New Scenarios in the Treatment of HIV/HCV Co-Infection

Abstract

The introduction of Highly Active Antiretroviral Therapy (HAART) dramatically improved the survival of HIV patients; however, an important cause of morbidity and mortality is the liver failure in patients with HIV-HCV co-infection. In an analysis on the adverse events of anti-HIV drugs, 1,246 patients out of 23,441 died over a 5-year follow-up period and liver failure constituted 15% of the mortality with over 50% of deaths occurring despite optimal HIV suppression. Therefore, more effective treatment for chronic hepatitis C virus infection become pivotal to a favorable outcome in HIV co-infected patients. The eradication of the Hepatitis C Virus (HCV) with novel HCV antiviral offers new therapeutic opportunities. At the same time, these drugs arise new challenges as drug interaction with HAART, overlapping toxicities and the high costs of treatment. This review focuses on the current state of the art of these new and promising therapeutic options for HIV/HCV co-infected individuals.

Keywords: Human Immunodeficiency Virus; Hepatitis C Virus; Chronic hepatitis C Interferon-free; Directly Acting Antivirals; Co-infection; Sustained Virological Response; End-Stage Liver Disease

Introduction

Chronic hepatitis by C virus infection is emerging as an increasing burden to health and as an important cause of morbidity and mortality worldwide, with an estimated global number of chronic carriers up to 180 million [1]. Among these, an estimated 5 to 10 million individuals solely in the western world are co-infected with Human Immunodeficiency Virus (HIV) [2]. HIV/HCV co-infection is associated to high rates of liver fibrosis, cirrhosis, hepatocellular carcinoma, and overall mortality [3,4]. After the decline in AIDS-related mortality since the introduction of HAART, end-stage liver disease (ESLD) emerged as a frequent overlapping toxicities and the high costs of treatment. This review focuses on the current state of the art of these new and promising therapeutic options for HIV/HCV co-infected individuals.

Up to recently interferon in combination with ribavirin was the main treatment for hepatitis C, but eligibility, safety, tolerability, and effectiveness of this pharmacological regimen were partial. The development of direct-acting antiviral drugs towards NS3/4A protease, NS5B polymerase, and NS5A replication complex has progressed, during the last few years, tremendously and now allows physician to have an interferon-free therapies strategy. The improvement of treatment strategies also yielded to the improvement of SVR rate, defined as undetectable levels of HCV RNA in plasma after 12 weeks of achievement therapy. However, co-infected individuals usually showed a lower SVR rate than the mono-infected one. In this context, the novel drugs for HCV treatment seem to be revolutionary because elicits high response rate to treatment both in mono-infected and co-infected individuals. In this review, we focused on the present and future of the therapeutic options for HIV/HCV co-infected individuals.

Discussion

The guidelines recommend HCV therapy before starting with HAART when CD4 T lymphocytes are > 500/µL in order to avoid the less responsiveness which occurs in individuals with CD4 T lymphocytes < 500/µL, in this case HAART is initiated prior to HCV treatment [2,8-10]. HCV therapies changed quickly in the last two years, but Pegylated interferon (Peg-IFN) will still remain the back bone of some HCV therapy combinations (especially in genotypes 2 and 3 of mono and co-infected individuals with mild fibrosis), although it more likely that this drug will be abandoned as therapeutic option in a near future [2]. In 2011, the FDA (USA) approved the first directly Acting Antivirals (DAAs). This class of drugs consist in NS3/4A protease inhibitors, telaprevir and boceprevir, which are currently used together with Peg-IFN and ribavirin.

Although the approval of DAAs for the treatment of HCV genotypes 1 and 4, was made 4 years ago, these drugs seems to be already outdated and no longer useful because they poor tolerability and adherence due to the high pill burden and to several pharmacokinetic interactions with the other antiretroviral drugs. Replacement of these compounds with the nucleotide analogue, sofosbuvir (SOF), used in combination with ribavirin (RBV) plus or not Peg-IFN has proved to be the best therapeutic option in both 1 and 4 HCV genotype infections. The addition SOF to Peg-IFN/RBV (triple therapy) for 24 week increases the 12-week post-treatment termination SVR rate (SVR12) to 76% [2]. Encouraging results also stemmed from the PHOTON-1 study, which was performed on223 patients harboring chronic HCV genotypes 1, 2, or 3 with HIV co-infection [11]. In this clinical trial, the efficacy of the all-oral regimen of SOF plus RBV (weight-based dose) was studied in naive and experienced patients. The inclusion criteria in the enrolled patients were: CD4+ count greater than 500/µL and HCV genotype 1, 2, or 3 for naive patients, while CD4 count greater...
than 200/µL with stable antiretroviral therapy, undetectable HIV RNA levels and HCV genotype 2 or 3 for experienced patients. Cirrhotic patients were also included in the trial but the number was not more than 20% of the total subjects enrolled.

