

Current status and emerging challenges in the treatment of hepatitis C virus genotypes 4 to 6

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Abstract

Hepatitis C virus (HCV) genotypes 4, 5 and 6 are mainly present in Africa, the Middle East and Asia and they have been less extensively studied with respect to epidemiology, natural disease history and therapeutic endpoints. Response rates to a 48-wk combined peginterferon/ribavirin treatment range to 40%-69% for HCV 4, 55%-60% for HCV 5 and 60%-90% for HCV 6. Response-guided schedules are recommended to optimize the outcomes of peginterferon/ribavirin treatment in HCV 4 and, in form of preliminary

data, for HCV 6, but no data are yet available to support such an individualization of therapy for HCV 5. Recently, the direct-acting antivirals (DAAs) with pan-genotypic activities simeprevir, sofosbuvir and daclatasvir have been recommended in triple regimens with peginterferon/ribavirin for the treatment of HCV genotypes 4 to 6 infections. In the future, DAA-based interferon-free therapies are awaited to drastically improve treatment outcomes in HCV. However, efforts to improve treatment outcomes with peginterferon/ribavirin should continue, as the HCV 4-6 infected population is mainly based in resource-limited settings with restricted access to the costly DAAs.

Key words: Hepatitis C virus; Genotype 4; Genotype 5; Genotype 6; Pegylated interferon; Ribavirin; Direct-acting antivirals

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Core tip: Hepatitis C virus (HCV) 4, 5 and 6 are lesser known genotypes mainly encountered in Africa, the Middle East and Asia. Studies, mostly retrospective, have reported response rates to a 48-wk peginterferon/ribavirin combination ranging to 40%-69% for HCV-4, 55%-60% for HCV-5 and 60%-90% for HCV-6. Increasing evidence has supported a response-guided approach for HCV-4, whereas no robust data are yet available concerning tailoring of treatment duration for HCV-5 and HCV-6. Direct-acting antivirals may significantly improve treatment outcomes in HCV, but use of these agents in countries endemic for HCV 4-6 is currently precluded by the very high costs.

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INTRODUCTION

Hepatitis C virus (HCV) remains a major health problem worldwide with over 170 million persons chronically infected and a burden of 300000 deaths annually^[1,2]. Phylogenetic analyses of viral genomic sequences have identified at least 6 major HCV genotypes (and more than 70 subtypes), each with a distinct geographical distribution and sensitivity to antiviral treatment^[3,4]. HCV 1, 2 and 3 are widely disseminated genotypes and have been thoroughly assessed with regard to epidemiology, natural disease history and treatment outcomes. Conversely, HCV 4, 5 and 6 have a restricted geographical distribution, mainly based in countries with limited resources and research facilities, thus epidemiological reports and treatment advances for these genotypes have been generally deficient. Prevalence of HCV genotypes 4 to 6 across different countries is summarized in Table 1. Genotype 4 is encountered throughout Middle East and Africa^[5-12], whereas a spread of the infection has been described in other countries^[13-15], particularly in Southern Europe^[16-20]. HCV 5 is rare outside South Africa^[21-23], but its sporadic presence has been reported in different parts of the world^[11,15,24-28], including a pocket of the infection in Southeast Greece^[29]. Lastly, HCV 6 and its subtypes are found mainly in Asia^[30-35]. Crucially, due to the phenomenon of globalization, the prevalence of the HCV 4 to 6 genotypes outside of these “typical” areas is awaited to increase in forthcoming years.

During the past decade, a dual combination of pegylated interferon (PegIFN) and ribavirin (RBV) has represented the standard of care (SOC) for treating chronic hepatitis C (CHC). In 2011, introduction of first generation direct-acting antivirals (DAAs), the NS3/4A protease inhibitors (PIs) boceprevir and telaprevir, has boosted rates of sustained viral response (SVR; *i.e.*, negative HCV-RNA at 6 mo or more after cessation of treatment) in both naïve and treatment-experienced patients, although this only regarded the most difficult-to-treat CHC genotype 1^[36]. Latter, in 2013, approval of the second generation DAA, NS5B polymerase inhibitor (PI) sofosbuvir, has been a further step forward due to its pangenotypic effect on HCV, better pharmacokinetics and improved resistance profiles^[37]. In the light of the rapidly changing paradigm of treating CHC, new drugs were recently approved or await approval. However, in the era of DAAs, optimal treatment of HCV genotypes 4 to 6 remains, more than ever before, to be defined. Indeed, most treatment data rely on retrospective studies, extrapolations using other HCV genotypes as reference, and expert opinions.

