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Tacrolimus as an Induction Agent for Proliferative Lupus Nephritis Is as Effective as Cyclophosphamide Sanjay Gupta,[1] Sheel Bhadra Jain,[1] Uma Kumar,[2] Amit K. Dinda.[1] *[1]Nephrology, AIIMS, India; [2]Medicine, AIIMS, India.*

Background: Conventional therapy for lupus nephritis has limitations, cyclophosphamide (cyclo) carries the risk of severe infections, ovarian failure and malignancies mycophenolate has risk of infections. Less toxic treatment with at least equal efficacy is necessary. Tacrolimus (tac) target B cells indirectly by interfering with T cell help by inhibiting IL-6, IL-10 production. The aim of study was to assess the efficacy and safety of Tacrolimus as induction therapy in class III and IV lupus nephritis and compare it with cyclo.

Methods: In an open label non randomized control trial involving 40 female patients with biopsy proven class III and class IV lupus nephritis, we compared the Tac in combination with steroid as an induction therapy with cyclo monthly pulses (NIH protocol). Twenty patients were treated with Tacrolimus, starting at 0.1 mg/kg/day in divided doses maintaining trough levels 5-8 ng/ml and prednisolone at 0.6 mg/kg/day for 6 weeks and then tapered. Response rate and adverse effects were compared with 20 consecutive patients treated with IV cyclo.

Results: The tac group and cyclo group had similar baseline characteristics. Histopathology was similar, in tac group class III in 10, IV in 9 & III+V in 1 and in cyclo group class III in 6, IV in 13 & IV+V in 1. After 6 months in Tac group, complete remission was achieved in 11(55%), partial response in 4 (20%) and no response in 5 (25%) while it was 8(40%), 9 (45%) and 3 (15%) in Cyclo respectively (p=0.23). Proteinuria decreased from 2.2±0.8 to 0.85±1.1 gm/day in tac group & 2.8±2 to0.78±1.2gm/day in Cyclo group(p=0.8) & S albumin increased from 3.1±0.7 to 4.1±0.5 g/dl in tac group & from 2.8±0.8 to 4±0.7 in cyclo group(p=.46). In both groups there was significant improvement in C3 level and decline in dsDNA (IU/ml) titre from baseline. There were more infections in Cyclo group, total 6 episodes (including 2 tubercular) versus 3 episodes in tac group (p=.45). There was no case of hyperglycemia or nephrotoxicity in both groups.

Conclusions: Induction with Tac is as effective as cyclo for proliferative lupus nephritis. It is an option for females desirous of preserving ovarian function or not tolerating Cyclo.

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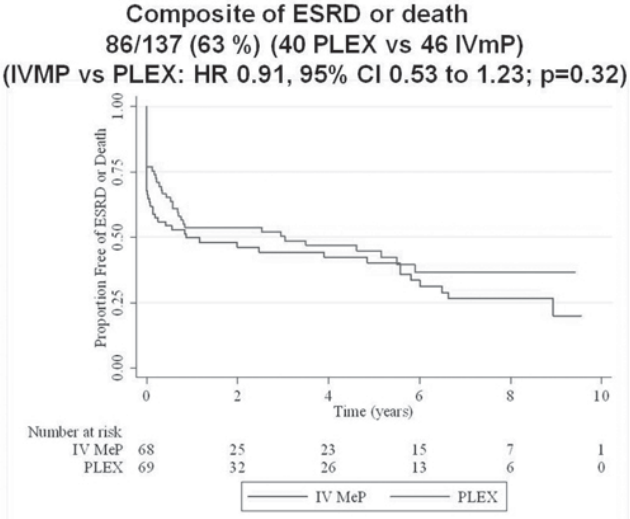
A Long-Term Analysis of the MEPEX Trial: Plasma Exchange for Severe Renal ANCA Vasculitis Alina L. Casian,[1] Michael Walsh,[2] David R.W. Jayne.[1] *[1]Vasculitis, Cambridge University NHS Foundation Trust, United Kingdom; [2]Epidemiology and Biostatistics, McMaster University, Hamilton, Canada.*

Background: Whether plasma exchange (PLEX) reduces end-stage renal disease (ESRD) and mortality in patients with severe ANCA vasculitis (AAV) is unclear. We examined the effect of PLEX on patient outcomes in the long term follow-up of the MEPEX trial.

Purpose of study: To determine whether PLEX compared to IV methylprednisolone (IVMeP) reduces the composite endpoint of ESRD or death or the endpoint of relapse in severe AAV.

Methods: Patients in MEPEX had severe AAV with a serum creatinine >500 μmol/L (5.8 mg/dl). They were randomized to receive either 7 treatments of PLEX or 3 pulses of IVMeP as adjunctive therapy to oral cyclophosphamide and prednisolone. Differences in ESRD/death between the groups were assessed using Cox proportional hazards models and differences in relapse were assessed using competing risk time to event models.

Results: 137 patients were included with a median follow-up time of 4 years. 70 (51%) developed ESRD, 56 (41%) died, and 26 (19%) experienced at least one relapse. The hazard ratio (HR) for the primary composite endpoint of ESRD and death was 0.91 (95% CI 0.53 to 1.23; p=0.32) for PLEX vs IVMeP.



