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

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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) infection.

LEE are 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-marking 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.it).

The aim of the present work is to analyse the incidence of LEE events in naive PLWHV, according to their first-line antiretroviral regimen in the ICONA cohort.

We performed a retrospective analysis of the ICONA prospective database, including all PLWHV who initiated their first antiretroviral regimen with 2 nucleoside reverse transcriptase inhibitors (NRTI) plus a ritonavir-boosted protease inhibitor (PIV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an INSTI.

LEE was defined as an increase of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of at least grade 2, confirmed in two consecutive blood samples. Grade 2 LEE was defined as ALT or AST ≥ 2.5 x upper normal limit (UNL); grade 3 ALT as AST ≥ 5 x UNL and grade 4 as ALT or AST > 10 x UNL, for patients with baseline ALT or AST in the normal range. The definition of LEE (H-IRIS) was based on literature data [1-10] and aim at analysing the possible episodes of H-IRIS, in HCV or HBV co-infected PLWHV starting their first line cART.

For the analysis of IRS events, only PLWHV co-infected with HCV (HCV-RNA positive) or with HBV (HBsAg positive) undergoing treatment 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 log10, and CD4+T lymphocytes recovery of 125 cells/jl or greater, in the first 6 months after the beginning of cART, in people coinfected with HIV and HBV or HCV. This definition was based on median HIV-RNA drop and CD4+T 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 (categorical), sex, smoking, body mass index, CDC stage C, HIV and HBV status and history of HIV infection, use of tenofovir/efavirenz (TDF/FTC) as background antiretroviral regimen, level of bilirubin, GGT, ALT and ALFB4 score, current antiretroviral drug use, and calendar year of cART initiation.

Results

Patients description and incidence of LEE

Overall, 6575 ART-naive patients were included, 2384 (36.3%) initiating 2NRTI+NNRTI, 2436 (37.1%) NRTI+PI/ITR and 1756 (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 2072 PY (Incidence rate of LEE= 8.8 (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.

Table 2:Multivariable analysis showed only 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 or heterosexual. Both patients in treatment with PIR and with NNRTI were more likely to experience LEE compared with patients treated with INSTI (Table 1). No differences were found in patients using TDF/FTC as a backbone, as compared to other NRTIs (Table 1).

Cases of H-IRIS

- Only 5 patients experienced H-IRIS according to the study definition, with an overall incidence rate of 0.15, 1000 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 compared as NNRTI or PIR.

- 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


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