Non Response to Peginterferon Alfa and Ribavirinin IL28B CC & CT Patients can be Overcome by High Dose Continuous Interferon Alfa-2b Administration in Combination with Ribavirin for Chronic Hepatitis C

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Study Design

A (n=10)	Screening	12 MU IFN –α2b QD continuously Ribavirin 15 mg/kg/day	Follow-up
B (n=10)	Screening	9 MU IFN –α2b QD continuously Ribavirin 15 mg/kg/day	Follow-up
C (n=10)	Screening	6 MU IFN –α2b QD continuously Ribavirin 15 mg/kg/day	Follow-up

Week   -4   0   48   72

Baseline Characteristics

Treatment Arm	Total	6MU	9MU	12MU	P value
IL28b genotype (rs12979860)					0.863
CC	3	1	1	1	
CT	20	6	6	8	
TT	6	2	3	1	
Male (%)	22 (73)	7 (70%)	6 (60%)	9 (90%)	0.303
Age (years)	46.9	46.1	48.2	46.5	0.685
Race					0.399
Caucasian /non-Caucasian	27/3	8/2	9/1	10/0	
Genotype 1 vs. 4	24/6	8/2	8/2	8/2	1.000
Cirrhosis (%)	13 (43)	3 (30)	3 (30)	7 (70)	0.114
BMI in kg/m^2 (mean)	27.5	26.6	28.7	27.2	0.664
Response to previous treatment					0.980
Non response	20	6	7	7	
Breakthrough	3	1	1	1	
Relapse	7	3	2	2	
Mean log HCV RNA	5.45	5.25	5.67	5.46	0.397
Bilirubin in µmol/L	12.0	10.2	12.5	13.2	0.790
ALT in U/L	88.3	88.9	88	88	0.717
GGT in U/L	113.5	151.3	81.9	107.2	0.245

Viral Decline at Week 4 Per IL28b Genotype
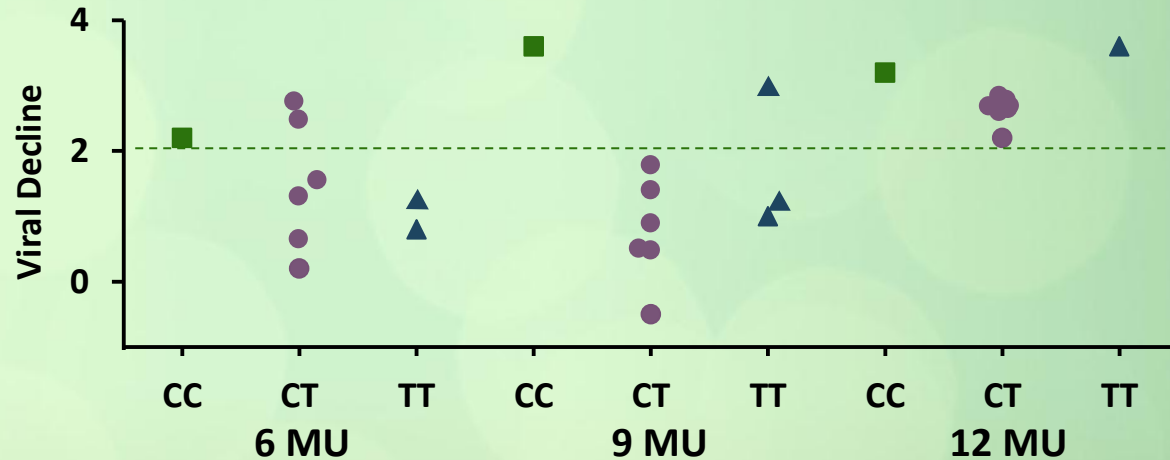
At wk 4, a mean HCV RNA decline of 2.91 (95% CI 2.06-3.76), 1.57 (95% CI 1.12-2.02) and 1.60 (95% CI 0.62-2.57) log10 IU/ml was found in the CC, CT and TT groups respectively (CC vs. CT/TT, P=0.04). Furthermore, in the high dose group receiving 12 MU IFN/day, all 10 patients had more than 2 logs viral decay at week 4 of treatment regardless of their IL28B genotype.

Factors Associated with Viral Decline at Week 4

Variables	Correlation Coefficient (R)	*P* value
IL 28B genotype (rs12979860) cc vs. ct/tt	1.333	0.04
Female Gender	0.339	0.381
Age	-0.06	0.874
Viral genotype 1 vs. 4	0.06	0.724
Cirrhosis	-0.038	0.928
Interferon alfa -2b dose	0.687	<0.003
Baseline viral load	0.053	0.864
Baseline GGT	0	0.886
Baseline ALT	-0.02	0.635

Factors Associated with Viral Decline at Week 4

Results

- In this cohort 100% of CC patients achieved EVR during treatment compared to 15 and 33% of CT and TT patients *(P*=0.015). Out of 30 patients, 6 achieved SVR: 2 in the CC group (one in each of the 6 and 9 MU group) and 4 subjects in the CT group, who all received 12 MU IFN/day. In the multivariate linear regression analysis both IL28B SNP *(P*=0.017) and IFN dose *(P*=0.004) were significantly associated with viral decline at week 4.

