Fig 2. P=0.018 Graft survival in patients with CsA-based triple agents according to TGF-β1 codon10 polymorphism. (In CsA-based dual group, P=NS)

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2241 EFFECT OF GENETIC POLYMORPHISMS OF MRP2 AND UGT2B7 ON GASTROINTESTINAL SYMPTOM RATING SCALE IN KIDNEY TRANSPLANT RECIPIENTS TAKING MYCOPHENOLIC ACID

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Background: Gastrointestinal (GI) symptoms are the most common complications with mycophenolic acid (MPA) therapy. MRP2 and UGT2B7 which are involved in the excretion and production of the metabolites of MPA respectively may play a role in the presentation of GI symptoms.

Objectives: To determine the relationship between single nucleotide polymorphisms in MRP2 and UGT2B7 and the incidence and severity of the GI symptoms in patients receiving MPA. Methods: Genotypes of MRP2 C-24T and UGT2B7 C802T were determined and the incidence and severity of GI symptoms were assessed using the validated Gastrointestinal Symptom Rating Scale (GSRS) at baseline, 2 weeks, 1 month, 3 months and 6 months post transplant. The mean overall GSRS score and subscale score for diarrhea were compared using Student's t-test and linear regression was performed to determine the predictors of GI symptoms.

Results: Fifty-six kidney transplant recipients were included in the study. The overall GSRS score was not significantly different between the MRP2 C-24T heterozygous variant and the homozygous wild type (1.6 vs 1.8, p=0.084). However the GSRS subscale score for diarrhea was significantly lower in the MRP2 C-24T heterozygous variant compared to the homozygous wild type (1.2 vs 1.7, p=0.004). For the UGT2B7 C802T, the overall GSRS score (1.6 vs 1.8, p=0.158) and diarrhea subscale score (1.4 vs 1.8, p=0.127) were not significantly different between the heterozygous and homozygous variant and the homozygous wild type. When the genotypes for MRP2 and UGT2B7 are considered together, the variant MRP2 C-24T and UGT2B7 C802T had significantly lower overall GSRS (1.5 vs 1.9, p=0.032) and diarrhea subscale score (1.1 vs 1.8, p=0.014) compared to the wild type. There were however no differences in the scores between patients receiving either mycophenolate mofetil or enteric-coated mycophenolate sodium; and patients receiving the different calcineurin inhibitors.

Conclusion: This study demonstrates that among patients receiving MPA, those with MRP2 C-24T and UGT2B7 C802T variant genotypes are potentially protected from the GI side effects, in particular diarrhea, regardless of the formulation administered.

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2242 SYSTEMS BIOLOGY IN DONOR KIDNEYS OF RECIPIENTS WITH POST-TRANSPLANT ANEMIA

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Post-Transplantation anemia is a common phenomenon after renal transplantation, and the cause is usually multi-factorial. Molecular mechanisms leading to anemia after renal transplantation are not fully understood. Focus of this present study was to further elucidate the biological processes of anemia in the post-transplantation setting.

The analysis of 52 renal transplant recipients (25 treated with ESAs within the first year after transplantation and 27 without ESA treatment) will be presented. The analysis include genome-wide gene expression profiles of donor kidney biopsies with subsequent systems biology approaches such as transcription factors analysis, regulatory networks, and protein-protein interaction data. Multivariable logistic regression analysis was used to quantify the association of genes identified in the systems biology studies with the outcome ESA use adjusted for clinical predictors such as donor age, biopsy confirmed acute rejection (BCAR) and glomerular filtration rate.

Unsupervised hierarchical clustering of experimental data suggests a distinct molecular signature associated with activated inflammation in the donor kidney biopsies with subsequent ESA requirement. Selection of 1.5fold differentially upregulated genes in the ESA group yielded 28 significant sequences that can be categorized according to PANTHER ontologies into three main biological processes: Cell adhesion-mediated signalling ($p<0.004$), immunity and defense ($p<0.004$), oncogenesis ($p<0.007$). In the multivariable analysis, several genes were found to be independent predictors of post-transplant anemia.

Our data suggest that genes involved in the inflammation cascade predict post-transplant anemia.

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2243 INFLUENCE OF MRP2 AND UGT1A9 POLIMORPHISMS IN THE MPA PHARMACOKINETICS IN RENAL TRANSPLANT RECIPIENTS. RESULTS OF THE PHARMACOGENETIC SUBSTUDY WITHIN THE SYMPHONY STUDY.

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Introduction: Mycophenolic acid (MPA) is an effective immunosuppressant used in renal transplantation and is mainly metabolized by uridine diphosphate-glucuronosytransferases (UGTs). The latter metabolites are excreted trough the kidney at least in part by multidrug resistance protein 2 (MRP2), which play an important role in the enterohepatic recirculation of the MPA. Furthermore, the inhibition of MRP2 by cyclosporine (CsA) is the main mechanism responsible for the interaction between CsA and MPA. The Symphony study compares 4 immunosuppressant regimens in renal transplant patients in terms of clinical outcomes. Patients included in the Pharmacogenetic sub-study had complete cyclosporine (CsA) and mycophenolic acid (MPA) pharmacokinetic assessments (in the Symphony PK sub-study) and they were genotyped for MRP2 and UGT1A9.

Objective: To determine the relationship between single nucleotide polymorphisms (SNPs) in the MRP2 (C-24T and C3972T) and UGT1A9 (UGT1A9*3 and UGT1A9-2152) genes and the MPA pharmacokinetics in renal transplant recipients of the Symphony Pharmacogenetic sub-study.

Subjects And Methods: 70 renal transplant recipients (58.6% males; mean age: 47.9±11.8 years) at 8 Spanish centres were randomized to 4 branches of immunosuppressive regimen: low and standard dose of CsA (N=30), tacrolimus (Tac) (N=13) and sirolimus (SRL) (N=23) all in addition to mycophenolate mofetil and steroids. Low and standard dose of CsA were summed into one group for the present analysis. Patients were genotyped for SNPs in MRP2, C24T and C3972T, and for SNPs in UGT1A9, *3 and 2152. Pharmacokinetic sampling was done before administration and at 20, 40, 75 min, 2, 3, 6, 8, 10 and 12 hours post-dose at scheduled intervals during the study (7, 30 and 90 days). Association of different Area Under Curve (AUC) plasma samplings with the presence of MRP2 and UGT1A9 polymorphisms and with the immunosuppressive regimens were studied using ANOVA analysis (Kruskal-Wallis).

Results: At 90 days, MPA AUC was associated with the presence of C24T (CC: 82.3 ± 48.3; *T: 50.6 ± 21.0; p= 0.009; N= 48) and with treatment with CsA (Tac and SRL: 82.9 ± 46.9; CsA: 52.9 ± 518.5; p= 0.003; N= 54). MPAG AUC was associated with the presence of UGT1A9*3 at 30 days (C*: 857.3 ± 558.6; TT: 1496.9 ± 888.2; p= 0.036; N= 53) and at 90 days (C*: 321.2 ± 22.2; TT: 972.2 ± 518.5; p= 0.024; M= 57). MPA AUC was associated with the presence of UGT1A9*3 at 30 days (C*: 68.3 ± 19.1; TT: 50.5 ± 26.6; p= 0.056; N= 53) but not at 90 days.

Conclusions: Renal transplant recipients with C-24T MRP2 SNPs were associated with a reduced MPA exposure in the steady-state conditions and CsA treated patients showed a reduction in MPA AUC in the steady-state conditions.