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DOES EPIGENETIC REGULATION PLAYS ROLE IN STEROID NON-RESPONSIVENESS IN LUPUS NEPHRITIS PATIENTS

Ashish Srivastav

Department of Department of Medicine, AIIMS, Gorakhpur, India, India

Objectives: Steroid resistance is one of the most common challenges for clinicians to manage Lupus Nephritis (LN) patients. Other than genetic effects; P-glycoprotein (P-gp) has been linked with steroid resistance; HDAC2 has been reported to be reciprocally related to P-gp and reduced HDAC2 may up-regulate the expression of P-gp which might result in steroid non-responsiveness. Our aim was to evaluate the gene expression of P-glycoprotein and HDAC2 on PBMCs in Lupus Nephritis patients.

Methods: 51 patients were recruited at baseline (before initiating steroid therapy); After 4 weeks of steroid therapy 33 patients responded to steroids responsive; whereas 18 patients did not respond to steroids. mRNA expression was analyzed on PBMCs in LN patients. qPCR was performed using SYBER green technology with SYBER primex relative gene expression levels calculated and normalized by the GAPDH gene. P-gp expression was measured by flow cytometry using a commercially available kit (EFLUXX-ID® Green multidrug resistance assay kit).

Results: Expression of P-gp mRNA was significantly lower in subjects who achieved remission as compared to baseline and those who were resistant to steroids ($P < 0.005$). Out of steroid-resistant patients, 13 achieved complete remission following tacrolimus therapy and their P-gp expression and activity were reduced. Whereas HDAC2 expression was increased significantly ($P < 0.005$). Out of the 33 patients who achieved remission, 10 relapsed whose P-gp mRNA expression and activity were increased; whereas expression of HDAC2 was decreased. Expression of HDAC2 mRNA was significantly higher at baseline and at remission following 4-weeks of steroid therapy. HDAC2 expression was significantly decreased in resistant patients as compared to that of the remission group ($P < 0.005$).

Conclusions: Reduced HDAC2 gene expression may increase the expression of P-gp which might promote steroid non-responsiveness in LN.