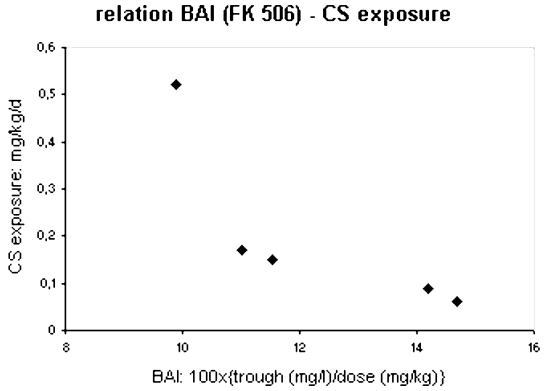
and 11 (range, 114 - 1432 umol/L) did not influence exposure. Indicators of hepatic function including bilirubin (1 - 39 umol/L), AST (7 - 283 U/L), ALT (3 - 373 U/L), and albumin (25 - 46 g/L) did not impact on exposure. CL/F was not different in diabetics (n = 31) compared with nondiabetics. CL/F was also not influenced by comedication with the beta-blockers atenolol (n = 29), labetolol (n = 16), metoprolol (n = 41), propranolol (n = 14). **Conclusions:** (1) Dose adjustment of FTY on the basis of weight (mg/kg) does not appear necessary; (2) FTY blood concentrations remained stable despite changes in renal function posttransplant; (3) Concomitant use of beta-blockers did not alter the pharmacokinetics of FTY; (4) No special patient populations were identified in this analysis for which FTY dose regimens need to be modified.

Abstract# 706

ORAL BIOAVAILABILITY OF FK 506 RAISES PARALLEL WITH DECREASING CORTICOSTEROID DOSES IN RENAL TRANSPLANT PATIENTS. Wim Lemahieu,[1] Kathleen Claes,[1] Pieter Evenepoel,[1] Dirk Kuypers,[1] Bart Maes,[1] Yves Vanrenterghem.[1] [1]*Internal Medicine, Division of Nephrology, UZ Gasthuisberg KULeuven, Belgium.*

Background: Catabolism by intestinal and hepatic cytochrome P450 3A4 (cyp 3A4) and excretion by P-glycoprotein (Pgp) is considered to have a major influence on oral bio availability of FK 506. Since it is known that high doses of corticosteroids (CS) induce both enzymes, the effect of changing CS exposure on the oral bio availability of FK506 was studied. **Methods:** A cohort of 203 renal transpant patients was analysed. At transplantation (tx), all received induction with steroids (500 mg methylprednisone) in addition to FK506 and MMF. Afterwards, CS doses, starting from 20 mg/d, were progressively tapered. CS exposure was calculated as mean daily dose in mg/kg body weight during the time intervals: day 0-30, 31-60, 61-90, 91-180 and 181-365 post tx. Bio availability of FK506 was calculated as an index (BAI): {through level (mg/l) / dose (mg/kg)}multiplied by 100 at 30, 60, 90, 180 and 365 days post tx. CS exposure and BAI were compared at the given time intervals with one way ANOVA. **Results:** CS exposure dropped significantly ($p<0.0001$) from 0.58 at 1 month to 0.17, 0.15, 0.09 and 0.06 at 2, 3, 6 and 12 months post tx respectively. Parallel, BAI raised by 11% from 9.9 at 1 month to 11 at 2 months ($p=0.0003$), by 16% to 11.54 at 3 months, by 43% to 14.2 at 6 months and by 48% to 14.69 at 12 months post tx ($p<0.0001$). As shown in the figure, BAI increases in correlation with decreasing corticoid exposure in function of time after tx. **Conclusions:** In renal transplant patients higher doses of CS were associated with lower oral bio availability of FK506, suggestive for the inducing effects of CS on cyp 3A4 and Pgp.



