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CLINICAL RESEARCH

Long-Term Follow-Up of Cyclical Cyclophosphamide and Steroids Versus Tacrolimus and Steroids in Primary Membranous Nephropathy

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Introduction: Kidney Disease: Improving Global Outcomes (KDIGO) 2012 recommends cyclical cyclophosphamide plus glucocorticoids (GC) (modified Ponticelli regimen) or calcineurin inhibitors (CNIs) such as tacrolimus (TAC) or cyclosporine as the first-line agents for the management of primary membranous nephropathy (PMN) that is resistant to antiproteinuric therapy with renin-angiotensin system blockers. However, the long-term outcome of patients treated with CNIs is not known.

Methods: We report the outcomes of 70 patients randomized 1:1 to receive modified Ponticelli regimen or TAC/GC for renin-angiotensin system–resistant PMN who were prospectively followed for 6 years. Patients were followed monthly for 12 months, then quarterly for 12 months, and then every 6 months through the end of 6 years.

Results: At the end of 6 years, 21 (61.76%) and 9 (28.12%) patients maintained relapse-free remission in modified Ponticelli regimen and TAC/GC groups, respectively (relative risk [RR]: 2.19, 95% confidence interval [CI]: 1.23 to 4.15), and 30 (88.23%) and 17 (53.12%) patients were in remission (including relapses) in modified Ponticelli regimen and TAC/GC groups (RR: 1.66; 95% CI: 1.21 to 2.45), respectively. There was no significant difference in the proportion of patients who had a 40% decline in the estimated glomerular filtration rate (eGFR), death, or end-stage kidney disease between the groups. None of the patients treated with modified Ponticelli regimen reported a solid organ or hematological malignancy.

Conclusions: To conclude, in the long-term, modified Ponticelli regimen is superior to TAC/GC as first-line therapy for the management of antiproteinuric-resistant PMN.

Kidney Int Rep (2021) **6,** 2653–2660; https://doi.org/10.1016/j.ekir.2021.07.028
KEYWORDS: calcineurin inhibition; cyclophosphamide; modified Ponticelli regimen; PLA2R; primary membranous nephropathy; tacrolimus

See Commentary on Page 2537

PMN is the most common cause of adult-onset nephrotic syndrome in India.[1] KDIGO 2012 recommends either cyclical cyclophosphamide/glucocorticoids (modified Ponticelli regimen) or CNIs as first-line therapy for the management of antiproteinuric therapy-resistant PMN.[2–4]

At least two studies evaluated the long-term outcome of PMN patients treated for 6 months with cyclical alkylating therapy and glucocorticoids.[5,6] Both studies highlighted the positive impact of this approach in preventing chronic kidney disease-grade 5 dialysis dependent in patients with PMN compared to no immunosuppressive therapy.[5,6] In contrast, data are lacking regarding the long-term outcome of patients treated with CNIs. There are at least three randomized trials in PMN that compared the remission rates using

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Received 17 June 2021; revised 19 July 2021; accepted 26 July 2021; published online 10 August 2021

cyclical cyclophosphamide–based therapy or placebo to CNI-based therapy[7-9]; however, none of these reported the long-term outcomes. We studied this issue and previously reported remission rates of 71% and 77% at 12 months in tacrolimus/steroids (TAC/GC) and modified Ponticelli regimen-treated patients, respectively.[10] At the end of 24 months, 43% and 80% of the patients who received TAC/GC and modified Ponticelli regimen as initial therapy, respectively, maintained relapse-free remission.[10,11] Patients treated with CNIs are at risk of relapse after cessation of the drug. In addition, patients treated with cyclophosphamide continued to go into remission even after stopping the drug. Because CNIs are nephrotoxic, it is important to understand the long-term outcome of patients initially treated with CNIs. To address this evidence gap, we report the outcomes in an extended 6-year follow-up of a cohort of PMN patients randomized to receive TAC/GC or modified Ponticelli regimen,[11] focusing on relapse rates and long-term adverse events.

