with Ad-κB, an adenoavirus expressing a mutated κB molecule which blocks NFκB signaling. The inhibitory effect of LPS and IFNγ on IL-4 and TGFβ expression was abrogated in cells co-transfected with Ad-κB and AdIL4/AktGFG compared to AdIL4 or AdGFG alone, indicating that the inhibitory effect is NFκB dependent. This study demonstrates that the interaction of transfected macrophages with the inflamed microenvironment can result in an attenuation of transgene expression, an observation that has important implications for gene therapy in inflammatory disease.

**O146 dispose PROTEASOMES ARE THE TARGET OF ANGIOTENSIN II INHIBITION THERAPY**

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The transcriptional factor NF-κB plays a key role in inflammatory glomerular diseases. Under specific stimuli the complex IKB/NF-κB is dissociated and NFκB translocates into the nucleus where, by binding specific DNA consensus sequences, it initiates the transcription of pro-inflammatory factors. The intracytoplasmic proteases proteasomes regulate NF-κB activation by modulating the degradation of ubiquitinated IκB.

Since we recently demonstrated that ACE-inhibitors (ACE-I) and Angiotensin II receptor antagonists (AT1-RA) down-modulate in mesangial cells (MCs) the effects induced by aberrantly glycosylated IgA, we aimed to evaluate the role of NF-κB by its nuclear translocation in electrophoretic mobility shift assay (EMSA) and immunoperoxidase and by evaluating the NF-κB gene transcription in RT-PCR.

2) The IκB polyubiquitination (proteasome system activity) by western blot. Desialylated and degalactosylated IgA (deSia/deGal IgA) significantly increased the NF-κB mRNA synthesis (relative units compared to GAPDH mRNA) (by 66% in comparison to basal values) and particularly increased the NF-κB mRNA synthesis (relative units compared to GAPDH mRNA) (by 66% in comparison to basal values) and particularly increased the NF-κB mRNA synthesis (relative units compared to GAPDH mRNA) (by 66% in comparison to basal values) and particularly increased the NF-κB mRNA synthesis (relative units compared to GAPDH mRNA) (by 66% in comparison to basal values) and particularly increased the NF-κB mRNA synthesis (relative units compared to GAPDH mRNA) (by 66% in comparison to basal values) and particularly.

Our data suggest that the Ang II antagonism inhibits NF-κB activation in mesangial cells stimulated by aberrantly glycosylated IgA by blocking the proteasome activity, a new interesting tool of molecular therapy.

**O147  dispose EFFECT OF TIMING OF ADMINISTRATION ON THE ANTIPROTEINURIC ACTIVITY OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR**

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To assess whether timing of administration can influence the antiproteinuric effect of angiotensin-converting enzyme inhibitor (ACEI), 42 proteinuric Japanese patients with various underlying etiologies and mildly reduced renal function were studied with ambulatory blood pressure monitoring and measurement of protein in timely collected urine. Trandolapril (TRP), 3 mg, was given at 7 AM once daily initially, then at 10 PM once daily, and finally the dose of 1 mg was administered three times daily after meal for 4 weeks of each regimen interspersed with the washout period of 2 weeks in a double-blind crossover fashion. The circadian rhythm of their blood pressure was almost same during each regimen, while antiproteinuric effects were the most prominent during the period of the night administration when compared with at the morning once daily (the mean reduction rate in daily proteinuria of -67.4% by the night morning vs. -49.9% by the morning one). The efficacy of Trandolapril during the period of the tid. administration varied among the individuals.

The changes in the levels of the blood neurohormones was same among three regimen, while natriuresis, kaliuresis, and urinary makers for the activity of the intra-renal RAS was the most prominently enhanced during the period of the night regimen. Interestingly, those with the poor response to the max-dose of Trandolapril during the morning administration (the reduction rate of the proteinuria less than -10%) showed a significant response after the change to the night regimen (the response rate up to -34.4%). The ACE gene polymorphisms did not explain the improvement. Our results have shown the clinically important results of considering the time on administrating of ACEI.

