Impact of diabetes on the risk of serious liver events and liver-related deaths in people living with HIV and hepatitis C co-infection: data from the ICONA Foundation Cohort Study.

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Running title

Serious liver events and liver-related deaths in HIV/HCV co-infected patients with diabetes

Key Words

HIV/HCV co-infection, serious liver events, liver-related deaths, diabetes mellitus

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Abstract

To investigate the association between diabetes and HCV infection in persons living with HIV and to determine the impact of diabetes on the occurrence of serious liver events (SLE) and liver-related deaths (LRD) among HIV/HCV co-infected patients. Patients were included if they had at least one follow up visit. In a cross-sectional analysis among all HIV patients, we have investigated the association between diabetes and HCV infection. A further longitudinal analysis was performed in the population of HIV/HCV co-infected free from SLE with FIB-4 index <3.25 at baseline, using the following endpoints: A) first event between SLE and LRD; B) liver fibrosis progression defined as the first of two consecutive FIB-4>3.25; C) first event between SLE, LRD and liver fibrosis progression. Data from 15,571 HIV patients were analysed: 2,944 (18.9%) were HCV-Ab positive and 739 (4.7%) presented a diagnosis of diabetes at their last follow-up. Among HIV/HCV co-infected population, 107 patients had a diagnosis of diabetes. Viremic HCV co-infected patients had 3-fold risk of diabetes onset than HCV uninfected patients. On HIV/HCV co-infected population, 85 SLEs/LRDs occurred over 20,410 PYFU, for an IR of 4.2/1000 PYFU (95%CI 3.4-5.2). Diabetic patients had 3-fold risk of pooled SLE and LRD than patients without diabetes. Furthermore, viremic HCV infection was independently associated with higher risk of SLE/LRD (aIRR 3.35 [95%CI 1.14-9.83]). In HIV-infected patients, viremic HCV co-infection is a strong predictor of diabetes. Among HIV/HCV co-infected population, diabetic patients showed an increased risk of SLE/LRD compared with those without diabetes.

Introduction

Combination antiretroviral therapy (cART) has significantly reduced the mortality and morbidity among HIV-infected patients [1]. The improvement in AIDS-related survival rates resulted in an increase of non-HIV-related deaths, including liver-related deaths and especially those due to chronic hepatitis C (CHC) [2]. HIV/HCV co-infected patients have an increased risk of liver fibrosis progression compared to those with HCV monoinfection [3]. Furthermore, HCV infection seems to be associated with an increased incidence rate (IR) of diabetes mellitus, which itself plays a major role in the acceleration of liver disease and in the increased probability of liver-related complications. Indeed, glucose abnormalities, including insulin resistance and diabetes, are associated with an increased occurrence of severe liver fibrosis due to increased oxidative stress and inflammatory cytokine secretion [4]. The aim of our study was firstly, to investigate the association between diabetes and HCV infection in the HIV population, and, secondly, to determine the risk factors of serious liver events (SLE) and liver-related deaths (LRD) and fibrosis progression among HIV/HCV co-infected patients enrolled in a large Italian cohort.

Patients and Methods

Study participants

Patients were selected from the Italian Cohort of Antiretroviral-Naïve patients (ICONA) Foundation Cohort Study, which is a multicenter prospective observational study of HIV-infected patients who enter clinical care when still antiretroviral-therapy-naïve that was set up in April 1997. Demographics, medication, and disease history are recorded using an electronic data collection form (www.icona.org) at enrolment and updated on a 6-monthly basis. Cohort details have been previously reported [5]. For the purpose of this study, all patients free from SLE at baseline, enrolled since January 1997 up to December 2018 were included if they had at least one follow up visit.

Study outcomes

The main outcome is to explore the association between diabetes and HCV infection in the HIV population. Secondly, we investigated the predictors for SLE and LRD occurrence in HIV/HCV patients. Furthermore, we evaluated the impact of diabetes on the liver fibrosis progression in the co-infected population (Figure 1).

Definitions

HCV infected population included all subjects with at least one HCV-Ab positive and/or HCV-RNA positive test. All anti-HCV-treated (interferon and direct-acting antiviral based regimens) and -untreated patients were included. Type 2 diabetes was defined at the time of the first of two consecutive fasting blood glucose levels of >126 mg/d or use of antidiabetic drugs. SLE included the following complications: ascites, gastrointestinal

bleeding, hepatic encephalopathy, hepatocellular carcinoma (HCC), hepatopulmonary syndrome, hepatorenal syndrome, spontaneous bacterial peritonitis. LRD was defined as death associated with liver cirrhosis or its complications. Liver fibrosis was defined using the FIB-4 score, and was calculated by Sterling's formula: age (years) × AST (U/l)/(platelets (10^9/l) × (ALT (U/l))$^{1/2}$). Advanced liver fibrosis was defined by two consecutive FIB-4 score ≥3.25 [6]. AIDS diagnosis was defined using the 1993 Centers for Disease Control and Prevention criteria [7]. Body Mass Index (BMI) was calculated according to the following formula: (weight in kilograms)/(height in meters^2). Alcohol consumption was categorized into 3 groups: abstainers, occasionally, and every day consumers.

