Hepatitis C virus genotype 6: Virology, epidemiology, genetic variation and clinical implication

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Abstract

Hepatitis C virus (HCV) is a serious public health problem affecting 170 million carriers worldwide. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and is the primary cause for liver transplantation worldwide. HCV genotype 6 (HCV-6) is restricted to South China, South-East Asia, and it is also occasionally found in migrant patients from endemic countries. HCV-6 has considerable genetic diversity with 23 subtypes (a to w). Although direct sequencing followed by phylogenetic analysis is the gold standard for HCV-6 genotyping and subtyping, there are also now rapid genotyping tests available such as the reverse hybridization line probe assay (INNO-LiPA II; Innogenetics, Zwijnaarde, Belgium). HCV-6 patients present with similar clinical manifestations as patients infected with other genotypes. Based on current evidence, the optimal treatment duration of HCV-6 with pegylated interferon/ribavirin should be 48 wk, although a shortened treatment duration of 24 wk could be sufficient in patients with low pretreatment viral load who achieve rapid virological response. In addition, the development of direct-acting antiviral agents is ongoing, and they give high response rate when combined with standard therapy. Herein, we review the epidemiology, classification, diagnosis and treatment as it pertain to HCV-6.

Key words: Hepatitis C virus; Genotype 6; Epidemiology; Clinical; Treatment

Core tip: Hepatitis C virus (HCV) genotype 6 is restricted to South China, South-East Asia, and it is occasionally found in migrant patients from endemic countries. Treatment response rates are lower than those of genotype 3 but higher than those of genotype 1. Based on current evidence, the optimal treatment duration of HCV-6 should be 48 wk. Shortened treatment duration of 24 wk could be sufficient in patients with low pretreatment viral load who achieve rapid virological response. The development of direct-acting antiviral agents is ongoing, and they give high response rate when combined with standard therapy. We review the epidemiology, classification, diagnosis and treatment.
INTRODUCTION

Hepatitis C virus (HCV) infection is an important worldwide public health problem. Most HCV cases become chronic hepatitis C (CHC), which may advance to liver fibrosis, cirrhosis, and hepatocellular carcinoma. The global prevalence of HCV infection is estimated at more than 170 million people\[^1\-\[^3\]\], and some studies estimate that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next two decades\[^4\].

Hepatitis C virus is a member of the Flaviviridae family and belongs to the genus Hepacivirus. HCV is classified into six major genotypes (1-6) and subdivided into various subtypes named in alphabetical order from a to z. Currently, sequencing of HCV isolates has identified more than 83 subtypes from the six genotypes\[^5\]. The genomes among HCV genotypes differ from each other by approximately 30%-35% while the genomes among the subtypes differ by 15%-20%. The prevalence of HCV genotypes varies geographically: HCV-1 is found worldwide including developed regions such as North America and Europe. HCV-2 has high prevalence in Central and West Africa as well as some western countries, while HCV-3 is predominantly found in the Far Eastern countries and the Indian subcontinent\[^6\]. Meanwhile, HCV genotypes 4, 5 and 6 are endemic to specific geographical areas: HCV-4 is mainly found in Egypt and Sub-Saharan Africa, HCV-5 in South Africa\[^7\], and HCV-6 in South China and South-East Asian countries\[^8\]-\[^10\] (Figure 1).\[^10\]-\[^34\]

HCV-6 is highly diverse with 23 subtypes currently known\[^8\]-\[^34\]. This genetic diversity may be the result of a long period of viral circulation\[^14\]. In addition, repeated viral exposure through activities such as intravenous drug use leads to more than one viral strain circulating in the host, which in turn increases the chance of viral recombination events among circulating HCV genotypes and strains. The high variation and accumulation of HCV-6 in Southeast Asia also supports the idea that this area may be the origin and worldwide distribution center of this genotype.

