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MINIREVIEWS

Hepatocellular carcinoma in patients co-infected with hepatitis C virus and human immunodeficiency virus

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Core tip: Hepatitis C virus and human immunodeficiency virus co-infected patients with Hepatocellular carcinoma, undergo the same therapeutic protocol as their mono-infected counterparts, but special issues such as interaction between regimens, withdrawal of therapy and choice of immunosuppressive agents, demand a careful approach by specialists.

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Abstract

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share a common route of transmission so that about one third of HIV infected individuals show HCV co-infection. Highly active antiretroviral therapy has offered a longer and better life to infected patients. While has removed AIDS-related diseases from the list of most common causes of death their place has been taken by complications of HCV infection, such as cirrhosis, end stage liver disease and hepatocellular carcinoma (HCC). HIV/HCV co-infection requires complex management, especially when HCC is present. Co-infected patients with HCC undergo the same therapeutic protocol as their mono-infected counterparts, but special issues such as interaction between regimens, withdrawal of therapy and choice of immunosuppressive agents, demand a careful approach by specialists. All these issues are analyzed in this minireview.

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INTRODUCTION

Co-infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is a common problem both in the United States as well as in Europe, for two main reasons. Firstly, both viruses share a common route of transmission (sexual or intravenous). Secondly, the introduction of highly active anti-retroviral therapy (HAART) has extended life expectancy for HIV infected individuals. These positive results, however, make these patients vulnerable to opportunistic infections or infections such as HCV. Furthermore, HCV/HIV co-infected patients cannot fully tolerate anti-HCV treatment due to adverse effects of the combination with HAART. While HIV subjects receiving HAART are at lower risk of dying from acquired immunodeficiency syndrome (AIDS)-related diseases, for those with HCV co-infection, end stage liver disease and hepatocellular carcinoma (HCC) have emerged as leading causes of morbidity and mortal-

ity. In the present report we try to evaluate epidemiological characteristics of co-infected patients, the risk of development of HCC, as well as the suggested treatment modalities presented in the pertinent literature.

EPIDEMIOLOGY

In the United States, about 25% to 35% of patients with HIV are co-infected with HCV, totaling nearly 300000 people, while less than ten years ago this number was only about 50000, with a higher prevalence among United States military veterans[1-4]. The prevalence of HCV infection among HIV infected individuals varies, with the co-infection rate being higher when transmission occurs *via* the parenteral route compared to infection through sexual contact. HIV infected individuals who receive the virus through intravenous drug abuse or blood/blood products transfusion have a prevalence of HCV co-infection rate of between 75% to 90%[3,5]. Bollepalli *et al*[6] reported that intravenous drug abuse, sharing toothbrushes or razors, being in prison and tattooing are the most common non-sexual related risk factors while among the sexual related risk factors, sex for money or drugs, sex with intravenous drug abusers and men having sex with men, are significant risk factors. However, it is very difficult to determine the true contribution of the above mentioned risk factors, as many of them interfere with one another. It is, though, true that the absolute number of patients with HCV/HIV co-infection is increasing and as the AIDS-related causes of death are minimized, the complications of HCV infection (end stage liver disease and HCC) have become the main cause for the morbidity and mortality in this subgroup of patients.

CLINICAL IMPACT

As described above, in the recent years there have been major efforts in the treatment of HIV infected individuals, maximizing therapy by introducing HAART. In the era of HAART, HIV infected subjects avoid the progression towards AIDS and its lethal complications, and achieve a prolonged viral suppression, significant immune system restoration, improvement of quality of life and a resultant prolongation of life expectancy[7-10]. As HIV and HCV share common routes of transmission, and HIV infected individuals under HAART face no longer the risk of death due to AIDS-related conditions, HCV infection and its complications have become the major issue.

A further issue is that the interaction between the two viruses and their impact on liver surgery is not completely understood. HCV is not directly cytotoxic and the pathogenesis of liver injury is believed to be result of host immune-mediated cytolytic response[11]. The presence of HIV infection alters the natural history of HCV infection. After acquiring HCV, the infection becomes chronic in almost 90% of HIV patients and once chronic infection is established liver fibrosis progresses much faster, resulting in higher frequency of cirrhosis and its complications, compared to mono-infected HCV patients[12,13]. A meta-analysis including 8 studies with 1871 HCV-positive patients showed, in the subgroup of those co-infected with HIV patients, a relative risk of 2.92 for more severe disease, 2.07 for histological cirrhosis and 6.14 for decompensated liver disease[12]. Similarly there is a higher incidence of HCC in co-infected patients[14,15]. Co-infected patients are younger and have a shorter duration of HCV infection than patients with HCC and HCV mono-infection. Another characteristic of this group of patients is that tumors commonly show an infiltrative pattern and an advanced stage at presentation as well as more frequent extranodal metastases[16]. Therefore an effective treatment of both viruses is the gold standard for achieving a favorable outcome in co-infected patients.

