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REVIEW

Hepatitis C virus infection: Are there still specific problems with genotype 3?

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Abstract

Hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease and the main indication for liver transplantation worldwide. As promising specific treatments have been introduced for genotype 1, clinicians and researchers are now focusing on patients infected by non-genotype 1 HCV, particularly genotype 3. Indeed, in the golden era of direct-acting antiviral drugs, genotype 3 infections are no longer considered as easy to treat and are associated with higher risk of developing severe liver injuries, such as cirrhosis and hepatocellular carcinoma. Moreover, HCV genotype 3 accounts for 40% of all HCV infections in Asia and is the most frequent genotype among HCV-positive injecting drug users in several countries. Here, we review recent data on HCV genotype 3 infection/treatment, including clinical aspects and the underlying genotype-specific molecular mechanisms.

Key words: Hepatitis C; Genotype 3; Direct-acting antivirals; Interferon; Hepatocellular carcinoma

Core tip: This article reviews the complex relationship between hepatitis C virus (HCV) genotypes and the possible complications in chronically infected patients. We discuss recent updates on the epidemiology and clinical aspects of HCV genotype 3 infection, including the currently available therapies. We also describe model systems to study the HCV genotype-specific molecular mechanisms.

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INTRODUCTION

Currently, about 3% of the world population is infected by the hepatotropic virus responsible for hepatitis C[1]. Thanks to intense research during the last two decades, hepatitis C virus (HCV) life cycle is now well known[2-4]. HCV is a small enveloped virus belonging to the *Flaviviridae* family and the hepacivirus genus, with a plus-strand RNA genome of about 9.6 kb. The HCV genome consists of a single open reading frame that encodes a large polyprotein of approximately 3000 amino acids. This polyprotein is processed by host and viral proteases to generate three structural (core, E1, E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B)[5]. Due to the error-rate of its RNA-dependent RNA polymerase NS5B, the high levels of viral replication and the pressure exerted by the host immune response, HCV sequence is highly variable, resulting in its classification in seven genotypes (GT) and 67 subtypes[6].

Two recent studies estimated the global burden of HCV infection and genotype distribution[7,8]. GT-1 is the most prevalent worldwide (46%), followed by GT-3 (22%). HCV genotype distribution shows geographic variations that reflect transmission mode differences and ethnic variability. Genotype diversity also directly affects the infected patients' outcome due to genotype-specific differences in response to treatment and disease severity. Until recently, HCV GT-3 was considered to be an easy-to-treat infection by using the standard combination of pegylated interferon α (PEG-IFN) and ribavirin (RBV), with higher cure rates (about 70%) than the other viral genotypes (particularly GT-1)[9]. In 2011, the approval of the first HCV protease inhibitors, in combination with PEG-IFN and RBV, greatly improved the treatment of HCV GT-1 in Europe and the United States. However, due to the side effect profiles and costs per sustained virologic response (SVR), this triple combination is no longer recommended by the European Association for the Study of the Liver (EASL recommendations 2015[10]). Indeed, several more effective and better tolerated direct-acting antivirals (DAAs) are now in clinical development[11], or have been approved by the Food and Drug Administration and the European Medical Agency (EMA). Among them, a nucleotide analog inhibitor of the HCV RNA-dependent RNA polymerase (sofosbuvir), a second-generation protease inhibitor (simeprevir) and two HCV-NS5A inhibitors (daclatasvir and ledipasvir) can be used in combination therapies.

Despite the wide range of new DDAs, few therapeutic options are effective for HCV GT-3. Moreover, the high cost of the new treatments implies a careful patient selection and will limit treatment delivery in some regions of the world. Here, we discuss the specific features and current issues of HCV GT-3 infection/treatment, including clinical aspects and the underlying molecular mechanisms.

