

HIV AND HCV CO-INFECTION IN HEMOPHILIA

Second Edition

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HIV and HCV Co-infection in Hemophilia

J. T. Wilde

Introduction

Prior to the development of viral inactivation procedures in the mid-1980s, virtually all hemophilic patients who had previously received large pool plasma-derived factor concentrates were infected with hepatitis C virus (HCV). A considerable number of these patients were also infected with human immunodeficiency virus (HIV). Before the introduction of highly active antiretroviral treatment (HAART) in the mid-1990s, HIV was considered to be the most significant viral infection in co-infected patients and the importance of HCV infection was underplayed. However, since HIV infection has been so effectively controlled by HAART, there has been a heightened awareness of the potentially life-threatening effects of chronic HCV infection in co-infected patients – in particular the progression to cirrhosis and end-stage liver failure and the development of hepatocellular carcinoma. Consequently, management of HCV infection in this patient cohort is now actively encouraged. This paper will discuss the interactions between HIV and HCV and cover aspects concerning the management of these viruses in co-infected hemophilic patients.

Interaction of HIV and HCV

Effect of HIV on HCV

It is well recognized that HIV accelerates the progression of chronic liver disease to liver failure and death in co-infected patients. Makris et al observed a higher rate of progression of HCV liver disease to cirrhosis in co-infected individuals in a cohort of U.K. hemophilic patients and this observation has recently been confirmed in a U.S. study [1, 2]. In another U.S. hemophilia cohort, Eyster et al reported that progression to HCV-associated liver failure was accelerated by HIV [3]. Telfer et al reported that, after a median time of 15 years from the initial exposure to factor concentrate, co-infected hemophilic patients were 21 times more likely to develop hepatic decompensation when

compared with HCV-monoinfected individuals [4]. In 1997, Darby et al published a retrospective study of the U.K. hemophilia cohort in which, as of January 1, 1993, the cumulative deaths from liver disease since first HCV exposure in HIV-infected patients were four times that of HIV-negative individuals (6.5% and 1.4% respectively) [5]. In a more recent study of 134 hemophilic patients, Lesens et al reported a sevenfold overall increased death rate in co-infected individuals, as compared with the HCV-monoinfected group, with an even higher rate in patients who progressed to acquired immune deficiency syndrome (AIDS) [6]. Liver cancer is another well-recognized complication of chronic HCV infection that appears to develop after a shorter period of infection in co-infected patients [7].

The exact way in which HIV accelerates chronic HCV liver disease has not been explained. As HIV itself does not appear to cause inflammation of the liver directly, its effect is presumably mediated via suppression of the immune response against HCV. However, although the amount of HCV in the blood (HCV viremia) does tend to be higher in HIV-positive patients as compared with those with HCV-monoinfection (both in hemophilic and non-hemophilic cohorts [8, 9]), there is no conclusive evidence that the level of HCV viremia is directly related to the severity of HCV liver disease [10].

Regardless of HIV status, there is evidence to suggest that HCV genotype 1 may be associated with more rapid progression to cirrhosis than other genotypes [11].

Effect of HCV on HIV

Whether or not HCV infection accelerates the progression of HIV infection to AIDS and death remains unclear. Three studies conducted during the early 1990s concluded that HCV co-infection did not adversely influence survival in HIV-infected individuals [12-14]. Similarly, four further studies, one before and three after the advent of HAART, concluded that HCV

infection did not accelerate immunological and clinical progression of HIV disease [15-18]. However, in a French study of 119 co-infected patients and 119 HIV-monoinfected individuals, Piroth et al observed that clinical progression of HIV was more rapid in the co-infected cohort [19].

In 2000, Greub et al published a prospective study of over 3,000 HIV-positive patients on HAART (the Swiss HIV Cohort Study) [20]. At a median follow-up of 28 months, 6.6% of HIV-monoinfected patients had progressed to AIDS, as compared with 9.7% and 15% of HCV-seropositive patients who were past or active intravenous drug users, respectively. The relative risk of developing an AIDS-defining illness or death in the co-infected group was 1.7, as compared with HCV-seronegative patients. Following initiation of HAART, co-infected patients had impaired CD4 cell count recovery, as compared with HIV-monoinfected individuals. In a study of a subset of patients, the level of HCV viremia was not found to be an influencing factor in CD4 cell count recovery. This observation was confirmed in a similar study of a cohort of HIV-infected hemophilic patients starting on HAART [21]. In the Swiss Cohort Study, HCV genotype 3 was associated with a more blunted CD4 cell count recovery [20]. However, in a U.K. study, Sabin et al reported that HIV-infected hemophilic patients co-infected with HCV genotype 1 had a worse prognosis, as compared with those infected with other genotypes [22].

