points. The 2 groups were comparable for main donor and recipient characteristics. Rejection rate (everolimus=11% vs. tacrolimus=3%, p=NS), HCV recurrence rate (everolimus=54% vs. tacrolimus=33%, p=NS), and one-year mortality (everolimus=18% vs. tacrolimus=19%, p=NS) were comparable between groups. Immunosuppression conversion rate was higher in the everolimus group (57% vs. 23%, p=0.01). One-year post-LT serum creatinine levels were comparable between groups. The most frequent side effect in the everolimus group was lower limb edema (everolimus=54% vs. tacrolimus=11%, p=0.001). The prevalence of other complications was similar between groups. A de-novo CNI-free immunosuppressive regimen seems feasible, but without significant overall improvement compared to a CNI-based immunosuppression.

O-203 INCIDENCE OF INTERSTITIAL LUNG DISEASE WITH EVEROLIMUS IN TWO LARGE, RANDOMIZED, MULTICENTER STUDIES IN DE NOVO HEART OR KIDNEY TRANSPLANT RECIPIENTS

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Background: mTOR-inhibitors have been associated with interstitial lung disease (ILD), a serious non-infectious lung disorder. Rare cases have been reported for everolimus (EVR) in kidney and heart transplantation (KTx, HTx), but no systematic evaluation of study databases has been published to date.
Methods: A2310 and A2309 are two 24-month (M), multi-center, randomized, open-label studies comparing efficacy and safety in de novo HTx- (A2310) or KTx (A2309) recipients receiving EVR dosed at 1.5 or 3mg/day (C0: 3-8 or 6-12ng/mL) with reduced-dose cyclosporine versus MMF/MPA with standard-cyclosporine. The study adverse event (AE) databases were searched for terms covering a wide range of pulmonary events. Identified cases were reviewed to assess likelihood of drug-induced ILD based on symptoms, history, concurrent conditions, diagnostic test results and possibility of treatment-relation. Concomitant infectious lung disease was ruled out.
Results: Safety populations for A2310 and A2309 consisted of 714 HTx- (EVR 1.5mg=279, EVR 3mg=167, MMF=268) and 825 KTx-recipients (EVR 1.5mg=274, EVR 3mg=278, MPA=273). Three cases were identified as possible ILD in A2310: one event of pulmonary toxicity (EVR 1.5mg) prompted EVR discontinuation. The event continued but the patient could be discharged. One ILD event (EVR 3mg) resolved 21 days after EVR termination. One mild AE reported by the investigator as ILD (EVR 3mg), did not lead to treatment adjustment but was reported as continuing at M12. One patient (EVR 1.5mg) in study A2309 experienced pulmonary alveolar proteinosis resulting in EVR dose reduction. This patient subsequently died from pneumonia and sepsis (Table 1).
Conclusion: Four cases (0.4%) of interstitial lung disease/pulmonary alveolar proteinosis were identified in this series of 998 HTx- and KTx-recipients receiving everolimus. ILD is a potentially serious event and rare occurrence needs to be considered with EVR-based immunosuppression.

O-204 ADVERSE EVENTS ASSOCIATED WITH mTOR INHIBITION: RESULTS FROM THE A2310 STUDY COMPARING EVEROLIMUS AND MMF IN DE NOVO HEART TRANSPLANT RECIPIENTS

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Background: Everolimus can reduce the development of cardiac allograft vasculopathy, a major contributor to long-term mortality after heart transplantation (HTx). However, mTOR-inhibitors have been associated with class-related complications possibly limiting treatment adherence.
Methods: A2310, a 24-month (M), multi-center, randomized, open-label study compared efficacy and renal function at M12 in de novo HTx recipients receiving everolimus (EVR) dosed at 1.5 or 3mg/day (C0: 3-8 or 6-12ng/mL) with reduced dose cyclosporine (CsA) or MMF 3g/day with standard dose CsA. All patients received steroids. Center-specific induction therapy (basiliximab/thymoglobulin/no induction) was allowed. Most relevant adverse events (AEs) were compared between groups.
Results: 714 HTx recipients constituted the safety population (EVR 1.5mg N=279, EVR 3mg N=167, MMF N=268). Enrollment in the EVR 3mg arm was prematurely terminated due to higher mortality. This analysis only compares low-dose EVR (1.5mg) and MMF patients. The EVR1.5mg group showed an increased incidence of new onset diabetes, pericardial effusions, proteinuria, stomatitis/mouth ulcerations, and thrombotic/thromboembolic events. Incidence of neutropenia and leukopenia was more frequent in the MMF group (Table 1). Management of these AEs rarely required the discontinuation of treatment (<3%). Incidence of serious infections (any infection) was 28.3% (64.9%) for EVR 1.5mg and 25.0% (63.1%) for MMF with serious bacterial infections being more frequent with EVR 1.5mg (14% vs. 8.6%) and serious viral infections more frequent with MMF (2.5% vs. 10.8%). Rates of serious fungal infections were 3.6% with EVR 1.5mg vs. 3.4% with MMF.

