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Evaluation of IL-17 and TAK-1 mediated P-gp and MRP-1 expression on lymphocytes and Plasma cells in refractory lupus nephritis patients

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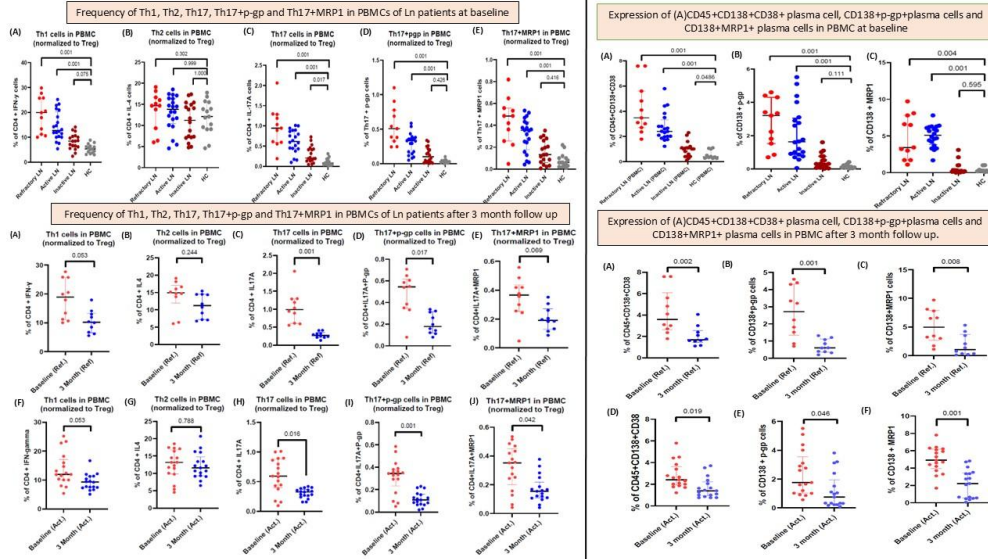
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Objectives : To evaluate the frequency of peripheral blood PCs and Th17 cells expressing p-gp and MRP-1 in LN compared with healthy controls (HCs).

Methods : p-gp+ and MRP-1+PCs, p-gp+ and MRP-1+ Th17 lymphocytes were determined in patients with LN. U266B1 cell treated with anti-IL-6, anti-IL-17, in combination and with TAK1 inhibitor in the presence of rIL-6+rIL-6R+rIL-17 in combination for 24hr, after that qRT-PCR was performed.

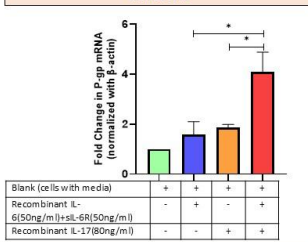
Results : Forty-nine patients with LN [11 refractory [mean SLEDAI-2K 11.9 (10.41)], 20 active (10 treatment naïve), 18 inactive LN] {median age 30 (24-37), 45 female and 4 males}, 15 healthy controls (HCs) {median age 27 (24-33)} were recruited. In blood, overall PCs were elevated in refractory LN, CD45+CD138+CD38[4.196(1.906)vs0.991(.54), p<0.0009]; CD138+p-gp[2.759(1.348)vs0.515(0.501), p<0.0009]; CD138+MRP-1[3.04(2.86)vs0.441(0.389), p<0.0851] as compared to inactive. Ratio of Th17/Tregs [1.08(0.86)vs0.249(0.159), p<0.0009]; p-gp+Th17/treg [(1.354(0.606)vs0.416(0.399), p<0.0009] and MRP-1+Th17 lymphocytes [1.156(0.676) vs 0.431(0.311), p<0.1651] were significantly increased in refractory compared to inactive LN. Cytokine levels of NGAL [406.287(243.710)vs99.583, p<0.0008], IL-17[157.727(78.34)vs50(27.389), p<0.005]; IL-6[238.85(169.11)vs47.471(26.674), p<0.008]; TNF- α [50.651(22.936)vs26.611(21.259), p<0.03]; IL10[88.935(30.765)vs172.283(65.493), p<0.338]; CXCL12[735.931(347.284)vs513.756(91.533), p<0.03] and CXCL13[513.031(621.981)vs340.170(342.663), p<0.05] (Figure:1) were also elevated in refractory LN compared to inactive LN. In PCs cell line (U266B1), increase mRNA expression of P-gp(p<0.03) and MRP-1(p<0.05) after stimulation with the combination of rIL-6+sIL-6R+rIL-17(Figure:2). While by the inhibitory effect of anti-IL-6 and anti-IL-17 in combination downregulated the expression of P-gp(p=0.04) and MRP-1(p=0.005) as compared to either alone (Figure:2). The effect of (5Z)-7-Oxozeanol(TAK-1 inhibitor) in combination with anti-IL17 decreased the expression of P-gp(p=0.006) and MRP1(p=0.05) gene (Figure:2).

Conclusions : There is an increased frequency of P-gp and MRP-1-expressing PCs and Th17+P-gp lymphocytes in LN. IL-17 in the presence of IL-6 might be increases the expression of P-gp and MRP-1 on PCs and facilitates the non-responsiveness to the treatment.

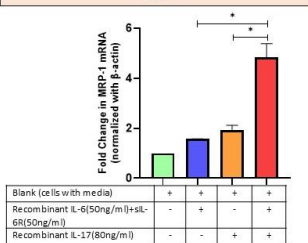


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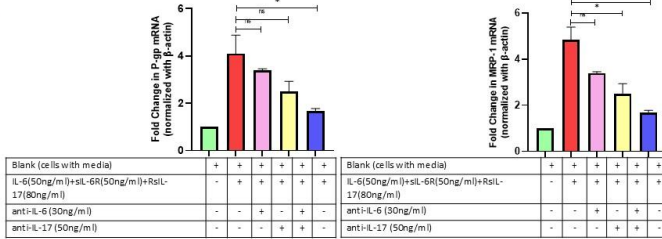
P-glycoprotein activation in the presence of IL-6 and IL-17A in U26681 cells



MRP-1 activation in the presence of IL-6 and IL-17A in U26681 cells



Therapeutic modulation with Anti-IL-6(tocilizumab), Anti-IL-17(Secukinumab) on P-glycoprotein and MRP-1 expression



Therapeutic modulation with TAK-1, Anti-IL-6(tocilizumab) and Anti-IL-17(Secukinumab) on P-glycoprotein and MRP-1 expression

