and OV/BV, and ObS/BS as dependent variables, showed the independent variables to be significantly predictive of the dependent variables, however positively for iPTH and inversely for Fetuin A. MGP was below the normal average: in hyperparathyroidism, mixed osteodystrophy and low turnover, was not significantly different (3.94±0.86, 3.40±0.99 and 5.64±2.4 nmol/L, respectively). By dividing MGP serum values in tertiles, the mean values of OV/BV were different (ANOVA $p<0.04$), with higher value in the higher MGP tertile. One for each type of osteodystrophy, a significant correlation between BFR/BS and MGP serum values was found ($p<0.05$). A significant correlation was also found between MGP and the variable Trabecular Thickness (Tb.Th).
Conclusions: Fetuin-A and MGP have a direct effect on bone formation, presumably mediated by the TGF-β/BMP system. Fetuin-A, as opposed to MGP, inhibits bone turnover and bone cell activity by inhibiting the TGF-β/BMP complex, a protein cytokine system which appears to be an important regulator of bone formation and probably a factor playing important role in renal osteodystrophy.

MO016 EFFECTS OF SEVELAMER AND CALCIUM CARBONATE ON BONE MINERALISATION AND TURNOVER IN CHRONIC MAINTENANCE HAEMODIALYSIS PATIENTS

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Introduction and Aims: A 1-year, randomised, open-label bone biopsy study was conducted to compare the effects of phosphate binder therapy with sevelamer hydrochloride (S) versus calcium carbonate (C) on bone.
Methods: Adult patients on haemodialysis ≥3 times/week (for ≥3 months) with hyperphosphataemia up to 2.6 mmol/l (8.1 mg/dl) receiving treatment with a phosphate binder underwent 2 bone biopsies one year apart (taken from the iliac crest following double tetracycline labelling). Patients were stratified according to bone turnover status (high versus low/normal) and randomised to S or C. Bone mineralisation was assessed by changes in mineralisation lag time (Mlt) and osteoid thickness (OTh) while bone turnover was determined by changes in activation frequency (Acf), number of osteoblasts and osteoclasts/bone perimeter and bone formation rate/bone surface (BFR/BS). Trabecular microarchitecture was assessed by changes in cancellous bone volume (BV/TV) and trabecular separation (TbSp).
Results: Sixty-eight patients completed the study (S=33; C=35). Treatment groups were comparable with regard to baseline demographics. During the study, serum phosphorus, calcium and iPTH were well-controlled in both groups, although serum calcium was consistently lower and serum iPTH higher in the S group. More patients could receive vit D and the mean dose of vit D increased in S but was unchanged in C (p=0.03). At study end, there were no significant changes from baseline in Mlt with either S or C (-3.3 ± 42.6 vs 7.9 ± 98.9 days). OTh significantly increased in S and C (1.4 ± 5.9 and 1.1 ± 5.2 μm; p=0.03) but there was no significant difference between treatments. Baseline median Acf was below normal (0.47-0.72/year) in both groups. There were no significant changes from baseline or between groups in median Acf or any of the parameters used to assess bone turnover, with the exception of a significant increase in BFR/BS in the S group (median change 0.5 ± 2.9 mm^3/cm^2/year; p=0.02 vs baseline). Fewer S patients developed below normal Acf levels during the study (3% S vs 14% C) while more S patients increased BV/TV towards normal (24% S vs 14% C). Seven out of 10 S patients with abnormally high TbSp at baseline were within the normal range at the end of the study. This was not found in any C patient. Percentage of patients with low bone turnover went from 63% to 54% in S and from 54% to 51% in C. There were no significant differences in development of predominant hyperparathyroid bone disease. In one C patient, a severe mineralisation defect was seen at baseline but no such defect was seen in S or C patients at the end of the study.
Conclusions: Serum phosphorus and iPTH levels were well-controlled in both S and C. There was a trend towards less suppression of bone turnover and improvement in microarchitecture in S but not in C. No development of osteomalacia was seen with S or C.

Late breaking trials

MO017 RENAL BIOREPLACEMENT THERAPY IS ASSOCIATED WITH A REDUCTION IN MORTALITY IN PATIENTS WITH ACUTE RENAL FAILURE: RESULTS OF A RANDOMIZED, MULTI-CENTER, PHASE II TRIAL