Following Greub's publication, a U.S. study of almost 2,000 HIV-infected patients with a similar median follow-up reported that HCV co-infection was not associated with an increased risk of progression to AIDS or death or impairment of the immunological response to HAART [23].

The differences between the Swiss and U.S. studies may be explained by variability in the patient groups. In the Swiss study, HCV-infected patients tended to be younger, white, and female, whereas in the U.S. study, patients were older and more likely to be African-American.

If HCV infection does worsen the outcome of HIV infection, the mechanism has not been

explained. Possible mechanisms that have been suggested include HCV-mediated impairment of CD4 cell production in lymphoid tissue and sensitization of CD4 cells to premature programmed cell death [24].

Effect of HAART on HCV infection

Two European studies, one of a cohort of hemophilic patients, reported that the initial period of HAART was not associated with significant elevations in serum liver enzyme (transaminase) levels (an indication of liver damage) and HCV viremia [25, 26]. However, other studies have reported contrary observations. In a study of 21 co-infected hemophilic patients, Ragni and Bontempo observed an increase in HCV viremia in 17 individuals during a 96-week period following commencement of HAART [27]. However, this was not associated with evidence of progression to HCV liver disease, although one patient did progress to liver failure during the first year of HAART. Other studies have observed rises in HCV viremia and transaminase levels following commencement of HAART [28-30]. In a study by Vento et al, which included 51 co-infected patients followed up for a nine-month period, there were transient rises in HCV and transaminase levels following commencement of HAART, which peaked at one month. Patients who underwent liver biopsy had a tendency to develop increased liver inflammation consistent with reactivation of an immune-mediated attack on HCV, as a consequence of restoration of immune function. Seven of the patients in this study progressed to decompensated liver disease during the study period and discontinued HAART.

Effects of HIV drugs on the liver

If worsening of pre-existing transaminitis or new transaminitis occurs in co-infected patients who have started on HAART, direct drug-related toxicity must be considered as a possible cause and not assumed to be due to increased inflammatory activity against HCV. Pre-existing liver disease predisposes to HIV drug-induced liver toxicity, and a recent study has shown an increased frequency of HAART-related hepatotoxicity in patients who have active HCV co-infection, compared to patients who have had

HCV successfully treated prior to starting HAART [31].

All the licensed nucleoside reverse transcriptase inhibitor drugs (NRTIs) can cause elevation of liver enzymes and have been associated with hepatic steatosis and liver enlargement [32]. Stavudine and didanosine (DDI) are the most likely NRTIs to be associated with hepatic steatosis and the associated elevation of lactic acid levels or, occasionally, potentially life-threatening lactic acidosis. Abacavir may be associated with a disturbance in liver function due to a multi-organ hypersensitivity reaction which can develop within a few days or weeks of beginning treatment. Liver function test abnormalities associated with the other drugs in this group result from direct drug toxicity likely caused by a poisoning of the liver cell mitochondria.

The licensed non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine have also been associated with liver toxicity. Efavirenz can cause direct liver cell damage with elevation of liver enzymes, especially in patients with hepatitis B or C. Nevirapine can cause derangement of liver function, with potentially life-threatening fulminant hepatitis as part of a generalized immune-mediated hypersensitivity reaction which can occur within the first two months of treatment. The risk of nevirapine-associated hypersensitivity is directly correlated with the CD4 cell count, reducing as immune function declines. Nevirapine can also cause direct dose-dependent liver toxicity occurring after at least four months of therapy, especially in patients with HCV co-infection.

Although the earlier protease inhibitor drugs (PIs) indinavir, ritonavir, and saquinavir were associated with liver toxicity, this does not appear to be a problem with the newer agents amprenavir, fosamprenavir, nelfinavir, lopinavir, atazanavir, tipranavir, and darunavir.

