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Hepatitis C genotype 6: A concise review and response-guided therapy proposal

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Abstract

Hepatitis C genotype 6 is endemic in Southeast Asia [prevalence varies between 10%-60% among all hepatitis C virus (HCV) infection], as well as also sporadically reported outside the area among immigrations. The diagnosis of HCV genotype can be inaccurate with earlier methods of genotyping due to identical 5′-UTR between genotype 6 and 1b, hence the newer genotyping methods with core sequencing are preferred. Risk factors and clinical course of HCV genotype 6 do not differ considerably from other genotypes. Treatment outcome of HCV genotype 6 with a combination of pegylated interferon and ribavirin is superior to genotype 1, and nearly comparable to genotype 3, with expected sustained virological response (SVR) rates of 60%-90%. Emerging data suggests that a shorter course 24-wk treatment is equally effective as a standard 48-wk treatment, particularly for those patients who attained undetectable HCV RNA at week 4 (RVR). In addition, baseline and on-treatment predictors of response used for other HCV genotypes appear effective with genotype 6. Although some pan-genotypic direct-acting antivirals have completed phase Ⅱ/Ⅲ studies (sofosbuvir and simeprevir) with clinical benefit demonstrated in small number of patients with genotype 6, broad availability of these agents in Southeast Asia may not be expected in the near future. While awaiting the newer therapy, response-guided therapy seems appropriate for patients with HCV genotype 6. Patients with RVR (representing > 70% of patients) are suitable for 24-wk treatment with expected SVR rates > 80%. Patients without RVR and/or those with poor response predictors may benefit from 48 wk of therapy, and a detectable HCV RNA at week 12 (with no early virological response) serves as a stopping rule. This treatment scheme is likely to have a major economic impact on HCV therapy, particularly in Southeast Asia, wherein treatment can be truncated securely in the majority of patients with HCV genotype 6.

Key words: Hepatitis C; Genotype 6; Epidemiology; Southeast Asia; Treatment; Pegylated interferon; Ribavirin; Response-guided therapy

Core tip: Hepatitis C genotype 6 is endemic in Southeast Asia [prevalence varies between 10%-60% among all hepatitis C virus (HCV) infection], as well as also sporadically reported outside the area among immigrations. The diagnosis of HCV genotype can be inaccurate with earlier methods of genotyping due to identical 5′-UTR between genotype 6 and 1b, hence the newer genotyping methods with core sequencing are preferred. Risk factors and clinical course of HCV genotype 6 do not differ considerably from other geno-

types. Treatment outcome of HCV genotype 6 with a combination of pegylated interferon and ribavirin is superior to genotype 1, and nearly comparable to genotype 3. Emerging data suggests that a shorter course 24-wk treatment is equally effective as a standard 48-wk treatment, particularly for those patients who attained undetectable HCV RNA at week 4.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a worldwide health problem in that it has a global prevalence rate of approximately 3% and affects over 170 million individuals. It is a leading cause of chronic liver disease and hepatocellular carcinoma worldwide in both industrialized and developing countries[1]. However, geographic differences in the overall prevalence and distribution of HCV genotypes have been well recognized[1]. The majority (87%) of HCV-infected individuals are from Western Pacific countries (62.2 million), Southeast Asia (32.3 million), Africa (31.9 million), and Eastern Mediterranean countries (21.3 million)[2,3]. The prevalence of HCV infection is especially higher in Southeast Asia with an estimate prevalence of 2%-12% among general population in some countries[4], compared to the estimated prevalence of 1.6% in western countries such as the United States[5]. Hepatitis C genotypes 1, 2, and 3 are widely distributed globally and have been the focus of most experimental and clinical studies. Genotypes 4 and 5 are found mainly in the Africa and Middle East. Genotype 6 and its subtypes are found mainly in Southeast Asia[2-4,6]. In some countries in Southeast Asia, such as Thailand, Vietnam, and Myanmar, HCV genotype 6 is one of the most common genotype, detected in 10%-60% of all HCV patients[7-14]. In the past, HCV genotype 6 was believed to be confined to Southeast Asia, but in the changing era of increasing migration of populations, it has been recently reported in nearby areas of Asia, such as China, Taiwan, and Hong Kong (China)[6,15], and as far as western countries, such as United States, Canada[16], and Germany[15]. As globalization (*e.g.*, immigration, travel, and cultural diversity) potentially impacts the epidemiology of HCV, the numbers of patients with HCV genotype 6 seen outside Southeast Asia is expected to increase.

