Effects of Frequent In-Center Hemodialysis: The Frequent Hemodialysis Network (FHN) Daily Trial Nathan W. Levin,[2] Glenn M. Chertow,[3] Alan S. Kliger.[4] *[1]and the FHN Trial Group; [2]Renal Research Institute; [3]Stanford University; [4]Hospital of St. Raphael, Yale University.*

Background: We conducted a randomized clinical trial to determine if frequent in-center ("daily") hemodialysis resulted in changes in left ventricular mass (LVM), self-reported physical health and other intermediate outcomes in patients on maintenance hemodialysis.

Methods: Patients were randomized to 6x *versus* 3x-per-week hemodialysis for 12 months. The co-primary composite outcomes were 1) death or change (baseline to 12 months) in LVM by cardiac magnetic resonance imaging (death/LVM); and 2) death or change in the RAND Physical Health Composite (PHC) from the SF-36 (death/PHC). Secondary outcomes included cognitive performance, self-reported depression, laboratory markers of nutrition, mineral metabolism and anemia, blood pressure and rates of hospitalization and vascular access interventions.

Results: Patients randomized to the 6x-per-week arm completed an average of 5.2 sessions per week; the weekly standard Kt/V_{urea} was significantly higher in the 6x-per-week arm (3.54 ± 0.56 *versus* 2.49 ± 0.27). As expected, per-session ultrafiltration volume and interdialytic weight gain were lower, and corresponding weekly values higher, in the 6x-per-week arm. Frequent hemodialysis resulted in favorable changes in both co-primary composite outcomes (death/LVM hazard ratio (HR) 0.61, 95% confidence interval (95% CI) 0.46 to 0.82 and death/PHC HR 0.70, 95% CI 0.53 to 0.92). Patients randomized to 6x-per-week hemodialysis were more likely to undergo vascular access interventions (HR 1.71, 95% CI 1.08 to 2.73). Frequent hemodialysis resulted in improved control of hypertension and hyperphosphatemia; there were no significant effects on cognitive performance, self-reported depression, serum albumin or the use of erythropoiesis-stimulating agents.

Conclusions: Frequent hemodialysis resulted in favorable changes on death/LVM and death/PHC, but prompted more frequent vascular access interventions.

Disclosure of Financial Relationships: Employer: Renal Research Institute, New York; Ownership: Fresenius Medical Care North America; Honoraria: RoFAR, Roche, Affymax, Merck; Scientific Advisor: ISN Council, KDIGO Executive, DOPPS Advisory

Effects of Nocturnal Home Hemodialysis: The Frequent Hemodialysis Network (FHN) Nocturnal Trial Michael V. Rocco,[2] Alan S. Kliger.[3] *[1]and the FHN Trial Group; [2]Wake Forest University, Winston-Salem, NC; [3]Hospital of St . Raphael, Yale University, New Haven, CT.*

Background: A randomized, clinical trial was performed to determine if frequent nocturnal home hemodialysis improved left ventricular (LV) mass and health related quality of life.

Methods: Subjects were randomized to thrice weekly hemodialysis (2.5-5 hrs/session) or nocturnal home hemodialysis (6.0-8.0 hrs/session) 6 times per week. The co-primary composite outcomes were death or 12 month change in 1) LV mass by magnetic resonance imaging and 2) the RAND Physical Health Composite (PHC). Secondary outcomes included cognitive performance, self-reported depression, laboratory markers of nutrition, mineral metabolism and anemia, blood pressure and rates of hospitalization and vascular access interventions.

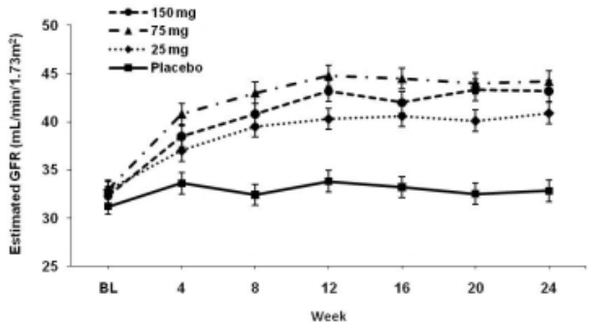
Results: The achieved mean (SD) weekly standard Kt/V, number of hemodialysis sessions/week and adherence to >80% of hemodialysis sessions in the conventional arm (n=42) were: 2.59 (0.69), 2.93 (0.07) and 100%, respectively; corresponding values in the nocturnal arm (n=45) were: 4.72 (1.18), 5.07 (0.79) and 75.0% respectively. There was no significant benefit of frequent nocturnal home hemodialysis for either of the two co-primary outcomes (LV mass: Hazard ratio (HR) 0.68, 95% confidence interval (CI) of 0.44 to 1.07, p=0.095; death/PHC: HR=0.91, 95% CI 0.58 to 1.43, p=0.68). Patients randomized to the nocturnal arm experienced improved control of hyperphosphatemia and hypertension but no significant improvements in the other main secondary outcomes and a trend for an increase in vascular access events. The treatment effects on LV mass and PHC should be interpreted in the context of their wide confidence intervals. For LV mass, the large confidence interval contains the estimated effect of other randomized controlled trials showing reduced LV mass with frequent dialysis. Similarly, the change in PHC within the nocturnal arm was similar to the effect seen in the FHN Daily Trial.