EPIDEMIOLOGY

Although persistent HCV infection is one of the leading causes of liver-related morbidity and mortality, possibly accounting for up to 0.5 million deaths every year[12], its epidemiology remains poorly understood in many countries. As the efficacy of current and new therapies differ according to the HCV genotype, epidemiological data on the infected populations and the HCV genotype distribution have important clinical implications. Several recent studies on the global, regional and national prevalence and genotype distribution of HCV infection highlighted significant geographical differences[7,13-15] (summarized in Table 1). Specifically, HCV GT-3 accounts for 40% of all HCV infections in Asia, with a high prevalence in India, Malaysia and Pakistan (54%, 59% and 79%, respectively)[8]. HCV GT-3 is also predominant (> 43%) in some European countries (Denmark, Finland and United Kingdom) and might represent 50% of all HCV infections in Norway[14] and about 36% in Australasia[8]. The genotype distribution in a country may change from one year to the other, partly due to the migration of infected individuals and therefore, needs to be regularly updated. For instance, a recent study conducted in the southern part of Turkey reported a HCV GT-3 prevalence of 46%, a rate remarkably higher than that from previous Turkish findings[16] (Table 1). Updated data from four regions of Thailand and from Southeast Asia also indicate variations in the distribution of HCV genotypes and subtypes, notably in the 3a/3b subtype ratio[17] (Table 1). Phylogenetic analysis of HCV subtype 3a, the prevalent subtype in Thailand, showed that the genotypes of HCV samples from infected Thai and Indian/Pakistani patients cluster in close proximity, supporting the hypothesis of a close relationship between the HCV subtype 3a viruses that circulate in these countries[18].

Over the last ten years, GT-3 was reported as the most frequent genotype among HCV-positive injecting drug users (IDUs) in several countries[19-21]. In 2011, Nelson *et al*[22] performed a global systematic review of HCV prevalence among IDUs and found that about 10 million IDUs worldwide might be HCV-positive. China, the United States and the Russian Federation have by far the largest HCV-positive IDU populations. Thus, IDUs are now at the heart of the HCV epidemics in developed countries[23,24]. More specifically, HCV subtype 3a, which originated from Asia, has spread widely among IDUs and also among other patient groups in industrialized countries[25]. Recently, a prospective, multicenter cohort study on the treatment of HCV/HIV-positive patients after liver transplantation in Spain indicated that co-infected patients were

Table 1 Reported prevalence of hepatitis C virus genotype 3

Country, Region	Viremic population	Genotype 3 prevalence	Ref.
Asia			
India	6026 (3157-7174)	54.4%	[8]
	8666 (5150-15449)	64.0%	[14]
Malaysia	237 (47-1216)	58.6%	[8]
Pakistan	7039 (1728-10524)	79.0%	[8]
Thailand	925 (633-1259)	44.2%	[8]
Thailand, North		23%/16% (3a/3b)	[17]
Thailand, South		38%/14% (3a/3b)	[17]
Europe, Western			
Denmark	21 (14-21)	43.0%	[8]
Finland	22 (16-27)	46.0%	[8,14]
Norway	29 (25-37)	28.1%	[8]
	22 (18-28)	50.0%	[14]
United Kingdom	210 (125-428)	43.8%	[8]
Middle East			
Turkey	434 (274-959)	4.9%	[8]
Turkey, province of Kahramanmaras		46.0%	[16]
Australasia			
Australia	234 (169-260)	36.8%	[8]
New Zealand	50 (27-72)	35.0%	[8,14]

younger and had more frequently HCV GT-3 than patients infected only by HCV[26].