Despite the significant burden of the disease, the creditable data regarding the epidemiology and treatment specifically for HCV genotype 6 are rather limited. This may be largely due to the fact that the majority of the HCV genotype 6-infected population is based in developing countries with limited research facilities and restricted access to publication. This review is aimed to summarize the current available data regarding the epidemiology and treatment of HCV genotype 6, as well as to propose a response-guided algorithm of treatment.

CLASSIFICATION AND DIAGNOSIS

Substantial genetic diversityled to the identification and classification of various genotypes and subtypes of the HCV among different geographical areas. Currently, 6 major genotypes and more than 80 subtypes have been identified from around the world; the previously reported HCV genotypes of 7, 8, and 9 that are endemic in Southeast Asia have been re-classified as subtypes of genotype 6[16,17]. Proper classification of HCV genotypes and subtypes is very important clinically and is dependent on nucleotide sequence disparity[6]. Though the ideal method to accurately identify HCV genotype is by directly sequencing of the entire genome, the current, commercially available methods typically use distinct motifs found within the HCV genome to either indirectly or directly genotype HCV, a more resourceful strategy[6]. Indirect method of HCV genotyping uses genotype-specific antibodies and competitive enzyme immunoassays (*e.g.*, Murex HCV Serotyping Assays, Murex Diagnostics, Dartfort, United Kingdom)[6]. Direct methods of genotyping include direct sequence analysis of 5'-UTR only (*e.g.*, TruGene HCV 5'NC, Visible Genetics, Toronto, Canada), restriction fragment length polymorphism analysis and reverse hybridization line probe assay for the 5'-UTR only (*e.g.*, INNO-LiPA HCV I , Innogenetics, Zwijnaarde, Belgium) or both 5'-UTR and core regions (INNO-LiPA HCV Ⅱ, Innogenetics, Ghent, Belgium)[6]. Selection of genotyping assay is crucial, especially for genotype 6 variants as genotype 6 shares identical 5'-UTR sequences with genotype 1b, thus making earlier genotyping methods based solely on 5'-UTR sequences alone unreliable and those tests with additional HCV core-sequencing preferable[6,18-21]. Among the newer genotyping methods, INNO-LiPA HCV Ⅱ assay is one of the most widely used globally. It has been developed on INNO-LiPA HCV I platform with additional sequencing of core regions and demonstrated significant improvement in genotyping accuracy, particularly to differentiate between HCV genotype 1 and genotype 6 variants (about 100% success rate)[6,18-21].

EPIDEMIOLOGY OF HCV GENOTYPE 6

Epidemiologic studies regarding HCV genotype 6 from different parts of the world are summarized in Table 1. In brief, HCV genotype 6 is particularly common in Southeast Asia (prevalence among all HCV infections are 9%-31% in Thailand[7-10], 21%-49% in Myanmar[11,12], 32%-46% in Vietnam[13,14], > 90% in Lao PDR[22], and 56% in Cambodia[23]), and is the most common HCV genotype is some of these countries. In addition, geo-

Table 1 Prevalence of hepatitis C virus genotype 6 in Asia

Country of origin	Population	Genotyping method	Prevalence of HCV genotype 6	Author
Thailand	*n* = 236; Blood donors throughout the country	Reverse hybridization	18.0%	Kanisanon *et al*[7]
	n = 58; Volunteers from four hospitals located in the North, North-east, South and Center of the country	Core sequencing	8.9%	Sunanchaikarn *et al*[8]
	n = 126; Blood donors in the Northern Thailand	Core sequencing	31.0%	Jutavigittum *et al*[9]
	n = 375; Blood donors in the Central Thailand	Core and NS5B sequencing	18.9%	Akkarathamrongsin *et al*[10]
	n = 40; Immigrant workers from Cambodia (*n* = 25) and Myanmar (*n* = 15) in Thailand	Core and NS5B sequencing	56% among Cambodian workers and 26.7% among Myanmar workers	Akkarathamrongsin *et al*[23]
Myanmar	*n* = 110; Blood donors in Yangon and its suburbs	NS5B sequencing	20.9%	Shinji *et al*[11]
	n = 145; Volunteers from four different border cities of Myanmar	Core sequencing	49% (Genotype 6 was mostly found in the Northern cities)	Lwin *et al*[12]
Vietnam	*n* = 308; Patients from urban community-based GI practice in Southern Vietnam	Core sequencing	31.5%	Nguyen *et al*[13]
	n = 135; Blood donors in Hanoi (Northern Vietnam	Core (*n* = 70) and NS5B (*n* = 65) sequencing	45.9%	Pham *et al*[14]
Lao PDR	*n* = 45; Blood donors in Lao PDR	Core and NS5B sequencing	95.6%	Hübschen *et al*[22]
Hong Kong	*n* = 1055; 949 non-IVDU and 106 IVDU from all over Hong Kong	Core sequencing	27.1% (23.6% among non-IVDU and 58.5% among IVDU)	Zhou *et al*[26]
	n = 212; Blood donors	NA	27%	Prescott *et al*[25]
China	*n* = 148; Patients from nine regions in China	Core and NS5B sequencing	13% (Genotype 6 was only observed in the South)	Lu *et al*[24]