Conclusions: Frequent nocturnal hemodialysis did not significantly improve the primary or main secondary outcomes except for hyperphosphatemia and hypertension.

Disclosure of Financial Relationships: Consultancy: Amgen, DaVita

Effect of Bardoxolone Methyl on Renal Function in Patients with Chronic Kidney Disease (CKD) and Type 2 Diabetes Mellitus Pablo E. Pergola,[1] Colin Meyer,[2] Eric B. Grossman,[2] Melissa Krauth,[2] Heidi Christ-schmidt,[3] Barbara Richardson,[2] Janet Wittes,[3] David G. Warnock.[4] *[1]Renal Associates, PA, San Antonio, Texas, United States; [2]Reata Pharmaceuticals, Inc., Irving, Texas, United States; [3]Statistics Collaborative, Inc., Washington, D.C., United States; [4]University of Alabama, Birmingham, AL.*

Bardoxolone methyl is an antioxidant inflammation modulator that has shown to improve estimated glomerular filtration rate (eGFR) and other markers of renal function in patients with moderate to severe CKD. In an ongoing multicenter, double-blind trial, 227 adults with CKD (eGFR 20-45 mL/min/1.73m²) and type 2 diabetes mellitus were randomized to receive either placebo or bardoxolone methyl (at three titrated doses of 25, 75, and 150 mg) once daily. The primary outcome was change in kidney function following 24 weeks of treatment. Large, dose-dependent increases in eGFR, ranging from 8.3±1.1 to 11.5±1.1 mL/min/1.73m², were observed in each bardoxolone methyl group relative to a 0.1±1.1 change in placebo (p<0.001). Over 73% of patients in each bardoxolone methyl group had at least a 10% increase in eGFR, and approximately 25% had more than a 50% increase, compared with one patient (2%) in placebo. The increases translated to an improvement in CKD stage in the majority of patients, including those with Stage 4 disease. Significant reductions were observed in other kidney function markers, including blood urea nitrogen, serum phosphorus, and uric acid, that inversely correlated with increased eGFR. Bardoxolone methyl was generally well-tolerated; most adverse events were mild to moderate in severity and clinically manageable. These results indicate that bardoxolone methyl is a promising agent in the treatment of CKD. The study continues to capture outcomes at 52 weeks to confirm the sustainability of these demonstrated kidney function improvements.



Disclosure of Financial Relationships: nothing to disclose

Results of the Multicenter FSGS Clinical Trial in Children and Young Adults Debbie S. Gipson,[1] Howard Trachtman,[3] Frederick J. Kaskel,[2] Tom H. Greene,[4] Jennifer J. Gassman,[5] Milena Radeva,[5] Marva M. Moxey-Mims,[6] Richard N. Fine,[7] John Paul Middleton,[8] V. Matti Vehaskari,[9] Susan L. Hogan,[10] Ronald J. Hogg,[11] Sandra L Watkins,[12] Patricia Flynn,[2] June Mcmahan,[5] Leslie Powell,[10] Suzanne M Vento,[3] Aaron L. Friedman.[13] *[1]Univ Michigan; [2]Children's Hosp Montefiore; [3]Cohen Children's Hosp; [4]Univ Utah; [5]Cleveland Clinic; [6]NIH-NIDDK; [7]Stony Brook Univ Med Ctr; [8]Duke Univ; [9]Louisiana State Univ; [10]Univ North Carolina; [11]Children's Hosp at Scott & White; [12]Univ Washington; [13]Univ Minnesota.*

The recently completed NIH/NIDDK-funded FSGS Clinical Trial compared two active pharmacological interventions' effects on inducing and sustaining remission in patients with FSGS. Eligibility criteria included biopsy-confirmed primary FSGS, steroid resistance (Up/c >1.0 after a minimum of 4 wks of steroid therapy), and eGFR > 40 ml/min/1.73m².

