22-24 MAGGIO 2018 ERGIFE PALACE HOTEL, ROMA

10° CONGRESSO NAZIONALE ICAR

Presidenza del Congresso
Massimo Andreoni, Roma
Andrea Antinori, Roma
Carlo Federico Perno, Milano

Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali

Italian Conference on AIDS and Antiviral Research

10 ANNIVERSARY

P 1

Fondazione Icona ITALIAN COHORT NAIVE ANTIRETROVIRALS

Liver enzyme elevations according to the first line cART regimen: real life data from the ICONA cohort.

Lucia Taramasso (1), Patrizia Lorenzini (2), Antonio Di Biagio (3), Miriam Lichtner (4), Giulia Marchetti (5), Roberto Rossotti (6), Giuseppe Lapadula (7), Davide Minisci (8), Francesca Vichi (9), Andrea Antinori (2), Stefano Bonora (10), Antonella D'Arminio Monforte (5) for ICONA Foundation Study Group.

1 Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; 2 HIV/AIDS Clinical Department, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy; 3 Infectious Diseases Clinic, Policlinico San Martino Hospital, Genoa, Italy; 4 Department of Infectious Diseases, Sapienza University, Polo Pontino, Latina, Italy; 5 Department of Health Sciences, Clinic of Infectious and Tropical Diseases, University of Milan, Milan, Italy; 6 Infectious Diseases Department, ASST GOM Niguarda, Milan, Italy; 7 Infectious Diseases Unit, Ospedale San Gerardo , Monza, Italy; 8 Department of Infectious Disease, L. Sacco University Hospital, Milan, Italy; 9 Unit of Infectious Diseases, Santa Maria Annunziata Hospital, Florence , Italy; 10 Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

Introduction

- Liver enzyme elevations (LEE) are common in course of Human Immunodeficiency Virus (HIV) infection and have been historically linked to Hepatitis B (HBV) or C (HCV) co-infection.
- LEE have often a multifactorial etiopathogenesis, and the possibility of drug toxicity should always be investigated in patients developing LEE.
- LEE that develops soon after combined antiretroviral therapy (cART) initiation in patients co-infected with HBV or HCV can also be driven by the immune recovery that occurs in the first weeks after starting cART, when a fast CD4+T-lymphocyte rise and a rapid HIV-RNA decline can cause an immune reconstitution syndrome (IRIS).
- Although LEE are now less frequently observed than in the past, few data are available on new drug classes such as integrase strand transfer inhibitors (INSTI), especially in the clinical post-marketing phase.

Study Aims and definitions

- ICONA collects data starting from the data of entry in the cohort till last available follow-up of all patients aged ≥ 18 years old who agree to participate and sign consent forms (www.icona.org).
- The aim of the present work is to analyse the incidence of LEE events in naïve PLWHIV, according to their first-line antiretroviral regimen in the ICONA cohort.
- We performed a retrospective analysis of the ICONA prospective database, including all PLWHIV who initiated their first antiretroviral regimen with 2 nucleoside reverse transcriptase inhibitors (NRTI) plus a ritonavir-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an INSTI.
- LEE was defined as an increase of alanine aminotrasnferase (ALT) or aspartate aminotranferase (AST) of at least grade 2, confirmed in two consecutive blood controls. Grade 2 LEE was defined as ALT or AST rise ≥ 2.5 x upper normal limit (UNL); grade 3 LEE as ATL or AST > 5 x ULN and grade 4 as ALT or AST >10 x ULN, for patients with baseline ALT or AST in the normality range. The corresponding figures for patients with baseline values > ULN were grade 2: ALT or AST ≥ 2.5 x baseline value; grade 3: ALT or AST > 3.5 x baseline value; grade 4 : ALT or AST > 5 x baseline value. Moreover, we propose a definition of hepatic IRIS (H-IRIS) based on literature data [1-10] and aim at analysing the possible episodes of H-IRIS, in HCV or HBV co-infected PLWHIV starting their first line cART.
- For the analysis of IRIS events, only PLWHIV co-infected with HCV (HCV-RNA positive) or with HBV (HBsAg positive) initiating an antiretroviaral therapy with CD4+T lymphocyte count ≤350 cells/µl were considered.
- H-IRIS was defined in our study as a LEE (grade ≥2) in concomitance of HIV-RNA drop of at least 2.8 $\log_{10}$ and CD4+T lymphocytes recovery of 125 cells/µl or greater, in the first 6 months after the beginning of cART, in people confected with HIV and HCV or HBV. This definition was based on median HIV-RNA drop and CD4+ rise reported in H-IRIS in the literature [1-10].

