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REVIEW

Predictive factors associated with hepatitis C antiviral therapy response

Lourianne Nascimento Cavalcante, André Castro Lyra

Lourianne Nascimento Cavalcante, André Castro Lyra, Hospital Sao Rafael - Gastro-Hepatology Service, Salvador, Bahia 41253-190, Brazil
André Castro Lyra, Department of Medicine, Federal University of Bahia, Salvador, Bahia 40026-010, Brazil

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Correspondence to: Lourianne Nascimento Cavalcante, MD, Hospital Sao Rafael - Gastro-Hepatology Service, Diretoria Científica, 6° andar Sao Rafael Av. 2152 - Sao Marcos, Salvador, Bahia 41253-190, Brazil. lourianne@gmail.com
Telephone: +55-71-32816432
Fax: +55-71-32816855

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Abstract

Hepatitis C virus (HCV) infection may lead to significant liver injury, and viral, environmental, host, immunologic and genetic factors may contribute to the differences in the disease expression and treatment response. In the early 2000s, dual therapy using a combination of pegylated interferon plus ribavirin (PR) became the standard of care for HCV treatment. In this PR era, predictive factors of therapy response related to virus and host have been identified. In 2010/2011, therapeutic regimens for HCV genotype 1 patients were modified, and the addition of NS3/4a protease inhibitors (boceprevir or telaprevir) to dual therapy increased the effectiveness and chances of sustained virologic response (SVR). Nevertheless, the first-generation triple therapy is associated with many adverse events, some of which are serious and associated with death, particularly in cirrhotic patients. This led to the need to identify viral and host predictive factors that might influence the SVR rate to triple therapy and avoid unnecessary exposure to these drugs. Over the past four years, hepatitis C treatment has been rapidly changing with the development of new therapies and other developments. Currently, with the more recent generations of pan-genotipic antiviral therapies, there have been higher sustained virologic rates, and prognostic factors may not have the same importance and strength as before. Nonetheless, some variables may still be consistent with the low rates of non-response with regimens that include sofosbuvir, daclatasvir and ledipasvir. In this manuscript, we review the predictive factors of therapy response across the different treatment regimens over the last decade including the new antiviral drugs.

Key words: Hepatitis C; Direct acting antivirals; Antiviral therapy; Interferon; Sustained virologic response

Core tip: Treatment of chronic hepatitis C has been changing very rapidly in recent years. The chances of cure have increased with the new drugs. Predictive factors of sustained treatment response in the "age" of based-interferon therapy is becoming less important with the arrival of the direct acting antivirals, however, viral genotype, cirrhosis and viral kinetics may still

impact on therapy outcome with the new available drugs.

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INTRODUCTION

Hepatitis C virus (HCV) is an important etiology of chronic hepatitis and cirrhosis and is the leading indication for liver transplantation (LT) in adults around the world[1,2]. Therefore, early recognition and effective management of the disease can modify its natural history. HCV infection may lead to significant liver injury, and viral, environmental and host factors, including immunologic and genetic susceptibilities, may contribute to differences in the disease expression and treatment response[3]. This genetic susceptibility has a significant part in developing of HCV infection, from viral antigen recognition and presentation to the type of immune response developed against the pathogen[3].

The natural history of HCV genotypes 1, 2 and 3 infection appears to be similar, and patients are at risk for developing liver cirrhosis, decompensation of liver disease and hepatocellular carcinoma. HCV genotype 3 is also associated with an increase in hepatic steatosis, which is believed to be related to viral interference in host lipid metabolism[4].

The predictive factors of therapy response are also related to the virus and hosts, and they can be classified as clinical, immunologic and genetic factors. HCV genotype 1, male gender, advanced liver fibrosis, human immunodeficiency virus (HIV) and HBV coinfection, insulin resistance, poor treatment adherence, high viral load (⩾ 600.000 UI/mL) and African ancestry have been related with the failure of interferon (IFN) based therapies, particularly with dual therapy (pegylated interferon and ribavirin)[1,5].

Gene polymorphisms that encode or regulate the host molecular expression may be useful as disease evaluation markers and therapy response predictors; moreover, they could provide helpful information for understanding the complex mechanisms underlying the virus-host interaction and the variations observed in antiviral therapy responses. The interleukin-28B (IL28B) polymorphisms were considered the strongest baseline identified predictors of dual therapy response (pegylated interferon and ribavirin); they are also predictors of viral kinetics and spontaneous clearance in acute HCV infection. IL28B polymorphisms differs among different ethnic backgrounds[6,7].

Along the last four years, hepatitis C treatment has rapidly changed with the development of new therapies and other advancements, and the chances of cure are significantly increasing. Initially, with the first-generation direct acting antivirals (DAA) boceprevir and telaprevir, individuals with HCV genotype 1 achieved sustained virologic response (SVR) rates of nearly 70% or greater, and the viral kinetics and hepatic fibrosis were the main predictors of response[8,9]. Currently, with the more recent generations of pangenotipic antiviral therapies, there have been even higher SVR rates, and prognostic factors may not have the same importance and strength as before. Nevertheless, viral kinetics, the presence of liver cirrhosis and HCV genotype 3 may still be relevant factors that influence the rates of SVR[9].

PROGNOSTIC FACTORS IN DUAL PEGYLATED INTERFERON PLUS RIBAVIRIN THERAPY ERA

Early in 2000s, dual therapy using a combination of pegylated interferon-alpha plus ribavirin (PR) was the standard of care for HCV treatment. HCV genotype 1 infection used to be the most difficult genotype to treat, with relatively low SVR rates compared to current rates, and required an expected duration of therapy of 48 wk that could be extended to 72 wk for partial responders. Conversely, for genotypes 2 and 3 HCV infected patients, the recommended treatment time was 12 to 48 wk, and superior SVR rates were reached compared with HCV genotype 1[1,5,10]. The sustained virological response proportion for HCV genotype 1 infected patients were 40%-50%, whereas for HCV genotype 2 and 3 infected subjects it was, approximately, 75%-80%[1].

In the PR era, predictive factors of therapy response related to virus and host have been identified. Clinical host characteristics possibly correlated with the response to dual regimen are gender, age, dyslipidemia, insulin resistance, liver fibrosis stage, ancestry, 25(OH) vitamin D status, coinfection with HBV and/or HIV. Immunologic elements related with response to PR treatment are cytokines and interferon-gamma inducible protein 10 (IP-10); in addition, genetic factors such as IL28B polymorphisms, other genes associated with JAK-STAT pathway polymorphisms and genetic ancestry markers have also been described as predictors of response[11]. The HCV features associated with therapy antiviral response are genotype, baseline viral load and viral kinetics at specific time-points throughout the treatment. The single most important viral factor that influences the response to antiviral treatment is HCV genotype, and the most important host factors are IL28B genotype and liver fibrosis[12-14].

Pegylated interferon alpha-2a and -2b

Both pegylated interferons may be used during PR therapy. In the Ideal study, which included 3070 HCV genotype 1 infected patients, the SVR rates were similar among the schemes with pegylated interferon alpha 2a or 2b; the SVR rates were 40.9% and 39.8%, respectively, without statistically significant differences[15].

