NEW APPROACHES TO THE MANAGEMENT OF HEPATITIS C IN HEMOPHILIA

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ORIGINAL ARTICLE

New approaches to the management of hepatitis C in haemophilia in 2012

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Summary. Hepatitis C virus (HCV) infection is common in patients with Haemophilia. As in other patients, its natural history is characterized by disease progression towards cirrhosis and hepatocellular carcinoma. Many patients with hereditary bleeding disorders infected with HCV are also infected with HIV which is a factor of faster liver disease progression. In the past years, major progress has been made in the management of hepatitis C with the development of non invasive tools to assess liver fibrosis stage, i.e. fibroscan and biomarkers. With these tools, it is now possible to predict with good accuracy the liver disease stage and to take treatment decision. The landscape of antiviral therapy has evolved rapidly, especially for patients infected with HCV genotype 1. Triple therapy with interferon, ribavirin and protease inhibitors has been approved recently, the results of clinical trials showing a clear added benefit in terms of sustained virologic response in naive patients compared to interferon - ribavirin combination therapy. However, results are less promising in cirrhotic patients who failed a previous line of therapy, with a higher rate of side effects and a lower rate of virologic response in patients who qualified as null responders to IFN based therapy. Clinical trials with triple therapy are ongoing in HCV-HIV coinfected patients. Furthermore, new IFN free regimen relying on the combination of direct acting antivirals are currently being evaluated in HCV genotype 1 and non-1 infected patients. These advances provide new hope in the management of chronic hepatitis C, including patients with hereditary bleeding disorders.

Keywords: hepatitis C, haemophilia, antiviral therapy, interferon, ribavirin, protease inhibitors

Introduction

HCV infection acquired from factor concentrates in the 1970s and early 1980s is a major health issue in patients with hereditary bleeding disorders. A significant number of patients have been infected with HCV via administration of pooled factor concentrates, cryoprecipitate or fresh frozen plasma [1]. Around 20% of patients naturally eradicate their HCV infection. Patients who do not clear the virus have a chronic infection. Chronic liver inflammation may lead to slowly progressive hepatic fibrosis and clinically significant liver disease during prolonged follow-up. At least 30% of chronically infected bleeding disorder patients have developed progressive fibrosis culminating in cirrhosis, end-stage liver disease and hepatocellular carcinoma which may lead to liver transplantation [2]. A significant number of bleeding disorder patients are coinfected with HIV and HCV. Highly active antiret-

roviral therapy (HAART) has revolutionized the prognosis of HIV infection so that the HCV infection has become of major clinical importance, as liver disease is now the most common cause of death in patients with HIV/HCV coinfection [3].

The main aim of HCV treatment is to eradicate the virus and prevent disease progression. Ideally, cure should be achieved prior to the development of cirrhosis, not only to avoid progression to end-stage liver disease but also to reduce the risk of HCC.

Identification of HCV cases

The majority of patients exposed to blood components and factor concentrates prior to the introduction of viral inactivation procedures in the mid 1980s have been tested for HCV infection at their treatment centres. However, it is likely that there are a significant number of patients with mild disorders, who have received concentrate on a single or several occasions and contracted HCV, but have not been followed up and tested.

All patients with bleeding disorders who received blood products before 1992 should be tested for HCV antibody using a third generation ELISA test. Patients

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who are HCV antibody positive should undergo HCV RNA PCR testing to determine if they have a chronic infection. Quantification of HCV RNA and HCV genotyping are required for the pretreatment evaluation of the patients [2]. HCV RNA negative patients who have cleared the infection naturally should be counselled, but long-term hepatology follow-up is usually not required.

Assessment of liver disease severity

Major progress has been made recently in the investigation and management of HCV. Non-invasive methods and techniques, such as biomarkers and liver transient elastography (fibroscanning) have been developed as an alternative to liver biopsy for assessment of HCV-associated liver fibrosis.

A number of algorithms based on biochemical test results, including the aspartate aminotransferase to platelet ratio index (APRI score), Fibrometer, FIB-4 and Fibrotest have been developed to predict the severity of the liver disease. These non-invasive tests are useful in defining patients with cirrhosis or with only mild liver disease, but present limitations in the assessment of intermediate stages of disease [4]. Few studies have been performed assessing these methods in HCV-infected haemophilia patients.