Source: Ref. [6], with permission. IVDU: Intravenous drug users; NA: Not available; HCV: Hepatitis C virus; GI: Gastrointestinal; PDR: People's Democratic Republic; NA: Not available.

graphical differences of HCV prevalence in each individual country were observed in which genotype 6 appears to be more prevalent in the Northern areas of Thailand, Myanmar, and Vietnam, when compared with the central and southern regions[9,10,12-14]. It should be noted that the earlier reports of the prevalence of HCV genotype with previous version of HCV genotypic assays may have underestimated the prevalence of HCV genotype 6 (misclassified with genotype 1). Outside Southeast Asia, HCV genotype 6 is also observed in the nearby areas, particularly Hong Kong and the Southern parts of China[24-26]. Interestingly, HCV genotype 6 is somewhat uncommon in the many countries in Southeast Asia, such as Indonesia, Philippines, and Singapore, as well as in the surrounding countries, such as India, Pakistan, Taiwan, and South Korea[4,18]. Apart from the aforementioned areas, HCV genotype 6 encountered elsewhere (*e.g.*, United States, Canada, and Germany) were mostly immigrants from Southeast Asia[15,16].

Nowadays in the Western countries, HCV infections are primarily due to intravenous or nasal drug use and, to a lesser degree, to unsafe medical/surgical procedures, tattooing or acupuncture with unsafe materials, and male homosexual activity[27]. This contrasts with the principal routes of HCV transmission prior to 1990's of blood transfusion and unsafe injection procedures. Despite conflicting published data, several studies have found that many Asian HCV patients have no identifiable risk factor (up to 50%) of HCV acquisition[27]. Intravenous or nasal drug use does not seem to be a major contributing factor to HCV infection. Therefore, inadequately sterilized medical equipment and cultural practices such as acupuncture or cosmetic tattooing are presumably implicated in the transmission of HCV a significant proportion of patients[18]. A cross-sectional study of 308 Southeast Asian Americans with HCV (41% with genotype 6) reported that risk factors for acquisition for HCV genotype 6 are similar to that of other genotypes, with 41% of patients who could not recall any specific exposure risk[28]. Nevertheless, higher prevalence of HCV genotype 6 has been described in some certain populations including intravenous drug users and patients with thalassemia major[10,26,29]. In Hong Kong, HCV genotype 6 was predominantly observed in 58.5%-62.5% among intravenous drug users and 50% among patients with thalassemia major[26,29]. Correspondingly, Seto *et al*[30] reported that statistically significant larger proportion of patients with HCV genotype 6 were infected through intravenous drug injections when compare to those with genotype 1 (28.2% *vs* 8.7%, respectively).

CLINICAL FEATURES

There is limited data that specifically addresses the clinical features and natural history of HCV genotype 6. A cross-sectional study performed in 308 Southeast Asians in California found no significant differences in the clinical and virological characteristics (*e.g.*, age, risk factors of

HCV acquisition, alcohol consumption, family history of liver disease, liver functions tests, white blood cell and platelet count, HCV RNA viral load, and liver histology) between HCV genotype 6 and other genotypes. Yet, several studies have suggested that Asian patients tend to be older, have lower body mass index (BMI), consume less alcohol and tobacco, and have more advanced liver histology at presentation than non-Asians[18,31]. Late presentation in Asian patients may be secondary to the lack of awareness of appropriate screening and the low proportion of patients presenting with identifiable risk factors[18].