Herein, we aimed to a concise overview on the treatment of HCV 4 to 6, including recent proposals for a response-guided treatment approach as well as the available data and future perspectives on the use of DAAs with respect to these lesser known HCV

genotypes.

TREATMENT OF HEPATITIS C

GENOTYPES 4 TO 6

Combination therapy with PegIFN and RBV

Hepatitis C virus genotype 4: HCV 4 has been traditionally considered a difficult to treat genotype, mainly because of the disappointing SVR rates (5%-25%) obtained in the early clinical trials using conventional interferon monotherapy^[38,39]. Later introduction of RBV, used in conjunction with PegIFN, has significantly increased the efficacy of treatment, although response rates were still lower as compared to genotype 2 and 3 patients. Figure 1 summarizes results of prospective studies evaluating a fixed 48-wk treatment using standard-dose PEGIFN and RBV (PegIFN α -2a 180 μ g or PegIFN α -2b 1.5 mg/kg and RBV 1-1.2 g/d) in HCV 4^[40-46]. Overall, SVR rates ranged between 40% and 69%. However, a significant discrepancy could be noted between the SVR rates reported in highly endemic countries (SVR 60%-69% in studies conducted in Egypt and the Middle East)^[40,42,43,47-50] and those (generally < 60%) reported in European populations infected with HCV 4; including 55% in Spain^[51], 40.3% in France^[52] and 43.5% in a cohort from Greece^[53]. This difference has prompted the hypothesis of an impact of ethnicity on antiviral response, with 2 French analyses suggesting Egyptian (*vs* European) origin as a favorable prognostic indicator for SVR^[52,54]. However, no solid pathogenetic basis has been provided for this phenomenon, although genetic or immunological ethnic-specific differences have been put forward^[55,56]. Unlike the French observations, we could not identify any influence of Greek ($n = 101$) *vs* Egyptian ($n = 76$) origin on treatment outcomes^[57], and only age ≥ 45 years [odds ratio (OR) = 0.42, $P = 0.01$], presence of diabetes (OR = 0.23, $P = 0.007$), advanced liver fibrosis (Metavir F3-F4; OR = 0.39, $P = 0.01$) and treatment suspension (OR = 0.17, $P = 0.007$) were independent negative associations, in line with previous studies assessing predictors of response in HCV 4^[40,42,43,52,54,58-63] (Table 2). The importance of metabolic factors has been highlighted by the observation of a beneficial effect of using an insulin-sensitizing agent, such as pioglitazone, in conjunction with antiviral treatment in patients with insulin resistance (homeostasis model assessment index > 2)^[64]. Congruently, presence of hepatic steatosis, known to be a poor predictor of treatment in CHC, has been linked to host metabolic factors in HCV 4 rather than to a direct viral steatogenic effect as in the case of HCV 3 infection^[65,66]. Other host factors, including the IL-28B TT genotype and high values of the interferon-c inducible protein 10 (IP-10) have been associated with a poor therapeutic outcome^[59]. Interestingly, Boglione *et al.*^[67] have recently proposed use of the IL-28B polymorphisms upstream as a genuine basis for the identification of patients

Table 1 Indicative reports of hepatitis C virus genotype 4 to 6 prevalence in different continental areas