CLINICAL COURSE

Pathologies frequently associated with HCV genotype 3

Most HCV infections are asymptomatic. Consequently, infected individuals are not aware of their illness until the appearance of severe and irreversible liver disease, often several decades after the initial infection. Steatosis, characterized by lipid droplet accumulation in the cytoplasm of hepatocytes, is an extremely common histological finding in patients with chronic HCV (from approximately 40% to 80%, depending on the studies) and its prevalence is two times higher than in the general population[27]. Several risk factors for steatosis and liver injuries in HCV infection (*i.e.*, high fat diet, chronic alcohol consumption, dyslipidemia, obesity, chronic drug consumption, diabetes, insulin resistance, *etc.*) are the same as for alcoholic and non-alcoholic steatohepatitis, thus rendering the precise relationship between steatosis and HCV difficult to determine[28,29]. Nevertheless, in 1997, a study on the liver histopathological lesions in 90 HCV-positive patients revealed a significantly higher prevalence of steatosis among patients infected by HCV GT-3a than by GT-1a or 1b[30]. Since then, several other works confirmed this association and provided evidence of a HCV GT-3-specific cytopathic effect[31,32]. In a later study, Rodriguez-Torres *et al*[33] reported that among 614 patients, those with HCV GT-3 infection were more likely to have steatosis than patients infected by HCV GT-2 (79% *vs* 59%). This HCV genotype was qualified as steatogenic. Indeed, several studies reported a significant improvement in steatosis in HCV GT-3 patients who achieved sustained viral clearance after antiviral therapy[34-36], Furthermore, GT-3 patients tend to have hypocholesterolemia and hypobetalipoproteinemia[37-39], thus accounting for a direct effect of the virus on lipid metabolism. HCV GT-3 infection also promotes liver fibrosis development/progression[40-43]. However, the coexistence of host and viral factors contributing to liver steatosis and fibrosis in the same patient impair the analysis of their independent involvement and this issue remains controversial[44,45].

Moreover, chronic HCV induces multiple defects in the upstream components of the insulin signaling pathway in the liver, thus contributing to the observed prevalence of insulin resistance (IR) and type 2 diabetes mellitus in infected patients[46-48]. A genotype-specific association between IR and HCV was recently confirmed in a study on 497 HCV GT-1-positive patients and 541 GT-2/3-positive patients who received IFN-based therapy and in whom IR was measured before and 12 wk after the treatment using the homeostasis model assessment of IR (HOMA-IR)[49]. SVR was associated with a reduction in the HOMA-IR value in HCV GT-1-positive patients, but not in those with HCV GT-2 or GT-3 infection. Of note, IR was identified as an independent predictor of advanced fibrosis in patients with chronic HCV GT-3 infection[45]. However, the mechanism of HCV-mediated IR and the genotype-specific association remains unclear.

Evidence that viral factors, such as the HCV genotype, may affect the risk of progression to cirrhosis or to hepatocellular carcinoma (HCC) is scarce. Larsen *et al*[50] investigated the risk factors for these severe liver diseases in HCV-infected drug abusers in France between 2001 and 2007 and showed that HCV GT-3 infection is associated with severe liver disease in drug abusers, independently of age, sex, duration of infection, alcohol consumption and co-infection with HIV. In 2011, Nkontchou *et al*[51] reported the association of HCV GT-3 infection and higher HCC incidence in patients with cirrhosis in France. A strong association between chronic HCV GT-3a infection and HCC was also found in Pakistan[52]. This finding was recently confirmed by the analysis of patients' data from the Veterans Affairs HCV clinical registry showing that the risks of cirrhosis and HCC were significantly higher in HCV GT-3- than in GT-1-infected patients[53].

Conversely, HCV GT-3 was not reported as a significant factor influencing post-liver transplantation hepatitis, contrary to HCV GT-1, although the genotype influence on HCV recurrence after liver transplantation remains controversial[54].

Extra-hepatic manifestations

Besides liver disease, HCV infection can also cause a variety of extra-hepatic problems (autoimmune and/or

Table 2 Factors associated with poor response to pegylated interferon α/RVB in hepatitis C virus GT-3- infected patients