For the endpoint of ESRD alone, the HR was 0.64 (95% CI 0.4 to 1.05, p=0.08) and for the endpoint of death alone the HR was 1.08 (95% CI 0.67 to 1.73). 37 out of 137 patients were alive and not ESRD at 5 years, with a median creatinine of 176 μmol/L in the PLEX group vs. 158 μmol/L in the IVMeP group (p=0.43). When considering the competing risk of death, the HR for relapse was 0.56 (95% CI 0.26 to 1.21, p=0.14) in patients treated with PLEX compared to IVMeP.

Conclusions: We were unable to demonstrate a long-term benefit of PLEX over IVMeP. Further trials are needed to determine if PLEX reduces the occurrence of clinically important outcomes in patients with AAV

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Aberrations in Genes Encoding CFHR5 and Terminal Complement Pathway Components in Patients with Atypical Hemolytic Uremic Syndrome Dineke Westra,[1] Katherine Anne Vernon,[2] Elena Volokhina,[1] Matthew C. Pickering,[2] Cees van Kooten,[3] Nicole Van De Kar,[1] Lambertus V. Heuvel.[1,4] *[1]Radboud University Nijmegen Medical Centre, Netherlands; [2]Imperial College, United Kingdom; [3]Leiden University Medical Centre, Netherlands; [4]University Hospital Leuven, Belgium.*

Background: Atypical HUS (aHUS) is a rare and severe renal disorder thought to be caused by predisposing aberrations in complement proteins. Previously, complement deficiencies in *CFH*, *CFI*, *MCP*, and *CFB*, or the presence of αFH were identified in 37% of our cohort of Dutch and Belgian patients. More than 4% of the patients carried an alteration in more than one gene. In this study, we identify potentially pathogenic aberrations in the regulator CFHR5 (*CFHR5*) and the terminal complement complex (TCC) components C8α (*C8A*), C8β (*C8B*), and C9 (*C9*).

Methods: Mutational screening was performed in *CFHR5*, *C8A*, *C8B*, and *C9* in 65 aHUS patients. Potential pathogenicity of genetic alterations was checked in literature, evolutionary conservation, and *in silico* mutation prediction programs. Influence of mutations in *C8A* on protein structure was analyzed with respect to available structural data. Hemolytic assays were performed for functional analysis of aberrations in TCC proteins. CFHR5 was detected in available serum by means of western blotting analysis and ELISA.

Results: In eleven patients (16.9%) we identified a potentially pathogenic sequence variation in a TCC gene or in *CFHR5*. The p.Arg444His aberration in C8α, located in the proximity of the interface with C8γ and in the binding site for CD59, results in increased hemolytic activity. Serum levels of CFHR5 were not altered. In three patients, a genetic defect was also found in one of the previously screened genes (*CFH*, *CFHR5*, and *C8A*: 2x; *CFHR5* and *CFH*: 1x).

Conclusions: A potentially pathogenic genetic abnormality in one of the components of the membrane attack complex or in *CFHR5* was observed in 16.9% of the patients. In total, in 51% of the patients at least one potentially pathogenic defect was identified in one of the complement genes screened in this cohort. The combined genetic defects identified in 9.2% might partly explain the incomplete penetrance described in the disease.

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Podocyturia Is an Early Marker That Distinguishes among Normotensive Pregnancy, Gestational Hypertension, and Preeclampsia Iasmina Craici,[1] Steven Wagner,[1] Juan C. Calle,[1] Christina Wood-Wentz,[3] Kent R. Bailey,[3] Stephen T. Turner,[1] Joseph P. Grande,[2] Vesna D. Garovic.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [3]Biostatistics, Mayo Clinic, Rochester, MN.*

Background: Preeclampsia (PE) is a disorder of hypertension and proteinuria that affects 3% to 5% of pregnancies. We have previously shown that podocyturia, the shedding of live podocytes, is present at delivery in patients with PE. We aim to test whether podocyturia is predictive of later development of PE, and whether it can differentiate among normotensive pregnancies, gestational hypertension (GHTN), and PE.

Methods: From a prospective cohort of 315 patients, 15 developed PE and 15 developed GHTN. Forty four normal controls were selected. Blood pressure and protein/creatinine ratios were checked at mid-gestation prior to the onset of PE or GHTN. Urine sediments collected in mid pregnancy, prior to 210 days gestation, were cultured for 24 hours to select for viable cells. Podocytes were then identified on the basis of podocin staining.

Results: Age was not different between groups. At mid-pregnancy, the patients who later developed PE or GHTN had higher mean arterial pressure (MAP). There was an insignificant trend toward a higher protein:creatinine ratio in those who later developed PE. Of the 15 patients who later went on to develop PE, all had positive podocyturia early in pregnancy. None of the 44 normal pregnancies or 15 pregnancies complicated by gestational hypertension had podocyturia before 210 days gestation (Table 1).

Table 1

	Normotensive	GHTN	PE	p (anova)
Maternal age (years)	28.8 ± 4.4	29.9 ± 3.5	29.3 ± 6.4	0.72
Mid gestation MAP (mmHg)	77.6 ±7.1	84.0 ± 7.4	84.1 ± 8.4	0.002
Protein:creatinine ratio	0.06 ± 0.12	0.04 ± 0.02	0.25 ± 0.76	0.17
Podocyturia N (%)	0/44 (0%)	0/15 (0%)	15/15 (100%)	

Conclusions: Mid pregnancy, podocyturia is a highly accurate test for prediction of later development of PE. Podocyturia can also differentiate between later development of GHTN and PE. We postulate that the high accuracy of this test further supports the role of podocyte loss in the mechanism of proteinuria in preeclampsia.