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ORIGINAL ARTICLE

Identification of Biomarkers That Predict Response to Treatment of Lupus Nephritis With Mycophenolate Mofetil or Pulse Cyclophosphamide

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Objective. **There is a need to identify clinical characteristics and/or biomarkers that can predict treatment outcome in lupus nephritis. To this end, we utilized data from the Aspreva Lupus Management Study to identify possible baseline and early predictors of renal response to mycophenolate mofetil (MMF) or intravenous (IV) cyclophosphamide (CYC).**

Methods. **Patients with class III–V lupus nephritis were randomized to MMF or IV CYC. We assessed predictors of renal response, including baseline demographic, clinical, laboratory, and histologic characteristics, as well as early clinical and laboratory data, obtained within the first 2 months of therapy. Odds ratios (ORs) and 95% confidence intervals for renal response were calculated for each putative predictor.**

Results. **Normalization of C3, C4, or both by week 8 was strongly predictive of renal response at week 24 (ORs 2.5, 2.6, and 2.9, respectively; $P < 0.05$). Reduction in proteinuria by ≥25% by week 8 was predictive of renal response at week 24 (OR 3.2, $P < 0.05$). Reduction in anti–double-stranded DNA (anti-dsDNA) by week 8 was not predictive of renal response. Only 3 baseline characteristics (C4 level, time since diagnosis of lupus nephritis, and estimated glomerular filtration rate [GFR]) were predictive of renal response; the remaining characteristics (age, age at lupus nephritis onset, time since diagnosis of systemic lupus erythematosus, sex, histopathologic class, anti-dsDNA antibody level, C3 level, level of proteinuria, and use of angiotensin-converting enzyme inhibitors, statins, or hydroxychloroquine) were not.**

Conclusion. **This study demonstrates that baseline C4 level, time since diagnosis of lupus nephritis, baseline estimated GFR, early normalization of complement, and reduction in proteinuria independently predict renal response to therapy at 6 months.**

INTRODUCTION

Lupus nephritis is a common manifestation of systemic lupus erythematosus (SLE) that contributes to significant morbidity and mortality. Although the prognosis of lupus nephritis has improved over the past few decades, 10–15% of patients still progress to end-stage renal disease within 10 years (1). The heterogeneous and unpredictable nature of nephritis along with the potential toxicity associated with treatment have spurred great interest in identifying clinical or biologic factors that predict renal outcome and response to therapy. In this regard, two types of characteristics might provide useful renal prognostic information: baseline factors that are present at the initiation of therapy and changes in biologic indicators of disease activity during the early stages of treatment. Identification of these factors might aid in the prediction of overall responsiveness to treatment as well as help predict which patients will respond to a particular therapy. The over-

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arching hope is that a patient's treatment regimen might eventually be tailored according to early prognostic information. In this way, risks of prolonged and toxic therapy can be lessened.

To address these issues, we analyzed data from the Aspreva Lupus Management Study (ALMS), one of the largest randomized controlled trials to date for the treatment of lupus nephritis. ALMS is an international trial of 370 patients with class III–V lupus nephritis comparing pulse monthly intravenous (IV) cyclophosphamide (CYC) to mycophenolate mofetil (MMF) for the induction of renal response (2,3). The data from this trial provided a rare opportunity to analyze a large population of prospectively followed, well-characterized, ethnically diverse lupus nephritis patients who were treated with two commonly used immunosuppressive agents.

PATIENTS AND METHODS

Study design. ALMS was a randomized, open-label, multinational, multicenter clinical trial. Details of the study design have been previously published (2,3). The institutional review boards at each participating center approved the study. All of the study subjects gave written informed consent prior to randomization.

Patients. Patients were eligible for the study if they had a biopsy-proven diagnosis of class III–V lupus nephritis within 6 months of study entry. Patients with class III or V nephritis must have had proteinuria of at least 2 gm/day. Exclusion criteria included treatment with MMF or IV CYC within the previous year, continuous dialysis for >2 weeks before study entry, and pulse IV corticosteroids within 2 weeks of study entry.

