Prevention of Hepatitis C Virus Infection and Liver Cancer

E. J. Lim and J. Torresi

1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer-related death worldwide (Lafaro et al. 2015). Incidence of HCC is highest in the less developed countries of Asia and Africa, with China accounting for over 50% of cases (Petrick et al. 2016). However, the rates of HCC have been increasing rapidly in America, Europe and Australia (Petrick et al. 2016), where the majority of HCC cases are attributable to chronic hepatitis C (HCV) infection (Choo et al. 2016). Of the more than 42,000 new cases of HCC in the United States in 2018 (http://seer.cancer.gov), an estimated 50–60% are related to HCV (El-Serag and Kanwal 2014). Although a strong association exists between chronic HCV and the development of HCC, the precise mechanisms by which HCV infection promotes HCC are uncertain. There is, however, good evidence to suggest that eradication of the virus in both cirrhotic and noncirrhotic HCV-infected patients reduces the subsequent risk of developing HCC (Morgan et al. 2013).

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2 Hepatitis C Infection

It is estimated that over 71 million individuals are chronically infected with HCV worldwide (Blach et al. 2017). HCV is transmitted via infected blood. Currently, in Western countries, acquisition of HCV occurs primarily through intravenous drug use and tattoos (Razali et al. 2007), whereas in Asia and Africa, infection mainly occurs through the use of contaminated blood products and medical instruments. In contrast to these modes, HCV transmission via sexual and perinatal routes is infrequent (Razali et al. 2007).

Following infection with HCV, up to 80% of patients are unable to clear the virus, resulting in chronic infection which may ultimately progress to cirrhosis in approximately 20% of individuals (Westbrook and Dusheiko 2014). The natural history of HCV infection is summarized in Fig. 1. The majority of chronically infected patients remain asymptomatic for many years, thus delaying both the diagnosis and treatment. It is often not until the development of complications of cirrhosis such as hepatic decompensation and HCC that these patients present to medical care, and around 15% of patients with chronic HCV will develop HCC (Rein et al. 2011).

3 Hepatitis C Virology

HCV belongs to the genus *Hepacivirus* in the *Flaviviridae* family (Forns and Bukh 1999). It has a single-stranded linear RNA genome of approximately 9600 nucleotides that encodes a large polyprotein of approximately 3000 amino acids (Bartenschlager et al. 2011). The structure of the HCV genome and functions of the various viral proteins are summarized in Fig. 2. HCV exists as six major genotypes with genotype 1 being the dominant genotype in the United States, Europe and Australia (Messina et al. 2015). Genotype 2 is primarily found in West Africa, genotype 3 is more prevalent in India and Southeast Asia, whereas genotype 4 is more commonly seen in the Middle East and Africa (Gower et al. 2014). Each

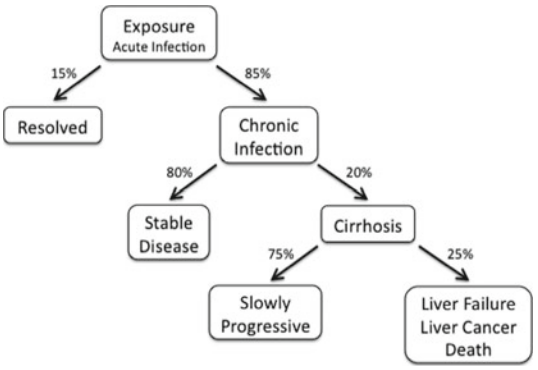

Fig. 1 Natural history of HCV infection. Adapted from Alter (1995)

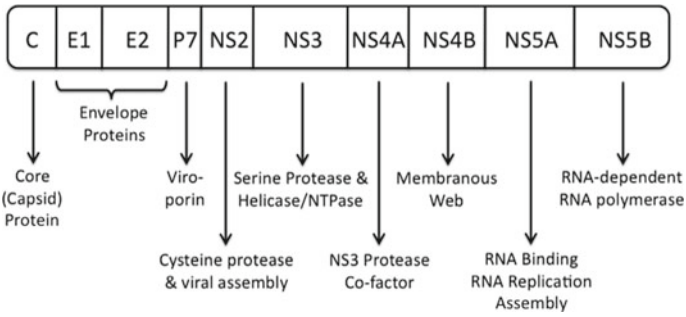

Fig. 2 HCV genome structure and functions of viral proteins. Adapted from Bartenschlager et al. (2011)

genotype contains multiple subtypes according to viral sequencing, identified with lower case letters (a, b, c, etc.). The HCV genotype may influence treatment response, severity of liver disease, and risk of HCC development, but the data are contradictory. A meta-analysis found that genotype 1b HCV infection was associated with a doubling of the risk of HCC development compared to infection with other genotypes (Raimondi et al. 2009). However, in a more recent cohort study of 100,000 patients, those chronically infected with genotype 3 HCV were found to have an 80% greater risk of HCC compared with genotype 1 chronic infection (Kanwal et al. 2014).

Like other RNA viruses, the RNA polymerase protein of HCV lacks proofreading ability and as a consequence, replication of the viral genome is error-prone resulting in a high mutation rate. The result is great genetic heterogeneity that leads to the evolution of diverse viral quasi-species. This viral diversity interferes with the development of effective host humoral immune responses against the virus thereby promoting viral persistence within infected individuals (Forns and Bukh 1999).

4 Hepatitis C and Associated Risk Factors for HCC Development

HCV is recognized as a major cause of HCC globally. In a large population-based prospective study, infection with HCV conferred a 20-fold increased risk of developing HCC compared to HCV-negative individuals (Sun et al. 2003). In another large prospective cohort study, HCV infection conferred a cumulative lifetime risk of HCC of 24% in men and 17% in women (Huang et al. 2011). This strong association between chronic HCV and HCC has been noted since the early 1980s, when the virus was known as non-A, non-B hepatitis (Kiyosawa et al. 1984). Almost all HCV-related HCCs occur in the setting of established cirrhosis, with cirrhosis itself being a strong independent risk factor for developing HCC (Tsukuma et al. 1993). Consequently, HCC develops many years (often 2–3

decades) after initial HCV infection. In the setting of HCV-induced cirrhosis, HCC develops at an annual rate of 1–5% (Westbrook and Dusheiko 2014), with an 11.5% 4-year risk of HCC (Serfaty et al. 1998), emphasizing the importance of HCC screening in this population.

However, not all HCV-related HCCs occur in patients with pre-existing cirrhosis. In a large prospective study, about 17% of HCV-positive patients with HCC were not cirrhotic but were noted to have at least an Ishak fibrosis score of 3 or more on serial liver biopsies (Lok et al. 2009), indicating that even in the absence of cirrhosis, HCC tends to develop in HCV-infected individuals with established chronic hepatitis and advanced liver fibrosis. Indeed, 20% of HCV-infected patients with Metavir fibrosis stage 3 (noncirrhotic) have been noted to develop HCC (Alkofer et al. 2011). More recently, a small retrospective study noted that 10% of HCCs developed in HCV-infected patients who only had a Metavir fibrosis stage of F0 to F2 (Lewis et al. 2013).

