Natural history of hepatitis C

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Summary

There has long been evidence that hepatitis C can lead to persistent infection in a high proportion of infected individuals, and can progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). The transition from acute to chronic hepatitis C is usually sub-clinical. Accurate studies of the time course for clearance of acute hepatitis C are difficult to carry out because of the silent onset of the acute disease. The likelihood of spontaneous HCV resolution is associated with several genetic factors, including *IL28B* inheritance and the DQB1*0301 allele of the major histocompatibility complex class II. Most data suggest that resolution in the acute phase without progression to chronic disease is not accompanied by significant disease, but minor histological lesions have been observed in anti-HCV positive, HCV RNA negative individuals. The risk of reinfection remains a possibility after clearance of acute hepatitis C. High rates of sexually-transmitted infection are being reported in HIV positive men who have sex with men (MSM). Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world. The natural history of the chronic disease remains incompletely defined. It is generally a slowly progressive disease characterized by persistent hepatic inflammation, leading to the development of cirrhosis in approximately 10–20% of patients over 20–30 years of HCV infection. However, the published data indicate varying progression rates to cirrhosis. Overall, once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation. Following an episode of decompensation the risk of death in the following year is between 15% and 20%. The high number of chronically infected individuals, the burden of disease, and the absence of a vaccine indicates that treatment will form part of the disease control but the impact, effectiveness and outcomes of treatment in various groups remain uncertain. Several studies and meta-analysis have concluded that eradication of HCV with antiviral therapy reduces the risk of HCC in patients with chronic hepatitis C, independent of fibrosis stage, but the risk is not eliminated.

Introduction

Non-A non-B hepatitis was formerly identified as a putative viral hepatitis occurring after transfusion of blood products or intravenous drug use. There was evidence that non-A non-B hepatitis could lead to persistent infection in a high proportion of infected individuals, and could progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). HCV was discovered to be the major cause of non-A non-B hepatitis in 1989, and is now known to be a leading cause of chronic liver disease in both industrialised and developing countries. Within Europe the sero-prevalence increases with age with a peak prevalence occurring in 55–64 year old patients; Southern and Eastern Europeans have the highest peak prevalence [1].

The high number of chronically infected individuals, the burden of disease and the absence of a vaccine indicates that treatment will form part of the control of the disease. However the majority of those with persistent infection are unaware of the infection, and screening programs to identify patients will be required to prevent silent progression of the disease [1,2]. The high prevalence and incidence of hepatitis C necessitates that treatment to prevent disease forms part of the perceived strategy to limit control of the disease, but the impact, effectiveness and outcomes of treatment in various groups remains uncertain. The overall impact of treatment for patients with mild or advanced disease may differ, and the effect of widespread treatment on the future burden of disease will need ongoing evaluation, particularly to reduce the prevalence of infection and disease.

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Key Points

Acute hepatitis C
- Up to 4 million people are newly infected with HCV annually

- The acute illness is clinically mild and is typically unrecognised and undiagnosed

- Between 18-34% of infected individuals spontaneously clear HCV

- Acute resolution of HCV is not associated with any long-term sequelae

- Treatment is indicated in patients who are deemed to develop chronic hepatitis

Chronic hepatitis C
- Is the leading cause of end-stage liver disease, hepatocellular carcinoma and liver related deaths in the Western world

- The effects of chronic hepatitis C extend beyond liver related morbidity and impact on the overall quality of life

- Fibrosis progression rates are extremely variable and are influenced by host, viral and environmental factors

- Achievement of a sustained virologic response (SVR) is associated with a reduction in portal hypertension, hepatic decompensation, hepatocellular carcinoma and liver related mortality

- Following liver transplantation fibrosis rates are accelerated with graft cirrhosis rates of 30% at 5 years

Acute hepatitis C

Populations at risk of acute hepatitis C are patients who received blood transfusions, blood products or anti D immunoglobulin in pregnancy prior to 1990, before routine screening of blood products for HCV, intravenous drug users and intra nasal cocaine users, patients with tattoos or body piercings, heath care workers, dialysis patients, and those partaking in high risk sexual activities. Since the introduction of routine screening of blood products and sterile injection needles the principal cohorts of newly infected patients has changed. The majority of patients presenting as new cases in developed countries now are people who inject drugs and men who have sex with men [3]. Estimates of the annual incidence indicate that three to four million persons are newly infected each year and 350,000 people die annually from HCV related causes [4]. The acute illness is clinically mild and typically unrecognised and thus, it is only infrequently diagnosed, particularly in those who progress to chronic hepatitis. After six months of persistence of HCV RNA within the blood the infection is defined as being chronic. The transition from acute to chronic hepatitis C is usually sub-clinical. The initial features of the acute illness are non-specific flu-like symptoms.

They are not diagnostic of HCV in particular, as they are common to many acute viral infections. More specific symptoms of viral hepatitis can be encountered in a minority of individuals: jaundice, dark urine, anorexia, aversion to smoking among smokers and abdominal discomfort may occur. Physical findings are usually minimal, apart from jaundice in a third of patients. Chronic hepatitis is the most common outcome, usually characterized by raised serum aminotransferases and may lead to fibrosis and cirrhosis in the liver. Thus chronicity is the major complication of acute hepatitis C.