Statistical analysis

Descriptive statistics were expressed as median and interquartile range (IQR) for continuous variables or as proportions for categorical variables. For the analyses database was freezed on December 2018. Two different analyses were performed. Firstly, a cross-sectional analysis was performed to investigate, in persons living with HIV, the association between diabetes and HCV-Ab and HCV-RNA positivity, by means of multivariable logistic regression. Patients were observed at their last follow up**.** A second longitudinal analysis was performed in the population of HIV/HCV co-infected patients free from SLE and with FIB-4 index <3.25 at baseline, using the following endpoints: A) first event between SLE and LRD; B) liver fibrosis progression defined as the first of two consecutive FIB-4>3.25; C) first event between SLE, LRD and liver fibrosis progression. The baseline of this analysis was the date of first HCV-Ab positivity. Patients were followed until onset of first SLE or LRD or last available clinical follow-up, whichever occurred first. Type 2 diabetes diagnosis was used as time-dependent covariate. The IR was calculated as number of events over person-years of follow-up (PYFU) and expressed per 1000 PYFU. The risk of the outcome in patients with diabetes was estimated by means of Poisson regression multivariable model, adjusting for main confounders. The following covariates at baseline were explored at univariable analysis: gender, age, nationality, mode of HIV transmission, duration of HIV infection, HBV co-infection, AIDS diagnosis, BMI, smoke status, alcohol use, blood hypertension, nadir CD4+ cell count, CD4+ cell count and HIV-RNA at the baseline, FIB-4, total and HDL cholesterol, triglycerides, cART exposure, HCV-RNA and HCV genotype. All models were adjusted for all variables except for HCV genotype. In particular age was not retained as covariate when the outcome included FIB-4. All analyses were performed using the software STATA 15.1.

Ethics

The ICONA study was approved by the institutional review boards or ethics committees of each clinical site. All patients provided their written informed consent at the enrolment. All procedures of the study were performed in accordance with the 1964 Helsinki Declaration and its later amendments (October 2013 revision).

Results

Patients' characteristics

We included 15,571 HIV patients, and among these, 2,944 (18.9%) individuals were HCV-Ab positive. Table 1 shows the main characteristics of the study population. In brief, the median age was 43 (IQR 36-51) years; 11,927 (76.6%) patients were male; 2,573 (16.5%) patients became HIV-infected through injection drug use (IDU), 5,926 (38.1%) patients were infected through homosexual contact, and 5,981 (38.4%) through heterosexual contact; 754 (4.8%) patients were found to be HBsAg positive. Median (IQR) CD4+ cell count at baseline was 591 (387-820) cells/mmc and median (IQR) HIV-RNA at baseline was 1.6 (0-2.7) $\log_{10}$ copies/ml; 2,136 (13.7%) patients had an AIDS diagnosis at baseline. Almost all of the patients (97.1%) had available baseline FIB-4 index: 11,767 (75.6%) patients had a FIB-4 <1.45, 2,579 (16.6%) patients had an index between 1.45 and 3.25, and 778 (5.0%) patients had a FIB-4 >3.25, respectively.

Diabetes

Over 15,571 HIV-infected patients, 739 (4.7%) presented a diagnosis of diabetes at their last follow-up. Among HIV/HCV co-infected population, 107 patients had a diagnosis of diabetes (29 patients were diabetic at baseline and 78 patients developed diabetes during the follow-up). Viremic HCV co-infection was independently associated with diabetes diagnosis (adjusted odds ratio [aOR] 3.35 [95%CI 2.38-4.71]). Other factors independently associated with diabetes diagnosis were older age (45-55 years old: aOR 1.79 [95%CI 1.43-2.24] and >55 years old: aOR 2.15 [95%CI 1.64-2.82] vs <45 years old, respectively), higher BMI values (BMI ≥30: aOR 4.93 [95%CI 2.71-8.98], respectively), HIV-RNA detectable at baseline (≤50 copies/ml: aOR 3.08 [95%CI 2.25-4.22] and >50 copies/ml: aOR 5.79 [95%CI 4.17-8.03], respectively), higher FIB-4 score (FIB-4 1.45-3.25: aOR 1.32 [95%CI 1.05-1.65] and FIB-4 >3.25: aOR 1.48 [95%CI 1.07-2.03], respectively), hypertension (aOR 2.33 [95%CI 1.83-2.96]), hypercholesterolemia (aOR 1.29 [95%CI 1.04-1.59]), and hypertriglyceridemia (aOR 3.66 [95%CI 2.99-4.48]) (Table 1).