	Genotype 4		Genotype 5		Genotype 6	
	Country	Prevalence	Country	Prevalence	Country	Prevalence
Africa	Egypt ^[10]	91%	South Africa ^[22,23]	40%		
	Gabon ^[12]	71%				
	Cameroon ^[7]	76%				
	Nigeria ^[8]	60%				
Middle East	Saudi Arabia ^[11]	60%	Syria ^[25]	10%		
	Lebanon ^[9]	30%	Saudi Arabia ^[11]	1%		
	Syria ^[5]	30%				
	Iraq ^[6]	35.40%				
Asia	China ^[33]	0-1.7%			Hong Kong ^[33-35]	10%-30%
					Vietnam ^[30]	14%
					South Korea ^[31]	1.40%
					China ^[32,35]	0-50%
Europe	France ^[15]	4%-10%	France ^[15,26]	3%-14.2%		
	Spain ^[17,20]	1.4%-14%	Belgium ^[28]	1%-5%		
	Italy ^[16,19]	1.4%-3.1%	Spain ^[27]	0-10.3%		
	Greece ^[18]	13.2%-15.2%	Italy ^[24]	0-0.1%		
			Greece ^[18,29]	0.4%-1.9%		
America	United States ^[13,14]	0-2%				

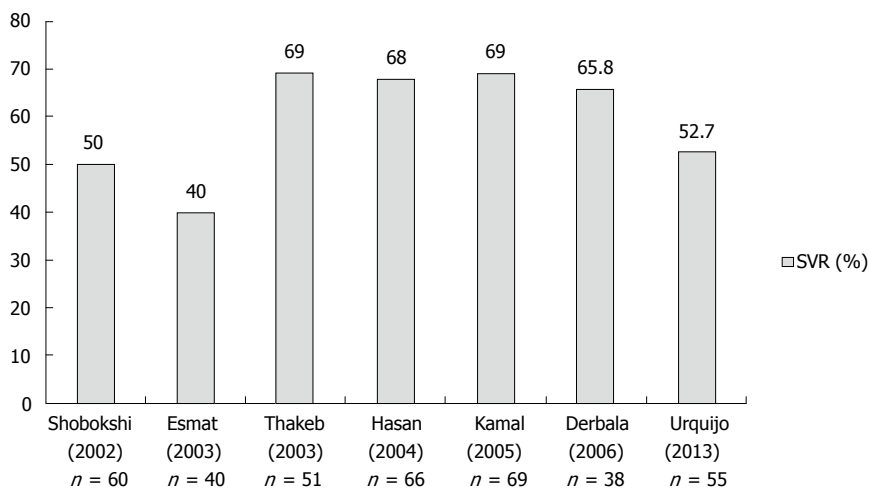


Figure 1 Prospective studies evaluating a fixed 48-wk treatment using a standard dose of pegylated interferon and ribavirin in patients with hepatitis C genotype 4. SVR: Sustained viral response.

Table 2 Predictors of response to antiviral treatment in patients with hepatitis C virus genotype 4 infection

Predictor	Ref.
Age	[57]
Liver histopathology (advanced fibrosis/severe steatosis)	[40,52,54,60]
Baseline viral load ¹	[42,43]
Ethnicity	[52,54]
Diabetes/Insulin resistance	[49,54,57]
IL28B polymorphisms	[58,63]
Plasma levels of IP-10 ²	[59]
HCV 4 subtypes	[52]
Co-infections (HIV, Schistosomiasis)	[38,61]

¹Most studies used a cut-off value of 400,000 IU/mL; ²Interferon-c inducible protein 10. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IP-10: Inducible protein 10.

unlikely to respond to standard dual therapy, and thus candidates for a DAA regimen. This individualized approach merit further robust assessment.

