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Treatment Patterns Among Adults and Children With Membranous Nephropathy in the Cure Glomerulonephropathy Network (CureGN)

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Introduction: The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis recommend that patients with membranous nephropathy (MN) at risk for progression receive immunosuppressive therapy (IST), usually after 6 months of observation. A cyclophosphamide (CYC) or calcineurin inhibitor (CNI)–based regimen is recommended as first-line IST. However, the extent to which KDIGO recommendations are adopted in practice remains largely unknown.

Methods: We evaluated prescribing practice among patients with primary MN (diagnosed 2010–2018) enrolled in the Cure Glomerulonephropathy Network (CureGN) cohort study. We also evaluated the availability of testing for phospholipase A2 receptor (PLA2R) in the contemporary era.

Results: Among 361 patients (324 adults and 37 children) with MN who were IST-naïve at biopsy and had at least 6 months of follow-up, 55% of adults and 58% of children initiated IST <6 months after biopsy. Of these, 1 in 5 had no indication for (i.e., urine protein-to-creatinine ratio [uPCR] <4 g/g) or an apparent contraindication to (i.e., an estimated glomerular filtration rate [eGFR] <30 ml/min per 1.73 m^2) IST. As first-line IST, half of treated patients received either CYC (16% of adults; 0% of children) or a CNI (40% and 46%, respectively), whereas 1 in 5 received corticosteroid monotherapy (20% and 27%, respectively) and 1 in 6 rituximab (15% and 15%, respectively). More than 80% of surveyed centers had access to PLA2R testing.

Conclusion: These findings suggest that providers are not aware of, or lack confidence in, current KDIGO guidelines for MN. Treatment patterns observed in this cohort might critically inform the drafting of planned updates to KDIGO guidelines.

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Primary MN is a leading cause of nephrotic syndrome in adults worldwide but is much rarer in children.[1,2] The clinical presentation and natural history of MN are highly variable, with up to one-third of patients entering remission spontaneously without

treatment,[3,4] but many others experiencing progressive decline in kidney function.[5,6] The KDIGO clinical practice guidelines for MN recommend initiation of IST after 6 months of observation if patients have not entered remission spontaneously,[7] or sooner if severe disease complications develop. However, it is recommended that IST be avoided entirely in patients expected to have a good prognosis without IST (i.e., <4 g/24 hours of proteinuria) or in those whose disease is already too advanced (i.e., those with a serum creatinine >3.5 mg/dl or an eGFR <30 ml/min per 1.73 m^2). The KDIGO guidelines also recommended specific first- and second-line IST approaches based on limited data from randomized controlled trials. However, the extent to which these recommendations regarding the necessity, timing, and choice of IST in MN are adopted in clinical practice remains unknown.

Because KDIGO guidelines for glomerulonephritis were published in 2012, understanding of the pathophysiology and treatment of MN has advanced considerably, in particular since the discovery that M-type PLA2R antibodies are implicated in most cases of primary MN.[8–13] Accordingly, based on a recent KDIGO consensus report, nearly all MN treatment recommendations will have to be revisited.[14] The discovery of anti-PLA2R has also sparked new interest in B-cell–targeted IST strategies for MN.[15,16] However, contemporary practices with respect to testing for PLA2R antigen in biopsy specimens and/or PLA2R antibodies in serum, and prescribing of B-cell–targeted IST strategies, among patients with biopsy-proven primary MN, has not to our knowledge been reported.

Recognizing these knowledge gaps, our study aimed to describe contemporary practice patterns with respect to the timing and choice of IST in adults and children with MN enrolled in the CureGN, to compare observed practice patterns with current KDIGO treatment guidelines, and to determine accessibility to PLA2R antigen/antibody testing among nephrologists caring for patients with MN.

METHODS

Study Design and Population

CureGN is an ongoing international cohort study[17] aiming to enroll 2400 adults and children with minimal change disease, focal segmental glomerulosclerosis, MN, or IgA nephropathy, diagnosed by kidney biopsy within the 5 years before study enrollment. Institutionalized patients, those with end-stage renal disease at screening, or with diabetes, a prior organ/hematopoietic transplant, hepatitis B or C, HIV, malignancy, or systemic lupus erythematosus at time of biopsy, are excluded. Patients are recruited from 70 sites (65 in the United States, 3 in Canada, 1 in Italy, and 1 in Poland) and are identified either through receiving nephrology care at one of these sites or through referral from a primary treating nephrologist in the community. Enrollment and subsequent annual visits are conducted in person; interval 4-monthly study visits can be conducted in person or remotely (i.e., by telephone or e-mail). Research coordinators conduct all study visits and enter data, under the supervision of the site clinical principal investigator.

All children and adults with MN enrolled in CureGN by June 5, 2018, were considered for study inclusion. We restricted our study population to patients who were naïve to IST before kidney biopsy so as to focus on patients we were confident were prescribed IST for management of newly diagnosed glomerular disease and not another indication. However, because it is common practice to treat children with nephrotic syndrome with glucocorticoids (GCs) empirically before performing a kidney biopsy, we regarded children who had received a maximum of 6 weeks of GC monotherapy immediately before kidney biopsy as also being treatment-naïve. All study subjects provided written informed consent. This study was approved by each institutional review board in agreement with the Declaration of Helsinki.