Statistical Methods

- A standard survival analysis was used to calculate the hazard ratios (HR) for LEE according to different antiretroviral regimens, by means of a Cox regression model.
- The multivariable model for the analysis was run adjusting for age, gender, mode of HIV transmission, body mass index, CDC stage C, HBV and HCV status, duration of HIV infection, use of tenofovir/emtricitabine (TDF/FTC) as backbone, baseline levels of bilirubin, GGT, AST and ALT, FIB4 score, current alcohol and drug use, calendar year of cART initiation.

Results

Patients description and incidence of LEE

- Overall, 6575 ART-naïve patients were included, 2384 (36.3%) initiating 2NRTI+NNRTI, 2436 (37.1%) NRTI+PI/r and 1755 (26.7%) NRTI+INSTI.
- Patients were 80.8% male, 26% had <200 CD4+T-cells/µl at baseline and median age was 39 (32-47) years. HBsAg and HCV-RNA were detected in 3.9% and 5.8% of the study population.
- One hundred and eighty three LEE occurred over 20722 PYFU (Incidence rate of LEE= 8.8 x 1000 PYFU, 95%CI 7.6-10.2), 93 events of grade 2 (50.8%), 42 (23.0%) of grade 3 and 48 (26.2%) of grade 4. LEE occurred after a median time of 17 (6-38) months.

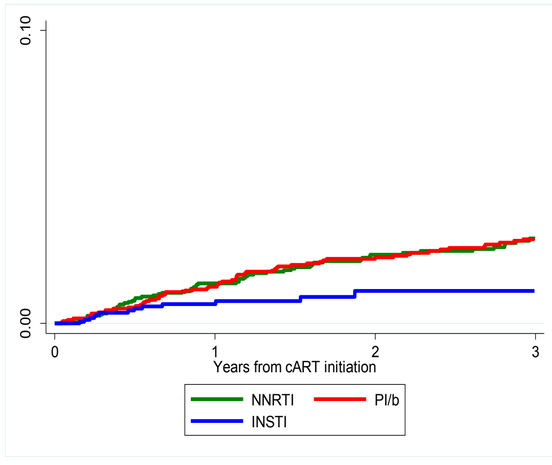
Table 1:Crude and adjusted relative hazards (RH) for liver enzyme elevations (LEE) from fitting a Cox regression model.

