



Review Article

# Direct-acting Antiviral Regimens for Patients with Chronic Infection of Hepatitis C Virus Genotype 3 in China

Xiaozhong Wang<sup>1</sup> and Lai Wei<sup>2\*</sup>

<sup>1</sup>Department of Hepatology, Affiliated Hospital of Traditional Chinese Medicine of Xinjiang Medical University, Urumqi, Xinjiang, China; <sup>2</sup>Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

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## Abstract

Hepatitis C virus (HCV) genotype (GT)3 infection is associated with a more rapid hepatic disease progression than the other genotypes. Hence, early HCV clearance slows down the disease progression and is important for improving prognosis in GT3-infected patients. Nevertheless, compared with other genotypes, GT3 is difficult-to-treat with direct-acting antivirals, especially in the presence of cirrhosis. Current guidelines recommend several regimens which have been proven to be effective in GT3-infected patients from the Western world (North America, Europe, and Oceania). In China, GT3 infection comprises 8.7–11.7% of the 10 million patients infected with HCV and has strikingly different characteristics from that in Western countries. Unlike the Western countries, where GT3a is the predominant subtype, GT3a and 3b each affect roughly half of Chinese GT3-infected patients, with 94–96% of the GT3b-infected patients carrying A30K+L31M double NS5A resistance-associated substitutions. Phase 3 clinical trials including GT3b-infected patients have suggested that GT3b infection is difficult to cure, making the regimen choice for GT3b-infected patients an urgent clinical gap to be filled. This review includes discussions on the epidemiology of HCV GT3 in China, recommendations from guidelines, and clinical data from both Western countries and China. The aim is to provide knowledge that will elucidate the challenges in treating Chinese GT3-infected patients and propose potential solutions and future research directions.

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**Keywords:** Cirrhosis; Direct-acting antivirals; Hepatitis C; Genotype 3; Resistance-associated substitutions.

**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; CLV, coblopassvir; CMA, Chinese Medical Association; DAA, direct-acting antiviral agent; DCV, daclatasvir; EASL, European Association for the Study of the Liver; EBR, elbasvir; FDA, Food and Drug Administration; GLE, glecaprevir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; LDV, ledipasvir; mITT, modified intention-to-treat; NHSA, National Health Security Administration; PegIFN, pegylated interferon; PI, protease inhibitor; PIB, pibrentasvir; PWID, people who inject drugs; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir; WHO, World Health Organization.

\*Correspondence to: Lai Wei, Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, 168 Litang Rd, Changping District, Beijing 102218, China. Tel: +86-10-56118881, Fax: +86-10-56118566, E-mail: weelai@163.com

## Introduction

Direct-acting antivirals (DAAs), with their proven efficacy and safety, have replaced pegylated interferon (PegIFN) plus ribavirin (RBV) as the first-line treatment for chronic hepatitis C virus (HCV) infection in international guidelines.<sup>1–4</sup> However, compared with patients infected with other genotypes (GTs) of HCV, GT3-infected patients, especially those with cirrhosis, tend to achieve lower rates of sustained virological response (SVR) from DAA regimens.<sup>5</sup> Given that China has drastically different distributions of HCV GT3 subtypes and resistance-associated substitutions (RASs) from those of Western countries,<sup>6</sup> it remains unclear whether findings from clinical studies on DAAs in GT3-infected patients from those countries would be generalizable to Chinese patients. This article will discuss the epidemiology of HCV GT3 in China and review guidelines recommendations as well as clinical data from GT3-infected patients on DAAs, to provide direction for treatment and research among the Chinese and the broader Asian GT3-infected population.

## HCV GT3 epidemiology in China

There are currently over 71 million HCV-infected patients worldwide,<sup>7</sup> of which 44–46% are of GT1 and 25–30% are of GT3.<sup>7,8</sup> South and Southeast Asian countries like Pakistan, India, and Malaysia see a higher proportion of GT3 infection, with 79% of the Pakistani HCV-infected patients being of GT3.<sup>7</sup> China has around 10 million HCV-infected patients,<sup>7</sup> with the most common genotypes being GT1b (52.2–62.8%) and GT2a (16.7–28.7%).<sup>7,9–11</sup> GT3 comprises 8.7% to 11.7% of all the local infections,<sup>7,9,11</sup> with both incidence and prevalence showing an increasing trend in recent years.<sup>10,11</sup> For instance, one retrospective study conducted at a hospital in Shanghai, China found that the percentage of GT3-infected patients increased from 13.4% in 2011 to 22.6% in 2014.<sup>12</sup> Geographically, GT3 has spread from the south and southwest regions to the entire country over the last two decades,<sup>11,13</sup> albeit with an uneven distribution across different regions; up to 38% of HCV-infected patients in the southwest region are of GT3, while that percentage is only 3% in the northeast region.<sup>9</sup> GT3a and GT3b subtypes each constitute about 50% of the Chinese GT3-infected population,<sup>6,9,11</sup> with the southwest region reporting up to 70% of GT3-infected patients carrying the GT3b subtype.<sup>9</sup> The GT3b subtype comprised 90%