Patients with HCV genotype 1 belonging to the naïve group and experienced patients with HCV genotype 2 or 3 received a 24-week treatment course. Instead, naïve patients harboring HCV genotype 2 or 3 were treated for a 12-week course. The SVR 12 rate in HVC genotype 1 resulted in 76% while in HCV genotype 2 and 3 the value was 88% and 67%, respectively. The SVR 12 for experienced patients harboring HCV genotype 2 and 3 resulted in 92% and 94%, respectively. The study showed that SOF plus RBV therapy clearly brings benefit also to patients harboring HCV genotype 3 infection when the pharmacological treatment was enlarged from 12 to 24 weeks. These data are a starting point for the future management of the co-infected HIV/HCV patients. Both naïve and experienced patient obtained exceptional SVR rates with SOF plus RBV in the all-oral regimen.

Extending of knowledge concerning this new pharmacological strategy was made thanks to the multi-centric PHOTON-2 study in which among the 274HIV/HCV genotyping 1,2,3 also HIV/HCV genotyping 4 patients were included. The all-oral regimen of SOF plus weight-based RBV was given for 24-weeks to all naïve patients with HCV genotype 1,3 or 4 and experienced patients with genotype 2, whereas naïve patients with HCV genotype 2 received the therapy for 12 weeks. Among the enrolled patients, 81% were HCV naïve treatment and 20% cirrhotic. They displayed a mean CD4 count was 588/µL and 97% were on anti retroviral therapy with tenofovir -emtricitabine plus one of the following drugs: efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine, or raltegravir. The higher SVR12 rates was achieved in co-infected patient HCV genotyping 1,2,3 equals to 89% followed by 88% for HCV genotyping 2 and 85% and 84% for HCV genotyping 1 and 4, respectively. It is worth to note that the treatment responses between naïve and experienced patients were similar [12,13].

These two studies highlight the efficacy of the all-oral regimen of the combined therapy. The small, open-label, non-randomized, clinical trial called ERADICATE combine ledipasvir (LDV), an oral NS5A inhibitor, plus SOF ± RBV as therapeutic regimen in HIV/HCV genotyping 1 co-infected patients without liver cirrhosis [14,15]. The study enrolled 50 patients dividing them into two cohorts: patients in cohort 1 were not receiving antiretroviral therapy (n=13), while patients in cohort 2 were receiving antiretroviral therapy (n=37). In this latter group, patients were allowed to receive tenofovir-emtricitabine plus either efavirenz, raltegravir, rilpivirine, rilpivirine plus raltegravir, or efavirenz plus raltegravir. Data collected in the cohort 1 showed an SVR12 achieved by 100% of the patient who were not taking anti retroviral therapy. In the cohort 2, the SVR12 was achieved by 97% of patients who were taking anti retroviral therapy. These findings suggest that LDV plus SOF ± RBV is very effective in HIV/HCV genotyping 1 co-infected patients.

The safety of those promising drugs regimen is monitored in the TURQUOISE-I study, a still ongoing randomized, open-label, trial that focuses on both safety and efficacy of a combination therapy. In this study, the all-oral regimen treatment studied is i) ABT-450 Paritaprevir: NS3/4A serine protease inhibitor, 150 mg boosted with RTV 100 mg plus ABT-267 Ombitasvir: NSSA inhibitor; 25 mg all once daily; ii) ABT-333 Dasabuvir: non nucleoside NSSB polymerase inhibitor; 250 mg twice daily, plus ribavirin for period of time of 12 or 24 weeks.

Patients included in the TURQUOISE-I study are required to have CD4 count of 200/µL (or at least 14%) and an HIV RNA level less than 40 copies while receiving atazanavir or raltegravir HIV antiretroviral regimen. The patients' enrollment included also people with compensated cirrhosis, called Child-Pugh class A and patients with prior treatment with Peg-IFN plus RBV. The SVR12 rate at 12-week arm, was achieved by 93.5% and at 24-week by the 90.6%. In the 12-week arm, five patients were not able to achieve an acceptable SVR12, one patient withdrew from the study prematurely and one worsened at week 4 showing resistance at 3 viral targets (D168V in NS3/4A, M28T in NSSA and S556G in NSSB).

