Efficacy and Safety of Everolimus Based Immunosuppression on De Novo Kidney Transplantation with 5 Years Follow-up Especially in Protocol Biopsy Findings and Donor Specific Antibody Production

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OBJECTIVES

The impact of everolimus (EVR) based immuno-suppression in De Novo Kidney Transplantation was evaluated in clinical outcomes, protocol biopsies findings and donor specific antibody (DSA) production with 5 years follow-up

METHODS

During March 2008 and August 2009, twenty-four recipients were enrolled to compare the safety and efficacy between EVR based and mycophenolate mofetil (MMF) based immunosuppression as a part of A1202 study. EVR group received reduced-exposure cyclosporine (CsA; target C0 25-50ng/ml after 6 months) + steroid, and EVR-C0 were adjusted 3-12ng/ml. MMF group received standard-exposure cyclosporine (CsA; target C0 100-250ng/ml after 6 months) + steroid. Both groups received basiliximab induction.

RESULTS

Study Protocol

EVR group (n=13)
EVR 1.5mg/day (C0=3-12ng/mL) + Reduced CsA
+ Basilixmab
+ Steroid

Target C0 (ng/mL): 100-200 | 75-150 | 50-100 | 25-50

MMF group (n=13)
MMF 2g/day + Standard CsA
+ Basilixmab
+ Steroid

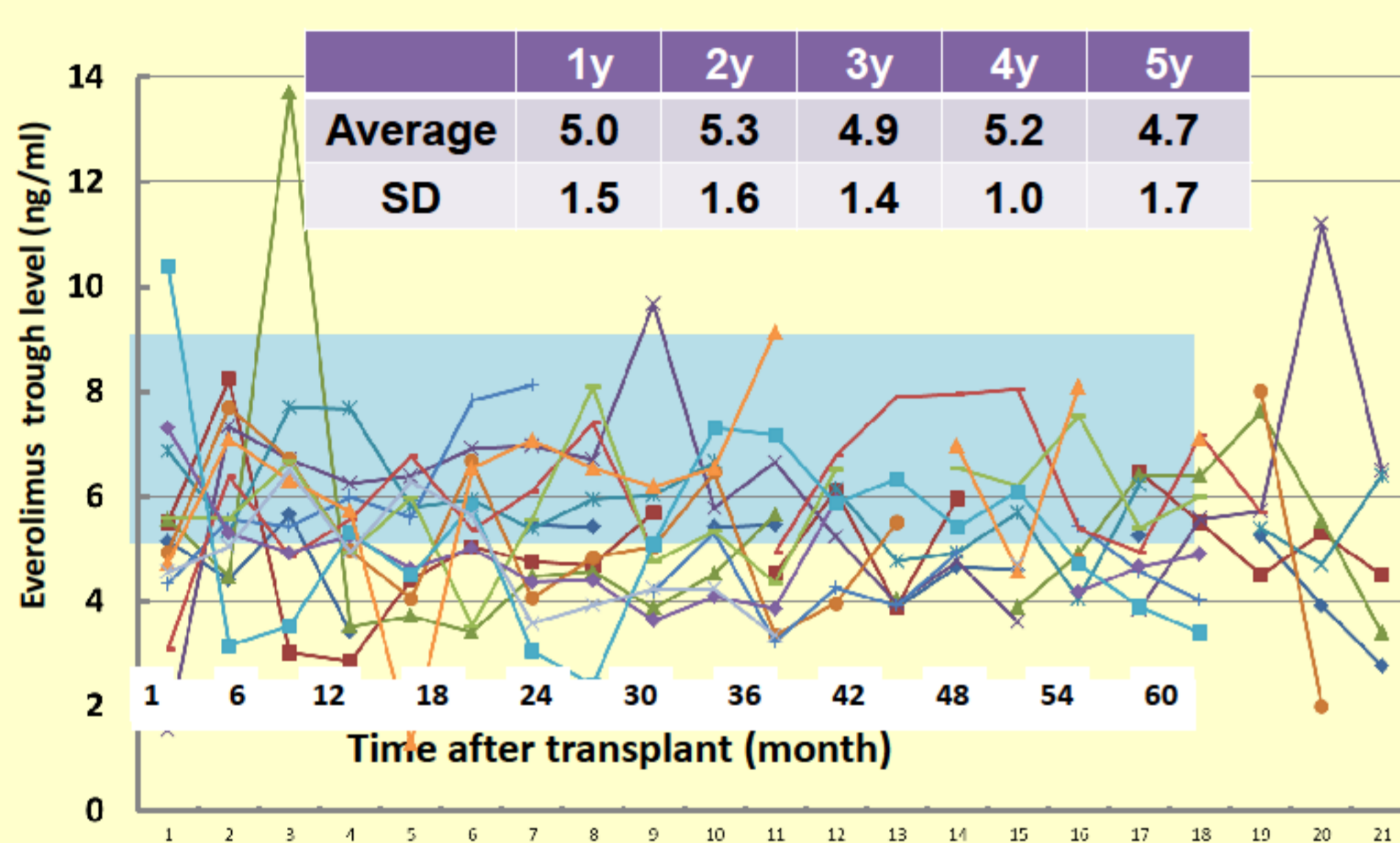Target C0 (ng/mL): 200-300 | 100-250

Tx 2M 4M 6M

[Patient's characteristics]

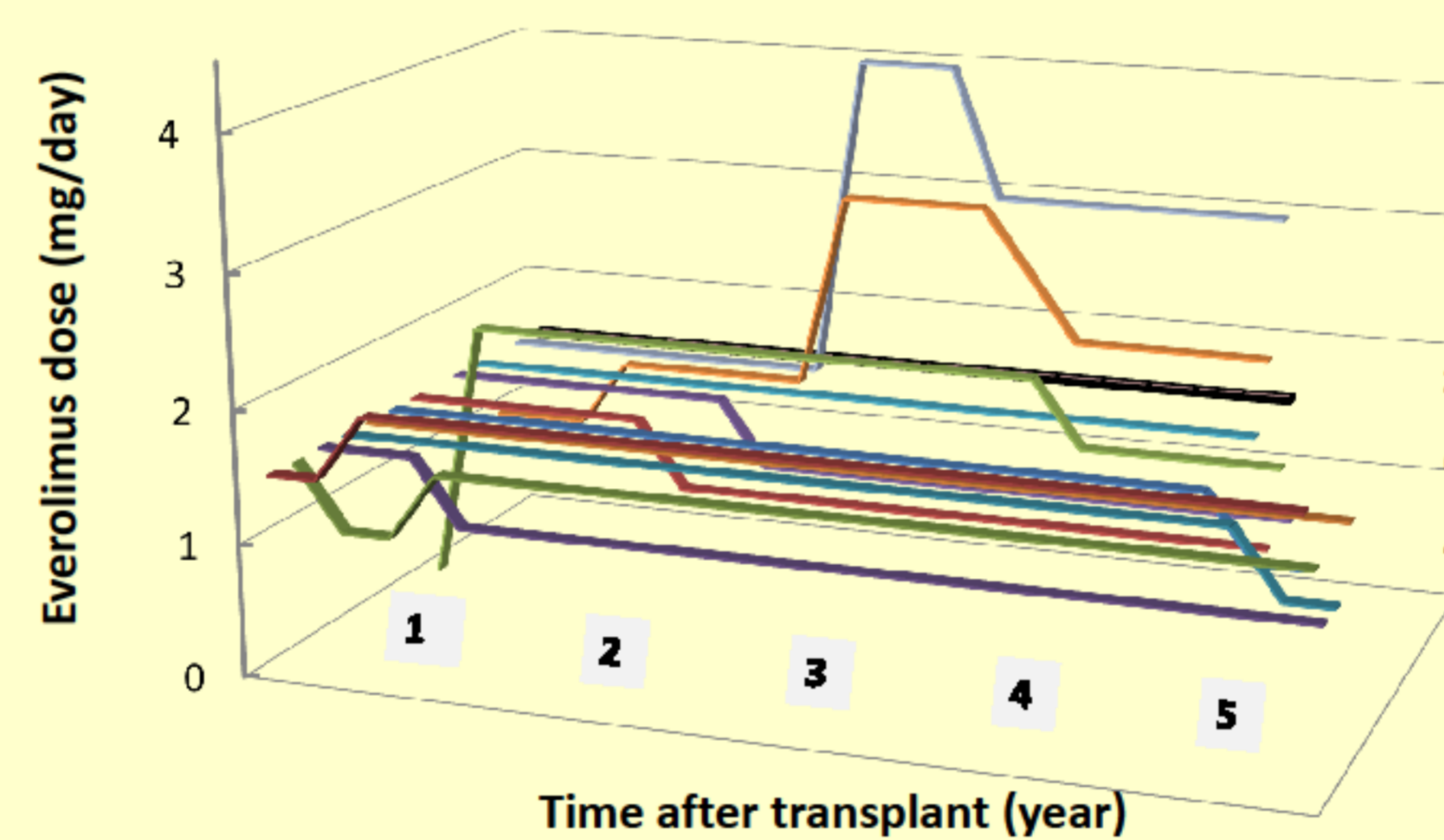|	Everolimus(EVR) group	MMF group
Age (year)	13	11
Sex (M/F)	22-61 (44±15)	22-49 (35±9)
Sex (M/F)	8/5	7/4
Original disease	CGN 4 / IgA nephropathy 4 / Renal sclerosis 1 / Interstitial nephritis 1 / ADPKD 1 / Sponge kidney 1 / Reflux N 1	CGN 3 / IgA nephropathy 4 / Diabetes mellitus 2 / FSGS 1 / Reflux N 1
Body Mass Index	17.5-27.7 (21.7±3.1)	17.0-30.0 (21.0±3.1)
Observation period	53 – 69 (61±6)	53 - 70 (61±6)
Patient & Graft Survival	100% / 100%	100% / 90.9% (one graft loss at 5.5y PO)