Data Collection and Definitions

Immunosuppressive Medications

At study enrollment, data were collected regarding all ISTs used to treat glomerular disease before study enrollment, including start and stop dates. Thereafter, medication lists were updated at each study visit. We categorized IST as follows: GC alone, CNI-based therapy, CYC-based therapy, rituximab (RTX)-based therapy, mycophenolate mofetil (MMF)–based therapy, or combination IST. If GCs were prescribed concurrently with another IST, we considered this to be therapy based on the other IST. Therapies started within 30 days of one another were considered part of the same regimen.

Other Demographic, Clinical, and Laboratory Measures

We defined adults as those ≥18 years at time of biopsy. Glomerular disease subtypes were defined according to their original biopsy report diagnosis. Whenever available, laboratory values measured between time of symptom onset and time of enrollment were collected and recorded. The eGFR was calculated using the Bedside Schwartz formula in children[18] and the Chronic Kidney Disease–Epidemiology Collaboration formula in adults.[19] There were missing data for race, uPCR, hematuria, serum albumin, and eGFR (see Table 1 for frequencies).

Table 1. Characteristics of IST-naïve patients at the time of biopsy

Characteristics	Adults (n = 324)	Children (n = 37)	P
Age at biopsy (yr)	53 (40, 63)	14 (12, 16)	<0.001
Follow-up time after biopsy (mo)	33 (18, 56)	23 (10, 33)	0.006
Female	122 (38)	21 (57)	0.02
Race			0.08
Asian	28 (9)	1 (3)	
Black/African American	46 (14)	8 (22)	
Native American	1 (0)	1 (3)	
White/Caucasian	235 (73)	23 (62)	
Multiracial	5 (2)	2 (5)	
Unknown	9 (3)	2 (5)	
Hispanic ethnicity	26 (8)	12 (32)	<0.001
uPCR (g/g)	5.9 (3.5, 8.7)	3.0 (1.2, 7.1)	0.005
Unknown	102 (31)	8 (22)	
Hematuria (≥1+)	122 (67[a])	20 (77[a])	0.25
Unknown	141 (44)	11 (30)	
Serum albumin (g/dl)	2.6 (2.1, 3.5)	2.2 (1.6, 3.0)	0.005
Unknown	95 (29)	3 (8)	
eGFR (ml/min per 1.73 m^2)	83 (60, 106)	107 (84, 128)	<0.001
Unknown	66 (20)	4 (11)	
Thromboembolism before biopsy	16 (5)	1 (3)	0.54

eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; uPCR, urinary protein-to-creatinine ratio.
[a]Among those with available urinalysis results from time of kidney biopsy.
Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as n (%).

Alignment With KDIGO Treatment Guidelines

KDIGO clinical practice guidelines for patients with MN recommended IST if urinary protein excretion exceeds 4 g/d AND remains at over 50% of the baseline value AND is not progressively declining, during an observation period of at least 6 months, but some exceptions were described.[7] If IST is indicated, a 6-month course of alternating monthly oral/i.v. GC and oral CYC is recommended; a CNI (cyclosporine or tacrolimus) is suggested for patients intolerant of, or with contraindications to, CYC.

We explored alignment of treatment practices for CureGN participants with MN with KDIGO guidelines, both for the overall cohort (primary analysis) and among patients who underwent kidney biopsy either after July 1, 2012, or after July 1, 2013 (i.e., 0 and 12 months, respectively), after the guidelines were published (sensitivity analysis). Patients who received a first-line IST other than CYC or a CNI were considered to deviate from KDIGO guidelines. Among patients who initiated IST <6 months following kidney biopsy, we examined factors that might appropriately or inappropriately have prompted earlier IST (i.e., severity of proteinuria/hypoalbuminemia, severity of kidney impairment, duration of symptoms >6 months, development of a thromboembolic event). Patients with less than 6 months of follow-up between their biopsy and their most recent study visit were excluded from these analyses.

Survey of Access to PLA2R Testing

A request to complete a survey regarding access to biopsy staining for PLA2R, and serum testing for antibodies to PLA2R, was distributed by e-mail to all CureGN participating centers (n = 70) in May 2018. A reminder e-mail was sent in July 2018. CureGN investigators were asked to complete the survey online. A copy of the survey is provided in the Supplementary Figure S1.

Statistical Analyses

Descriptive analyses were performed using frequencies with percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Unadjusted comparisons across groups (adults vs. children, treated vs. untreated) were made using χ^2 and Kruskal-Wallis testing, as appropriate. Times from biopsy to initiation of first-line IST, stratified by IST regimen, were estimated using the Kaplan-Meier method. Times from first- to second-line IST, and the composition of second-line IST strategies, were also reported. All analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 419 patients (370 adults and 49 children) with MN had been enrolled in CureGN at time of manuscript preparation. Forty-six (12%) of these adults and 12 (24%) of these children received IST (other than a maximum of 6 weeks of corticosteroids, in the case of children) before kidney biopsy and were excluded from our study cohort (Figure 1).