Table 1. Incidence of relevant adverse events, n (%)

	EVR 1.5 mg (N=279)	MMF (N=268)
Thrombocytopenia	33 (11.8)	29 (9.3)
Leukopenia	34 (12.2)	62 (23.1)
Neutropenia	44 (15.8)	94 (35.1)
Hyperlipidemia	83 (29.7)	60 (22.4)
New onset diabetes	27 (9.7)	16 (6.0)
Sternal wound complication	68 (24.4)	52 (19.4)
Pericardial effusion*	121 (43.4)	76 (28.4)
Pericardial effusion with hemodynamic compromise*	20 (7.2)	4 (1.5)
Pleural effusion	78 (28.0)	62 (23.1)
Peripheral edema	151 (54.1)	133 (49.6)
Proteinuria	9 (3.2)	5 (1.9)
Stomatitis, mouth ulceration	23 (8.2)	13 (4.9)
Thrombotic and thromboembolic events	43 (15.4)	25 (9.3)

*P<0.01.

Conclusion: The occurrence of mTOR-inhibitor associated AEs should be expected during treatment of HTx recipients with everolimus, although management of the event will rarely require discontinuation of everolimus. The use of systematic postoperative pericardial drainage may reduce the incidence of pericardial effusions.

Experimental immunosuppression

O-205 PHOSPHOSPECIFIC FLOW CYTOMETRY TO MONITOR P38 MAP KINASE ACTIVITY IN T LYMPHOCYTES OF RENAL TRANSPLANT PATIENTS

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Introduction: Transplant patients frequently suffer from lack of efficacy by immunosuppressive medication or from toxicity, which can be attributed to inter-individual variation in drug sensitivity. This problem can be overcome by pharmacodynamic monitoring, which focuses on measuring the biological effects of drugs. We used phosphospecific flow cytometry to study the effect of tacrolimus (TAC) on P38 MAP kinase (MAPK), the activator of NFAT (nuclear factor of activated T cells), in T cells.
Materials & Methods: Freshly obtained whole blood samples were stimulated with PMA/Ionomycin, and P38 MAPK phosphorylation was measured by flow cytometry.
Results: In vitro TAC inhibited P38 MAPK in a dose dependent manner: the IC50 in T cells was 37 ng/mL (95% CI 32 to 44 ng/ml).
In healthy volunteers (N=4), 2 hours after an oral dose of 10 mg TAC, the P38 MAPK activation was inhibited by 35.3% (median, range 16.4–60.3%) and

Abstract O-203 – Table 1. Identified cases of ILD in studies A2310 and A2309

HTx/KTx (treatment)	Event name (preferred term) / causality with treatment	Event start date / stop date or continuing	Severity / AE or SAE	Comments
HTx (EVR 1.5 mg)	Pulmonary toxicity / suspected	Day 110 / cont.	Severe / SAE	Ground glass opacities in CT scan. EVR discontinued Day 323
HTx (EVR 3 mg)	ILD / suspected	Day 94 / Day 127	Severe / SAE	Diagnosis by CT scan. Resolved after EVR discontinuation Day 106
HTx (EVR 3 mg)	ILD / suspected	Day 31 / cont.	Mild / AE	No diagnostic evidence provided. No action taken
KTx (EVR 1.5 mg)	Pulmonary alveolar proteinosis / not suspected	Day 316 / cont.	Moderate / SAE	Diagnosis by CT scan and bronchoscopy. EVR reduced. Death from pneumonitis/sepsis

cont., continuing; SAE, serious AE.