Abstract# 707

PERIPHERAL BLOOD FTY720 PHARMACOKINETIC/ PHARMACODYNAMIC (PK/PD) MODELING IN RENAL TRANSPLANTED RECIPIENTS. Sung I. Park,[1] Cláudia R. Felipe,[1] Paula G. Machado,[1] Riberto Garcia,[1] Andrej Skerjanec,[2] Robert Schmouder,[2] Hélio Tedesco-Silva,[1] José O. Medina-Pestana.[1] [1]*Hospital do Rim e Hipertensão - Nephrology Division, Universidade Federal de São Paulo, São Paulo, SP, Brazil;* [2]*Novartis Pharmaceuticals, East Hanover, NJ.*

INTRODUCTION: FTY720 is a lymphocyte homing drug that induces peripheral blood lymphopenia. The relationship between FTY720 dose or blood concentration and peripheral lymphopenia is not clear. This study investigates models of FTY720 PK/PD relationships in the blood compartment. **METHODS:** 23 kidney transplant recipients were randomized to receive FTY720 (0.25, 0.5, 1.0 or 2.5 mg QD) or MMF (2gm/day) in combination with Neoral and steroids. FTY720 was administered for 12 weeks post-transplant. FTY720 dose, blood concentrations and peripheral blood lymphocyte counts were obtained weekly in all 5 groups, before and at weeks 4 to 12 after transplantation. Peripheral blood lymphocyte counts from MMF group were used to calculate the effect when FTY720 dose or concentrations were equal to zero. The PD effect was calculated as a % reduction compared to the lymphocyte count before the administration of the first dose of FTY720 or MMF. FTY720 blood concentrations were measured by HPLC/MS/MS method. PK/PD modeling was utilized to find the best-fit model of the correlation between % reduction in peripheral lymphocyte count and increasing doses or blood concentrations of the FTY720. **RESULTS:** Mean age was 40 years, 61% white, 61% males and mean BMI was 22.8±2.6 kg/m². FTY720 dose associated with best efficacy in preventing acute rejection was 2.5 mg/day. Mean FTY720 concentrations were 0.36±0.05 (0.25 mg), 0.73±0.12 (0.5 mg), 3.26±0.51 (1 mg), and 7.15±1.41 ng/mL (2.5 mg). Between weeks 4 to 12, best-fit PK/PD modeling for dose-effect or concentration-effect relationship was the simple E_{max} model [$E = (E_{max} * C) / (C + EC_{50})$, where E is the effect at a given concentration C, Emax is the maximum effect attributed to the drug, and EC_{50} is the drug concentration which produces 50% of maximum effect]. For dose-effect relationship, $E_{máx}$=87,8±5,3% and ED_{50}=0,48±0,08 mg (r^2=0,94). For concentration-effect relationship $E_{máx}$=78,3±2,9% and EC_{50}=0,592±0,091 ng/mL (r^2=0,89). **CONCLUSION:** According to the PK/PD model, EC_{50} was achieved at FTY720 doses of 0.5 mg and blood concentrations of 0.6 ng/mL. Since FTY720 PK are dose-linear and effective doses of FTY720 are 2.5 and 5 mg/day, the immunosuppressive effect of FTY720 may depend upon induction of high degree of lymphopenia (~80%) and/or be associated with other FTY720 effects out of the blood compartment, perhaps in secondary lymphoid tissues where lymphocyte home.

Abstract# 708

PHARMACOKINETICS OF MYCOPHENOLATE MOFETIL IN RENAL TRANSPLANT IMMUNOSUPPRESSION: RISKS OF USING A FIXED DOSE REGIMEN. Kazuharu Uchida,[1] Yoshihiro Tominaga,[1] Toshito Haba,[1] Akio Katayama,[1] Susumu Matsuoka,[1] Norihiko Goto,[1] Tsuneo Ueki,[1] Tetsuhiko Sato,[1] Asami Takeda,[1] Kunio Morozumi,[1] Takaaki Kobayashi,[2] Hirosi Takagi,[3] Akimasa Nakao.[2] [1]*Dept. of Transplant Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan;* [2]*Dept. of Surgery II, Nagoya University, Nagoya, Aichi, Japan;* [3]*Surgery, JR Tokai General Hospital, Nagoya, Aichi, Japan.*