Chronic HCV infection can be associated with various extrahepatic manifestations, including lymphoproliferative (*e.g.,* mixed cryoglubulinemia and lymphoma) and immunological disorders of various organ systems[32]. The prevalence of lymphoproliferative disorders associated with HCV seems to be geographical heterogeneity[32,33]. Without clear reasons, it is more prevalent in Southern Europe (with an increased prevelence in patients infected with HCV genotype 2) than in Northern Europe, North America, and Asia[32,33]. To date, there have been no specific epidemiological and clinical data regarding extrahepatic manifestations of HCV genotype 6. From our experiences, clinically significant extrahepatic manifestations of HCV are rare in Thailand (especially when compared to the relatively high prevalence of HCV in this area).

TREATMENT

Treatment outcomes

A combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) has been the standard treatment for patients with chronic HCV. These drugs are administered for either 48 wk (for HCV genotypes 1, 4, 5, and 6) or for 24 wk (for HCV genotypes 2 and 3), inducing sustained virologic response (SVR) rates of 40%-50% in those with genotype 1, and of > 70-80% in those with genotypes 2 and 3 infections[27,34]. It should be noted that HCV treatment outcome with PEG-IFN/RBV in Asians seems to be superior to that of non-Asian populations, and this may be due to several factors, such as favorable *IL28B* genotype, low body weight, and HCV genotype misclassification (6 to 1) [18]. More recently, the treatment durations can be modified according to the virological responses (response-guide therapy)[27], and in 2011, direct-acting antiviral (DAA)-based triple combination therapies (boceprevir or telaprevir plus PEG-IFN/RBV) have been approved and shown to improve virological outcomes in HCV genotype 1 patients, with an SVR of up to 65%-75% in treatment-naïve patients[35]. Once achieved, an SVR is associated with long-term clearance of HCV infection, which is regarded as a "cure," as well as with significant improvement of morbidity and mortality of the patient[27,35]. Among several predictors of SVR to therapy, HCV genotype is considered one of the most robust independent predictors[27]. Compared to other genotypes, data regarding the treatment of HCV genotype 6 are scant and mostly generated retrospectively. The available studies suggest that SVR rates in patients infected with HCV genotype 6 (60%-90%) are superior to those in patients with genotype 1 and comparable to patients infected with genotypes 2 and 3[36-43] (Table 2). The question whether a high treatment response rates in HCV genotype 6 is due to viral factor itself or partialy due to host factor, especially favorable *IL28B* genotype among Asians, remains unclear.

Treatment regimens

The optimal dose and treatment duration of HCV genotype 6 have not been well-established. Most of the earlier studies applied PEG-IFN for 48 wk duration with weight-based RBV dose for HCV genotype 6 reported conflicting results with studies comparing 48-wk *vs* 24-wk treatment duration (Table 3). In a retrospective cohort of Nguyen *et al*[44], SVR was significantly higher in patients treated for 48 wk than in those treated for 24 wk (75% *vs* 39%, respectively; $P = 0.044$). However, a randomized controlled study from Lam *et al*[45] ($n = 60$) found no significant difference in SVR rates in patients treated with PEG-IFN α-2a/RBV for 48 wk *vs* 24 wk (79% *vs* 70%, respectively; $P = 0.45$). Based on this conflicting evidence, differences in treatment duration recommended by the available guidelines are observed. The 2009 American Association of the Study of Liver Disease[34] and the 2012 Asian Pacific Association for the Study of the Liver[46]. Practice Guidelines have recommended 48 wk duration of treatment for patients with HCV genotype 6, as for those with genotype 1, whereas the 2011 European Association for the Study of the Liver Practice Guideline has suggested response-guided therapy for HCV genotype 6 with the same algorithm as genotype 2 and 3[27]. In 2012, the largest randomized controlled trial to date of patients with HCV genotype 6 ($n = 105$) has been published. This study found no statistically significant difference in SVR rates between the genotype 6 patients treated with 24 and 48 wk of PEG-IFN α-2a/RBV (60% *vs* 71%, $P = 0.24$ in the intention-to-treat analysis; 72% *vs* 79%, $P = 0.46$ in the per-protocol analysis)[47].