MATERIALS AND METHODS

Patient Selection

The present report is the 6-year follow-up of patients randomized according to the modified Ponticelli regimen and TAC/GC at the Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. Briefly, participants were those fulfilling the diagnosis of PMN on histology and were resistant to antiproteinuric treatment or who were having complications of the nephrotic syndrome.[11] Patients having clinical features/serology suggestive of secondary membranous nephropathy and those with serum creatinine >2.5 mg/dl were excluded.[11] The current report is an investigator-initiated study (CTRI/2013/10/004061) and approved by the Institute Ethics Committee (INT/IEC/16/901). Patients provided written informed consent, and the study conduct was according to the Good Clinical Practice guidelines.

Therapy

Patients were randomized to receive sufficient TAC to maintain a trough level of 5 to 10 ng/ml (mean: 7.46 ng/ml) for 12 months plus oral prednisolone (0.5 mg/kg per day for 6 months), or alternating cyclical cyclophosphamide (2 to 2.5 mg/kg per day) (months 2, 4, and 6), and GC (methyl prednisolone 1 g intravenous from days 1 to 3 and oral prednisolone (0.5 mg/kg) from days 4 to 30 (month 1, 3, and 5) as previously described.[11] The cumulative dose of oral cyclophosphamide did not exceed 180 mg/kg per day. All the patients continued to receive antiproteinuric treatment in the form of renin-angiotensin system blockers with or without statins. After the first year of therapy, treatment was at the discretion of the treating nephrologist. The eGFR was calculated as per the Modified Diet in Renal Disease formula.[12]

Highlights

Seventy patients were enrolled in the primary study that ran from September 2011 to December 2013. The 6-year follow-up of the last patient was completed in December of 2019. Patients who relapsed following the withdrawal of TAC were treated with either modified Ponticelli regimen or rituximab, except for one patient who received azathioprine and GC. Patients who received modified Ponticelli regimen and relapsed were given a second course of modified Ponticelli regimen or rituximab. Patients who did not achieve an initial remission with TAC/GC or modified Ponticelli regimen were treated interchangeably with modified Ponticelli regimen or TAC or rituximab.

Definitions

Nephrotic syndrome was defined as a proteinuria of >4 g/day or ≥2.0 g/day (if serum albumin was< 2.5 g/dl) with hypoalbuminemia and edema.[5,11] Complete remission (CR) and partial remission (PR) were as per the KDIGO guidelines.[2,3] Relapse is defined as a nephrotic range for proteinuria following any remission (CR or PR). Anti–M-type phospholipase A_2 receptor antibodies (anti-PLA2R) were measured in most patients, and a titer of >14 RU/ml was considered positive.[13] Relapse-free remission was considered for remission (either CR or PR) without any further relapse of nephrotic syndrome. Patients were considered to be therapy resistant if they did not achieve CR or PR at any time during the study. Clinicoserological dissociation is when patients (PLA2R-related PMN) with resistant disease despite negative anti-PLA2R antibodies or clinical remission with persisting autoantibodies (>14 RU/ml).

Statistical Analysis

Patients lost to follow-up were deleted from any further analysis. Categorical values were presented as absolute values or percentages. The analysis for relapse-free remission was performed using a Pearson chi square or Fisher exact test to estimate RR and 95% CIs. For other additional analysis unpaired Student *t* tests or Pearson chi square tests were used to compare two groups as appropriate. Nonparametric data were compared with the Mann–Whitney test. A simple linear regression was performed to see the association between the changes in eGFR levels over time in two groups of patients. Time to event (relapse) analysis was performed with Kaplan-Meier survival curve and the magnitude of effects reported as hazard ratios (Cox-

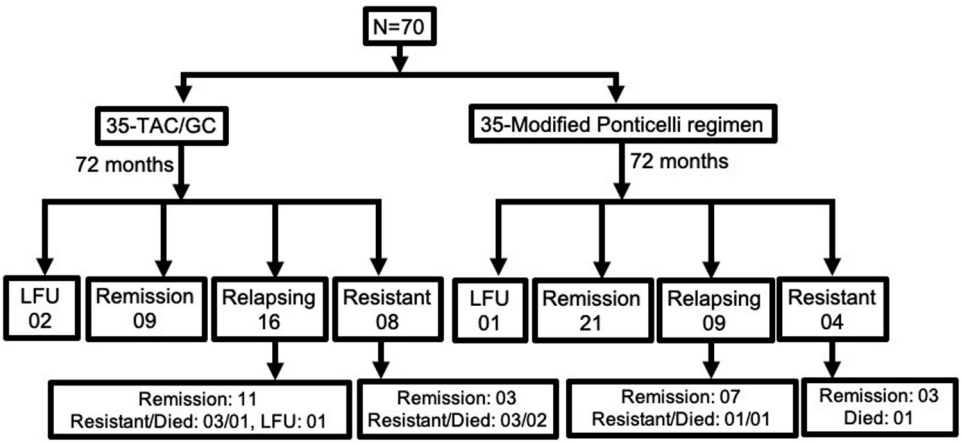

Figure 1. Study outcome.