Pivotal pharmacokinetic studies that evaluated Mycophenolate Mofetil (MMF) in renal transplantation have demonstrated low intrapatient and interpatient variability resulting in the adoption of fixed dose recommendations for MMF therapy. We investigated comparative pharmacokinetics, including intrapatient and interpatient variability over time up to the 6th postoperative week; to evaluate the MMF fixed dose regimen in renal transplantation . Study population and Methods: The study included 45 de novo renal transplant recipients treated with prednisolone, MMF and CNI's, (CsA = 24, FK= 21). Drug exposure in the first four hours post-dose (AUC) of CNI's and mycophenolic acid (MPA) were measured once or twice a week from the 4th postoperative day to the 6th postoperative week; to evaluate the MMF fixed dose regimen in renal transplantation . Study population and Methods: The study included 45 de novo renal transplant recipients treated with prednisolone, MMF and CNI's, (CsA = 24, FK= 21). Drug exposure in the first four hours post-dose (AUC) of CNI's and mycophenolic acid (MPA) were measured once or twice a week from the 4th postoperative day to the 6th postoperative week. MMF dosing was initiated with a fixed dose at 3g/day (BID) from the 2nd postoperative day, with a dose change to 2 g/ day from the 15th or 29th postoperative day. Results&Conclusion: The study data demonstrate that interpatient variability in MPA pharmacokinetics is high (CV; 50-80%), although intrapatient variation is lower (CV; 25-45%). The MPA C0 level increased gradually, reaching a steady state at the 2nd-3rd postoperative week (2-3 fold from baseline), and lowered after changing the dose to 2 g. The MPA AUC in the same patients remained steady without declining even after decreasing the dose from 3 g/day to 2 g/day. Our evaluation of MPA pharmacokinetics demonstrates that MPA interpatient variability is high, and that the trough level elevates gradually over time without MMF dose changes. The MPA AUC changes are not dose-dependant. These results indicate a potential risk for variable MPA exposure with a MMF fixed dose regimen, and suggest TDM of MPA for individualization of MMF doses.

1. MPA mean values plus inter-patient variation for C0 (mcg/mL) and AUC0-4h (mcg·h/mL)

Day(MMF dose)	#4d (3g)	#14d (3g)	#35 (2g)	#42d (2g)
Mean C0 (%CV)	1.3±0.7(75.8)	0.8±2.1(76.7)	3.7±3.0(82.5)	3.7±2.3(61.0)
Mwan AUC(%CV)	39.1±21.7(55.5)	37.7±18.6(49.3)	44.5±22.5(50.6)	45.5±21.1(46.4)

2. Intrapatient variability during the administration period for 3 g/day and 2 g/day fixed doses per patient

	3g-period	2g-period
Mean C0 (%CV)	2.6±1.6(45.8)	3.1±1.5(39.8)
Mean AUC(%CV)	41.9±12.0(26.9)	40.2±10.1(25.1)

Abstract# 709

DIFFERENCES IN HEALTH INSURANCE ARE ASSOCIATED WITH ACCESS TO THE KIDNEY TRANSPLANT WAITLIST.

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Background: Previous studies have assessed cadaveric renal transplantation rates among different patient groups, and multivariate analyses have shown that minorities, females, the elderly, and diabetics were relatively less likely to receive a renal transplant. This analysis examines the relationship between the type of insurance (primary and secondary) at initiation of dialysis (ESRD) and access to the transplant waitlist. **Methods:** We used national (CMS) data for insurance status and characteristics of all dialysis patients at time of first dialysis and SRTR data for time of first waitlisting. The study population consists of 258,391 dialysis patients (age < 65) beginning dialysis between 1995 and 2001. Relative rates of waitlisting (RR-WL) from ESRD onset were calculated for kidney dialysis patients by type of insurance using a Cox regression model of time to waitlisting (censored at death, living donor transplant, or end of study on 6/30/2002). Pre-emptive waitlists were excluded. The model was adjusted for age, gender, diagnosis, race, incidence year, ethnicity, 20 comorbidities, type of dialysis facility, and geography (state). **Results:** The table below shows the relative waitlisting rate by type of insurance coverage. Patients with Medicare only, Medicaid only, or Medicare and Medicaid only have significantly lower waitlisting rates than do other patients.