Definition of the optimal treatment duration is paramount to reduce costs and improve treatment tolerability without compromising the therapeutic efficacy. Due to the consistently lower response rates with 24 wk of therapy, a 48-wk treatment duration has been recommended as the SOC for genotype 4, similar to genotype 1^[43,48,68]. A further refinement has been use of early viral responses to allow for shorter treatment durations in highly responsive patients (*i.e.*, response-guided approach). In a double-blind randomized study, Kamal *et al.*^[43] showed that in patients achieving a complete early viral response (EVR; defined as a negative HCV-RNA at week 12 of treatment), the SVR rate was 86% with a 36-wk therapy and 92% with 48 wk of therapy ($P = 0.8$), whereas PegIFN dose reductions were significantly more common in the 48-wk group. Two randomized controlled trials, one including exclusively genotype 4^[69] and one including a mixture of both genotype 1 or 4 patients^[70] have assessed the utility of a

Table 3 Studies reporting rates of sustained virological response to 48-wk interferon-based combination therapy in patients with hepatitis C genotype 5

Author/Country/Year	No. patients	Regimen	SVR
Legrand-Abrevanel/France/2004 ^[75]	12	Standard/Pegylated IFN plus RBV	63.60%
Delwaide/Belgium/2006 ^[74]	6	Standard/Pegylated IFN plus RBV	83%
Bonny/France/2006 ^[78]	87	Standard/Pegylated IFN plus RBV	60%
¹ Antaki/Syria/2008 ^[77]	26	Standard/Pegylated IFN plus RBV	54%
D'Heygere/Belgium/2011 ^[79]	38	Standard/Pegylated IFN plus RBV	55.30%
Karatapanis/Greece/2012 ^[29]	10	Pegylated IFN plus RBV	60%
Antaki/Syria/2012 ^[76]	49	Standard/Pegylated IFN plus RBV	49%
Mauss/Germany/2012	24	Pegylated IFN plus RBV	58%
Papastergiou/Greece/2014 ^[81]	27	Pegylated IFN plus RBV	63%

¹Thirteen out of 26 patients received 24 wk of treatment due to personal, financial or medical reasons. IFN: Interferon; RBV: Ribavirin; SVR: Sustained virological response.

response-guided tailoring of treatment. Based on the results of these studies, a 24- and 36-wk treatment duration have been established as sufficient in patients with a rapid viral response (RVR, defined as negative viral load at week 4 of treatment) and EVR respectively. Contrarily, Ferenci *et al.*^[71] showed that a 72-wk extended-duration therapy may benefit slow responders; *i.e.*, those non achieving RVR but attaining at least a partial (*i.e.*, a $\geq 2\log_{10}$ drop in serum HCV-RNA) EVR and a negative HCV-RNA at week 24. Critically, a suboptimal PegIFN alpha-2a dose (135 $\mu\text{g}/\text{wk}$ after week 48) may have compromised SVR rates in this study. Patients with detectable viral load at the end of week 24 are unlike to respond to treatment, and therefore assessment based on serum HCV-RNA at this time-point may serve as a futility rule, as indicated by its 92.8% negative predictive value on SVR^[53]. To date, no robust conclusions can be drawn regarding efficacy of PegIFN alpha-2a vs alpha-2b in patients infected with HCV 4^[72].

Hepatitis C virus genotype 5: Mainly due to its low worldwide prevalence, HCV 5 probably represents the less studied HCV genotype with respect to therapeutic endpoints. Epidemiological reports from France, Belgium, Canada, Syria and Greece argue that patients infected with HCV 5 have specific epidemiological characteristics: they are predominantly females of advanced age and they are characterized by high baseline viremia and advanced hepatic fibrosis^[25,29,73-75]. Despite presence of these classical negative predictors of treatment response, SVR rates have been reported to 55%-60%^[29,74-81], although most of the therapeutic studies on HCV 5 (Table 3) have had inherent limitations, including the retrospective design, small sample and extreme heterogeneity with respect to treatment modalities^[74-76,78] and patient sampling^[79]. Currently, a fixed 48-wk course of combined PegIFN and RBV is recommended for patients with HCV 5. However, the intrinsic sensitivity of HCV to combined antiviral therapy, and thus the ideal treatment duration, remains controversial. In a retrospective study by Antaki *et al.*^[77], 13/26 patients were treated for 24 wk