Treatment protocol. Patients were randomized in a 1:1 fashion to receive oral MMF or IV CYC. MMF was initiated at a dose of 500 mg twice daily, increased to 2 gm/day in week 2, and then to a maximum of 3 gm/day at week 3. IV CYC was administered as monthly infusions of 0.5–1.0 gm/m^2 according to the National Institutes of Health protocol for a total of 24 weeks. All of the patients received prednisone starting at a maximum dosage of 60 mg/day. The prednisone dosage was decreased by 10 mg/day every 2 weeks until a dosage of 40 mg/day was reached, and then by 5 mg/day every 2 weeks until a dosage of 10 mg/day was reached. Angiotensin-converting enzyme (ACE) inhibitors were permitted, but were to remain at a stable dose throughout the trial period. The protocol did not outline specific guidelines about blood pressure control, the use of lipid-lowering medications, or the use of hydroxychloroquine.

Trial outcome measures. The primary efficacy outcome measure was renal response at 24 weeks as defined in the following manner: a decrease in the urine protein to creatinine ratio on a 24-hour collection to <3 in patients with baseline nephrotic range proteinuria, or by ≥50% in patients with subnephrotic range proteinuria, and stabilization or improvement in serum creatinine levels. Responder status was assessed by a clinical end points committee.

Baseline predictors of renal response. Prior to analyzing the ALMS data, we selected several demographic, clinical, serologic, and histopathologic factors that we hypothesized might predict renal response in the entire intent-to-treat (ITT) population and within each treatment arm. These characteristics included: age, age at lupus nephritis onset, time since diagnosis of lupus nephritis, time since diagnosis of SLE, sex, renal biopsy class, estimated glomerular filtration rate (GFR), 24-hour urine protein to creatinine ratio, anti–double-stranded DNA (anti-dsDNA) antibody concentration, C3 and C4 complement levels, presence of anticardiolipin antibodies, and background medication (including the use of an ACE inhibitor, hydroxychloroquine, or a statin) (Table 1). In a previous analysis of race and ethnicity, Isenberg et al reported that patients of African descent and Hispanic patients were more likely to respond to MMF than IV CYC (4). We therefore did not include race and ethnicity in our list of possible baseline predictors.

For the purpose of statistical analysis, continuous independent variables were recoded into categories. For age, these were ≤20 years, 21–30 years, 31–40 years, and ≥41 years. For time since diagnosis of lupus nephritis, these were <1 year, 1–5 years, and ≥6 years. For time since diagnosis of SLE, the categories were <1 year, 1–4 years, and ≥5 years. For baseline proteinuria, the categories were based on the urine protein to creatinine ratio on a 24-hour collection: ≤1, >1 to 3, and >3. Hypocomplementemia was defined as a C3 level of <90 mg/dl or a C4 level of <16 mg/dl; anti-dsDNA antibody level was categorized as <30, 30–60, >60 to 200, or >200 IU/ml, and the presence of anticardiolipin IgG antibody was defined as a titer of ≥10 mg/dl.

Improvement in biologic factors within the first 8 weeks of treatment. In addition to the baseline factors described above, we identified several indicators that we hypothesized might provide early clues regarding the likelihood of success in meeting the primary outcome measure of the ALMS trial. Specifically, we determined if normalization of complement C3 or C4 levels or both, improvement in proteinuria, or improvement in anti-dsDNA levels at week 8 predicted renal response at week 24 in the ITT population. The C3 and C4 analysis was restricted to those subjects with a low complement at baseline, defined as a C3 level of <90 mg/dl or a C4 level of <16 mg/dl. Reduction in proteinuria was defined as a decrease of ≥25%. Reduction in anti-dsDNA was defined as a decline to ≤60 IU/ml for subjects with baseline anti-dsDNA of >200 IU/ml or to ≤30 IU/ml for subjects with baseline anti-dsDNA of ≤200 IU/ml.

