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Two-Year Follow-up Study of Membranous Nephropathy Treated With Tacrolimus and Corticosteroids Versus Cyclical Corticosteroids and Cyclophosphamide

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Introduction: Both cCTX/GCs and CNIs are recommended as first-line agents in the management of PMN. The present study is an extended report of patients randomized to receive TAC/GCs or cCTX/GCs at 2 years post randomization.

Methods: Seventy patients enrolled in the clinical trial Tacrolimus Combined With Corticosteroids Versus Modified Ponticelli Regimen in Treatment of Idiopathic Membranous Nephropathy: Randomized Control Trial were followed quarterly between 12 and 24 months. At the end of 24 months, 3 patients were lost to follow-up.

Results: At 18 months, 66% and 89% ($P = 0.04$) were in remission in TAC/GCs and cCTX/GCs groups, respectively. At 18 and 24 months, 60% and 86% ($P = 0.03$) of cases were in remission in the TAC/GCs and cCTX/GCs groups, respectively. At 18 months, 57% and 83% ($P = 0.03$) of the patients in TAC/GCs and cCTX/GCs groups were in remission without need of any additional immunosuppression (persistent remission) and, at 24 months, 43% and 80% ($P = 0.002$) were in persistent remission in TAC/GCs and cCTX/GCs groups, respectively. Relapse rate after any remission was 40% and 6.7% in TAC/GCs and cCTX/GCs groups, respectively ($P = 0.007$). There was an association of aPLA2R titers with remission or resistance ($P = 0.006$) in relapsing PMN. The significant decrease in eGFR after 12 months of TAC/GCs therapy normalized at 18 and 24 months.

Discussion: At 2 years after randomization, relapse rates are higher for TAC/GCs compared with cCTX/GCs in PMN patients. Thus, cCTX/GCs are better than TAC/GCs in the longer term in PMN patients.

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Both calcineurin inhibitors (CNIs) and cyclical cyclophosphamide (cCTX) with glucocorticoids (GCs) (CTX/GCs) are recommended in the management of primary membranous nephropathy (PMN).[1] The 2 regimes are equally efficacious, but have different adverse event profiles.[1,2]

We reported a remission rate at the end of 1 year of 77% and 71% with cCTX/GCs and tacrolimus (TAC) with steroids, respectively.[3] At least 3 other randomized controlled trials have reported the 12-month remission rates of 65% to 89% and 44% to 69%,[4–6] with TAC/GCs and cCTX/GCs, respectively.

Cattran *et al.*[7] reported a remission rate of 75% after 6-month treatment with cyclosporine and steroids. The remission rates fell to 46% and 39% at 12 and 24 months once cyclosporine was stopped. In other studies, the relapse rates after stopping TAC/cyclosporine and cCTX/GCs range from 47% to 50% and 20% to 31%, respectively.[7–10] The high rates of relapse compounded with nephrotoxicity of long-term use of CNIs, makes it worthwhile to study the remission rates

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Table 1. Clinical outcome at various time points

	18 mo		24 mo	
	TAC/GCs (n = 35)	cCTX/GCs (n = 35)	TAC/GCs (n = 35)	cCTX/GCs (n = 35)
Remission (ITT)[a]	23 (65.7)[b]	31 (88.6)[c]	21 (60)[d]	30 (85.7)[e]
CR	15 (42.8)	20 (57.2)	12 (34.3)	20 (57.2)
PR	08 (22.8)	11 (31.4)	09 (25.7)	10 (28.5)
Resistant	07 (20.0)	04 (11.4)	07 (20.0)	03 (8.6)
Relapse	05 (14.3)[f]	NA[g]	07 (20.0)[h]	02 (5.7)[i]
Remission[j]	20 (57.1)[k]	29 (82.8)[l]	15 (42.8)[m]	28 (80)[n]

Values are n (%).
cCTX, cyclical cyclophosphamide; CI, confidence interval; CR, proteinuria <500 mg/d with normal serum albumin (≥3.5 g/dl) and serum creatinine; GCs, glucocorticoids; ITT, intention to treat; NA not applicable; PR, proteinuria ≥500 mg/d, but <2 g/d or <50% of baseline with normal serum albumin (≥3.5 g/dl) and serum creatinine; TAC, tacrolimus.
[a]Included all remission irrespective of the use of second line agents, TAC/GCs, and cCTX/GCs.
[b*c]0.24 (95% CI: 0.07–0.86; $P = 0.04$).
[d*e]0.25 (95% CI: 0.07–0.80; $P = 0.03$).
[f+h versus g+i]$P = 0.007$.
[j]Cases with remission without any need of any further immunosuppression.
[k*l]0.27 (95% CI: 0.08–0.87; $P = 0.03$).
[m*n]0.18 (95% CI: 0.06–0.54; $P = 0.002$).

after stopping the drug. The present study reports the remission rates at 18 and 24 months.