Liver transient elastography (fibroscanning) is becoming an alternative to liver biopsy and appears preferable in patients with hereditary bleeding disorders [5]. A probe is placed over the liver and delivers an ultrasound pulse wave. The degree of propagation of the ultrasound shear wave is recorded as a numerical value, the fibroscan score, which is inversely proportional to the elasticity of the liver so is a measure of fibrosis

deposition. Transient elastography may be unsuccessful in patients with high BMI in whom serum markers of fibrosis or liver biopsy may provide an alternative means of assessing liver fibrosis stage. However, a probe suitable for the examination of obese patients is now available (XL Probe).

The combination of biomarkers and fibroscanning (Fig. 1) may be useful to improve the accuracy of liver fibrosis prediction [6]. Both types of method indicate fibrosis severity but not the cause of the fibrosis. When the cause of the liver disease remains uncertain or multifactorial, examination of liver histology may be necessary.

Treatment of chronic HCV infection with pegylated interferon and ribavirin

The pharmacological treatment of HCV in patients with hereditary bleeding disorders is no different from that of other infected individuals and should follow established guidelines, such as those recently published by the American Association for the Study of Liver Diseases [2] and the European Association for the Study of the Liver [7].

Pegylated interferon (PegIFN) and ribavirin combination therapy is the present standard treatment for HCV infection with non-1 genotype. This regimen should be offered to treatment-naive patients with chronic HCV-related liver disease, and patients who have failed to respond to or relapsed following previous interferon monotherapy or standard interferon and ribavirin combination therapy.

It is recommended that HCV RNA levels are checked at 4 weeks and 12 weeks to assess the initial viral
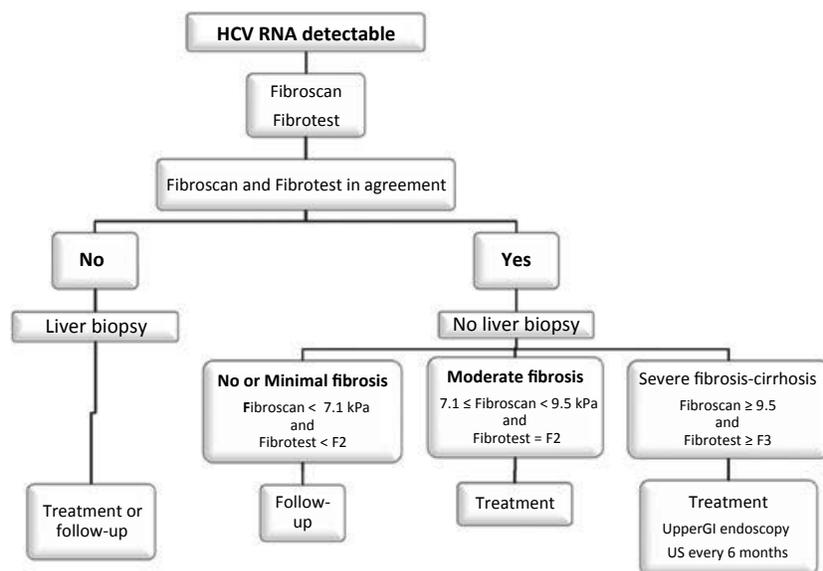

Fig. 1. Proposed algorithm for patient management according to Fibrotest and Fibroscan results [11].

kinetic responses to treatment [7,2]. A rapid virological response (RVR – defined as clearance of HCV at 4 weeks) is highly predictive of achieving a sustained virological response (SVR – defined as undetectable HCV RNA 24 weeks following discontinuation of therapy) independent of genotype. Early virological response (EVR – defined as at least a two log reduction in viral load) is assessed at 12 weeks. Absence of an EVR is highly predictive of failure to achieve SVR, especially in patients with genotype 1 and treatment should be discontinued. Patients not achieving a complete EVR (undetectable HCV at week 12) should be retested at 24 weeks and if HCV RNA is still detectable treatment should be discontinued. Patients with genotypes 2 and 3, who achieve either an RVR or complete EVR should be treated for 24 weeks.

Genotype 1 patients who have an RVR can also discontinue therapy at 24 weeks, without reducing their chances of achieving an SVR. However, it is recommended that patients with genotype 1 infection who do not have an RVR, but achieve complete EVR should be treated for a total of 48 weeks.

In patients with genotype 1 infection who achieve a partial EVR (>2 log reduction in viral load at 12 weeks but not complete clearance) and eventually clear their virus between 12 and 24 weeks consideration can be given to extending treatment to 72 weeks to improve the chances of achieving an SVR. However, standard practice is to stop treatment at 48 weeks and if SVR is not maintained to consider retreatment with newer HCV medications.