Statistical analysis. The number and percentage of responders and nonresponders were calculated for each factor, overall and by treatment group. Univariate odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using SAS, version 9.2, PROC LOGISTIC (5). Analyses were conducted on an ITT basis; all randomized

Table 1. Baseline demographics and disease characteristics of patients, by renal response*

	All subjects (n = 370)	Responders (n = 202)	Nonresponders (n = 168)
Age, years			
≤20	50 (14)	31 (15)	19 (11)
21–30	124 (34)	63 (31)	61 (36)
31–40	120 (32)	69 (34)	51 (30)
≥41	76 (21)	39 (19)	37 (22)
Age at diagnosis of lupus nephritis, years			
≤20	76 (21)	45 (22)	31 (18)
21–30	132 (36)	71 (35)	61 (36)
31–40	105 (28)	53 (26)	52 (31)
≥41	57 (15)	33 (16)	24 (14)
Females	313 (85)	175 (87)	138 (82)
Renal biopsy class			
III only	23 (6)	7 (3)	16 (10)
III and V	35 (9)	23 (11)	12 (7)
IV only	27 (7)	12 (6)	15 (9)
IV and V	225 (61)	129 (64)	96 (57)
V only	60 (16)	31 (15)	29 (17)
Proteinuria (n = 360), mg			
≤1,000	32 (9)	16 (8)	16 (10)
>1,000 to 3,000	130 (36)	69 (35)	61 (37)
>3,000	198 (55)	112 (57)	86 (53)
Estimated GFR <30 ml/minute per 1.73 m^2 (n = 369)	32 (9)	6 (3)	26 (15)
Anti-dsDNA antibody (n = 358), IU/ml			
<30	58 (16)	31 (16)	27 (17)
30 to <60	51 (14)	30 (15)	21 (13)
60–200	97 (27)	54 (28)	43 (26)
>200	152 (42)	80 (41)	72 (44)
Complement C3 level <90 mg/dl (n = 361)	272 (75)	152 (77)	120 (74)
Complement C4 level <16 mg/dl	234 (63)	138 (70)	96 (59)
Anticardiolipin antibody ≥10 mg/dl	67 (18)	36 (18)	31 (18)
Concurrent treatment†			
ACE inhibitor treatment	167 (45)	90 (45)	77 (46)
Statin treatment	53 (14)	30 (15)	23 (14)
Hydroxychloroquine treatment	99 (27)	50 (25)	49 (29)
Time since lupus nephritis diagnosis, years			
<1	236 (64)	143 (71)	93 (55)
1–5	80 (22)	29 (14)	51 (30)
≥6	54 (15)	30 (15)	24 (14)
Time since SLE diagnosis, years			
<1	149 (40)	92 (46)	57 (34)
1–4	94 (25)	47 (23)	47 (28)
≥5	127 (34)	63 (31)	64 (38)

* Values are the number (percentage). GFR = glomerular filtration rate; anti-dsDNA = anti–double-stranded DNA; ACE = angiotensin-converting enzyme; SLE = systemic lupus erythematosus.
† Assessed at the first study drug administration. More than one concurrent medication is possible.

patients with at least one posttreatment evaluation were included, with missing information from followup assessments imputed by carrying forward data from the last nonmissing observation. ORs and 95% CIs for renal response were calculated for each putative predictor in the overall study population and within each treatment group.

In order to ascertain the extent to which the statistically significant predictors were independent of each other, we conducted a multivariable logistic regression analysis. Our candidate covariates included all significant predictors from the univariate regressions. To avoid multicolinearity, we examined a correlation matrix of all candidate covariates; groups of covariates that were more correlated with each other than response to treatment were inspected to identify the covariate that was most highly correlated with response to treatment. All other covariates in the group were excluded from the multivariable regression. In order to ascertain whether the predictors included in the regression were independent of race and ethnicity, we ran a second multivariable logistic regression that also included race and ethnicity.

RESULTS

Baseline predictors of response. A total of 370 patients were enrolled in the ALMS, and 306 patients (82.7%)

Table 2. Univariate baseline predictors of responsiveness for the entire ITT population*

