Keynote lecture: Mesenchymal stromal cell therapy in ischemia/reperfusion injury: review of the experimental and clinical evidence

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5th Session: IRI and cells

O13 ADMINISTRATION OF THIRD-PARTY MESCENHYMAL STROMAL CELLS AT THE TIME OF KIDNEY TRANSPLANTATION: INTERIM SAFETY ANALYSIS AT ONE-YEAR FOLLOW-UP

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Introduction: Mesenchymal stromal cells (MSC) therapy has been suggested in kidney transplantation (KTx). We report on the 1-year follow-up of an open-label phase I trial using MSC at the time of KTx.

Patients and Methods: On postoperative day 3 (D3), third-party MSC (2.0 ± 10^6/kg) were administered to 7 non-immunized first-transplant recipients from deceased donors, under standard immunosuppression (Basiliximab, Tacrolimus, MMF and steroids). No HLA matching was required for MSC donors. In parallel, 7 comparable KTx recipients were included as controls.

Conclusions: No hemodynamic or immune-allergic side-effect was noted at the time of MSC injection. Still, 1 patient with a history of ischemic heart disease had a NSTEMI –3 h after MSC infusion. Ten months after KTx, 1 MSC patient had type B aortic dissection and STEMI. Four MSC patients had at least 1 opportunistic infection, whereas 3 controls had polyoma-BK viremia. Three MSC patients were affected by at least 1 (pulmonary) infection, whereas 2 controls had urinary infection. No MSC engraftment syndrome was observed. At D14, eGFR in MSC and control groups was 47.1 ± 6.8 and 39.7 ± 5.9 ml/min, respectively (p = 0.05). Nevertheless, eGFR in MSC and control groups at 1 year was 43.1 ± 17.8 and 53.9 ± 13.4 ml/min, respectively (p = 0.25). At 3-month protocol biopsy, borderline rejection (BR) was evident in 1 MSC patient. Later on, 1 BR and 1 AR were diagnosed at D1240 and D350, respectively. No biopsy-proven AR was noted in controls. Three patients developed anti-HLA antibodies against MSC (n = 1) or shared kidney/MSC (n = 2) mismatches.

Conclusions: MSC infusion was safe in all patients except one. Incidence of opportunistic and non-opportunistic infections was similar in both MSC and control groups. No MSC engraftment syndrome was documented. No difference in eGFR was found at 1 year between both groups. No MSC engraftment syndrome was documented. No difference in opportunistic and non-opportunistic infections was similar in both MSC and control groups.

5. Background: Ischemia reperfusion injury (IRI) contributes to acute kidney injury (AKI) and to delayed graft function (DGF) after kidney transplantation. After initial activation of myofibled cells in the first 48 h after IRI, T-cells invading the renal tissue are relevant players of the pro-inflammatory mediator IL-17A. In this project, we evaluated the role of T-cell subsets (vs versus gd T-cells) and IL-17A on inflammation and fibrosis induced by ischemia reperfusion injury in mice.

Methods: IRI was induced by unilateral clamping of the renal pedicle for 45 min and mice were sacrificed after 7 days when infiltrating T-cells were detected. In a second model IRI induced delayed graft function (DGF) was studied after allogeneic transplantation (ktx) and again leukocyte composition was studied at 7 and compared to IRI alone. T-cell receptor (TCR-gd) and IL-17A deficient and wildtype (WT) mice were used. We performed the IRI model as well. FACS analysis, histology and immunohistochemistry for inflammation and fibrosis as well as qPCR were done.

Results: IRI and ktx resulted in substantial T-cell infiltration but the distribution of T-cell subsets were different. In IRI ab T-cell infiltrates were 2.5 fold higher compared to gd T-cells whereas in the combination of IRI with ktx ab T-cell infiltrates were about 8 fold higher compared to gd T-cell infiltrates. The gd T-cells contributed substantially to elevated IL-17A production. Surprisingly, gd T-cells and IL-17A deficient mice were not protected from IRI and showed progressive renal fibrosis similar to WT mice. In both mouse strains (TCR-gd and IL-17A deficient mice) IL-17A production of gd T-cells was totally abrogated in ex vivo T-cell stimulation with PMA/ionomycin.

Conclusion: Surprisingly, neither gd T-cell nor IL-17A deficient attenuated IRI, inflammation or tissue fibrosis.

O15 CONTRIBUTION OF GD T-CELL SUBSETS AND IL-17A ACTIVATION TO RENAL ISCHEMIA REPERFUSION INJURY IN MICE

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Introduction: Ischemia reperfusion injury (IRI) contributes to acute kidney injury (AKI) and to delayed graft function (DGF) after kidney transplantation. After initial activation of myofibled cells in the first 48 h after IRI, T-cells invading the renal tissue are relevant players of the pro-inflammatory mediator IL-17A. In this project, we evaluated the role of T-cell subsets (vs versus gd T-cells) and IL-17A on inflammation and fibrosis induced by ischemia reperfusion injury in mice.