Accurate studies of the time course for clearance of acute hepatitis C are difficult to carry out because of the silent onset of the acute disease. Studies to determine the rate of persistence are few and may be biased by the mode of ascertainment. They frequently involve the prospective study of symptomatic individuals, who are more likely to clear the virus [5,6]. Asymptomatic individuals are more difficult to identify for obvious reasons. In the studies that are available, it is frequently stated that 15–40% of individuals resolve their acute disease and do not progress to chronic hepatitis, based largely on retrospective studies of post-transfusion hepatitis. This range points to a degree of uncertainty. Factors such as the immune response, determined by host genetics, gender, mode of acquisition, the severity of the acute illness, presentation with jaundice, a poorly defined weak immune response, immunosuppression with for example corticosteroid treatment, which can affect clearance of HCV, HIV co-infection, are all determinants of the acute response. This means that the time course of clearance is difficult to establish with certainty. The likelihood of spontaneous HCV resolution is associated with several genetic factors, including *IL28b* inheritance and the DQB1*0301 allele of the major histocompatibility complex class II2 [5,7,8].

Grebely *et al.* showed among 632 individuals with acute hepatitis C that spontaneous clearance occurred in 173 of 632, and at 1 year after infection, 25% had cleared HCV [6]. Among those with clearance, the median time to clearance was 16.5 weeks with 34%, 67%, and 83% demonstrating clearance at 3, 6, and 12 months. Female sex was associated with clearance. Although there have been few opportunities for longitudinal studies of acute hepatitis, those which are available show considerable variance: a review of 675 individuals showed that clearance of infection ranged from 0% to 80% with a weighted mean of 26% [9]. Females were more likely to clear than males (40% *vs.* 22%) and patients with identified clinical infection were more likely to clear than those that were identified through serological incidence studies (revealed by seroconversion from negative to positive anti-HCV) (31% *vs.* 18%). Wang *et al.* indicated that 18% of 67 individuals had spontaneously cleared hepatitis C after 6 months of follow up [9]. Yeung *et al.* showed that 28% of 157 children cleared HCV [10]. Importantly Cox *et al.* studied 179 anti-HCV negative injection drug users [11]. After prospective evaluation 62 (34%) had seroconverted to anti-HCV. HCV RNA was measured by Cobas Amplicor test (RT PCR) and by transcription mediated amplification (TMA, Chiron). Detectable RNA typically preceded detection of the antibody by 5–6 weeks and HCV RNA detection typically preceded elevation of ALT [11]. In a subset of the cohort, 20 patients cleared viraemia. Viral recovery was defined as the presence of anti-HCV antibody with HCV RNA undetectable by the COBAS assay obtained during at least 2 consecutive visits more than 300 days after initial detection of viraemia. Their paper illustrates several patterns of viraemia during acute hepatitis C. No

subjects had jaundice. It is however noteworthy that although ALT increases from baseline were noted for several individuals, the early increases in ALT concentrations (from baseline) still fell within the normal range. In subjects with viral persistence, a stable level of HCV RNA was noted within 60 days of initial detection of viraemia, but in others, stable viraemia was not apparent until more than 1 year later. In subjects with long-term viral clearance HCV RNA became undetectable as early as 94 days but as late as 620 days after initial viraemia. Some patients showed patterns of viraemia in which periods of detectable viraemia were separated by intervals in which HCV RNA could not be detected (viral sequence data excluded reinfection, but re-infection could be detected in one subject with persistence). These data point to a spectrum of viral load declines and variable rates of clearance of acute hepatitis C. A similar proportion of patients with genotype 4 may clear the acute infection [12].

In persistently infected persons neutralizing antibody responses have been shown to be broader in persons who controlled viraemia and were detected earlier [13]. A strong IFN-gamma-mediated antiviral NK cell response was associated with a self-limited course of acute hepatitis C in HIV positive patients [14]. IFNL4 ss469415590 polymorphism has been strongly associated with response to IFN therapy in HCV-positive HIV-negative individual's but not in HIV-positive patients.

Most data suggests that resolution in the acute phase without progression to chronic disease is not accompanied by significant disease, but minor histological lesions have been observed in anti-HCV positive, HCV RNA negative individuals. Haydon *et al.* found that ten of 12 patients who were RT-PCR negative for HCV RNA in serum were RT-PCR positive in liver; however, this group had significantly lower intrahepatic HCV concentrations and serum ALT levels. Some had cirrhosis. The significance of these lesions and their relationship to acute resolved hepatitis C remains doubtful [15]. The impact of ongoing alcohol use in anti-HCV positive, HCV RNA negative individuals remains important: McMahon *et al.* compared survival data from subjects that were chronically infected with those who recovered from HCV infection, stratified by alcohol use. No difference was discerned among heavy alcohol users in the incidence of liver related deaths or end stage liver disease in those with chronic HCV, compared with those recovered from HCV infection [16].

The effects of treatment of acute hepatitis C

Treatment is indicated in patients who are deemed to develop chronic hepatitis. This time frame is somewhat arbitrary because the transition between acute and chronic hepatitis C is not clearly delineated as some patients remain viraemic for longer than six months during the acute phase. Although it is important to recognise the disease in the acute phase, it is frequently unrecognised. Intervention with IFN, or IFN and RBV for hepatitis C, to reduce the risk of chronic hepatitis, is required and indeed is frequently applied in patients with acute hepatitis C before six months of viraemia have ensued. Pegylated IFN (PEG IFN) with or without ribavirin (RBV) for 24 weeks or longer induces high rates of viral clearance. The optimal treatment regimen and guidelines for the appropriate time to treat have not yet been standardized. Symptomatic hepatitis C is less likely to progress to chronic hepatitis C. Response rates are lower in patients treated later than 20 weeks post infection. If the HCV RNA remains positive after 12 weeks of

observation it is reasonable to consider that therapy should be initiated. There may be a benefit in treating all viraemic patients who have not spontaneously cleared the virus by 12 weeks after onset because of the risk of loss to follow-up in at risk patients. Newer antiviral agents may alter this thinking.

