WHAT'S HOT WHAT'S NEW - AN UPDATE FROM THE IPNA 2016 MEETING

Idiopathic Nephrotic syndrome

1) The results of the placebo controlled levamisole trial for frequently relapsing and steroid-dependent nephrotic syndrome pediatric patients, conducted in Europe and India. Levamisole is a safe and effective steroid-sparing option in maintaining remission in patients with frequently relapsing forms of disease.

FP-S25-11 - Levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome: results of a multi-center, double-blind, placebo-controlled, randomized clinical trial.

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Objectives: Levamisole has been considered the least toxic and expensive drug for preventing relapses of steroid sensitive idiopathic nephrotic syndrome (SSINS). However, evidence is limited, as previous randomized clinical trials (RCTs) were found to have methodological limitations. This is why we conducted an appropriate RCT to reassess its usefulness in prevention of SSINS relapses in children.

Methods: The study was conducted in an international multi-center, placebo-controlled, double blind RCT for one year, in order to evaluate efficacy and safety of levamisole in children with SSINS and frequent relapses.

Results: The intention to treat population (ITT) consisted of 99 patients from 6 countries. Time to relapse (primary endpoint) was significantly increased in the intervention group compared to placebo (p-value 0.22 [95% CI 0.11-0.43], p-value 0.001 after 100 days post-randomization). After 12 months of treatment, remission persistence was more frequent in levamisole than in the placebo group (26% vs 6 %: p = 0.012). The most frequent serious adverse event (SAE) (4/50) possibly related to levamisole was asymptomatic moderate neutropenia (500-1000 cells/µL), reversible spontaneously or after treatment interruption. Rare, severe side effects of levamisole reported in treatment of SSINS included hepatitis, convulsions or antineutrophil cytoplasmic antibody (ANCA) vasculitis were not observed in this study. However, ANCA-related arthritis was reversible with levamisole interruption, and reported in one patient.

Conclusions: In children with SSINS and frequent relapses, levamisole prolongs time to relapse and also prevents recurrence for one-year of treatment in 20% of patients. Regular blood controls are necessary for safety issues.

2) A study identifying a biomarker for response to rituximab in pediatric patients with focal segmental glomerulosclerosis from the group of Prof Yap in Singapore, recently published in CJASN (ref).

FP-S14-1 - Hyporesponsive T-cell activation subsets predict favorable rituximab response in patients with focal segmental glomerulosclerosis (FSGS)

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Objectives: The use of rituximab in refractory idiopathic nephrotic syndrome especially FSGS has met with variable success. As B-cell depletion can impact T-cell function, this study aimed to characterize T-cell subsets in FSGS patients in order to identify an immunological signature predictive of favorable response to rituximab therapy.

Methods: 22 consecutive FSGS patients (median age 14.4 years, range 6.2- 25.0 years) who received rituximab as third line therapy following steroids and calcineurin inhibitors (CNI), were included in the study. Clinical parameters including urinary protein excretion and serum albumin, as well as immunological subset monitoring were performed at baseline, 14-days, 1-month, and subsequently 3-monthly until relapse. Baseline immunological subsets were compared between rituximab responders and non-responders, as well as 22 patients with minimal change nephrotic syndrome (MCNS) in relapse and 30 healthy controls, using Mann-Whitney U Test. Paired comparison was done using Wilcoxon signed rank test.

Results: 12 of 22 patients (54.5%) responded to rituximab therapy, defined as resolution of proteinuria and ability to wean off steroids and CNI at 3 months following rituximab treatment. Mitogen-stimulated T-cell activation subset expressions are shown in the Table 1 below. Mitogen-stimulated CD154+CD4+CD3+ expressions before rituximab were significantly lower in FSGS responders compared to non-responders and controls. IFN-γ+CD3+ and IL-2+CD3+ were similarly decreased in FSGS responders compared to nonresponders, MCNS and controls. Significant recovery of all 3 subsets in FSGS responders occurred 6 months post-rituximab treatment. Using ROC analysis, activated CD154+CD4+CD3+ (AUC 0.81, 95% CI 0.61-1.01), IFN-γ+CD3+ (AUC 0.90, 95% CI 0.75-1.05) and IL-2+CD3+ (AUC 0.78, 95% CI 0.57- 0.98) were good predictors of response to rituximab. & Table 1: T-cell activation subsets pre-rituximab and 6 months postrituximab in FSGS rituximab responders and non-responders compared to MCNS patients in relapse and healthy controls.

Conclusions: T-cell subset hyporesponsiveness to mitogen stimulation predicted a favorable response to rituximab in FSGS patients.

3) The identification of a new murine model of minimal change disease, with a knock-in mutation of the adaptor protein Sh3BP2 involved in activation of both NFkB abd NFAT. The phenotype appears to faithfully reproduce MCD both clinically (low serum albumin, proteinuria) and histologically (foot process effacement).

FP-S02-2 - Is minimal change disease (MCD) caused by dysregulation of SH3BP2- mediated immune activation?

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Objectives: Immunopathogenesis of MCD remains unclear. Serum TNFα is increased in MCD. TNFα-dependent inflammation is observed in transgenic mouse (Ki/Ki) with P416R mutation in sh3bp2 gene. SH3BP2 is an adaptor protein that binds to tyrosine kinasesABL, SYK,VAV, etc. to regulate immune activation ofMϕ, T- and B-cells. Sh3bp2 knock-in mice are used as amodel to study "cherubism" in children which improves post-puberty like MCD. The Ki/Ki mouse phenotype is abrogated when crossed with TNFα KO or MyD88 KO mouse suggesting a role for immune system. We showed that podocytes express TLR-MyD88-NFkB innate immune signaling pathway. Therefore, we planned to assess Sh3bp2Ki/Kimouse as amodel to studyMCD.

Methods: We compared urine, serum, renal histology and serum cytokine profile from wild type (+/+), heterozygous (Ki/+) and homozygous (Ki/Ki) mice at 4 and 12 wks.

Results: Ki/Kitransgenic mice showed higher urine albumin, lower serum albumin, increased mesangial cellularity and decreased slits/GBM length by 12 wks. IL2, IFNγ,MIP1α and IL17 were elevated at 12 wks, while IL1α and CXCL1 remained unchanged (Table and Figure). Podocytes and mesangial cells express sh3bp2, Myd88 and TNFαR by qRT-PCR.