Various factors determine treatment response. In the case of host factors, age, sex, race, fibrosis and steatosis level all have important influences on treatment outcome\[^15\]-\[^17\], while the most important viral factors for predicting response to IFN-based therapy are genotype and viral load at baseline. In the past 10 years, the standard treatment of HCV patients has been a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) with a 24 to 48 wk regimen depending on the viral genotype of each infected individual. Thus, HCV genotype is considered one of the most robust independent predictors for sustained virological response (SVR). Most clinical studies on PEG-IFN/RBV efficacy have been based on common genotypes such as genotype 1, 2 and 3, while scant clinical data has been generated concerning genotype 6. However, due to this genotype's extreme genetic diversity, it may be important to study it in a controlled, clinical setting in order to gauge the standard therapy's efficacy\[^5\].

Currently, the few available studies suggest that treatment with the longer 48-wk regimen may lead to a higher rate of SVR. On the other hand though, treatment with the 24-wk regimen may also lead to a similar SVR rate in subgroups of patients, as in the case of patients with genotypes 2 and 3\[^18\]. In 2011, newer agents known as direct-acting antivirals (DAA) were approved for use in conjunction with PEG-IFN and RBV for the treatment of HCV-1. However, the efficacy and safety of DAA in the treatment of the HCV-6 patients still needs to be assessed.

This study aimed to review the virology, epidemiology, genetic variation and clinical implication of HCV genotype 6. All data were retrieved and selected from related HCV-6 topics from PubMed database.

EPIDEMIOLOGY

Within endemic countries, HCV-6 shows variability in subtype prevalence. Vietnam has reported HCV-6 prevalence of 51%-54.4% in Ho Chi Minh City and 47.1% elsewhere with the most common subtypes being 6a followed by 6c and 6l. In total, 12 subtypes have thus far been identified in Vietnam (6a, 6c, 6e, 6f, 6h, 6k, 6l, 6n, 6o, 6p, 6r and 6t)\[^9\]-\[^10\]. Although there is limited information regarding HCV epidemiology in Laos and Cambodia, a few studies have reported a high proportion of HCV-6 in these countries also. Among Laos blood donors, 95.6% of the HCV RNA positive samples were classified as HCV-6 with various subtypes being found including 6b, 6h, 6k, 6l, 6n, 6o, 6q and unclassified subtype\[^12\]-\[^13\]. A study of Cambodian migrants in Thailand reported that HCV seroprevalence in this group is similar to their guest country (2.3%). It was also found that HCV-6 is the most dominate genotype in Cambodian migrants with 52% of the HCV-RNA carriers testing positive for this genotype with the subtype breakdown as the following: 6e (20%), 6r (20%), 6f (8%) and 6p (4%)\[^14\]. Similar to its neighboring countries, Thailand also has several endemic HCV-6 subtypes (6b, 6c, 6e, 6f, 6l, 6m and 6n) along with novel subtypes (6u and 6v), which are found in the North and Northeast\[^15\]. However, unlike the Cambodian migrant population in Thailand, this genotype contributes a lower proportion (20.1%) of overall infection in comparison with HCV-3 and HCV-1\[^15\]. In Myanmar, HCV-6 prevalence has grown from being the third most prevalent HCV genotype in 2004 to the first after analysis of a large number of blood samples from 2007. HCV-6 is especially prevalent in the Northern part of Myanmar.
Figure 1  The prevalence of the various hepatitis C virus genotypes varies considerably between countries and regions\textsuperscript{[10-34]}. 