	N	Renal response, no. (%)	OR (95% CI)
Age, years			
≤20 (ref.)	50	31 (62)	–
21–30	124	63 (51)	0.6 (0.3–1.2)
31–40	120	69 (58)	0.8 (0.4–1.6)
≥41	76	39 (51)	0.6 (0.3–1.3)
Age at diagnosis of lupus nephritis, years			
≤20 (ref.)	76	45 (59)	–
21–30	132	71 (54)	0.8 (0.5–1.4)
31–40	105	53 (50)	0.7 (0.4–1.3)
≥41	57	33 (58)	0.9 (0.5–1.9)
Sex			
Male (ref.)	57	27 (47)	–
Female	313	175 (56)	1.4 (0.8–2.5)
Renal biopsy class			
III/III and V (ref.)	58	30 (52)	–
IV/IV and V	252	141 (56)	1.2 (0.7–2.1)
V only	60	31 (52)	1.0 (0.5–2.1)
Proteinuria (n = 360), mg			
≤1,000 (ref.)	32	16 (50)	–
>1,000 to 3,000	130	69 (53)	1.1 (0.5–2.5)
>3,000	198	112 (57)	1.3 (0.6–2.8)
Estimated GFR (n = 369), ml/minute per 1.73 m^2			
≥30 (ref.)	337	195 (58)	–
<30	32	6 (19)	0.2 (0.1–0.4)
Anti-dsDNA antibody (n = 358), IU/ml			
<30 (ref.)	58	31 (53)	–
30–60	51	30 (59)	1.2 (0.6–2.7)
>60 to 200	97	54 (56)	1.1 (0.6–2.1)
>200	152	80 (53)	1.0 (0.5–1.8)
Complement C3 level (n = 361), mg/dl			
≥90 (ref.)	89	46 (52)	–
<90	272	152 (56)	1.2 (0.7–1.9)
Complement C4 level (n = 360), mg/dl			
≥16 (ref.)	126	59 (47)	–
<16	234	138 (59)	1.6 (1.1–2.5)
Anticardiolipin antibody, mg/dl			
<10 (ref.)	303	166 (55)	–
≥10	67	36 (54)	1.0 (0.6–1.6)
Concurrent treatment†			
No ACE inhibitor treatment (ref.)	203	112 (55)	–
ACE inhibitor treatment	167	90 (54)	0.9 (0.6–1.4)
No statin treatment (ref.)	317	172 (54)	–
Statin treatment	53	30 (57)	1.1 (0.6–2.0)
No hydroxychloroquine treatment (ref.)	271	152 (56)	–
Hydroxychloroquine treatment	99	50 (51)	0.8 (0.5–1.3)
Time since lupus nephritis diagnosis, years			
<1 (ref.)	236	143 (61)	–
1–5	80	29 (36)	0.4 (0.2–0.6)
≥6	54	30 (56)	0.8 (0.4–1.5)
Time since SLE diagnosis, years			
<1 (ref.)	149	92 (62)	–
1–4	94	47 (50)	0.6 (0.4–1.0)
≥5	127	63 (50)	0.6 (0.4–1.0)

* ITT = intent-to-treat; OR = odds ratio; 95% CI = 95% confidence interval; GFR = glomerular filtration rate; anti-dsDNA = anti–double-stranded DNA; ACE = angiotensin-converting enzyme; SLE = systemic lupus erythematosus.
† Assessed at the first study drug administration. More than one concurrent medication is possible.

completed the 6-month induction treatment period. Demographic and clinical baseline characteristics of the study population are summarized in Table 1, and have been described previously (3).

Baseline predictors of responsiveness are shown in Table 2. Slightly more than 50% of the subjects in each treatment group met the criteria for a renal response at 24 weeks (3). The baseline characteristics of age, age at lupus nephritis onset, time since diagnosis of SLE, sex, histopathologic class, anti-dsDNA antibody level, complement C3 level, level of proteinuria, or use of ACE inhibitors, statins, or hydroxychloroquine were not predictive of renal response at 24 weeks. Only 3 baseline characteristics, i.e., low estimated GFR, time since diagnosis of lupus nephritis, and C4 levels, correlated with renal response. Only 19% of individuals with an estimated GFR of <30 ml/minute per 1.73 m^2 responded to therapy, whereas 58% of those with an estimated GFR of ≥30 ml/minute per 1.73 m^2 responded (OR 0.2, 95% CI 0.1–0.4). Thirty-six percent of subjects with a time since diagnosis of lupus nephritis of 1–5 years responded to therapy compared to 61% of subjects with a time since diagnosis of lupus nephritis of <1 year (OR 0.4, 95% CI 0.2–0.6); however, the rate of response for subjects with a duration of lupus nephritis of ≥6 years (56%) was similar to subjects with a duration of <1 year, and the OR for that comparison (0.8) was not statistically significant. Among subjects with a low baseline C4 level (<16 mg/dl), 59% met the response criteria as compared to 47% of the patients with a normal C4 level (OR 1.6, 95% CI 1.1–2.5).