Factors	Study design	Number of patients	Characteristics	Ref.	Comments
Viral factors					
High baseline viral load (> 8 × 10^5 UI/mL)	Prospective	426 (all GT-3)	223 patients with viral load > 8 × 10^5 UI/mL	[56]	Combined with non-RVR
High baseline viral load (> 6 × 10^5 UI/mL)	Retrospective	107 (all GT-3)	45 non-SVR/62 SVR	[71]	Combined with advanced fibrosis
High baseline quasi-species complexity and diversity	Retrospective	10 (all GT-3)		[58]	
Mutations in NS5A	Prospective	49 (all GT-3)	25 non-SVR/24 SVR	[62]	Significant mutations at positions 2309 (Ala to Ser) and 2326 (Gly to Ala)
Host factors					
Fibrosis/Cirrhosis	Prospective	91 (all GT-3)	17 cirrhotic/74 non-cirrhotic	[63]	Also associated with increased risk of post-treatment relapse
	Retrospective	604 (all GT-3)	145 cirrhotic/459 non-cirrhotic	[64]	Response not affected by ethnicity
	Retrospective	180	108 GT-3/72 GT-2	[66]	Lack of SVR associated with fibrosis and GT-3
	Retrospective	107 (all GT-3)	45 non-SVR/62 SVR	[71]	Combined with high baseline viral load
Steatosis	Prospective	224	182 GT-3/42 GT-2	[69]	Lower SVR in GT-3
	Retrospective	932	505 GT-3/427 GT-2	[70]	Associated with higher relapse rates in GT-3 patients who had RVR
Ethnicity	Retrospective	103	66 Caucasians/38 Asians	[74]	Poor response could reflect more advanced liver disease at baseline in Asian patients
	Retrospective	604 (all GT-3)	305 non-Asians/299 South Asians	[64]	No correlation between ethnicity and treatment relapse
IFNL3 gene polymorphisms	Retrospective	107 (all GT-3)	45 non-SVR/62 SVR	[71]	No correlation between IFNL3 polymorphisms and SVR
	Prospective	293 HCV RNA- positive	65.87% GT-3/32.08% GT-1	[78]	CC and TT alleles strongly associated with SVR in GT-3 patients
Intrahepatic ISG15 expression/IFNL4 gene polymorphisms	Retrospective	92	36 GT-3/56 GT-1	[79]	In GT-3, low ISG15 expression and good-responder IFNL4 genotype associated with high SVR rates

GT: Genotype; SVR: Sustained virologic response; RVR: Rapid virologic response; NS5A: Non-structural 5A protein; IFNL: Interferon lambda; ISG: Interferon-stimulated gene; HCV: Hepatitis C virus.

lymphoproliferative disorders as well as cardiovascular, renal, metabolic and central nervous system diseases) in up to 74% of patients[55]. To the best of our knowledge, there is no evidence of a significant association between extra-hepatic diseases and HCV genotype.

HCV GENOTYPE 3 AND RESPONSE TO THE STANDARD TREATMENT

High SVR rates are observed in HCV GT-3-infected patients who receive the standard-of-care treatment (PEG-IFN/RVB). Accordingly, this genotype has been considered as "easy to cure" and grouped with GT-2 in clinical studies. However, increasing evidence indicates that differently from GT-2, some patients infected by HCV GT-3 respond poorly. Several viral or host factors could be associated with this reduced response (summarized in Table 2).

Viral factors

The baseline viral load is critical for treatment outcome. Indeed, HCV GT-3-infected patients with high pre-treatment viral load (> 8 × 10^5 IU/mL) are unlikely to show an SVR[56]. Moreover, it is well known that the high degree of genetic diversity of the HCV genome is associated with viral sensitivity or resistance to IFN-based therapy[57]. Accordingly, high HCV quasi-species complexity/diversity might negatively influence the outcome of IFN-based therapy in patients with chronic HCV GT-3 infection[58]. Viral genetic polymorphisms, especially within the non-structural 5A protein (NS5A) regions, may also be involved in the response to PEG-IFN/RVB therapy[57,59-61]. Specifically, in a small cohort of 49 non-responder and responder HCV GT-3a-infected patients, Mansoor *et al*[62] identified NS5A mutations that allow predicting the response to treatment.

Host factors

Several studies suggest that liver fibrosis and cirrhosis have a negative effect on the treatment response in HCV GT-3-infected patients[63,64] and that they are associated with an increased risk of hepatitis relapse after treatment[63]. Recently, a multicenter, open-label, randomized trial (*n* = 136 patients) showed that patients infected by HCV GT-3 and with advanced fibrosis do not benefit from extended therapy (48 wk) with PEG-INF/RBV[65]. Moreover, in a small cohort

of 180 Canadian patients, Powis *et al*[66] found a significant interaction between cirrhosis and HCV GT-3 (*vs* GT-2), leading to poor antiviral response. However, this association was also reported for other genotypes[67].