A pilot study of combination therapy with telaprevir, PEG IFN, and RBV in acute genotype 1 HCV infection in HIV-infected men has been completed. In the telaprevir group, 84% (16/19) of men achieved SVR 12% *vs.* 63% in a prior comparator group. Most patients (81%) who achieved SVR in the telaprevir group received 12 weeks of treatment [17].

Reinfection after clearance of acute hepatitis C

The risk of reinfection remains a possibility after clearance of acute hepatitis C. High rates of sexually-transmitted infection are being reported in HIV positive men who have sex with men (MSM). Re-screening for active hepatitis C will be necessary in HIV positive MSM after a single antibody test or following spontaneous or treatment-induced resolution because of the substantial incidence of hepatitis C in this group [18]. The Australian Trial in Acute Hepatitis C (ATAHC) defined re-infection and super-infection as detection of infection with an HCV strain distinct from the primary strain after spontaneous or treatment-induced suppression. Among 163 patients, 111 were treated, and 60% achieved SVR. However, recurrence was observed in 19%: 12 with relapse and five with reinfection (4.7 cases per 100 person-years). Reinfection occurred more frequently in those with ongoing injecting drug use. Reinfection in intravenous drug users, has been described, based on Sanger sequencing. However, interestingly pyrosequencing has suggested that previously undetected variants present in the post-treatment sample could represent the emerging dominance of pre-existing minority variants rather than reinfection [19].

Relative prevalence reductions have been predicted with varying treatment rates and sustained virological response rates in people with injecting drug use (PWID). The impact on prevalence will hopefully be increased with higher rates of treatment and higher rates of SVR; reinfection rates may however increase with simpler IFN free treatments, unless behavioural changes accompany treatment [20]. Prevention models are being examined. MSM who clear HCV infection remain at high risk of reinfection [21].

Chronic hepatitis C, its outcome and the effect of treatment

Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world. It is generally a slowly progressive disease characterized by persistent hepatic inflammation leading to the development of cirrhosis in approximately 10–20% of patients over 20–30 years of HCV infection. However, the published data are variable with progression rates to cirrhosis quoted from as low as 2–3% to as high as 51% over 22 years [22,23]. It is not uncommon for patients to remain undiagnosed with hepatitis C until they present with the complications of end stage liver disease. Once cirrhosis is established the disease progression remains unpredictable: cirrhosis can remain indolent for many years in some patients whilst progressing in others to hepatocellular

carcinoma, hepatic decompensation and death. Overall once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation. Following an episode of decompensation the risk of death in the following year is between 15% and 20%.

The natural history of the disease remains incompletely defined. Patient cohort studies have included heterogenous populations and often have many co-founders, which can impact on the progression of hepatic fibrosis. The above complexities have resulted in the majority of published studies being retrospective, with prospective studies limited due to the difficulty identifying patient cohorts and the long length of follow-up required to reach meaningful end points. Retrospective data regarding the natural history of hepatitis C after treatment have several limitations. First, it is likely to be skewed towards patients whose disease has resulted in hepatic complications and hence sought medical input. The timing of the initial infection will be based on patient's recall of first contact with blood products or intravenous drug abuse which can often be inaccurate. In retrospective studies, cirrhosis rates have been reported to be between 17% and 55%, HCC rates 1% and 23%, and liver related death 1% and 23% over an estimated infection period between 20 and 30 years [22,24,25].

Prospective data are available regarding the natural history of hepatitis C but it are limited by relatively short follow-up periods and are only available in well-defined patient cohorts. Data obtained from prospective studies typically show lower complication rates as these studies are not reliant on patients seeking medical care to be identified. One such cohort were women infected with hepatitis C following administration of anti D immune globulin during pregnancy. Over a follow-up period of 18–20 years the incidence of histologically confirmed cirrhosis was reported to be between 1% and 2% and bridging fibrosis between 2% and 10% [26]. A further community based study in America identified hepatitis C antibodies in over 1500 young intravenous drug abusers who were followed for a median of 8.8 years [27]. Over this time period 10% of patients spontaneously cleared the virus, 4.4% developed end stage liver disease and a further 2% were identified as having cirrhosis histologically [27].

Recent data have demonstrated that development of hepatic fibrosis in hepatitis C is multi-factorial and many co-factors have been identified which increase an individual's risk of developing significant fibrosis or cirrhosis. These include age at infection, male gender, alcohol consumption, obesity, insulin resistance, type 2 diabetes, co-infection with hepatitis B or HIV, immunosuppressive therapy and genetic factors. Regressive variables that influence fibrosis rates may change with time and hence disease progression of hepatitis C is not necessarily linear [28].

Due to the complex array of variables influencing disease progression it is thus difficult to define prognosis at an individual level and hence, the overall impact of treatment at various stages and patterns of disease. An understanding of the natural history of chronic hepatitis C and its long-term consequences is critical to enable appropriate decisions regarding monitoring *vs.* the need and urgency for treatment and the risks and benefits of treatment.

Although hepatitis C causes persistent hepatitis, the RNA viral genome does not integrate into the host genome and viral replication can be curtailed and a virological cure achieved by treatment. Accepted cure is defined as undetectable HCV RNA in serum at 12–24 weeks following completion of treatment (sustained virological response, SVR). Our understanding of the

natural history of the disease is also important in estimating the benefits of a treatment and the effect of achieving an SVR.