regression). eGFR loss was defined as loss of eGFR of 30% or more between years 1 and 6. Logistic regression analysis was used to test the association between eGFR loss (≥30% between years 1 and 6) with disease status (resistant, relapse, or CR/PR), persistent proteinuria (2 g/day at more than six time points from years 1 to 6), initial therapy (TAC/GC or modified Ponticelli regimen), and eGFR at the end of year 1. Statistical analyses were using Graph Pad Prism 8 (San Diego, California, USA) IBM SPSS Statistics for Windows, Version 23.0 (IBM, Armonk, New York, USA), and Stata 12.0, 2011 (StataCorp LP, College Station, Texas, USA). A two-sided P value < 0.05 was considered significant.

RESULTS

Of the 35 patients randomized to each group, 30 in the modified Ponticelli regimen group and 25 in the TAC/GC group were in remission at 1 year or later.[10,11] Four (5.71%) patients were lost to follow-up, three in year 1 (two from the TAC/GC group and one from the modified Ponticelli regimen group) and one patient was lost to follow-up from the TAC/GC group at 24 months. The baseline parameters of both groups were comparable.[11] At 1 year, 71% and 77% of the patients from each group were in remission, respectively. The patients were then observed over a 72-month period post-randomization. Beyond 1 year, none of the patients treated with TAC/GC remitted, but three additional patients treated with the modified Ponticelli regimen went into remission.[10] Relapses were observed in 16 and 9 patients treated with TAC/GC and the modified Ponticelli regimen, respectively. At the end of 6 years, 21 (61.76%) and 9 (28.12%) patients in the modified Ponticelli regimen and TAC/GC arms, respectively, had relapse-free remission and did not require any additional therapy to maintain remission (Figure 1). The RR for maintenance of remission was 2.19 with a 95% CI of 1.23 to 4.15 in favor of the modified Ponticelli regimen over TAC/GC (Table 1). At last follow-up (78.5 ± 17.8, median 84 months), 20 (57%) and 9 (26%) never relapsed (RR: 2.09, 95% CI: 1.16 to 3.97) in the modified Ponticelli regimen and TAC/GC groups, respectively. At the end of 6 years, 30 (88.23%) and 17 (53.12%) of patients were in remission in the modified Ponticelli regimen and TAC/GC groups (RR: 1.66; 95% CI: 1.21 to 2.45), respectively. At the end of last follow-up (median: 84 months), 30 (88.23%) and 23 (71.85%) of patients were in remission in the modified Ponticelli regimen and TAC/GC groups (RR: 1.22; 95% CI: 0.96 to 1.64), respectively. Among the patients in remission, CR rates at 6 years were higher in the modified Ponticelli regimen compared to the TAC/GC-treated patients (RR: 1.61: 95% CI: 0.93 to 3.20) (Table 1).

Proteinuria, Serum Albumin, and Creatinine

The proteinuria, serum albumin, and serum creatinine levels at various time points are shown in Table 1. The median proteinuria was significantly higher in the TAC/GC compared to the modified Ponticelli regimen group at 36, 48, and 60 months and at 6 years (Table 1). Proteinuria began to diverge between treatment arms at 12 months. The serum albumin was significantly lower in the TAC/GC group compared to the modified Ponticelli regimen groups at 48 months and 6 years (Table 1). No patients developed chronic kidney disease –G5D by 6 years. Results from linear regression suggest no difference in mean eGFR levels at 6 years compared to 1 year in both TAC/GC ($P = 0.09$) and modified Ponticelli regimen ($P = 0.23$). On logistic regression analysis, disease status at 6 years was not predictive of 30% glomerular filtration rate loss (odds ratio: 3.09; 95% CI: 0.46 to 20.8; $P = 0.246$). Approximately 70% patients from the TAC/GC group received rituximab or modified Ponticelli regimen in the follow-up. Persistent proteinuria (odds ratio: 0.19; 95% CI: 0.3 to 1.49), eGFR at 1 year (odds ratio: 0.96; 95% CI: 0.92 to 1.02), and