A total of 192 children and adults age 2 to 40 years were enrolled at 66 sites across the U.S. and Canada. A total of 138 patients were randomized to a 12-month treatment regimen, 72 to cyclosporine (CSA) and 66 to a combination of oral pulse dexamethasone and mycophenolate mofetil (MMF/DEX). The primary outcome was assessed at 12 months based on complete remission (CR) Up/c < 0.2; partial remission (PR) Up/c < 50% of baseline and Up/c< 2; or no remission (NR). Participants with NR at 6 months were defined as treatment failures for the primary outcome. The main secondary outcome was sustained remission 6 months after withdrawal of the CSA or MMF/DEX.

Baseline characteristics of the patients were: 41 (30%) 2–12 years of age, 47 (34%) 13–17 years of age, 50 (36%) 18 or older; 53 (38%) African American; 73 (53%) male; mean eGFR 135 ml/min/1.73m² (range 42.0–408.8); mean Up/c 5.97 (range 1.04–31.77).

The FSGS-CT is the largest controlled trial of FSGS to date. We present the results of the primary and secondary analysis of the FSGS Clinical Trial as well as results of analyses of the safety of the regimens and of the progression of renal disease in these patients.

Disclosure of Financial Relationships: nothing to disclose

Results from a Composite Safety Endpoint Used To Evaluate the Cardiovascular Safety of Hematide™/Peginesatide in Patients with Anemia Due to Chronic Renal Failure Steven Fishbane,[1] Anatole Besarab,[1] Brigitte Schiller,[1] Robert Provenzano,[1] Adrian C. Covic,[1] Iain C. Macdougall,[1] Francesco Locatelli,[1] Andrzej Wiecek,[1] Carol Francisco,[2] Krishna R. Polu,[2] Martha Mayo,[2] Anne-Marie Duliege.[2] *[1]AFX01-12/14 Peginesatide Study Groups; [2]Affymax, Inc., Palo Alto, CA.*

Background: Peginesatide, a PEGylated, investigational, peptide-based erythropoiesis-stimulating agent (ESA), has been studied for treatment of anemia of chronic renal failure (CRF). A Composite Safety Endpoint (CSE) was prospectively defined in the 4 Phase 3 randomized controlled peginesatide trial protocols. Pooled (across-study) analyses of the CSE were prespecified to evaluate cardiovascular safety of peginesatide relative to comparators (darbepoetin alfa, epoetin alfa/beta). Peginesatide met the noninferiority primary Hb endpoint in all 4 studies.

Methods: Six CSE events were defined: all-cause death, stroke, myocardial infarction, and serious AEs of congestive heart failure, unstable angina, and arrhythmia; a blinded independent committee adjudicated the events. The noninferiority criterion was defined as an upper limit of the 2-sided 90% CI for the HR of ≤1.3 for the pooled analysis.

Results: Peginesatide met the noninferiority criterion compared to comparators in the pooled analysis. In the dialysis subpopulation, results were consistent with this finding. In the nondialysis subpopulation, an increased HR for peginesatide was observed, primarily due to a higher rate of CSE events of death, unstable angina, and arrhythmia.

Underline represents presenting author/disclosure.

	Dialysis+Nondialysis		Dialysis		Nondialysis	
	Peginesatide (N=1722)	Comparators (N=869)	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)
Patients w/CSE Events	22%	22%	23%	24%	22%	17%
Hazard Ratio (90% CI)	1.06 (0.91, 1.23)		0.95 (0.79, 1.13)		1.34 (1.03, 1.73)	

Conclusions: The overall cardiovascular safety profile of peginesatide was noninferior to comparator ESA in patients with anemia of CRF. Further, in the dialysis population, the CSE was not significantly different from epoetin. Differences in the CSE in non-dialysis patients for peginesatide compared to darbepoetin warrant further evaluation.

Disclosure of Financial Relationships: Consultancy: Roche, Watson; Grant/Research Support: Affymax, Takeda, Dynavax, Luitpold, Rockwell; Honoraria: AMAG, Abbott; Scientific Advisor: Affymax, AMAG, Rockwell

Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (PEARL 1 and PEARL 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents Iain C. Macdougall,[1] Robert Provenzano,[1] Pablo E. Pergola,[1] Raja Zabaneh,[1] Amit Sharma,[1] Bruce S. Spinowitz,[1] Andrzej Wiecek,[1] Diogo S. Belo,1 Chao H. Sun,[1] John Durham,[1] Rebecca J. Schmidt,[1] Carol Francisco,[2] Martha Mayo,[2] Anne-Marie Duliege,[2] Steven Fishbane.[1] *[1]AFX01-11/13 Peginesatide Study Groups; [2]Affymax, Inc., Palo Alto, CA.*

Background: Peginesatide, a PEGylated, peptide-based erythropoiesis-stimulating agent (ESA), has been studied for treatment of anemia due to chronic renal failure (CRF). PEARL 1 and 2 were Phase 3 randomized controlled trials that evaluated safety and efficacy of peginesatide compared to darbepoetin alfa for anemia in CRF patients not receiving dialysis or ESA treatment.

