

**Methods:** To achieve a steady state 3 groups of Lewis rats (n=8/group) were treated daily with oral CsA (8mg/kg), TRL (4 mg/kg) or vehicle for a week before daily oral treatment with MMF (20mg/kg). Combined treatment with either CsA+MMF, TRL+MMF or MMF+vehicle was continued for a week (days 8-14). Thereafter MMF treatment was continued for another week, but CsA and TRL treatments were stopped after day 14. Blood samples were collected at days 7 (after a single MMF dose), 14 (after multiple MMF doses) and 21 (after CsA/TRL wash out).

**Results:** During TRL treatment and in the MMF+Vehicle group the PK-profile showed a second peak, consistent with enterohepatic recirculation of MPA. The PK profiles of the CsA+MMF treated animals did not show a second peak. On Day 14, the mean MPA-AUC(0-24) for the CsA treated animals was significantly less than MPA exposure for the TRL and the vehicle group. Furthermore, in contrast to other groups, co-administration of CsA and MMF significantly increased MPAG-AUC(0-24). Serum creatinines did not differ among the three groups.

**Conclusions:** CsA, but not TRL, decreased MPA plasma levels and increased MPAG-AUC. These data suggest that CsA inhibits MPAG excretion into bile and explain increased MPA exposure in patients after switching from CsA to TRL.

36

#### ISATX247: A NOVEL CALCINEURIN INHIBITOR

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Cyclosporine A (CsA) is a widely used immunosuppressive agent due to its preferential effect on T-cell mediated reactions. Chronic treatment with CsA is associated with serious dose-related adverse effects, of which nephrotoxicity is of primary concern. Investigators at Isotechnika Inc., have developed a more potent analogue of CsA with fewer side effects. This novel semi-synthetic calcineurin (CN) inhibitor is designated ISATX247. The efficacy of ISATX247 as an immunosuppressive agent was examined using an *in vitro* calcineurin assay and an *in vivo* rat heterotopic heart transplant model. Compared to CsA, ISATX247 exhibited up to a 3-fold greater inhibition of calcineurin activity and prolonged graft survival 3-fold in the rat when both drugs were administered at equivalent doses (1.75 mg/kg). Long term *in vivo* studies using rats, rabbits, dogs, and primates to assess the multiple dose toxicity of ISATX247 indicated that the drug is significantly less toxic than CsA even at doses up to 100-fold in excess of that required for immunosuppression. In addition, the drug caused fewer renal side effects than that observed for CsA. In particular, no signs of interstitial fibrosis, consistent with chronic CsA nephrotoxicity, were found in the kidneys. Single and multiple dose Phase 1 clinical trials have been conducted. No significant AEs have been noted at a single dose up to 6.0 mg/kg and a multiple dose of 2 mg/kg/day BID for 7 days. The pharmacokinetic parameters observed suggest that ISATX247 has a similar bioavailability and half-life as other CN inhibitors. The absence of nephrotoxicity, coupled with increased potency suggests that ISATX247 has a broader safety margin/therapeutic index as compared to CsA, making it a more desirable agent for use in both transplantation and autoimmune diseases. Phase 2 trials with ISATX247 are expected to commence in 2001.

37

#### EOTAXIN AND PREDNISOLONE CONCENTRATIONS REGULATE THE MOBILISATION OF PERIPHERAL BLOOD EOSINOPHILS PRECEDING HEART ALLOGRAFT REJECTION

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There is a generic relationship between early changes in peripheral blood eosinophil counts (EOS) and the development of clinically significant rejection following solid organ transplantation. In a randomized, controlled trial of EOS monitoring in 80 heart transplant (HTx) recipients we have further shown that suppression of EOS can be used as a highly cost-effective guide to corticosteroid administration in the control of rejection within the first 6 post-operative weeks. We have now assessed the relative impact of immunosuppressive drugs, including the plasma prednisolone (PRL) concentration (HPLC assay), as well as plasma concentrations of two eosinophil chemotactic and activating peptides that act through the CC-chemokine receptor-3 (CCR3), eotaxin and RANTES (immunometric assay), on the diagnostic changes in EOS that precede treated HTx rejection (usually ISHLT Grade  $\geq$  3A). The first 46 consecutive HTx recipients recruited to our randomised trial, with a median follow-up of 90 days, were included in the study. Univariate regression analysis showed that cyclosporin dose, blood cyclosporin concentration, azathioprine dose and plasma RANTES concentration were not related to EOS. Factors related to changes in EOS included plasma PRL, endogenous cortisol and eotaxin concentrations. Multivariate linear regression analysis, accounting for within and between-patient correlations, revealed that the most important factors influencing EOS were PRL (-31% change in EOS per 50 $\mu$ g/L increase in PRL; 95% CI -21, -40%; P<0.001) and eotaxin (+22% change in EOS per 100 $\mu$ g/L increase in eotaxin; 95% CI +6, +41%; P=0.006) in a negative and positive manner, respectively. Changes in EOS that precede HTx rejection are controlled by a balance between eotaxin-induced mobilisation and corticosteroid-induced suppression. The use of new selective CCR3 antagonists may help to elucidate the pathophysiological significance of eosinophils in allograft rejection.

38

#### CYCLOSPORINE VERSUS TACROLIMUS IN HEART TRANSPLANTATION: AN ISHLT/UNOS REGISTRY ANALYSIS

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The use of tacrolimus (Tac) as a principle immunosuppressive agent is increasing in heart transplantation. While small series of patients (pts) have shown variable results, the impact of using Tac in place of cyclosporine (CsA) on mortality is not established. The Joint ISHLT/UNOS Thoracic Registry was analyzed for the effects of Tac versus CsA in pts discharged on one of these two agents as the primary analysis. Subset analysis included the effects of mycophenolate (MMF) or azathioprine (AZA) on the primary groups and pts on the same drug both at discharge and first follow-up or death. Analysis was limited to US pts trans-