In HCV genotypes 2 and 3, ribavirin doses (800 mg/d compared to 1000-1200 g/d adjusted for weight (kg) did not produce any difference in SVR rates when patients were treated for at least 24 wk[13,16].

On the other hand, a meta-analysis of 26 studies included, 11 were randomized and 15 were non-randomized, with a total number of 18260 patients (8125 patients were treated with PEG-IFN alpha 2a and 10135 were treated with PEG-IFN alpha-2b) and showed that dual therapy with PEG-INF-alpha 2a was associated with a greater SVR than PEG-IFN-alpha 2b in HCV monoinfected patients, particularly for genotypes 1 and 4. An analysis of randomized clinical trials, including HCV-type 1 and 4 patients, showed SVR rates of 43.2% for the PEG-IFN-alpha 2a group and 38.7% for the PEG-IFN-alpha 2b and ribavirin group. In the HCV genotypes 2 and 3 group, the SVR rates among patients treated with PEG-IFN-alpha 2a was 82.6% and 75.5% for the PEG-IFN-alpha 2b and ribavirin group[17].

Ancestry/race and SVR

Ancestry is an important marker of response to IFN-based treatments in people chronically infected by HCV. People of African descent have lower chances of success with dual antiviral therapy compared with Caucasians. These findings were observed in more homogeneous populations, with low rates of racial admixture assessed by self-reported ancestry; similar findings were found in admixed populations when ancestry was assessed using genetic markers[18]. Although people of African descent are most commonly infected by HCV genotype 1, randomized studies ruled out the possibility that HCV genotype infection was the reason for the lower response to antiviral treatment in this group. The immunological and genetic background appear to be the reasons for this suboptimal response because these differences did not occur as a result of therapy adherence, viral genotype, histopathological changes, type of IFN or social or the economic status of the patients[19,20]. The IL28B polymorphisms are most likely influenced by ancestry, and these variables may modify IFN-based therapy outcomes[21].

IL28B polymorphisms

Genome Wide Association Studies (GWAS) described single nucleotide polymorphisms of genes in the area of the IFN-λ as powerful predictors of therapy response with double regimen with peg-IFN PR in patients infected by hepatitis C genotype 1 and of spontaneous viral clearance during acute HCV infection[6,7,18,21-24]. In HCV genotypes 2 and 3 infected individuals, the outcomes were somewhat controversial; some studies showed that IL28B polymorphisms are associated with rapid virologic response (RVR) and not SVR, whereas others showed that IL28B polymorphisms are associated with SVR only in patients who did not get RVR[24].

The most studied IL28B genetic polymorphisms are IL28B (IFN-λIII) rs12979860 single nucleotide polymorphism (SNP) (T > C) and rs8099917 (T > G), which are separated by 4378 nucleotides. In genetic studies with hepatitis C infected patients, both IL28B variants (rs12979860 and rs8099917) are in linkage disequilibrium, and in HCV genotype 1 patients treated with pegylated IFN PR, the IL28B C/C genotype in rs12979860, T/T in rs8099917 and A/A in rs12980275 were associated with sustained virological response[7,25].

According to GWAS, SNP rs12979860 IL28B C/C genotype was strongly related with superior chances of SVR, and it was observed that ancestry had affected the results. Individuals with European ancestry and C/C genotype had two times superior chances of achieving SVR than did subjects with T/T genotype; IL28B C/C African Americans had three times higher chances of achieving SVR than IL28B T/T genotype African Americans, and among Hispanics, the C/C genotype was associated with a twofold higher chance of SVR compared to the T/T genotype[26]. Data revealed that African Americans with chronic hepatitis C genotype 1 and Il28B C/C have better SVR rates compared to European Americans (north American Caucasians) without the IL28B C/C genotype[27]. The C allele is more common in populations of European and Asian ancestries, and this supports the hypothesis that some of the differences in SVR rates among people of African descent and Caucasians can be explained by the variance in the frequency of the C allele in these populations. Asians infected with hepatitis C genotype 1 virus had higher SVR rates compared with Caucasians, African Americans and Hispanics, and the frequency of the IL28B alleles is a possible explanation for this difference[7].

An analysis of the Brazilian admixed population showed that the *IL28B* gene polymorphisms, rs12979860 and rs8099917, were also predictors of SVR to PR dual therapy consistent with results of studies conducted in populations with low levels of racial admixture[18]. However, in the studied admixed population, the association among ancestry, IL28B polymorphisms and therapy response was detected only when ancestry was assessed using genetic markers[18].

Liver fibrosis

Liver fibrosis is a host factor that has consistently been associated with response rates to IFN-based therapies. Patients with advanced liver fibrosis (Metavir F3 or F4) have a lower chance of SVR compared to subjects with milder liver fibrosis. Invasive (liver-biopsy) and non-invasive methods may be used to assess the fibrosis stage[25].

IP-10

The combination of serum IP-10 and IL28B SNPs may increase the predictive value of the treatment response. The IP-10 (IFN - IP-10) is also called CXCL10 and belongs to the CXC chemokine family. IP-10 is a indicator of liver inflammation and fibrosis in individuals with chronic hepatitis C. Low pre-treatment IP-10 levels have been related with SVR and on the other hand, increased levels

have been associated with therapy failure. A baseline IP-10 level > 600 pg/mL was determined to be greatly predictive of an unfavorable therapy outcome[26,27].

Vitamin D

Studies including HCV genotypes 1 and 4 infected patients have revealed that low vitamin D status is related with inferior probabilities of achieving SVR following peg-IFN alpha PR therapy[28,29]. Nevertheless, a recent published systematic review and meta-analysis did not confirm these findings[30]. The authors found no significant association between the baseline mean 25(OH) D level and SVR (OR = 1.44; *P* = 0.11), either in patients infected with HCV genotypes 1, 4, 5 (OR = 1.48; *P* = 0.09) or genotypes 2/3 (OR = 1.51; *P* = 0.65).

Statin use

The role of metabolic factors as well overweight and visceral obesity, hepatic steatosis, insulin resistance and diabetes, in the response to antiviral therapy has been studied widely in the last decade[30]. To assessing the role of statins on HCV response rate to treatment, several studies analyzed the addition of fluvastatin to the HCV treatment (peg-IFN and ribavirin)[31,32]. The use of statins significantly improved SVR (OR = 2.02, 95%CI: 1.38-2.94), RVR (OR = 3.51, 95%CI: 1.08-11.42) and early virologic response (OR = 1.89, 95%CI: 1.20-2.98). The SVR rate substantially improved for HCV genotype 1 (OR = 2.11; 95%CI: 1.40-3.18). There was not an important increase in adverse events reports and withdrawn with the adding of statins.

Gender

Females overall appear to have higher chances of achieving SVR. Nevertheless, several studies have suggested that in HCV genotype 1 infected women, menopause is related with an increased severity of liver fibrosis, and with a lower likelihood of response to therapy with peg-IFN and ribavirin[33-36].

