Towards a decline in hepatitis related mortality in persons living with HIV?

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Keywords: HCV, HBV, HIV, Cirrhosis, Hepatocellular Carcinoma, Interferon, Ribavirin

ABSTRACT

Liver related mortality is the second cause of death in persons living with HIV (PLHIV) in developed countries; it has showed a stable trend since from 2000, but a decline of HBV related mortality has been observed during this time period probably because of the large usage of anti HIV drugs with dual anti HBV and anti HIV activity. Hepatitis C coinfection is the main cause of liver related death, but its prevalence in PLHIV in Italy is declining. HIV worsens the course of HCV, but this effect could be reduced by early HAART. The negative effect of HAART in the short term (hepatotoxicity) and long term (steatosis, insulin resistance) could be reduced by the usage of new antiretrovirals. Optimization of anti HCV treatment by: response and human genotype guided therapy, usage of higher doses of Ribavirin, selection of concurrent HAART and pre-treatment management of metabolic side effects of HAART might increase the rate of SVR and patients survival. Screening of cirrhotics for HCC, aggressive treatment of decompensated cirrhosis and liver transplantation might increase survival in patients with advanced liver disease. In the next future the implementation of new anti HCV drugs in clinical practice, by increasing the rate of response to treatment, could additionally improve the prognosis of HIV/HCV coinfected patients.

Liver diseases are the second single cause of death in Persons living with HIV n developed countries. However in the next years it is conceivable that we will see a decrease in liver related mortality in persons living with HIV in Italy. Epidemiological trends, characteristics of anti HIV and anti HCV treatment, the implementation of a more aggressive management of advanced liver disease and finally the availability of new anti HCV drugs are the issues that support this prediction.

Epidemiological Trends

In 2006 the D:A:D study has showed that hepatitis coinfections were the major cause of non AIDS related death in the first 10 years of HAART era causing more than 13% of death in developed countries[1]. A French study from the GERMIVIC cohort showed the trend over time of the proportion of death due to liver disease in HIV infected persons: in this cohort in 2003 proportion of liver related death showed a slight decrease and there was a stabilization from 2001 to 2003 after some years of progressive increase. In the same period the proportion of liver related death occurring in HBsAg positive subjects showed a sharp decrease[2]. These data indirectly support the hypothesis that HBV related mortality is decreasing with the availability of anti-retrovirals with anti HBV activity and that this decrease is one of the causes in the stabilization of liver related mortality observed in HIV infected patients in some very recent reports. This hypothesis was also supported by a multicohort study[3] . In order to assess the impact of exposure to antiretrovirals with dual activity on liver related mortality this study retrospectively analyzed data from 13 cohorts recruiting 2041 HBsAg positive persons living with HIV with a median follow up of 4 years[3]. Fifty seven liver related deaths occurred during this time period. Lamivudine exposure was independently associated with a 23% decrease of the risk of liver related death This association was independent from CD4 counts, age and diagnosis of decompensated liver disease. Exposure to antiretroivirals without anti HBV activity was not associated with a significant change in liver related mortality. Lamivudine withdrawal was associated with an 11 times higher risk of liver death.

However the prevalence of hepatitis coinfection in Europe is not homogeneous over time and space. In the EuroSIDA cohort. 9 % of HIV infected patients are co-infected by HBV without geographical heterogeneity. Thirty three per cent are co-infected by HCV with a north to south and north to east gradient of prevalence varying from 24% in northern Europe to more than 40% in southern and eastern Europe according to the different prevalence of intravenous drug use as risk factor for HIV. But times they are changing and so the prevalence of co-infections. The prevalence of co-infections in patients of Master cohort in Italy whose date of the first HIV positive tests has been collected has been analyzed. The proportion of patients with HCV co-infection, has sharply declined in the last 20 years from 80 to 20%. There was a mild decline in the proportion of HCV co-infected patients both in IDU and in persons with sexual exposure, however this sharp decline is due to the decrease in the proportion of patients with parenteral risk exposure among those diagnosed as HIV infected in the last years. On the contrary the proportion of HBV co-infected patients was stable over time.
Thus in conclusions liver related mortality is the second cause of death in HIV: but it has a stable trend since from 2000. This stable trend is due to the decline of HBV related mortality related to the usage of anti HIV drugs with dual activity. Hepatitis C coinfection remain the main cause of liver related death, but its prevalence in persons living with HIV in Italy is declining. Thus it could be hypothesized that these epidemiological trend might produce a progressive decline in liver related death.