Methods: PEARL 1 enrolled 490 US patients; PEARL 2 enrolled 493 US and EU patients. Patients were randomized 1:1:1 to SC peginesatide once monthly (starting dose 0.025 or 0.04 mg/kg) or SC darbepoetin every 2 wks (starting dose 0.75 µg/kg), titrated to maintain Hb of 11-12 g/dL. Patients were to be dosed ≥52 weeks.

Results: In both studies, peginesatide was noninferior to darbepoetin in increasing Hb. In PEARL 2, approximately twice as many peginesatide patients received RBC transfusions; in PEARL 1, transfusion rates were similar in all treatment groups. Pooled analysis of the studies identified more deaths, unstable angina, and arrhythmia events for peginesatide than for darbepoetin.

	PEARL 1			PEARL 2		
	Peginesatide		Darbepoetin	Peginesatide		Darbepoetin
	0.025*	0.04*		0.025*	0.04*	
Mean Increase in Hb: BL to Wks 25-36, g/dL	1.4	1.6	1.4	1.5	1.7	1.4
% Pts w/Transfusions Through Wk 36	6	7	5	11	10	5
% Pts w/Hb Response[1]	93	94	94	91	93	95

*Starting dose (mg/kg). [1]Hb increase ≥1.0 g/dL and a Hb ≥11 g/dL during first 36 wks w/o transfusions in previous 8 wks.

Conclusions: The observed safety imbalance between peginesatide and darbepoetin in nondialysis CRF patients not previously receiving ESAs warrants further evaluation.

Disclosure of Financial Relationships: Consultancy: Amgen, Roche, Affymax, Takeda, Astellas, Vifor Pharma; Grant/Research Support: Amgen, Affymax, Vifor Pharma; Honoraria: Amgen, Roche, Affymax, Takeda, Astellas, Vifor Pharma; Scientific Advisor: Amgen, Affymax, Takeda, Astellas, Vifor Pharma

Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (EMERALD 1 and EMERALD 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin Alfa or Epoetin Beta Brigitte Schiller,[1] Francesco Locatelli,[1] Adrian C. Covic,[1] Edouard R. Martin,[1] Roderick V Clark,[1] Steven Zeig,[1] Marializa Bernardo,[1] Claudia E. Hura,[1] Nathan W. Levin,[1] Mark Kaplan,[1] Iain C. Macdougall,[1] Carol Francisco,[2] Krishna R. Polu,[2] Anne-Marie Duliege,[2] Anatole Besarab.[1] *[1]AFX01-12/14 Peginesatide Study Groups; [2]Affymax, Inc., Palo Alto, CA.*

Background: Peginesatide, a PEGylated, investigational, peptide-based erythropoiesis-stimulating agent (ESA), has been studied for treatment of anemia of chronic renal failure (CRF). EMERALD 1 and 2 were Phase 3 randomized controlled trials designed to evaluate safety and efficacy of peginesatide in hemodialysis (HD) patients previously treated with epoetin alfa or beta.

Methods: EMERALD 1 enrolled 803 US patients; EMERALD 2 enrolled 823 US and EU patients. Patients who received HD for ≥3 months and IV or SC epoetin for ≥8 wks were eligible for randomization. Patients were randomized 2:1 to receive IV or SC peginesatide once monthly or epoetin 1-3 times weekly. Peginesatide starting dose was determined using a conversion table based on screening epoetin dose, with doses titrated to maintain target Hb levels of 10-12 g/dL. Patients were to be dosed ≥52 weeks.

Results: In both studies, peginesatide met the primary endpoint and demonstrated noninferiority for efficacy in maintaining Hb; other efficacy endpoints were similar except for proportion in the target range in EMERALD 1. Hb excursions, excessive rates of rise, and important safety events such as death, stroke, and myocardial infarction had similar frequencies for peginesatide and epoetin.

	EMERALD 1		EMERALD 2	
	Peginesatide	Epoetin	Peginesatide	Epoetin
Mean Hb, g/dL				
Baseline	11.3	11.3	11.2	11.2
Weeks 29-36	11.1	11.3	11.1	11.1
% Pts w/Transfusions Through Week 36	10	9	8	10
% Pts w/Mean Hb in Target (Weeks 29-36)	63	72	64	66

Conclusions: Peginesatide is noninferior to epoetin in the maintenance treatment of anemia in dialysis patients. The safety profile of peginesatide is similar to that of epoetin in this population.

Disclosure of Financial Relationships: Scientific Advisor: Affymax, Inc.; Other: spouse employee at DaVita, Inc.