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Introduction and Aims: The mortality rate for patients with acute renal failure (ARF) remains unacceptably high despite advances in dialysis therapy and acute medical care. Although dialysis therapy removes waste products and corrects fluid imbalance, it does not provide critical functions normally performed by human renal tubule epithelial cells (HREC). The extracorporeal delivery of HREC has the potential to replace the absorptive, metabolic, endocrine and immunologic function of normal kidney tubular elements which are absent in ARF. Renal Bioreplacement therapy (RBT) is a cell-based therapy comprised of a conventional hemofilter lined by a monolayer of HREC. We hypothesized that short-term (up to 72 hours) replacement of renal tubular function with RBT would improve survival in patients with ARF when compared to conventional CVVH therapy alone.
Methods: Study RAD-002 was a randomized, controlled, open-label trial conducted at 10 centers in the United States. Fifty-eight patients (age 18–80 years) with ARF requiring dialysis therapy in the ICU were randomized (2:1) to receive CVVH + RBT (n=40) or CVVH alone (n=18). Patients were required to have received CVVH for a minimum of 4 hours (maximum 48 hrs), anticipated to remain in the ICU for at least 96 hours, and to have in addition to ARF, at least one non-renal organ failure or the presence of sepsis. The primary endpoint was all-cause mortality at day 28. All-cause mortality at day 90 and day 180, time to recovery of renal function, time to ICU and hospital discharge, and safety were also assessed.
Results: Baseline demographics and clinical characteristics were well balanced between treatment groups. At day 28, the mortality rate was 33% in the CVVH + RBT group and 61% of the CVVH group (p=0.08). Survival through day 180 was greater in the CVVH + RBT group (p=0.04) and the Cox hazard ratio indicated that the risk of death was 50% of that observed in the CVVH alone group. RBT therapy was also associated with more rapid recovery of kidney function, faster discharge from the ICU and a reduction in the time to hospital discharge (p= 0.08 to 0.11). Treatment with RBT therapy was well-tolerated and the adverse event profile was consistent with that expected for a seriously ill patient population with ARF.
Conclusions: The results of this Phase II study demonstrate that treatment with RBT for up to 72 hours resulted in a marked improvement in survival in patients with ARF which was sustained throughout the 6 month study. RBT has the potential to improve patient survival while decreasing the cost of care for this important unmet medical need.

MO018 IgACE: FIRST MULTICENTRIC PROSPECTIVE DOUBLE BLIND RANDOMIZED AND PLACEBO CONTROLLED STUDY ON ACE-INHIBITORS (ACE-I) ADMINISTRATION IN MODERATELY PROTEINURIC IgA NEPHROPATHY (IgAN) IN THE YOUNG

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Introduction and Aims: The benefits of ACE-I in IgAN were deducted from retrospective studies, that evidenced the advantages particularly in hypertensive patients (pts) with nephrotic proteinuria (pto). The only prospective randomized controlled trial (RCT) in literature enrolled 44 adult pts referred to a single centre, with pto between 0.5 and 5.5 g/day and wide range of kidney function.
Methods: In the project Biomedicine and Health Research for the EC we designed the first multicentric prospective double blind RCT, choosing children and young pts (<35 yrs) with IgAN, mild and stable pto (>1g and < 3.5 g/1.73m^2/day) and GFR >60 ml/min/1.73m^2 (DOQI 1e2). Fifty-seven pts, mean age 19.9 yrs (ranging 9 – 35 yrs), randomized to receive

Benazepril (ACE-I, 23 pts) or placebo (PL, 34 pts) completed the trial (mean follow-up 42 months). The primary outcome was represented by progression of the kidney damage expressed as decreasing of 30% of the basal GFR and/or worsening of pto until the nephrotic range (>3.5g and 1.73 m^2/day). Secondary outcome was pto remission (<0.5 g/1.73m^2/day), until disappearance (<160 mg/1.73m^2/day). The survival was evaluated by Kaplan Meier univaried analysis and Log rank test.
Results: A single patient (4.3%) in the ACE-I group and 5 pts (14.7%) in the PL group showed a worsening of GFR > 30% (P = 0.18). No pts treated with ACE-I developed nephrotic syndrome, vs 7 pts (20.6%) in PL group. The primary outcome resulted significantly different between two groups: 1 patient in ACE-I and 9 (26.5%) in PL (Log rank P = 0.035). A stable remission of the proteinuria for> 6 months was observed in 13/23 (56.5%) ACE-I pts vs 3/34 (8.8%) of PL pts (Log rank P = 0.0330), with regression in 17.4% of the ACE-I pts and in none of the PL pts (Log rank P = 0.029). The multivariate Cox analysis showed that the treatment with ACE-I was the only positive predictive factor while no effects were observed for sex, age, GFR and both basal values of blood pressure or proteinuria.
Conclusions: In conclusion, in the young with mild pto ACE-I treatment showed a protective effect against the worsening of the kidney function that reached levels of statistical significance considering the primary outcome of functional decline and appearance of nephrotic syndrome. The extremely significant effect in inducing a complete pto remission underlines the potential benefits of this therapy in the long term.