Risk factors that may contribute to the progression of HCV-associated liver disease to cirrhosis and HCC include concurrent alcohol consumption, older age at the time of infection, male gender, coinfection with HIV or hepatitis B, immunosuppression, associated insulin resistance or non-alcoholic steatohepatitis, and a higher degree of inflammation and fibrosis on liver biopsy (Chen and Morgan 2006).

Significant alcohol intake of >40 g alcohol/day in women and >60 g of alcohol/day in men for more than 5 years is associated with a 2- to 3-fold increased risk of cirrhosis and decompensated liver disease in HCV-infected individuals (Wiley et al. 1998). Furthermore, the risk of developing HCC is doubled in HCV-infected individuals who consume >60 g of alcohol/day compared to those consuming <60 g/day (Donato et al. 2002). Also, the presence of chronic HCV infection has been associated with more advanced liver disease and increased mortality in alcoholic individuals compared to alcoholic patients with chronic hepatitis B infection (Mendenhall et al. 1991).

Age of infection is also an independent risk factor for the development of more severe liver disease in chronic HCV. After controlling for duration of HCV infection, patients who acquire HCV infection at an older age (>40 years old) are significantly more likely to progress to advanced liver fibrosis than individuals infected at a younger age (Poynard et al. 1997). The incidence of HCC is up to 29 times higher for individuals who become infected with HCV after 39 years of age compared to those infected before the age of 19 years (Pradat et al. 2007). HCV-infected men have a 2–4 fold higher risk of developing HCC than HCV-infected women (El-Serag and Kanwal 2014).

In the setting of HIV–HCV coinfection, a low CD4 count is associated with higher HCV viral loads as well as increased hepatic fibrosis and accelerated progression to cirrhosis (Di Martino et al. 2001). Other causes of immunosuppression, such as organ transplantation, have also been associated with more rapid liver fibrosis progression (Berenguer et al. 2000). Individuals coinfected with HCV and hepatitis B virus (HBV), also have a higher risk of HCC development (Shi et al. 2005). Kruse et al. showed that individuals with HCV/HBV-coinfection but without detectable HBV DNA had a risk of HCC equivalent to HCV-monoinfected patients.

However, in coinfected patients with detectable HBV replication, the risk of HCC was doubled (Kruse et al. 2014).

Curiously, daily coffee consumption may have a protective effect on HCV-induced HCC (Wakai et al. 2007). HCV-infected individuals with HCC who drank at least one cup of coffee a day were noted to have a 69% lower mortality compared to individuals who did not drink coffee (Kurozawa et al. 2005).

4.1 Hepatitis C Viral Hepatocarcinogenesis

How HCV infection results in the development of HCC is not entirely clear. There is evidence to suggest that HCV may interact with various intracellular signal transduction pathways or affect epigenetic changes thereby altering hepatocyte physiology to directly promote malignant transformation. HCV core protein has been strongly implicated in hepatocarcinogenesis. Core protein expression has been noted to promote HCC development in transgenic mice in the absence of hepatic inflammation or fibrosis indicating that viral proteins themselves may directly have a carcinogenic effect (Moriya et al. 1998). Core protein is noted to interact with the mitogen-activated protein (MAP) kinase signalling pathway (Hayashi et al. 2000) and upregulate mTOR (Tholey and Ahn 2015), thereby promoting cell proliferation. Core protein has also been shown to inhibit p53 tumour suppressor protein allowing the proliferation of genetically aberrant hepatocytes (Kao et al. 2004).

The non-structural proteins of HCV have also been implicated in hepatocarcinogenesis. NS3 (Ishido and Hotta 1998) and NS5A (Lan et al. 2002) have been shown to bind to p53, perhaps inhibiting p53-mediated apoptosis of malignant cells. The NS5A protein was noted to activate the beta-catenin signalling pathway (Park et al. 2009) and mTOR pathway (Peng et al. 2010) to promote cell proliferation. While the NS5B protein has been found to downregulate retinoblastoma (Rb) protein, a key tumour suppressor protein that regulates cellular response to DNA damage, by targeting Rb for proteasome degradation (Munakata et al. 2005).

Also, it has been shown that the tumour suppressor gene p16INK4A in tumour tissue resected from the livers of HCV-infected patients with HCCs is hypermethylated, and this results in the inactivation of p16INK4A, a feature not seen in non-HCV-associated HCCs (Li et al. 2004).

Second, immune-mediated liver inflammation and the promotion of apoptosis of HCV-infected hepatocytes result in a compensatory stimulation of cell proliferation to replace dead hepatocytes. The increased cell turn-over permits the accumulation of genetic mutations within hepatocytes, and this together with the surrounding inflammatory liver milieu promotes HCC development (Hino et al. 2002; Budhu and Wang 2006). Indeed, inflammation-mediated hepatocyte apoptosis with compensatory cell proliferation was shown to enhance HCC development in mice (Qiu et al. 2011), and increased inflammatory activity within the liver parenchyma has been associated with a poorer prognosis in patients with HCV-associated HCC (Maki et al. 2007).

5 Prevention of HCC in Patients with Hepatitis C-Induced Cirrhosis

The incidence of HCV-related HCC continues to rise worldwide because of the high number of individuals with chronic HCV infection, the presence of associated co-morbidities, and the longer survival of patients with advanced liver disease as a result of improved management of the complications of liver failure. A recent meta-analysis showed that the successful clearance of HCV in patients with advanced liver disease was associated with a reduction in the risk of subsequent HCC development from 17.8 to 4.2%, indicating that despite already having cirrhosis, successful antiviral therapy of HCV-infected patients will still reduce the future risk of HCC (Morgan et al. 2013). However, as the risk of HCC is not completely eliminated despite achieving viral eradication, ongoing HCC screening is still indicated in patients with cirrhosis (Aleman et al. 2013). There appears to be no benefit of therapy on reducing HCC risk if viral eradication was not successful. A systematic review not only found that SVR was related to a reduced incidence of liver failure and HCC, but successful viral eradication may lead to cirrhosis regression (Ng and Saab 2011).