Baseline characteristics at time of biopsy for the 361 adults and children who were treatment-naïve at biopsy are presented in Table 1 (Supplementary Table S1 for data of the entire cohort). Median age at biopsy was 53 (IQR, 40–63) years in adults and 14 (IQR, 12–16) years in children. Female sex was less frequent in adults (38%) than children (57%), P = 0.02. Most adults and children self-reported as white. At biopsy, comparing adults with children, median uPCR was higher (5.9 vs. 3.0 g/g, P = 0.005), and median eGFR was lower (83 vs. 107 ml/min per 1.73 m^2, P < 0.001).

Non-immunosuppressive Therapy Approaches in Adults and Children

Among 324 IST-naïve adults, 93 (29%) were receiving renin-angiotensin-aldosterone system blockade and 76 (23%) were receiving diuretics at time of biopsy. Thereafter, 274 (85%) and 208 (64%) ever received renin-angiotensin-aldosterone system blockade or diuretics, respectively, after a median of 33 (IQR, 18–56) months postbiopsy. Among 37 IST-naïve children, 3 (8%) were receiving renin-angiotensin-aldosterone system blockade

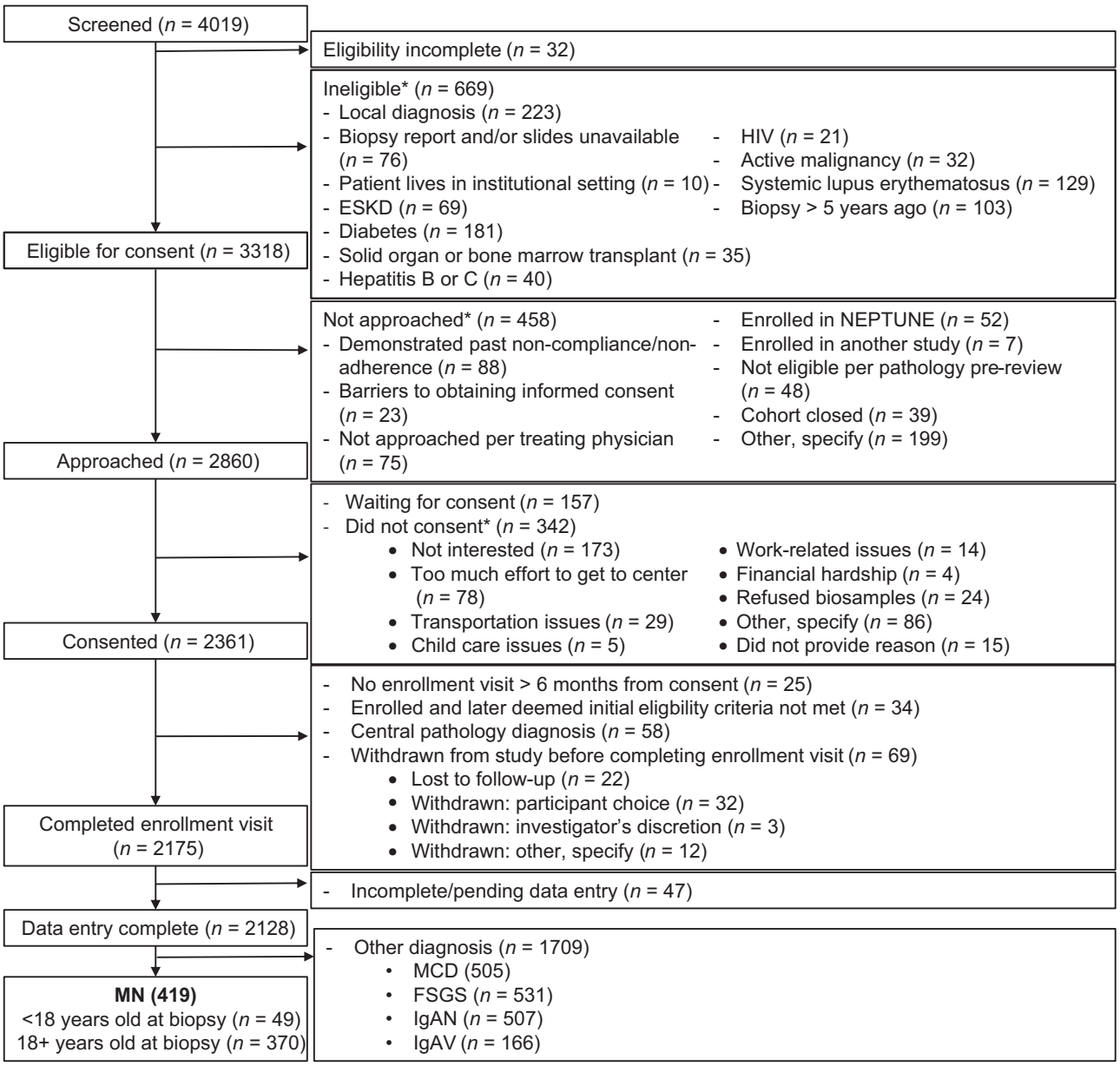

Figure 1. Flowchart of included patients. Data as of June 5, 2018. *Could provide more than 1 reason. ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; IgAV, IgA vasculitis; MCD, minimal change disease; MN, membranous nephropathy; NEPTUNE, Nephrotic Syndrome Study Network.

and 1 (3%) was receiving diuretics at time of biopsy. Thereafter, 27 (73%) and 12 (32%) ever received renin-angiotensin-aldosterone system blockade or diuretics, respectively, after a median of 23 (IQR, 10–33) months.