Early improvement in biologic parameters as predictors of renal response. A rapid decline in proteinuria was the strongest early predictor of the likelihood of meeting the response criteria at 24 weeks (Table 3). Overall, 204 patients had a decline in proteinuria of ≥25% within the first 8 weeks of treatment. Among these subjects, 68% went on to meet the criteria for a renal response at 24 weeks. In contrast, among 141 subjects who did not experience a 25% decline in proteinuria within 8 weeks, only 40% went on the meet the response criteria (OR 3.2, 95% CI 2.1–5.1). Among hypocomplementemic subjects, early normalization of C3 and/or C4 was also predictive of a better outcome. Among patients who normalized their C3 within 8 weeks, 72% went on to achieve a renal response, compared to a response rate of 51% in patients who did not immediately correct their C3 (OR 2.5, 95% CI 1.4–4.2). Similarly, among patients who normalized their C4 within 8 weeks, 73% ultimately achieved a renal response, compared to 51% in patients whose C4 concentration did not correct within 8 weeks (OR 2.6, 95% CI 1.5–4.5). Reduction in proteinuria and normalization of complement levels were equally predictive of renal response in the MMF and IV CYC subgroups. Reduction in anti-dsDNA antibody at week 8 was not predictive of renal response at week 24 (Table 3). The positive predictive values of reduction in proteinuria, normalization of C3, normalization of C4, and normalization of C3 and C4 at 8 weeks for a renal response at 24 weeks were 68%, 72%, 73%, and 76%, respectively.

ORs for early improvement markers, stratified by treatment group, are shown in Table 4. Similar relationships between each factor and renal response were evident for both groups; however, stronger relationships existed within the IV CYC group, in which all of the statistically significant relationships described in Table 3 persisted. The MMF group did not exhibit statistically significant relationships for normalization of C4 or C3 when examined separately.

Table 3. Early improvement in biologic parameters as predictors of renal response for the entire ITT population*

Characteristic	N	Renal response, no. (%)	OR (95% CI)
Reduction in proteinuria†			
Yes	204	139 (68)	3.2 (2.1–5.1)
No	141	56 (40)	
Normalization of C3‡			
Yes	99	71 (72)	2.5 (1.4–4.2)
No	162	82 (51)	
Normalization of C4‡			
Yes	100	73 (73)	2.6 (1.5–4.5)
No	129	66 (51)	
Normalization of C3 and C4‡			
Yes	86	65 (76)	2.9 (1.7–5.2)
No	199	102 (51)	
Reduction in anti-dsDNA§			
Yes	136	81 (60)	1.2 (0.8–2.0)
No	151	82 (54)	

* ITT = intent-to-treat; OR = odds ratio; 95% CI = 95% confidence interval; anti-dsDNA = anti–double-stranded DNA.
† Reduction in proteinuria analysis restricted to subjects with nonmissing protein results at baseline and week 8. Proteinuria reduction is defined as a decrease of 25% or more.
‡ Normalization of complement analyses restricted to subjects with low complement levels (C3: <90 mg/dl, C4: <16 mg/dl) at baseline and a nonmissing value at week 8.
§ Reduction in anti-dsDNA analysis restricted to subjects with anti-dsDNA >30 IU/ml at baseline and a nonmissing value at week 8. Anti-dsDNA reduction is defined as ≤30 IU/ml at week 8 for individuals with baseline ≤200 IU/ml, and ≤60 IU/ml at week 8 for individuals with baseline >200 IU/ml.