Spontaneous resolution of chronic hepatitis C is relatively rare, but can occur. Although only a few longitudinal or retrospective studies have been reported, the majority of HCV RNA patients remain positive. Watanabe *et al.* followed 435 HCV RNA positive patients for a follow-up period of a mean of 7.2 years [29]. 16/453 patients (3.7%) became RNA negative. Rates of 0.5% loss per year per person were observed. Aminotransferase normalization was always preceded by clearance of serum HCV RNA, which remained negative throughout the follow-up. HCV RNA was found in the peripheral blood lymphoid cells, but not in the serum after convalescence. These results imply that HCV RNA can persist at very low levels in the serum, peripheral lymphoid cells and brain, and that an intermediate replicative form of the HCV genome can persist in peripheral blood mononuclear cells for many years after apparently complete spontaneous or antiviral therapy-induced resolution of chronic hepatitis C.

In asymptomatic patients who test positive for anti-HCV antibodies, small quantities of HCV RNA commonly persist, even in patients who test negative for HCV RNA in serum by commercial tests. These viral genomes may however be defective. Moreover, it is known that hepatitis C can persist without apparent liver disease or raised serum ALT. Low-grade hepatitis, and even low-grade fibrosis can occur in those patients with HCV and "normal serum aminotransferases" (which are actually higher when compared to a cohort of healthy individuals) but fibrosis progression may be less rapid in females with low or normal ALT [30]. Moreover, in HCV patients with "a normal ALT" who received antiviral therapy, further decline in ALT is observed in virological responders.

Fibrosis progression in HCV

Chronic hepatitis C infection causes cirrhosis in approximately 16% of patients over 20 years [28]. However, fibrosis progression rates are extremely variable and can be influenced by host, viral and environmental factors. The rates of progression are not linear and may vary between fibrosis stages and accelerate with duration of infection or aging [31,32]. In patients who have had hepatitis for 30 years cirrhosis rates are estimated at 41%, almost 3 times higher than the rates predicted at 20 years duration [28].

Serial biopsies in patients with hepatitis C have shown annual rates of fibrosis progression to be between 0.1 and 0.2 stages per year [33,34]. Several factors have been identified, which increase an individual's risk of fibrosis progression. These factors include age, male gender, alcohol consumption of more than 50 g/day, obesity, insulin resistance, type 2 diabetes, co-infection with hepatitis B or HIV, immunosuppressive therapy, and host genetic factors. The rates of fibrosis progression increase significantly with age and data suggest that progression rates can be up to 300 fold higher in patients affected in their 7th decade compared to those infected in their 3rd decade of life. Male gender increases fibrosis rates up to ten fold, independent of age [35] and hepatic steatosis is associated with more severe inflammatory activity, fibrosis progression and a higher incidence of HCC [36,37].

Thein *et al.* have tried to address risk of fibrosis progression on an individualized level. They reviewed 111 studies totalling over 33,000 patients and developed models to calculate specific

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progression rates and cirrhosis risk for individual patients to help further stratify monitoring and surveillance. Once cirrhosis is established, patients have a 1–5% annual risk of HCC ad a 3–6% annual risk of hepatic decompensation (variceal haemorrhage, ascites, encephalopathy). Following an episode of decompensation the risk of death in the following year is between 15% and 20% [28].

Hepatitis C and HIV can share routes of transmission. Among patients infected with HIV, the HCV prevalence is 72–92% amongst IVDU's, 1–12% in men who have sex with men and 9–27% in heterosexuals. Co-infection with HIV has a negative impact on the natural history of HCV. Higher levels of circulating HCV RNA levels occur with a decreased response to IFN treatment, resulting in a more rapid progression of fibrosis and 2–3 times increased risk of cirrhosis and its associated complications [38,39]. Moreover, with improvement in anti-retroviral therapies for patients with HIV, liver related morbidity and mortality due to hepatitis C has become a major cause of mortality in the HIV-HCV co-infected patient population.

Hepatitis B and hepatitis C co-infection is also a frequent (and probably underestimated) occurrence due to shared modes of transmission and shared geographical areas where both viruses are endemic. The estimated prevalence of HBV-HCV co-infection is 5–20% in HBsAg positive patients and 2–10% in HCV positive patients, but with marked geographical variation [40]. The interaction between HBV and HCV is largely undefined due to the large number of virological and host variables making definitive conclusions difficult. There are data to support a higher prevalence of co-infection in patients with cirrhosis, hepatic decompensation and HCC although a recent meta-analysis did not confirm these findings [41,42].

Effects of treatment and SVR on fibrosis and inflammation

The majority of patients (57–94%) demonstrate marked improvements in their necro-inflammation and fibrosis scores following SVR [43–46]. However, a small minority (1–14%) of patients have demonstrated fibrosis progression following a sustained virological response [44,45,47]. Young age and platelet count at SVR are predictive of fibrosis regression. SVR was associated with improvement in activity scores and a mean reduction in the fibrosis score in patients with SVR and a lower rate of fibrosis progression in 187/487 patients who achieved SVR than those who did not attain SVR or in untreated patients [48].

The HALT C study showed that although serum aminotransferases, HCV RNA and histologic necroinflammatory scores all decreased significantly with maintenance of IFN treatment, there was no significant difference between the groups in the rate of any primary outcome. The percentage of patients with at least one serious adverse event was 38.6% in the treatment group and 31.8% in the control group. Long-term therapy with PEG-IFN did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, who did not have a response to initial treatment with PEG-IFN and RBV.