Insurance Coverage	N	%	RR-WL	p-value
Medicare Only	19,784	7.7	1.00	ref
Medicaid Only	51,989	20.1	0.93	<.01
Medicare and Medicaid Only	19,871	7.7	0.88	<.01
Employer Group Health Insurance Only	18,041	7.0	1.97	<.01
Medicare and Any Other Insurance	75,026	27.2	1.27	<.01
Other Medical Insurance	41,603	16.1	1.55	<.01
No Medical Insurance Listed	36,909	14.3	1.03	0.20

Patients with only Medicaid insurance had an overall waitlisting rate 34% lower (RR-WL=0.66, p<0.01) than patients with all other types of insurance. Although this RR-WL varied by state (22% to 68% lower), it remained statistically significant in 43 states. **Conclusions:** These newly reported results by state reveal dramatic geographic differences in access to the kidney transplant waitlist by patient insurance status at initiation of dialysis.

Abstract# 710

KIDNEY TRANSPLANTATION RATES FROM THE WAITLIST REVEAL DISPARITIES IN ACCESS BY INSURANCE STATUS.

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[1]University of Michigan, Ann Arbor, MI; [2]URREA, Ann Arbor, MI; [3]Massachusetts General Hospital, Boston, MA; [4]Virginia Commonwealth University, Richmond, VA; [5]Lifelink Transplant Institute, Tampa, FL.

Background: Minorities, females, and the elderly have been shown to be less likely to receive cadaveric donor kidney transplants. This analysis looks at the relationship between patient insurance at the time of entry onto the transplant waitlist and cadaveric transplant access. **Methods:** Transplant rates (RR-Tx) for waitlisted patients were calculated using a Cox regression model (censored at removal from waitlist or end of study [6/30/02]) among 112,319 registrants entering the kidney waiting list for the first time from 1995-2001. Waitlist dates before first dialysis were moved to onset of ESRD. Pre-emptive transplants were excluded. The model was adjusted for age, gender, diagnosis group, blood type, race, ethnicity, waitlist year, previous transfusions, state of residence, initial PRA, time from first dialysis to waitlisting, dialysis modality at waitlist, and HLA antigens. **Results:** The table below shows adjusted transplantation rates by type of insurance coverage. Patients with Medicare only, Medicaid only, and HMO/PPO only have significantly lower waitlisting rates than do patients with private or multiple types of insurance.

Insurance Coverage	N	%	RR-Tx	p-value
Medicare Only	13,009	11.0	1.00	ref
Medicaid Only	7,171	6.1	0.99	0.68
Medicare + Other	40,627	34.4	1.09	<.01
Private Only	24,147	20.4	1.05	0.01
HMO/PPO Only	6,602	5.6	0.86	<.01
Private/HMO/PPO + Other	19,717	16.7	1.11	<.01
Other source of payment	5,860	5.0	1.05	0.09
Missing source of payment	1,046	0.9	0.85	0.20

Waitlisted patients with only Medicaid insurance had an overall transplantation rate in the U.S. 10% lower (RR=0.90, p<0.01) than patients with all other types of insurance. The disparity was greater than 10% for 20 states (3 of them with p<0.05), while in 6 states Medicaid patients had significantly higher rates (p<0.05). **Conclusions:** These results indicate substantial disparities in access to cadaveric transplantation for waitlisted patients by insurance type and by geography. These disparities are less extreme than those observed in access to the waitlist itself. Patients with insurance types (HMO/PPO only, Medicare only, and Medicaid only) at waitlist are most disadvantaged.

Abstract# 711

COST EFFECTIVENESS OF EXTENDED MEDICARE COVERAGE OF IMMUNOSUPPRESSIVE MEDICATIONS TO LIFE IN RENAL TRANSPLANTATION.