IST Approaches in Adults

Among 324 IST-naïve adults at time of kidney biopsy, 244 (75%) initiated IST at any time during a median follow-up of 33 (IQR, 18–56) months, and 167 (55%) of the 302 adults with at least 6 months of follow-up after kidney biopsy had initiated IST within the first 6 months following kidney biopsy (Table 2). The median time from biopsy to IST initiation was 4.3 months.

Focusing on any exposure to IST, 176 (54%) of adults were ever exposed to GC, either alone (8%) or consecutively/concurrently (92%) with other IST (Table 2). Thereafter, CNIs, RTX, and CYC were the most frequently prescribed ISTs (44%, 31%, and 27% exposed, respectively), followed by MMF, adrenocorticotropic hormone, and azathioprine (10%, 7%, and <1%, respectively). Single-agent oral GCs were used earliest in the disease course (median 31 days from kidney biopsy; IQR, 9–175 days), followed by CNI-based regimens (Figure 2).

Focusing on first-line IST, CNI-based regimens were the most frequently prescribed (40% of the 244 treated

Table 2. Exposure to IST among adults and children who were IST-naïve at time of kidney biopsy

	Adults (n = 324)	Children (n = 37)	P
Ever treated			
Any IST	244 (75)	26 (70)	0.45
Steroids	176 (54)	21 (57)	0.78
Oral steroids	169 (52)	20 (54)	0.83
I.v. steroids	30 (9)	2 (5)	0.43
Calcineurin inhibitors	142 (44)	16 (43)	0.95
Mycophenolate mofetil	33 (10)	6 (16)	0.26
Cyclophosphamide	87 (27)	1 (3)	0.001
Oral CYC	83 (26)	1 (3)	0.002
I.v. CYC	10 (3)	0 (0)	0.28
Rituximab	102 (31)	6 (16)	0.05
Azathioprine	1 (0)	0 (0)	0.74
ACTH	23 (7)	0 (0)	0.09
RAAS-blockade	274 (85)	27 (73)	0.07
ACE-inhibitors	144 (44)	24 (65)	0.02
Angiotensin receptor blockers	147 (45)	7 (19)	0.002
Diuretics	208 (64)	12 (32)	<0.001
Treated in the first 6 months after biopsy[a]	Adults (n = 302)	Children (n = 31)	
Any IST	167 (55)	18 (58)	0.85
Steroids	112 (37)	12 (39)	0.86
Oral steroids	109 (36)	12 (39)	0.77
I.v. steroids	8 (3)	0 (0)	0.36
Calcineurin inhibitors	86 (28)	11 (35)	0.41
Mycophenolate mofetil	10 (3)	4 (13)	0.01
Cyclophosphamide	47 (16)	0 (0)	0.02
Oral CYC	42 (14)	0 (0)	0.03
I.v. CYC	6 (2)	0 (0)	0.43
Rituximab	31 (10)	3 (10)	0.92
Azathioprine	1 (0)	0 (0)	0.75
ACTH	4 (1)	0 (0)	0.52
RAAS-blockade	172 (57)	17 (55)	0.82
ACE-inhibitors	91 (30)	15 (48)	0.04
Angiotensin receptor blockers	82 (27)	2 (6)	0.01
Diuretics	131 (43)	5 (16)	0.003

ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone; CYC, cyclophosphamide; IST, immunosuppressive therapy; MN, membranous nephropathy; RAAS, renin-aldosterone-angiotensin system.
[a]Cohort restricted to those with at least 6 months of follow-up.
Categorical variables expressed as n (%).

adults; Table 3). Thereafter, 49 patients (20% of treated adults) received single-agent GC for at least 30 days as their first-line IST. Frequency of use as first-line IST was similar for both RTX and CYC (15% and 16% of treated adults, respectively). Other ISTs, including MMF, adrenocorticotropic hormone, and azathioprine, were much less frequently prescribed as a first-line IST (4%, 0%, and 0%, of patients, respectively). Overall, among the 244 adults who ever received IST, only 138 (57%) received either CYC or a CNI. Restricting the cohort to adults biopsied on or after July 1, 2013, did not reveal any meaningful differences (102 of 179 patients, 57%).