A cohort of HCV patients treated with dual therapy revealed that SVR was independently related with female gender, younger age, IL28B C/C genotype, viral genotype and low baseline levels of serum HCV-RNA[35]. However, females older than 50 years infected with HCV genotype 1 achieved lower rates of SVR. The possible reason was that, at baseline, females older than 50 years included in cohort had high body mass index and visceral obesity, metabolic alterations and severe histological liver damage, findings more frequently observed in the menopause females. In genotype 2 and genotype 3 patients, gender usually does not affect the SVR[37].

RVR

As reported in several studies, RVR (HCV RNA viral load undetectable at week 4) is associated with a notably higher rate of SVR. Some trials have observed that patients infected with HCV genotypes 2 or 3 achieve RVR in higher proportions than patients infected with genotype 1. However, regardless of the HCV genotype, patients who reach RVR have the highest rates of SVR. In the study by Fried *et al*[37] RVR was achieved by 16% of patients with genotype 1, 71% of genotype 2 and 60% of genotype 3. Among individuals who reached RVR, the SVR rate was high across all HCV-genotypes and ranged from 88% to 100% (genotypes 1-4). Baseline predictive factors of RVR comprised genotype, low baseline viral load, high alanina aminotransferase ratio, nonexistence of advanced fibrosis, and younger age. RVR was the most important predictor of SVR based on logistic regression analysis[37]. Among HCV genotype 3 infected patients, if RVR is present, the treatment period may be shortened. In a previous trial, among patients with RVR - week 4, SVR was 81.6% among patients treated for 24 wk and 82.5% among them treated for 12 wk. In patients without RVR, SVR was 52.1% if the treatment duration was 24 wk and 61.7% if the duration was 36 wk. According to this study, HCV genotype 3 patients with RVR may be treated for 12 wk if the appropriate ribavirin doses are used; in patients without RVR, the SVR rates were higher with 36 wk of treatment compared with 24 wk[38].

FIRST WAVE OF DIRECT ACTING ANTIVIRAL (TELAPREVIR AND BOCEPREVIR)

In 2010/2011, therapeutic regimens for HCV genotype 1 patients were modified, and the adding NS3/4a protease inhibitors to dual therapy increased the effectiveness and chances of SVR. The grouping of pegylated IFN, ribavirin and a protease inhibitor (boceprevir or telaprevir) significantly improved the SVR rates compared with dual treatment (approximately 70% to 80% *vs* 40% to 50% SVR, respectively)[9,39,40]. Protease inhibitors should not be used as monotherapy, due to the development of resistance and genetic modification of the host barrier. With triple therapy, there is the possibility of shortening treatment as guided by viral kinetics. Individuals with IL28B (rs12979860) genotype C/C have higher chances of achieving shortened response guided therapy. Randomized trials have suggested that patients with unfavorable IL28B genotypes (C/T and T/T, rs12979860) had significantly improved SVR rates when protease inhibitors were combined with dual therapy[9,39,41-45] (Tables 1 and 2).

Nevertheless, the first generation triple therapy is associated with many adverse events, some of which are serious and associated with death, especially in cirrhotic patients. This led to the need to identify viral and host predictive factors that might influence the SVR rate to triple therapy, and additionally, it was important to determine whether a subdivision of patients might have a higher likelihood of response to dual therapy so that the use of first-generation protease inhibitors with their associated adverse effects and high costs could be

Table 1 Risk factors associated with response (sustained virologic response 12) to first-generation direct acting antivirals in naive patients

	SVR12 rates (%)				
	Boceprevir			Telaprevir	
Predictive variables	PR48	BOCRGT	BOCPR48	PR48	T12PR48
Naïve	40	67	66	44	75
Mild-moderate fibrosis	38	67	67	47	118.5
Advanced fibrosis	38	41	52	33	62
Black race	23	42	53	25	62
HCVRNA viral load < 800.000 IU/mL	64	76	85	36	74
IL28B C/C	78	82	80	64	90
Il28B C/T	28	65	71	23	71
IL28B T/T	27	55	59	25	73
HCV genotype 1a	35	59	63	41	71
HCV genotype 1b	40	66	70	4	79
BMI < 25	47	58	67	44	83
BMI ⩾ 30	33	48	66	41	71
Relapse	22	9	9	28	9

Data obtained, analyzed and adapted from Ref. [8,9,44]. PR48: Standard therapy with pegylated interferon plus ribavirin for 48 wk; BOCRGT: Boceprevir with therapy possibly shortened by response guided therapy; BOCPR48: Boceprevir with treatment fixed time for 48 wk; T12PR48: Telaprevir by 12 wk and standard therapy for 48 wk; IL28B: Interleukin-28B; BMI: Body mass index; HCV: Hepatitis C virus; SVR: Sustained virologic response.

Table 2 Risk factors associated with therapeutic response to first-generation direct acting antivirals in patients previously treated with pegylated interferon and ribavirin

	SVR rates (%)				
	Boceprevir			Telaprevir	
Predictive variables	PR48	BOCRGT	BOCPR48	PR48	T12PR48
Previous relapser	29	69	75	24	83
Previous partial-responder	7	40	52	15	59
Previous null responder				5	29
Mild-moderate fibrosis	23	63	68	16	76
Advanced fibrosis	13	44	68	11	49
Black race	8	61	63	10	55
HCVRNA viral load > 800.000 IU/mL (baseline)					
IL28B C/C	46	79	77	29	79
Il28B C/T	17	61	73	16	60
IL28B T/T	50	55	72	13	61
HCV genotype 1a	24	5	61		
HCV genotype 1b	22	65	73		
BMI < 25	20	6	68		
BMI ⩾ 30	11	56	65		
Relapse	15	59	54		

Data obtained, analyzed and adapted from Ref. [40,41,44,45]. PR48: Standard therapy with pegylated interferon plus ribavirin for 48 wk; BOCRGT: Boceprevir with therapy possibly shortened by response guided therapy; BOCPR48: Boceprevir with treatment fixed time for 48 wk; T12PR48: Telaprevir by 12 wk and standard therapy for 48 wk; IL28B: Interleukin-28B; BMI: Body mass index; HCV: Hepatitis C virus; SVR: Sustained virologic response.

avoided.

SVR rates to treatment regimens containing protease inhibitors vary with the type of prior non-response to treatment. Naïve individuals reach response rates between 67% and 75% (Table 1), and among relapsers to previous dual PR therapy, the response rates vary between 69% and 88%; for previous partial responders, the response rates are between 40% and 59%, and for previous null responders, the SVR rates vary between 23% and 38%[9,39,41,45]. However, the response rates are lower among individuals with liver cirrhosis (SVR = 11%-68%) and are higher among subjects with IL28B genotype C/C (Table 2).

In two phase 3 trials including boceprevir, baseline predictors of SVR in previously treated patients include former treatment response (previous relapse rather than previous partial nonresponse), nonexistence of cirrhosis, use of triple therapy rather than PR, low viral load at baseline and lack of cirrhosis. In previously naive patients, based on multivariate analysis, baseline predictors of SVR were triple therapy, non-black race, low viral load at baseline (< 400.00 UI/mL), age (⩽ 40 years), statin use and absence of cirrhosis. In both studies, a 1 $\log_{10}$ IU/mL decline in HCV-RNA viral load

after the 4-wk (lead-in) on-treatment was the greatest predictor of SVR[8,45,46].

