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Introduction: Current guidelines do not mention tacrolimus (TAC) as a treatment option and no consensus has been reported on the role of tacrolimus in active LN. Recent clinical trials have reported positive effects of tacrolimus-based regimens for treatment of lupus nephritis (LN). In order to translate these trials into clinical practice, we systematically reviewed all clinical studies published thus far that investigated TAC regimens in LN patients and performed a meta-analysis.
Methods: We identified from various databases every clinical study investigating TAC regimens in LN. Studies were summarized on the basis of treatment target (induction or maintenance), concomitant immunosuppression and quality of the data. A meta-analysis was performed for the efficacy of TAC regimens as induction treatment.
Results: 239 studies were identified from which 24 were clinical studies performed in LN patients: 6 case series, 9 cohort studies, 3 case-control studies (CCS) and 6 randomized controlled trials (RCTs). Further analysis of the 9 controlled trials showed that 7 studies investigated tacrolimus in combination with steroids and 2 tacrolimus with mycophenolate plus steroids. 4 RCTs investigated TAC regimens as induction treatment and 2 RCTs as maintenance treatment. Strikingly, there was no consensus in any of the studies regarding tacrolimus dosing and target trough levels. Importantly, all the studies were performed in LN patients of Asian ethnicity. A meta-analysis of TAC regimens for induction treatment showed a significantly higher complete response (RR 1.18, 95% CI 1.04-1.34, $p = 0.01$) and a significantly lower no response rate (RR 0.71, 95% CI 0.56-0.90, $p<0.01$). With respect to safety, no clear differences between TAC regimens and conventional treatment were observed.
Conclusions: Current studies on TAC regimens for LN are limited, heterogeneous and predominant uncontrolled studies in patients of Asian ethnicity. A significant clinical efficacy of TAC regimens as induction treatment was found. However, this cannot be extrapolated beyond Asian LN patient groups. Clearly, these results mandate further confirmation in multi-ethnic, randomized trials.

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LEARNING ABOUT HUMAN KIDNEY IMMUNOLOGY FROM THERAPEUTIC MONOCLONAL ANTIBODY-INDUCED KIDNEY INJURY: EFFECT OF PD1 BLOCKADE

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Introduction: Human renal microvascular endothelial cells (RMEC) normally express high levels of HLA class II, even when no inflammation is present by histology. Previous work in the lab with isolated (cultured) RMEC showed that the cells present peptide in a DR restricted manner to activate antigen-specific T cells. T cell proliferation and cytokine secretion were decreased by CD40 and CD58 antibodies and increased with CD274 (PD-L1) antibodies. We hypothesized that RMEC express T cell inhibitory molecules in vivo to prevent or limit T cell activation to HLA class II presented peptides.

Nivolumab, a programed death 1 (PD1) inhibitor, is a new immunotherapy option for a growing number of cancer types, including lung cancer, advanced renal cell carcinoma, and metastatic melanoma. It selectively binds PD1 to prevent interaction with its ligands PD-L1 (CD274, B7H1) and PD-L2 (CD273, B7H2). PD-1 is expressed on activated T and B lymphocytes and myeloid cells. Binding to its ligands transmits an inhibitory signal which reduces the proliferation of these cells. Expression of PD1 ligands on tumor cells enables them to suppress lymphocyte responses to tumor antigens. Monoclonal antibodies targeting PD1 removes this suppression, thereby enhancing T-cell responses to promote anti-tumor activity.
Methods: Flow cytometry was used to identify RMEC and assess their expression of PD1 ligands and T cell co-stimulatory proteins. Medical records and pathology slides were reviewed for patients who developed acute kidney injury while being treated with nivolumab.
Results: Flow cytometry studies identified high levels of PD-L1 on RMEC from normal human kidneys.

Four patients were identified who developed acute kidney injury while receiving PD1 blocking antibody therapy for their cancers. Three underwent renal biopsy which showed interstitial nephritis with intense inflammation around capillaries. Other causes of interstitial nephritis were not identified from clinical history.
Conclusions: Our interpretation of RMEC's ability to activate T cells in a class II-peptide dependent manner, their high levels of inhibitory ligand PD-L1 (CD274) and now the development of interstitial inflammation in some patients receiving anti-PD1 monoclonal therapy is that RMEC are poised to present peptide from circulating antigen as an immune surveillance system, with the PD1 pathway functioning to restrain T cell activation. Other human organs also express high levels of HLA class II on microvascular endothelial cells. Hence our hypothesis of a kidney capillary endothelium forming an immune surveillance system may also pertain to other organs.

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VITAMIN D RECEPTOR ACTIVATION REDUCES INFLAMMATORY CYTOKINES AND PLASMA MICRORNAS IN MODERATE CHRONIC KIDNEY DISEASE–A RANDOMIZED TRIAL

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Introduction: Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease (CVD), partly due to endothelial dysfunction, and chronic inflammation. Disturbed function of the immune system in CKD patients is witnessed through the high levels of cytokines in the plasma, and epigenetic modifications such as micro RNAs (miRs) expression contribute to the disease process. Vitamin D supplementation or treatment, protect endothelial function and may improve outcome in these patients. In the SOLID-trial, we showed that treatment with a vitamin D receptor activator, (VDRA; paricalcitol) is followed by a maintained endothelial function and capillary blood flow. Here, we report the effect of paricalcitol on pro-inflammatory cytokines and miRs in plasma from patients in the SOLID-trial.
Methods: 36 patients with eGFR of 15-59 mL/min/1.73 m2, calcium < 2.6 mmol/L, and PTH level of 35-500 pg/mL were randomized to 12 weeks treatment with placebo, 1 μg, or 2 μg paricalcitol.