[Donor & Matching]

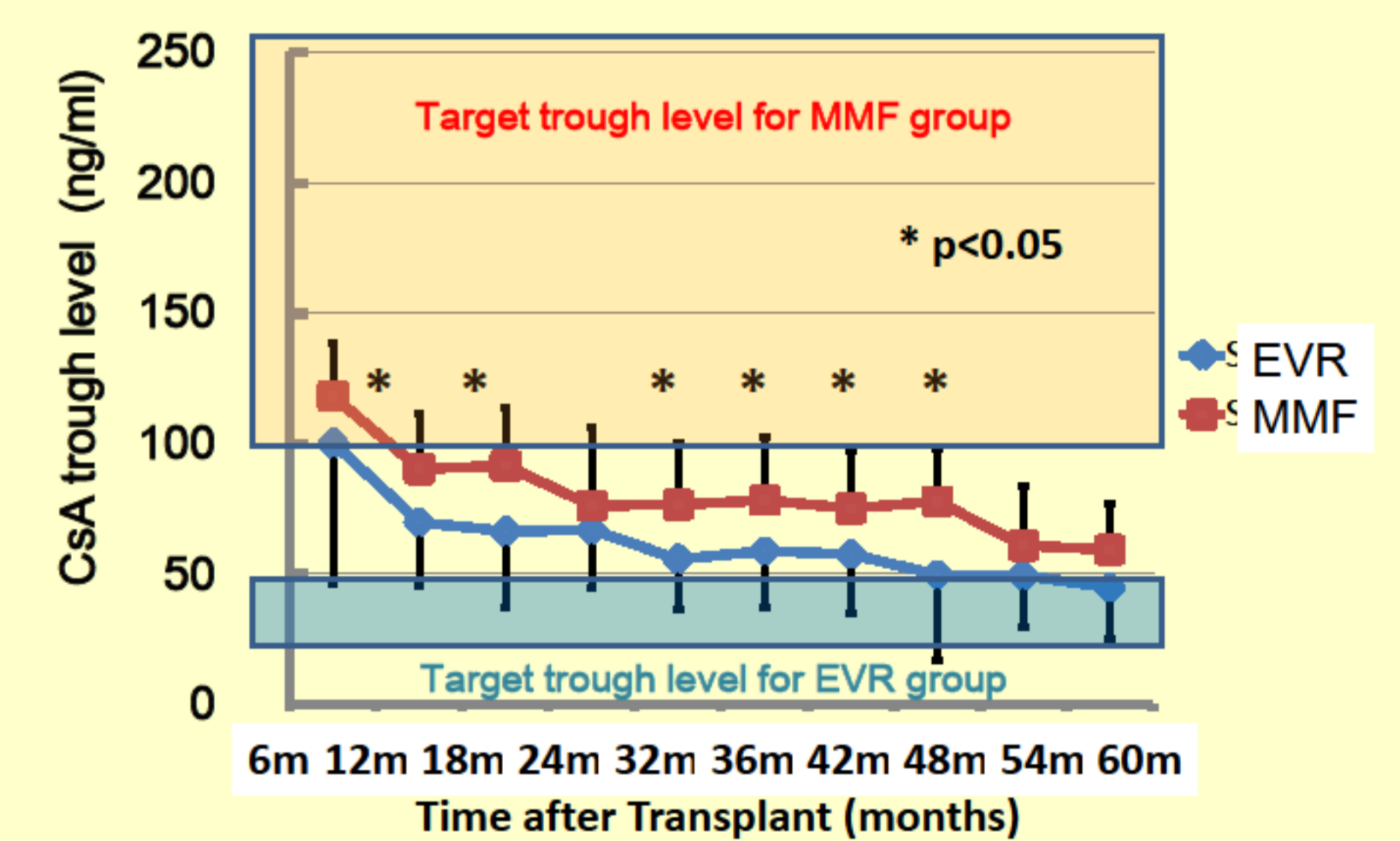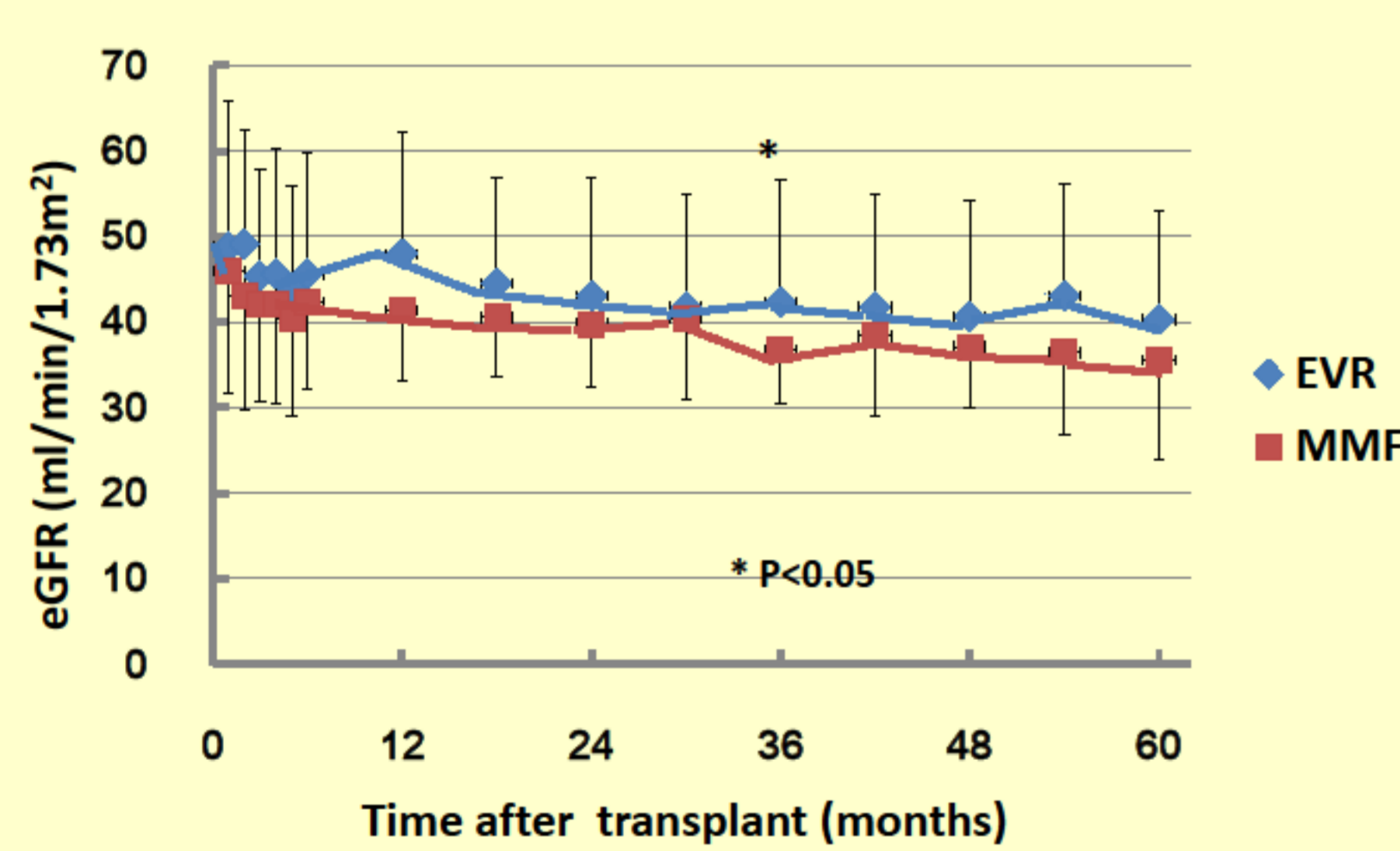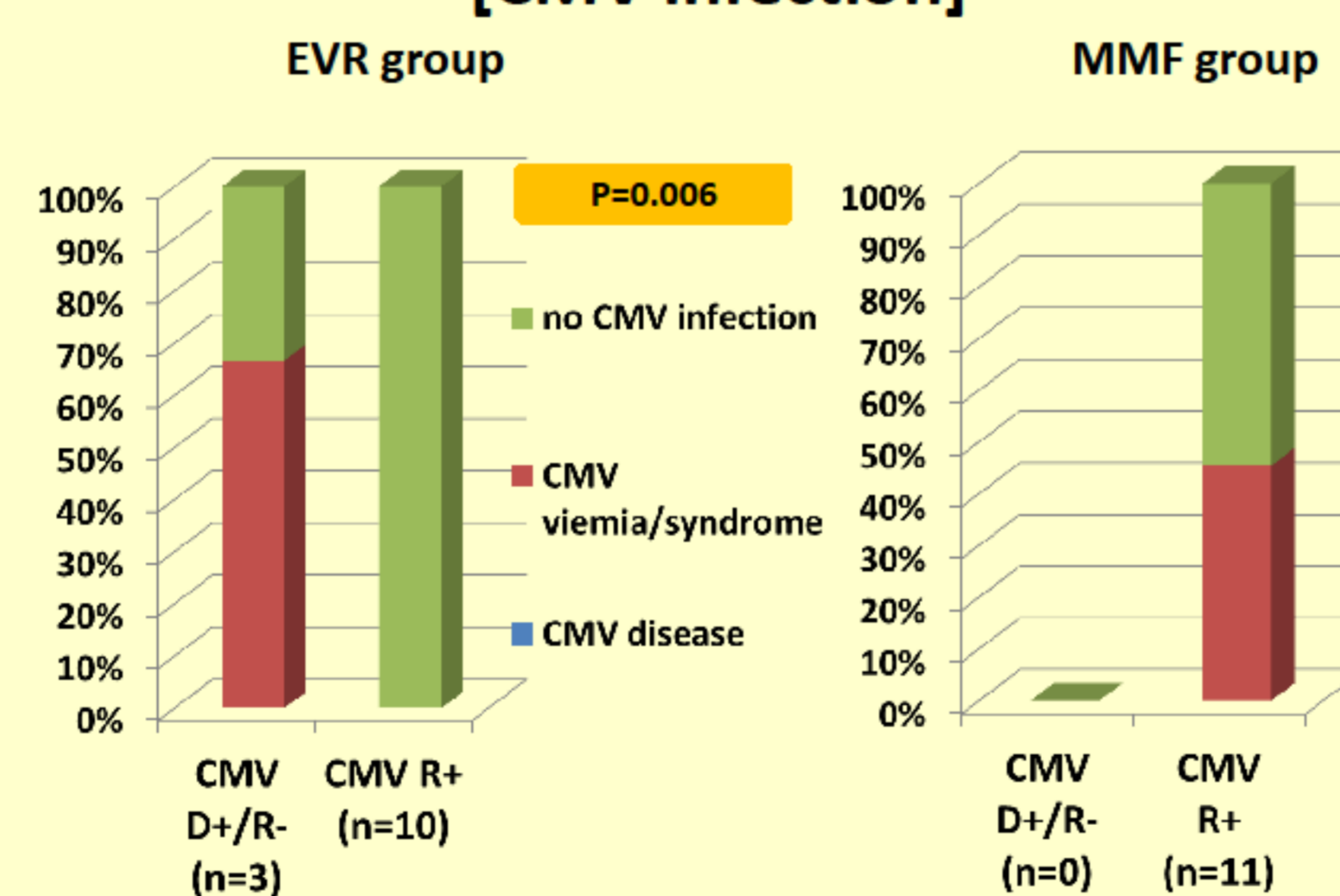|	EVR group	MMF group
Sex (M/F)	7/6	4/7
Age	34-63 (52±8)	43-62 (55±6)
Relationship	Spouse 6 / Parents 5 / Sibling 2	Spouse 2 / Parents 2 / Sibling 1
HLA mismatch Class I	1.9±0.7 (1 – 3)	1.6±0.7 (0 – 2)
HLA mismatch Class II	1.2±0.6 (0 – 2)	0.8±0.6 (0 – 2)
CMV serology	D+/R+ 9 (69.2%) / D-/R+ 1 (7.7%) / D+/R- 3 (23.1%)	D+/R+ 10 (92.3%) / D- /R+ 1 (7.7%) / D+ /R- 0 (0%)