Untreated subjects with unfavorable predictive variables of therapy response to PR treatment have improved the chances of cure with the addition of telaprevir. Patients with advanced fibrosis (bridging fibrosis or cirrhosis), older age, diabetes mellitus, and HCV RNA levels of 800000 IU/mL or higher, black race and C/T and T/T *IL28B* genotypes showed improved chances of an HCV cure[9]. Studies with telaprevir-based triple therapy including previously treated patients evaluated previous partial responders, relapsers and null responders. The SVR rates during treatment were higher in patients who had previous relapse or partial response than in patients who had null response. Based on these analyzes, advanced fibrosis appears to be associated to unsuccessful, especially among patients with no response or a partial response to previous treatment, although there was no such effect on prior relapsers. The lead-in phase with peguilated IFN alpha-2a PR before telaprevir intake did not improve the response rate[41] (Table 2).

Lead in phase as a predictor of SVR

Clinical trials have suggested that the lead-in phase, by evaluating the sensitivity to IFN, is able to predict the efficacy of triple therapy using first generation DAA[47]. Lead-in phase consists of four weeks of pegylated IFN and ribavirin treatment before triple therapy. A viral load decline > 1 log after lead-in was the strongest predictor of SVR in both naïve and previously treated patients with boceprevir[44]. Notably, in individuals with a viral load decline less than 1 log after lead-in phase, the chances of achieving SVR were lower, which may reflect resistance to IFN. In the Sprint-2 trial, patients who achieved more than a 2 log viral load decline after lead-in had an SVR rate greater that 80%.

The rationale for performing a lead-in phase is to avoid adverse effects associated with triple therapy with boceprevir or telaprevir in patients with few chances of SVR, particularly in cirrhotic and previous experimented patients. Poor-IFN sensitive patients without RVR at week 4 after lead-in and with other unfavorable predictors to SVR may avoid the disadvantages of triple therapy with boceprevir or telaprevir and should be treated with new IFN-free therapies.

A multivariate analysis to evaluate the baseline markers that predict this IFN response after the lead-in phase, accessing previously untreated patients, showed that baseline markers of good response involved the following: IL28B C/C genotype, low baseline viral load, absence of cirrhosis, and lower body mass index (BMI). In previous treatment-failures, baseline predictors of good response after lead-in were IL28B C/C genotype and previous relapse to PR therapy. Statistically significant differences in SVR rates for patients who did not reach a 1 Log IU/mL decline after lead-in were observed such as the following: patients with genotype 1b *vs* 1a (47% *vs* 25%), METAVIR score F0/1/2 *vs* F3/4 (38% *vs* 17%), and baseline viral load ⩽ 800000 *vs* > 800000 (69% *vs* 31%). Gender, race (black *vs* nonblack), age, BMI and steatosis score were not associated with response in this subgroup of patients[44].

First generation DAA and IL28B

The IL28B C/C genotype is a strong predictor of IFN response with PR therapy, however, with first wave *DAA* IFN-based triple therapy IL28B C/C genotype is a good marker of early response in naïve or previous treatment experimented patients and viral kinetics is the strongest predictor of SVR.

Sprint-2 and Respond-2 were phase Ⅲ studies that evaluated the effectiveness of triple therapy with pegylated IFN, ribavirin and boceprevir in naïve and previous treated patients, respectively. Subanalysis of these studies assessed the impact of the IL28B polymorphism (rs12979860) as a predictor of therapy response[41,43,47,48]. The genotype C/C IL28B was the best predictor of treatment response at week 4 (after lead-in) and week 8. Considering the IL28B C/C and RVR (HCVRNA < 100 IU/mL at week 8 and 12), the duration of treatment with triple therapy was reduced in approximately 90% of previously treated and treatment-naïve patients. In the IL28B C/C genotype group in the Sprint-2 study, the SVR rates were higher in all three treatment studied arms (dual therapy, response-guided triple therapy with boceprevir and triple therapy with boceprevir fixed dose)[8]. However, in this cohort, the IL28B genotype C/C was a more important predictor of shortening treatment; 89% of patients cleared the virus at week 8 of treatment. IL28B C/C was a predictor of SVR in a limited model analysis with covariates (Respond-2: OR = 2.2, P = 0.025 and Sprint-2: OR = 4.5, P < 0.001), but when a model of logistic regression analysis was performed, the response after lead-in (week 4) was a stronger variable for predicting SVR than any other, including IL28B C/C, based on the baseline evaluation. In a combined Sprint-2 and Respond-2 studies analysis, early response to pegylated IFN and ribavirin, *i.e.,* response after week 4, was the best predictor of SVR in patients with unfavorable *IL28B* genotypes C/T and T/T. In the response-guided therapy, the duration of therapy was based on the detection of HCV-RNA at week 8 and patients who had undetectable HCV at this time point were eligible for shortening their therapy. The majority of C/C patients treated with boceprevir had undetectable HCV-RNA viral load by week 8 (89% in Sprint-2, and 76% in Respond-2), and consequently was eligible for abbreviated treatment. On the other hand, a fewer number of patients with the C/T and T/T *IL28B* genotypes had undetectable viral loads at week 8 (CT, 53% in Sprint-2 and 46% in Respond-2/TT, 42% in Sprint-2 and 63% in Respond-2). The SVR rate for patients in the boceprevir groups who became undetectable by week 8 was 81%-100%, regardless of the IL28B genotype[8,45].

Table 3 Cupic study evaluation of the risk/benefit of the treatment cirrhotic patients with telaprevir or boceprevir triple therapy considering the chances of death or severe complications and sustained virologic response 12 according to cutoffs of serum albumin level and platelet count *n* (%)

Factors	Platelet count > 100000/mm^3	Platelet count ⩽ 100000/mm^3
Serum albumin level > 35 g/L		
Patients with severe complications or death)	19 (6.2)	9 (12.2)
SVR12	168 (54.9)	27 (36.5)
Serum albumin level > 35 g/L		
Patients with severe complications or death	5 (16.1)	19 (51.4)
SVR12	9 (29.0)	10 (27.0)

Adapted from Hézode *et al*[50]. SVR12: Sustained virologic response at 12 wk after ending of treatment.