In a meta-analysis of patients with HCV-induced cirrhosis who develop HCC, it was found that after curative treatment of HCC via local ablative therapy or surgical resection, successful eradication of HCV with interferon therapy was associated with a reduced risk of HCC recurrence from 61 to 35% (Singal et al. 2010). Furthermore, successful treatment with pegylated interferon and ribavirin was associated with an improved hepatic functional reserve and increased survival (96 vs. 61% at 3 years) in this cohort (Ishikawa et al. 2012). These studies indicate that antiviral therapy is also useful in the secondary prevention of HCC in HCV-induced cirrhosis. In patients undergoing liver transplantation for HCV-associated HCC, interferon therapy for recurrent HCV post-liver transplant was found to decrease subsequent HCC recurrence from 27 to 4% (Kohli et al. 2012). More recently, the newer direct-acting antiviral (DAA) drugs have also been shown to be highly efficacious in clearing HCV post-liver transplantation, with a 98.5% success rate reported regardless of viral genotype and fibrosis stage (Pyrsopoulos et al. 2018). DAA regimens have been shown to be highly effective in eradicating post-liver transplant HCV with minimal side effects and a durable response on long-term follow-up (Beinhardt et al. 2018).

6 Prevention of Cirrhosis and HCC in Patients with Hepatitis C-Induced Chronic Hepatitis

The potential long-term benefits of successful antiviral therapy of HCV-infected patients with chronic hepatitis include the normalization of serum transaminase levels with resultant reduction in hepatic necroinflammation and fibrosis, the improvement in health-related quality of life, and the reduction in HCC risk, all of

which enhance patient survival (Patel et al. 2006). We know that HCC primarily develops in HCV-infected patients with cirrhosis. In order to reduce the risk of developing HCV-related HCC, the aim would be to provide treatment to eradicate HCV prior to the development of cirrhosis. Indeed, studies have shown that successful viral clearance with antiviral therapy results in clinical and histological improvement in the vast majority of patients (Marcellin et al. 1997), with an associated reduction in the risk of subsequent development of cirrhosis and HCC (Pradat et al. 2007).

In a large multicentre European study of largely noncirrhotic (89%) HCV-infected patients, successful viral eradication was associated with the progression to cirrhosis in only 2.3% of patients with no patients developing HCC, whereas a failure to achieve viral clearance was associated with progression to cirrhosis in 20% of patients and development of HCC in 4.2% (Pradat et al. 2007). In another study of HCV-infected patients, the majority of whom (90%) did not have cirrhosis, successful viral clearance with interferon therapy was associated with a 10-fold reduction in the risk of subsequent HCC development from 2.31 to 0.24%/year (Maruoka et al. 2012). The meta-analysis by Morgan et al. concluded that achieving sustained virological response (SVR), defined as having an undetectable HCV RNA 12 weeks post-completion of antiviral therapy, resulted in a 4.6% absolute reduction in HCC development regardless of fibrosis stage (Morgan et al. 2013). Indeed, attaining SVR is associated with a 54% reduction in all-cause mortality in HCV-infected individuals (Backus et al. 2011). In patients with no evidence of significant hepatic fibrosis, SVR is thought to be associated with an improvement in liver histology back to normal and a reduction in the risk of HCC back to population levels. As such, these patients may be discharged from ongoing surveillance (Westbrook and Dusheiko 2014).

7 Antiviral Treatment of Hepatitis C

A vaccine for the prevention of HCV is not yet available, and therefore the only effective means to prevent the development of liver cirrhosis and HCC is with antiviral therapy. The aim of such treatment is to eradicate the virus, resulting in the clearance of HCV from the body, and thereby halt the progression of liver injury and fibrosis. On long-term follow-up of patients achieving SVR, more than 99% remained HCV negative, essentially equating SVR with a cure for HCV infection (Simmons et al. 2016).

7.1 Pegylated Interferon Alfa and Ribavirin

For many years, the only available treatment for chronic HCV infection was the combination of pegylated interferon alfa and ribavirin. Interferon alfa induced the transcription of genes involved in cell cycle regulation, apoptosis, and promotion of

an antiviral state within hepatocytes (Thomas et al. 2003). Besides the direct effect against virally-infected host cells, interferon alfa is also involved in modulating the immune system by enhancing the CD8+ cytotoxic T cell response against infected cells, as well as promoting the proliferation of B cells to augment the production of antibodies against HCV (Thomas et al. 2003). Treatment was frequently associated with a myriad of side effects resulting in patient morbidity (Chevaliez and Pawlotsky 2007) and despite a prolonged treatment duration of 48 weeks, viral clearance was only achieved in 52% of patients with genotype 1 HCV (Hadziyannis et al. 2004). These regimens are no longer recommended for HCV treatment in the US (Chung et al. 2015) or Europe (Liver 2018).

7.2 Direct-Acting Antiviral Agents

The recent advent of DAA drugs has vastly improved the landscape of antiviral therapy for chronic HCV and has provided a more effective approach to the long-term prevention of HCV-associated HCC. Indeed, combinations of these oral agents are now considered the standard of care for HCV treatment (Chung et al. 2015). These DAAs targets and inhibit specific HCV proteins, including the viral protease (NS3/4A protein), polymerase (NS5B protein), and the NS5A protein, thereby disrupting the HCV replication cycle (Poordad and Dieterich 2012). These DAAs have resulted in significant improvements in achieving SVR, resulting in the rapid normalization of hepatic inflammation and regression of liver fibrosis (Tada et al. 2017) (Table 1).

The first DAAs to be released were the protease inhibitors telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck Sharp and Dohme) in 2011. Both were only effective in patients infected with genotype 1 HCV and were unable to affect SVR alone. As such, they had to be added to pegylated interferon alfa and ribavirin treatment (Hezode et al. 2014), thereby increasing the number and severity of side effects but also augmenting the SVR rates in both treatment naive and treatment-experienced patients. Telaprevir increased SVR rates from 44 to 75% compared to standard therapy alone and boceprevir enhanced SVR rates from 38 to 66% compared to pegylated interferon and ribavirin alone. Common side effects of telaprevir therapy include skin rash, anaemia, and gastrointestinal symptoms, while common side effects of boceprevir include anaemia and dysgeusia (Jacobson et al. 2011; Poordad et al. 2011).