Among the severe liver injuries linked to HCV, steatosis negatively influences the response to antiviral therapy[68], particularly in HCV GT-3-infected patients[69], and is an independent predictor of relapse after rapid virologic response in these patients, irrespectively of the viral load[70]. However, using the database of a large prospective clinical trial in patients with HCV GT-2 or GT-3 infection, Rodriguez-Torres *et al*[33] found that liver steatosis did not affect the viral response in patients treated with PEG-IFN/RBV for 16 or 24 wk. A major limitation of many studies on SVR predictors is that they evaluated HCV GT-2- and GT-3-infected patients together. Therefore, Marciano *et al*[71] performed a retrospective multicenter study on 107 HCV GT-3-infected patients in Argentina and showed that advanced fibrosis and high pre-treatment viral load were associated with poor response to PEG-IFN/RBV in the patients who did not achieve an SVR.

Several studies focused on ethnic features that may influence the efficacy of IFN-based therapy, mainly by comparing Asian and Caucasian patients[72,73]. In 2008, a small study found a lower SVR rate in South Asian patients infected by HCV GT-3 than in Caucasians[74]. The influence of Asian ethnicity on the response to therapy for HCV GT-3 infection appears to be a major issue because this HCV genotype accounts for 40% of all infections in Asia. However, this association remains controversial because a retrospective analysis of 604 patients infected by HCV GT-3 and undergoing therapy in four United Kingdom centers (where many patients originate from the Indian subcontinent) showed that the response to antiviral therapy was affected by age, cirrhosis and diabetes, but not by the patient ethnicity (South Asian *vs* Caucasian)[64].

Polymorphisms of the interleukin-28B gene (*IL28B*, also named *IFNL3* for IFN lambda 3) located on chromosome 19 may affect both the natural history of HCV infection and the patient response to IFN-based therapy[75,76]. A recent systematic meta-analysis revealed a weak correlation between treatment outcome and IFNL3 genotype in patients infected by HCV GT-3 or GT-2[77]. However, in most studies analyzed in this review, these two genotypes were included in the same subgroup, thus rendering difficult to draw conclusions exclusively for GT-3. The recent study by Marciano *et al*[71] on 107 HCV GT-3-infected patients in Argentina did not find any association between *IFNL3* polymorphisms and SVR, while a study on HCV GT-3 infected patients in India showed that two favorable single nucleotide polymorphisms (SNPs) (rs12979860 and rs8099917) are strongly associated with SVR[78]. Holmes *et al*[79] evaluated the association between *IFNL3* and *IFNL4* (a variant upstream of *IFNL3* identified as a new *IFNL* gene[80]) genotypes, intrahepatic expression of IFN-stimulated genes (ISGs) and PEG-IFN/RBV treatment outcome in HCV GT-1 and GT-3-infected patients. Interestingly, this retrospective analysis of 259 patients treated with PEG-IFN/RBV in a single large tertiary center in Australia between 2004 and 2011 clearly highlights fundamental differences in the host response to HCV GT-1 and GT-3 infection, with a central role for intrahepatic ISG15 expression, independently of the *IFNL4* genotype. The lowest ISG15 level was observed in HCV GT-3-infected patients with the good-responder *IFNL4* genotype and the highest SVR. Conversely, the highest ISG15 level was detected in HCV GT-1-infected patients with the poor-responder *IFNL4* genotype and the lowest SVR rates. Robinson *et al*[81] compared gene transcription profiles in liver biopsies from uninfected and HCV GT-1- or GT-3-infected patients and confirmed the reduced predictive value of the *IFNL* genotype for HCV GT-3. Moreover, investigation of the host-pathogen interactions that underlie the genotype-specific clinical outcomes of chronic HCV infection[82] showed elevated ISG transcription in peripheral blood mononuclear cells from HCV GT-1-, but not from GT-3-infected patients, thus confirming the genotype-specific host-pathogen interactions.