The phase Ⅲ study Advance analyzed triple therapy with pegylated IFN, ribavirin and telaprevir in treatment-naïve patients with genotype 1 chronic hepatitis C[49]. Retrospective analysis of the Advance study evaluated SVR rates based on *IL28B* genotypes in 42% (*n* = 454/1088) of patients from the study population, all Caucasians based on self-reported ancestry. In the group with IL28B C/C, 90% of subjects (*n* = 45/50) achieved SVR with triple therapy *vs* 64% SVR among those who received pegylated IFN and ribavirin in the control group. The genotypes C/T and T/T patients had SVR rates of 71% and 73%, respectively in the group treated with triple therapy compared with SVR rates of 23% and 25% in those treated with dual therapy. The C/C patients achieved higher rates of extended RVR (eRVR) characterized by HCVRNA viral load < 1000 IU/mL at week 4 and 12 of treatment; subjects with eRVR were eligible for shortened therapy. In this study, eRVR was the best predictor of SVR, although, notably, individuals with the IL28B C/C genotype also had high rates of SVR. The overall SVR rate in the group with eRVR was 91%, but among individuals who also had the IL28B C/C genotype, the SVR rate increased by 6% (97%); among those who did not achieve eRVR, the SVR rate was significantly lower (43%), but in those without eRVR and with genotype C/C IL28B, the SVR was 63%.

The phase Ⅲ study Realize compared the efficacy, safety and tolerability of telaprevir (with or without lead-in) in combination with pegylated IFN and ribavirin, with the control group treated with pegylated IFN and ribavirin in patients non responsive to prior treatment, including relapsers, as well as partial and null responders. In a retrospective analysis, the association between the IL28B genotype (rs12979860) and SVR was investigated in 527 (80%) patients included in the study; however, the IL28B C/C genotypes were not predictors of SVR among individuals treated with triple therapy. SVR rates were greater in telaprevir treated groups *vs* PR for all *IL28B* genotypes (CC: 79% *vs* 29%, CT: 60% *vs* 16%, TT: 61% *vs* 13%, respectively)[42].

Role of advanced liver fibrosis in first wave DAA treatment regimens

Although triple therapy combining the protease inhibitors (telaprevir or boceprevir), pegylated-IFN and ribavirin have increased the chances to eliminate HCV in many groups of patients, its efficacy remains suboptimal in treatment experienced cirrhosis patients. These patients are considered difficult-to-treat, and lower SVR rates than noncirrhotics are achieved; they have an enlarged risk of developing serious adverse events. Moreover, cirrhosis patients were underrepresented in first generation DAA clinical trials.

A real life study analyzed a total of 660 cirrhosis patients who were previous relapsers, partial responders and null responders to pegylated IFN and ribavirin treatment, including 299 treated with telaprevir and 212 with boceprevir. Patients were included in each group at the discretion of the physician[50]. The first endpoint (SVR 12) achieved among patients treated with telaprevir was 74.2% for relapsers, 40.0% for partial responders and 19.4% for null responders. Among individuals treated with boceprevir, 53.9% of relapsers, 38.3% of partial responders and none of null responders got SVR at week 12. A late virologic breakthrough during therapy was observed after discontinuing TVR in 16.4% of the cases, a relapse in 14.7%, and 4.7% patients failed for other reasons (7 were lost to follow-up, 4 died, and 3 were missing HCV-RNA level measurements). Among the 121 patients who failed boceprevir treatment, virologic breakthrough during therapy was observed in 9%, 17% relapsed and 1.9% patients failed for other reasons (2 deaths and 2 missing HCV-RNA level measurements).

Variables associated with SVR 12 among patients treated with telaprevir were HCV subtype 1b and RVR. In the group treated with boceprevir, HCV subtype 1b, 1 Log HCV-RNA decline after lead in (week 4), 3 Log HCV-RNA decline or undetectable viral load at week 8 were good predictors of SVR12. In multivariate analysis, factors associated with SVR12 included previous response to previous treatment, HCV subtype 1b and baseline platelet count greater than 100000/mm^3.

Serious adverse events occurred in 49.9% of cases, comprising hepatic decompensation, severe infections in 10.4%, and death in 2.2%. According to multivariate analysis, baseline serum albumin level less than 35 g/L and platelet counts of 100000/mm^3 or less predict serious side effects or death. Among patients with serum albumin levels < 35 g/L and platelet counts ⩽ 100.000/mm^3, the proportion of severe complications or death was 51.4%, and therefore, this treatment is not advisable for this subgroup of patients (Table 3)[50].

In the Cupic study, the long follow-up period (60 wk) of subjects treated with telaprevir or boceprevir revealed a large number of serious adverse events (SAE), such as severe infection or hepatic decompensation and death in 10.6% of patients. These SAE were attributed, in part, to

a higher mean age of the study population compared to phase 3 studies, as well as a more severe liver disease and portal hypertension. Therefore, treatment with first-generation DAA is not recommended for patients with advanced cirrhosis and severe portal hypertension[50].

First wave DAA and drug resistance

The emergence of drug-resistant variants is a concern with the utilization of antiviral drugs. A large amount of genetically different variants, or viral quasispecies may occur in a unique individual, considering that about 10^{12} HCV are produced daily with a mutation rate of approximately 1×10^{4} to 1×10^{-5} per nucleotides[51]. These resistant variants can be selected in antiviral treatment as the level of wild-type HCV decreases.

The most common resistance variants related to therapy failure are comparable for telaprevir and boceprevir. V36A/M, T54A/S, R155K/T and A156S/T are clinically expressive variants that are resistant to both drugs[52]. The V55A and A156V are variants associated with boceprevir only. In patients treated with telaprevir or boceprevir, diverse resistance patterns are identified for the HCV genotype 1 subtypes (1a and 1b). Genotype 1b is correlated with a low-resistant variant selection rate, the higher genetic barrier and superior response to triple therapy in comparison with genotype 1a[53]. The most probable reason for these differences are the lower genetic barriers to resistant variants at key-sites on the HCV NS3 protease in genotype 1a patients in comparison to patients with genotype 1b.

In phase 3 trials, patients who did not reach SVR with telaprevir and boceprevir triple therapy, resistant variants were identified in 86% and 55% of genotype 1a patients, respectively; 56% and 47%, of those with genotype 1b, respectively[54]. Genotype 1b-resistant variants sustained for a median of 1-2 mo comparatively with 8-11 mo for genotype 1a, in phase 3 clinical trials with telaprevir[54]. In phase 1b trials, ultradeep sequencing showed more variants in patients treated with telaprevir or boceprevir: R117H in patients treated with telaprevir, S174F in boceprevir-treated patients and A87T in both groups; they were only found in genotype 1b, and the effect of these variants on triple therapy is undetermined.

If patients do not get SVR with telaprevir-based therapy, telaprevir-resistant variants are often increased at the end of treatment. Population sequencing revealed that the telaprevir-resistant variants are typically not detectable at baseline (prevalence of patients $\leqslant$ 5%) and the majority of the variants present at the time of treatment failure are no longer detectable at the end of the study. The analysis performed in the Realize study using a deep-sequencing technique showed that before treatment, telaprevir-resistant variants (T54A, T54S, or R155K) were detected in 2% of patients and that these variants were not essentially detected at the time of treatment failure. Analysis of 49 patients, deep-sequencing technique, revealed the presence of variants V36A/L/M, T54S or R155K in 16 patients (33%) at the end of the study[55].