It soon became apparent that single DAA agents were not only insufficiently potent to achieve SVR on their own, but single-agent use quickly led to the development of antiviral resistance due to the rapid selection of drug-resistant HCV variants (Conteduca et al. 2014). The answer came from utilizing regimens consisting of combinations of DAAs with different mechanisms of action in order to prevent the development of antiviral resistance (Pawlotsky 2016). Furthermore, by utilizing multiple DAAs together, treatment duration has generally been shortened to 12 weeks for most regimens regardless of HCV genotype, degree of hepatic

Table 1 Summary of the outcomes of Phase 3 clinical trials with Zepatier, Epclusa, Vosevi and Maviret

DAA regimen	Population	Treatment history	Treatment	Endpoint/Outcome SVR12	References
Zepatier GPV/EBV					
C-EDGE-TN	Gt 1a, 1b, 4 NC or C	TN	GPV/EBV 12w	92% Gt 1a 99% Gt 1b 100% Gt 4 97% noncirrhotic 94% cirrhotic	Zeuzem et al. (2015)
C-EDGE TE	GT14,6, NC or C ± HIV	TE-PR	GPV/EBV ± 12w GPV/EBV ± 16w	12w: 92% Gt 1a 100% Gt 1b 16w: 94% Gt 1a 98% Gt 1b	Kwo et al. (2017)
C-SURFER	GT1, NC or C ± CRD	TN	GPV/EBV 12w	99.1%	Bruchfeld et al. (2017)
C-EDGE COINFECTION	GT1, NC ± HIV	TN	GPV/EBV 12w	97% Gt 1a 96% Gt 1b 96% Gt 4	Rockstroh et al. (2015)
Epclusa SOF/VEL					
ASTRAL-1	GT 1,2,4,5,6 NC or C	TN (68%) or TE (32%)	SOF/VEL 12w	99% Overall 98% Gt 1a 99% Gt 1b 100% Gt 2 100% Gt 4 97% Gt 5 100% Gt 6	Feld et al. (2015)

(continued)

Table 1 (continued)

DAA regimen	Population	Treatment history	Treatment	Endpoint/Outcome SVR12	References
ASTRAL-2 & 3	Gt 2,3 NC or C	TN TE-PR	SOF/VEL 12w or SOF/RBV 12w	99% Gt 2, SOF/VEL 95% Gt 3, SOF/VEL 94% Gt 2, SOF/RBV 80% Gt 3, SOF/RBV	Foster et al. (2015)
Vosevi SOF/VEL/VOX					
POLARIS-1	Gt 1,2,3,4,5,6 NC or C	TE-DAA	SOF/VEL/VOX 12w	96% Overall 96% Gt 1a 100% Gt 1b 100% Gt 2 95 Gt 3 91 Gt 4 100 Gt 5 100 Gt 6	Bourliere et al. (2017)
POLARIS-4	Gt 1,2,3,4 NC or C	TE-DAA	SOF/VEL/VOX 12w or SOF/VEL 12w	98% Overall S/V/V 98% Gt 1a S/V/V 96% Gt 1b S/V/V 100% Gt 2 S/V/V 96% Gt 3 S/V/V 100% Gt 4 S/V/V 90% Overall S/V 89% Gt 1a S/V	Bourliere et al. (2017)

(continued)

Table 1 (continued)

DAA regimen	Population	Treatment history	Treatment	Endpoint/Outcome SVR12	References
				95% Gt 1b S/V 97% Gt 2 S/V 85% Gt 3 S/V	
Maviret (GLE/PIB)					
ENDURANCE-1	GT1, NC ± HIV	TN or TE-PRS	GLE/PIB 12w GLE/PIB 8w	99.7% 99.1%	Zeuzem et al. (2018)
ENDURANCE-2	GT2, NC	TN or TE-PRS	GLE/PIB 12w	[a]99.5% 100%	Asselah et al. (2018)
ENDURANCE-3	GT3, NC	TN	GLE/PIB 8w GLE/PIB 12w DCV/SOF 12w	94.9% 95.3% 96.5%	Zeuzem et al. (2018)
ENDURANCE-4	GT4,5,6, NC	TN or TE-PRS	GLE/PIB 12w	99% overall	Asselah et al. (2018)
EXPEDITION-4	GT1-6, NC or C ± CRD	TN or TE-PRS	GLE/PIB 12w	98%	Gane et al. (2017)
ENDURANCE-5,6	GT4,5,6 NC or C	TN or TE-PRS	GLE/PIB 8w GLE/PIB 12w	Overall, 97.6% 99% 89% (cirrhotic)	Asselah et al. (2019)

[a]DAA-treatment-experienced cohort; *RCTs* Randomized control trials; *PRS* Pegylated interferon, ribavirin and/or sofosbuvir; *NC* Noncirrhotic; *C* Cirrhotic; *TE* Treatment-experienced; *TN* Treatment naive; *CRD* Chronic renal disease; *DCV* Daclatasvir; *SOF* Sofosbuvir; *GLE/PIB* Glecaprevir/Pibrentasvir; *GPV/EBV* Grazoprevir/Elbasvir; *SOF/VEL* Sofosbuvir/Velpatasvir; *SOF/VELVOX* Sofosbuvir/Velpatasvir/Voxilaprevir; *RBV* Ribavirin

fibrosis, or previous antiviral treatment failure (Table 1). These all-oral regimens are also far better tolerated than interferon-containing regimens.

DAA drugs are relatively safe and well-tolerated and there are few absolute contraindications to therapy, with the main issue being drug interactions. Hence it is essential to determine what medications the patient is on, taking into account herbal and over-the-counter drugs, and check for interactions prior to commencement of DAA therapy. Drugs with the potential to cause toxicity should be ceased or switched to another drug in the same class that does not have interaction for the duration of DAA therapy. The University of Liverpool website (www.hep-druginteractions.org) is a useful resource for the screening of potential drug interactions with DAAs. Specific DAA regimens are discussed below.

8 Zepatier® (Elbasvir 50 mg + Grazoprevir 100 mg, Merck & Co.)

Zepatier is a once-daily, single-tablet regimen combining elbasvir and grazoprevir. This treatment is only effective for genotype 1 and 4 HCV infection (Zeuzem et al. 2015). Elbasvir is a potent inhibitor of the NS5A protein which is crucial for viral RNA replication and assembly (Coburn et al. 2013). Grazoprevir is a potent inhibitor of the NS3/4A protease, required for the proteolytic cleavage of the viral polyprotein into the mature proteins which are essential for HCV replication. Grazoprevir has been shown to be effective against common NS3 resistance-associated substitutions (Summa et al. 2012). Although 12-week treatment with Zepatier is highly efficacious in both treatment naive and treatment-experienced patients with a reported SVR rate of over 95% (Zeuzem et al. 2015), in certain difficult to treat cohorts such as treatment-experienced patients or treatment naive patients with pre-existing NS5A resistance-associated substitutions, the recommendation is to extend therapy to 16 weeks and add weight-based ribavirin (Kwo et al. 2017). This is because the presence of NS5A resistance-associated substitutions may result in resistance to elbasvir, thereby reducing the efficacy of this regimen. However, Lawitz et al. showed that by extending treatment duration and adding ribavirin, SVR rates in this cohort was increased from 91 to 100% (Lawitz et al. 2015). In patients with advanced chronic renal disease and infected with HCV genotype 1, a 12-week treatment course of Zepatier has been shown to be safe and produce an SVR of 99% (Bruchfeld et al. 2017). Similarly, in treatment-naive HIV-coinfected patients, Zepatier has been shown to produce an SVR of 96% (Rockstroh et al. 2015). Zepatier is generally well-tolerated with only a small proportion of patients experiencing headaches (17%), fatigue (15%) or nausea (9%) (Zeuzem et al. 2015), however, when combined with ribivirin, these adverse effects were more frequent, together with an increased rate of anaemia (8%) and other cytopenias (Forns et al. 2015), necessitating ribavirin dose-reduction in affected patients. Zepatier can be used safely in patients with renal impairment even up to stage 5 chronic kidney disease on

haemodialysis (Roth et al. 2015), but it is contraindicated in patients with Child-Pugh B or C cirrhosis as it contains a protease inhibitor (Vermehren et al. 2018).