METHODS

The present report is an extended (2-year) follow-up of patients enrolled in a randomized controlled trial that compared tacrolimus combined with corticosteroids and cCTX/GCs (Tacrolimus Combined With Corticosteroids Versus Modified Ponticelli Regimen in Treatment of Idiopathic Membranous Nephropathy: Randomized Control Trial; CTRI/2013/10/004061) carried at the Department of Nephrology, PGIMER, Chandigarh, India.[3] Briefly, the study included adults with biopsy-proven PMN and persistent nephrotic syndrome in spite of 6 months of nonimmunosuppressive symptomatic treatment with full angiotensin-blockade.

Therapy

Patients received either oral prednisolone (0.5 mg/kg/d for 6 months and subsequent taper by 0.1 mg/kg/wk) and *TAC* (trough level = 7.46 ± 1.28 ng/ml for the first 6 months and 4.83 ± 0.59 ng/ml for next 6 months)[3] for 12 months, followed by taper by 50% every 2 weeks to stop or cCTX/GCs (6-month course of alternate months of steroid and cyclophosphamide).[3,11]

Endpoint

A total of 70 patients were enrolled in the study starting from September 21, 2011 to December 2, 2013. Two-year follow-up was completed by December 2015. The primary endpoint of the trial was remission rate at the end of 6 and 12 months.[3] At the end of 12 months, 71% (n = 25) and 77% (n = 27) of the study participants achieved remission.[3] During the study it was decided to continue the follow-up of the enrolled patients without any prespecified interventions. Patients were followed quarterly from months 12 to 24 with proteinuria, serum creatinine, and albumin. The Institute Ethics Committee approved the study, and all subjects provided written informed consent.

Definitions

Nephrotic syndrome: Proteinuria of >4 g/d or ≥2.0 g/d along with serum albumin <2.5 g/dl.[3,11] Complete remission: Proteinuria <500 mg/d with normal serum albumin (≥3.5 g/dl) and serum creatinine. Partial

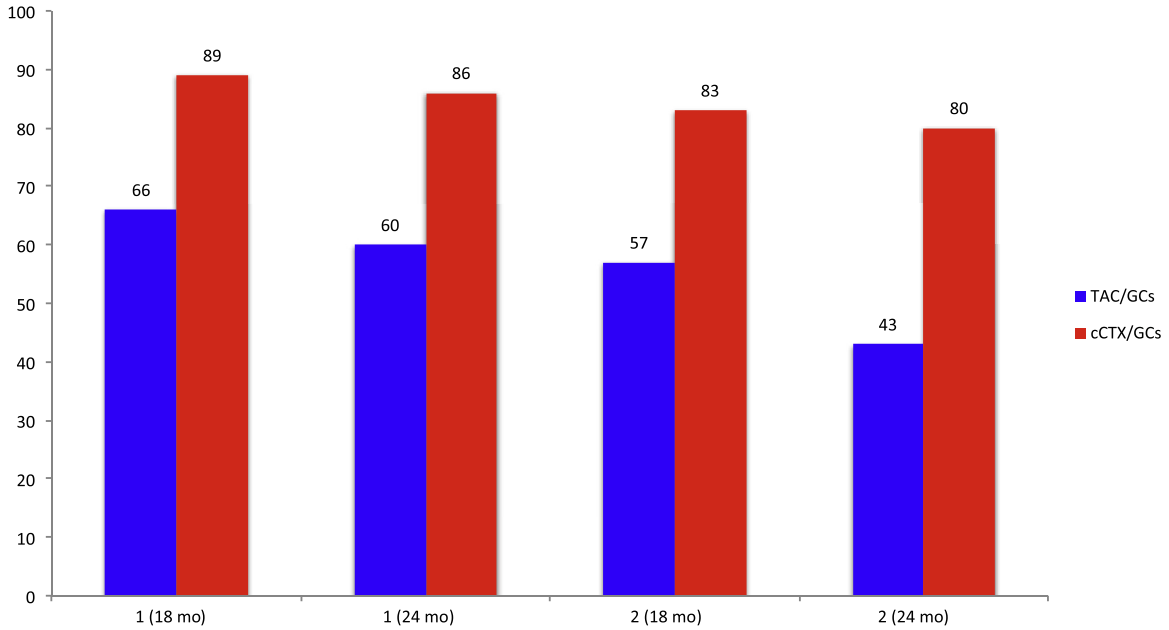

Figure 1. Remission rate at various time points (1—intention to treat; 2—remission without any secondary immunosuppression). cCTX, cyclical cyclophosphamide; GCs, glucocorticoids; TAC, tacrolimus.