Focusing on second-line IST, 118 (48%) of the 244 adults who started a first-line IST ultimately transitioned to a second-line IST, after a median of 5 months (range, 1–71 months) (Supplementary Table S2A). The proportion of patients proceeding to a second-line IST was highest for single-agent GC (71% of patients), intermediary for CNI-, CYC-, or MMF-based regimens (48%, 47%, and 50% of patients, respectively), and lowest for RTX-based regimens (27% of patients), $P < 0.001$. Time from initiation of first-line IST to initiation of second-line IST was shortest for single-agent GC (median, 68 days; IQR, 35–131 days) or MMF-based regimens (median, 64 days; IQR, 45–287 days), and longest for CNI-based regimens (median, 328 days; IQR, 135–622 days). To account for differences in follow-up time between groups, hazards for transitioning to second-line IST were compared across first-line IST groups. Comparing with CYC-based regimens, hazard ratios (HRs) for transitioning to a second-line IST were significantly higher for single-agent GC (HR, 3.4; 95% confidence interval, 1.9–6.0) but similar for other comparator first-line IST strategies: CNI-based HR 1.0 (95% confidence interval, 0.6–1.7), RTX-based HR 0.6 (95% confidence interval, 0.3–1.4), and MMF-based HR 0.9 (95% confidence interval, 0.4–2.4). With respect to the choice of second-line IST, substantial variability was evident (Supplementary Table S2A).

IST Approaches in Children

Among 37 IST-naïve children (allowing inclusion of children with a maximum of 6 weeks of GC monotherapy immediately before kidney biopsy), 26 (70%) initiated IST at any time during a median follow-up of 23 (IQR, 10–33) months, and 22 (59%) of 31 children with at least 6 months of follow-up following kidney biopsy initiated IST within the first 6 months after kidney biopsy. The median time from biopsy to IST initiation was 1.9 months.

Focusing on any exposure to IST, 21 (57%) of 37 children were ever exposed to GC, either alone (24%) or consecutively/concurrently with other treatments (76%; Table 2). Thereafter, CNIs (43%), MMF (16%), and RTX (16%) were the most frequently prescribed ISTs, followed by CYC, adrenocorticotropic hormone, and azathioprine (3%, <1%, and <1%, respectively). Single-agent oral GCs were used earliest in the disease course (median 3 days from kidney biopsy; IQR, −27 to 59 days), followed by RTX- and CNI-based regimens (Figure 2).

Focusing on first-line IST, CNI-based regimens were the most frequently prescribed (46% of the 26 treated children; Table 3). Thereafter, 7 children (27% of treated children) received at least 30 days of single-agent GC as first-line IST: 3 had started GC before kidney biopsy and IST was transitioned to another IST

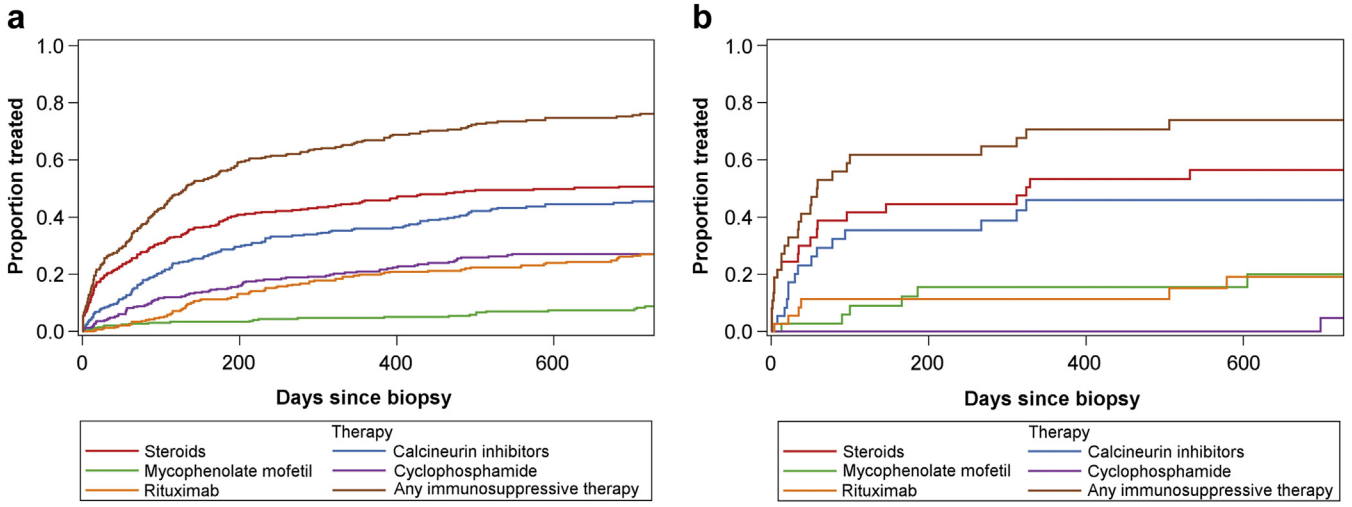

Figure 2. Time to immunosuppressive therapy (IST) initiation after biopsy among adults (a) and children (b) with membranous nephropathy who were IST-naïve at the time of kidney biopsy. Any IST also includes adrenocorticotropic hormone and azathioprine.

within 30 days after biopsy; however, the remaining 4 initiated single-agent GC after confirming a diagnosis of MN by kidney biopsy. Frequency of use as first-line IST was higher for RTX than MMF (15% and 8% of treated children, respectively), whereas CYC, adrenocorticotropic hormone, and azathioprine were much less frequently prescribed as first-line IST (<1% of patients) in children. Overall, among the 26 children who ever received IST, only 12 (46%) received a CNI or CYC (none received CYC), as recommended by KDIGO, as a first-line IST. Restricting the analysis to children who were biopsied on or after July 1, 2013, did not reveal any meaningful differences (11 of 24 children, 46%). Focusing on *second-line IST*, 7 (27%) of the 26 children who started a first-line IST ultimately transitioned to a second-line IST (Supplementary Table S2B).