9 Epclusa® (Sofosbuvir 400 mg + Velpatasvir 100 mg, Gilead Sciences)

Epclusa is a single-tablet, daily dose regimen consisting of velpatasvir and sofosbuvir. The nucleoside-analogue sofosbuvir binds to and inhibits the active site of the HCV NS5B polymerase, the structure of which is highly conserved across all HCV genotypes (Buhler and Bartenschlager 2012), thus giving sofosbuvir pan-genotypic efficacy with a high drug resistance barrier (Sofia et al. 2010). Velpatasvir is a second-generation NS5A inhibitor which also has pan-genotypic potency, effective even in patients with detected NS5A resistance-associated substitutions, and has a high barrier to resistance (Cheng et al. 2013). Hence, Epclusa is the first of the pan-genotypic DAA regimens effective against all 6 HCV genotypes, with SVR rates of between 97 and 100% achieved after 12 weeks of treatment regardless of the presence of cirrhosis (99% SVR overall) (Feld et al. 2015). Epclusa is well-tolerated with no statistically significant difference seen between the treatment and placebo groups in the commonly reported side effects of headache, fatigue and nausea, however, cytopaenias were reported in 1% of patients receiving treatment (Feld et al. 2015). This regimen is approved for use in decompensated cirrhosis, usually in combination with ribavirin if tolerated (Vermehren et al. 2018), where the addition of ribavirin to 12-week treatment with Epclusa was noted to increase the SVR rate in this cohort from 83 to 94% (Curry et al. 2015). Addition of weight-based ribavirin should also be considered in treatment-experienced genotype 3 patients as this cohort is known to have a suboptimal response to Epclusa alone (Foster et al. 2015). As Sofosbuvir is mainly renally-excreted, its use is contraindicated in patients with a glomerular filtration rate of <30 ml/min, and Epclusa is not recommended for patients with severe renal impairment.

10 Vosevi® (Sofosbuvir 400 mg + Velpatasvir 100 mg + Voxilaprevir 100 mg, Gilead Sciences)

This single daily tablet fixed-dose regimen adds voxilaprevir, to the NS5B inhibitor/NS5A inhibitor combination of Epclusa. Voxilaprevir is a new generation pan-genotypic reversible inhibitor of the HCV NS3/4A protease with enhanced activity against the common NS3 resistance-associated substitutions (Taylor et al. 2015). This 12-week regimen was shown to be effective in patients who failed to respond to prior NS5A inhibitor-containing DAA treatment, achieving SVR in 91–100% of patients with genotype 1–6 HCV (Bourliere et al. 2017). In

treatment-experienced patients not previously exposed to an NS5A inhibitor, Vosevi achieved SVR in 98% of genotype 1–3 patients, whereas Epclusa achieved SVR in 90% of these patients (Bourliere et al. 2017), indicating that the addition of a protease inhibitor to Epclusa improved viral clearance in this cohort. Commonly reported side effects to Vosevi treatment include headache, nausea, diarrhoea and fatigue, but no treatment cessation resulted from adverse events. Currently, the triple DAA combination of Vosevi is recommended as salvage therapy after failure of dual DAA regimens, especially in the setting of previous NS5A inhibitor use, rather than first-line therapy, with data showing that Vosevi was effective regardless of the presence of resistance-associated substitutions prior to commencing therapy obviating the need for pre-treatment resistance testing (Bourliere et al. 2017). With 80% of sofosbuvir being renally-excreted, Vosevi is not recommended in patients with severe chronic kidney disease. As Vosevi contains a protease inhibitor, its use is contraindicated in decompensated cirrhosis (Vermehren et al. 2018).

11 Maviret® (Glecaprevir 100 mg + Pibrentasvir 40 mg, AbbVie)

Maviret is a single-tablet once-daily regimen consisting of glecaprevir and pibrentasvir effective against all 6 HCV genotypes with reported SVR rates of 95–99% across all genotypes with 12-week therapy (Asselah et al. 2018; Zeuzem et al. 2018). Glecaprevir is a new generation NS3/4A protease inhibitor which has high antiviral potency across all HCV genotypes and does not seem to be as prone to the development of resistance as the previous generation protease inhibitors (Ng et al. 2018). Pibrentasvir is a new generation NS5A inhibitor with potent pan-genotypic activity and efficacy against the common NS5A resistance-associated substitutions (Ng et al. 2017). The presence of cirrhosis did not adversely impact treatment efficacy with Maviret with reported SVR rates of 98–100% in cirrhotic patients with genotype 1–6 HCV, with no patient developing hepatic decompensation on treatment (Forns et al. 2017; Wyles et al. 2017). However, in treatment-experienced patients, especially with prior NS5A inhibitor exposure, extension of Maviret therapy from 12 to 16 weeks may be beneficial. In treatment-experienced genotype 3-infected patients, SVR rates of 91 and 95% were reported for 12 and 16-week treatment, respectively (Wyles et al. 2017). While NS5A-treatment-experienced genotype 1-infected patients showed SVR rates for 12 and 16-week treatment of 88 and 94% respectively (Poordad et al. 2018). Maviret has also been shown to produce high SVR rates in patients infected with genotypes 5 and 6 (Asselah et al. 2019). In this phase, 3b study patients without cirrhosis received 8 weeks of Maviret while patients with compensated cirrhosis received 12 weeks of treatment. Patients were either treatment naive or had prior treatment with pegylated interferon with or without ribavirin or sofosbuvir. Overall, an SVR12 was achieved in 97.6% of patients(Asselah et al. 2019).

Maviret treatment is well-tolerated with commonly occurring adverse events of headache and fatigue not statistically different between the Maviret treatment group and placebo group (Asselah et al. 2018). Maviret has been shown to be safe in severe chronic kidney disease as both glecaprevir and pibrentasvir have negligible renal excretion (Gane et al. 2017). As Maviret contains a protease inhibitor, its use is contraindicated in decompensated cirrhosis (Vermehren et al. 2018).