IL28b Genotypes Per Treatment Arm
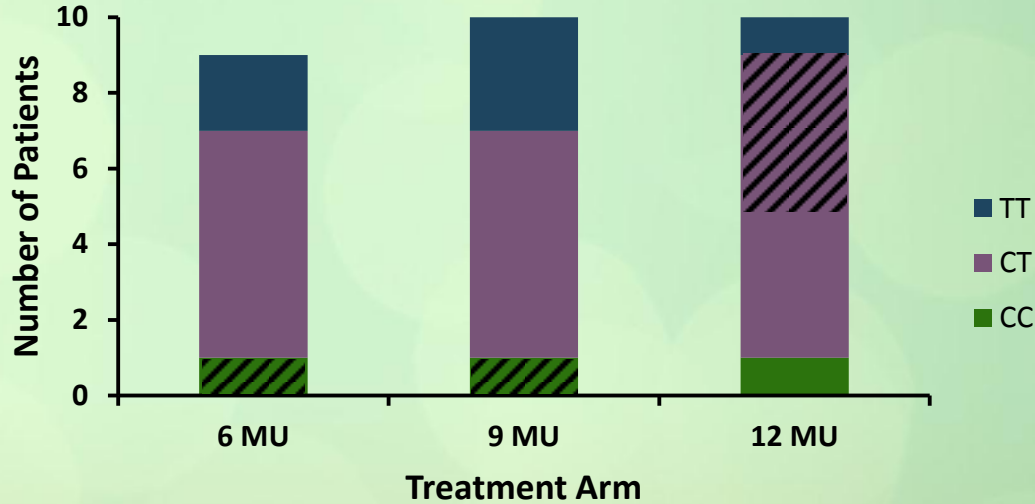
IL28b (rs12979860) genotype distribution per treatment arm. The stripped boxes represent the patients with SVR. In the 6 and 9 MU groups both SVR patients had the rs12979860 CC genotype. In the 12 MU group all SVR patients had genotype CT. In 1 patient genotyping failed.

Virological Responses During According to IL28b Genotype (rs12979860)
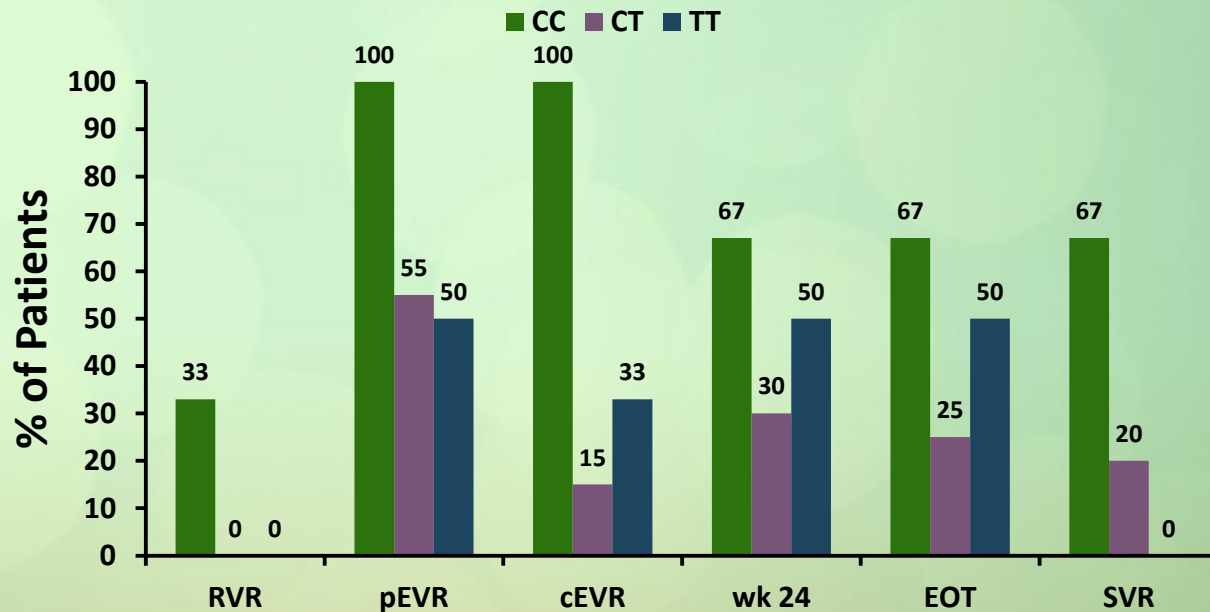
Virological Responses During According to IL28b Genotype (rs12979860)

Conclusions

1. IL28b is a strong predictor of response during retreatment in patients with non response to previous therapy

2. Continuous delivery of interferon in previous therapy failures can be a successful treatment strategy especially in patients with IL28b genotype CC & CT

3. High doses of interferon can overcome the innate lack of interferon sensitivity that is predicted on the basis of the IL28b genotype