Most of the studies on the effect of treatment on fibrosis have been limited by lack of long-term follow up after treatment *vs.* untreated patients. Ongoing co-factors such as alcohol and metabolic syndrome are likely to play a significant role. This highlights the importance of ongoing follow-up of patients with advanced fibrosis and attempting to address all hepatic risk factors.

Achievement of SVR is associated with a reduction in portal hypertension, hepatic decompensation, and hepatocellular carcinoma [47,49,50]. Veldt *et al.* reported the outcomes in consecutively treated patients with chronic hepatitis C with histologically proven advanced fibrosis or cirrhosis. SVR was correlated with clinical outcomes, including death (liver or non-liver related), liver failure and hepatocellular carcinoma. Of 479 patients, 29.6% had sustained virologic response. The median follow-up was 2.1 years. SVR was associated with a statistically significant reduction in the hazard of events, an effect which was largely attributable to a reduction in liver failure.

Effects of treatment on portal hypertension and liver failure in HCV

Cirrhosis and portal hypertension are major determinants impairing SVR in IFN treated patients. Thus, disease severity is a major independent determinant of the rate of SVR in patients with advanced chronic hepatitis C, but arresting disease severity is the critical focus of treatment. Portal hypertension results as a consequence of progressive fibrosis and architectural remodelling of the liver as a response to ongoing inflammation. Hepatic fibrosis creates resistance to sinusoidal blood flow and results in increased portal venous pressure. Gastric and oesophageal varices develop as a result of the increased portal venous pressure. Overall gastro-oesophageal varices are present in 50% of patients with cirrhosis, but their incidence correlates with the severity of liver disease with a prevalence of 85% in patients with Child-Pugh C cirrhosis. Bleeding from ruptured oesophageal varices is the second highest cause of mortality, after HCC, in cirrhotic patients with hepatitis C [51,52].

In patients with hepatitis C the prevalence of upper gastrointestinal varices is approximately 16% with Ishak grade 3 to 4 fibrosis and 39% in patients with biopsy proven cirrhosis. In a recent study of 1016 patients only 12 (0.01%) had large varices (impingement of >50% of lumen). Furthermore, although many subjects with bridging fibrosis had varices, these were generally small or medium size with no high risk stigmata for bleeding. The incidence of varices in patients with cirrhosis or advanced fibrosis is estimated to be 6.5% per year, with a 1% per annum risk of variceal haemorrhage. In patients with pre-existing varices the annualized rate of progression was 8.8% [50,53].

Non-cirrhotic patients who have achieved SVR will not progress to liver failure or portal hypertension and do not need ongoing endoscopic surveillance. Patients with HCV cirrhosis who achieve SVR have a reduction in their portal pressure measurements when compared to non-responders [54]. Although achieving an SVR prevents the development of oesophageal varices in the majority of patients with compensated HCV cirrhosis, a recent prospective study showed that although the risk of developing varices post SVR was vastly reduced it was not eliminated, with a small number of patients developing small oesophageal varices (2/57) [55].

Effects of treatment on the HCC risk in patients with HCV

The incidence of HCC amongst HCV infected patients is between 1% and 3% at 30 years [56]. Once cirrhosis is established, *de novo* HCC develops at a rate between 1% and 4% per annum, with rates

highest in patients contracting hepatitis C from contaminated blood products [56,57]. Host factors, which increase an individual's risk of developing HCC, are similar to those factors described to increase progression rates to cirrhosis, and include HIV, HBV, alcohol and diabetes [57]. Once cirrhosis is established male sex, increasing age and severity of cirrhosis all increase the likely hood of HCC.

Interesting data regarding the incidence of HCC was obtained from the HALT C study. The overall rates of HCC development in cirrhotic patients was 7% over 4.8 years. Importantly, a significant number of patients with Ishak grade 3 or 4 fibrosis also developed HCC raising questions regarding what defines need for screening in cirrhotic and non-cirrhotic patient cohorts.

A key question is the efficacy of IFN plus RBV therapy in patients with HCV cirrhosis, and the development of HCC. The cumulative incidence of HCC in 132 HCV-cirrhotic patients receiving IFN alpha, during a median follow-up period of 37 months, has been reported: HCC developed in fewer patients with SVR suggesting that achieving SVR may decrease the incidence of HCC in patients with HCV-related cirrhosis [58]. Similarly, Ikeda *et al.* reported that the hazard ratio of developing HCC was reduced in IFN treated patients. In 606 patients with persistent normal ALT with or without HCV-RNA clearance the risk of HCC was significantly lower than that in untreated patients and those with abnormal aminotransferases [59].

Several studies and meta-analysis have concluded that eradication of HCV with antiviral therapy reduces the risk of HCC in patients with chronic hepatitis C, independent of fibrosis stage [60,61]. It has been suggested that achieving an SVR in patients with cirrhosis provides a 20% reduction rate in the incidence of HCC [62].

A recent meta-analysis published in Annals of Internal Medicine included 30 studies comprising of 31,528 patients from 17 different countries [60]. This study reported a 4.6% absolute reduction in developing HCC following SVR. Furthermore in patients with advanced liver disease achieving an SVR reduced the overall risk of developing HCC from 17.8% to 4.2% with a reduction in incidence from 3.3% per person year to 1.05% (CI 0.7–1.5%) per person year. Prospective data extracted from the HALT C cohort corroborated the above findings: following SVR the incidence of HCC reduced from 8.8% down to 1.1% over approximately 7 years follow-up.

