ESPN Journal Club – Idiopathic nephrotic syndrome

The papers selected for this month's Journal Club pertaining to idiopathic syndrome.

The first one is a paper published very recently in Nature Medicine by J Reiser's group, highlighting the potential pathogenic role of suPAR-producing immature myeloid cells in determining proteinuria in mice.

1) Hahm E, Wei C, Fernandez I, Li J, Tardi NJ, Tracy M, Wadhwani S, Cao Y, Peev V, Zloza A, Lusciks J, Hayek SS, O'Connor C, Bitzer M, Gupta V, Sever S, Sykes DB, Scadden DT, Reiser J.

Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease.

Nat Med. 2017 Jan; 23(1):100-106

ABSTRACT

Excess levels of protein in urine (proteinuria) is a hallmark of kidney disease that typically occurs in conjunction with diabetes, hypertension, gene mutations, toxins or infections but may also be of unknown cause (idiopathic). Systemic soluble urokinase plasminogen activator receptor (suPAR) is a circulating factor implicated in the onset and progression of chronic kidney disease (CKD), such as focal segmental glomerulosclerosis (FSGS). The cellular source(s) of elevated suPAR associated with future and progressing kidney disease is unclear, but is likely extra-renal, as the pathological uPAR is circulating and FSGS can recur even after a damaged kidney is replaced with a healthy donor organ. Here we report that bone marrow (BM) Gr-1lo immature myeloid cells are responsible for the elevated, pathological levels of suPAR, as evidenced by BM chimera and BM ablation and cell transfer studies. A marked increase of Gr-1lo myeloid cells was commonly found in the BM of proteinuric animals having high suPAR, and these cells efficiently transmit proteinuria when transferred to healthy mice. In accordance with the results seen in suPAR-associated proteinuric animal models, in which kidney damage is caused not by local podocyte-selective injury but more likely by systemic insults, a humanized xenograft model of FSGS resulted in an expansion of Gr-1lo cells in the BM, leading to high plasma suPAR and proteinuric kidney disease. Together, these results identify suPAR as a functional connection between the BM and the kidney, and they implicate BM immature myeloid cells as a key contributor to glomerular dysfunction.

The second is a paper published in JASN and presented in September at the ESPN meeting in Brazil, by the group of H Yap. They assessed children receiving rituximab for FSGS, and identified a subset of patients with FSGS bearing an immunologic signature (hyporesponsiveness to T cell stimulation) who respond better to rituximab.

2) Chan CY, Liu ID, Resontoc LP, Ng KH, Chan YH, Lau PY, Than M, Jordan SC, Lam KP, Yeo WS, Yap HK. **T Lymphocyte Activation Markers as Predictors of Responsiveness to Rituximab among Patients with FSGS.**

Clin J Am Soc Nephrol. 2016 Aug 8; 11(8):1360-8

ABSTRACT

BACKGROUND AND OBJECTIVES:

Rituximab is used with variable success in difficult FSGS. Because B cell depletion significantly affects T cell function, we characterized T cell subsets in patients with FSGS to determine if an immunologic signature predictive of favorable response to rituximab could be identified.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:

Twenty-two consecutive patients with FSGS (median age =14.4 years old; range =6.2-25.0 years old) and age of onset of nephrotic syndrome 1-18 years old receiving rituximab for clinical indications between October of 2009 and February of 2014 were studied. Indications for rituximab were lack of sustained remission despite calcineurin inhibitors (CNIs) and mycophenolate in steroid-resistant patients and lack of steroid-sparing effect with cyclophosphamide and CNI or CNI toxicity in steroid-dependent patients. Exclusion criteria were infantile onset, known genetic mutations, and secondary causes. Rituximab (375 mg/m (2)) was given fortnightly up to a maximum of four doses. Immunologic subset monitoring was performed at baseline and regular intervals until relapse. Median follow-up duration postrituximab was 26.7 months (range =6.5-66.5 months). Baseline immunologic subsets were examined for association with rituximab response defined as resolution of proteinuria with discontinuation of prednisolone and CNI 3 months postrituximab.