In patients with chronic HCV infection which have progressed to cirrhosis, the risk of development of HCC is 3–6% per year [8]. The relative risk of HCC is significantly reduced in treated compared with untreated patients. Although the relative risk in patients successfully treated with interferon/ribavirin is low compared with non-responders, as the risk remains patients with cirrhosis who achieve SVR should continue to be monitored at 6-monthly intervals for the development of HCC.

A meta-analysis of the treatment of chronic HCV infection in haemophilic patients has reported that the overall SVR rate to PegIFN/ribavirin was 61% in HIV-negative individuals with a rate of 45% for genotype 1 and 79% for non-1 genotypes [9,10].

Patients with normal transaminases

HCV RNA PCR positive patients with persistently normal ALT are more likely to have slower progression of liver disease and earlier stages of liver fibrosis.

However, they should undergo an assessment of liver fibrosis similar to patients with elevated transaminase levels to enable appropriate management decisions to be made.

Patients with cirrhosis and liver failure

Patients with established cirrhosis are especially difficult to treat and should be managed in specialist hepatology units.

Patients with liver failure, especially with associated features including ascites, variceal bleeding, encephalopathy, leucopenia and thrombocytopenia should not receive PEG interferon/ribavirin treatment as the risk of serious adverse events, such as life-threatening infection and acceleration of hepatic decompensation is high [11]. These patients should be referred to Hepatology units working with a liver transplantation programme.

Predictors of response

Factors which are associated with a reduced chance of achieving SVR include a high pretreatment HCV viral titre, failure to achieve RVR or EVR, genotype 1 infection, presence of cirrhosis, older age at the time of infection and African racial origin.

A genetic polymorphism near the IL28B gene encoding for interferon-λ-3 has been identified as being associated with a twofold difference in response to PegIFN/ribavirin treatment [12]. Testing for the IL28B polymorphism can now be performed in most hepatology reference centres and can provide useful information to decide which treatment regimen to start.

HIV/HCV co-infected patients

HCV RNA should be assessed in all HIV-positive persons, as approximately 6% of these individuals fail to develop detectable HCV antibodies so a negative antibody test result should not be interpreted as indicating that the patient does not have HCV infection.

The management of these patients has been reviewed recently in the UKHCDO guidelines [10]. Patients coinfected with HIV and HCV have an approximately twofold greater risk of developing cirrhosis, and progress more rapidly to liver failure compared with HCV monoinfected individuals. The importance of the need to treat HCV in this patient group should therefore be emphasized. To optimize response to anti-HCV treatment, HIV infection should be fully suppressed using HAART. HAART regimens should not include zidovudine (AZT) as this is contraindicated with ribavirin because of the potential for severe anaemia. Didanosine and stavudine should also be avoided because of the interaction with ribavirin and the risk of potentially fatal lactic acidosis. The impact of abacavir on treatment responses to HCV combination therapy is currently debated.

HIV non-progressors who are maintaining normal CD4 counts, not on HAART should also be encouraged

to undertake HCV treatment. Co-infected patients have lower SVRs with PegIFN/ribavirin treatment compared with monoinfected individuals. In the meta-analysis reported by Franchini, coinfected patients had an overall SVR of 29% [9].

Clinical trials of protease inhibitor based triple therapy are currently ongoing in HIV/HCV coinfected patients to assess, safety and efficacy, as well as drug–drug interactions which can be problematic in this patient population.

New anti-HCV agents

The first direct acting antivirals belonging to the class of protease inhibitors (boceprevir, telaprevir) have been recently approved, but are restricted to the treatment of HCV genotype 1 infections [13]. As a result of the viral genome variability which is responsible for the rapid emergence of drug resistant virus, when these drugs are administered in monotherapy, protease inhibitors have been approved in combination with pegylated interferon and ribavirin. The rates of sustained virologic response (SVR) have increased by 30% compared with previous standard of care, reaching approximately 75% in clinical trials for treatment naive patients (Figs 2 and 3) [7,14]. Trial results suggest combination therapies including PegIFN, ribavirin and protease inhibitors increase the SVR rates for genotype 1 naive patients compared with present standard treatment; moreover, using response guided regimens, shorter treatment periods can be given to those genotype 1 patients achieving RVR [14,15].

In treatment experienced patients, the SVR rates are approximately 80–90% in relapsers, 50% in partial responders and 30% in null responders [14,15]. Clinical studies are ongoing for the treatment of HIV co-infected patients. To our knowledge, no specific study has been reported so far in haemophilic patients.