Table 1. Clinical details at various time points

Trial entry	TAC/GC	Modified Ponticelli regimen
Age, years	38.6 ± 11.3 (18 - 60)	40 ± 10.6 (18 - 58)
M:F	27: 08	20:15
Anti-PLA2R positive	24 (69)	24 (69)
Baseline[11]	N = 35	N = 35
Proteinuria, g/day	6.29 (4.00 - 9.00)	4.70 (3.87 - 7.00)
Serum albumin, g/dl	2.10 (1.80 - 2.40)	2.20 (1.80 - 2.63)
Serum creatinine, mg/dl	0.80 (0.70,1.01)	0.80 (0.7,1.10)
1 year	N = 33	N = 34
Proteinuria, g/day	0.38 (0.22 - 1.89)	0.44 (0.21 - 1.80)
Serum albumin, g/dl	3.82 ± 0.64 (2.10 - 4.75)	3.86 ± 0.51 (2.60 - 4.80)
Serum creatinine, mg/dl	1.04 ± 0.29[a] (0.70 - 1.90)	0.90 ± 0.19[b] (0.60 - 1.70)
2 years	N = 33	N = 34
Proteinuria, g/day	1.54 (0.21 - 3.05)	1.18 (0.16 - 1.72)
Serum albumin, g/dl	3.69 ± 0.77[c] (2.16 - 4.74)	4.06 ± 0.53[d] (2.20 - 4.97)
Serum creatinine, mg/dl	0.99 ± 0.25 (0.7 - 1.95)	0.93 ± 0.18 (0.79 - 1.70)
3 years	N = 29	N = 32
Proteinuria, g/day	0.60[e] (0.26 - 2.34)	0.23[f] (0.15 - 0.74)
Serum albumin, g/dl	4.15 ± 0.68 (2.99 - 5.30)	4.10 ± 0.52 (2.60 - 4.92)
Serum creatinine, mg/dl	0.98 ± 0.25 (0.70 - 1.90)	0.91 ± 0.22 (0.70 - 1.70)
4 years	N = 29	N = 32
Proteinuria, g/day	0.42 (0.23 - 1.55)	0.25 (0.12 - 0.87)
Serum albumin, g/dl	3.90 ± 0.59[g] (2.12 - 4.92)	4.8 ± 0.39[h] (3.40 - 4.96)
Serum creatinine, mg/dl	1.00 ± 0.39 (0.70 - 2.30)	0.93 ± 0.25 (0.60 - 1.80)
5 years	N = 29	N = 32
Proteinuria, g/day	1.24[i] (0.30 - 3.10)	0.35[j] (0.20 - 1.37)
Serum albumin, g/dl	3.98 ± 0.64 (2.06 - 4.96)	4.15 ± 0.52 (2.35 - 5.10)
Serum creatinine, mg/dl	1.07 ± 0.59 (0.40 - 3.60)	0.90 ± 0.27 (0.60 - 1.70)
6 years	N = 29	N = 32
Proteinuria, g/day	2.71[k] (0.30 - 4.26)	0.26[l] (0.16 - 0.95)
Serum albumin, g/dl	3.84 ± 0.67[m] (2.20 - 4.79)	4.29 + 0.56[n] (2.90 - 5.50)
Serum creatinine, mg/dl	1.09 ± 0.44[o] (0.70 - 2.60)	0.92 ± 0.22[p] (0.60 - 1.70)
Relapse-free remission at 6 years	09 (28.12)[q]	21 (61.76)[r]
Complete remission	07 (21.87)	16 (47.06)
Partial remission	02 (06.25)	05 (14.70)
Remission (including relapses) at 6 years	17 (53.12)[s]	30 (88.23)[t]
Complete remission	07 (21.87)	20 (58.82)
Partial remission	10 (31.25)	10 (29.41)

F, female; GC, glucocorticoids; M, male; PLA2R, phospholipase A_2 receptor antibodies; TAC, tacroliumus.
Values are shown as median (interquartile range) or n (%). At the diagnosis of primary membranous nephropathy. a*b 0.02, c*d 0.02, e*f 0.009, g*h 0.03, i*j 0.02, k*l<0.001, m*n 0.006, o*p 0.05, q*r 0.007 and s*t 0.002.

initial therapy (odds ratio: 1.25; 95%. CI: 0.16 to 9.89) did not predict eGFR loss of 30% or more from years 1 to 6.