Whilst achieving an SVR reduces the risk of HCC in patients with advanced fibrosis or cirrhosis, there is clear evidence that the risk is not eliminated [61]. Patients with advanced fibrosis or cirrhosis can develop HCC as long as 8–10 years or beyond SVR implying that ongoing surveillance for HCC needs to be continued in patients with advanced fibrosis/cirrhosis [63].

A recent study has tried to risk stratify patients further, by creating a scoring system based on age, platelets, alpha fetoprotein and fibrosis score [64]. Patients were divided into low, medium or high risk dependent on their score. In the low risk group 9 out of 657 patients developed HCC over 9 years equating to a 0.17% risk *per annum*, an incidence which is well below the incidence where screening is deemed cost effective. If this score is validated then it may help identify which patients should be recommended for long-term HCC surveillance.

In patients without pre-existing significant liver disease a SVR is associated with resolution of risk from liver disease and these patients can be discharged from ongoing follow-up. In those patients with advanced fibrosis or established cirrhosis, clearance of the virus lowers an individual's risk of hepatic complications but they remain at risk of decompensation and development of HCC and hence patients with cirrhosis or advanced fibrosis require ongoing longitudinal follow-up and HCC surveillance.

Hepatitis C, liver transplantation and the effects of treatment

The end stage of the natural history of HCV infection is decompensated cirrhosis, HCC and ultimately death. Liver transplantation (LT) is the only potentially salvage treatment option for such patients. HCV is currently the leading indication for LT in the Western world. In those patients who have achieved SVR, recurrence of hepatitis C in the graft does not occur despite immunosuppression, and liver transplantation outcomes are comparable to or even better than those patients transplanted for other indications. In those who are undergoing treatment whilst on the LT waiting list and achieve HCV RNA negativity but have not yet achieved an SVR, HCV recurrence can be reduced to approximately 30% [65].

In those patients that are HCV RNA positive at the time of transplantation, HCV reinfection infection of the graft is almost universal. Disease progression occurs at an accelerated rate in the post-transplant population when compared to the immunocompetent patient population. The rapid progression to significant fibrosis seen in HCV recipients impacts negatively on outcome with an overall 20% increased risk of mortality and 30% increased risk of graft failure when compared to other LT indications [66]. Whilst HCV recurrence is universal post LT, multiple factors influence the severity and rates of fibrosis post-transplant.

The graft is infected at reperfusion from circulating virons. Detectable HCV propagation and replication is discernable within hours [67]. Primarily due to profound immunosuppression, HCV RNA concentrations within the first weeks post transplantation are generally 1 log higher than levels prior to transplantation. Most patients develop histological evidence of recurrent hepatitis C between 4 and 12 weeks post-transplant which is often accompanied by a further steep rise in circulating viral RNA [67]. Chronic hepatitis is established between 3 and 9 months after transplantation; the clinical, biochemical and histopathological findings are similar to those seen in non-transplant HCV patients. However the rate of progression to fibrosis is more rapid.

Serial biopsies in patients with recurrent hepatitis C post-transplant have shown annual rates of fibrosis progression to be between 0.3 and 0.6 stages/year, (F0–4) compared to rates between 0.1 and 0.2 in immunocompetent patients [68,69]. The severity of the histological necro-inflammatory activity at 12 months is the best predictor of risk for developing cirrhosis at 5 years [70,71]. Cirrhosis occurs in up to 30% of those transplanted for HCV by 5 years post-transplant, compared to the average time for the development of cirrhosis in the non-transplant patient being 30 years [69,70]. Once cirrhosis has developed, the rate of decompensation is also accelerated with reports of 40% at 1 year and >70% at three years compared to <5% and <10% respectively in the immunocompetent patients.

A small percentage of patients transplanted for hepatitis C (2–5%) develop a unique acute severe aggressive form of hepatitis C recurrence between 1 and 6 months post-transplant. The syndrome of fibrosing cholestatic hepatitis is characterized by elevated bilirubin (>6 mg/dl) and a raised alkaline phosphatase level in the absence of biliary obstruction. Histologically there

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is severe hepatocyte ballooning, intrahepatic cholestasis and ductular proliferation in the absence of significant lobular inflammation or lymphoid aggregates. HCV RNA concentrations are typically extremely high and although the pathogenesis is poorly understood it is thought to be due to a direct cytopathic effect following massive hepatocyte repopulation with HCV. Despite occasional case reports of successful outcomes with AVT, the majority of cases rapidly progress to graft failure and death within the first 12 months following liver transplantation [72].

Patient and graft survival in HCV positive recipients is therefore not surprisingly reduced when compared to those patients transplanted for other indications [73]. In 2002 a multicentre European study reported 7 year graft and patient survival to be 51% and 55% respectively in HCV-positive recipients compared to 67% and 70% in HCV negative recipients [74]. Reasons for poor outcomes post-transplantation in patients with HCV are not restricted to HCV recurrence. Patients transplanted for HCV have a higher incidence of associated HCC when compared to other indications. Over the last decade the understanding of factors, which may impact negatively on patient and graft survival in HCV recipients, has improved significantly. This has resulted in improved outcomes post LT for HCV patients however they remain inferior to patients transplanted for other indications.

