Assessment of Hepatic Antifibrotic Effect of Cenicriviroc in Patients With HIV

Abstract Number: 552

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Abstract

Background: Chronic liver disease is frequently observed in HIV-infected patients and is multifactorial. Attenuation of fibrotic progression may improve liver-related morbidity and mortality. Cenicriviroc (CVC) is an oral, dual antagonist of CCR2/CCR5, which are involved in key pro-inflammatory and fibrogenic pathways. We evaluated effects of 2 doses of CVC on serum hepatic fibrosis biomarkers in HIV+ subjects treated in a Phase 2b study (NCT01338883).

Methods: Patients with CCR5-tropic HIV-1 were randomized to receive CVC 100 mg (n=59), CVC 200 mg (n=56) or Efavirenz (EFV) (n=28), each combined with emtricitabine/tenofovir for 48 weeks. The Enhanced Liver Fibrosis (ELF) biomarker index was evaluated in a subset of patients who completed 48 weeks of treatment and had paired baseline and 48-week samples. The ELF index has been validated previously in patients with NASH, HCV and HBV infection, and by our lab in HIV patients with liver disease. The ELF index was calculated from the results of 3 serum biomarkers of collagen and extracellular matrix deposition: hyaluronic acid, propeptide of type III procollagen, and tissue inhibitor of metalloproteinase-1.

Results: Paired baseline and 48-week samples were randomly selected for 89/100 subjects completing the study: CVC 100 mg arm (n= 37 /42), CVC 200 mg arm (n= 36/41) and EFV controls (n= 16/17). No subjects were coinfected with HCV or HBV. Among subjects receiving CVC 100 mg and 200 mg, the ELF scores at baseline were 9.95 ± 0.93 and 9.90 ± 0.97 and after 48 weeks were 9.93 ± 1.00 and 9.09±1.3, respectively. Subjects who received EFV had a mean ELF score of 9.13±0.98 at baseline and 9.28 ± 1.06 after 48 weeks. ELF scores decreased significantly in patients who received CVC 200 mg after 48 weeks of treatment (p=0.0002) but remained unchanged in patients who received EFV or CVC 100 mg. HIV suppression was similar in all groups.

Conclusion: Daily administration of CVC 200 mg for 48 weeks was associated with a significant decrease in specific biomarkers of hepatic fibrosis encompassed by the ELF index. This was not observed in control subjects treated with EFV nor with the lower dose of CVC (100 mg) Clinical trials of CVC are underway in adults with NASH and liver fibrosis, using a new single tablet formulation of CVC 150 mg providing drug levels comparable to CVC 200 mg in the HIV Phase 2 trial. Evaluation of CVC in HIV patients who are at risk of liver fibrosis progression is warranted.

Objectives

Our aims were:

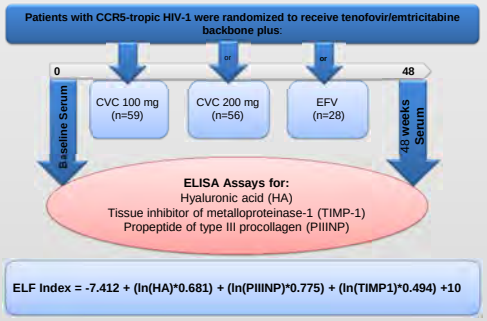
A. To validate ELF Index compared to liver biopsy histology

B. To utilize ELF Index to determine if exposure to cenicriviroc, a CCR2/CCR5 antagonist would decrease specific hepatic fibrosis markers at different doses in HIV-infected patients.

Methods:

- Paired serum samples were evaluated using the ELF Index at baseline and at treatment week 48, in the CVC 100mg, 200 mg and control (EFV) groups.
- Subjects coinfected with HCV or HBV, or any known active or chronic liver disease or cirrhosis; serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value Grade >2 or total bilirubin >upper limit of normal (ULN); CD4 count < 200 cells/mm^3 were excluded from the study.