Predictors of treatment response and response-guided therapy

For HCV in general, the strongest predictors of SVR are genetic polymorphisms in *IL28B*, genotype, the stage of fibrosis, and undetectable HCV RNA at week 4 of treatment (defined as rapid virological response; RVR)[27]. Other predictors of response include host factors (*e.g.*, age, BMI, insulin resistance, gender), baseline HCV RNA levels, co-infections, the dose and duration of therapy, virological responses during the treatment, and treatment adherence[27]. These predictors seem to be valuable for all HCV genotypes and may extrapolate to use for patients with HCV genotype 6 as well. With sparse available data, predictors of response in HCV genotype 6

Table 2 Treatment outcomes of hepatitis C virus genotype 6 (compared to other genotypes)

Ref.	Design/treatment	Genotype	*n*	SVR	*P* value[1]
Dev *et al*[36]	Retrospective	6	33	82.5%	NR
	IFN + RBV 52 wk	1	17	61.9%	
Hui *et al*[37]	Prospective	6	16	62.5%	0.04
	IFN + RBV 52 wk	1	24	29.2%	
Cheng *et al*[43]	Retrospective	6	13	69.2%	0.026
	PEG-IFN + RBV (duration not reported)	1	61	32.8%	
		2	18	77.8%	
Fung *et al*[38]	Prospective	6	21	85.7%	0.019
	PEG-IFN + RBV 52 wk	1	21	52.4%	
Nguyen *et al*[40]	Retrospective	6	34	74.0%	0.016
	PEG-IFN + RBV (48 wk for genotype 1 and 6; 24 wk for genotype 2/3)	1	70	49.0%	
		2/3	63	75.0%	
Seto *et al*[30]	Retrospective IFN/PEG-IFN + RBV 52 wk	6	26	92.3%	NR
	IFN/PEG-IFN + RBV 52 wk	1	21	42.9%	
Tsang *et al*[41]	Retrospective	6	70	75.7%	NR
	PEG-IFN + RBV 48 wk	1	70	57.1%	
Zhou *et al*[42]	Retrospective	6	22	81.8%	0.068
	PEG-IFN + RBV (48 wk for genotype 1b; 24 wk for genotype 2/3 and 6)	1b	39	59.0%	
		2/3	42	83.3%	
Tangkijvanich *et al*[48]	Prospective	6	34	76.5%	0.309
	PEG-IFN + RBV (RGT[2] for genotype 6; 48 wk for genotype 1; 24 wk for genotype 3)	1	16	62.5%	
		3	16	81.3%	

[1]*P*-value between genotype 6 *vs* genotype 1; [2]Response-guided therapy (RGT) define as 24 wk for patients with rapid virological response and 48 wk for those without. PEG-IFN: Pegylated interferon; RBV: Ribavirin; SVR: Sustained virological response.

Table 3 Treatment outcomes of hepatitis C virus genotype 6 by the treatment duration

Ref.	Design/treatment	Duration (wk)	*n*	SVR	*P* value
Nguyen *et al*[44]	Retrospective	24	23	39%	0.044
	PEG-IFN 2a/2b + WB-RBV	48	12	75%	
Lam *et al*[45]	Randomized (1:1)	24	27	70%	0.450
	PEG-IFN 2a + WB-RBV	48	33	79%	
Thu-Thuy *et al*[47]	Randomized (1:2)	24	35	60%	0.240
	PEG-IFN 2a + WB-RBV	48	70	71%	
Tangkijvanich *et al*[48]	Prospective	24 if RVR achieved	25	88%	NR
	PEG-IFN 2a + WB-RBV	48 if no RVR	9	44%	

PEG-IFN: Pegylated interferon; RBV: Ribavirin; WB: Weight-based; SVR: Sustained virological response; RVR: Rapid virological response.

have been observed among studies of HCV genotype 6 include younger age (< 40-50 years)[40,42], low BMI (< 25 kg/m^2)[40], treatment adherence[40] and RVR[42,45]. Among these predictors and concordant with observations in other HCV genotypes, RVR was a strong independent predictor of SVR in HCV genotype 6, wherein the positive predictive value (PPV) in achieving SVR in patients with RVR has been 80%-90%[42,45,47,48]. In Thu thuy *et al*[47] study, RVR was common (in up to 80% of patients) with a high PPV (75%-86%) and negative predictive value (NPV) for the prediction of SVR (0%-8%), regardless of the treatment duration. Thus, none of the patients who did not have undetectable HCV RNA at week 12 of treatment (defined as early virological response; EVR) subsequently achieved SVR[47]. Thus, in those who completed treatment protocol, the importance of RVR in the prediction of SVR has been further substantiated; PPV for SVR was 96% with 48-wk treatment group, and was 91% with 24-wk treatment. In addition, a retrospective analysis by Zhou *et al*[42] demonstrated that the PPV and NPV of RVR and EVR in patients with HCV genotype 6 are comparable with those in patients with genotype 2/3 infection.