**Table 1. Approved DAA agents in China**

DAA agent	Therapeutic class	Indicated GTs
Asunaprevir <sup>a</sup>	NS3/4A protease inhibitor	1b
CLV <sup>a</sup>	NS5A inhibitor	1, 2, 3, 6
Danoprevir/ritonavir <sup>a</sup>	NS3/4A protease inhibitor+CYP3A inhibitor	1b
Dasabuvir <sup>a</sup>	None-nucleotide analogue NS5B polymerase inhibitor	1
DCV <sup>a</sup>	NS5A inhibitor	1–6
SOF <sup>a</sup>	Nucleotide analogue NS5B polymerase inhibitor	1–6
EBR/GZR	NS3/4A protease inhibitor+NS5A inhibitor	1, 4
GLE/PIB	NS3/4A protease inhibitor+NS5A inhibitor	1–6
LDV/SOF	NS5A inhibitor+Nucleotide analogue NS5B polymerase inhibitor	1–6
Ombitasvir/paritaprevir/ritonavir <sup>a</sup>	NS5A inhibitor+NS3/4A protease inhibitor+CYP3A inhibitor	1, 4
SOF/VEL	Nucleotide analogue NS5B polymerase inhibitor+NS5A inhibitor	1–6
SOF/VEL/VOX	Nucleotide analogue NS5B polymerase inhibitor+NS5A inhibitor+NS3/4A protease inhibitor	1–6

<sup>a</sup>The drug needs to be used in combination with other medications to treat chronic HCV infection; more details can be found in the relevant prescribing information.

of the GT3-infected patients in a hospital-based study conducted in Myanmar bordering southwest China.<sup>14</sup> These are markedly different from the patient composition pattern in the Western world (North America, Europe, and Oceania), where close to 99% of the GT3-infected patients carry the GT3a subtype.<sup>15</sup>

Prior research in South Korea and the USA has shown that compared with GT1- or GT2-infected patients, GT3-infected patients tend to have a more rapid hepatic disease progression, with a higher risk of liver complications, such as hepatocellular carcinoma.<sup>16–18</sup> Similarly, the Chinese prospective, observational cohort study “CCgenos” reported that the median time from infection to disease progression was shorter in GT3b-infected patients than in GT1-infected patients (27.1 vs. 35.6 years).<sup>19</sup> The aforementioned study at the Shanghai hospital also reported a younger age and a shorter duration of infection in cirrhotic patients with GT3 infection,<sup>12</sup> lending further evidence to the rapid disease progression associated with GT3.

NS5A RASs such as Y93H, A30K, L31M as well as A30K and L31M double substitutions can affect the efficacy of NS5A inhibitor-based DAA regimens,<sup>20</sup> and are thus a potential key consideration when choosing DAAs for HCV treatment. The global prevalence of the Y93H RAS in GT3a-infected patients is 6%.<sup>15</sup> The phase 3 clinical trials of ALLY-3 in the USA and ASTRAL-3 in Europe, Northern America, and Oceania both reported a Y93H prevalence of 9% among GT3-infected patients.<sup>21,22</sup> However, only 1.6% of GT3-infected and 3.3% of GT3a-infected patients in China have the Y93H RAS.<sup>6,23</sup> As for GT3b, both Chinese and global patient populations have reported a very low prevalence of Y93H.<sup>15,23</sup> In China, 94–96% of GT3b-infected patients carry both A30K and L31M RASs,<sup>6,23</sup> which confer high resistance to currently-approved NS5A inhibitors, as shown by the elevated half maximal effective concentrations for HCV with the RASs.<sup>20</sup>

Injection drug use is a strong risk factor for HCV infection worldwide.<sup>24</sup> A 2017 global meta-analysis reported an HCV antibody prevalence of 43.1% among Chinese people who inject drugs (PWID),<sup>25</sup> while a 2019 study focusing on HCV high-risk populations in China found the prevalence to be 72.4% among PWID.<sup>26</sup> Most of the early GT3-infected patients in China contracted the virus via this route.<sup>11</sup> GT3 is still highly prevalent among the HCV-infected PWID in China, with a 2015 study reporting that GT3 accounted for

55% of HCV-infected PWID.<sup>27</sup> A recent study in heroin users undergoing methadone maintenance therapy in Jiangsu Province reported that up to 74.0% of these patients were HCV antibody-positive,<sup>28</sup> with GT3a and GT3b comprising 24.6% and 41.7% of the cohort with viremia, respectively.<sup>28</sup>