Prevention of Dialysis Catheter Lumen Occlusion with rt-PS Versus Heparin (Preclot): A Randomized Trial Brenda Hemmelgarn,[1] Louise M. Moist,[2] Charmaine E. Lok,[3] Marcello Tonelli,[4] Braden J. Manns,[1] Rachel M. Holden,[5] Martine Leblanc,[6] Paul E. Barre,[7] Nairne William Scott-Douglas.[1] *[1]Univ of Calgary; [2]Univ of Western Ontario; [3]Univ of Toronto; [4]Univ of Alberta; [5]Queen's Univ; [6]Univ of Montreal; [7]McGill Univ.*

Background: Central venous catheters (CVCs) are used for vascular access by more than 75% of incident, and up to 50% of prevalent, hemodialysis patients in North America. The optimal solution for locking CVCs to decrease the risk of catheter malfunction and bacteremia, the major complications of CVCs, is unknown.

Methods: We conducted a multi-centre, randomized controlled trial in 225 chronic hemodialysis patients with a newly inserted central venous hemodialysis catheter. The primary objective was to determine if substituting rt-PA (1 mg per lumen) for heparin once per week as a catheter locking solution would decrease the incidence of catheter malfunction, compared to locking with heparin alone (5000 units per mL). Secondary outcomes included catheter-related bacteremia. The study treatment period was six months; participants, investigators and trial personnel were blinded to treatment allocation.

Results: Catheter malfunction occurred in 40 (34.8%) patients assigned to heparin and 22 (20.0%) patients assigned to rt-PA, with an almost two-fold increased risk of catheter malfunction for patients treated with heparin compared to rt-PA (hazard ratio [HR] 1.91; 95% confidence interval [CI], 1.13 to 3.22; P=0.015). Catheter-related bacteremia occurred in 16 (13.9%) patients assigned to heparin and 5 (4.6%) assigned to rt-PA (1.02 and 0.32 episodes per 1,000 patient-days in heparin and rt-PA groups; p=0.027). The risk of all-cause bacteremia was three-fold higher in the heparin compared to t-PA arm (HR 3.16; 95% CI 1.16 to 8.61; P = 0.025). The risk of adverse events, including bleeding, was similar in the two groups.

Conclusions: The use of once weekly rt-PA compared to heparin as a locking solution for CVCs significantly reduced the incidence of both catheter malfunction and bacteremia.

Disclosure of Financial Relationships: nothing to disclose

Should We Reduce LDL Cholesterol in Patients with Chronic Kidney Disease? The Results of the Study of Heart and Renal Protection (SHARP) The Sharp Collaborative Group, *c/o Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom.*

Background: Reducing low-density lipoprotein cholesterol (LDL-C) has been shown to reduce the incidence of atherosclerotic events in many types of patients, but it remains unknown whether it is beneficial for people with chronic kidney disease (CKD).

Methods: Patients with advanced CKD (blood creatinine above 1.7 mg/dL in men or 1.5 mg/dL in women) and without known history of myocardial infarction or coronary revascularization were randomized to receive ezetimibe 10mg plus simvastatin 20mg daily versus matching placebo. The pre-specified key outcome was major atherosclerotic events (defined as first nonfatal myocardial infarction or coronary death, non-haemorrhagic stroke, coronary or non-coronary revascularization).

Results: 9438 patients were randomized, of whom one third were on dialysis. Mean age was 61 years, two thirds were male, one fifth had diabetes mellitus, and one sixth had vascular disease. Among patients not on dialysis, two fifths were Kidney Disease Outcomes Quality Initiative stage 3, two fifths stage 4, and one fifth stage 5. Baseline LDL-C was 108 (SD 34) mg/dL and, compared with placebo, allocation to ezetimibe/simvastatin yielded an average LDL-C reduction of 33 mg/dL during mean follow-up of 4.1 years. Over this period, there were 1146 first major atherosclerotic events, which included 443 nonfatal myocardial infarctions or coronary deaths, 305 non-haemorrhagic strokes, and 638 revascularizations (with some patients having more than one such event). Allocation to ezetimibe/simvastatin yielded a highly significant 16% (95% CI 6-26%; p=0.002) reduction in the incidence of major atherosclerotic events. Similar reductions were observed among patients who, at baseline, were or were not on dialysis. During follow-up, there were about 2100 cases of end-stage renal disease, 2000 total deaths and 900 incident cancers. Ezetimibe/simvastatin did not increase the risks of non-vascular mortality or cancer incidence.

Conclusions: Reducing LDL-C with ezetimibe/simvastatin safely produces substantial reductions in the risks of major atherosclerotic events among patients with CKD.