Following transplantation, immunosuppression therapy negatively impacts on graft fibrosis rates and survival. Immunosuppression is one of the only factors to impact on graft survival, which can be modified post transplantation, however, the optimal immunosuppressive strategy remains largely undefined and is still an area of uncertainty due to a lack of good evidence supporting superiority of individual or combinations of agents over others [75]. Fibrosis, secondary to hepatitis C recurrence, is expedited by the use of repeated boluses of corticosteroid therapy, and anti-lymphocyte antibodies used to treat rejection. Low dose steroids and slow tapering are associated with better outcomes than high dose maintenance or slow tapering. There are no data to support superiority of CyA vs. tacrolimus on HCV recurrence rates, however, tacrolimus is associated generally with better post-transplant outcomes when compared with cyclosporin. There may be a beneficial effect on long-term use of azathioprine in conjunction with tacrolimus, demonstrated in a randomised single centre controlled study. The mTOR inhibitors, sirolimus, and everolimus have been associated with significantly less fibrosis progression in animal models when compared to calcineurin inhibitor (CNI) therapies. Retrospective non-randomised studies in humans support this finding however but good quality studies are lacking.

Achievement of SVR with antiviral therapy significantly improves graft survival in hepatitis C virus mono-infected liver transplant (LT) patients. The benefit of HCV therapy in HCV-human immunodeficiency virus (HIV) co-infected liver transplant recipients are less well established. The low SVR rate and serious adverse event rate in this group highlight the crucial need for better tolerated and more efficacious HCV therapies for both mono infected and HCV-HIV co-infected transplant recipients [76,77].

IFN treatment of recurrent hepatitis C has not consistently improved histologic disease after virologic response, and carries a risk of allograft rejection [78]. Telaprevir and boceprevir have been utilised to treat post-transplant recurrent HCV. Preliminary reports indicated that higher SVR rates than achieved with PEG-IFN and RBV. Severe toxicity, particularly anaemia and sepsis, and drug-drug interactions with the calcineurin inhibitors

complicate the use of boceprevir and telaprevir. Discontinuation rates of up to 40 percent have been encountered.

There is therefore an urgent need to improve graft survival and patient outcomes in patients transplanted for hepatitis C or hepatitis and HCC. Unfortunately, IFN is contraindicated in patients with decompensated cirrhosis, and few patients can be treated therefore with IFN and RBV or IFN plus a direct acting antiviral to achieve a pre-transplant SVR. Fortunately, IFN treatment is being displaced by better tolerated and more effective combination direct antiviral (DAA) therapies. A preliminary report of the use of pre-transplant sofosbuvir and RBV for up to 48 weeks, to the day of transplant for patients transplanted for HCV and HCC (within Milan criteria), has resulted in a 64% post-transplant SVR rate. The duration of undetectable HCV RNA pre-transplant was the best predictor of response. The application of more potent regimens including the combination of sofosbuvir and an NS5a inhibitor, either daclatasvir or ledipasvir, or sofosbuvir plus simeprevir is likely to further reduce the risk of post-transplant recurrence. However, the safety, efficacy and duration of DAA combinations in patients with decompensated liver disease and high MELD scores has not been established. The outcomes after SVR in patients on a transplant waiting list are not yet known. It is possible that an SVR in patients may stabilize a proportion of patients. However, the proportion of patients who can be delisted, and the optimal duration of treatment, regimens and criteria that predict not only SVR but clinical improvement have yet to be ascertained. Similarly, the outcomes and safety in patients with decompensated cirrhosis not on a transplant waiting list are not yet known.

Sofosbuvir and RBV have been used for the treatment of recurrent post-transplant hepatitis C (all genotypes). Virological response rates of 77% after 24 weeks of treatment have been reported. Recently Kwo et al. reported that 96% of patients with genotype 1 post-transplant hepatitis C and mild (less than or equal METAVIR F2 fibrosis) treated with ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID RBV plus or minus RBV have SVR. CNI dosing was manageable over the duration of study. It is not yet clear how applicable this regimen would be for cholestatic hepatitis or decompensated cirrhosis. These landmark treatments, which will be improved with time, may greatly reduce the risk and complications of post-transplant HCV. Further follow-up to ensure the durability of response and effect on post-transplant HCV will be required and more information on drug-drug interactions are needed. The need for re-transplantation should be reduced. It is possible that all post-transplant recurrent hepatitis C will be treated rather than deferring treatment until the advent of severe disease. The optimal strategy to reduce post-transplant recurrence and the inclusion criteria to avoid decompensation during treatment pretransplant will be required as a matter of urgency.

Effect on extra-hepatic consequences of hepatitis C infection

Chronic infection with hepatitis C is known to cause several extra hepatic manifestations. Several diseases including sicca syndrome, lichen planus, type 2 diabetes and non-Hodgkin's lymphoma, have been reported. Overall 15–35% of patient with chronic HCV have circulating cryoglobulins. Of these between 5% and 25% will develop clinical consequences including mixed essential cryoglobulinemia, systemic vasculitis, peripheral

neuropathy, Raynaud's phenomenon, and membranoproliferative glomerulonephritis. The risk of developing a non-Hodgkins B cell driven lymphoma is increased, likely as a consequence of long-term B cell stimulation by the HCV. HCV is also recognized to influence several metabolic pathways, with patients more likely to develop insulin resistance, type 2 diabetes and increased rates of vascular disease [79,80].

Achieving SVR results in the resolution of immune complex extrahepatic manifestations, reduces the incidence of lymphoma, decreases the risk of type 2 diabetes and its associated complications and improves patients overall quality of life [81,82]. Due to reduction in the complications above, a sustained virological response is associated with a reduction in all cause mortality of 54%. Antiviral treatment with IFN-α leads to resolution of cryoglobulinemia and vasculitis symptoms in most patients who show a response to antiviral treatment [83]. A full analysis of the methodology of the studies, documenting the outcomes of these extrahepatic manifestations after resolution of the disease, is not possible in this review.