due to personal, financial or medical reasons, and no impact of treatment duration (24 wk vs 48 wk) was found on SVR. In support of a 24-wk treatment, some retrospective data^[75,78] suggested that response of HCV is similar to that observed for genotypes 2 and 3, although this was disputed in more recent studies^[76,79]. Clearly, extrapolations using other HCV genotypes as reference are not an appropriate basis for treatment standardization. In a prospective, open label, single-arm trial we have evaluated 27 patients with HCV 5 and the SVR was 63%, whereas non-response was mainly due to relapse (26.1%)^[81]. To our knowledge this is the only prospective therapeutic trial using exclusively a combination of PegIFN and RBV and including only treatment-naïve patients. The most striking finding of our study was the excellent predictive value of early viral responses on SVR: the positive predictive value (PPV) of RVR was 93.8%, whereas the negative predictive value when not achieving EVR was 100%. Based on these data, a response-guided schedule may be a viable option for patients with HCV 5^[82]. Thus, it merits appropriate consideration in future trials, possibly conducted on a multi-center basis.

Hepatitis C virus genotype 6: Small studies, using a combination of either standard interferon^[83,84] or PegIFN^[85,86] and RBV have examined treatment outcomes in HCV 6. Overall, SVR rates have ranged to 60%-90%, indicating a more favorable response in comparison to HCV 1 and comparable to that of HCV 2 and 3. Crucially, a favorable IL28B status among Asians patients may have contributed significantly to these good results^[87]. Apart from baseline viral load and the degree of hepatic fibrosis, which represent classical predictors of treatment response in CHC, other host factors such as age, BMI and adherence to treatment schedule have been identified as relevant in cohorts of patients with HCV 6^[88]. To date, optimal treatment duration for HCV 6 has been a matter of controversy, with studies comparing a 48- vs a 24-wk regimen providing equivocal results (Figure 2)^[86,89-91]. Most studies investigating therapeutic outcomes in HCV 6 have applied 48-wk treatment duration^[83-85].

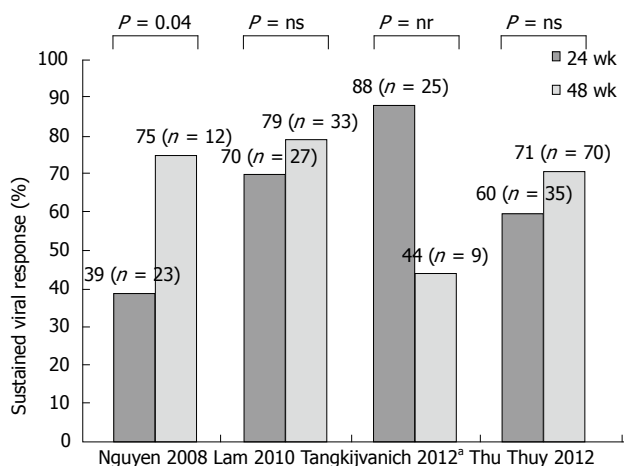


Figure 2 Studies comparing outcomes of 24 vs 48 wk of therapy with pegylated interferon and ribavirin in patients with hepatitis C virus genotype 6. ^aTreatment duration was tailored according to viral response at week 4: Patients with negative hepatitis C virus-RNA received 24 wk of treatment; the remainder received 48 wk. ns: Non-significant; nr: Not reported.

Moreover, in a retrospective analysis by Nguyen *et al.*^[86], the SVR rates were significantly lower with a 24-wk treatment schedule (39% vs 75%, $P = 0.044$). However, two randomized controlled trials including 60 and 105 patients have shown non-inferiority with a 24-wk (vs a 48-wk) regimen of PegIFN alpha/2a and RBV^[89,91]. As in case of other HCV genotypes, individualization of treatment duration based on early viral dynamics may allow for reduction to drug exposure and in treatment costs. In an open-label randomized study by Thu Thuy *et al.*^[91], RVR occurred in about 80% of patients and had a 75%-86% PPV on SVR irrespective of treatment duration; nonetheless, among those with no RVR, even a 48-wk treatment achieved low SVR rates (8%). Efficacy of a response-guided approach based on RVR has been evaluated by Tangkijvanich *et al.*^[90]: in a pilot study including 34 patients with CHC genotype 6, the SVR rate in patients with RVR who underwent a 24-wk treatment was 88%. Based on these data, patients with a RVR may benefit with 24 wk of therapy. On the other hand, interruption of treatment may be the most reasonable option in patients with a detectable viral load by week 12 of therapy (non-EVR), as these patients are unlikely to respond to a 48-wk course^[89,91,92] whereas there is no data to support they might benefit from longer treatment duration. Additionally to the use of early viral responses, evaluation of baseline parameters such as age, the degree of liver fibrosis, viral load and BMI may further rationalized choice of the optimum treatment duration^[88]. Larger randomized trials are awaited to optimize treatment schedules for HCV 6.