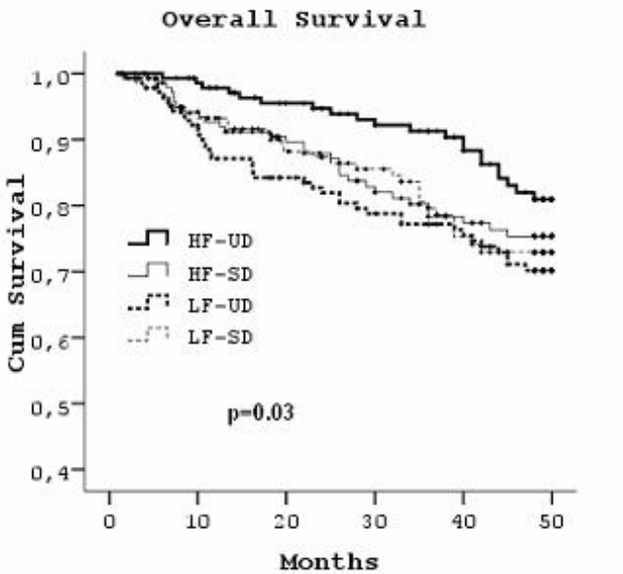
Disclosure of Financial Relationships: nothing to disclose

Underline represents presenting author/disclosure.

The Impact of Membrane Permeability and Quality of Dialysate on Cardiovascular Outcomes in Hemodialysis Patients Gulay Asci,[1], Mehmet Ozkahya,[1], Huseyin Toz,[1], Soner Duman,[1], Mustafa Cirit,[2], Selen Bayraktaroglu,[1], Savas Sipahi,[1], Hamad Dheir,[1], Devrim Bozkurt,[1], Sinan Erten,[3], Ali Basci,[1], Ercan Ok.[1] *[1]Ege University, Turkey; [2]Ataturk Hospital, Turkey; [3]Bozyaka Hospital, Turkey.*

Introduction: The effect of high-flux dialyser (HF) use on survival is controversial, while the effect of ultrapure dialysate (UD) use has never been investigated.

Methods: In this prospective, randomized, controlled trial, we examined the impact of membrane flux and dialysate quality on survival along with cardiovascular (CV) surrogate markers (coronary artery calcification-CAC, carotid artery intima-media thickness-IMT). We randomly assigned 704 prevalent hemodialysis (HD) patients to either HF or low-flux (LF) dialyser and either UD or standard dialysate (SD) arms by 2x2 factorial design. Follow-up was 4 years. Primary outcome was composite of fatal and non-fatal CV events. **Results:** Despite trends favoring HF and UD, primary outcome was not different between HF and LF groups and between UD and SD groups, as well as overall and CV survival and progression of CAC and IMT. In patients with arterio-venous (AV) fistula (n=576), composite CV event-free survival was higher in HF group compared to LF group (p=0.02); also overall and CV survival was better in HF group. In adjusted models, HF use was associated with a 39% risk reduction for composite CV events (95% CI 0.38-0.97, p=0.03). Composite CV event-free survival was higher in UD group than SD group among patients with HD duration longer than 3 years (n=399) (adjusted HR 0.55, 95% CI 0.31-0.97, p=0.04); CRP levels and CAC progression within 4 years were lower in UD group. Combined treatment with HF and UD had best overall survival rate in patients with AV fistula.



Conclusions: Use of HF membrane improves survival in patients with AV fistula; UD provides better outcomes in patients with longer HD duration.

Disclosure of Financial Relationships: nothing to disclose

The Effect of Pyridorin on the Progressive Renal Dysfunction of Overt Type 2 Diabetic Nephropathy Edmund J. Lewis, Julia Lewis, Tom H. Greene, Robert C. Atkins, Itamar Raz, Lawrence G. Hunsicker. *for The Collaborative Study Group, Chicago, IL.*