**O148  dispose EFFECTS OF LOSARTAN AND AMLODIPINE ON PROTEINURIA AND URINARY TGF-β1 EXCRETION IN PATIENTS WITH IGA NEPHROPATHY**

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TGF-β1 is the major profibrotic cytokine involved in the development and progression of various renal diseases. Angiotensin II upregulates TGF-β1 and also contributes to the appearance of proteinuria. Urinary TGF-β1 reflects TGF-β1 production in the kidney, and urinary TGF-β1 excretion is known to be increased significantly in patients with IgA nephropathy. The aim of the present study was to compare the effects of losartan and amlodipine on proteinuria, as well as on serum and urine TGF-β1 levels in IgA nephropathy patients. Thirty six biopsy proven hypertensive IgA nephropathy patients with proteinuria and serum creatinine less than 3mg/dl were enrolled in double blind, controlled trial for 12 weeks using losartan 50 mg (n=20) or amlodipine 10 mg (n=16) daily. Both treatments controlled blood pressure to a similar degree, but only losartan significantly reduced urine protein excretion (2.3 ± 1.5 g/day at baseline and 1.2 ± 1.5 g/day at 12 week, p<0.05) without significant change in nPNA (1.3 ± 0.3 g/kg/day at baseline and 1.2 ± 0.3 g/kg/day at 12 week). Losartan also significantly reduced urinary TGF-β1 excretion (38.3 ± 36.3 pg/mg creatinine at baseline and 21.2 ± 14.8 pg/mg creatinine at 12 week, p<0.05). In contrast, amlodipine had no affect on urinary TGF-β1 excretion.

Both losartan and amlodipine failed to reduce serum TGF-β1 levels. Renal function and other biochemical parameters did not change during the study period. The results indicate that with similar control of blood pressure, losartan and amlodipine have different effects on urinary protein and TGF-β1 excretion. These differences might be important for the management of IgA nephropathy.

**FC26 Hepatitis**

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Hepatitis B vaccination in chronic failure (CRF) patients results in low protective antibody levels and low rates of seroconversion. A randomized controlled trial was carried out to study the effect of GM CSF given along with Inj. Engerix B vaccine in patients with CRF, 54 patients of CRF (S. Creatinine varying from 2 mg/dl to > 8 mg/dl and / or on dialysis) were randomized to two groups(Gps). 28 (Gp A) patients (20 males & 8 females) were given 30μg of GM-CSF weekly for 5 weeks post vaccination. The other group of 26 patients (Gp B) received placebo. The virological response (HbsAg negativity) was noted in 14/28 patients in Gp A and 0/26 patients in Gp B. This study demonstrated that GM-CSF vaccination is safe and effective in CRF patients with low antibody responses to the current hepatitis B vaccine.
females) received only 3 doses of 2 ml of Inj. Engerix B at 0,1,2 months and 26 (Gp B) patients (18 males & 8 females) received 150 μg each of GM CSF (Leucomax) s/c with 3 doses of Inj. Engerix B at 0,1,2 months. The antibody levels in each subject was measured by Elisa method at 4th month & 12th month. Antibody titers > 10 IU/L were considered seroconverted. Those patients who had not seroconverted at 4th month received 4th dose of Engerix along with GMCSF and their antibody titers were measured after 1 month and then at 1 year. The antibody titers at 4th month and at 1 year were compared. Patients were characterized by s.creatinine values as 2-4 mg/dl, 4-8 mg/dl and more than 8 mg/dl and / or on dialysis as subgroups I, II & III respectively. The antibody titers in various gps at 4th month and at 1 year respectively are: Gp A I 96 ± 29 IU/L and 19±4.9 IU/L, Gp II 64±19 IU/L and 16±8 IU/L, Gp A III 44±16 IU/L and 21±7 IU/L and Gp B I 663± 221 IU/L and 203±72 IU/L, Gp B II 478±184 IU/L and 146±55 IU/L; Gp B III 137±46 IU/L and 71±25 IU/L. 5 patients, 4 of Gp A and 1 of Gp B lost their protective antibody titers at 1 year (P<0.05). All except two (both Gp B III) seronegative patients seroconverted to 4th dose of Engerix + GMCSF. None of the patients in both gps developed HBV hepatitis. We conclude that GM CSF potentiates seroconversion to HB vaccination in CRF leading to higher and longer lasting protective antibody titers.

RIBAVIRIN/ INTERFERON COMBINATION THERAPY IN HEMIDIALYSIS PATIENTS. A NEW THERAPEUTICAL OPTION?


Background: This prospective pilot study was carried out to evaluate the response, side effects and pharmackinetics of a combination therapy with interferon alpha2b (IFN- α2b) and ribavirin in hemidialysis patients (HD patients).

Methods: HD patients with positive HCV-RNA were treated with IFN-α2b (3 million units (mU) 3 times per week) and received ribavirin after hemodialysis. Patients who continued to have circulating HCV-RNA after 24 weeks of therapy were dropped out, patients regarding a negative RNA continued the therapy for 6 months at least and followed for six months after cessation of therapy. A complete response was defined as absence of HCV-RNA at month 12 (CR), a nonresponder was HCV-RNA positive at month 6 (NR). Drug trough levels of Ribavirin (HPLC) and blood values were monitored (ribavirin dosage was adapted) and compared with patients without renal insufficiency. Pharmacokinetic data of Ribavirin were evaluated.