NEW WAVES OF DAA

Currently, the hepatitis C virus antiviral therapy challenge is the development of drugs and therapy regimens with markedly antiviral activity, high genetic barrier to resistance, few side effects and short duration. An improved understanding of the HCV genome lifecycle led to the discovery of many potential targets for antiviral therapy. The polyprotein processing and replication, viral entry and fusion, the RNA virus translation, assembly and release of host cells and numerous other factors are attractive targets for new and alternative antiviral therapies. Combinations of antiviral agents with different action mechanisms have brought about IFN-free treatment regimens, with expressive rates of sustained response, better tolerability and fewer side effects[56]. Some characteristics of the new DAA are summarized in Table 4.

Sofosbuvir

Sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase, with HCV pangenotypic action.

The phase 3 NEUTRINO trial evaluated sofosbuvir (400 mg/d) in combination with PEG-IFN and weight-based RBV (1000 mg to 1200 mg daily) for 12 wk[57]. In the NEUTRINO study, of the 456 patients with HCV genotype 1, 4, 5, or 6, 291 had HCV genotype 1 and 327 began treatment. A total of 17% of patients were black, 71% were non-CC *IL28B* genotype, and 17% had cirrhosis. The SVR rate at 12 wk after treatment was 90%. The variables associated with therapy response were cirrhosis, *IL28B* (rs12979860) genotype and ribavirin exposure. The SVR12 for patients with genotype 1 infection was 89.4% (SVR12 91.6% to HCV subtype 1a and 81.9% to HCV 1b); SVR12 was inferior in patients with cirrhosis (80%) than in those without cirrhosis (92%). Subjects with IL28B CC achieved a 97.9% SVR12 compared to 87.1% among non-CC *IL28B* genotypes[57].

In the FISSION study, 499 patients with HCV genotype 2 or 3 began treatment and 20.5% of patients in all groups had cirrhosis[57]. In this phase 3 trial, among patients receiving sofosbuvir-ribavirin, the predictive factors associated with SVR12 were HCV genotype, presence of cirrhosis, HCV-RNA viral load at baseline and ribavirin exposure. The response rates were lower among patients with HCV genotype 3 than among those with genotype 2 (55.7% *vs* 97.1%); in addition, SVR rates observed were worse for cirrhotic patients than for those without cirrhosis (46.9% *vs* 72.1%), and patients with HCVRNA $\geqslant$ 6 $\log_{10}$ UI/mL at baseline also had lower SVR rates at week 12 (61.6% *vs* 78%).

In both Neutrino and Fission trials, known variables such as older age, black race (self-reported), body mass index $\geqslant$ 30 kg/m^2 that are commonly associated with failure of previous IFN-based treatments were not

Table 4 Characteristics of the "New-wave" direct acting antivirals and the most important variables associated with sustained virological response

Drug	Characteristics	Resistance-associated	SVR predictive factors	OR[1]	*P*-value[1]	
Sofosbuvir	Nucleotide analogue HCV NS5B	HCV mutation S282T	Genotype 1			McHutchison *et al*[15]
	Polymerase inhibitor		Cirrhosis: no *vs* yes	3.93	0.0018	Neutrino study
	Against all HCV genotypes		IL28B: CC *vs* CT/TT	7.99	0.006	
			RBV exposure (mg/kg per day)	1.39	0.0005	
			Genotypes 2 and 3			
			HCV genotypes 2 *vs* 3	42.49	< 0.0001	Fission study
			Cirrhosis: no *vs* yes	2.94	0.005	
			HCV RNA baseline: < *vs* ⩾ 6 Log IU/mL	2.33	0.009	
			RBV exposure (mg/kg per day)	1.26	0.002	
Simeprevir	NS3/4A serine protease inhibitor	Q80K-HCV subtype 1a	HCV 1a: Q80K: no *vs* yes	0.19	1.7×10^{-5}	Jacobson *et al*[61]
	HCV genotype 1	R155K	F0-F2 *vs* F3-F4	2.09	0.029	Quest-1 study
		D168V - HCV subtype 1b	IL28B: CC *vs* CT/TT	5.11	1.3×10^{-4}	
			HCV RNA baseline: ⩽ *vs* > 800.000 IU/mL	3.13	0.028	
Daclatasvir	NS5A replication complex inhibitor	NS3 polymorphisms	HCV genotype 1a *vs* 1b	2.82	0.025	Hézode *et al*[63]
	Against all HCV genotypes	NS5A-A30K	HCV genotypes 2 *vs* 3	1.31	0.740	Sulkowski *et al*[46]
Ledipasvir	HCV NS5A replication complex inhibitor					Afdhal *et al*[67]
	HCV genotype 1					
ABT-450	NS3/4A protease inhibitor		Treatment *vs* placebo	7.19	4.3×20^{-11}	Feld *et al*[70]
Ritonavir	HCV NS5A replication complex inhibitor					
Ombitasvir	HCV NS5A inhibitor (Pangenotipic)		HCV genotype 1a			
Dasabuvir	HCV NS5B RNA non-nucleoside polymerase inhibitor		Ribavirin: with *vs* without	3.50	0.038	Ferenci *et al*[69]
	HCV genotype 1					

[1]Statistical analyses were performed using Fisher's test, two-tailed. An alpha error < 5% was considered. IL28B: Interleukin-28B; HCV: Hepatitis C virus; SVR: Sustained virologic response; RBV: Ribavirin.

associated with SVR based on the multivariate logistic regression.

Notably, 28 patients from NEUTRINO study and the 74 patients from FISSION study who received sofosbuvir relapsed after a virologic response at the end of treatment; however, the reason for this non-response is unknown. Testing for viral resistance did not find the S282T HCV mutation associated with Sofosbuvir.

Daily sofosbuvir (400 mg) and weight-based ribavirin plus weekly pegylated IFN for 12 wk is one of the recommended treatment regimens for IFN-eligible subjects with HCV genotype 1, 2 and 3 infection[58,59].

Cost-effectiveness exploratory analysis showed that in developed countries the strategy of treating all individuals with genotype 1 and 4 chronic hepatitis C with Peg-IFN alpha-2a, ribavirin and sofosbuvir (12 wk) as well as treating HCV genotype 2 and 3 patients with sofosbuvir PR (12 wk) would be cost-effective when compared to no treatment or to restricting therapy according to stage of fibrosis (⩾ F2, analyzed by non-invasive tests). This analysis has considered other treatment options and has showed that treating everyone would be cost-effective if the overall increase in treatment reached up to about £ 37500, but not over. If costs increased to greater than £ 37500 the strategy to restrict the treatment for patients with METAVIR ⩾ F2 would be the most cost effective. Unfortunately these results can't be extrapolated to developing countries, where local cost-effectiveness analyzes need to be evaluated[60].

Simeprevir

Simeprevir is a specific inhibitor of the HCV NS3/4A serine protease, which is used to treat HCV genotype 1 patients. The recommendations have comprised a treatment regimen of simeprevir plus PR for HCV infected patients, especially HCV genotype 1b. If the IFN-based treatment is not appropriate for patients, combination with sofosbuvir ± ribavirin should be considered.