Pyridorin (Pyr) inhibits formation of advanced glycosylation end products and scavenges reactive oxygen species and toxic carbonyls. We report a double-blind, randomized, placebo-controlled Phase 2b trial of 307 subjects with type 2 diabetic nephropathy with serum creatinine (Scr) [1.3-3.3 mg/dl in females; 1.5-3.5 mg/dl in males] and urine protein:creatinine ratio (PCR) ≥ 1200 mg/g. Subjects were randomized to oral twice daily placebo, Pyr 150 mg or Pyr 300 mg for 52 weeks. Stable ACE/ARB dosage and stable blood pressure with concomitant antihypertensive therapy were maintained. The primary endpoint was change in Scr from baseline to 52 weeks. To determine the effect of Pyr according to severity of kidney disease, prespecified analyses were employed to study baseline Scr subgroups. Patient demographics included: age 63.9 ±9.5 (SD) BMI 33.6±6.5; diabetes duration 17.6 ±8.5 yrs; nephropathy duration 5.3±4.5 yrs, systolic BP 138.4 ±13.9; Scr 2.2 ±0.57 mg/dl; PCR 3030±1971 mg/G and were balanced among the 3 groups. Primary results revealed the mean change in Scr at week 52 was: placebo (n=103) 0.36 mg/dl; Pyr 150 (n=99) 0.43 mg/dl; Pyr 300 (n=105) 0.35 mg/dl (both Pyr groups vs placebo p=0.651). Analysis of covariance for treatment interaction with baseline Scr as a continuous variable revealed Pyr 150 vs placebo (p=0.006); Pyr 300 vs placebo (p=0.012); Pyr (both groups) vs placebo (p=0.002). Examination of baseline Scr tertiles revealed the change in Scr at 52 wks in the lowest Scr tertile (Scr 1.3 – 1.86 mg/dl): placebo (n=33) 0.28 ±0.62 mg/dl; Pyr 150 (n=33) 0.06 ±0.22 mg/dl; Pyr 300 (n=36) 0.14±0.2 mg/dl (Pyr both groups vs placebo p=0.046). There was no significant treatment effect in the middle (Scr 1.86-2.44) (p=0.573) or upper (Scr >2.44) (p=0.097) tertiles. There were no significant adverse events associated with Pyr. We conclude that Pyr failed to significantly alter the progression of Scr at one year follow-up in the total patient population studied. However slowing of progression in that subgroup with the most intact renal function (Scr 1.3-1.86 mg/dl) reached statistical significance.

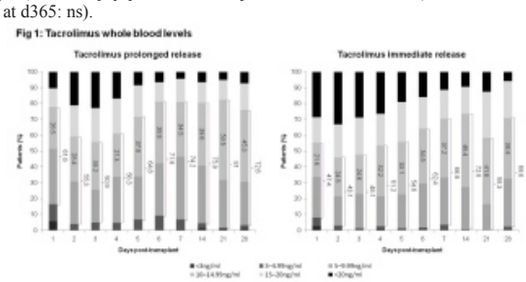
Disclosure of Financial Relationships: Grant/Research Support: NephroGenex

Early Post-Transplant Blood Levels in *De Novo* Renal Recipients on Tacrolimus Prolonged Release (TacQD) v Tacrolimus Immediate Release (TacBD) in a Phase III Double-Blind Double-Dummy Study Bernd Krüger,[1] Bernhard Banas,[2] Philippa C Tomlinson,[3] Bernhard K. Krämer.[1] *[1]Mannheim University Hospital, Germany; [2]University Regensburg, Germany; [3]Astellas Pharma Europe Ltd, United Kingdom.*

Introduction: Rapidly achieving consistent therapeutic blood levels prevents rejection and toxicity in renal recipients. This analysis compares Tac whole blood trough levels (TL) for 28 days (d) post-transplant with TacQD or BD.

Methods: Patients were randomised to TacQD (*n*=331) or BD (*n*=336) at 0.2mg/kg/d with MMF (2g/d to d14 then 1g/d) and 3-month steroid taper (20–0mg/d, d2–85) without induction. The first doses of TacQD/BD and MMF were given pre-transplant. Target levels for Tac were 10–15ng/ml (d1–28), 5–15ng/ml (d29–168) and 5–10ng/ml to d365. Tac TL, time to target and dose changes to remain in target were determined.

Results: More patients on Tac QD were in target range and in 5–15ng/ml throughout the study. Median time to target (2 consecutive TL in target ±10% or 3 if period between TL ≤2d) was 9d for both TacQD and BD; mean number of dose changes were 3.0 (3.0) and 3.5 (3.0), respectively. Fewer patients (%) on TacQD than BD were exposed to TL ≥20ng/ml: d1 (10.2 v 28.6), 4 (16.9 v 26.4), 7 (4.5 v 11.3), 14 (6.5 v 9.3), 21 (5.1 v 12.7), and 28 (7.4 v 5.8). A minority of patients had TL <5ng/ml; TL <3ng/ml were infrequent. Mean dose during wk 4 was higher with TacQD (0.21 v 0.17mg/kg/d), TL similar (12.3 v 12.8ng/ml), and biopsy-proven acute-rejection-free rate similar (0.83 v 0.87 at d28; 0.79 v 0.83 at d365: ns).



Conclusions: Initiating therapy with TacQD preoperatively resulted in more patients attaining and remaining in target early post-transplant than with TacBD. Time to target and number dose changes to remain in target were no different to TacBD. Fewer patients on TacQD were exposed to potentially toxic blood levels, especially in wk 1.

