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The Effect of Interleukin-2 in HIV-1 Patients with HBV and HCV co-infection: Associations between Fibrosis Biomarkers at Baseline and Clinical Outcomes in the ESPRIT Study

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BACKGROUND

The ESPRIT study was a randomized trial that tested the safety and efficacy of interleukin 2 (IL-2) plus antiretroviral therapy (ART) compared to ART alone (control group) in HIV-1 patients with a CD4+ cell count >300 cells/µl at study entry. Although adjunctive IL-2 therapy was associated with a significant increase in CD4+ cell count compared to ART alone, it did not result in overall clinical benefit (ESPRIT Study, NEJM 2010).

Previous studies in patients with HCV infection suggested that IL-2 therapy lowered HCV viral load and normalized liver enzymes in some patients, although any clinical significance of this is uncertain (Pardo et al, Hepatology 1997; Tedaldi et al, J Viral Hepatitis 2005).

OBJECTIVES

The aim of this study was to investigate the effect of IL-2 on clinical outcomes in the HIV/hepatitis co-infected population in the ESPRIT study, and determine whether stage of liver fibrosis, as measured by three liver fibrosis markers, influenced clinical outcomes.

METHODS

Participants

All participants positive at baseline for HCV-RNA (>615 IU/mL; denoted HCV+) and/or HBsAg (denoted HBV+) were included in the study.

Fibrosis markers

Stored plasma collected at entry to ESPRIT and at month 24 and 60 of follow-up were tested for the liver fibrosis marker hyaluronic acid (HA) using a commercial enzyme linked binding protein assay (Corgenix, Colorado, USA) with a HA range in a healthy population between 0-75 ng/mL. Each HA level was measured in duplicate according to the manufacturers specifications. The fibrosis indices APRI (AST to platelet ratio index) and FIB-4 [age x AST/(platelets x $ALT^{1/2}$)] were calculated based on locally collected data. Only data at study entry were available. Biomarkers were categorized according to levels of fibrosis using previously reported cut-points (HA >100 ng/ml, FIB-4 >3.25, APRI >1.5) for significant fibrosis (Metavir F2-F4.)

Statistical methods

Adjusted and unadjusted hazard ratios (HRs) were estimated using Cox models. Adjustment was for age, gender, race, injecting drug use, AIDS, and nadir and baseline CD4+ count. To facilitate comparisons among biomarkers HRs per 1-standard deviation (SD) change in the $\log_{10}$-transformed marker were estimated. Associations were studied in the IL-2 and control groups separately.

Table 1

Baseline Characteristics

	Pts w/ data	IL-2	Control	P
HBV+ (n)	621	83	102	
HCV+ (n)	625	213	216	
HBV+ and HCV+ (n)	618	6	8	
Age , median years (IQR)	628	38 (34, 43)	40 (35, 44)	0.07
Female sex (%)	628	19.2	21.5	0.48
Black race (%)	628	8.3	10.1	0.43
Injecting drug use (%)	628	53.0	45.1	0.05
Prior AIDS (%)	628	28.5	28.8	0.92
HIV-RNA ≤500 copies/ml (%)	627	76.2	84.6	0.008
CD4+, median cells/µl (IQR)	628	435 (364, 535)	434 (364, 559)	0.49

Table 2

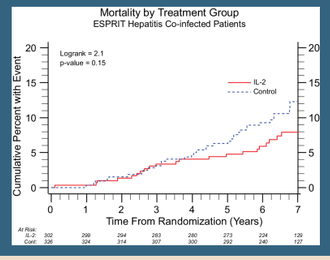
Causes of Death

	IL2	Control
Hepatic	6	10
Malignancy	2	6
CVD	3	6
AIDS	0	2
Infection	1	1
Others*	0	3
Substance abuse	4	2
Accident/suicide	2	3
Cause unknown	6	4

*CNS, hematological, gastrointestinal
CVD: cardiovascular disease

Figure 1

Cumulative Risk of Death



RESULTS

Baseline characteristics

Out of 4,111 participants in ESPRIT, 628 (15.3%) were hepatitis co-infected. 185 (29.5%) were HBV+, 429 (68.3%) were HCV+ and 14 (2.2%) were both HBV+ and HCV+. Compared with the control group (ART alone), the IL-2 group were younger (38 vs. 40 years), more likely to be injecting drug users (53.0 vs. 45.1%) and less likely to have HIV-RNA ≤500 copies/ml (76.2 vs. 84.6%), **table 1.**