Table 3. First-line IST in adults and children who were treatment-naïve at time of kidney biopsy

First therapy	*n* (%)	Days from biopsy until onset, median (IQR)	Days from biopsy until onset, range
Adults, $n = 324$			
Never received therapy[a]	80 (25)	N/A	N/A
CNI-based Therapy	98 (30)	88 (18, 202)	2–1700
Steroids alone	49 (15)	31 (9, 175)	0–2049
CYC-based therapy	40 (12)	61 (18, 153)	0–855
Rituximab-based therapy	37 (11)	133 (75, 277)	15–1964
MMF-based therapy	14 (4)	72 (11, 384)	6–1016
Combination of ISTs	6 (2)	69 (26, 132)	14–207
Children, $n = 37$			
Never received therapy[a]	11 (30)	N/A	N/A
CNI-based therapy	12 (32)	43 (15, 173)	4–324
Steroids alone	7 (19)	3 (−27, 59)	−30 to 96
Rituximab-based therapy	4 (11)	37 (20, 272)	4–506
MMF-based therapy	2 (5)	57 (13, 100)	13–100
Combination of ISTs	1 (3)	2 (2, 2)	2–2

ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitor; CYC, cyclophosphamide; IST, immunosuppressive therapy; MMF, mycophenolate mofetil; N/A, not applicable.
[a]Never received any of the following therapies: steroids (oral or i.v.), calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide (oral or i.v.) rituximab, azathioprine, ACTH. A new therapy started within 30 days of a previous therapy is considered to start at the same time.

Comparison of Patients Treated Versus Not Treated With IST During the First 6 Months Following Kidney Biopsy

Restricting the cohort to patients with at least 6 months of follow-up following kidney biopsy ($n = 302$ adults and $n = 31$ children), we compared characteristics between patients who did versus did not initiate IST within the first 6 months following kidney biopsy (Table 4). Aside from a higher proportion of male individuals in the treated group (32% vs. 47% female sex, $P = 0.008$), adults treated with IST within the first 6 months following kidney biopsy were demographically similar to adults who were not treated. However, treated adults had more severe biochemical features of the nephrotic syndrome, with a higher median uPCR (7.0 vs. 3.8 g/g; $P < 0.001$) and a lower median serum albumin (2.3 vs. 3.2 g/dl; $P < 0.001$) at time of biopsy. The proportion of adults with a uPCR 8 to 12 g/g or >12 g/g at biopsy was also higher in the treated group, although 21 (17%) patients who received IST earlier than 6 months following kidney biopsy had a uPCR <4 g/g before IST initiation. The proportion of patients with an eGFR <30 ml/min per 1.73 m^2 was low in both groups (8 [6%] of treated and 7 [7%] of untreated patients, $P = 0.22$). Adults who were treated versus untreated within the first 6 months following biopsy were not any more likely to have had a thromboembolic event (15 [9%] vs. 11 [8%]; $P = 0.80$).

In contrast to the adult population, uPCR and serum albumin levels were very similar among children who

Table 4. Characteristics of adults and children with MN who were IST-naïve at time of kidney biopsy and who had at least 6 months of follow-up after kidney biopsy, comparing those who were treated versus untreated with IST within the first 6 months following kidney biopsy