The role of anti HIV treatment
HIV coinfection worsens the course of hepatitis C by increasing[6]:

- the rate of chronicity of acute infection
- the rate of evolution of chronic hepatitis toward cirrhosis especially with low CD4 counts
- the rate of decompensation of liver cirrhosis
- mortality in decompensated cirrhosis and HCC

D:A:D study clearly demonstrated an inverse correlation between CD4 counts and the risk of liver related death showing a linear increase in the risk of liver related death starting from less than 500 CD4/mmc[1]. Several studies confirmed this relationship between progression of liver disease and low CD4 counts[6]: in addition another study demonstrated a relationship between HIVRNA levels and progression of liver disease[7]. So HIV may increase the progression of liver disease in HCV coinfected patients indirectly by CD4 depletion but also by a putative direct profibrotic activity. Two recent papers have offered interesting hypothesis to explain the relationship between HIV and increased progression of fibrosis in liver disease. In the first paper it has been demonstrated that HIV promotes liver disease by enhancing microbial trans location because of CD4 depletion of the gut[8]. In another paper it has been demonstrated in vitro that HIV-gp120 modulates different aspects of Human Stellate Cells biology, including directional cell movement and expression of pro-inflammatory cytokines probably through binding to CCR5r. Hepatic Stellate Cells play a pivotal role in liver fibrogenesis thus these results identified a direct pathway possibly linking HIV infection with liver fibrogenesis via envelope proteins[9].
Thus earlier anti HIV treatment by suppressing HIV replication and enhancing CD4 restoration by maintaining CD4 counts higher than 500 cells/mmc could have a major role in slowing down the progression of liver disease and thus in decreasing liver mortality in HIV-HCV coinfected patients. In fact most of the recent guidelines support the initiation of HAART in HCV coinfected patients when CD4 decrease below 500 cells /mmc[10].
In the D:A:D study, adjusting the linear regression model for the last CD4 count thus for the effect of HAART on CD4 , the risk of liver related death increased by 16% per year of exposure to HAART[1]. In fact HAART could be associated to liver damage by drug induced hepatotoxicity in the medium-short term and by steatosis associated to metabolic disturbances in the long term[10]. However new antiretrovirals have a better profile than older anti HIV drugs in term of both hepatotoxicity and metabolic toxicity[10]. Thus in the future it is conceivable that HAART will have o a prevalent favourable effect on liver diseases in HIV infected persons.

The role of anti HCV treatment
The rates of sustained virologic response to combination anti HCV treatment in studies performed in person living with HIV are highly heterogeneous ranging from 27 to 50%[6]. By the meta analysis of all these studies some issues could be clearly identified:

- the best results have been obtained in: later studies, registrative studies (where the participating centres have been selected by a drug company) and in single centre study where the study was drawn, performed and published by the same group of physician: thus the first determinant of treatment success is the experience of treating physician probably in terms of patients' selection and management of side effects
- in patients infected with HCV genotype 1 and 4 the best results have been obtained in studies where high doses of ribavirin have been used (ie 1-1,2 g/d) so another determinant of success is the usage of high doses of ribavirin especially in patients with HCV G21 and G4 coinfection
- in patients infected with HCV G3 the lowest relapse rates have been obtained in studies where these patients have been treated for 48 weeks so another determinant of success is the prolongation of treatment to 48 weeks in patients infected by HCV G3 especially if they are treated with low ribavirin.