RESULTS:

Twelve patients (54.5%) responded to rituximab. Mitogen-stimulated CD154(+)CD4(+)CD3(+) subset before rituximab was significantly lower in FSGS responders compared with nonresponders (54.9%±28.1% versus 78.9%±16.4%; P=0.03). IFN-γ(+)CD3(+) and IL-2(+)CD3(+) were similarly decreased in responders compared with nonresponders (0.6%±0.8% versus 7.5%±6.1%; P=0.003 and 0.2%±0.5% versus 4.0%±4.7%; P<0.01, respectively). Recovery of all three activation subsets occurred 6 months postrituximab treatment (CD154(+)CD4(+)CD3(+), 74.8%±17.2%; IFN-γ(+)CD3(+), 7.1%±7.7%; and IL-2(+)CD3(+), 7.9%±10.9%; P<0.01). Receiver-operating characteristic analysis using optimal cutoff values showed that activated CD154(+)CD4(+)CD3(+) <83.3% (area under the curve [AUC], 0.81; 95% confidence interval [95% CI], 0.61 to 1.00), IFN-γ(+)CD3(+)<2.5% (AUC, 0.90; 95% CI, 0.75 to 1.00), and IL-2(+)CD3(+)<0.3% (AUC, 0.78; 95% CI, 0.57 to 0.98) were good predictors of rituximab response.

CONCLUSIONS:

We have identified prognostic markers that define a subset of patients with FSGS bearing an immunologic signature representing hyporesponsiveness to T cell stimulation and therefore, who respond better to rituximab.

The third is a paper on the role of mycophenolic acid blood levels to optimize therapy with MMF in children with INS by J Harambat's group, suggesting the optimal levels to maintain control of disease.

3) Tellier S, Dallocchio A, Guigonis V, Saint-Marcoux F, Llanas B, Ichay L, Bandin F, Godron A, Morin D, Brochard K, Gandia P, Bouchet S, Marquet P, Decramer S, Harambat J. **Mycophenolic Acid Pharmacokinetics and Relapse in Children with Steroid-Dependent Idiopathic Nephrotic Syndrome.**

Clin J Am Soc Nephrol. 2016 Jul 21

ABSTRACT

BACKGROUND AND OBJECTIVES:

Therapeutic drug monitoring of mycophenolic acid can improve clinical outcome in organ transplantation and lupus, but data are scarce in idiopathic nephrotic syndrome. The aim of our study was to investigate whether mycophenolic acid pharmacokinetics are associated with disease control in children receiving mycophenolate mofetil for the treatment of steroid-dependent nephrotic syndrome.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:

This was a retrospective multicenter study including 95 children with steroid-dependent nephrotic syndrome treated with mycophenolate mofetil with or without steroids. Area under the concentration-time curve of mycophenolic acid was determined in all children on the basis of sampling times at 20, 60, and 180 minutes

postdose, using Bayesian estimation. The association between a threshold value of the area under the concentration-time curve of mycophenolic acid and the relapse rate was assessed using a negative binomial model.

RESULTS:

In total, 140 areas under the concentration-time curve of mycophenolic acid were analyzed. The findings indicate individual dose adaptation in 53 patients (38%) to achieve an area under the concentration-time curve target of 30-60 mg·h/L. In a multivariable negative binomial model including sex, age at disease onset, time to start of mycophenolate mofetil, previous immunomodulatory treatment, and concomitant prednisone dose, a level of area under the concentration-time curve of mycophenolic acid >45 mg·h/L was significantly associated with a lower relapse rate (rate ratio, 0.65; 95% confidence interval, 0.46 to 0.89; P=0.01).

CONCLUSIONS:

Therapeutic drug monitoring leading to individualized dosing may improve the efficacy of mycophenolate mofetil in steroid-dependent nephrotic syndrome. Additional prospective studies are warranted to determine the optimal target for area under the concentration-time curve of mycophenolic acid in this population.

Regarding therapy, it is also worth mentioning that in October the Cochrane review for treatment of SRNS was published (Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Hodson EM, Wong SC, Willis NS, Craig JC. Cochrane Database Syst Rev. 2016 Oct 11;10:CD003594. Review.).

Briefly, these are the AUTHORS' **CONCLUSIONS:**

To date RCTs have demonstrated that calcineurin inhibitors increase the likelihood of complete or partial remission compared with placebo/no treatment or cyclophosphamide. For other regimens assessed, it remains uncertain whether the interventions alter outcomes because the certainty of the evidence is low. Further adequately powered, well designed RCTs are needed to evaluate other regimens for children with idiopathic SRNS. Since SRNS represents a spectrum of diseases, future studies should enrol children from better defined groups of patients with SRNS.