Direct-acting antivirals

First generation protease inhibitors: Telaprevir and boceprevir are first generation NS3/4 PIs firstly approved in 2011 for patients infected with HCV 1.

Although both drugs are not approved for HCV 4, telaprevir has shown a modest activity against this genotype. A phase IIa trial (study C210) has assessed the activity of telaprevir on early viral dynamics^[21]. Twenty four patients with HCV 4 were randomized to three groups: telaprevir alone; PegIFN plus RBV; and a triple regimen comprising telaprevir plus PegIFN/RBV. By day 15 of therapy telaprevir monotherapy induced only a 0.77 log₁₀ decline in HCV-RNA levels (vs 4.77 log₁₀ for HCV 1). The viral decline was more pronounced (4.32 log₁₀) when telaprevir was administered together with PegIFN/RBV indicating a synergic effect. A descriptive subanalysis of the C210 study showed that the most frequent mutation accounting for the limited antiviral efficacy of telaprevir monotherapy was the T54A/T previously described for HCV 1^[93]. Interestingly, this mutation has limited or no impact on the efficacy of subsequent treatment with dual PegIFN/RBV.

Indeed, emergence of resistant variants has generally precluded monotherapy with first generation PIs. However, use of these agents in conjunction with PegIFN/RBV still depends on interferon sensitivity, requires a high pill burden and a complex treatment algorithm. Moreover, both drugs may enhance or induce a set of considerable side effects. Anemia, neutropenia and dysgeusia are the most common side effects with boceprevir, whereas anemia, skin rash and anorectal symptoms are more frequently associated with telaprevir. Anemia, occurring in about 40%-50% of cases, may lead to discontinuation of treatment despite management with ribavirin dose adaptations, use of erythropoietin alpha or blood transfusions. Skin rash specifically related to telaprevir is generally mild and manageable using emollients and topical corticosteroids, although, in about 5% of cases, a severe life-threatening cutaneous reaction may lead to treatment discontinuation^[94].

Better-tolerated new generation DAAs with improved pharmacokinetics (allowing once-daily administration) and favorable resistance profiles (allowing interferon-free, all-oral regimens) were recently approved or await approval. These agents, with activities against HCV 4 to 6, will be discussed below.

Simeprevir (TMC435): It is a second generation NS3/4A PI, active against genotypes 1, 2, 4, 5 and 6. It is administered as a once-daily tablet orally and has demonstrated a favorable safety profile and limited drug-drug interactions^[95]. It was approved in November 2013 by the United States Food and Drug Administration (FDA) and in Japan in September 2013.

RESTORE, a phase III, multicenter, single-arm, open-label study, conducted in France and Belgium, evaluated simeprevir (150 mg once-daily for 12 wk in combination with PegIFN/RBV, followed by 12-36 wk of PegIFN/RBV only) in 107 patients with HCV 4, either naïve or treatment-experienced^[96]. Overall, SVR

at week 12 was observed in 65.4% of patients, with rates being particularly high among treatment-naïve (82.9%) and prior-relapsers (86.4%). Both these patient groups were eligible to a shorter (totally 24 wk) treatment duration if they achieved a HCV-RNA < 25 IU/mL at week 4 and undetectable at week 12. These response-guide criteria were met by 88.6% of treatment-naïve and 90.9% of prior relapsers; among them 93.5% and 95% respectively achieved a SVR at week 12. Notably, none patient had a detectable Q80K substitution in the NS3 protease sequence at baseline, associated with decreased efficacy in patients with HCV 1a.

