KSN 2020
FULLY VIRTUAL MEETING

Abstract Submission No. : IL-9137

Pharmacogenomic aspect of steroid resistance in Nephrotic Syndrome

Narayan Prasad
Sanjay Gandhi Postgraduate Institute of Medical Sciences,Lucknow, India

Lecture title: Pharmacogenomic aspect of steroid resistance in Nephrotic Syndrome
Presenting Author: Prof. Narayan Prasad
Professor & Head
Department of Nephrology and Renal Transplantation
Sanjay Gandhi Post Graduate Institute of Medical Sciences
Lucknow, INDIA
Pin- 226014
Email: narayan.nephro@gmail.com
Mobile No. +91-9415403140
Phone No. +91-522-2495187

Steroid-resistant nephrotic syndrome (SRNS) is one of the most frequent cause of chronic kidney disease. During course of steroid therapy 15% remain primary non responder, 30% become frequent relapser, 25 % steroid dependent and 3-5% of them become late non-responder. Approximately 50% of SRNS patients progressed to end stage renal disease in 10 yrs. SRNS also carries a 33% risk of relapsing after renal transplant, thereby again added to the list of CKD.

Non-responsiveness to steroid possibly because of -histological transformation from MCD to FSGS; genetic Mutations (WT1, INF2, LAMB2, ACTN4, NPHS1, and NPHS2 gene); and pharmacogenomic alteration leading to development of SRNS. Herewith, I present a pharmacogenomic aspect of steroid response in NS patients.

Pharmacogenomics of SRNS comprises of three important aspects: 1 Multi Drug Resistant-1 (MDR-1) gene polymorphism and P-glycoprotein (P-gp), 2. Multidrug resistant associated protein-1 (MRP-1) efflux pump, another protein of ABC transporter family, and 3. Histone Deacetylase 2 (HDAC2) which is a class of enzymes that remove acetyl groups from an amino acid on histone protein of DNA, close the chromatin and stops transcription of genes.

P-gp, a product of MDR-1 gene expressed on blood–brain barrier, liver, kidney, intestine and peripheral blood lymphocytes (PBLs) etc., which acts as an efflux pump for xenobiotics/drugs in an energy dependent manner and removes steroid from inside cells to outside the cell, limiting the availability of drug to act at the site of action and causing steroid resistance.

Way back, in 2011 we showed that patients with NS carrying homozygous mutants of single nucleotide polymorphism (SNP) G2677T/A are prone to develop SRNS. The synergistic effect of mutant genotypes of SNPs G2677T/A and C3435T in different combinations increase the risk of developing steroid resistance in patients with NS and published in NDT (Nephrol Dial Transplant (2011) 26: 3968–3974). Further, we have analyzed P-gp expression on different types of T helper cells and found steroid therapy in INS induces decreased P-gp expression on lymphocytes along with increased frequency and cytokine response of T-regulatory cells, and reduced frequency and respective cytokine response of Th1 and Th2 cells during remission. However, reversal in the frequency and respective cytokines of T-regs, Th1 and Th2, and P-gp expression on PBLs occurs during relapses on follow-up. Wasilewska AM et. Al. 2006, Doaa M Youssef et. al. 2013 and several others have also supported our findings that is worse response to steroid or dependency may be due to overexpression of P-gp.

We have also found P-gp and MRP-1 expression on CD4 and CD8 cells was high in SRNS patients. On AUC-ROC curve we have found P-gp expression on PBLs with a cutoff value of 7.13% predicted steroid resistance with a sensitivity of 86.4% and specificity 90%. Similarly, MRP-1 expression on PBLs with a cutoff value of 9.62% predicted steroid resistance with a sensitivity of 80.7% and specificity of 80%.

Recently we have published our findings in "Frontiers in Pharmacology" on HDAC2 role in SRNS. We

found reduced HDAC2 and increased P-gp/MRP-1 activity may play a role in response to steroids in childhood NS. HDAC2 and P-gp/MRP-1 are in reciprocal relationship with each other. We have also found that mRNA expression of P-gp and MRP-1 decreases with increasing molar concentration of HDAC2 stimulator "Theophylline" however mRNA expression of HDAC was increasing. The reverse association in transcripts of P-gp and MRP-1 increases with increasing molar concentration of HDAC2 inhibitor "Trichostatin A" in both SRNS and steroid sensitive NS. In conclusion, MDR-1 gene, and its protein product P-gp affects steroid response and C2677T/A gene polymorphism is associated with increased P-gp expression and steroid resistance in our patient population. Tacrolimus is substrate as well as inhibitor of P-gp. This may be possible explanation of response of steroid after adding Tac in SRNS and steroid dependent patients. HDAC stimulator (Theophylline) may also play an important role in sparing steroid response, however it needs to confirmed.

Figure 1: Pharmacokinetic Variability with P-gp (A), P-gp expression at remission, during relapse, at SRNS and in control (B).