12 Risk of HCC Development with DAA Therapy

Initial reports raised concern that HCV eradication via DAA treatment may in fact increase the risk of developing HCC. Conti et al. found that in their cohort of HCV cirrhotic patients, the majority of whom did not have a history of previous HCC, 8% were found to have developed HCC within 24 weeks of completing DAA therapy (Conti et al. 2016). Another small study of HCV-infected individuals treated with DAA therapy that specifically excluding patients with previous HCC found a HCC incidence rate of 9% developing within 6 months of DAA therapy (Ravi et al. 2017). These rates were higher than the 1–5% annual reported rate of HCC development in cirrhotic patients with untreated HCV (Westbrook and Dusheiko 2014). The rate of HCC recurrence was also noted to be high after the DAA treatment of HCV. Reig and colleagues noted in their cohort of HCV cirrhotics who had previous curative treatment of HCC, 28% developed evidence of HCC recurrence within 6 months of DAA treatment completion (Reig et al. 2016). In patients who received liver transplantation for HCV-associated HCC, pre-transplant DAA therapy was also associated with an increased rate of HCC recurrence within the transplanted liver (Yang et al. 2016). This promotion of tumourogenesis may be due to immune dysregulation caused by DAA therapy (Meissner et al. 2016), with the rapid viral clearance effected by DAAs perhaps resulting in impaired immune surveillance of tumour cells (Nault and Colombo 2016). It was noted that this increased risk of HCC development was not seen with interferon-based treatments (van der Meer et al. 2012), and interferon therapy has been shown to reduce the risk of HCC recurrence (Singal et al. 2010) purportedly due to the immune stimulant properties of interferon. However, it must be noted that due to the propensity of interferon to cause hepatic decompensation, interferon-based therapy was only used in well-compensated cirrhotics, unlike DAA therapy which may be used safely in more advanced patients, who are innately at higher risk of developing HCC.

However, subsequent large studies and meta-analyses have refuted these claims. In a large retrospective cohort study of 22,500 patients treated with DAAs, achieving SVR was associated with a significant reduction in HCC risk, with the annual HCC incidence rate falling from 3.5 to 0.9% compared to patients who did not achieve SVR (Kanwal et al. 2017). A meta-analysis including over 13,000 patients across 41 studies showed no statistical difference in the rate of HCC development following SVR with DAA regimens compared to interferon-based

treatment (Waziry et al. 2017). Furthermore, Tsai et al. noted that in HCV-infected patients post-curative treatment of HCC, treatment with pegylated interferon and ribavirin was also associated with a significance rate of HCC recurrence (22.9%) within 6 months after antiviral therapy (Tsai et al. 2017), indicating the predilection of HCC to redevelop early regardless of the type of antiviral therapy used. Another meta-analysis analyzing more than 31,000 HCV-infected individuals showed that achieving SVR with DAA therapy reduced the risk of HCC at all stages of hepatic fibrosis (hazard ratio 0.24, $p < 0.001$) (Morgan et al. 2013). A large retrospective study involving over 62,000 patients in the US not only showed that DAA therapy for HCV was not associated with an increased risk of HCC development compared to interferon-based therapy, but achieving SVR with DAA therapy also decreased the subsequent risk of HCC by 71%, and subsequent HCC development was related to advanced disease stage rather than treatment used (Ioannou et al. 2018). To answer the question of post-liver transplant HCC recurrence, a study of HCV-infected individuals who received DAA therapy prior to undergoing liver transplantation for HCC was performed and only 8.5% of patients developed tumour recurrence at 24 months post-transplant (Donato et al. 2017).

13 Risk of Hepatitis B Reactivation and Flare with DAA Therapy

In patients infected with both HCV and HBV, the HCV viral replication often dominates resulting in a low to undetectable HBV viral load (Yu et al. 2015). DAA therapy for HCV has been found to promote HBV flares by rapidly removing the suppressive effect of HCV on HBV replication while having no antiviral activity against HBV. In one study using all-oral DAA therapy in patients coinfected with HCV and HBV, on-treatment development of hepatitis occurred in 30% of HBsAg-positive patients, with 10% progressing to liver failure (Wang et al. 2017), but this did not adversely affect HCV SVR rates. Even in patients with previous HBV infection (HBcAb positive but HBsAg negative and HBV viral load undetected), DAA treatment for HCV has been associated with on-therapy HBV reactivation resulting in significant hepatitic flares. Reactivation causing fulminant hepatitis requiring liver transplantation has even been reported (Ende et al. 2015).

The most recent AASLD guidelines (hcvguidelines.org) and EASL guidelines (Liver 2018) both recommend screening for HBV status with HBsAg, HBsAb and HBcAb prior to the initiation of DAA therapy. Patients with a detectable HBV viral load are at risk of a hepatitis flare on DAA treatment and should receive prophylactic HBV nucleoside-analogue therapy which should be continued for a further 12 weeks after cessation of HCV DAA therapy. Patients with previous HBV infection (HBcAb positive only) should be monitored for the loss of HBsAb or detection of HBsAg while on DAA therapy, indicating the presence of HBV reactivation.

14 Prevention of the Acquisition of HCV in High-Risk Patients

14.1 Preventative Vaccines

Despite HCV being discovered over 20 years ago, there is currently still no effective vaccine to prevent HCV infection, and the development of a preventative vaccine remains an area of intense research. Recent advances in the treatment of HCV with DAAs have significantly improved SVR rates. However, these treatments will not prevent re-infection particularly in high-risk populations where re-infection rates of up 30% have been reported (Bate et al. 2010; Sacks-Davis et al. 2013; Midgard et al. 2016).

Simulation models of hepatitis C dynamics in high-risk populations have all predicted that the introduction of a vaccine, even with modest efficacy, will have a significant effect on reducing the incidence of HCV. Moreover, vaccination after successful treatment with DAAs is also predicted to be as effective at reducing HCV prevalence as vaccinating an equivalent number of people who inject drugs (PWID) in the community (Scott et al. 2015).

A vaccine producing sterilizing immunity is not required in order to achieve HCV elimination. In a US study, a vaccine with an efficacy of 80% and a high vaccination rate of 1% per month targeted to high-risk individuals is predicted to reduce the incidence of HCV from 13.5 to 2.3% per person-years 30 years after vaccine introduction. Even a vaccine of modest (65%) efficacy and vaccination coverage of 0.6% per month would produce a fall in the incidence of chronic HCV to 2.9% after 30 years (Hahn et al. 2009). A UK study showed that by achieving annual vaccination rates of 162, 77 and 44 per 1000 people who inject drugs (PWID) for low (50% protection for 5 years), moderate (70% protection for 10 years), and high (90% protection for 20 years) vaccine efficacies resulted in a halving of chronic HCV prevalence over a 40 year period (Stone et al. 2016). The introduction of DAAs is not a reason to overlook the potential benefit of a vaccine. The introduction of a vaccine of 60–90% efficacy in the era of DAAs is predicted to significantly reduce HCV prevalence especially in populations with high (50%) to very high (75%) chronic HCV prevalence (Scott et al. 2015). A preventative vaccine in a combined approach with DAAs and harm minimization strategies will be the only way to enable us to fulfill the goal of eliminating HCV as a global health burden.