Study Design



Results

A. Validate ELF Index compared to liver biopsy histology

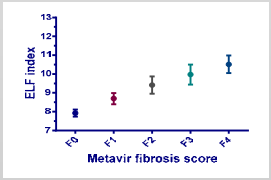


Figure 1. Validation of Enhanced Liver Fibrosis (ELF) index in patients at different liver fibrosis stages. The ELF index was significantly different between the 5 groups using the Kruskal-Wallis test (p= 0.0038). The ELF index in the F0 group was significantly different from F2,F3 and F4 group (p≤0.05). There was a significant linear correlation between the Metavir fibrosis score and the ELF Index (r= 0.645, p=< 0.0001).

B. ELF index in HIV patients treated with Cenicriviroc

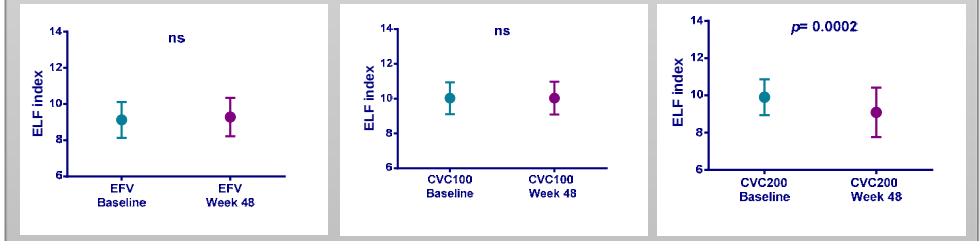


Figure 2. ELF index in CVC treated and Efavirenz groups. Wilcoxon matched-pairs signed rank test showed significantly lower ELF levels in HIV patients receiving 200 mg of CVC (N=36) (p= 0.0002). The difference in the Efavirenz treated group (N=16) and in patients receiving 100 mg of CVC (N=37) before and after treatment was not significant. The mean ELF baseline value for patients enrolled in the EFV arm were significantly lower from the CVC 100 and 200 group (p≤0.05).

Results

Table 1: Baseline demographics, virological and clinical characteristics of subjects

18	EFAVIRENZ ARM	CVC100 mg ARM	CVC 200 mg ARM
N	16	37	36
Demographics			
Age, years			
Mean (range)	33 (20-49)	34 (19-63)	38 (25-57)
Race, n (%)			
White	11 (69)	23 (62)	28 (78)
African American	5 (31)	13 (35)	4 (11)
Other	0	1 (3)	4 (11)
Gender, n (%)			
Male	13 (81)	35 (95)	36 (100)
Female	3 (19)	2 (5)	0
Virological and clinical data			
BMI			
Mean (range)	25.51 (18.11-34.26)	26.15 (19.14-34.59)	26.78 (19.76-37.53)
CD4$^+$ T-cell count, cells/mm^3			
Mean (range)	357.7 (177.0-605.0)	392.9 (207.0- 774.0)	417.4 (190.0-1017)
HIV-1 RNA load, copies/Ml			
Mean (range)	53337 (2050-342000)	43450 (2870-201000)	66424 (947.0-347000)
ALT level, U/L			
Mean (range)	23.25 (9.00-49)	27.35 (9-69)	26.08 (14-50)
AST level, U/L			
Mean (range)	21.81 (13-42)	26.46 (14-63)	25.81 (14-44)
HIV <50 copies/ml after 48 weeks (%)	50	68	64

Conclusion

- Daily administration of CVC 200 mg for 48 weeks was associated with a significant decrease in specific biomarkers of hepatic fibrosis encompassed by the ELF index.
- The difference in ELF is not explained by HIV response which was comparable between groups.
- Clinical trials of CVC are currently underway in adults with NASH and liver fibrosis, using a new single tablet formulation of CVC 150 mg providing drug levels comparable to CVC 200 mg utilized in the HIV Phase 2 trial. Evaluation of this CVC formulation in HIV patients who are at risk of liver fibrosis progression from any etiology appears warranted.

department of Internal Medicine

Funding: This work supported by R56AI065256 to KES from the NIH NIAID.

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