TREATMENT STRATEGIES

The achievement of optimal treatment of HCV in HIV patients is a challenge. An initial assessment of viral load of HIV and HCV along with a CD4 count should be performed. The current recommendation is to suppress HIV before starting anti-HCV treatment[16]. The combination of pegylated interferon and ribavirin seems to be the treatment of choice in order to stop progression of fibrosis and prevent liver-related disease and death in mono-infected patients[16,17]. However, adverse effects lead to discontinuation of treatment or doses modification in the majority of patients. The most common side effects are flue-like symptoms while about one third of patients experience a drop in hematological parameters[18-20]. The treatment of HCV in HIV co-infected patients is more complicated due to the additive drug toxicities of ribavirin and the nucleoside reverse transcriptase inhibitors didanosine, zidovudine and stavudine[21-23]. Recent studies, however, reveal that a nucleoside-free HAART is feasible in the context of anti-HCV therapy and it is at least not disadvantageous for the patients, and could also provide great improvements in treatment response rates[24].

HCC ISSUES

The result of HCV infection is, in the majority of cases, the development of liver cirrhosis. Once cirrhosis is established, the annual risk of HCC, liver disease progression and death in HCV infected patients reaches approximately 1% to 7%, 5% and 2% respectively[25]. As described above, co-infected patients have been shown to develop liver cirrhosis more quickly than HCV mono-infected individuals and demonstrate a more aggressive course of HCC. In a study by Benhamou *et al*[13], HIV-HCV co-infected patients had a mean rate of fibrosis progression of 0.181 fibrosis units per year, which translated into a mean duration from HCV infection to cirrhosis of 26 years. HCV mono-infected patients had a mean rate of fibrosis progression of 0.135 fibrosis units per year, or a mean duration of 38 years from HCV infection to cirrhosis. Thus the eradication of HCV in these pa-

tients remains the gold standard of treatment.

According to current guidelines, treatment of HCC is the same for patients with and without HIV infection although the outcome seems to be worse for HIV-positive patients than their HIV-negative counterparts[26]. Chemotherapy seemed not to be a favorable treatment strategy until recently as HCC was considered as a chemoresistant tumor. However, sorafenib is a new tyrosine kinase inhibitor targeted against several biological factors (including vascular endothelial growth factor, platelet derived growth factor and Raf kinase) which demonstraties the ability to inhibit tumor proliferation and angiogenesis *in vitro*. Monotherapy with oral sorafenib (400 mg twice daily) prolonged median overall survival and delayed the median time to progression in patients with advanced hepatocellular carcinoma, according to the results of a randomized, double-blind, placebo-controlled, multicenter, phase Ⅲ trial (the Asia-Pacific trial)[27]. Two hundred and seventy-one patients from 23 centers in China, South Korea and Taiwan were enrolled in the study. Of these, 226 patients were randomly assigned to the experimental group (n = 150) or to the placebo group (n = 76). Median overall survival was 6.5 mo in patients treated with sorafenib, compared with 4.2 mo in those who received placebo. Median time to progression was 2.8 mo (2.63-3.58 mo) in the sorafenib group compared with 1.4 mo (1.35-1.55 mo) in the placebo group[27]. Sorafenib has been approved both in Europe Union and United States and has changed the natural course of unresectable HCC.

The efficacy of sorafenib, however, has not been proved in the setting of HCC in HCV-HIV co-infected patients as there are only individual cases described in the pertinent literature and no larger trials. In these cases there has been a remarkable prolongation of patient survival after administration of sorafenib[27]. Furthermore, metabolism of sorafenib occurs primarily in the liver, mediated *via* cytochrome P450, and concomitant administration of cytochrome inducers or inhibitors could alter the active sorafenib concentration[28]. Some agents (fosemprenavir and ritonavir) used in the HAART are cytochrome inhibitors and this could mediate a potent increase in the active dose of Sorafenib, resulting in a favorable outcome for the patient. Further studies are needed in order to strengthen these results.

