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Efficacy of prolonged release tacrolimus, administered once daily, in maintaining remission of calcineurin inhibitor dependent steroid sensitive nephrotic syndrome in children

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Objectives : To examine the efficacy of a PR tacrolimus formulation (ODVenta®) in maintaining stable remission (no or infrequent relapses) over 6 months follow-up, in patients with calcineurin (CNI) dependent steroid-sensitive nephrotic syndrome (SSNS)
Methods : This investigator-initiated, single-center, single-limb interventional study enrolled patients aged 5-18 years with stable remission while receiving therapy with immediate release (IR) tacrolimus for CNI-dependent SSNS (CTRI/2022/01/039427). Patients with cumulative CNI >30 months, frequent relapses on IR tacrolimus, and estimated GFR <60 ml/min per 1.73 m^2 were excluded. Eligible and consenting patients on twice daily IR-tacrolimus were switched to ODVenta® on 1:1 mg basis. Primary outcome was the proportion of patients with stable remission. Secondary outcomes included proportion of children with sustained remission or treatment failure, number of relapses and adverse events. Pharmacokinetics included tacrolimus trough levels (C0), dose-to-trough ratio (TDD/C0) and CYP3A5 polymorphism. Area under the curve (AUC0-24) was calculated after 2 weeks using tacrolimus concentration at 0,0.5,1,2,4,6,8, 12 and 24-hours in every third patient enrolled.
Results : Of 48 children screened for eligibility, 20 (85% boys) were enrolled at median (interquartile range) age of 130 (98.5, 184.5) months. At 6-months follow up, 17 (85%) patients showed stable remission, with sustained remission in 50%. Three patients had treatment failure (FR-2; late steroid resistance-1). There were no significant changes from baseline in estimated GFR, HbA1c, serum magnesium and total cholesterol (Table 1). TDD/C_0 was higher at 6-months in comparison to baseline (P=0.01). Median AUC_{0-24} (7 patients) was 130.3 (81.6, 158.6) hr*ng/ml (Fig. 1). Ten (50%) patients were CYP3A5 expressors (*01*03) and showed a higher TDD/C_0 in comparison to non-expressors (*03*03) at 2 weeks follow-up (P=0.02).
Conclusions : Therapy with PR-tacrolimus effectively maintains stable remission in patients with CNI-dependent SSNS. Pharmacokinetic profile is comparable. CYP3A5 polymorphism influences the pharmacokinetic profile. Controlled large studies should evaluate its efficacy in SSNS and steroid-resistant NS in children.

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Parameter	Baseline	6 months	*P*
Hemoglobin (g/dL)	12.5 (11.7, 12.9)	12.8 (11.8, 13.6)	0.05
Estimated GFR (ml/1.73 m^2/min)	115.9 (78.6, 141.9)	113.2 (86.1, 132.6)	0.90
Serum magnesium (mg/dL)	1.85 (1.7-1.9)	1.8 (1.7, 2.0)	0.13
Glycated hemoglobin Hba1c (%)	5.3 (5.0, 5.4)	5.1 (4.8, 5.5)	0.83
Total cholesterol (mg/dL)	128 (116.5, 175.8)	142 (125, 195)	0.17
Tacrolimus trough level (ng/ml)	3.9 (3.5, 5.6)	3.8 (3, 4.1)	0.06
Total daily dose/ tacrolimus trough concentration (TDD/C0)	0.65 (0.57, 0.94)	0.89 (0.61, 1.61)	0.01
Incidence of relapses per person-year	0.7 (0.28, 1.44)	1.2 (0.62, 2.1)	0.26

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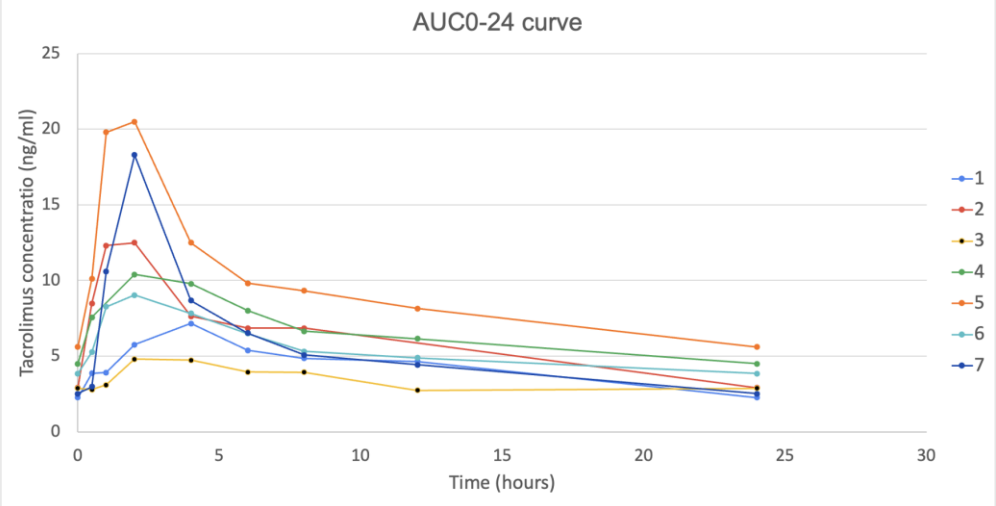
AUC0-24 curve
Tacrolimus concentratio (ng/ml)
Time (hours)
0
5
10
15
20
25
30
1
2
3
4
5
6
7