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A substantial number of renal transplant recipients lose Medicare coverage of immunosuppressive medications after 36 months post-transplant. One's ability to afford these medications is correlated with non-adherence to treatment and graft loss, especially among patients of lower socioeconomic status. Woodward et al.(AJT 1:69-73, 2001) determined that extending Medicare immunosuppression coverage from one to three years correlated with a 27% greater improvement in graft survival in the majority of patients stratified by income. We sought to compare the economic costs and quality of life benefits of extension of immunosuppressive coverage to life. Methods: The United States Renal Data System (USRDS) was analyzed for recipients of renal transplants from 1995-1999. A Markov model was designed to assess the outcomes of patients who receive a renal transplant. This model compared current immunosuppressive coverage of 3 years to a model representing lifetime immunosuppressive medication coverage, both measured over a 20-year period. Probabilities of all outcomes were calculated including graft function, graft loss with death, graft loss with return to dialysis, and death. Costs, calculated from the perspective of Medicare, along with quality adjusted life year (QALY) benefits, were estimated according to each associated outcome. Results: The previously reported graft loss reduction from extending immunosuppression coverage translates into an increase in overall survival from 55.4% with current coverage to 61.7% after 20 years with lifetime coverage. In addition, lifetime immunosuppressive medication coverage produced an average of 0.30 additional QALYs per individual transplant over existing coverage. Since Medicare spends approximately $79,400 per QALY to care for wait-listed patients on dialysis, we felt it reasonable to follow that precedent for renal transplantation. We found that the QALY benefit of lifetime immunosuppression coverage would be cost-effective relative to dialysis if the average annual cost of immunosuppression to Medicare were $5,570. Conclusions: The average annual cost of immunosuppression can be considerably higher than the cost-effective threshold calculated here. However, providing lifetime coverage through Medicare as secondary insurance, available to patients without alternatives, those truly at risk, may yield the previously observed benefits of extended coverage while bringing the average cost of lifetime coverage down to cost-effective levels.

Abstract# 712

DID INSURANCE REDUCE RACIAL DISPARITIES IN KIDNEY GRAFT SURVIVAL?

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Purpose: It had been previously reported that the additional two years of immunosuppression insurance benefits Medicare added between 1993 and 1995 effectively eliminated graft survival differences associated with income disparities. (*Am J Transplant*, 2001) The current study determined whether that same additional immunosuppression coverage had an equally beneficial effect on the graft survival differences associated with ethnicity. **Methods:** We first merged patient-level clinical data from the USRDS-distributed UNOS registry with median family income for each patient's ZIP code from the 1990 Census. We then compared only the first cadaveric single-organ renal transplants performed in 1992-3 in the highest and lowest income quartiles with the similar transplants performed in 1995-7. We used Cox Proportional Hazards models to compare graft survival in the second and third years post-transplant among i) the 4,441 patients transplanted in 1992 and 1993 that survived at least one year and ii) the 6,496 set of similar patients transplanted between 1995 and 1997. (Medicare maintenance immunosuppression insurance benefits were available only to the second of these 2 cohorts.) **Results:** In a model controlling for other significant donor, recipient, and transplant characteristics, the extra two years of Medicare immunosuppression insurance more than eliminated the 23% (Hazard Ratio Confidence Interval, HRCI, 1.05 to 1.44; P=0.009) greater graft loss associated with the lowest incomes. But the extra Medicare insurance produced no such beneficial impact on the greater graft loss associated with black ethnicity. Black ethnicity was associated with a 42% additional graft failure (HRCI 1.09 to 1.85, P=0.009). On top of that, the lowest income black recipients were associated with an additional 32% graft loss (HRCI 1.02 to 1.72; P=0.037). All variables testing for the value of the extra Medicare insurance benefits to blacks generally and to low-income blacks in particular were highly insignificant. **Conclusions:** Gaston (*Am J Transplant*, 2002) and others have expressed