<table>
<thead>
<tr>
<th>Country</th>
<th>Genotype Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>565</td>
</tr>
<tr>
<td>United States</td>
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<tr>
<td>Brazil</td>
<td>2953</td>
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<tr>
<td>Egypt</td>
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<tr>
<td>France</td>
<td>9801</td>
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<td>United Kingdom</td>
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<td>South Africa</td>
<td>315</td>
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<td>China</td>
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<td>Vietnam</td>
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<tr>
<td>Japan</td>
<td>583</td>
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<td>Thailand</td>
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<td>Australia</td>
<td>2025</td>
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<tr>
<td>Russia</td>
<td>655</td>
</tr>
<tr>
<td>Myanmar</td>
<td>1186</td>
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<tr>
<td>India</td>
<td>190</td>
</tr>
<tr>
<td>South Korea</td>
<td>3768</td>
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<tr>
<td>Hong Kong</td>
<td>344</td>
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<tr>
<td>China</td>
<td>830</td>
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<tr>
<td>Indonesia</td>
<td>675</td>
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<tr>
<td>Indonesia</td>
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<td>Thailand</td>
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<td>South Korea</td>
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<td>Hong Kong</td>
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<td>Japan</td>
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<tr>
<td>China</td>
<td>22245</td>
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<td>Indonesia</td>
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<td>South Korea</td>
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<td>South Africa</td>
<td>958</td>
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<tr>
<td>Germany</td>
<td>753</td>
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<td>United States</td>
<td>830</td>
</tr>
<tr>
<td>Canada</td>
<td>3565</td>
</tr>
</tbody>
</table>

Figure 1  The prevalence of the various hepatitis C virus genotypes varies considerably between countries and regions\textsuperscript{[10-34]}. 

Thong VD et al. Hepatitis C virus genotype 6
with subtypes 6f, 6n and 6m predominating\cite{44-47}. Despite
is ubiquitous presence in the above-mentioned countries,
however, HCV-6 is only rarely reported in other proximal
countries. For example, only three samples of subtype 6g
(previously designated as genotype 1a) have been report-
ed in Indonesia since 1996\cite{58}, while only a single recent
report of subtype 6n has been found in Kuala Lumpur,
Malaysia, and notably, this patient was co-infected with
HIV-1 and had a history of IVDU\cite{49}.

HCV-6 can also be found outside of the immediate
South East Asian region in countries such as South
China, Hong Kong and Taiwan (Figure 2)\cite{28,40,46,48,50-55,59}.

Intravenous drug abuse is the transmission route sus-
pected of being most responsible for the high frequency
of this genotype in certain parts of Asia and the factor
driving a continuous discovery of new subtypes. In Chi-
na, HCV is frequently found in the South in patients with
HIV-1 co-infection and IDU history\cite{56}. For example,
prevalence of HCV-6 in chronic hepatitis cases is 12.9% to
14.2% while being 28.2% to 51.5% in IDUs. In addi-
tion, similar to Vietnam, 6a is the major subtype in IDUs
from all study groups\cite{17,57,58}. A similar trend of HCV-6
infection can also be observed in Hong Kong. More
than half of infected IDU have this genotype (53.2% to
58.5%)\cite{52,59}, which is much higher than the prevalence
in the general population (23.6%)\cite{53}, and subtype 6a is the
most common subtype\cite{52,59}. In Taiwan, there has been no
report of HCV-6 until 2010, but since then there is a
growing prevalence of HCV-6 and subtype 6a along with
novel subtypes being reported in prisoners and IDUs\cite{53,59}.

**EVOLUTION OF HEPATITIS C VIRUS GENOTYPE 6**

There is now considerable evidence to support the hy-
pothesis that HCV-6 originated in Southeast Asia. First,
this genotype is mainly observed in countries such as Viet-
nam, Cambodia, Laos, Myanmar and Thailand with the
prevalence of HCV-6 in these countries ranging from ap-
proximately 20% to more than 50% of all genotypes. Sec-
ond, there are a great number of known and novel sub-
types circulating within these populations\cite{11}. Third, when
HCV-6 is found outside of its endemic area, such as in
countries like US, Canada and Australia, the virus is almost
exclusively isolated from Asian immigrants\cite{70,76}. Fourth, a
study in Laos showed that HCV-6 is highly divergent from
other genotypes, and that it has distinct genetic differences
from other strains, which suggests that there may yet be
uncharacterised subtypes existing in this area. Thus, the ac-
cumulation of such genetic heterogeneity suggests that this
genotype has circulated, adapted and evolved in this area
for a long period of time (Table 1)\cite{39,64,66,67}.