Relapsing Disease

At the last follow-up, a total of 26 patients (25 at 6 years) relapsed after achieving a CR or PR (at or after year 1). Relapse rates were higher in the TAC/GC-treated patients than the modified Ponticelli regimen–treated patients (64% vs. 33%, $P = 0.03$). The probability of relapse was lesser in the TAC/GC group as compared to the modified Ponticelli regimen (HR: 0.36; 95% CI: 0.16 to 0.80: $P = 0.012$) (Figure 2).

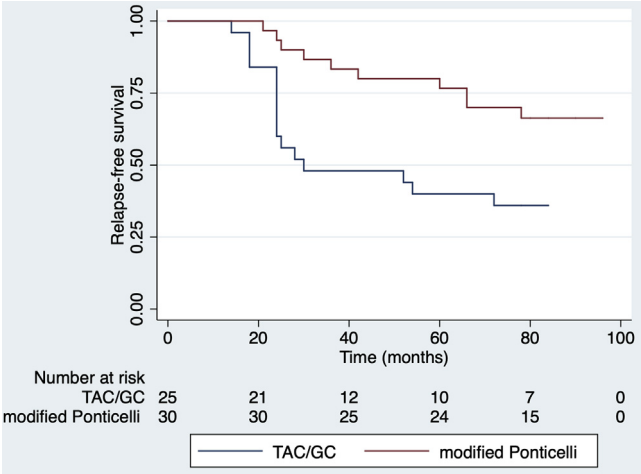

Figure 2. Kaplan-Meier curve showing relapse-free survival in both groups. Log-rank test, $P = 0.008$. GC, glucocorticoids; TAC, tacrolimus.

Of the 26 patients who relapsed (25 at 6 years), seven patients did not receive any second-line immunosuppressive treatment. Of the seven, three spontaneously remitted, two died, one refused any further treatment, and one was lost to follow-up. The 19 remaining patients had 22 episodes of relapse (three patients had two relapses each) (Supplementary Table 1) and were treated. Relapses were treated with rituximab (n = 9), modified Ponticelli regimen (n = 12), or azathioprine/steroids (n = 1). Seventeen (77.27%) patients achieved remission within 1 year of being re-treated (rituximab, n = 6; modified Ponticelli regimen, n = 10; and azathioprine, n = 1) (Supplementary Table 1). Two patients did not have anti-PLA2R antibody titers pre- and post-treatment (patients 1 and 11, Supplementary Table 1). Four patients had clinicoserological dissociation (patients 3, 4, 14, and 17, Supplementary Table 1), two patients (patients 3 and 4, Supplementary Table 1) with serological remission and resistant disease at 1 year achieved clinical remission on an extended follow-up, and the other two patients (patients 14 and 17, Supplementary Table 1) with clinical remission despite persisting antibodies relapsed 1 year from initiation of the modified Ponticelli regimen.

Resistant Disease

Of the 12 patients with resistant disease, 11 received immunosuppressive therapy for resistant disease. One patient received TAC/GC as the first therapy, which was followed by modified Ponticelli regimen (patient

27, Supplementary Table 1). This, in turn, was followed by rituximab for the resistant disease. Unfortunately, the patient was resistant to both therapies. One patient with resistant disease, citing financial issues, did not receive any second-line agent. Anti-PLA2R was available before and after month 6 of therapy initiation. Three patients achieved clinical and serological remission. Three patients had clinicoserological dissociation (patients 29, 30 [TAC as the rescue therapy], and 31, Supplementary Table 1). Two-patients (patients 30 and 31, Supplementary Table 1) with clinical remission and persisting antibodies relapsed subsequently, and one patient (patient 29, Supplementary Table 2) with persistent anti-PLA2R at month 6 (and clinical remission), achieved serological remission at month 12; however, the patient tested negative for autoantibodies at 24 months, when testing was performed for a different project. Both of the above-mentioned patients (patients 30 and 31, Supplementary Table 1) with relapse responded favorably (both clinical and serological remission) to rituximab therapy. One patient (patient 32, Supplementary Table 1) who had a relapse after a clinical and serological remission with the modified Ponticelli regimen responded to rituximab therapy. These clinical and serological details are depicted in Supplementary Table 1.