However treatment schedules could be additionally modulated on kinetics of viral response offering shorter treatment period to patients with rapid HCVRNA negativization during treatment and longer treatment schedules in those with later HCVRNA negativization[6]. This approach is defined as response guided treatment and has been indicated by the most recent European guidelines as the standard of care. According to this schedule all patients should be treated with Pegylated Interferon (alfa 2 a at a flat dose of 180 mcg per week and alfa 2b with a weight based dose of 1.5 mcg /kg per week) in combination with 1.-1,2 g/d of Ribavirin. Patients infected with HCV G3 or 2 with HCVRNA negativization after 4 weeks of treatment and without cirrhosis or elevated baseline HCVRNA levels (> 500.000 IU/mL) could be treated for 24 weeks; patients infected with HCV G1 or 4 without HCVRNA negativization after 12 weeks of treatment can be treated for 72 weeks and all the remaining patients should be treated for 48 weeks[6]. Recently a single nucleotide polymorphism (SNP) near theIL28B gene (rs12979860) has been shown to predict treatment response in HCV-monoinfected patients carrying genotype 1. A recent paper has demonstrated that this SNP is associated with HCV treatment response in HIV-infected patients with chronic hepatitis C due to genotypes 1 or 4. Thus IL28B genotyping has been included in an algorithm including other baseline characteristics (such as HCV genotype, HCVRNA levels and fibrosis stage that allows to predict the probability of response to anti HCV treatment of each individual and that has been validated in HIV infected persons. The combination of the analysis of baseline characteristics and on treatment data in the next future could probably help to highly improve the assessment cost effectiveness of anti HCV treatment and its optimal schedule for each individual with HIV/HCV coinfection[11].

Concurrent antiretroviral treatment could also be optimized in patients undergoing to anti HCV treatment[6]. If didanosine usage is to avoid according to all guidelines, there are consistent data on the increased toxicity of anti HCV treatment supporting the suggestion to avoid usage of zidovudine and stavudine[6]. There are also concerns on the potential negative interaction of abacavir with ribavirin that suggest to avoid usage of this drug especially in patients assuming low dose of ribavirin. Finally there are data on the increased neurological toxicity of efavirenz and on the increased hyperbilirubinemia in patients taking atazanavir, but these potential interactions should be managed on an individual basis. There are some papers showing an association between insulin resistance and a lower response to anti HCV treatment, thus HAART should be preliminary adapted to minimize insulin resistance before starting anti HCV treatment. The impact of hypercholesterolemia on response to anti HCV treatment on the contrary seems to be favourable (probably because of the putative interference of lipoproteins with HCV entry in hepatocytes) so normalization of HAART induced alterations on lipid metabolism dose not seem to play a role in facilitating response to anti HCV treatment[6].

Treatment of advanced liver disease[12-13]

Al patients with cirrhosis should be identified and screened for Hepato Cellular Carcinoma (HCC) with upper abdomen ultrasound performed every 6 months and for Oesophageal Varices with Endoscopy performed every 2 years. An appropriate and intensive management of patients with decompensated liver disease conducted by a team including hepatologists and HIV doctors could increase their survival . The main steps of this intensive approach are the following:

1. Treatment of underlying liver disease (ie alcoholic liver disease or hepatitis B)
2. Treament of HIV coinfection
3. Reduction of portal pressure and treatment of esophageal varices
    - Beta blockers
    - Varices ligation
    - Trans Iugular Porto Systemic Shunts
4. Improvement of the systemic hyperdynamic circulatory state with the usage of:
    - Antibiotics
    - Albumin
    - Vasoconstrictors
5. Treatment of Hepato Cellular Carcinoma
6. Liver Transplantation that has given very good results in HBV coinfected patients but worse results in HCV coinfected persons because of the rapid progression of the relapse of HCV infection in transplanted livers.

Future Developments

The implementation of new anti HCV drugs in anti hepatitis treatment of persons living with HIV in the next few years will probably allow to increase the rates of response to standard of care by addition of antivirals and maybe to treat with combinations of antivirals free of interferon and/or ribavirin patients non responders or intolerant to standard of care. These therapeutic innovations will probably change completely the scenario of HCV/HIV coinfection allowing to treat and cure the majority of coinfected patients, to slow down the progression of advanced liver disease ad to transplant HCV coinfected patients preventing and/or treating HCV relapse as we treat and prevent HBV relapse on transplanted liver.

In conclusion there are many elements which allow to predict a decline in liver related mortality in persons living with HIV in Italy . Most of these elements are probably new challenges for patients , doctors and for the health system but we know from the history of the management of HIV that together we can and we will face also these challenges.

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