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Hepatitis C in Haemophilia: Time for treatment for all

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The infection of tens of thousands of haemophilic individuals with hepatitis C through their treatment is one of the largest medical treatment disasters in history. Most of these infections occurred before the introduction of viral inactivation of clotting factor concentrates in 1985 and the chronic problems of this infection are still with us today. A revolution in the treatment of this infection means that eradication of hepatitis C from the haemophilia community is within reach.

The introduction of clotting factor concentrates prepared from pooled donations of plasma in the 1960s and 1970s transformed the lives of persons with haemophilia. Since these pools of plasma contained up to 30,000 donations, it was almost invariable that recipients of non-virally inactivated concentrates were infected with hepatitis C and often with HIV as well. The introduction of viral inactivation was highly efficient in destroying the virus so the problem of hepatitis C in haemophilia is largely seen in individuals treated with concentrates prior to 1985. Around 15-20% of those infected cleared the HCV virus spontaneously (within 6 months of infection) but in the remainder chronic infection which virtually never cleared spontaneously ensued(1).

The problem with chronic HCV is the patient's propensity to develop liver cancer or liver failure decades after infection. Previous cohort studies have shown that up to 20-30% of the infected patients develop end stage liver disease(2)(3). Current data reported to the European Haemophilia Safety Surveillance (EUHASS) program up to 2015, show that hepatocellular cancer is the commonest cancer in patients with haemophilia and liver disease is the commonest cause of death in these individuals (personal unpublished information). The mortality data usually report liver disease when this was the main cause of death but they hide the problem of morbidity where patients with advanced cirrhosis die due to another cause.

Attempts to eradicate HCV in haemophilia started in 1987 with interferon monotherapy but the chance of sustained virological response (ie long term clearance) was less than 10%(4,5). The introduction of ribavirin, pegylated interferon, telaprevir and boceprevir led to a stepwise increase in clearance of up to 50-70%(6). The problem with these treatments has been the frequency of adverse events, the duration of the treatment of up to 1 year and the inconvenient dosing regimens of injections and tablets(4,5).

A dramatic change in the treatment of HCV is however upon us with multiple new highly effective agents such as sofosbuvir, daclatasvir, ledipasvir, simeprevir, ombitasvir, paritaprevir and dasabuvir (7). The current interferon-free treatments which are often once daily oral treatments for 8-12 weeks achieve clearance in excess of 95% with virtually no side effects. As a result most studies of HCV treatment nowadays are reporting consistent clearance in over 95% of treated patients (6,8)(9).

The field is developing so rapidly that 100% clearance with a single tablet taken for 6-8 weeks with virtually no side effects and covering all genotypes is now close to reality. For experienced haemophilia clinicians and infected patients this major advance in the treatment of HCV can be difficult to comprehend and I often wonder whether the treatment can really be that good? The answer most certainly appears to be yes.

The remarkable efficacy of these regimens in patients with bleeding disorders is documented in the study of U.S. patients by Walsh et al published in this issue of the journal [10. Walsh C et al]. Only one of the 120 treated patients did not have a documented sustained response at 12 weeks. He was a treatment-naïve patient with genotype 3 HCV. Five of five patients with compensated cirrhosis and prior treatment responded. The treatment was well tolerated, including in the 22% of patients who were HIV positive. These data confirm that except for patients with uncompensated cirrhosis or coinfection with hepatitis B, treatment of hepatitis C in haemophilia patients is highly effective.

The downside of the HCV treatment is the price which at first appears incredibly high at around £40,000 ($49,300; €46,600) per course of treatment (11). Worldwide there are large numbers of HCV infected patients and understandably governments view the potential costs of HCV treatment with horror. The pharmaceutical industry explains the very high cost of treatment as the result of the high development costs and the fact that this is a cure rather than disease suppression, as for HIV, where they can continue to make profits from selling the drugs long term. It has been suggested that it cannot cost so much to manufacture a drug but this is no longer a relevant issue when it comes to the price of drugs. Whilst 50 years ago the price of a drug related to the manufacturing cost, nowadays this cost is a tiny component of the price and the pharmaceutical companies state that the cost is now largely to cover their investment in research and development. Cynics, however, believe that the cost of a drug is determined by the pricing of the last similar drug to appear on the market.

A number of countries have introduced health technology assessments (HTAs) to evaluate all new treatments and the HCV therapies are undergoing evaluation. Initial data suggest that health care systems are likely to fund these treatments but their introduction is likely to be rationed. Unfortunately, none of these HTAs consider the case for haemophilia separately. Persons with haemophilia argue that theirs is a special case based on a moral issue since the treatment provided by health care systems, resulted in their HCV infection in the first place. A stronger case can however be made on clinical grounds, since firstly the infection has been present for at least 30 years and thus more likely to progress and secondly there are additional costs in terms of clotting factor concentrate to manage the complications of HCV. Once a person with haemophilia develops cirrhosis, they bleed more frequently due to reduction in clotting factors which are all made in the liver as well as due to thrombocytopenia secondary to portal hypertension. Every time a patient with haemophilia has an endoscopy to look for and treat oesophageal varices or perform a paracentesis to examine for spontaneous bacterial peritonitis, there will be an additional financial cost for the concentrate to normalise the clotting and thus cover the procedure. Although initially the one-off cost of HCV eradication of £40,000 appears high, this is relatively small in comparison to the ongoing annual costs of severe haemophilia where the concentrate is often in excess of £100,000 per year.

Another concern with the high cost drugs is that most of the world population lives in less affluent countries which are unlikely to be able to afford them. Pharmaceutical manufacturers cognisant of the criticisms of their pricing, have come up with methods to make the drugs more affordable and available in poorer countries. Examples of such schemes include the provision of the anti-HCV drug free of charge to every person in the country of Georgia as a test case to see if it is possible to eliminate HCV from a whole country and the supply of the drug at a great discount to Egypt where 10 million HCV patients reside(12).

Our aim as a haemophilia community should be to eradicate HCV from every infected individual as early as possible and thus to avoid the ongoing and constant complications of this pernicious infection. Where access is initially rationed, it should be possible to prioritise on the basis of likely progression using non-invasive imaging with instruments such as the fibroscan. Individuals with cirrhosis and significant fibrosis should be prioritised for treatment but ultimately all persons should be treated irrespective of their degree of fibrosis or liver function disturbance.

Declaration of Interest

MM has attended a single advisory board meeting for Gilead. BAK has nothing to declare.

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