Evolutionary analysis of HCV-6 subtypes hypothesizes
that these subtypes evolved from a common ancestor
more than 1000 years ago, and that some subtypes may
have maintained their endemcity via local epidemics dur-
ing the 20th century initiated and propagated by modern
medicine, blood transfusion and IVDU\cite{51}. However, each

of the subtypes seems generally restricted to different
locations such as subtype 6d in Vietnam, 6f in Thailand,
6g in Indonesia and 6r in Cambodia. In addition, strains
isolated from the same country tend to cluster together
in a HCV-6 phylogenetic tree (Figure 3)\cite{67,68}.

HCV-6 has spread through other East Asian countries
by multiple transmission routes with one of the most
effective routes being IDU. In the general population,
HCV-1 is still the predominant genotype across Asia.
However, HCV-6 - and especially subtype 6a - is the
dominant genotype among IVDUs\cite{53,58,59}. An example of
this is the phylogeographic and coalescent analysis of
HCV-6's spread through China. Analysis shows that sub-
type 6a and some other Chinese strains may have origi-
nated in Vietnam and spread to neighboring Guangxi
and Yunnan provinces\cite{53,60,61}. Finally, since Guangdong is
a major gateway to China, this province may have been the
origin of subtype 6a dispersion throughout other regions
of the country\cite{53}.

Similar to other RNA viruses, HCV has a high ten-
dency for genetic heterogeneity due to a lack of proof
reading activity by its viral RNA polymerase. This genetic
drift results in an accumulation of viral mutations, which
will then be selected for by forces of environmental
pressure. Thus, only the fittest strains survive and become
the major circulating viral population. Of course, however,
this process of fixation requires a relatively long period
of time. Meanwhile, viral recombination can result in
novel strains overnight, although the drastic nature of
recombination can be a danger to viral survival. So far, the
evidence suggests that novel HCV strains mainly accu-
culate through genetic drift by collecting viral mutation
instead of recombination, as there have only been two
reported cases of HCV-6-specific recombination occur-
ing\cite{57,68}, recombinants RF_2i/6p and RF_2b/6w from a
Vietnamese blood donor and an IDU in Taiwan, respec-
tively\cite{5,60,69}.

**METHODS USED FOR GENOTYPING**

Since HCV genotype is such an important consideration
for predicting an effective treatment regimen, several dif-
ferent genotyping methods have been developed. These
methods include direct nucleic acid sequencing\cite{76}, a re-
verse hybridization line probe assay (LiPA)\cite{79}, subtype-
specific reverse transcription (RT)-PCR\cite{80}, DNA restric-
tion fragment length polymorphism\cite{81} heteroduplex
mobility analysis\cite{82}, primer-specific and mispair extension
analysis\cite{83}, melting curve analysis with fluorescence reso-
nance energy transfer probes\cite{78} and serologic genotyping
(Figure 4)\cite{75,76}.

However, not every method is equal. The Asian Pa-
cific Association for the Study of the Liver states that
genotype discrimination based on primers from the 5' un-
translated region (5'UTR) do not distinguish some of
the HCV-6 subtypes prevalent in Southeast Asia, and that
these subtypes should instead be classified as genotype 1
or 1b\cite{70,79}, available methods generally use distinct motifs
Figure 2  Distribution of the prevalence of subtype of hepatitis C virus-6 in the world 

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>n = 273</td>
</tr>
<tr>
<td>United States</td>
<td>n = 39</td>
</tr>
<tr>
<td>France</td>
<td>n = 3</td>
</tr>
<tr>
<td>Vietnam</td>
<td>n = 694</td>
</tr>
<tr>
<td>Taiwan</td>
<td>n = 22</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>n = 205</td>
</tr>
<tr>
<td>Singapore</td>
<td>n = 6a</td>
</tr>
<tr>
<td>Cambodia</td>
<td>n = 141</td>
</tr>
<tr>
<td>Laos</td>
<td>n = 105</td>
</tr>
<tr>
<td>South China</td>
<td>n = 1022</td>
</tr>
<tr>
<td>Indonesia</td>
<td>n = 15</td>
</tr>
<tr>
<td>Vietnam</td>
<td>n = 6b</td>
</tr>
</tbody>
</table>