Overall, simeprevir has demonstrated favorable safety profile. By pooling data from phase III clinical trials (QUEST-1, QUEST -2 and PROMISE), discontinuation of treatment due to severe adverse events occurred in 2% of patients receiving a simeprevir plus PegIFN/RBV combination^[97-99]. Rates of adverse events, most commonly fatigue, influenza-like illness, headache, nausea and pruritus, were generally similar between simeprevir/PegIFN/RBV and placebo/PegIFN/RBV groups. Incidence of photosensitivity and rash has been slightly higher with simeprevir (vs placebo), although the vast majority of cases were graded 1/2 in severity. Transient moderate bilirubin increases were noted; however, no clinically relevant cases of hepatotoxicity were recorded.

Recent European guidelines have included a 24-48 wk simeprevir plus PegIFN/RBV combination as an option for HCV 4-related compensated liver disease (including cirrhotics), suggesting interruption of treatment if HCV-RNA levels are \geq 25 IU/mL at week 4, 12 or 24^[100].

Sofosbuvir: This is a nucleotide inhibitor of NS5B, with a pan-genotypic effect activity and a high barrier to resistance. It is administered as an oral 400 mg tablet/day with no food effect, whereas it has been proven safe and well-tolerated in phase II and III clinical trial including > 2000 patients. It was approved by FDA for HCV 1 in combination with PegIFN/RBV, and in HCV 2 and 3 in interferon-free regimens in December 2013 and in Europe in January 2014.

NEUTRINO, an open-label, single-arm, phase III trial, evaluated a 12-wk regimen, comprising sofosbuvir plus PegIFN/RBV, in 327 treatment-naïve patients with genotypes 1, 4, 5 and 6^[101]. However, the vast majority (89%) of the patient population had HCV 1. Overall, 27 out of the 28 (96%) patients with HCV 4, all 6 patients with HCV 6 and the single patient with HCV 5 achieved an SVR, 12 wk after the end of treatment. Currently, a sofosbuvir-based triple combination for 12 wk appears as the most efficacious and easy-to-use interferon containing option for the treatment of HCV genotypes 4 to 6, without the risk for selecting resistant variants in case of treatment failure^[100]. Critically, rates of SVR were relatively lower in cirrhotics in the NEUTRINO trial (80% vs 92% in

patients without cirrhosis), whereas no data with this regimen has been presented in treatment-experienced patients. Thus, it remains unknown whether longer treatment duration may be required for these more difficult-to-treat patient populations.

More recently, promising data have emerged on the efficacy of an interferon-free combination of sofosbuvir plus ribavirin in patients with HCV 4. Ruane *et al.*^[102] randomized (1:1) 60 patients of Egyptian ancestry (treatment-naïve: 28, treatment-experienced: 32; 23% cirrhotics; 17% with the IL28B CC genotype), stratified by prior treatment status and cirrhosis, to receive 12 or 24 wk of sofosbuvir (400 mg/d) plus RBV (1200 mg/d). After 12 wk of treatment, SVR rates were 11/14 (79%) in treatment-naïve and 10/17 (59%) in treatment-experience patients. However, extending the duration of treatment to 24 wk resulted in higher SVR rates in both treatment-naïve (14/14; 100%) and -experienced (13/15; 87%) groups. Thus, a dual sofosbuvir/ribavirin combination given for 24 wk is currently recommended for HCV 4 patients who are interferon-intolerant or -ineligible^[100].

As evident in phase III clinical trials, sofosbuvir in combination with RBV represents a well-tolerated option with rates of treatment discontinuation as low as 1%-2%^[103]. Drug-related adverse events attributable to RBV such as fatigue, insomnia and anemia were the most common, and headache was also frequent. Unsurprisingly, incidence of adverse effects commonly associated with interferon, such as influenza-like illness and depression, was significantly lower and hematological abnormalities were less prominent among patients who receive sofosbuvir/RBV than among those who receive the standard PegIFN/RBV combination^[101]. Consistently, health-related quality of life and health utilities of patients have been shown to be only minimally affected by sofosbuvir/RBV irrespectively to treatment duration^[104,105].