Multivariable analysis. We entered all of the significant baseline and early improvement predictors into a correlation matrix that also included response at 24 weeks (data not shown) in order to identify variables to be excluded to avoid multicollinearity. All of the complement variables correlated more closely with each other than with the outcome variable, so we only included the variable that had the highest correlation with the outcome variable (normalization of C3 and C4 at week 8) in the multivariable logistic equation. The following covariates were included: baseline estimated GFR <30 ml/minute per 1.73 m^2, time since diagnosis of lupus nephritis (1–5 years versus <1 year and ≥6 years versus <1 year), >25% reduction in proteinuria at week 8, and normalization of C3 and C4 at week 8. The results are shown in Table 5 (model 1); listwise deletion of observations with missing values for any of the covariates resulted in the exclusion of 98 observations from the analysis (26% of the entire sample). All 4 covariates remained statistically significant in the multivariate analysis, with only a slight attenuation in the ORs for reduction in proteinuria (2.7 versus 3.2) and normalization of C3 and C4 (2.6 versus 2.9) when compared to the univariate analyses, and estimates for the other two ORs remaining constant. The similarities in parameter estimates and statistical significance for these covariates indi-

Table 4. Early improvement in biologic parameters as predictors of renal response for the entire ITT population, stratified by treatment arm*

Characteristic	MMF N	MMF Renal response, no. (%)	MMF OR (95% CI)	IV CYC N	IV CYC Renal response, no. (%)	IV CYC OR (95% CI)
Reduction in proteinuria†						
Yes	110	75 (68)	3.0 (1.6–5.8)	94	64 (68)	3.4 (1.8–6.4)
No	63	26 (41)		78	30 (38)	
Normalization of C3‡						
Yes	51	36 (71)	2.0 (0.9–4.2)	48	35 (73)	3.0 (1.4–6.4)
No	73	40 (55)		89	42 (47)	
Normalization of C4‡						
Yes	48	33 (69)	1.5 (0.7–3.3)	52	40 (77)	4.2 (1.9–9.2)
No	57	34 (60)		72	32 (44)	
Normalization of C3 and C4‡						
Yes	41	31 (76)	2.6 (1.2–5.9)	45	34 (76)	3.3 (1.5–7.2)
No	96	52 (54)		103	50 (49)	
Reduction in anti-dsDNA§						
Yes	63	39 (62)	1.3 (0.6–2.5)	73	42 (58)	1.2 (0.6–2.4)
No	78	44 (56)		73	38 (52)	

* ITT = intent-to-treat; MMF = mycophenolate mofetil; IV = intravenous; CYC = cyclophosphamide; OR = odds ratio; 95% CI = 95% confidence interval; anti-dsDNA = anti–double-stranded DNA.
† Reduction in proteinuria analysis restricted to subjects with nonmissing protein results at baseline and week 8. Proteinuria reduction is defined as a decrease of 25% or more.
‡ Normalization of complement analyses restricted to subjects with low complement levels (C3: <90 mg/dl, C4: <16 mg/dl) at baseline and a nonmissing value at week 8.
§ Reduction in anti-dsDNA analysis restricted to subjects with anti-dsDNA >30 IU/ml at baseline and a nonmissing value at week 8. Anti-dsDNA reduction is defined as ≤30 IU/ml at week 8 for individuals with baseline ≤200 IU/ml, and ≤60 IU/ml at week 8 for individuals with baseline >200 IU/ml.

cate that they are independent predictors of response at week 24. When we added the race/ethnicity variable into the multivariable equation (model 2), the parameter estimates were almost identical to model 1. We therefore concluded that all 4 covariates of interest were also independent of race and ethnicity as predictors of response at week 24.

Table 5. Baseline and early improvement parameters as predictors of renal response (multivariable models) for the entire ITT population (n = 272)*

Characteristic	Model 1, OR (95% CI)	Model 2, OR (95% CI)
Time since lupus nephritis diagnosis, years		
<1 (ref.)	–	–
1–5	0.3 (0.2–0.6)	0.3 (0.1–0.6)
≥6	0.6 (0.3–1.4)	0.7 (0.3–1.6)
Estimated GFR <30 ml/minute per 1.73 m^2	0.2 (0.1–0.6)	0.2 (0.1–0.5)
Reduction in proteinuria†	2.7 (1.5–4.6)	2.9 (1.6–5.1)
Normalization of C3 and C4‡	2.6 (1.4–4.9)	2.7 (1.4–5.0)

* Model 1 was adjusted by all of the characteristics included in table; model 2 was adjusted by all of the characteristics included in table and race/ethnicity. ITT = intent-to-treat; OR = odds ratio; 95% CI = 95% confidence interval; GFR = glomerular filtration rate.
† Reduction in proteinuria analysis restricted to subjects with nonmissing protein results at baseline and week 8. Proteinuria reduction is defined as a decrease of 25% or more.
‡ Normalization of complement analyses restricted to subjects with low complement levels (C3: <90 mg/dl, C4: <16 mg/dl) at baseline and a nonmissing value at week 8.