Results: After 24 weeks of therapy the amount of HCV was reduced (2/9) negative (6/9) or unchanged (1/9); 4/9 patients had a weight loss > 2.5 - 6%. Maximum decrease in hemoglobin between 0.5 and 2.0 g/dl. LDH, haptoglobin and bilirubin are not effective in monitoring hemolysis. Ribavirin serum levels could not be reduced by hemodialysis in a significant way. Ribavirin drug trough levels between 10 and 20 μMol/l could be achieved without significant side effects.

Conclusions: Drug monitoring of ribavirin and an erythropoetin therapy are important steps to perform the combination therapy (ribavirin and IFN-α2b) in hemodialysis patients to reveal toxic side effects of ribavirin in this patient group.

KIDNEY TRANSPLANTATION (KT) FOR PATIENTS WITH POSITIVE HB s Ag: LOOKING BEYOND THE GRAFT SURVIVAL

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Whether KT should be done for HBV infected patients or not is debatable. Our objectives are to determine the outcome of KT for HBsAg positive ESRD patients(HB+)and compare with that of the HB+, who are also transplant candidates, but still remain on hemodialysis. Also, the impacts of mode of therapy on the status of viral replication are determined.

The survival of HB+ who were registered as waiting list during 1987-2001 was studied. Patients who had signs of overt liver disease(portal hyper-tension,precirrhosis/cirrhosis) were excluded. Patients who received KT were classified as Gr1 while those remaining on dialysis as Gr2. Survival analysis was done by Kaplan-Meier and Cox proportional hazard model. Markers of viral replication were evaluated by cross-sectional study that tested for plasma ALT, HBsAg, HBV DNA and HBV viral load (AmplicoR®). 52HB+ were enrolled with informed consent(29 as Gr1 and 23 as Gr2). Liver related death (before graft failure) occurred in 5 of Gr1. Five year patient survival was 80 and 94% for Gr 1 and 2(p=0.12). Cox analysis revealed that KT was significantly associated with increased risk of death within 12 months (R=16; p=0.003) and decreased risk thereafter(R=0.06; p=0.002) of both groups had el-evation of plasma ALT. Prevalence of precore mutants HBV [HBsAg(-) but HBV DNA(+)] was 60% and 62% for Gr1 and 2. The proportion of Gr1 who had high viral load (106 copies/ml or more) was higher than Gr2(75% VS 25%; p=0.001). We conclude that KT and hemodialysis treatment for the HB+ may have indifferent efficacy but different time-dependent risk of death. The high prevalence of precore mutant HBV should lead to awareness concerning the use of appropriate markers to define active viral replication when considering KT for the HB+.

LONG-TERM RESULTS OF HBV AND HCV INFECTION IN RENAL ALLOGRAFT RECIPIENTS

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The effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection on renal transplant outcome remains controversial. The aim of our study was to evaluate HBV and HCV infection as predictors of graft loss in 331 pts (mean age 38 yrs, range 15-71 yrs, 140 female and 191 male) who received renal allograft between 1991 and 1993. Maintenance immunosuppression consisted of Prednisone, Cyclosporine and Azathio-prine. Follow-up time was up to ten years. At the day of transplantation 73 (22%) pts were positive for HBsAg and 177 (53%) pts were positive for anti-HCV antibodies. The endpoint of the study was graft loss defined as requiring of dialysis. In statistical analysis we used Kaplan-Meier estimator and proportional hazards analysis for the evaluation relative risk of graft loss. HCV infection increased the risk of graft loss in 44% (p<0.05) and HBV infection increased the risk of graft loss in 9% (p<0.01) independent of baseline patients parameters. Ten years graft survival in HCV seropositive group was significantly lower as compared with seronegative group 53% versus 64% (p<0.05). No significant difference was seen between a group of patients infected with HBV and noninfected. In conclusion HCV infection has deleterious effect on long-term outcome in renal allograft recipients.
LAMIVUDINE THERAPY FOR ACTIVATED HEPATITIS B VIRUS INFECTION IN RENAL TRANSPLANT PATIENTS

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Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Its efficacy, good tolerance and absence of immunomodulatory effects, allowed its safe use in renal transplant patients (RT pt).