All HIV medications should be used with caution in patients with HCV-associated liver disease, with regular monitoring of liver function. Patients on NRTIs or NNRTIs should be monitored closely for the possible development of hepatic steatosis, elevation of

lactic acid levels, and lactic acidosis. Medications should be suspended or permanently discontinued if deterioration in liver function occurs.

Management of HCV in HIV infection

HIV-infected hemophilic patients are likely to have been screened previously for HCV infection using an HCV antibody test. Virtually all of these patients will have a positive test consistent with past exposure to HCV in factor concentrates. However, around 15% of individuals will naturally eradicate the virus and, therefore, it is important to determine if HCV infection is still present in the blood by performing a polymerase chain reaction (PCR) test for HCV RNA. If the patient is HCV RNA-positive, quantitation of the virus should be performed and the genotype determined. HIV-infected patients who are antibody-negative should also have an HCV RNA test, as false-negative antibody tests can occur as a consequence of immunosuppression [33].

Co-infected patients with intermittently or persistently elevated liver enzymes should be considered for HCV eradication therapy. Histological analysis of a liver biopsy remains the gold standard in the assessment of HCV infection. Liver tissue can be obtained by either a percutaneous, transjugular, or laparoscopic approach [34]. There has been concern in the past over the safety of this procedure in hemophilic patients due to the potential for bleeding [35]. However, provided effective factor concentrate replacement protocols are followed, the risk does not appear to exceed that of patients who do not have a bleeding disorder [34, 36]. Conventionally, patients with hemophilia are kept in hospital for overnight observation following liver biopsy. However it has recently been reported that with appropriate factor concentrate cover, percutaneous and transjugular biopsies can be performed safely as day case procedures in this patient group [2, 37].

Due to the potential for HCV infection to progress to end-stage liver disease, a good case can be made for initiating HCV treatment without information on liver histology. However, histological findings can be very useful in helping both the clinician and the

patient make informed management decisions. Occasionally, minimal liver inflammation may be present, making it unlikely that HCV infection will progress at any time in the future to cirrhosis and liver failure. In this situation, treatment could be withheld reasonably. Equally, if advanced cirrhosis is present, a decision may be made not to proceed with treatment due to the reduced chances of HCV eradication.

In HCV RNA-positive patients with persistently normal liver enzymes, a liver biopsy should be considered as progressive liver disease cannot be excluded [38]. HCV therapy should only be offered if there is evidence of active liver disease on histology [33].

Due to the cost and perceived risk of liver biopsy in patients with hemophilia, there has been an increasing shift towards the use of non-invasive tests to assess the severity of HCV liver disease. These include algorithms based on abnormalities of laboratory test variables such as the Fibrotest [39], FibroMeter [40], and tests specific for HIV/HCV co-infected patients [41]. The presence of liver fibrosis can also be assessed with a test of hepatic elasticity, the fibroscan [42].

Treatment of HCV in HIV infection

HCV treatment strategy in HIV-infected patients is the same as in HIV-negative patients. Individuals with stable HIV infection and well-preserved CD4 cell counts who are not on HAART should be strongly advised to consider HCV treatment in an attempt to eradicate HCV infection. Eradication of HCV at this stage will remove the potential adverse influence of HCV on HIV infection and prevent the development of liver disease, which may lead to problems with HAART therapy if it is required in the future. HIV-infected patients who are stable on HAART should be assessed on an individual basis. HCV treatment should be considered for stable patients with CD4 counts greater than $200 \times 10^6/L$. Co-infected individuals with progressive HIV disease and low CD4 counts should have HAART commenced as a priority. HCV treatment should be considered only when HIV infection is stabilized and CD4 counts improve. Patients with advanced HIV infection

and a failing liver should not be considered for HCV treatment.

The treatment of choice for HCV is combination therapy with pegylated interferon (Peg-IFN) and ribavirin. Peg-IFN is a formulation of alpha-interferon combined with polyethylene glycol (Peg). It is administered subcutaneously and the formulation results in sustained therapeutic interferon levels which allow a once-weekly dosing schedule. Currently, there are two preparations, peg-alpha-2b interferon (Pegasys®, Roche) and peg-alpha-2a interferon (Peg-Intron™, Schering-Plough). Ribavirin, an analogue of the DNA base guanosine, is taken orally twice daily. To optimize therapy, it is important that ribavirin is prescribed at the correct dose for the body weight [43]. Patients started on combination therapy should be advised to abstain from alcohol.