Another very serious issue regarding HCC is recurrent disease after initial treatment. Several treatment modalities have been introduced, with interferon the most popular among them. A meta-analysis examining the effect of interferon on patient survival, was favorable to interferon with a pooled risk ratio of 0.65, and without statistical heterogeneity. Interferon treatment also significantly reduced the risk of tumor recurrence with a pooled risk ratio of 0.86[17]. The significant positive effect of interferon is, however, diminshed by its moderate or severe side effects. Interferon possesses several properties including antiviral, immunomodulatory, antiproliferative and antiangiogenic actions. Such activities could explain why the beneficial effect of interferon is greater for survival than for tumor recurrence. In particular the antiviral effect might delay further progression of cirrhosis and deterioration of liver function.

The last but very interesting issue in the setting of HCV-HIV co-infection with the presence of HCC, is the possibility of liver transplantation (LTx). Previously the presence of HIV infection was a contraindication for LTx despite the fact that LTx is the treatment of choice for end-stage liver disease or HCC. However, during the last decade things have changed dramatically and in the HAART era, 1- and 3-year survival rates after LTx have reached 87% to 91% and 64% to 73%, respectively[29]. Further epidemiological studies reveal that the outcome after LTx in HIV-HCV co-infected patients is worse than mono-infected either with HIV or HCV[30,31]. Norris *et al*[30] reported that at 12 mo, 4 of 7 (57.1%) of those coinfected with HCV were still alive, but by 25 mo a further 2 had died. The survival rate of HCV/HIV co-infected individuals was clearly lower than in the HCV mono-infected candidates who received organs during the same period. The latter had actuarial 1- and 2-year survival rates of 87.5% and 83.9%, respectively.

Several factors regarding the outcome of LTx in HIV infected individuals should be highlighted. Firstly should be pointed out that HIV-positive individuals with hepatitis B or hepatitis C virus infections should be referred to transplant centers at an early stage, in order for the transplant experts to choose the optimal time for transplantation (not too late and not too early, depending on the cause of liver failure). The criteria for LTx are the same for both HIV-positive and for HIV-negative patients, requiring low virus load and absolute CD4 cells not less than 100 cells/mL. Similarly, opportunistic infections previously considered as a contraindication now should be evaluated before decisions on transplantation are made[32].

Another controversial issue is the choice of immunosuppressive regimen after LTx. Two issues require special attention, the first being the avoidance of rapid withdrawal of steroids in the HCV co-infected population, due to the evidence of accelerated fibrosis. The second issue is the interaction between immunosuppressive treatment and HAART, as many of the immunosuppressive medications are metabolized in the cytochrome P450 system. Some antiretroviral drugs (*e.g.*, ritonavir) can reduce metabolism of calcineurin inhibitors (cyclosporine, tacrolimus), so that dosage of these agents must be reduced by up to 75%. On the other hand immunosuppressive agents like mucophenolate mophetil interact with nucleotide analogues altering the activity of antiviral medication[33,34].

CONCLUSION

HIV infection is a serious social problem, in developed countries as well as in the developing world, and as any vaccine is still far from everyday clinical practice, this is becoming ever more dangerous. HIV and HCV share common routes of transmission, resulting in about 30% of HIV infected individuals being co-infected with

HCV. Treatment of HIV/HCV co-infected subjects is more complicated for than mono-infected individuals. In the HAART era, HIV infected subjects live longer and enjoy a very good quality of life, so that the complications of HCV infection (cirrhosis, end stage liver disease and HCC) are the most common causes of mortality and morbidity in the co-infected subgroup of patients. Treatment of HCV and its complications in co-infected patients is a difficult dilemma due to interactions between medications and frequent withdrawal of therapy or dose modification due to adverse effects. Treatment of HCC in co-infected patients is the same as in other HCC patients, including surgical techniques, chemotherapy with sorafenib, palliative treatment modalities and liver transplantation.

Future directions can be divided into two main categories. In the first category are clinical and experimental studies, ranging from new therapeutic agents to vaccination. Until this becomes reality, we should follow the second category which includes a very close clinical and laboratory examination of co-infected patients and an early reference to centers of expertise.

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