Disclosure of Financial Relationships: nothing to disclose

Carnitine Improves Gait Speed (GS)and Sit-to-Stand (STS) Measures in Chronic Hemodialysis (HD) Patients with Low Baseline SF36 Physical Composite Scores Alison Leah Steiber *Department of Nutrition, Case Western Reserve University, Cleveland, OH.*

Patients on HD experience decreased nutritional and functional status leading to decreased quality of life. The purpose of this study was to determine the efficacy of carnitine on functional status in HD patients with low SF36 physical composite scores(PCS). This was a 24 week, double blind, RCT conducted at dialysis centers in the Midwest. Study inclusion criteria were: > 19 years old, > 6 months on dialysis, HD treatments 3 times a week for > 3 hours, a SF36 PCS of <40, and a free carnitine of <40µmol/L. Primary outcomes were: functional status measured as GS, STS, and 6-minute walk (MW), subjective global assessment (SGA), and SF36. Statistical analysis was done with SPSS and significance was defined as p<0.05. Patients were screened from 8 centers, 93 agreed to participate, 67 met criteria, and 13 were lost to attrition. Patients were randomized to either treatment with IV carnitine at 20mg/kg or placebo (50cc D5W). There were no significant differences between parameters at baseline. The mean age, BMI, and serum albumin were 69±14 years, 28±6 and 3.8±0.4mg/dl, respectively. The sample was 46% female, 73% Caucasian, 23% African American and 4% Hispanic. 48% had type 2 diabetes and 35% had hypertension as their primary etiology. Baseline PCS, CRP, total, free and AC were 31.5±7.5, 15.2±19.5µg/dL, 36.04±11.7µmol/L, 20.4±7.6 µmol/L, and 15.8±6.0 µmol/L. Using a multiple linear regression (MLR) model with group, baseline PCS, SGA and CRP as independent and GS change as dependent variables, carnitine treatment was a significant predictor of GS change (group β=-0.4; R2 = 0.5, p=001). Similarly, in a MLR model with group and CRP as independent and STS change as the dependent variable, carnitine was a significant predictor of STS change (β=0.4, R2 = 0.2, p=0.05). Group was not a significant predictor of MW or PCS change. In this study, HD patients with low PCS demonstrated significant improvements in clinically relevant parameters due to carnitine treatment.

Disclosure of Financial Relationships: Consultancy: Pentech Inc.; Grant/Research Support: Genzyme Inc, Abbott, Sigma Tau Pharmaceuticals Inc.; Honoraria: Pentech Inc; Sigma Tau Pharmaceuticals, Abbott; Scientific Advisor: Nephroceuticals

Underline represents presenting author/disclosure.

The Efficacy and Safety of Lixivaptan in Patients with Euvolemic Hyponatremia: Results of the LIBRA Study William Abraham,[1] Peter Gross,[2] Daniel G. Bichet,[3] Johannes Hensen,[4] Deodatta Chafekar,[5] Richard Josiassen,[6] Lawrence Mcdermott,[7] Barry Ticho,[8] Cesare Orlandi.[7] *[1]The Ohio State University, Columbus, OH; [2]Universitatsklinikum C.G. Carus, Dresden, Germany; [3]Hopital du Sacre-Coeur, Montreal, Canada; [4]Klinikum Hannover-Nordstadt, Hannover, Germany; [5]Shri Samarth Hospital, Nasik, India; [6]Drexel University College of Medicine, Philadelphia, PA; [7]Cardiokine Biopharma, Philadelphia, PA; [8]Biogen Idec, Weston, MA.*

Background: Hyponatremia is the most common laboratory abnormality in hospitalized subjects and is associated with increased mortality, cognitive impairment, gait disturbances, falls, and fractures. No prospective study has evaluated the relationship between hyponatremia symptoms and serum sodium concentrations (SNa). Lixivaptan is a vasopressin receptor antagonist that increases SNa in patients with hyponatremia without detrimental effects on vital signs, renal function, and electrolytes.

Methods: LIBRA was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the impact of lixivaptan on SNa and cognitive function in patients with euvolemic hyponatremia associated with the syndrome of inappropriate antidiuretic hormone secretion. Hospitalized patients with euvolemic hyponatremia (SNa <130 mEq/L) were randomized to receive lixivaptan or placebo in addition to standard of care. Lixivaptan was titrated based on SNa from 50 mg QD to a maximum 100 mg QD or to a minimum of 25 mg QD. Patients were treated for a total of 30 days in inpatient and outpatient settings. Symptomatology was carefully evaluated at baseline to better characterize the population. The primary endpoint was change from baseline in SNa at day 7. Secondary endpoints included assessment of SNa at other time points and patients' cognitive function using the Trail-Making Test-Part B and Medical Outcomes Study-6 cognitive function scale.

Results: From 30 July 2008 to 16 March 2010, 106 patients were enrolled in LIBRA. Results from LIBRA will be presented.

Conclusions: LIBRA will further characterize the population with euvolemic hyponatremia and establish the efficacy and safety of the vasopressin receptor lixivaptan in the treatment of this condition.

Disclosure of Financial Relationships: Consultancy: Cardiokine

Underline represents presenting author/disclosure.