In HIV-negative non-hemophilic patients, Peg-IFN/ribavirin combination therapy can achieve HCV eradication rates of just over 40% for HCV genotype 1 and up to 80% for genotypes 2 and 3 [44, 45]. In a recent literature review of HCV treatment studies in hemophilic patients, Posthouwer et al report an overall 57% sustained response rate to this therapy in a total of 167 HIV-negative individuals [46]. Studies looking at the efficacy of Peg-IFN/ribavirin in co-infected non-hemophilic patients report lower sustained response rates compared to monoinfected individuals of 27% in two studies and 40% in another [47-49].

So far, there is little published data on the treatment experience in co-infected hemophilic patients. Posthouwer has reported a single-centre study in which HCV was successfully treated in 2 of 10 co-infected hemophilic patients [50]. Of the 11 co-infected hemophilic patients included in a multicentre trial reported by Shire in which patients were treated for 72 weeks, 3 patients achieved sustained virological response [51].

As well as eradicating HCV, combination therapy reportedly reduces the degree of hepatic fibrosis [45, 52]. Even in non-responders, a course of interferon therapy may slow fibrosis progression and reduce the risk of end-stage liver disease and the development of liver cancer [53].

Factors predictive of a favourable response to interferon/ribavirin combination therapy in co-infected patients include a CD4 cell count of more than $500 \times 10^6/L$ and plasma HIV RNA levels of less than 10^4 copies/mL [54]. Other favourable predictive factors shared with HCV-monoinfected patients include non-genotype 1 infection, low HCV load (less than 3.5×10^6 copies/mL), age less than 40, minimal hepatic fibrosis, and abstinence from alcohol [43, 55].

Patients started on Peg-IFN/ribavirin should have an HCV RNA test performed at three and six months. Although the majority of responders become HCV RNA-negative by three months, it has been recommended that treatment should be continued in those who remain RNA-positive as later responses have been reported [56]. If the six-month RNA test is positive, therapy should be discontinued as a response beyond this time is very unlikely. A recent trial has suggested that persistence of detectable HCV RNA at three months is a strong predictor of response failure in co-infected patients [44]. Therefore, a case could be made for discontinuing therapy at this early stage in non-responders, avoiding unnecessary drug treatment and possible toxicity. Patients with genotype 1 infection who have cleared HCV RNA by 6 months should have their treatment continued for a full 12 months to consolidate the response. Responders with non-genotype 1 virus can have their treatment discontinued at six months [33]. Following cessation of therapy, responders should have regular HCV RNA monitoring and, if a relapse occurs, further combination therapy should be considered.

New drugs specifically targeted against different stages of the life cycle of HCV in hepatocytes have been developed. The most promising include HCV proteinase inhibitors, HCV RNA polymerase inhibitors, and HCV assembly inhibitors. However as single agents, these drugs have poor efficacy against HCV with a high rate of resistance development, so they have had to be combined with Peg-IFN and ribavirin for optimal effect. Results of initial trials using such combinations are promising, showing higher response rates than with Peg-IFN/ribavirin alone. Larger trials are ongoing but as yet these newer drugs have not been trialed in co-infected patients [57].

Side effects of HCV treatment and interactions with HAART drugs

The main side effects of Peg-IFN are similar to those of conventional IFN preparations and include flu-like symptoms, lethargy, depression, and reductions in blood cell numbers. IFN can induce a reduction of CD4 cell counts in some individuals. This effect is likely to be a consequence of the pooling of the lymphocytes within lymphoid tissue and is usually transient. Occasionally, the fall in CD4 count can be severe enough to necessitate cessation of IFN and may be irreversible [58]. Ribavirin is associated with the development of a dose-dependent hemolytic anemia. Hemoglobin levels can fall below 11g/dL in up to a third of patients [59]. The anemia is not usually clinically significant, but may be severe enough to cause symptoms. This effect of ribavirin may compound zidovudine-induced anemia in co-infected patients on this drug. Symptomatic patients can be treated effectively with recombinant human erythropoietin, which is preferable to reducing the ribavirin dose due to the potential for reduction of its anti-HCV effect [60, 61].