Clinical outcomes

The median follow-up was 80 months. The average CD4 difference (standard error) between the IL-2 and control groups during follow-up was 124.3 (17.2). In total 61 patients (24 in IL-2 and 37 in the control group) died. A breakdown of the causes of death by randomization group is shown in **table 2.** The rate of death was 1.19 vs. 1.72 per 100 person years of follow-up in the IL-2 and control groups, respectively. The IL-2/control hazard ratio for death was 0.69 (95% CI 0.41 - 1.15; p=0.15). Sixty-five patients in the IL-2 group experienced a grade 4 event compared to 73 patients in the control group, HR=0.98, 95% CI=0.70,1.37, p=0.91.

Associations between fibrosis markers and all-cause mortality

Four hundred sixty-three co-infected patients had data available for all three fibrosis markers at baseline (HBV n=140, 30.3%; HCV n=316, 68.3%; both HBV and HCV n=5, 1.1%). Overall 33 (13 in IL-2 and 20 in the control group) of these patients died during 2,972 person-years of follow-up (4 in IL-2 group and 5 in control group due to liver-related causes). In the control group, but not in the IL-2 group, each biomarker was significantly associated with all-cause mortality (**table 3**); of note, the rate of death was comparable between control and IL-2 group for those with normal biomarker levels. The interaction p-values for treatment group x $\log_{10}$ biomarker were 0.02, 0.02 and 0.11 for FIB-4, APRI and HA, respectively.

Changes in HBV-DNA, HCV-RNA and hyaluronic acid levels during follow-up

For the 463 patients with available fibrosis markers there were no differences between the IL-2 group and the control group with regards to follow-up plasma levels of HBV-DNA, HCV-RNA (**figure 2**) and hyaluronic acid (**figure 3**).

CONCLUSIONS

Liver fibrosis markers predicted mortality in HIV/hepatitis co-infected persons randomized to ART alone, but not in the group randomized to receive adjunctive IL-2 therapy. This suggests that IL-2 may dampen the clinical consequences of viral hepatitis-induced liver damage. However, this effect is not mediated through any longitudinal differences in HBV or HCV viral load or liver fibrosis marker levels.

Table 3

All-cause mortality by Treatment Group Defined by Baseline Fibrosis Marker Level

	IL-2 group			Control group		
Fibrosis marker	*Rate**	*HR (95% CI)*	*p*	*Rate**	*HR (95% CI)*	*p*
HA (ng/ml)						
≤100	0.76	Ref.		0.85	Ref.	
>100	1.68	1.46 (0.4 - 4.9)	0.54	5.79	7.50 (2.8 – 19.9)	<0.01
One SD increase**		1.15 (0.6 – 2.1)	0.64		2.77 (1.6 - 4.7)	<0.01
FIB-4						
≤3.25	0.96	Ref.		1.06	Ref.	
>3.25	0.00	-		10.02	9.79 (2.5 – 37.8)	<0.01
One SD increase**		0.88 (0.5 – 1.6)	0.68		2.00 (1.2 – 3.3)	0.006
APRI						
≤1.5	0.97	Ref.		1.16	Ref.	
>1.5	0.00	-		3.79	3.20 (0.9 – 11.5)	0.07
One SD increase**		0.87 (0.5 – 1.5)	0.61		2.14 (1.3 – 3.4)	0.002

*Rate=# of events per 100 person years , HR: hazard ratio; ** One standard deviation $\log_{10}$ increase in fibrosis marker level . Hazard ratios are adjusted for age, gender, race, injecting drug use, AIDS, and nadir and baseline CD4+ count

Figure 2

HBV-DNA and HCV-RNA Levels During Follow-up by Treatment Group

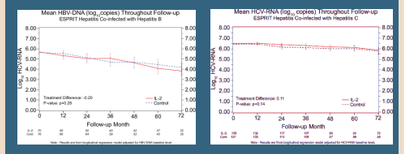
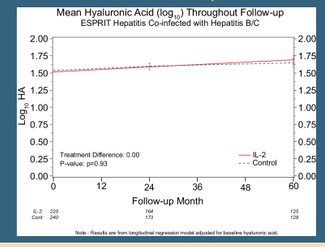


Figure 3

Plasma Hyaluronic Acid Levels During Follow-up by Treatment Group



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