Taken together, it is likely that baseline response predictors together with on-treatment response-guide therapy (RGT) can be utilized for the treatment of HCV genotype 6 in order to optimize treatment outcomes as well as cost-effectiveness (Figure 1). Based on available data, patients with RVR will benefit with 24 wk of therapy, particularly if they are young, with a BMI < 25 kg/m^2, and have a low viral load, whereas patients with older age, non-CC *IL28B* genotypes, obesity, advanced fibrosis, and high viral loads, would benefit from 48 wk of therapy. The SVR rates among HCV genotype 6 patients with RVR are expected to be at > 80%[42,45,47], and possibly up to > 90% in those who adhere to therapy[47]. Alternatively, patients who do not achieve RVR are expected to have low rates of SVR (0%-30%)[45,47]. If treatment continues, HCV RNA should be checked again at week 12. If HCV RNA is detectable at week 12 then

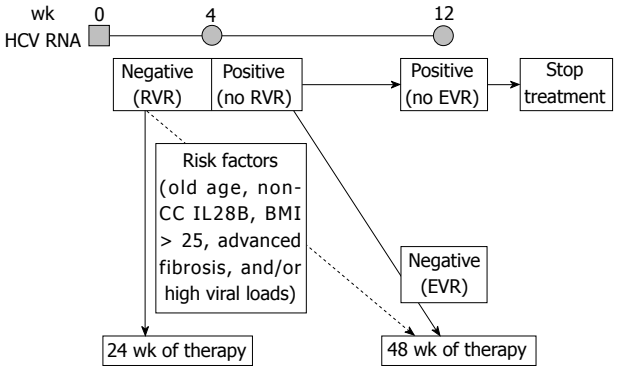

Figure 1 Response-guided therapy in patients with hepatitis C genotype 6. RVR: Rapid virological response; EVR: Early virological response; BMI: Body mass index; HCV: Hepatitis C virus; IL: Interleukin.

treatment should be discontinued, since SVR rates have shown to be near zero in non-EVR patients[42,45,47]. Correspondingly, a proof-of-concept study (n = 34) utilizing RGT for HCV genotype 6 patients with RVR has been firstly reported by Tangkijvanich *et al*[48]. In this study, 25 patients who achieved RVR were assigned to receive 24 wk treatment (RGT group) while the remaining 9 patients (no RVR) were assigned for standard 48 wk of PEG-IFN 2a/RBV therapy. SVR rates were significantly higher for RGT group when compared to 48-wk treatment group (88% *vs* 44%, respectively; P = 0.024)[48]. However, the precise role and protocol of RGT for HCV genotype 6 needs a larger prospective study to address.

Treatment adverse events

As previously reported in HCV treatment trials, the common side effects of HCV genotype 6 are of general non-specific symptoms and anemia, which are mild and manageable by supportive measures[45,47]. Though the incidence and types of side effects caused by therapy with PEG-IFN/RBV seem to be similar among patients of different HCV genotypes, side effect profiles appear to differ among patients of different ethnicities[6]. Several studies have reported that psychiatric adverse events were less common and ribavirin-induced anemia was more common in Asians than either white or Hispanic patients, and that there were no significant difference between whites and Asians with respect to required ribavirin or PEG-IFN dose reductions[18]. Notably, the lower rates of psychiatric adverse events in Asians may be partly explained from the potential for underreporting psychiatric problems and/or depression in Asian populations due to associated sociocultural stigma[49,50], as well as from the absence of confounders such as alcohol use and drug abuse[51].