Thong VD et al. Hepatitis C virus genotype 6
Table 1  Prevalence of hepatitis C virus-6 in Asians a (%) 

<table>
<thead>
<tr>
<th>Country</th>
<th>Ref.</th>
<th>Genotype 6 prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myanmar</td>
<td>Lwin et al[46]</td>
<td>1333 (49)</td>
</tr>
<tr>
<td>Vietnam (Hanoi, Vietnam)</td>
<td>Pham et al[46]</td>
<td>238 (47.1)</td>
</tr>
<tr>
<td>Thailand (blood donors throughout country)</td>
<td>Kanistanon et al[61]</td>
<td>NR (18)</td>
</tr>
<tr>
<td>Thailand (blood donors in northern Thailand provinces)</td>
<td>Jutavigittum et al[62]</td>
<td>326 (31)</td>
</tr>
<tr>
<td>Thailand (blood donors from central Thailand)</td>
<td>Akkarathamrongsin et al[63]</td>
<td>375 (30)</td>
</tr>
<tr>
<td>Hong Kong, China (Blood donors)</td>
<td>Leung et al[64]</td>
<td>910 (27)</td>
</tr>
</tbody>
</table>

NR: Not reported.

Figure 3  Phylogenetic relationships among subtypes hepatitis C virus-6. Phylogenetic tree constructed from whole genome sequence of all hepatitis C virus-6 subtypes (subtype 6a to 6w) which was analyzed by K2P model and MEGA version 5. Bootstrap value of 1000 replicates was indicated at each node.
found within the HCV genome for HCV genotype[5]. In addition, previous studies reported the mistyping of HCV-6 as genotype 1 by the INNO-LiPA assay (Innogenetics, Zwijnaarde, Belgium)[80,81]. However, the INNO-LiPA HCV II (Innogenetics, Zwijnaarde, Belgium) genotyping assay seems to overcome the deficiencies demonstrated by the INNO-LiPA assay, as it has shown remarkable improvement in genotyping accuracy and differentiation between HCV-1 and HCV-6 variants by using core sequencing data as well as 5' UTR data[82,83].

**CLINICAL CHARACTERISTICS**

Acute HCV infection is infrequently diagnosed and leads to chronic infection in about 80% of cases[84]. Clinical manifestations can occur, usually within 7 to 8 wk (range: 2-26 wk) after exposure to HCV, but the majority of persons have either no symptoms or only mild symptoms, and fulminant hepatic failure due to acute HCV infection is very rare. Although clinical features will be present in less than 25% of infected patients, symptoms of acute hepatitis include jaundice, malaise, nausea and right upper quadrant pain[85]. While the infection becomes chronic in most cases, chronic infection is either asymptomatic or has only mild nonspecific symptoms such as fatigue as long as cirrhosis and hepatocellular carcinoma are not present. Other clinical manifestations are possible, however, such as nausea, weakness, myalgia, arthralgia and weight loss[86]. Although there have been many papers describing HCV-6's epidemiology, the clinical characteristics have not been well described in these studies. Nguyen et al[87] reported that patients with HCV-6 presented similar clinical manifestations as those with genotype 1 or 2/3. They also found that people with HCV genotype 1 and 6 had a somewhat higher baseline viral load than those with other genotypes. However, when comparing HCV-6 patients with patients infected with other genotypes, these differences were not statistically significant with regard to host factors (e.g., age, history of smoking, alcohol use, family history of CHC, hepatitis B, hepatocellular carcinoma and liver-related death), baseline laboratory values (e.g., ALT, total bilirubin, albumin, white blood cell count, platelet count), and liver histology[85,88]. However, steatosis is a chief modulator of clinical course of HCV infection[89].