In the 24-week arm the patients response to drugs safety was not dissimilar; one had virologic break through with resistance at 3 viral targets (R155K in NS3/4A, Q30R in NSSA and S556G in NSSB), and two were been re-infected with HCV genotyping 1a strain distinct from the baseline HCV isolate after the complete treatment. Consider this in COSMOS study patients with chronic HCV genotype 1 infection were randomized to receive SOF plus the new simeprevir (SMV), with or without ribavirin, for either 12 or 24 weeks. The study included naïve and experienced patients divided in two cohorts and fixed the primary outcome at SVR12. Patients enrolled in cohort 1 were 80 with mild fibrosis (Metavir stage F0-F2) and were not responding to prior treatment with Peg-IFN plus RBV. Patients in cohort 2 were 87 with advanced fibrosis (Metavir stage F3-F4) who were treatment either naïve or not responders to prior treatment with Peg-IFN plus RBV. The overall SVR rates were very high in both cohorts: 90% and 94% in cohort 1 and 2, respectively [16].

In the panel of drugs of this category, daclatasvir (DCV), another HCV NSSA replication complex inhibitor, is used in a single daily dose. Results about efficacy and safety of SOF plus DCV for 8 or 12 weeks in HIV/HCV co-infected patients with HCV genotyping 1, 2, 3, 4, 5 or 6 is still ongoing in the ALLY-2 study. It is worth to mention that data regarding HCV genotype 5 and 6 are limited, however, SOF plus Peg-IFN plus RBV for 12 weeks in genotypes 5. A fixed-dose of combination therapy with LDV 90 mg/ Sof-400 mg in one tablet once daily for 12 weeks in HCV genotype 6, seem to be the best treatment option in this category of patients. The strategies combining different DAAs with or without RBV do not show difference in the SVR rates between HCV mono-infected and HIV/HCV co-infected patients. Recently C-WORTHY study was started, with the aims to evaluate the safety and the efficacy of the combination of the second-generation, HCV NS3/4A protease inhibitor MK-5172 ± the second-generation HCV NSSA inhibitor MK-8742 ± RBV for patients with HCV genotyping 1.

The enrolled patients were with and without HIV infection, underlining the concept that HIV infected patients not differ from the mono-infected in terms of SVR rate under novel and more potent oral IFN-free treatments. Preliminary data of this study appear to support this hypothesis [18,19]. A very important

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aspect of all these study is the unpredictability drug-drug interaction (DDIs) with HAART that needs to be concerned. Most of HIV infected patients are also treated for their HIV infection. An overview of the literature does not report up today severe DDIs occurring in the combine treatments between SOF and antiretrovirals [2]. However, with respect to DCV the reduction of the dose is recommended when administered with specific antiretroviral drugs [17]. Data are, in this specific concern limited and more studies are necessary to assess DDIs with anti retrovirals [2]. Many other studies are ongoing to evaluate the safety and efficacy of new IFN-free DAAAs regimens for HCV mono-infected patients as well as for the HIV/HCV co-infected populations [20-24].

Conclusion

Hepatitis C virus co-infection is common in HIV-positive patients worldwide, especially in USA and Europe. HIV and HCV viruses share the same transmission routes. Compared with patients with HCV infection alone, those with HIV and HCV co-infection have higher rates of cirrhosis, hepato cellular carcinoma, and hepatic de-compensation. It is now evident that HIV infection can accelerate progression of HCV-related liver disease and treatment for HVC is recommended. Virtually, all patients mono-infected or co-infected should be treated with the better therapeutic options without limitations, such as for example fibrosis stage. At this time, the studies mentioned in this review, showed that new drugs are able to increase dramatically SVR rate for all genotypes, also in cirrhotic patients, as well as in other different clinical setting of naïve or pre-treated patients. However, treatment with DAAAs is expensive and the high costs will most likely influence the treatment strategy choice, especially in the countries with economic crisis and in the poorest areas of the world.

Although, in US and in most European country DAAAs therapy is guaranteed to all patients IFN – free independently to Metavir score (that describe the grade of hepatic fibrosis). Italian roles put therapy limitations. In this concern, patients who have Metavir score F0-F2 (meaning with not advanced or severe liver disease) cannot be treated with IFN-free regimens. So that, for example patients with HCV genotype 2, F2 fibrosis must treated with Peg - IFN and ribavirin; it is evident that if there are elderly who have other significant comorbidities (I.e. diabetes) or patients suffering from mental illness cannot take interferon either, if they have F0-F2 fibrosis. This aspect is particular important because physicians cannot treat them at the time. Despite that, patients with advanced liver damage, having a Metavir score F3-F4 or cirrhosis can be treated with IFN-free regimens. This concern could be revised in order to change role for DAAs regimen. Another special issue that needs to be deeply investigated in the management of co-infected patients may be drug interactions between anti retroviral drugs and DAAAs (19). Finally, more studies are necessary to establish the real impact of DAAAs on the liver fibrosis and on the prevention of hepato cellular carcinoma.

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