	Adults (n = 302)			Children (n = 31)		
Characteristics	Treated (n = 167)	Untreated (n = 135)	P	Treated (n = 18)	Untreated (n = 13)	P
Age at biopsy (yr)	53 (42, 63)	53 (40, 63)	0.76	15 (11, 16)	14 (12, 15)	0.70
Follow-up time after biopsy (mo)	33 (19, 54)	40 (22, 60)	0.13	23 (13, 32)	30 (28, 38)	0.05
Time from biopsy to IST	1 (0, 3)	N/A	N/A	2 (0, 3)	N/A	N/A
Time from symptom onset to IST	5 (3, 8)	N/A	N/A	1 (0, 1)	N/A	N/A
More than 6 mo from symptom onset to IST	61 (37)	N/A	N/A	2 (11)	N/A	N/A
Female	53 (32)	63 (47)	0.008	9 (50)	9 (69)	0.28
Race			0.70			0.22
Asian	15 (9)	12 (9)		0 (0)	1 (8)	
Black/African American	27 (16)	17 (13)		4 (22)	3 (23)	
Native American	0 (0)	1 (1)		0 (0)	1 (8)	
White/Caucasian	120 (72)	98 (73)		13 (72)	5 (38)	
Multiracial	2 (1)	2 (1)		1 (5)	1 (8)	
Unknown	3 (2)	5 (4)		0 (0)	2 (15)	
uPCR at biopsy (g/g)	7.0 (4.9, 9.6)	3.8 (2.1, 6.0)	<0.001	3.3 (1.2, 7.4)	3.4 (1.3, 4.6)	0.60
<4	21 (17)	42 (53)		7 (50)	7 (70)	
4–7.9	53 (43)	27 (34)		4 (29)	2 (20)	
8–11.9	35 (28)	7 (9)		1 (7)	1 (10)	
≥12	15 (12)	4 (5)		2 (14)	0 (0)	
uPCR before IST onset (g/g)	6.9 (5.0, 9.5)	N/A	N/A	5.8 (1.0, 8.7)	N/A	N/A
<4	20 (17)	N/A	N/A	5 (36)	N/A	N/A
4–7.9	51 (44)	N/A	N/A	5 (36)	N/A	N/A
8–11.9	30 (26)	N/A	N/A	1 (7)	N/A	N/A
≥12	14 (12)	N/A	N/A	3 (21)	N/A	N/A
Hematuria (≥1+) at biopsy[a]	71 (75)	38 (54)	0.04	11 (92)	6 (67)	0.33
Serum albumin at biopsy, g/dl	2.3 (1.9, 3.0)	3.2 (2.5, 4.0)	<0.001	2.3 (1.6, 3.0)	2.1 (1.8, 3.0)	0.88
eGFR at biopsy, ml/min per 1.73 m^2	81 (57, 103)	88 (62, 108)	0.22	116 (89, 133)	100 (84, 114)	0.52
eGFR at biopsy <30	8 (6)	7 (7)		1 (6)	0 (0)	
Thromboembolism						
Before biopsy	8 (5)	7 (5)	0.88	0 (0)	0 (0)	0.99
In 6 mo postbiopsy[b]	7 (4)	4 (3)	0.58	1 (5)	0 (0)	0.39

eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; MN, membranous nephropathy; N/A, not applicable; uPCR, urinary protein-to-creatinine ratio.
[a]Among those with hematuria data at biopsy.
[b]Among those without thromboembolism before biopsy.
Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as n (%).

were treated versus untreated in the 6 months following kidney biopsy. Restricting to patients who were biopsied after July 1, 2012, or July 1, 2013, did not reveal any meaningful differences in median time to first IST, the proportion of patients who received IST within 6 months following kidney biopsy, or the proportion of patients who received either a CYC- or CNI-based regimen as first-line IST (although fewer patients received MMF and more received RTX in the more recent eras), despite overall similar laboratory measures of disease severity when compared with earlier cohorts (Supplementary Table S3).

Survey of Access to PLA2R Testing

A total of 31 centers (44%) responded to the survey between May 22, 2018 and August 21, 2018. They were all from the United States and Canada. Most (n = 26, 84%) routinely used anti-PLA2R blood testing, although only 7 of the 26 (27%) performed the testing locally. The earliest reported introduction date for anti-PLA2R blood testing was January 2014. PLA2R antigen staining by kidney biopsy was also used routinely in most centers (n = 25, 81%). In contrast to blood testing, most centers (21 of 25, 84%) performed this testing locally. The earliest reported introduction date for PLA2R antigen testing by kidney biopsy was June 2013.

DISCUSSION

In this international cohort of 419 prevalent adults and children with MN enrolled in CureGN, we identified frequent and early use of IST and generally poor alignment with KDIGO clinical practice guidelines. Among the 361 patients (324 adults and 37 children) who were treatment-naïve before kidney biopsy, more than half initiated IST within 6 months after kidney biopsy, despite KDIGO recommendations to "watch and wait" for at least 6 months to observe for spontaneous remission. Among those patients who ever

received IST (75% of adults and 70% of children), only 57% of adults and 46% of children received a CYC- or a CNI-based regimen as first-line IST, despite KDIGO recommendations to use these agents as first- and second-line IST, respectively. We further identified GC monotherapy as first-line IST for MN in a significant proportion of patients (20% of treated adults and 27% of treated children), despite proven inefficacy for MN.[20] Not surprisingly, the response rate for GC monotherapy as first-line IST also appeared to be poorer than for other ISTs within our cohort (71% of adults required a second-line agent, with an HR for requiring transition to a second-line agent of 3.4 when compared with CYC).

In this cohort, the median time from biopsy to IST initiation in adults was 4.3 months. When exploring possible explanations for earlier than recommended use of IST, we identified a number of findings. Among adults, 37% of patients who were treated earlier than 6 months following kidney biopsy had reported symptoms of nephrotic syndrome for longer than 6 months; thus, nephrologists might have been satisfied that the patient had already failed to enter remission spontaneously after 6 months of observation. Next, many of the adults treated earlier than 6 months after kidney biopsy had heavy proteinuria at the time of kidney biopsy (40% of treated vs. 14% of untreated patients had a uPCR of $\geq$8 g/g), and serum albumin was also lower in the treated group (median 2.3 vs. 3.2 g/dl): thus, severe and symptomatic nephrotic syndrome might have triggered IST initiation in these patients. Finally, 9% of patients treated with IST earlier than 6 months following kidney biopsy had experienced a thromboembolic event before or in the 6 months following kidney biopsy, representing a strong indication to initiate IST without delay. Overall, 44% of the 167 adults treated within the first 6 months after kidney biopsy had 1 or more identifiable relative indication for earlier IST initiation (i.e., symptom duration >6 months, a uPCR $\geq$8 g/g, or a thromboembolic event), whereas 30% lacked any of these indications (representing potential deviations from KDIGO guidelines), and 26% had insufficient data for evaluation (i.e., missing symptom duration or uPCR data). Conversely, 20% of adults treated <6 months after biopsy had no indication for, or a possible contraindication to, IST initiation according to KDIGO guidelines (17% had a uPCR <4 g/g at biopsy, and 6% had an eGFR <30 ml/min per 1.73 m^2 at biopsy, whereas 15% satisfied both these criteria). No significant differences between children treated versus untreated with IST in the first 6 months following kidney biopsy were identified, and numbers were too small to derive meaningful conclusions regarding guideline adherence.