MO019 ❋ ★ RESULTS OF A MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED TRIAL FOR THE TREATMENT OF AMYLOID A (AA) AMYLOIDOSIS-ASSOCIATED RENAL DISEASE WITH NC-503 (EPRODISATE DISODIUM)

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Introduction and Aims: Amyloid A (AA) amyloidosis is a relatively rare but potentially life-threatening complication of long standing chronic inflammatory conditions. Although insoluble amyloid deposits may be found systemically, renal involvement (nephrotic syndrome and progressive loss of GFR) dominates the clinical picture. Currently, there is no specific approved drug for the treatment of this disease. NC-503 (eprodisate disodium) belongs to a new class of anti-amyloid compounds. Results from in vivo models of AA amyloidosis showed that NC-503 could reduce amyloid tissue deposition. In order to evaluate the efficacy and safety of NC-503 we performed a multi-center, randomized, double-blinded, placebo-controlled trial in patients with AA amyloidosis presenting with renal involvement.
Methods: 183 adults with a biopsy confirmed diagnosis of AA amyloidosis from 27 centers were randomized 1:1 to NC-503 or placebo for 24 months. The primary outcome was a composite assessment of renal function to classify disease as worsened (50% reduction in CrCl, doubling of SCr, progression to dialysis, or death), improved (50% increase in CrCl and no parameters of worsened disease) or stable, compared to baseline.
Results: NC-503 treatment was associated with a 42% reduction in risk of renal decline or death (95% CI 37-93%, p=0.025). The risk reduction was independent of baseline CrCl, proteinuria, underlying disease, drugs acting on the renin-angiotensin system or SAA concentrations. The NC-503 treated patients experienced a 30.1% reduction in the annual rate of loss of renal function as measured by the slope of CrCl compared to placebo (-10.9 vs -15.6 ml/min/1.73m^2/year). as[LD1] well as a longer time to doubling of SCr (p=0.081), 50% decrease in CrCl (p=0.029) or progression to dialysis/ESRD (p=0.19). NC-503 and placebo treated patients had a similar incidence of serious or non-serious adverse events (36% vs 42%, and 98% vs 93%, respectively).
Conclusions: This first multi-center trial of an anti-amyloid agent for the treatment of AA amyloidosis found that NC-503 had clinically meaningful and statistically significant beneficial effects on renal disease progression.

MO020 INCREASED MORTALITY ASSOCIATED WITH CORONARY ARTERY CALCIUM SCORES AND CALCIUM CONTAINING PHOSPHATE BINDERS: LONG TERM RESULTS FROM A RANDOMIZED CONTROLLED TRIAL IN NEW DIALYSIS PATIENTS

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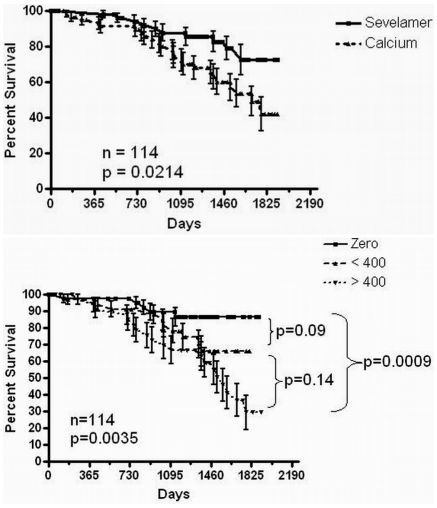
Introduction and Aims: Patients on hemodialysis given calcium containing phosphate binders (CCPB)experience accelerated vascular calcification as compared to those subjects given sevelamer hydrochloride (SEV). However, there has been no evidence of a clinical outcome difference in subjects given either calcium or non-calcium containing phosphate binders.
Methods: We enrolled new dialysis patients into an 18 month randomized clinical trial evaluating the use of either CCPB or SEV. Enrollment began in Sep 2000 and ended Jun 2001. Subjects underwent serial evaluation of coronary artery calcification with EBCT.
114 subjects had a qualifing baseline EBCT. Subjects were given either CCPB or SEV for up to 18 months. Follow up was assessed through Dec 31st, 2005.
Kaplan-Meier methodology was used to assess mortality. Subjects were censored at the time of death, time of kidney transplantation or if lost to follow up.
Results: The study population consisted of 114 adult hemodialysis pateints. Fifty-four were reandomized to SEV and 60 were randomized to CCPB. Mean age was 51 years, 49% were male, 44% were caucasian and 27% were african-american. Diabetes was the cause of ESRD in 56% and 28% had clinical evidence of ASCVD (history of MI, angina, angioplasty, known CAD, cerebrovascular disease, claudication, lower extremity intervention for atherosclerosis or aortic aneursym).
There was a significant difference in survival between subjects given SEV and CCPB as shown in Figure 1.There were significant differences in survival between subjects with no evidence of coronary artery calcium when compared to those with either modest or severe coronary artery calcification (calcium scores less than or greater than 400).



Conclusions: Coronary artery calcium score at entry into hemodialysis was strongly associated with survival. Furthermore, subjects randomized to CCPB experienced a marked increase in mortality as compared to subjects randomized to SEV.
Together with the data showing that provision of CCPB accelerates, while SEV attenuates, the progression of coronary artery calcification, these data support the use of SEV in subjects with evidence of vascular calcification.