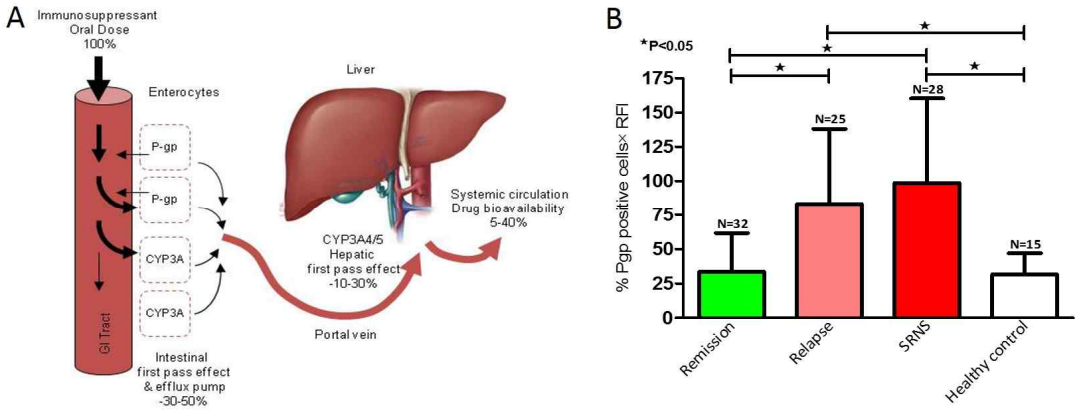
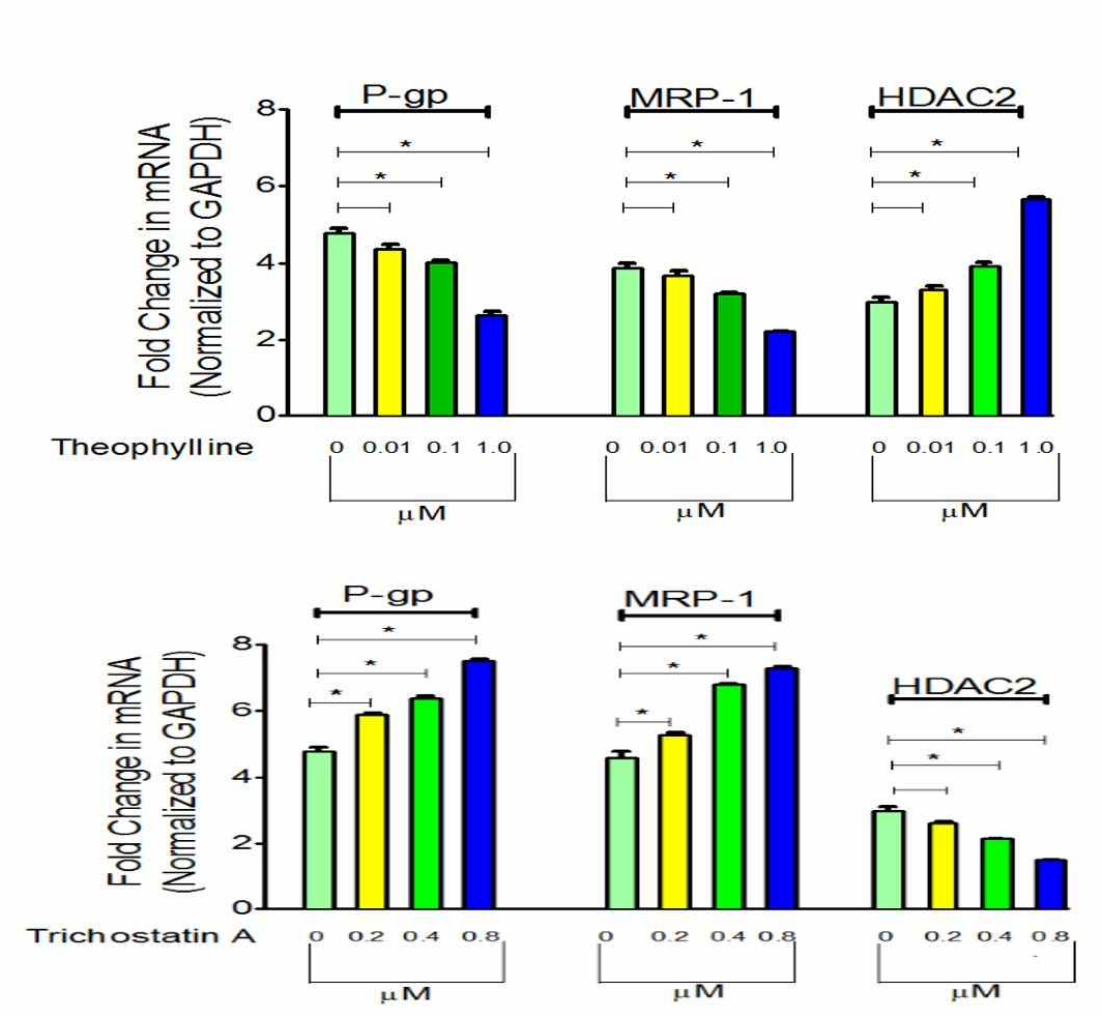


Figure 2: Effect of HDAC2 stimulator "Theophylline" and inhibitor "Trichostatin A" expression levels of P-gp, MRP1 and HDAC2 in SRNS patients.


P-gp
MRP-1
HDAC2
Fold Change in mRNA (Normalized to GAPDH)
0
2
4
6
8
*
Theophylline
0 0.01 0.1 1.0
μM
P-gp
MRP-1
HDAC2
Fold Change in mRNA (Normalized to GAPDH)
Trichostatin A
0 0.2 0.4 0.8
μM