Special Populations: Bleeding Disorders (and thalassemia)

It is debatable whether patients with hemophilia should be considered a special population, but these patients do have higher rates of HIV-HCV coinfection. Hemophilia is an inherited bleeding disorder caused by a deficiency of either factor VIII or IX in haemophilia A and B respectively. Patients suffer spontaneous and traumatic bleeds. Treatment is with intravenous replacement of these factors which until recently were prepared from plasma donations. Clotting factor concentrates are prepared from pools of plasma containing up to 30,000 donations and prior to 1985 were infused into recipients without any viral inactivation. Hemophiliacs exposed to non-virally inactivated concentrates prior to 1985 had an almost 100% chance of being infected with non-A, non-B hepatitis with their first exposure to concentrate. Thus patients treated prior to the introduction of viral inactivation in 1985 were commonly infected with hepatitis B, hepatitis C and HIV. Viral inactivation methods proved to be highly successful in eliminating both HIV and hepatitis C infection from concentrates. There are a number of other inherited bleeding disorders treated with concentrates including von Willebrand disease, and deficiencies of fibrinogen and factors II, VII, X, XI and XIII. The identification of hepatitis C in 1989 identified the prevalence of hepatitis C in haemophilic cohorts. Data from large cohorts indicate the prevalence of HCV genotype 1 in 45-74%, genotype 2 in 6-19%, genotype 3 in 10-42% and genotypes 4 and 5 in <4% of patients. Progression to end stage liver disease in patients with hemophilia is similar to HCV positive individuals in the general population.

Investigation of liver disease
The investigation of chronic liver disease in hemophilia is the same as in non-haemophilic individuals. Liver biopsies have been carried out since the late 1970s and have provided considerable information on the severity of the liver disease. More recently transjugular liver biopsies have enhanced the safety of the procedure. Non-invasive methods can be utilised to monitor disease progression with methods such as the Fibrotest and liver stiffness measurement by transient elastography. These tests are more accurate in predicting very mild fibrosis or cirrhosis; the test has been less widely studied in hemophiliacs.

The natural history of hepatitis C in Hemophilia
Virtually all hemophiliacs who were infected with HCV were infected by 1985 (the date of introduction of effective viral inactivation techniques). End stage liver disease (ESLD) may occur in patients who with chronic HCV; after 35 years of infection; ESLD develops in 11.5% of HIV negative and 35.1% of HIV/HCV co-infected individuals. Independent risk factors for ESLD included HIV co-infection, older age, alcohol abuse and infection with HCV genotype 1. Death from liver failure in HCV positive individuals is among the commonest causes of death in patients with inherited bleeding disorders. In patients with HCV related cirrhosis the risk of HCC is 3-6% per year, whilst it is approximately half this in individuals with advanced fibrosis. Patients with advanced liver disease should undergo surveillance for early detection of HCC.
Antiviral therapy

With the exception of unavailability of liver histology, the management of chronic hepatitis C in hemophilia is similar to the non-haemophilic population. Efficacy with interferon monotherapy, and ribavirin has been reported. Interferon monotherapy resulted in SVR in 95/434 (22%) patients, standard interferon plus ribavirin in 43% and pegylated interferon and ribavirin in 57% of individuals. Response to antiviral therapy in terms of SVR is associated with a marked difference in development of ESLD during long term follow-up. Patients with signs of decompensated cirrhosis should be considered for liver transplantation.

Higher rates of coinfection with HIV and HCV have occurred in hemophiliacs. HCV, with or without HIV, increasing the risk of insulin resistance and diabetes. Coinfection with HIV affects the natural history of HCV infection. Lower clearance rates (5% to 10%) are seen in HIV-seropositive individuals with acute HCV and HIV accelerates HCV disease progression. Cirrhosis is more prevalent among HIV-positive than -negative patients and is emerging as a major cause of morbidity and mortality in patients with HIV/HCV coinfection.

Antiretroviral agents for coinfected patients should be selected carefully, since some are more likely to induce hepatotoxicity. Important progress is being made in the development of new treatments, particularly in new specific inhibitors of hepatitis C and these are applicable to patients with hemophilia.

Several potential viral targets have been identified. In general patients with hemophilia are candidates for treatment with the first generation protease inhibitors. Patients with hemophilia and HIV-HCV coinfection are likewise candidates for treatment with new direct acting antivirals. Provisional data suggest that response rates are improved in coinfected patients, (to 70%) but larger studies are required to confirm these findings. Potential drug drug interactions in HCV-HIV coinfeated patients receiving antiretroviral agents (ARVs) requires careful selection of agents. The next phase of therapy for hepatitis C will evolve to interferon free regimens for many. Patients with thalassemia can be treated with first generation protease inhibitors but their propensity to anaemia will require additional transfusions.

Liver transplantation

Over 100 liver transplants have been carried out in PWH world-wide. FVIII/IX concentrate is administered immediately before the surgery either by bolus injection or continuous infusion and for the immediate post-operative period for 12-48hours, after which no further concentrate is required. Co-infection with HIV/HCV is not a contraindication to liver transplantation in hemophilia. The indications for liver transplantation in humans with hemophilia are the same as non-haemophilic individuals but the procedure has the major advantage of producing a phenotypic cure of the hemophilia as a result of FVIII production by the transplanted liver.

References