In the Quest-1 trial, patients with HCV genotype 1 were treated with simeprevir once daily plus peg-IFN alpha 2a and ribavirin compared to PR treatment[61]. Therapy period was 24 wk or 48 wk in the simeprevir group agreeing with response-guided therapy. The SVR12 from the Simeprevir group was higher when compared to the PR group (80% *vs* 50%, respectively), without worsening the adverse events associated with peg-IFN. RVR and SVR12 was better in the simeprevir group compared to the PR group independent of

baseline HCV RNA, HCV subtype (1a without Q80K or 1b), METAVIR score (F0-F2, F3, or F4), *IL28B* genotype (CC, CT, or TT) and race. Cirrhotic patients achieved 58% SVR12 in the Simeprevir group compared with 29% in the PR group; F0-F2 had 83% and 60% SVR12 in simeprevir and PR regimens, respectively; F3, achieved 78% SVR12 when treated with simeprevir and 26% SVR12 with PR treatment. Black or African-American patients in the simeprevir group achieved 63% SVR12 compared with 25% in the PR group; 59% black or African-American patients treated with simeprevir had RVR and 94% of them achieved SVR12. In the Quest-2 trial, simeprevir was added to peg-IFN alpha 2a or peg-IFN alpha 2b PR, and the combination improved SVR in treatment-naive patients with HCV genotype 1 infection[62].

In the Cosmos study, combination treatment with simeprevir and sofosbuvir, in an IFN-free regimen was evaluated in 167 patients with chronic HCV genotype 1 infection who had previously not response to peg-IFN and ribavirin or who were untreated[57]. There were two groups: cohort 1 (enrolled patients with a null response to PEG-IFN/RBV with Metavir fibrosis stage 0 or 2) and Cohort 2 (including patients who were treatment-naïve or with a previous null response with Metavir fibrosis stage 3 or 4). SVR12 were reached within 154 (92%) patients, 90% in cohort 1 and 94% in-group 2.

The ATTAIN phase Ⅲ study compared two treatments regimens, simeprevir plus PR and telaprevir plus PR in HCV genotype 1 patients who were previously treated with PR therapy. The SVR in the simeprevir group was achieved in 69.7% in partial responders and in 43.6% of previous null responders to PR. In the teleprevir group, the SVR was 68.5% among partial responders and 46.6% among the null responders[47,59].

For patients with HCV genotype 1a infection, the Q80K polymorphism is a negative predictive variable for achieving SVR, and baseline resistance testing may be considered because the mutation clearly modifies the probability of SVR to simeprevir. The SVR12 was 90% in the HCV genotype 1 group; however, in subtype 1a with Q80K polymorphism at baseline, SVR12 was 52% whereas in the 1a group without Q80K, SVR12 was 85%[61]. Most likely, the Q80K polymorphism does not prevent treatment with simeprevir plus sofosbuvir since SVR rate remains high in patients with genotype 1a/Q80K infection treated with this regimen (SVR 12 in cohort 1 was 86%)[57].

Patients treated with simeprevir who did not achieve SVR12 progressed with increasing number of mutations up to the time of failure in 92% (35 of 38) of patients. In HCV genotype 1a infected patients, the mutations were mainly R155K and for patients infected with HCV genotype 1b, the mutations were mainly D168V[57].

Daclatasvir

Daclatasvir is a HCV NS5A replication complex inhibitor that has great antiviral activity and is effective in patients infected with HCV genotypes 1, 2, 3 and 4. Treatment may be combined with peg-IFN PR or sofosbuvir PR and therapy duration varies between 12 and 24 wk.

The phase Ⅱb COMMAND-1 study analyzed HCV genotype 1 untreated patients and showed SVR rates of 87% in subtype 1b and 58% in subtype 1a patients[63]. This trial evaluated the combination of sofosbuvir and daclatasvir in HCV genotypes 1, 2 and 3 infected patients[46]. The results showed that once-daily oral daclatasvir plus sofosbuvir was related with increased rates of SVR among patients infected with HCV genotypes 1, 2 or 3, comprising those with no response to previous therapy with telaprevir or boceprevir. Among individuals infected by genotype 1, 98% of previously naive patients and 98% who did not achieve SVR with first-generation protease inhibitors had SVR12.Among HCV genotype 2 patients, 92% had SVR as well as 89% of HCV genotype 3 subjects. The SVR rates at 12 wk after treatment were similar in subgroups in accordance with viral subtype (genotype 1a, 98% *vs* genotype 1b, 100%), *IL28B* genotype (CC, 93% *vs* CT/TT, 98%), race (white, 97% *vs* black, 96% and other race, 90%), ribavirin presence (ribavirin, 94% *vs* without ribavirin, 98%) and, finally, previous treatment failure with telaprevir or boceprevir (98%)[46].

The virologic response was high despite the presence or absence of baseline NS3 mutations that confer resistance to telaprevir or boceprevir. At baseline, resistance analysis detected an NS5A-A30K existing polymorphism related with daclatasvir resistance at baseline; nevertheless, all of the patients with preexisting daclatasvir resistance variants achieved SVR[46,63,64].

Ledipasvir

Ledispavir is a NS5A inhibitor that has been associated with high rates of SVR among patients with HCV genotype 1. Multicentric trials have showed that combination treatment with sofosbuvir and ledipasvir for 12 wk was effective in patients with HCV genotype 1 infection[65-67].

In naïve patients, the SVR12 rate among those who were treated with 12 wk of ledipasvir plus sofosbuvir was 99%; among patients treated with 12 wk of ledipasvir plus sofosbuvir PR, the SVR rate was 97%. Among individuals who received 24 wk of ledipasvir plus sofosbuvir the SVR12 was 98%, while subjects treated with 24 wk of ledipasvir plus sofosbuvir PR had an SVR of 99%[65]. In this trial, the SVR rates were similar among known subgroups traditionally associated with low chances of SVR such as cirrhotic patients in whom SVR12 ranged from 94% to 100%[65]. Patients with HCV genotype 1a had 97%-99% rates of SVR; among those with a non-CC IL28B allele, the SVR12 rate also ranged between 97%-99%, and among black patients, the SVR12 ranged from 91% to 100%[65].

Good SVR rates were also detected when previous non-responders to IFN-based therapies (including protease inhibitors previous non-responders) were treated with sofosbuvir plus ledipasvir regimens. A trial with 440 patients previously non responders to IFN

associated treatment, including 20% cirrhosis patients and 79% HCV genotype 1a infected individuals, the SVR12 rates in treatment groups were as follows: 94% response in patients receiving 12-wk-ledipasvir sofosbuvir; 96% among those who received 12 wk of ledipasvir-sofosbuvir and ribavirin; 99% among patients who received 24 wk of ledipasvir-sofosbuvir; and 99% in the group that received 24 wk of ribavirin and ledipasvir-sofosbuvir[67]. Treatment was well tolerated with rare cases of breakthrough or relapse.