These regimens are associated with an increased rate of side effects, especially in cirrhotic patients, and subject to drug–drug interactions. Patient counselling through treatment education programme is therefore highly recommended to provide an optimal patient management.

Other classes of direct antivirals are being evaluated in clinical trials with the hope of developing interferon-
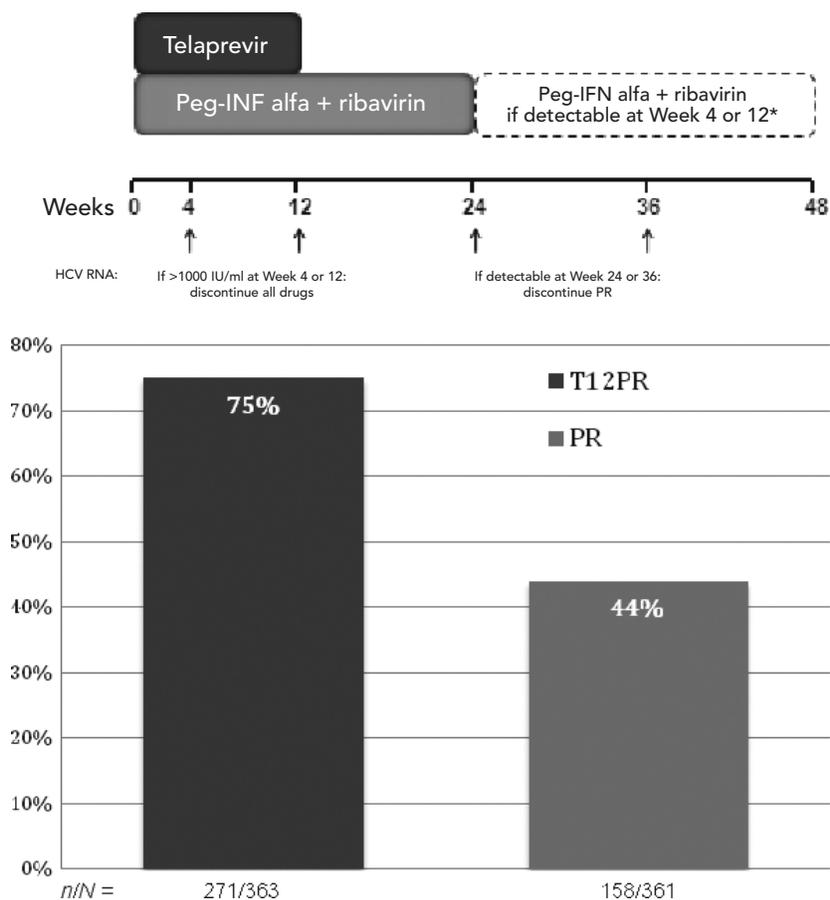