[Everolimus Trough Level]

	1y	2y	3y	4y	5y
Average	5.0	5.3	4.9	5.2	4.7
SD	1.5	1.6	1.4	1.0	1.7

Everolimus trough level (ng/ml) vs Time after transplant (month)

[Everolimus Dose]

Everolimus dose (mg/day) vs Time after transplant (year)

[CsA Trough(C0)]

Target trough level for MMF group / Target trough level for EVR group / * p<0.05 / CsA trough level (ng/ml) vs Time after Transplant (months): 6m 12m 18m 24m 32m 36m 42m 48m 54m 60m — EVR, MMF

[Changes of eGFR]

eGFR (ml/min/1.73m²) vs Time after transplant (months) — EVR, MMF, * P<0.05

[CMV infection]

EVR group: CMV D+/R- (n=3), CMV R+ (n=10) — P=0.006; MMF group: CMV D+/R- (n=0), CMV R+ (n=11). no CMV infection / CMV viremia/syndrome / CMV disease

[Proteinuria]

EVR group / MMF group — Proteinuria (g/day) vs Time: 1m 6m 12m 18m 24m 30m 36m 42m 48m 54m 60m

[Adverse Events]

	EVR group	MMF group	P value
Proteinuria >300mg/day	10/13(76.9%) Treated with ARB	6/11(54.5%) Treated with ARB	N.S.
Viral infection Other than CMV	Hemorrhagic cystitis 1 HCV infection 1	Herpes Zoster 2	N.S.
Lymphocele	0/13 (0%)	2/11 (18.2%)	N.S.
Aphthous ulceration	2/13 (15.4%)	0/11 (0%)	N.S.
Joint pain Edema Interstitial pneumonia	0/13 (0%)	0/11 (0%)	N.S.
NODAT	3/13 (23.1%) on medication, but not insulin therapy	0/11 (0%)	P=0.09

[Rejection and DSA production]

	EVR group	MMF group
Acute T cell Mediated rejection (ATMR)	Clinical : 0/13 (0.0%) Subclinical : 1/13(7.7%) *Borderline change on 6M protocol biopsy no treatment*	Clinical: 0/11 (0.0 %) Subclinical : 2/11 (18.2%) *Borderline change on 6&12M protocol biopsy no treatment*
Donor specific antibody (DSA) production	1/13 (7.7%) De novo DSA at 2y PO *DRB4 ; MFI 2700 & DQB1 ; MFI 8234*	3/11 (27.3%) De novo DSA at 3y PO *DQB1; MFI 14149* De novo DSA at 3y PO *DRB5; MFI 6318* De novo DSA at 5 y PO *DQB1; MFI 6422*
Antibody mediated rejection (AMR)	Acute AMR 0/11(0.0%) Chronic active AMR 0/13 (0.0%)	Acute AMR 0/11 (0.0%) Chronic active AMR (ptc3, ptcbm1), 1/11 (9.1 %) *Tx: DFPP, IVIG & Rituximab*

CONCLUSIONS

- EVR based immunosuppression provides equivalent clinical outcomes as well as the incidence of De Novo DSA production with MMF based immunosuppression with 5 years follow-up.
- CNI can be safely minimized with good graft function as well as a favorable outcome for incidence of CMV.
- Proteinuria, even nephrotic, could be treated with ARB without graft dysfunction.
- New onset diabetes need be carefully monitored.