HCV GT-3 infection after liver transplantation

Until recently, the treatment outcome of recurrent HCV GT-3 infection after liver transplantation was not precisely known. Faisal *et al*[83] demonstrated that the efficacy of the PEG-IFN/RBV combination for recurrent HCV GT-3 infection after liver transplantation is high and comparable with that in non-transplanted patients.

To improve the virologic response to IFN therapy, some combinations with other drugs were assessed. For instance, a case report indicated that the association of PEG-IFN/RBV and silibinin (an antiviral drug) resulted in an SVR after 24 wk in a treatment-naive patient who was reinfected by HCV GT-3 after liver transplantation[84].

Other drugs have been tested in combination with PEG-IFN and RBV. A prospective study on 179 treatment-naive patients with chronic HCV GT-1 or GT-3 infection indicated that fluvastatin (a 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitor of the statin family) combined with PEG-IFN/RBV improves the SVR in naive patients chronically infected by HCV GT-1 and high viral load, but not in patients infected by HCV GT-3[85]. Similarly, no significant benefit of statin in HCV GT-3 infection was found in a study based on the analysis of the United States Department of Veterans Affairs patient database[86].

Finally, severe side effects have been reported during IFN therapy and are one of the most frequent causes of treatment discontinuation[87,88]. Moreover, in specific groups of patients, IFN-based regimens are contraindicated or not applicable or failed repeatedly.

Table 3 Overview of direct-acting antiviral-containing treatments for hepatitis C virus genotype-3-infected patients

Drug combination	Recommendations[1]	Duration	Ref.
IFN-containing treatment			
PEG-IFN/RBV and SOF	For treatment-experienced patients, with or without cirrhosis	12 wk	[97]
PEG-IFN/RBV and DCV	Not yet recommended	12 or 16 wk	[98]
IFN-free treatment			
SOF and RBV	Suboptimal in treatment-experienced cirrhotic patients	24 wk	[99,100]
SOF and DCV	For patients without cirrhosis	12 wk	[101]
SOF/DCV and RBV	For treatment-naive and treatment-experienced patients with cirrhosis	24 wk	[102]
SOF/ledipasvir (single-tablet regimen)	Not yet recommended	12 wk	[104]
Promising therapeutic option			
GS-5816/SOF ± RBV	Under evaluation	12 wk	[107,108]

[1]According to the EASL Clinical Practice Guidelines in April 2015[10].

Therefore, IFN-free regimens need to be developed/tested in these patients.

GENOTYPE 3 IN DAA GOLDEN ERA

Until 2013 and given the relative efficacy of the standard-of-care treatment (PEG-IFN and RBV for 24 wk) for the other genotypes, research and drug development focused mainly on HCV GT-1. Currently, the introduction of DAAs has revolutionized HCV GT-1 therapy, while few effective treatment options are available for patients infected by HCV GT-3 who do not achieve an SVR with IFN (particularly, patients with cirrhosis), or have medical contraindications to IFN. First-generation, first wave NS3/4A protease inhibitors (telaprevir and boceprevir) are not efficient against HCV GT-3 infection[11,89,90]. For instance, Foster *et al*[89] reported that telaprevir alone or with PEG-IFN and RBV reduces the plasma levels of HCV RNA in patients with chronic HCV GT-2, but not GT-3 infection. Similarly, second-wave protease inhibitors, such as simeprevir (TMC435), are active against several HCV genotypes, but not GT-3[91,92]. The second generation of NS3-4A protease inhibitors, such as MK-5172[93], was developed to overcome the major limitations of first-generation antiviral drugs (*i.e.,* low barriers to resistance, dosing, clinically challenging side-effects and lack of pan-genotype activity)[94]. However, these drugs also are not effective against HCV GT-3 infection.