	Univariable			Multivariable*		
	HR	95%CI	p	HR	95%CI	p
Male gender	1.07	0.75-1.53	0.715			
Age						
<35	1.00			1.00		
35-45	1.00	0.72-1.40	0.987	0.90	0.63-1.27	
45+	0.69	0. 47-1.01	0.054	0.54	0.33-0.84	0.007
Mode of HIV transmission						
Heterosexual	1.00			1.00		
IVDU	3.88	2.53-5.93	<0.001	1.24	0.69-2.24	
MSM	1.41	1.00-1.98	0.050	1.61	1.06-2.45	0.025
Other/unknown	1.04	0.53-2.03	0.918	1.06	0.53-2.12	
BMI						
underweight	1.52	0.79-2.93	0.212			
normal	1.00					
overweight	1.03	0.66-1.59	0.906			
obesity	1.21	0.56-2.62	0.624			
CDC stage C	0.96	0.57-1.61	0.086			
HBsAg						
negative	1.00			1.00		
positive	1.75	0.97-3.16	0.064	2.33	1.26-4.32	0.007
missing	1.20	0.84-1.71	0.307	1.35	0.87-2.09	
HCVAb & HCVRNA						
HCVAb -	1.00			1.00		
HCVAb+ & HCVRNA-	0.44	0.06-3.19	0.42	0.44	0.06-3.23	
HCVAb+ & HCVRNA+	6.26	4.50-8.72	<0.001	8.43	5.41-13.15	<0.0001
HCVAb+ & HCVRNA ND	2.55	0.94-6.93	0.065	2.35	0.81-6.83	
missing	0.79	0.05-1.38	0.411	0.64	0.33-1.21	
Baseline CD4						
<200	1.00					
201-350	1.08	0.73-1.61	0.698			
351-500	1.01	0.67-1.52	0.972			
>500	1.18	0.56-2.29	0.669			
HIV RNA (log copies/mL)						
≤ 5	1.00					
>5	0.84	0.61-1.15	0.272			
Type of regimen						
NRTI + NNRTI	2.10	1.18-3.73	0.012	1.97	1.04-3.75	0.039
NRTI + PI/r	2.17	1.22-3.84	0.008	1.96	1.02-3.73	0.042
NRTI + INSTI	1.00			1.00		
BL ALT (for each 1IU/L)	0.99	0.99-1.00	0.068	0.98	0.98-0.99	<0.0001
FIB4 score						
<1.45	1.00					
1.45-3.25	0.97	0.66-1.42	0.881			
>3.25	1.35	0.71-2.57	0.361			
missing	1.25	0.66-2.34	0.497			
Alchol use						
absteiners	1.00					
occasional	1.05	0.71-1.54	0.808			
daily	1.56	0.96-2.55	0.074			
Current drug use						
no	1.00			1.00		
yes	2.77	1.50-2.13	<0.001	1.04	0.14-7.65	

•Multivariable analisys showed only variable significantly associated with LEE

Risk factors for LEE

- Relative hazards (RH) for LEE resulted significantly higher in younger patients, in HBV, HCV co-infected patients in those with lower baseline ALT levels and in those who acquired HIV through homosexual transmission vs heterosexual. Both patients in treatment with PI/r and with NNRTI were more likely to experience LEE when compared with patients treated with INSTI (Figure 1). No differences were found in patients using TDF/FTC as a backbone, as compared to other NRTIs (Table 1).



NNRTI:non nucleoside reverse transcriptase inhibitors; PI/r: ritonavir-boosted protease inhibitors; INSTI: integrase strand transfert inhibitos

Figure 1: Cumulative probability of LEE according to the third drug used in first-line cART

Cases of H-IRIS

- Only 5 patients experienced H-IRIS according to the study definition, with an overall incidence rate of 0.15 x 1,000 PYFU (95%CI 0.06-0.37). Three subjects started NNRTI, 1 boosted PI, 1 INSTI.

Conclusions

- In a real-life setting, we identified younger age, being men who have sex with men, HBV/HCV-coinfected as risk factors for liver toxicity once on ART.
- Starting on an INSTI-based regimen appeared to be protective toward LEE as compared to NNRTI or PI/r.
- H-IRIS in HCV or HBV co-infected patients is a very rare event and does not impact on the overall incidence rate of LEE.
- Taken together, these findings provide important information aimed at the most targeted and cautious clinical care in patients starting ART.

References

1. John M et al. AIDS 12: 2289–93, 1998
2. Zylberberg H et al. Clin Infect Dis 27: 1255–8, 1998
3. Carr et al. Lancet 349:995–6, 1997
4. Proia LA et al. Am J Med 108: 249–51, 2000
5. Mastroianni CM et al. AIDS 12: 1939–40, 1998
6. Velasco M et al. N Engl J Med 340: 1765–6, 1999
7. Mitsumoto et al. Intern Med. 2014;53:2165-70
8. Ratman I et al. Clin Infect Dis. 2006 ;42:418-27
9. Nigro L et al. Ital J Gastroenterol Hepatol. 1999;31:85-6
10. Yunihastuti et al. Clin Immunol.2010;139:32-39

Funding

- ICONA Foundation is supported by unrestricted grants from Gilead, Janssen, MSD and ViiV Healthcare

Icona Foundation Study Group