Risk of SLE/LDR

2670 HCV-Ab positive subjects with a FIB-4 <3.25 were selected for this analysis and observed for 20,410 PYFU, 85 SLEs/LRDs occurred. The IR was 4.2/1000 PYFU (95%CI 3.4-5.2). In detail, we observed 65 SLEs: 19 (29.2%) ascites, 10 (15.4%) hepatic encephalopathy, 9 (13.8%) HCC, 8 (12.3%) gastrointestinal bleeding, 3 (4.6%) hepatorenal syndrome, and 16 (24.6%) hepatic failure not specified; moreover, there were 20 (23.5%) LRDs. Diabetic patients had 3-fold IR of pooled SLE and LRD than patients without diabetes (IR 12.1/1000 [95%CI 5.8-25.4] and IR 3.9/1000 [95%CI 3.2-4.9], respectively. Diabetes was independently associated with higher risk of SLEs/LRDs (adjusted incidence risk ratio [aIRR] 3.06 [95%CI 1.30-7.19]). Additional predictors

were the following: female gender, HBV co-infection, AIDS diagnosis, viremic HCV co-infection, and higher FIB-4 at baseline (Table 2). When the composite outcome SLE/LRD/FIB-4 >3.25 was analysed, we found 424 events over 17,988 PYFU, corresponding to an IR of 2.4 (95%CI 2.1-2.6) per 100 PYFU. No differences in IR between diabetic and non-diabetic patients were observed (IR 2.8 [95% CI 1.5-5.0] and IR 2.3 [95%CI 2.1-2.6], respectively). Moreover, longer HIV history (> 10 years: aIRR 1.34 [95%CI 1.05-1.71], HBV co-infection (aIRR 1.90 [95%CI 1.31-2.76]), AIDS diagnosis (aIRR 1.71 [95%CI 1.22-2.39]), viremic HCV co-infection (aIRR 2.88 [95%CI 1.80-4.62]), higher FIB-4 at baseline (aIRR 2.71 [95%CI 2.38-3.10]), and every day alcohol use (aIRR 2.04 [95%CI 1.19-3.50]), but not diabetes (aIRR 0.92 [95%CI 0.49-1.70]) were independently associated with higher risk of SLE/LRD/FIB-4 >3.25 occurrence (Table S1).

Liver fibrosis progression

Multivariable analysis showed that HBV co-infection, AIDS diagnosis, viremic HCV co-infection, higher FIB-4 (per 1 point higher) at baseline, and every day alcohol use were independently associated with liver fibrosis progression. Conversely, diabetes was not associated with risk of liver fibrosis progression (aIRR 0.94 [95%CI 0.51-1.75]) (Table 2).

Discussion

In this analysis from the ICONA cohort, we evaluated the association between HCV infection and diabetes and further the risk of SLE and LRD in HIV/HCV co-infected patients with diabetes. We found that HCV infection was associated with a 3-fold increased risk of diabetes onset than uninfected patients. These results confirm those observed by others [8-12]. Among HCV-Ab positive patients, we observed that the probability of diabetes occurrence was independently associated with viremic HCV infection, whereas, although it does not reach significance, aviremic subjects had a 41% lower risk of developing diabetes. Similarly, in a previous ICONA study, De Luca et al. found that HCV-Ab positive/HCV-RNA positive status was independently associated with a higher incidence (adjusted relative rate [aRR] 1.73 [95%CI 1.08-2.78]) and prevalence (aOR 2.49 [1.08-5.74]) of diabetes, whereas HCV-Ab positive/HCV-RNA negative status was not [13]. Furthermore, we found that diabetes onset was independently associated with the liver fibrosis stage. These results are in line with those observed in other HIV cohorts [14, 15]. On this point, in a large French multicentre cohort, cirrhotic patients had a 2-fold increased risk of developing diabetes but not patients with CHC [15].

Overall, diabetic patients showed a significant increased incidence of major liver/renal-related events compared to non-diabetic patients. We found that ascites was the leading liver-related complication observed among our HCV/HIV co-infected patients. Diabetes is well-recognized risk factor for the development of ascites in cirrhotic patients [16]. Furthermore, cirrhotic patients with diabetes and refractory ascites had a poor outcome compared with those without diabetes. On this point, a retrospective French study that investigated the predictors

of prognosis in cirrhotic patients with refractory ascites found that the probability of survival at 1- and 2-years in diabetic patients was 32% and 18%, respectively, and 62% and 58%, respectively, in non-diabetic patients [17]. Moreover, we observed that HCC accounted for 12% of all SLE. Several studies confirmed that diabetes is an independent and strong predictor for the development of HCC. Moreover, diabetes negatively impacts on survival outcomes (overall survival rate and disease-free survival rate) in patients with HCC [18, 19].