Fig. 2. Telaprevir regimen in G1 HCV-infected patients: SVR rates in treatment naïve without cirrhosis.
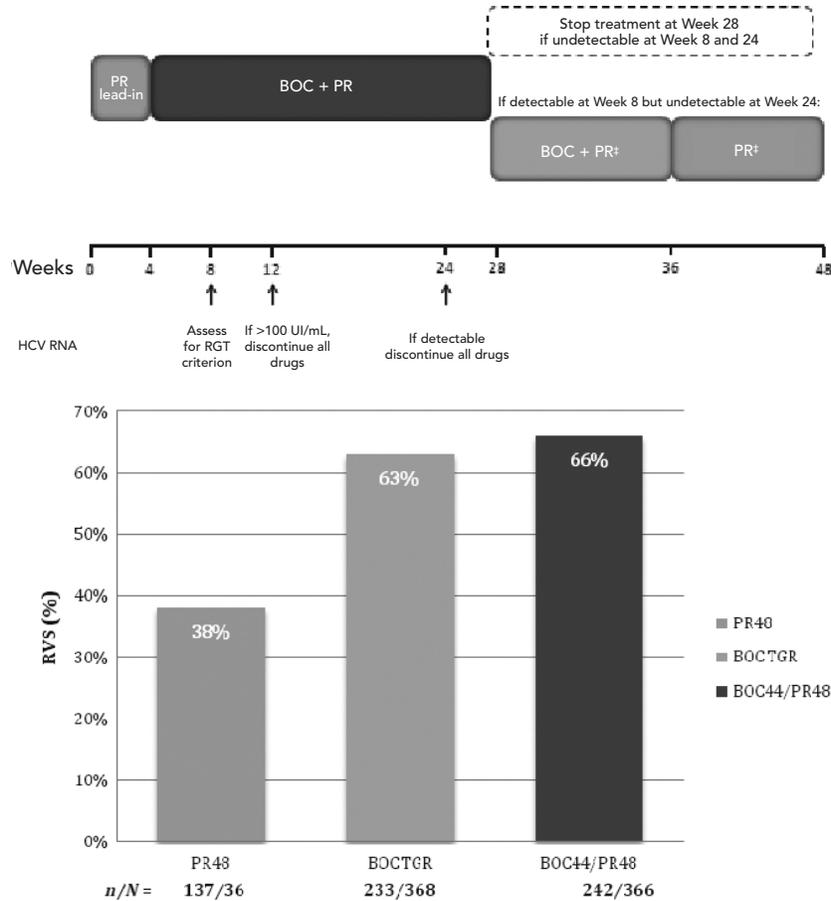
Fig. 3. Boceprevir regimen in G1 HCV-infected patients: SVR rates in treatment naïve without cirrhosis.
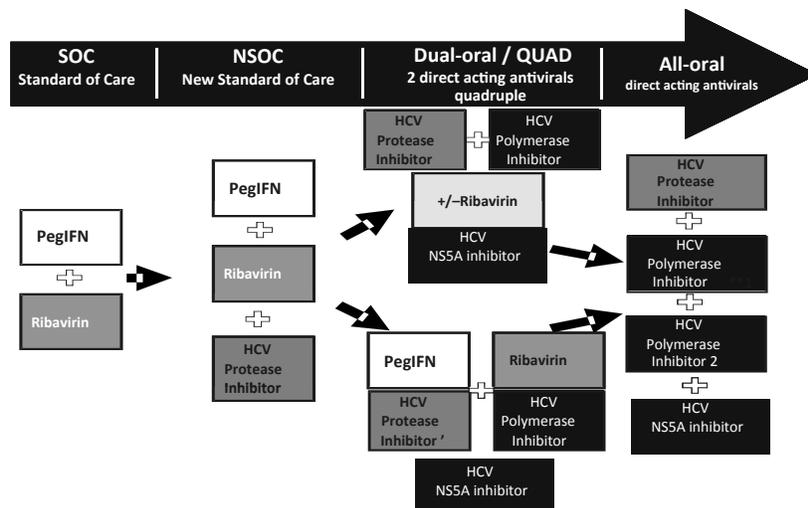
Fig. 4. Current and future HCV treatment regimens.

free regimen with even higher rates of SVR for all main HCV genotypes. These include new generation protease inhibitors, nucleoside and non-nucleoside polymerase inhibitors, NS5A inhibitors and other classes of antiv-irals. These new developments provide hope that in a near future chronic hepatits C will become a curable disease in most patients including the currently difficult to treat patients. A recent proof of concept study has

shown, in treatment-naive patients, that combination of an HCV protease inhibitor and polymerase inhibitor can be highly effective in suppressing HCV, providing new hope that future curative treatment regimens may be interferon free [16]. Another proof of concept study also showed that in patients who were null responders to a previous course of pegylated interferon and ribavirin, the combination of protease inhibitor and NS5A inhibitor without interferon may lead to clearance of viral infection in approximately 30% of these difficult to treat patients, whereas this SVR rate almost doubles when patients received a quadruple therapy including pegylated interferon and ribavirin [17].

Perspectives

Major advances have been made in the past 5 years in the management of chronic hepatitis C. The use of non-invasive methodologies for the assessment of liver disease severity has improved patient access to care and treatment; this had a clear impact on the management of patients with hereditary bleeding disorders. New treatment algorithms based on pre- and on-treatment predictive factors of response have been validated to optimize the chance of treatment success and to shorten treatment duration. The recent development of new direct-acting antivirals (HCV protease inhibitors) in combination with pegylated interferon and ribavirin provides an immediate treatment option for the most difficult to treat patients who are in need of treatment (patients infected with genotype 1 HCV with advanced fibrosis). Further studies are ongoing in special patient populations including HIV/HCV co-infected patients to increase the rate of SVR. There are still many challenges to decrease the risk of side effects and drug–drug interactions. On the other hand, clinical trials are currently ongoing with antivirals belonging to newer classes with the hope of interferon-free treatment regimens and pangenotypic activities (Figure 4). Doubtless, patients with hereditary bleeding disorders should benefit from these new developments in the near future.

Disclosures

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