Therefore, despite the wide range of potent antiviral drugs, therapies approved in the United States and Europe for the treatment of HCV GT-3 infection include only two pan-genotypic DAAs that target key proteins in HCV replication: the first-generation NS5A inhibitor daclatasvir (DCV)[95] and sofosbuvir (SOF), a nucleotide analogue targeting the NS5B polymerase[96]. Currently, SOF is considered to be the backbone for the treatment of HCV GT-2-4 infections. These IFN-free, all-oral treatments are attractive, especially to avoid the many IFN-induced adverse effects. Nevertheless, the treatment choice mainly depends on the liver fibrosis stage and on the previous therapies. In April 2015, the EASL Clinical Practice Guidelines[10] recommended only three treatment options with DAAs for HCV GT-3 infections, in addition to PEG-IFN/RBV, and two of them are IFN-free regimens (summarized in Table 3).

IFN-containing treatments

A combination of PEG-IFN once per week and daily RBV and SOF for 12 wk can be used. Indeed, a phase Ⅱ clinical trial on 47 HCV GT-2 or GT-3 patients showed that this regimen gives high SVR rates in treatment-experienced patients with HCV GT-3 infection, irrespective of their cirrhosis status, and is well tolerated[97]. Although not recommended yet by the EASL in May 2015, other combinations were recently tested in clinical trials. Notably, the treatment duration with PEG-IFN/RBV could be reduced to 12 or 16 wk when combined with DCV in HCV GT-3- infected patients[98].

IFN-free treatments

For patients for whom IFN is not an option (*i.e.,* who do not have an SVR with the 24-wk PEG-IFN/RBV treatment, and for patients with medical contraindications), only two IFN-free regimens could be efficient. Again, clear differences were highlighted when HCV GT-3 and GT-2-infected patients were compared. For instance, two randomized, phase Ⅲ clinical trials (FUSION and POSITRON)[99] reported the need to extend the duration of the SOF/RBV treatment to 16 wk for HCV GT-3 infection, particularly in cirrhotic or treatment-experienced patients, to obtain a high response rate. Conversely, 12 wk were sufficient to achieve an SVR in HCV GT-2-infected patients. In the VALENCE study[100], therapy with SOF/RBV was extended to 24 wk for HCV GT-3-infected patients (compared to 12 wk in HCV GT-2-infected patients), resulting in high SVR rates. However, this combination was suboptimal for treatment-experienced cirrhotic patients.

The second IFN-free regimen that gives satisfying results for GT-3 patients is the combination of SOF and DCV for 12 wk, but only in non-cirrhotic patients. Indeed, in the ALLY-3 phase Ⅲ clinical

trial in treatment-naive (n = 101) or treatment-experienced (n = 51) HCV GT-3 patients, an SVR was achieved in 96% of patients without cirrhosis after 12 wk of well-tolerated treatment, while only 58% of cirrhotic patients achieved an SVR[101]. Similar results were reported by a French multicenter study on the compassionate use of SOF/DCV ± RBV in patients with HCV GT-3[102]. A regimen with a single tablet that contains ledipasvir and SOF (the two first-generation NS5A inhibitors) was recently approved in the United States and Europe and represents a significant advance for HCV treatment[103]. However, published studies are lacking on its use for HCV GT-3 treatment. Based on the few available data[104] and on the low *in vitro* efficacy of ledipasvir on NS5A activity[105], this combination is not recommended yet by the EASL in May 2015[10]. Among the many combinations tested to date, Gane *et al*[106] recently reported results from a phase Ⅱ pilot study that assessed the safety and efficacy of RBV combined with grazoprevir and elbasvir (two potent NS3/4 and NSA5 inhibitors, respectively) in treatment-naive, non-cirrhotic patients with HCV GT-3 infection. This combination was poorly efficient in this population.

Overall, the available data suggest that subgroups of patients infected by HCV GT-3, particularly those with advanced liver fibrosis or a previous failure of IFN-based therapy, are more difficult to cure with the short IFN-free regimens available in 2015. As achieving an undetectable viral load is associated with decreased hepatic morbidity and mortality[53], it is critical to improve the treatment for these subgroups of patients. Among the currently evaluated DAAs that are active against GT-3, the pangenotypic NS5A inhibitor GS-5816, combined with SOF ± RBV is a promising therapeutic option[107,108].