**TREATMENT**

The current standard-of-care for treatment of HCV-infected patients is a combination of PEG-IFN and RBV. Among the various viral and host factors, HCV genotype is one of the most important predictors of response to treatment and is used to guide the duration of treatment. Patients with HCV genotype 1 are typically treated for 48 wk, whereas patients with genotype 2 and 3 are treated for 24 wk[85,86,80]. Limited studies have suggested that the response rate of HCV-6 may be at an intermediate level between those of genotypes 3 and 4[87,91,93].

Virological response kinetics during therapy has emerged as an important prognostic factor of treatment outcome in patients with chronic HCV infection[94,95]. Absence of an early virological response (EVR) at week 12 during therapy is the best negative predictor for nonresponse to treatment. In contrast, rapid virological response (RVR; defined as undetectable HCV RNA at week 4) is regarded as the most important predictor for SVR (defined as undetectable HCV RNA at week 24 after the end of therapy) and has emerged as an important milestone to guide the appropriate duration of therapy. For example, in patients with genotype 1, an individualized approach to therapy designed according to early viral kinetics has been adopted to optimize therapeutic outcome in patients. Recent clinical trials have used RVR to identify those patients with low baseline viral load that may benefit from shortened treatment duration of 24 wk[96-98].

**TREATMENT OUTCOMES OF HCV-6 VS OTHER GENOTYPES**

Currently, although the treatment outcome of patients with HCV-6 has so far not been exhaustively studied, a few studies exit which give hints as to what the standard course of care should be. Most previous studies have reported that genotype 6 behaves more similar to genotypes 2 and 3 (SVR rates of 76%-80%)[87,91,104] and thus responds better to therapy than genotype 1 (SVR rates of 46%-52%)[101]. For example, Nguyen et al[87] demonstrated that patients with HCV-6 had significantly better SVRs to PEG-IFN and RBV combination therapy than patients with genotype 1 (74% vs 49%). Furthermore, Tangkijvanich et al[102]...
OPTIMAL TREATMENT DURATION OF HCV-6

Most prior studies of HCV-6 included patients treated for 48-52 wk \cite{103-105}. A small study of Asian-American patients comparing a 48-wk to a shortened 24-wk regimen showed a significantly higher SVR rate in those treated by the 48-wk course (74% vs 49\%) \cite{86}. However, the limitation of the study was its retrospective design and the results were not analyzed with regard to an intention-to-treat method. A retrospective study conducted in China showed that the rate of SVR in 22 patients with HCV-6 treated for 24 wk was comparable to that of genotypes 2/3 (82% and 83\%, respectively) \cite{106}. In that study, the positive predictive values of RVR and EVR for HCV-6 were comparable with those for genotypes 2/3 (87\% vs 91\% and 86\% vs 87\%, respectively).

A randomized controlled trial of 60 patients with HCV-6 demonstrated that there was no significant difference in SVR rates in patients treated with 48-wk and 24-wk regimens (79\% and 70\%, respectively) \cite{107}. In that study, RVR was a significant predictor of SVR in the 48-wk group and tending towards significance in the 24-wk group, although a sizeable number of patients did not have RVR measurement performed. Recently, Thu Thuy et al. \cite{108} conducted an open-label randomized trial in Vietnam, which aimed at assessing the rate of SVR in HCV-6 chronic HCV following 48 and 24 wk of PEG-IFN and RBV combination therapy. They demonstrated that RVR was achieved in the majority of HCV-6 patients and similar and high rates of SVR were noted following 48- and 24-wk therapy (71\% vs 60\%, respectively, \(P = 0.24\)).