In a multivariable model, we found that patients with diabetes had a 3-fold increased risk of pooled SLE and LRD than those without diabetes. Our findings are consistent with those from other observational studies evaluating the prognostic impact of diabetes in patients with HCV infection. In a French retrospective study, including HCV-monoinfected and HIV/HCV co-infected cirrhotic patients, Elkrief et al. found that baseline diabetes was an independent prognostic factor for death and transplantation-free survival (hazard ratio [HR] 1.34 [95%CI 1.03-1.73]). Baseline diabetes was also associated with an increased risk of liver-related complications, such as ascites (HR 1.63 [95%CI 0.99-2.70]), renal dysfunction (HR 2.35 [95%CI 1.32-4.20]), bacterial infections (HR 2.10 [95%CI 1.23-3.59]), and HCC (HR 1.94 [95%CI 1.13-3.33]), during the follow-up [20]. Similarly, a large North-American retrospective study found that diabetic HIV/HCV co-infected patients had a 2-fold increased risk of developing liver decompensation (HR 1.88 [95%CI 1.38-2.56]) [21]. In addition, in an Asiatic study with a long follow-up including only CHC monoinfected patients, Huang et al. found that new-onset diabetes was independently associated with development of cirrhosis (HR 2.50 [95%CI 1.61-3.90]) and liver decompensation (HR 3.56 [95%CI 1.53-8.30]) [22].

In our cohort, we observed that liver fibrosis progression was related to well-recognized co-factors of liver damage such as consumption of alcohol and HBV co-infection. Furthermore, we found that patients with a viremic HCV infection had a 2.74 increased risk of fibrosis progression; indeed, it is known that HCV eradication significantly reduces liver-related morbidity and mortality [23, 24]. Finally, we found that diabetes was not associated with the risk of liver fibrosis progression. These results are in contrast with those of other studies that clearly showed a link between diabetes and cirrhosis development [22, 25]. These differences can be mainly explained by low rate of diabetes diagnosis among our HIV/HCV co-infected patients and high rate of patients who had a baseline a FIB-4 index between 1.45 and 3.25. Indeed, it is well known that FIB-4 index had a lower accuracy for FIB-4 values inside 1.45-3.25 range [26]. The major strengths of our study are that it is based on a large cohort of HIV-infected patients with a long follow-up. Furthermore, our study is one between few studies which evaluated the role of diabetes as predictor of SLE and LRD among HIV/HCV co-infected patients. However, our study has also some limitations that need to be taken into account. We have included a small number of patients with diabetes that can explain the lack in power to determine the role of diabetes in the liver fibrosis progression. Furthermore, we have not evaluated the impact of anti-HCV-therapy on the occurrence of diabetes and SLE/LDR. Finally, a general under-reporting of liver-related complications, as with all observational studies, is possible.

In conclusion, in our cohort, viremic HCV co-infection is independently associated with diabetes. Furthermore, among HIV/HCV co-infected population, diabetic patients showed an increased risk of SLE/LRD compared to who did not have diabetes. These results warrant further investigations to better characterize the role of diabetes as an independent prognostic factor for liver-related complications among HIV/HCV co-infected patients.

Compliance with ethical standards

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Conflict of interest

GO has received personal fees from Gilead Sciences and ViiV Healthcare; AC was a consultant for ViiV Healthcare, Gilead, Abbvie, BMS, Janssen, MSD; GG was a paid consultant or member of advisory boards for ViiV Healthcare, Gilead, Abbvie, BMS, Janssen, MSD; GM has been advisor for Gilead, Janssen and MSD and ViiV Healthcare and has received speakers' honoraria from BMS, Gilead, MSD, Janssen and ViiV Healthcare; ADB has been advisor for AbbVie, Gilead and MSD has received speakers' honoraria from BMS, Gilead, MSD, Janssen and ViiV Healthcare; MP was a consultant for Gilead, Abbvie, BMS, Janssen and MSD; AG has received grants and/or personal fees from BMS, Gilead, Janssen, MSD, ViiV Healthcare; ADM was a paid consultant or member of advisory boards for ViiV Healthcare, Gilead, Abbvie, BMS, Janssen, MSD. The remaining authors have no conflict of interests to disclose.

Ethical approval

The ICONA study was approved by the institutional review boards or ethics committees of each clinical site.

Informed consent

All patients signed an informed consent form before being enrolled at each local clinical site.

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