-finding study in LN,30 was shown in a placebo-controlled double-blind study in patients with active LN on steroids and MMF to be superior to placebo regarding complete renal response at week 52.31 Other agents expected to alter the playing field for the treatment of LN include B cell–depleting agents, such as rituximab or obinutuzumab, used in addition to MMF and steroids.32,33

This survey7 has highlighted some important considerations for those who treat LN in children and adolescents and may be the beginning of signposting next steps in terms of future studies, knowledge translation and dissemination, and model of care adoption to better ensure quality care for all children with cPLN. As a first step, all physicians treating patients with cPLN need to avail themselves of the current literature and guidelines and proceed with the best evidence-based approach to treatment in 2022 as outlined in this editorial. This is then followed by continual reassessment of therapy based on any new evidence or change in guidelines to ensure ongoing quality care for all patients with cPLN.

REFERENCES


