Immune Cell Phenotypes Associated with Successful Response to 2 Weeks of a Novel Non-Nucleoside Inhibitor CDI-31244 Concurrent with 6 Weeks of Sofosbuvir/Velpatasvir in Subjects with Chronic Hepatitis C Genotype 1 Infection.

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Background

The high cost of currently approved combination direct-acting antiviral (DAA) therapy of 8- and 12-weeks duration is a major barrier to the treatment of chronic hepatitis C (HCV) globally. Shorter duration therapy that maintains high cure rates of current therapy could reduce cost and improve adherence. Pretreatment identification of biomarkers that are associated with successful response to shorter duration therapy could aid this goal. The frequencies of circulating T cell and natural killer (NK) cell subsets have been shown to be associated with an ability to achieve either rapid virologic response or clearance using 12 weeks of DAA therapy.[1, 2]

Method

We investigated the association of specific immune cell biomarkers with sustained virologic response (SVR) or relapse in 12 treatment-native patients with chronic HCV genotype 1 infection without cirrhosis enrolled in a single center, phase 2a study to evaluate treatment with 2 weeks of a novel non-nucleoside inhibitor CDI-31244 (400 mg daily) concurrent with 6 weeks of sofosbuvir/velpatasvir (SOF/VEL) (Clinicaltrials.gov NCT# 03501550). Immunophenotyping with antibody staining and flow cytometry as well as degranulation assays were employed to investigate the frequency of both T cell and NK cell subsets[1,2] and their association with response to this regimen.

Results

Eight of 12 (67%) patients achieved SVR12 and SVR24. Patients that achieved SVR had significantly higher frequencies of terminally differentiated effector memory CD8+ T cells compared with those who relapsed at both baseline and at end-of-6-week treatment (Figure 1). At the same time, the frequency of naïve CD8+ T cells was lower while the frequency of effector memory CD8+ T cells was higher in SVR patients; however, these differences were not statistically significant. NK cell cytotoxic phenotypes determined by measuring expression of TRAIL and CD107a also did not differ between SVR and relapse patients, unlike another study that evaluated a different regimen for 12 weeks.[2]

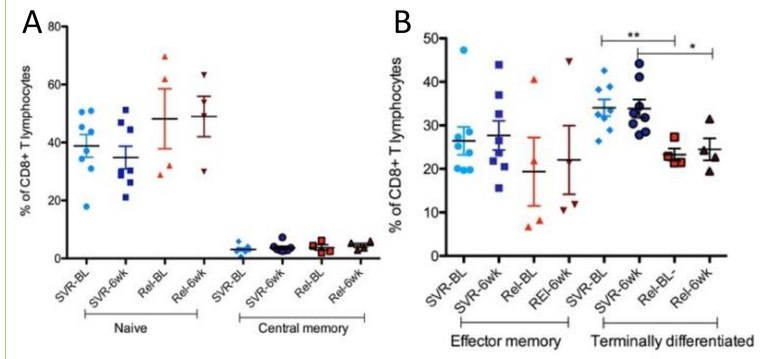
Subject Demographics

Subject #	Age	Gender	Race	HCV Genotype	IL28B Polymorphism	NS5A RAV	NS5B RAV	Fibrosis	Baseline HCV PCR (IU/mL)	Outcome
1	62	M	Black	1A	CT	-	G307R, S556G	F0-F1	457,000	Achieved SVR
2	43	M	White	1A	CC	Y93Y/N	-	F0	6,670,000	Achieved SVR
3	29	F	White	1A	TT	H58P	-	F0	2,340,000	Achieved SVR
4	56	F	Black	1A	CT	-	-	F0	6,500,000	Achieved SVR
5	51	M	Others	1A	CT	M28V	-	F0-F1	173,000	Relapsed posttreatment Week 4
6	40	F	Black	1A	CT	-	-	F0	558,000	Relapsed posttreatment Week 4
7	54	F	Black	1A	TT	-	-	F0	444,000	Achieved SVR
8	34	M	Black	1A	CC	M28V, Q30H	-	F0	8,120,000	Relapsed posttreatment Week 4
9	48	F	White	1A	CC	K24R	-	F1-F2	6,710,000	Achieved SVR
10	35	M	Black	1A	CT	-	-	F0	7,450,000	Relapsed posttreatment Week 4
11	49	F	Asian	1B#	CC	-	-	F0	13,200,000	Achieved SVR
12	28	M	Black	1B	TT	P58T	-	F0	716,000	Achieved SVR

Legend: HCV - Hepatitis C
M - Male
F - Female
RAV - Resistance associated variants detected at Day 1 (Baseline)
SVR - Sustained virologic response (both at posttreatment Week 12 and Week 24)
Screening HCV genotype detected as 1b (using 5'UTR and Core region amplification). Subsequent Day 1, HCV NS5A and NS5B drug resistance assay (using full length gene amplification and sequencing) did not fit any of 6 major genotypes, but was distantly related to HCV genotype 1 and 6 sequencing, and may represent a novel HCV strain.

Figure 1

Peripheral blood frequencies of CD8+ T cell subsets in SVR or relapsed patient groups.



Frequencies of **(A)** naïve (CCR7+CD45RO-) and central memory (CCR7+CD45RO+) CD8+; and **(B)** effector memory (CCR7-CD45RO+) and terminally differentiated effector (CCR7-CD45RO-) CD8+ T lymphocytes in patients that achieved SVR (blue) or those who relapsed (red).

SVR: Sustained virologic response; Rel: Relapse; BL: Baseline; 6wk: End of therapy time point.

Conclusion

CD8+ effector T cell phenotypes are associated with successful response to the novel NNI CDI-31244 in combination with SOF/VEL in treatment-naïve adults with chronic HCV genotype 1 infection without cirrhosis. Identifying these select patients may be valuable in the development of ultrashort duration HCV therapy.

REFERENCES:

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