DISCUSSION

The objectives of our current analysis of data from the ALMS trial of MMF versus IV CYC for the induction treatment of lupus nephritis were to identify baseline predictors of response to treatment and to determine if early improvement in biologic parameters after the institution of treatment predicted treatment response. We found that a rapid decline (>25%) in proteinuria within the first 8 weeks of treatment correlated strongly with achieving the response criteria at 24 weeks. Similarly, in patients who were hypocomplementemic at baseline, rapid restoration of normal serum complement levels was also predictive of a positive outcome. In contrast, early changes in anti-dsDNA concentration did not distinguish eventual responders from nonresponders.

With the exception of estimated GFR, time since diagnosis of lupus nephritis, and complement C4 level, the baseline characteristics proved not to be helpful in predicting response to therapy. These characteristics included age, age at lupus nephritis onset, time since diagnosis of SLE, sex, degree of proteinuria, anti-dsDNA antibody level, complement C3 level, the presence of anticardiolipin antibody, or background therapy with ACE inhibitors, statins, or hydroxychloroquine. These observations extend a recent report indicating that even his-

topathologic class did not predict outcome in the ALMS trial (6).

Interestingly, baseline C4 but not C3 correlated with treatment response. One possible explanation for this difference is that a low baseline C4 level might be reflective of underlying C4 deficiency and not consumption of C4. It is well known that C4 deficiency is common in patients with SLE; approximately 10% of people with complete C4 deficiency have SLE. We did not have access to genetic material for the ALMS subjects. Therefore, we were not able to determine if C4 deficiency played a role in our study findings.

Several studies have examined the prognostic benefit of early response to therapy in lupus nephritis. An analysis of 86 patients with lupus nephritis randomized to prednisone and oral CYC with or without plasmapheresis in the Lupus Nephritis Collaborative Study determined that resolution of serum creatinine elevation by week 48 predicted a favorable renal response at 100 weeks (7). Another study of 85 patients with lupus nephritis showed that response of proteinuria over the first year of treatment predicted long-term renal outcome (8). Finally, an analysis of 90 patients participating in the Euro-Lupus Nephritis Trial of low-dose IV CYC versus high-dose IV CYC for the induction treatment of lupus nephritis revealed that a decrease in serum creatinine and proteinuria of <1 gm/day at 6 months predicted long-term renal outcome to 10 years (9,10).

A major strength of our study is that we utilized data from ALMS, one of the largest controlled trials for the treatment of lupus nephritis. This ethnically diverse trial included patients that traditionally have poorer renal outcomes such as African American patients and patients with renal insufficiency. Unlike some other large-scale lupus nephritis trials, ALMS included patients with any combination of proliferative and/or membranous nephritis. A limitation of our study is that ALMS was designed to evaluate the induction phase of treatment with a 24-week timeframe. It is likely that 24 weeks is not long enough to determine a renal response to induction therapy with IV CYC or MMF. For example, one prior study suggested that the median time to renal response with IV CYC is 10 months (11). It is possible that with a longer followup period, baseline predictors such as the use of ACE inhibitors or statins might become more important. Therefore, it will be interesting to extend our analysis as more data become available from the maintenance phase of ALMS. Another limitation of our study is that it is a post hoc analysis. Although we identified the variables of interest prior to analyzing the data, none of our analyses was prespecified at the outset of the trial.

In conclusion, our study demonstrates that baseline C4 level, time since diagnosis of lupus nephritis, baseline estimated GFR, early normalization of complement, and reduction in proteinuria independently predict renal response to therapy at 6 months. However, despite the ability to define serologic and clinical predictors of renal response, the associations identified in this study are not sufficiently strong to influence therapeutic decision making in individual patients. Better biomarkers are needed to help define which patients will and will not respond to a particular treatment for lupus nephritis. The hope is that such prognostic information will enable us to provide more individualized care to our patients with lupus nephritis, thus resulting in better patient outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Dall'Era had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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