Adverse Events

Five patients (three in the TAC/GC group and two in the modified Ponticelli regimen group) died during the study period, all of whom were nephrotic and did not receive any immunosuppressive therapy in the last 3 months of life. One patient died due to disseminated tuberculosis and resulting respiratory failure, one patient died due to a traffic accident, and the other three patients had lower respiratory tract infections. At the end of year 1, 11 (six in the TAC/GC group and five in the modified Ponticelli regimen group) patients developed therapy-induced diabetes mellitus. This resolved in eight patients (four from each group) after completing therapy. One additional patient in the TAC/GC group developed diabetes mellitus at month 30. One patient (in the TAC/GC group) developed diabetes mellitus transiently when started on the modified Ponticelli regimen for resistant disease. Five patients developed an infection, necessitating clinical attention, two were dermatomycosis, two were urinary tract infections, and one was an upper respiratory tract infection. All the infectious episodes responded to appropriate antibiotic therapy. None of the patients developed a malignancy during the follow-up. At the last follow-up, 11 patients in the modified Ponticelli regimen group were amenorrheic, of which four and seven had menopause before and after initiation of therapy, respectively. All the patients with amenorrhea were ≥40 years old at the time of trial enrollment. In the TAC/GC group, five of the female patients were amenorrheic at the start of, or during, therapy. Details can be found in Supplementary Table 2.

DISCUSSION

The present report confirms the superiority of the modified Ponticelli regimen over TAC/GC in maintaining long-term remission in antiproteinuric-refractory PMN, without a higher incidence of adverse events or malignancies.

The KDIGO recommends modified Ponticelli regimen or CNIs as first-line therapies for the management of antiproteinuric-resistant PMN.[2-4] Patients with focal segmental glomerulosclerosis treated with CNIs often relapse after withdrawing the drug.[14,15] Further, the probability of additional complete or partial remissions after stopping the CNI is remote, in contrast to alkylating agents/glucocorticoids[5,6] and rituximab,[16] where patients can achieve remission months after therapy has ended. In the light of these facts, it is important to know the long-term response of patients treated with CNIs. Admittedly, long-term data are lacking for patients who receive CNIs. Whereas there are at least four trials which evaluated the short-term response to TAC (with or without steroids) in PMN, there is a conspicuous lack of long-term outcome data. Praga *et al.*[9] enrolled 48 cases of PMN to receive TAC (18 months) or conservative care. At the end of 18 months of therapy, 76% of the patients treated solely with TAC achieved clinical remission, which was significantly higher than the conservative group. However, 50% of the patients relapsed on stopping the TAC.[9] Chen *et al.*[8] randomized 73 patients with PMN to receive either TAC/GC or cyclophosphamide/steroids (noncyclical), and after 12 months, 79% and 69% responded in the TAC/GC and the cyclophosphamide/steroids groups, respectively. The investigators reported relapse in six and five patients in the TAC/GC and cyclophosphamide/steroid group, respectively. Most of the relapses in the TAC/GC group were within 3 months of stopping the drug, but the relapses in the cyclophosphamide/steroid were late. He *et al.*[7] randomized 56 patients to either cyclophosphamide or TAC/GC, 90% of the patients treated with TAC remitted by 12 months compared to two-thirds in the cyclophosphamide group, but no long-term data were reported. In the present study, the patients treated with TAC/GC had a significantly lower relapse-free remission period than the modified Ponticelli regimen group. In the recently published MENTOR (Membranous Nephropathy Trial of Rituximab) trial, of the 65 patients randomized to

receive cyclosporine, only 20% were relapse-free by 24 months.[16] Admittedly, there was no difference in the hard outcomes (cumulative incidence of chronic kidney disease–G5D /death or 40% decline in the eGFR between the two groups.[16] However, to find a meaningful difference in the progression to advanced kidney failure or death requires more than 2 years of follow-up in an indolent disease such as PMN. Nonetheless, there is an enhanced risk of complications of the nephrotic syndrome such as infection, malnutrition, chronic diuretic use for edema resolution, endothelial dysfunction,[17] and accelerated atherosclerosis[18,19] with repeated relapses. These comorbidities likely have an unfavorable influence on long-term kidney and patient health. Given these considerations, along with the relapse-free remission rates,[16,20] we advocate the use of CNIs as an adjunct therapy to other immunosuppression such as rituximab[21] for antiproteinuric-resistant PMN, as opposed to first-line single (or with GC) therapy.