We know that individuals who spontaneously clear HCV infection develop a strong and broadly cross-reactive CD4+ and CD8+ T cell responses against HCV core and non-structural proteins NS3, NS4 and NS5 (Lauer et al. 2004) as well as the production of cross-reactive neutralizing antibodies (NAb) (Pestka et al. 2007). The early induction of broad NAb is associated with control of viraemia and protection against HCV infection in chimpanzees, humanized uPa-SCID liver chimeric mice and humans (Dorner et al. 2011; Osburn et al. 2014). A strong NAb response is essential for a protective HCV vaccine. The importance of both CD4+

and CD8+ T cell responses in clearance of and protection against HCV has been borne out by numerous studies (Smyk-Pearson et al. 2006; Bharadwaj et al. 2009; Schulze Zur Wiesch et al. 2012; Swadling et al. 2014). Strong and broad HCV-specific T cell responses are important in the spontaneous clearance of HCV (Smyk-Pearson et al. 2006; Schulze Zur Wiesch et al. 2012). In contrast to persistent infection, spontaneous resolution of HCV infection has been temporally linked to the appearance of strong, long-lived, polyfunctional CD4+ and CD8+ T cell responses that are directed against multiple HCV antigens (Lechner et al. 2000). The role of T cell responses in HCV control is further reinforced by studies showing persistence of HCV in chimpanzees after viral challenge following the depletion of both CD4+ and CD8+ T cells (Grakoui et al. 2003).

As such, a preventative HCV vaccine would need to reliably generate all these responses against the various genotypes and quasi-species of HCV in inoculated individuals. Few vaccine strategies other than live attenuated viruses or virus-like particles (VLP) are likely to fulfill these criteria.

14.2 Recombinant Adenoviral and MVA Vaccines for HCV

Several HCV containing vaccine candidates that predominantly result in the production of HCV-specific T cell responses have now been described. These have included recombinant adenoviral and modified vaccinia Ankara (MVA), DNA and VLP vaccines in various prime-boost approaches (Folgori et al. 2006; Mikkelsen et al. 2011; Barnes et al. 2012; Swadling et al. 2014; Kumar et al. 2016).

Several studies have now been reported using recombinant adenoviral vectors encoding the non-structural proteins of HCV to produce live attenuated vaccines capable of producing CD4+ and CD8+ T-specific responses. These vaccines have been tested in various animal models and some have also progressed to clinical trials in humans. In early studies in mice, immunization with a replication-deficient recombinant adenovirus encoding HCV NS3 protein resulted in the production of strong HCV-specific T cell responses. This vaccine also resulted in protection against the recombinant vaccinia virus expressing the HCV NS3 and this protective response was correlated to CD8+ T-specific responses (Mikkelsen et al. 2011). A recombinant adenovirus vaccine encoding the NS3 gene of HCV has also been shown to induce strong CD8+ T cell responses in chimpanzees and this vaccine also resulted in the protection against challenge with a heterologous virus and the development of acute hepatitis in chimpanzees (Folgori et al. 2006). These studies demonstrated that recombinant adenoviral vaccines have the potential to prevent HCV in humans.

The earlier studies in primates paved the way for studies of recombinant adenoviral HCV vaccines in humans. In one of the first studies in healthy human volunteers, a vaccine consisting of recombinant human adenovirus 6 (Ad6) and chimpanzee adenovirus 3 (ChAd3) encoding the NS3-5B genes of genotype 1B of HCV produced CD4+ and CD8+ T cell responses against homologous and heterologous HCV non-structural proteins (Barnes et al. 2012). The vaccine also

produced polyfunctional memory CD4+ and CD8+ T cells in the vaccine recipients (Barnes et al. 2012). In a subsequent study, ChAd3 and MVA vectors encoding the NS3, NS4, NS5A, and NS5B proteins of HCV genotype 1b were tested in a prime-boost strategy in human volunteers. Vaccination with the ChAd3 vaccine followed by boosting with the MVA vaccine produced HCV-specific polyfunctional CD8+ and CD4+ T cell responses against homologous and heterologous HCV antigens together with long-lived memory T cell responses (Swadling et al. 2014).

A more recent study investigated immune responses in healthy human volunteers following vaccination with replication-defective ChAd3 and ChAd6 vectors followed by boosting with recombinant MVA vaccines delivering both HCV non-structural and HIV-1 conserved immunogens simultaneously (Hartnell et al. 2018). The co-administration of both HCV and HIV vaccines produced strong and broad polyfunctional CD4+ and CD8+ T cells responses that were similar to the responses produced using the different regimens alone. The immune responses were also maintained for up to 34 weeks after vaccination with HCV non-structural and HIV-1 conserved immunogens simultaneously. These vaccines, however, do not produce neutralizing antibody responses which are a central requirement for protection against HCV.

14.3 Recombinant Protein-Based Vaccines for HCV

The efficacy of an HCV vaccine will reside in its ability to produce broad NAbs (brNAb) in addition to CD4+ and CD8+ T cell responses. Recombinant protein and virus-like particle (VLP) based vaccines have been shown to produce brNAb responses. The vaccination of chimpanzees with recombinant E1 and E2 proteins produced in mammalian cells has been shown to prevent the development of persistent infection after homologous or heterologous virus challenge. This recombinant HCV E1E2 vaccine adjuvanted with MF59C has also been shown to be safe and immunogenic in humans resulting in the production of NAb and $CD4^+$ T cell responses (Frey et al. 2010). Furthermore, immunization of human volunteers with recombinant gpE1/E2 (HCV genotype 1a) resulted in the production of broad cross-neutralizing antibody responses (Law et al. 2013). It has also been shown that vaccination of mice and macaques with a genotype 1a HCV E2 glycoprotein and retroviral Gag pseudotypic particle vaccine produces high-titre NAb responses (Garrone et al. 2011).

Recombinant protein vaccines are also able to produce T cell responses against multiple antigenic targets. The co-administration of a recombinant HCV core, E1, E2, and NS3 protein vaccine in mice and African green monkeys has been shown to induce strong core and NS3 specific T cell responses. Furthermore, immune mice controlled viremia after challenge with a vaccinia virus expressing HCV structural proteins (Martinez-Donato et al. 2014).

14.4 Recombinant Virus-like Particle (VLP) Based Vaccines for HCV

Hepatitis C virus-like particles (HCV VLPs) have been shown to produce NAb and T cell responses in a number of animal models (Chua et al. 2012; Beaumont et al. 2013; Kumar et al. 2016; Earnest-Silveira et al. 2016a, b). HCV-specific NAbs recognize tertiary or quaternary structures (Giang et al. 2012) this makes VLPs attractive as a potential vaccine for HCV as VLPs present conformational epitopes in their native state (Garrone et al. 2011; Chua et al. 2012; Beaumont et al. 2013). HCV VLPs also produce stronger cytotoxic T cell responses in mice compared to DNA vaccines encoding HCV core, E1 and E2 (Murata et al. 2003).