HIV co-infected patients

There are limited data on the effect of achieving SVR on the HCC risk in patients with HIV. In papers by Berenguer and Limketkai there were no reports of HCC in 254 co-infected patients who achieved SVR. In contrast, recent reports confirm data similar to the non-HIV population with a significant proportion of HCC developing in patients who have achieved SVR, confirming the need for ongoing tumour surveillance in this group [84].

In addition to improved overall survival, antiretroviral therapy has reduced long-term liver-related mortality in co-infected patients. This survival benefit will be further improved by effective hepatitis C therapies in co-infected patients, whose prognosis will be further improved. HCC in patients with HIV co-infection is increasing in incidence and has a poor prognosis with studies reporting a 10 fold increase in mortality [85,86]. Co-infection with HCV accounts for 93% of cases of HCC occurring in patients with HIV.

Treatment effect on health-related quality of life

Chronic hepatitis C infection is recognized to negatively impact on patients' quality of life both physically, mentally, emotionally and socially and the effects of hepatitis C extend far beyond liver related morbidity [87,88]. Several studies suggest that people with HCV may have a lower quality of life due to depression, chronic fatigue, fibromyalgia, and anxiety in comparison to the general population. During IFN treatment quality of life indices deteriorate largely due to an increase in depression [89]. Bonkovsky and other authors have shown that patients who had a sustained response to IFN therapy experienced significant improvements in perceived wellness and functional status [90]. However the effect of treatment on these parameters requires further study in an era of interferon-free therapy.

Treatment effect in PWID

Successful treatment will hopefully have a profound effect on the incidence and prevalence of HCV infection in PWID. Increasing the proportion of injecting drug users hepatitis C treatment, achieving a sustained virological response (SVR) is likely to have an impact on transmission, as has been modelled; it is as yet uncertain whether these models will translate into a reduced rate of infection [91].

Overall benefit on treatment

The overall impact of HCV treatment on survival has relied on surrogate end points. More systematic reviews have called into question the methodology of these assessments and their validity of the findings. A Cochrane review systematically evaluated the benefits and harms of PEG IFN plus RBV vs. IFN plus RBV for patients with chronic hepatitis C. The primary outcomes were liver-related morbidity, all-cause mortality, serious adverse events, and adverse events leading to treatment discontinuation, other adverse events, and quality of life. Twenty seven randomised trials with 5938 participants were included. PEG IFN plus RBV vs. IFN and RBV seemed to significantly increase the number of participants achieving SVR. However, the authors concluded that there was insufficient evidence of the potential benefits on the quality of life in patients with achieved sustained virological response. Further high-quality research is need to impact on the confidence in the estimate of patient-relevant outcomes. The authors concluded that SVR is still an unvalidated surrogate outcome for patient-important outcomes. Innes et al. suggested that the benefit of SVR should be considered in terms of two patient-important outcomes: a percent-probability that SVR confers additional life-years, and the percent-probability that SVR confers additional healthy life-years. The benefit conferred by SVR was lowest for patients aged 60 years with initially mild fibrosis and was highest for patients with initially compensated cirrhosis aged 30 years [92].

Cost effectiveness of cure

An analysis of the cost effectiveness is beyond the scope of this article. Most analyses have concluded that patients treated with PEG IFN, benefit, with up to 46% of patients experiencing an SVR in one of the trials. PEG IFN also appears to be relatively cost effective with cost per QALY estimates remaining generally under £30,000. Additional studies are needed for newer DAA therapies, particularly in patients with mild fibrosis. The most cost effective policy for reducing the prevalence of hepatitis C infection and hepatitis C related disease is also being debated, and various models and scenarios are being proposed [91].

Conclusions

Cirrhosis is the major determinant of disease due to hepatitis C. Thus, arresting severe disease and preventing the onset of severe disease is the critical focus of treatment. The relatively low impact and effectiveness of IFN and PEG IFN combined with RBV on disease burden should be altered by the advent of more efficacious and effective DAA therapies. Surrogate events point to treatment conferring an advantage and an effect of cure on the progression of hepatic fibrosis and clinical events, and probably on some extra-hepatic manifestations of the disease.

IFN free treatments are more likely to be accepted and could have an impact on the complications of cirrhosis that will be discernable in a few years. It is to be hoped that not only the risk of cirrhosis, decompensated cirrhosis but also HCC, will be substantially diminished. The effects of chronic alcoholism no doubt also need to be mitigated to reduce the future burden of disease related to hepatitis C.

However, these disease outcomes will require careful measurement. It is likely that the first effects will be noted by a reduction in hospital admissions and requirements for liver transplantation if patients with cirrhosis are identified and treated. A "curative" response to therapy offers hope for millions. Policy makers will however want proof of impact in patients who have indolent and not life-threatening disease, because of the magnitude of the infected population and the cost of current DAA treatments. Further control of disease will also necessitate safe blood product use, reduced rates of transmission among PWID education, safe injections in developing countries, and possible vaccination.

Conflict of interest

Geoffrey Dusheiko has received research support from Gilead Sciences, BMS, GSK, Janssen and Abbvie and has acted as an advisor to Gilead Sciences, BMS, GSK, Janssen, and Abbvie. R.H. Westbrook has nothing to declare.

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