Patients in our cohort with a relapsing nephrotic syndrome predominantly received either modified Ponticelli regimen or rituximab. More than three-fourths of the TAC-treated patients who relapsed responded to the modified Ponticelli regimen and 50% of the patients with resistant disease responded to either the modified Ponticelli regimen or rituximab. The data on the management of resistant PMN are scanty. Arguably, both the modified Ponticelli regimen and rituximab are reasonably safe and efficacious in the management of resistant or relapsing disease.[22-24] However, a recently concluded randomized trial (STARMEN [Sequential Therapy With Tacrolimus and Rituximab in Primary Membranous Nephropathy] trial) reported superior remission rates with modified Ponticelli regimen as compared to a sequential TAC followed by rituximab therapy in PMN at high risk of progression.[25] In patients with relapsing and resistant disease, there was an association of anti-PLAR to clinical activity. Patients with anti-PLA2R in the third tertile had an unsatisfactory response to second-line agents, and this observation is similar to the prior reports.[26,27] Furthermore, we may hypothesize that the primary immunosuppressive therapy is critical in maintaining long-term remission.

The potential for future cancer in cyclophosphamide-treated PMN patients has been a matter of concern.[28] None of our patients developed a malignancy, consistent with two studies[5,29] that reported no cancers during long-term follow-up of patients treated with cyclical alkylating agent therapy. The oncogenic potential of cyclophosphamide is dose-dependent.[30,31] In a study from van den Brand, *et al.*,[28] the cumulative dose of cyclophosphamide leading to malignancy was 37 (range: 21 to 46) g compared to 13.5 g as the maximal dose in the modified Ponticelli regimen–treated cases of PMN.[5,11,29] We suggest that the risk of developing cancer with cyclophosphamide treatment may be exaggerated. A significant proportion of the TAC/GC-treated patients received the modified Ponticelli regimen; hence, it is not unexpected for the adverse effects to be similar in both groups at the end of 6 years.

The other main adverse event of concern in cyclophosphamide-treated patients is gonadal toxicity. Both age and the cumulative dose of cyclophosphamide predispose to infertility.[32,33] All of the patients who developed amenorrhea in the current study with cyclophosphamide were older than 40 years of age. Infertility may be mitigated by gonadal protection with Lupron or testosterone.[34]

This study had some limitations. The investigation was performed at a single center; therefore, generalizability remains to be determined. There was not a prespecified approach to manage relapsing disease. Finally, serum anti-PLA2R levels were generally not available on all patients annually during follow-up.

To conclude, on an extended follow-up, the modified Ponticelli regimen is superior to TAC/GC as the first-line therapy for the management of antiproteinuric resistant PMN. Relapse after withdrawal is a cause of serious concern in patients treated with TAC/GC. Based on our long-term findings, short-term studies in PMN may be insufficient to judge effects of a therapy on future kidney health; therefore, we suggest that future clinical trials incorporate a long-term follow-up protocol.

DISCLOSURE

RR received scientific grants from ICMR (No.5/4/7-5/14/NCD-II) and Indian Society of Nephrology for the study.

BR reports personal fees from Aurinia, Callidatis, Chemocentryx, Retrophin, Novartis, Morphosys, EMD Serono, Bristol Myers Squibb, Janssen, Astra Zenica, and Omeros; nonfinancial support from Lupus Foundation of America; and grants from NIH. VJ reports grants from Baxter Healthcare, GSK, NephroPlus, and others from Baxter Healthcare, Astra Zeneca, and Visterra.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Clinical and serological details of patients who relapsed or were resistant to initial therapy.

Table S2. Adverse events.

CONSORT Checklist

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