Seven RT pt were treated with lamivudine at our center. All of them were HBV positive before transplantation. DNA-HBV was negative or (2/7 pt) below 24 pg/ml and all had normal hepatic enzymes (HE). Hepatic histology was obtained in 4/7 pt: inflammation was moderate (2 pt) to minimal, and the former two were treated with -interferon.

After RT, all had HBV activation within 3 to 8 months, expressed by HE and viral markers enhancement. Lamivudine, 100 mg/day, was started before RT in 1 pt, and 8 months to 15 years after RT in the others. The reason for lamivudine treatment was HBV-associated graft glomerulonephritis (1 pt), fibrosing cholestatic hepatitis (1 pt), HBV activation after RT (4 pt), continuation of pretransplant treatment (1 pt). At this time HBs antigen was positive in 2 pt, alanine transaminase (ALT) increased up to 2-8 times the normal upper limit, and all had high levels of HBV-DNA, up to 46000 pg/ml.

There was a rapid and dramatic improvement after starting the treatment, particularly in the 2 cases of graft glomerulonephritis and fibrosing cholestatic hepatitis. In the first pt graft function significantly improved and the nephrotic syndrome disappeared. The latter normalized the laboratory markers of hepatic insufficiency, of cholestasis and the ALT level. DNA-HBV became negative in all the 7 pt after a mean interval of 5 months (3-8 months). All but one have normal HE levels. At present they all have a functioning RT and are still under lamivudine, 11 months evolved. We conclude that lamivudine is a promising therapy not only for activated HBV, but also for other severe expressions of the virus, like fibrosing cholestatic hepatitis or graft glomerulonephritis.

In conclusion, ribavirin therapy in RT recipients infected by HCV seems to be beneficial for renal function. By contrast, although it improves liver enzyme levels, it has no impact upon liver histology.

FC27 Uremia – Oxidative stress & atherosclerosis

O155 CHRONIC RENAL FAILURE INCREASES OXIDATIVE STRESS AND ACCELERATES ATHEROSCLEROSIS IN APOLIPOPROTEIN-E KNOCK-OUT (EKO) MICE

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In chronic renal failure (CRF), increased oxidative stress and consequent modifications of plasma proteins result in acceleration of atherosclerotic disease. We have shown that uremic patients have increased oxidative modifications of proteins, producing elevated plasma levels of advanced oxidation protein products (AOPP), that may trigger monocyte activation and represent an alternative pathway for increased atherosclerosis in CRF.

To create a novel experimental model of uremia-enhanced atherosclerosis, we induced CRF in EKO mice that spontaneously develop atherosclerotic lesions resembling human disease. The animals were fed usual lab diet. To create CRF, EKO mice (n=17) received electrocoagulation of the right renal cortex followed by left nephrectomy 2 weeks later, and control EKO mice (n=25) were sham operated. Seven weeks after surgery, CRF mice had higher levels (mean±SE) of plasma urea (324 vs. 9±1 mmol/L, p<0.001) and plasma AOPP (296±27 vs. 190±20 µmol/L, p=0.01) than control mice. Plasma total cholesterol and triglyceride levels were also higher in CRF than in control mice (20.5±1.53 vs. 12.8±0.94 and 1.28±0.20 vs. 0.58±0.07 mmol/L, p<0.001 for both). Induction of CRF in EKO mice did not alter the extent of established atherosclerosis in the aortic arch. However, CRF mice showed significantly increased atherosclerotic lesion formation in the descending aorta, taken from the arch to the last intercostal artery branch, compared with controls (2.2±0.7 vs. 0.8±0.2% of cross-section vessel surface area covered by lesions, p<0.04).

In conclusion, this new experimental model may provide a tool to study the role of oxidative stress and to evaluate new therapeutic strategies in the accelerated atherosclerosis associated with uremia.

O156 CHRONIC RENAL FAILURE ENHANCES AORTIC ATHEROSCLEROSIS IN APOLIPOPROTEIN E-DEFICIENT MICE

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Mortality from cardiovascular disease in patients with chronic renal failure (CRF) is 10 to 20 times higher than in the general population. Nevertheless, it remains controversial whether atherosclerosis is accelerated. The present study examined the effects of CRF on aortic atherosclerosis in homozygous apolipoprotein E-deficient mice. Seven-week old male mice were randomized to 5/6 nephrectomy (CRF, N=28), left-sided nephrectomy (sham, N=24), or no operation (controls, N=23). Aortic atherosclerosis was assessed 22 weeks later. Whole aortic plaque area was increased 6-fold (26.6±3.3 versus 4.5±0.6%, p<0.001), aortic cholesterol 5-fold (535±62 versus 100±9 mmol/area in