GENOTYPE 3 AND STUDY MODELS

Following the description of the association between HCV GT-3 infection and lipid accumulation in the liver in clinical studies, much effort has been made to understand the HCV genotype-specific pathogenic mechanisms. Detailed discussions of the different proposed molecular mechanisms are reviewed elsewhere and highlight the difficulties to identify pathological hallmarks of HCV GT-3 infection both *in vitro* and *in vivo* models[109,110].

Several evidences of perturbations induced specifically by HCV GT-3 infection, particularly the deregulation of lipoprotein metabolism, were obtained by analyzing liver biopsies and plasma samples from chronically infected patients[111-114]. As liver damage may be multifactorial, the major challenge in clinical research studies is to carefully exclude patients with risk factors for liver steatosis other than HCV (*i.e.*, patients with obesity, significant alcohol intake, diabetes, ongoing intravenous drug addiction, or use of steatogenic drugs).

In the last decade, it was suggested that the viral capsid core protein has a central and genotype-specific role. However, this hypothesis remains controversial[109]. Indeed, our current understanding of HCV GT-3 effects is largely based on studies using the human hepatoma Huh7 cell line that expresses the HCV GT-1b or GT-3a core protein[114-116]. However, these cell models do not mimic the liver physiological reality and complexity, or the viral infection processes and the specific intrinsic functions of other HCV GT-3 proteins.

Since 2005, a unique cell culture system based on the HCV GT-2a clone JFH1 and chimeric constructs allows the efficient replication of HCV and the *de novo* production of viral particles *in vitro* (HCVcc)[117]. Recently, we demonstrated that in well-defined culture conditions, adult primary human hepatocytes (PHH), isolated from liver tissue, support the complete infection cycle of natural HCV from patients' serum samples[118]. By testing the *in vitro* infectivity of about 120 HCV-positive serum samples in PHH cultures, we identified the highly infectious HCV GT-3a strain S310. We then cloned the full-length consensus genomic sequence of S310 and constructed a sub-genomic replicon, thus providing a new tool to study HCV GT-3a replication in Huh-7 cells[119]. We also identified critical mutations in subgenomic replicons that strongly promote viral replication and that were subsequently introduced in the full-length S310 HCV RNA. Kim *et al*[120] then demonstrated that full-length S310 clones replicate efficiently and produce infectious viral particles (HCVcc/S310) in Huh-7 cells, thus providing an unique infectious HCV GT-3a cell system. Interestingly, differences in HCV core protein localization and lipid content were observed in S310 (GT-3a)-infected and JFH1 (GT-2a)-infected cells. Moreover, the protease inhibitor telaprevir is less effective against S310- than JFH1-infected cells, as reported in the clinic.

Therefore, HCVcc/S310 particles represent a promising tool to determine the precise pathogenesis of HCV GT-3 infection and to understand the reasons of the effectiveness variations of different antiviral drugs. Further work is now needed to combine this HCV GT-3 strain with the most relevant host cell systems, such as primary cells, mouse models[121] or systems derived from tissue engineering[122].

CONCLUSION

Better understanding chronic HCV infection and the determinants of the treatment outcome appears nowadays as a key challenge. During the last few years, clinical research investigated mainly the interactions between viral and host factors, especially in HCV GT-3 infection. This genotype is significantly associated with severe liver disease and low response to most of the currently approved DAAs. The association of HCV GT-3 infection with the highest risk

of cirrhosis and HCC underscores the medical need for safe and effective treatment options for patients infected by HCV with this genotype. Luckily, recent clinical and basic research studies have been focusing more on HCV GT-3, in order to develop new strategies for providing timely and effective care for this high-risk population. Among the antiviral drugs under evaluation, host-targeted antivirals, like cyclophilin inhibitors, may be of great interest within the next few years.

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