ABT-450/r-ombitasvir and dasabuvir

A 12-wk treatment with the combination of ABT-450/r-ombitasvir, an NS5a inhibitor (a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir), dasabuvir, NS5B RNA non-nucleoside polymerase inhibitor (250 mg twice daily) and ribavirin according to body weight was tested in the HCV genotype 1 infected non-cirrhotic patients who achieved SVR12 rates of approximately 96%[68-71]. There was no difference in SVR12 among HCV genotype 1b or 1a. Among patients with HCV genotype 1b, the SVR rates were 99.5% including ribavirin in the regimen and 99.0% without ribavirin; on the other hand, among those with HCV genotype 1a, the addition of ribavirin appeared to increase the SVR rates (97.0% and 90.2%, SVR12 with and without ribavirin, respectively)[69]. Another trial analysed the efficacy of ABT-450/r-ombitasvir and dasabuvir ± ribavirin among HCV genotype 1b infected patients without cirrhosis and previously treated with peg-IFN and ribavirin. The SVR12 rate including ribavirin was 96.6% and without ribavirin, was 100%[71]. The SVR rates were 95.3% for previously relapsed patients, 100% among patients with previous partial response and 95.2% among those with a null response[71].

MK-5172 + MK-8742 ± RBV in HCV genotype 1

MK-5172 100 mg once daily plus MK-8742 50 mg once daily and RBV 1000-1200 mg divided twice daily is another treatment regimen, which is under evaluation for HCV genotype 1 patients. Therapy-naïve patients with HCV genotype 1 and cirrhosis were treated for 12 wk with MK-5172 + MK-8742 ± ribavirin and obtained SVR 4/8 rates of 90% with ribavirin containing regimen and 97% when ribavirin was not included. Groups in which patients were treated for 18 wk presented SVR rates of 97% with or without ribavirin. Previous HCV genotype 1 patients null responders to PR therapy when treated for 12 wk had a 94% SVR 4/8 rate in the regimen with ribavirin, and a 91% SVR 4/8 rate in the regimen without ribavirin. When treated for 18 wk, the SVR4/8 was 100% in the ribavirin-containing regimen group and 97% if ribavirin was not added to therapy[72].

LT

Treatment of HCV infection in the transplant scenario is indicated in two different situations: patients awaiting LT to prevent HCV infection of the graft; and patients with hepatitis C recurrence after LT in order to reduce the damage to the already infected graft.

Patients awaiting LT

Post-transplant recurrence of HCV is common in patients who have detectable HCV RNA at the time of transplantation. In patients waiting for LT, antiviral therapy may be indicated because it prevents graft infection if HCV RNA becomes undetectable at least 30 d prior to transplantation[59]. Current IFN-based treatments are not effective and safe in patients with advanced cirrhosis[73]. With the recent approval of sofosbuvir, simeprevir and daclatasvir in the United States and Europe, IFN-free regimens are being used in those cirrhotic patients with compensated liver disease awaiting LT. Guidelines have recommended antiviral therapy to Child-Pugh A patients in whom the indication for transplantation is HCC[59].

Sixty-one patients with hepatocellular carcinoma, HCV- any genotype, Child-Pugh score $\leqslant$ 7, on LT wait lists, were evaluated in an open-label phase 2 study, that aimed to avoid HCV recurrence after LT. Subjects received up to 48 wk sofosbuvir and ribavirin before LT. Among them, 46 received transplanted livers, 43 (93.5%) patients had HCV-RNA level less than 25 IU/mL at the time of transplantation; 30 of 43 subjects (70%) achieved a post-transplantation SVR at week 12. In this analysis, 10 (23%) had recurrent infection that was related inversely to the number of consecutive days of undetectable HCV RNA before transplantation. The authors concluded that sofosbuvir and ribavirin before LT can prevent post-transplant HCV recurrence[74].

In decompensated cirrhotic patients (Child-Pugh B or C) waiting for transplantation, antiviral therapy may be offered on an individual decision in experienced centers. Data about safety and efficacy data are still scarce and therefore there are no clear recommendations as well as there are insufficient data about time of treatment, post-LT relapse rate and safety. Of note, a few patients without HCC may be delisted they improve liver function and/or portal hypertension after achieving SVR.

Post-LT hepatitis C recurrence

Hepatitis C recurrence after transplantation is responsible for reduced post-transplant survival. Approximately 30% of patients with HCV develop severe recurrent acute hepatitis C after transplant which rapidly progress to liver cirrhosis; 5% to 7% have fibrosing cholestatic hepatitis and may rapidly progress to death[75,76]. Patients with HCV post-transplant recurrence should be considered for therapy. The treatment of recurrent HCV infection with combination of peg-IFN PR after LT is associated with low rates of SVR, ranging between 15%-35%, and with significant adverse effects[77]. The triple therapy adding boceprevir and telaprevir to PEG-IFN and ribavirin have improved the therapeutic efficacy in comparison with dual therapy, increasing in 30% the SVR rate, however, this is accompanied by an additional cost and high

toxicity with often serious adverse events and important drug interactions, especially with calcineurin inhibitors[78]. The new wave of DAA with fully oral schemes of simeprevir, sofosbuvir and/or daclatasvir has achieved significant SVR rates and better tolerability. Combination of sofosbuvir PR has been associated to better SVR rates as high as 70% and good tolerance[79].

All-oral sofosbuvir plus daclatasvir combination shows high virological efficacy in liver transplant recipients and appears not to interact with immunosuppressants[80]. Drug-drug interactions may be important in the post-transplant setting; until this moment, no clinically significant drug-drug interactions have been found between sofosbuvir, simeprevir or daclatasvir and cyclosporine and tacrolimus imunossupressants.

FINAL REMARKS

As the efficacy of new drug regimens used to treat chronic hepatitis C is improved, the influence of host and viral factors that may interfere with the chances of obtaining a SVR decreases.

Because IFN-based antiviral therapies were the main option, several studies searched for variables that are predictive of SVR in patients with chronic hepatitis C. Various viral factors, the host and the genetic variables, metabolic and immunological characteristics have influenced the response to IFN-based therapy. The most important viral factors that influence the response to IFN-based antiviral treatment appear to be HCV genotype and HCV RNA kinetics. Conversely, the strongest identified host baseline risk factor associated with SVR was IL28B polymorphisms, especially rs12979860 and rs8099917. Other important SVR risk factors at baseline were high viral load (> 600.000 UI/mL), older age, African ancestry, body weight, insulin resistance, steatosis, and advanced fibrosis stage. Viral kinetics is a strong predictor of SVR, particularly when the viral load is not detectable at week 4 (RVR).

With the arrival of first generation DAAs, some variables previously associated with SVR lost their value. Considering telaprevir and boceprevir, viral kinetics is the most important predictive factor of SVR. The IL28B was associated with greater chances to shorten therapy but not to achieve SVR.

With the new generation DAAs, it has been possible to identify treatment regimens that substantially improve SVR rates, including difficult to treat subgroups of patients such as patients with cirrhosis. Nonetheless, HCV subtype 1a, cirrhosis, some cases of HCV genotype 3 and "failure" of viral load decrease on-treatment may still indicate low rates of non-response with regimens that include sofosbubir, daclatasvir and ledipasvir.

It is expected that newer high genetic barrier drug treatment regimens will produce very high SVR rates with short therapy durations independent of the presence of the current known unfavorable host, viral and immunogenetic variables associated with response.

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