Our study is not without limitations. First, because much of our data came from chart extraction and patient interview regarding events that happened before study enrollment, we can only speculate regarding the exact reasons for earlier use of IST or IST choice. Although we could extract information regarding biochemical features of nephrotic syndrome, eGFR, and thromboembolic events for most patients, laboratory data were missing for some patients and severity of symptoms was missing for all patients, hampering our ability to truly determine the appropriateness of decisions whether and when to treat with IST. Nevertheless, we hypothesize that use of CNIs as first-line therapy in almost one-third of patients might have influenced the decision to start IST earlier than recommended, as CNIs are generally considered safer than CYC. Indeed, CYC was used rarely in our study population, especially in children, whereas RTX (which, at the time these patients were treated, had only been studied in case reports and series) was used more frequently than expected. It is worth noting, however, that some of the patients enrolled in CureGN were also enrolled in the MENTOR study of RTX use in MN.[16] Conceivably, in a treatment era that appears to have moved away from CYC as first-line IST for MN, in favor of "less toxic" CNI- or RTX-based regimens, a 6-month waiting period as recommended by KDIGO might be considered too long for many nephrologists and their persistently nephrotic patients. Indeed, the experience of CureGN participants highlights a potential need to reconsider current guideline recommendations regarding IST timing and choice. Finally, the influence of anti-PLA2R antibody levels on decisions regarding IST necessity and timing requires further exploration: although we did collect data regarding the general availability of testing for PLA2R at study sites, we did not collect data on whether testing was performed, and how it influenced decision-making, in each of the individual study participants.

Our study also illuminates understanding of MN treatment patterns in children, in whom MN is rare and randomized controlled treatment trials are lacking.[21,22] Indeed, treatment recommendations for children with MN are extrapolated from adult data, despite higher rates of spontaneous remission, lower rates of PLA2R positivity,[23,24] and more favorable renal outcomes[25,26] in children compared with adults. Uncertainty with respect to IST choice in children with MN is reflected in the wide variety of first-line IST choices observed in this cohort. Children rarely received CYC, which we hypothesize is due to concerns for toxicity, including

sterility. Further, the lack of discernible differences between children who were versus were not treated with IST within the first 6 months following biopsy suggests that consensus regarding indications for early treatment with IST in children is lacking. Accordingly, CureGN is now uniquely positioned to prospectively monitor outcomes and treatment responses in children with MN, which in turn can inform future clinical trials.

To conclude, we have described practice patterns with respect to the timing and choice of IST among a large cohort of adults and children with biopsy-proven MN. We report that only half of treated patients received a CNI- or CYC-based regimen as first-line IST, that 1 in 5 treated patients received GC monotherapy as first-line IST, and that RTX was more frequently prescribed than CYC in our patient cohort, representing apparent major deviations from KDIGO guidelines. Further, we report that more than half of patients in our cohort initiated IST <6 months following kidney biopsy: while many of these patients had an apparent indication for earlier treatment (i.e., symptoms for more than 6 months, severe nephrotic syndrome, or a thromboembolic event), 1 in 5 had an apparent contraindication to receiving IST (i.e., a uPCR <4 g/g or an eGFR <30 ml/min per 1.73 m^2). We consider these findings to represent a lack of awareness of, or confidence in, current KDIGO guidelines, factors that should be considered when updating these guidelines. Finally, we report widespread access to PLA2R testing among CureGN investigators and propose that future treatment guidelines incorporate available data regarding the role of PLA2R testing in determining the necessity and timing of IST initiation.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Copy of survey of access to PLA2R testing.

Table S1. Characteristics at the time of biopsy, including all patients irrespective of whether or not IST was received before kidney biopsy.

Table S2A. Transitions from first- to second-line IST among adults with MN who were treatment-naïve at time of kidney biopsy ($n = 324$).

Table S2B. Transitions from first- to second-line IST among children with MN who were treatment-naïve at time of kidney biopsy ($n = 37$).

Table S3. Characteristics of adults and children with MN who were treatment-naïve at time of kidney biopsy and who had at least 6 months of follow-up after kidney biopsy, comparing those who were treated versus untreated with IST within the first 6 months following kidney biopsy. Limited to kidney biopsies on or after July 1, 2013.

STROBE Checklist.

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