With regard to interactions with HIV drugs, ribavirin is known to inhibit the intracellular phosphorylation of zidovudine and stavudine *in vitro*. This has the potential to reduce the efficacy of these drugs *in vivo*, but there is no evidence that this interaction results in a failure of HIV therapy [62]. Ribavirin enhances the phosphorylation of didanosine [43]. Although this may enhance the anti-HIV effect of didanosine, there have been reports of an increased incidence of mitochondrial toxicity in patients on both drugs, manifesting clinically as weight loss, pancreatitis, hyperlactataemia, or, at its most extreme, lactic acidosis [63]. Stavudine, and to a lesser extent the other NRTIs, appear to have similar interactions with ribavirin [64]. Therefore, patients receiving HCV combination therapy and HAART regimens containing NRTIs should be monitored very closely and, for those on didanosine, consideration should be given to changing them to an alternative drug.

Liver transplantation for HCV liver disease in co-infected patients

Co-infected patients who develop HCV-related liver failure or localized hepatocellular carcinoma and who have stable HIV infection (on or off HAART) should be considered for liver transplantation. Prior to HAART, the prognosis in this group of patients was poor [65]. In the series reported by Gordon et al, the one-year and three-year survival in 6 co-infected patients was 67% and 23% respectively, which was significantly worse than that of the 19 HIV-negative patients (90% and 83% respectively) [66]. However, co-infected patients who remain stable on HAART post-transplant appear to have a better prognosis. At the time of writing, two co-infected hemophilic patients have been transplanted in Birmingham, U.K., and remain alive and well at eight and five years post-transplant [67]. Therefore, HIV infection should not be considered a contraindication to liver transplantation.

Conclusion

HIV infection worsens the prognosis of HCV liver disease. There is also evidence that HCV has a detrimental effect on the course of HIV infection. HCV infection should, therefore, be actively managed in co-infected patients. Patients who need treatment and who have stable HIV infection either on or off HAART with CD4 counts above $200 \times 10^6/L$ should be treated with Peg-IFN/ribavirin combination therapy. Close clinical and laboratory monitoring is recommended to screen for possible drug side effects and interactions. As in immuno-competent individuals, responders with genotype 1 virus should continue treatment for 12 months and those with non-genotype 1 virus for six months. Individuals with end-stage liver disease with stable HIV infection should be considered for liver transplantation.

Glossary

CD4 cell count: CD4 cells are white blood cells that, together with other parts of the body's immune system, help fight off invading viruses, bacteria and other causes of infection. HIV infects and destroys CD4 cells, effectively preventing the immune system from fighting the virus. The CD4 cell count is used as an indicator of the health of the immune system in HIV infection.

Cirrhosis: A disease of the liver caused by chronic damage, where the normal cells are replaced with fibrous, scar tissue.

Fulminant hepatitis: A severe form of hepatitis involving death of liver cells and, often, liver failure.

HAART: A combination of three or more drugs that, together, block HIV's ability to replicate.

Hepatic decompensation: A decrease in function caused by the liver's failure to repair itself from injury.

Hepatic steatosis (or "fatty liver"): An accumulation of fat in the liver that can progress to cirrhosis.

Hepatocellular carcinoma: The most common type of primary liver cancer.

Hyperlactatemia: An elevation in the levels of lactic acid in the blood that can lead to lactic acidosis (see below).

Hypersensitivity reaction: An inappropriate and excessive immune reaction to an allergen or drug.

Lactic acidosis: A potentially lethal accumulation of lactic acid in the blood. Certain HIV drugs have been associated with mitochondrial toxicity, which can lead to lactic acidosis.

Nucleoside reverse transcriptase inhibitors (NRTIs): Anti-HIV drugs that stop the virus from replicating by shutting down an important viral enzyme, reverse transcriptase.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Like NRTIs, these anti-HIV drugs stop the virus from replicating, but they have a different chemical structure, resulting in different side effects.

Pancreatitis: Inflammation of the pancreas.

Protease inhibitors: Anti-HIV drugs that help keep the virus from replicating by targeting an important viral enzyme, protease.

Transaminase: A liver enzyme. A laboratory test that measures transaminase levels is used to assess the functioning of the liver.

Transaminitis: The presence of elevated transaminases.

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