The feasibility of a response-guided therapy by individualizing the duration of treatment according to viral kinetics in patients with genotype 6 was first investigated by Fried et al. \cite{107}. In that pilot study, more than 70\% of patients with HCV-6 achieved RVR and received an abbreviated 24-wk regimen. Among them, the rate of relapse was approximately 10\%, and nearly 90\% of them eradicated the virus. These data were consistent with observations regarding treatment of HCV genotypes 1, 2, 3 and 4, which suggest that monitoring RVR might be useful to guide treatment duration for patients with HCV-6. In particular, therapy might be shortened to 24 wk in patients with low pretreatment viral load who achieve RVR, whereas a 48-wk course was appropriate for those who cleared the virus after week 4. The abbreviated regimen could offer advantages by reducing unnecessary medication exposure, which may make the treatment of HCV-6 more affordable and maximize the cost effectiveness of therapy. However, further prospective randomized trials are required to evaluate the response-guided strategy in a larger number of patients with HCV-6.

OPTIMAL DOSE OF RBV IN TREATING HCV-6

Although PEG-IFN represents the backbone of treatment, combination with RBV has been shown to help prevent relapse. Current guidelines recommend a weight-adjusted dose of RBV in combination with PEG-IFN for treating patients with genotype 1, while a flat, low dose of RBV (800 mg/d) is recommended for treating patients with genotype 3 \cite{98}. However, a weight-adjusted dose of RBV might be useful to enhance the response rate in patients with genotype 3 who do not achieve RVR and in those with RVR undergoing abbreviated therapy \cite{108,109}. Currently, the optimal dose of RBV for treatment of patients with HCV-6 is unknown. In previous studies, daily weight-based or fixed doses of RBV had been used, rendering comparisons rather complicated. Nonetheless, recent prospective trials adopted a weight-based dosage of RBV (1000-1200 mg/d) for abbreviated treatment (24 wk), which might result in achieving SVR equivalent to that obtained with longer treatment duration (48 wk) \cite{101}. These data might reflect the need of a weight-based dosage of RBV in patients with HCV-6 undergoing abbreviated therapy.

SAFETY AND SIDE EFFECT PROFILE OF TREATMENT

Treatment with PEG-IFN and RBV has been shown to be safe in patients with HCV-6, but treatment discontinuation or dose reduction due to side-effects is typical. Although HCV genotypes play a role in achieving SVR, there is no significant difference in the frequency or types of side effects experienced among patients of genotypes 1, 2, 3 or 6 \cite{87,104,103} taking PEG-IFN and RBV, although side effect profiles do appear to differ among patients of
different ethnicities. For example, compared with Caucasians, Asian patients are more likely to decrease their RBV dose or discontinue the therapy due to anemia. In addition, Asian patients reported symptoms of depression, more commonly than Caucasian patients\footnote{\cite{10,111}}. Other common side effects include flu-like symptoms (fever, fatigue, headache, malaise, and loss of appetite), dyspepsia and some cases with rash, weight loss, arthralgia and alopecia\footnote{\cite{103}}. However, these symptoms are often mild and tolerable and without the requirement for PEG-IFN and/or RBV dose modification.