Insect cell-derived VLPs expressing the core, E1 and E2 structural proteins of genotype 1a HCV have been shown to produce broad HCV-specific immune responses (Baumert et al. 1998, 1999; Murata et al. 2003; Steinmann et al. 2004).

Vaccination of mice with insect cell-derived HCV VLPs resulted in cross-neutralizing antibody responses against the HCV structural proteins (Baumert et al. 1998). Furthermore, vaccination of HLA-A2.1 transgenic and BALB/c mice with HCV VLPs produced strong humoral and HCV core-specific CD4+ and CD8+ T cell responses and protection against recombinant vaccinia virus expressing the HCV structural proteins (Baumert et al. 1998, 1999; Lechmann et al. 2001; Murata et al. 2003; Steinmann et al. 2004). The importance of CD4+ and CD8+ T cells in producing protective responses against vaccinia-HCV has also been shown in adoptive transfer experiments (Murata et al. 2003). In addition, the HCV VLPs were able to stimulate the maturation of human dendritic cells (Barth et al. 2005). The immunogenicity of HCV VLPs and the effects of novel adjuvants were further tested in a nonhuman primate model (Jeong et al. 2004). Baboons were immunized with HCV VLPs adjuvanted with AS01B developed HCV-specific antibody, CD4+ and CD8+ T cell responses (Jeong et al. 2004). A subsequent study of HCVVLPs in the chimpanzee showed that this vaccine produced HCV-specific CD4+ and CD8+ T cell responses and prevent progression to persistent infection following the HCV challenge (Elmowalid et al. 2007).

Genotype 1a HCV VLPs have also been produced in human hepatocyte-derived cells. These HCV VLPs possess the biochemical, biophysical properties and morphological characteristic of HCV virions (Gastaminza et al. 2010; Catanese et al. 2013; Earnest-Silveira et al. 2016a, b; Collett et al. 2019) and have been shown to produce NAb and HCV-specific T cell responses in mice (Chua et al. 2012; Earnest-Silveira et al. 2016a, b). In addition, the HCV VLPs bound neutralizing human monoclonal antibodies (HuMAbs) targeting conserved antigenic domain B and D epitopes of the E2 protein (Keck et al. 2004, 2008, 2011; Fauvelle et al. 2016; Keck et al. 2016). A genotype 3a HCV VLP vaccine has also been shown to produce broad humoral and cellular immune responses in mice (Kumar et al. 2016). An advance in the approach of HCV VLP vaccines has been the development of a quadrivalent genotype 1a/1b/2a/3a HCV VLP vaccine (Earnest-Silveira et al. 2016a, b). This vaccine has been shown to produce brNAb, memory B cell and T cell responses in mice and pigs (Christiansen et al. 2018a, b, 2019).

Vaccination of mice with recombinant retrovirus-based virus-like particles (retroVLPs) made of Gag of murine leukemia virus and pseudotyped with HCV E1 and E2 envelope glycoproteins produces strong homologous HCV-specific NAb and T cell responses (Huret et al. 2013). Also, the co-administration of this vaccine with retroVLPs displaying NS3 has been shown to produce strong HCV NS3 and E1E2 specific T cell responses (Huret et al. 2013). In a prime-boost immunization series using retroVLPs and a recombinant serotype 5 adenovirus (rAd5) expressing HCV-E1/E2 envelope glycoprotein (rAdE1E2) mice were primed with rAdE1E2 followed by boosting with retroVLPs. This approach resulted in stronger E2-specific antibody responses than retroVLPs alone (Desjardins et al. 2009; Garrone et al. 2011). The prime-boost strategy also produced cross-neutralizing HCV NAb against five genotypes of HCV (Garrone et al. 2011).

In an alternative approach, a chimeric HBs-HCV VLP vaccine containing E1–E2 heterodimers of genotype 1a HCV has been shown to produce cross-NAb responses against heterologous HCV genotypes (Patient et al. 2009; Beaumont et al. 2013, 2016; Beaumont and Roingeard 2015). The immunogenicity of the chimeric HBs-HCV particles was assessed in rabbits and shown to produce strong HCV E1 and E2 specific antibody responses and HCV neutralizing antibody responses against HCV genotypes 1a, 1b, 2a and 3 (Beaumont et al. 2013). The immunogenicity of the chimeric vaccine and the strength of the HCV E2 responses was not affected by pre-existing immunity to HBsAg (Beaumont and Roingeard 2015).

Modified HBsAg particles by carrying HCV-specific B and T cell epitopes in the 'a' determinant of the HBs protein have also been shown to produce HCV-specific immune responses in mice (Netter et al. 2001, 2003; Woo et al. 2006; Haqshenas et al. 2007; Vietheer et al. 2007). Vaccination of mice with a combination of particles carrying different HCV E2 HVR1 epitopes resulted in a stronger antibody response than vaccination with the individual particles (Netter et al. 2001). Finally, the presence of pre-existing anti-HBs antibody has been shown to have no effect on the production of anti-HVR1 antibody, suggesting that the vaccine could be used in individuals who have previously been vaccinated against HBV (Netter et al. 2001).

14.5 Public Health Measures

As a safe and effective preventative vaccine remains elusive, strategies to reduce HCV transmission among individuals at high risk of acquiring the virus should be employed. In particular, harm reduction measures to reduce unsafe injecting practices amongst intravenous drug users, such as behavioural interventions, the access to sterile needles and syringes, and the management of substance abuse, have been shown to reduce the risk of HCV infection by about 75% (Hagan et al. 2011). The universal screening of blood donors is also important to prevent transmission via contaminated blood products, as is adhering to universal precautions and strict needle-stick protocols within healthcare facilities.

15 Conclusions

HCV is currently a serious global health concern, chronically infecting about 3% of the world's population, leading to chronic hepatitis, cirrhosis, liver failure and HCC, thereby causing significant morbidity and mortality. Furthermore, HCV infection is a major cause of HCC in the Western world, with the majority of HCCs developing in the setting of cirrhosis. The new highly potent DAA combinations are able to cure HCV in the vast majority of infected patients, regardless of viral genotype, viral load, or fibrosis stage. Thus, it is imperative to identify at-risk individuals and provide antiviral therapy prior to the development of established cirrhosis in order to reduce the risk of subsequent HCC. Even after the development of cirrhosis, successful HCV clearance is still associated with reduced HCC risk. Preventative and therapeutic vaccines against HCV remain an area of ongoing research and hopefully, an effective vaccine will be available in the future.

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