Daclatasvir: This is an HCV NS5A oral PI with a pan-genotypic activity, but a lower barrier to resistance in genotype 1a^[106]. A recent phase II b double-blind, placebo-controlled study evaluated a triple combination comprising daclatasvir plus PegIFN/RBV including treatment-naïve patients with HCV 1 ($n = 365$) or 4 ($n = 30$)^[107]. Patients were randomly assigned (2:2:1) to daclatasvir 20 mg or 60 mg, or placebo once daily plus PegIFN/RBV. Overall, SVR rates (week 24 post-treatment) were 8/12 (66.7%) in HCV 4 patients receiving 20 mg, 12/12 (100%) in those receiving 60 mg and 3/6 (50%) in patients receiving placebo. Patients on daclatasvir did not have adverse events beyond those typical of PegIFN/RBV.

Based on this preliminary data, a daclatasvir (dose: 60 mg/d) plus PegIFN/RBV regimen has been included as an option for the treatment of genotype 1b and 4 patients^[100]. The triple combination should be administered for 12 wk. In those who do not achieve an HCV-RNA level < 25 IU/mL at week 4

and undetectable at week 10, all three drugs should be continued for an additional 12 weeks. Conversely, PegIFN/RBV should be continued alone between week 12 and 24 in those who achieve such response^[100].

Other DAAs evaluated in HCV 4: Phase II trials have evaluated other triple or quadruple drug combinations in patients infected with HCV 4. In the DAUPHINE trial, different dosing schedules of danoprevir boosted with ritonavir plus PegIFN/RBV for 12–24 wk achieved up to 100% of SVR in treatment-naïve patients with HCV 4^[108]. In yet another phase II b study, 25 HCV-4 patients were assigned to asunaprevir 200 mg or placebo twice daily plus PegIFN/RBV; the SVR rates were 89% in those receiving asunaprevir vs 43% in the placebo group^[109]. Lastly, two randomized placebo-controlled trials have evaluated use of mericitabine in combination with PegIFN/RBV including patients infected with HCV 4^[110,111]. In the JUMP-C trial, a 24-wk response-guided combination of mericitabine 1000 mg twice daily plus PegIFN/RBV was well-tolerated and more effective than a standard 48-wk PegIFN/RBV combination^[110].

EMERGING CHALLENGES

While standardization of dual PegIFN/RBV regimens for HCV 4 to 6 is still pending, interferon-based treatment of HCV has been superseded by the introduction of oral DAAs with pan-genotypic activities. These agents are characterized by improved antiviral efficacy and offer the perspective for short-course, all-oral and interferon-free therapies. However, as it is reasonable, most trials evaluating DAAs have focused on the more prevalent and difficult to treat HCV genotype 1. Given obvious difficulties in patient sampling, multi-centric efforts may be necessary to assess therapeutic sensitivity, optimize DAA schedules and establish cost-effective response-guided approaches for HCV 4 to 6. Crucially, the very high cost of HCV DAAs is a central barrier to their widespread use, thus interferon-based treatments are likely to continue to have a role as cost-containing options in low- or lower-middle income countries. This is particularly relevant in the case of genotypes 4 to 6 which are mainly based in resource-limited countries; but with large HCV epidemics, hence these genotypes represent > 20% of the global HCV burden. Therefore, unless low-cost DAAs become available, a large population of untreated patients will continue to spread HCV in these countries and worldwide. Furthermore, treatment with DAAs of special patient population (*e.g.*, patients with kidney disease, HIV coinfection, patients undergoing solid organ transplantation) remains a challenge, as few or no data are available.

In conclusion, it seems we need to wait for a while until arrangement of both practical and logistic issues will allow for low-cost, all-oral and interferon-free regimens, at a level to dramatically change the global epidemics of HCV 4 to 6. Until then, efforts to further

rationalize the use of the traditional PegIFN/RBV treatment should continue.

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