**PREDICTORS OF SVR**

As in studies of patients with other HCV genotypes, pretreatment predictors of response are useful for advising patients on their likelihood of SVR. Pretreatment host and viral characteristics affect early viral kinetics. Once treatment has been initiated, outcome depends on how fast HCV RNA becomes undetectable. Multivariante analyses have identified various predictors of response in HCV-6 such as youth (< 40-50 years)\footnote{\cite{100,105}}, low BMI, treatment adherence and RVR\footnote{\cite{105,106}}\footnote{\cite{113}}. Among these predictors - and concordant with observations in other HCV genotypes - the importance of RVR (undetectable HCV RNA after 4 wk of treatment) in the prediction of SVR has been further substantiated in HCV-6, wherein the positive predictive value to achieve SVR in patients with RVR has been 83%–87%\footnote{\cite{87,105}}\footnote{\cite{113}}. The role of IL28B testing in predicting treatment response in patients with HCV-6 is limited\footnote{\cite{113}}. A recent study from Hong Kong showed that patients carrying the CC genotype of one of these predictive SNPs (rs12979860) have a twofold (95%CI: 1.8-2.3) greater rate of SVR than patients who carry the TT genotype. Interestingly, the C allele frequency is much higher in white and Asian populations (78% for the CC genotype, 38% for the TC genotype, and 26% for the TT genotype). Interferron- lambda-3. Following antiviral treatment, patients carrying the CC genotype of one of these predictive SNPs (rs12979860) have a twofold (95%CI: 1.8-2.3) greater rate of SVR than patients who carry the TT alleles (78% for the CC genotype, 38% for the TC genotype, and 26% for the TT genotype). Interestingly, the C allele frequency is much higher in white and Asian populations than in black populations\footnote{\cite{112}}. More recently, a variant upstream of IFN3 creating a novel gene, designated as IFNL A, has been discovered\footnote{\cite{121}}. This region harbors a dinucleotide variant (ss469415590) that is found in two alternative forms (ΔG or TT alleles). The ss469415590 indel is more strongly associated with treatment response of HCV-1 infection in African-American individuals compared to rs12979860\footnote{\cite{113}}.

Data regarding the association of the SNPs with antiviral response in HCV-6 infected patients are still very limited. A recent study from Hong Kong showed that rs8099917, another IL28B polymorphism, was associated with response to PEG-IFN/RBV therapy in HCV-6 infected patients\footnote{\cite{114}}. In that report, the favorable TT genotype of rs8099917, when compared to the unfavorable TG genotype, was significantly associated with an increased SVR rate (96.2% and 62.5%, respectively) and was the only clinical parameter that predicted SVR.

**DAA**

In 2011, direct-acting antivirals (telaprevir and boceprevir) were approved by the US. Food and Drug Administration for treatment of HCV genotype 1. They are first generation NS3-4A protease inhibitors (PI), targeting the protease enzyme that cleaves the HCV polyprotein thus inhibiting the replication process. The addition of a DAA to PEG-IFN/RBV has reduced treatment duration and side effects, and improve efficacy and cost\footnote{\cite{115}}. Thus, the development of DAA represents a significant milestone in improving the efficacy of HCV treatment, especially in patients with HCV genotype 1.

Currently, clinical results of the use of DAAs for patients with HCV-6 are limited\footnote{\cite{115}}. For example, monotherapy with TMC 435, a second-generation NS3/4A PI with pan-genotype antiviral activity, could induce a significant mean viremia decrease of -4.35 log10 UI/mL after 8 days in patients with HCV-6. In addition, five patients with HCV-6 were included in the ATOMIC study and treated with sofosbuvir (GS 7977), a NS5B polymerase inhibitor, plus PEG-IFN/RBV for 24 wk. The RVR rate at week 4 and the SVR rate 12 wk after the end of the treatment were both 100%.

**CONCLUSION**

Three percent of the world’s population is infected with HCV. Of that 3%, HCV-6 accounts for a disproportionately high burden high of prevalence in Southeast Asia and the surrounding areas as well as in infection drug users and people with thalassemia major. Previous literature suggest older tests may have misclassified HCV-6 as genotype 1, but newer line probe assays have shown impressive improvement in genotyping accuracy and differentiation between HCV genotype 1 and HCV-6 variants. Clinical characteristics and predictors of poor response are similar for patients with HCV-6 and other HCV genotypes. Current data suggests that the response rate of HCV-6 may be at an intermediate level between those of genotypes 3 and 1. Thus, the optimal treatment duration of HCV-6 should be 48 wk, although shortened treatment duration of 24 wk could be sufficient in patients with low pretreatment viral load who achieve RVR. In addition, there are currently conflicting data on the role of IL28B testing in predicting treatment response in patients with HCV-6.

Further studies will be required to arrive at a sensitively diagnostic method for HCV-6/subtypes, optimal treatment duration, and early predictors for treatment response and drugs (DAA) to achieve higher SVR rates in patients with HCV-6.

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