Roles of IL28B

Single nucleotide polymorphisms (SNPs) near the *IL28B* gene responsible for encoding IFN-gamma are strongly associated with spontaneous and treatment-induced clearance of HCV[52,53]. A genome-wide association study of more than 1600 patients infected with HCV genotype 1 found the rate of SVR following PEG-IFN/RBV treatment to be approximately 80%, 40%, and 25% in *IL28B* genotypes CC, CT, and TT, respectively[52]. Notably, the favorable C allele is frequently found up to 80% in Asians, which is more common than in Caucasians, Hispanics and African Americans, respectively[52,54]. This may be part of the reason that SVR rates for HCV genotype 1 among Asian patients are higher (expected 60%-70%) compared to non-Asian populations[18]. However, the role of *IL28B* for the prediction of HCV clearance in non-1 genotypes is less clear. Studies from HCV genotypes 2, 3, and 4 yielded somewhat conflicting results, though most studies failed to show a significant association of *IL28B* variations with SVR[53]. Nevertheless, a preliminary study in Chinese genotype 6 HCV patients (n = 24) has demonstrated a significant association between *IL28B* polymorphisms (SNPs rs12979860 and rs8099917) and SVR rates[55].

Roles of viral genome mutations

Studies from Japan and Hong Kong have identified associations between genetic mutations around the interferon sensitivity-determined region (ISDR) of HCV genotype 1b and resistance to IFN-based treatment[56,57]. Accordingly, sequence diversity of HCV genotype 6a within the extended ISDR (covering 192 base-pairs upstream and 201 base-pairs downstream from the ISDR previously defined in genotype 1b) has shown correlation with antiviral treatment outcomes in a report from China[58]. However, it should be noted that this observation was not reproducible among HCV genotype 1b patients in Europe and United States[59,60], which may be partially explained by differences in genetic background, especially the *IL28B* genotypes.

Roles of DAA

At present, there has been no data on the efficacy of current, FDA-approved DAA, boceprevir and telaprevir, on HCV genotype 6. However, some investigational agents with pan-genotypic antiviral activities (*e.g.*, new generation protease inhibitors, NS5B, and cyclophilin inhibitors) have been shown to suppress HCV replication in HCV genotype 6[61,62]. Recently, sofosbuvir[63] and simeprevir (TMC435)[64] have demonstrated clinical benefit in a small number of patients with HCV genotype 6 in the phase Ⅱ/Ⅲ studies. However, further studies with larger number of genotype 6 patients are needed in order to establish the regimens and clinical efficacy in this group of patient. While awaiting clinical trials specifically for genotype 6, one would speculate that the use, or off-label use, of pan-genotypic DAA, especially sofosbuvir and simeprevir, for HCV genotype 6 patients may be seen soon, particularly for those who failed standard treatment with PEG-IFN/RBV. It should also be noted that the availability of DAA is currently very limited in most countries in Southeast Asia due to socio-economic

and other barriers.

CONCLUSION

Hepatitis C genotype 6 is endemic in Southeast Asia (prevalence varies between 10%-60% among all HCV infection), as well as also sporadically reported outside the area among immigrations. The diagnosis of HCV genotype can be inaccurate with earlier methods of genotyping due to identical 5'-UTR between genotype 6 and 1b, and the newer genotyping methods with core sequencing are preferable. Risk factors and clinical course of HCV genotype 6 do not considerably differ from the other genotypes. Treatment outcome of HCV genotype 6 with PEG-IFN/RBV is superior to genotype 1, and nearly comparable to genotype 3 (expected SVR rates of 60%-90%). Emerging data suggests that a shorter course 24-wk treatment may be effective as a standard 48-wk-treatment, particularly in those patients who attained RVR. In addition, baseline and on-treatment predictors of response used for other HCV genotypes seem to be useful for genotype 6. Although some pan-genotypic direct acting antivirals have completed phase Ⅱ/Ⅲ studies (sofosbuvir and simeprevir) with clinical benefit demonstrated in small number of patients with genotype 6, broad availability of these agents in Southeast Asia may not be expected in the near future. While awaiting the newer therapy, response-guided therapy seems to be appropriate for patients with HCV genotype 6. Patients with RVR (representing > 70% of patients) are suitable for 24 wk treatment with expected SVR rates > 80%. Patients without RVR and/or those with poor response predictors may benefit from 48 wk of therapy, and a detectable HCV RNA at week 12 (no EVR) can be served as stopping rule. This treatment scheme is likely to have a major economic impact on HCV therapy, particularly in Asia, wherein treatment can be truncated securely in the majority of patients with HCV genotype 6.

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