### Treatment recommendations for GT3-infected patients

All the DAAs currently approved in China can be found in Table 1. All of them except sofosbuvir (SOF) are available only as brand-name drugs in China. Seven DAA regimens have been approved in China for GT3-infected patients, namely SOF+RBV, SOF plus daclatasvir (DCV), SOF plus coblopasvir (CLV), ledipasvir (LDV)/SOF+RBV, SOF/velpatasvir (VEL), glecaprevir/pibrentasvir (GLE/PIB), and SOF/VEL/voxilaprevir (VOX); however, not all of them are recommended in the guidelines. The Chinese Medical Association (CMA), American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and World Health Organization (WHO) recently updated their HCV treatment guidelines.<sup>1–4,29</sup> The recommendations for GT3-infected patients without or with compensated cirrhosis are summarized in Table 2. It is worth noting that the international guidelines were formulated primarily based on clinical studies conducted in Western countries, where the GT3a subtype predominates among GT3-infected patients.<sup>15</sup> Therefore, the recommendations for “GT3-infected patients” in these guidelines would likely be more applicable to those with GT3a infection.

### Non-cirrhotic patients

According to the CMA, AASLD, EASL, and WHO guidelines, 12-week SOF/VEL is recommended for non-cirrhotic, GT3-infected patients, regardless of prior PegIFN+RBV treatment (Table 2).<sup>1–4</sup> Co-administration of RBV with SOF/VEL can be considered in GT3b-infected patients, according to the CMA guidelines.<sup>1</sup> GLE/PIB is recommended for non-cirrhotic, GT3-infected patients in the CMA, EASL and WHO guidelines, and the treatment duration is dependent on patient

**Table 2. Treatment recommendations for GT3-infected patients without and with compensated cirrhosis**

Cirrhosis status	Regimen	Treatment history	CMA <sup>1</sup> 2019	AASLD <sup>2</sup> 2019	EASL <sup>3,29</sup> 2018	WHO <sup>4</sup> 2018
No cirrhosis	SOF/VEL	Naïve	12 weeks <sup>b</sup>	12 weeks	12 weeks	12 weeks
		Experienced <sup>a</sup>	12 weeks <sup>b</sup>	12 weeks <sup>c</sup>	12 weeks	12 weeks
	GLE/PIB	Naïve	8 weeks	8 weeks	8 weeks	8 weeks
		Experienced <sup>a</sup>	16 weeks	–	12 weeks <sup>e</sup>	16 weeks
	SOF+DCV	Naïve	–	–	–	12 weeks
		Experienced <sup>a</sup>	–	–	–	12 weeks
Compensated cirrhosis	SOF/VEL	Naïve	12 weeks ±RBV	12 weeks <sup>d</sup>	12 weeks <sup>f</sup>	12 weeks
		Experienced <sup>a</sup>	12 weeks ±RBV	–	12 weeks <sup>f</sup>	12 weeks
	GLE/PIB	Naïve	12 weeks	8 weeks	12 weeks	12 weeks
		Experienced <sup>a</sup>	16 weeks	16 weeks	16 weeks	16 weeks
	SOF/VEL/VOX	Naïve	12 weeks	–	12 weeks	–
		Experienced <sup>a</sup>	12 weeks	12 weeks	12 weeks	–
	SOF+DCV	Naïve	–	–	–	24 weeks
		Experienced <sup>a</sup>	–	–	–	24 weeks

<sup>a</sup>Treatment “experienced” refers to prior treatment with PegIFN+RBV in the guidelines by AASLD, EASL and WHO, but with PegIFN+RBV±SOF or SOF+RBV in the CMA guidelines. <sup>b</sup>Consider the co-administration of RBV in GT3b-infected patients. <sup>c</sup>Baseline RAS testing for Y93H is recommended. When Y93H is present, RBV should be co-administered, or an alternative regimen (12 weeks of SOF/VEL/VOX or 16 weeks of GLE/PIB for those treatment-experienced) should be used. <sup>d</sup>Only applicable for patients without Y93H. When Y93H is present, another regimen should be used (12 weeks of SOF/VEL+RBV or SOF/VEL/VOX as alternatives for such patients). <sup>e</sup>The European prescribing information for GLE/PIB suggests a 16-week course for PegIFN+RBV-experienced, non-cirrhotic patients with GT3 infection. <sup>f</sup>Only applicable for patients without Y93H. If Y93H is present, an alternative regimen such as SOF/VEL/VOX should be used, or RBV should be co-administered with SOF/VEL when SOF/VEL/VOX is not available.

treatment history.<sup>1,3,4</sup> The regimen is also recommended by AASLD as a first-line treatment for treatment-naïve patients and as an alternative for PegIFN+RBV-experienced patients.<sup>2</sup> Recent clinical data showed that with 8 weeks of GLE/PIB in non-cirrhotic patients, a lower SVR12 rate was observed in GT3b-infected patients than in GT3a-infected patients,<sup>30</sup> indicating that 8 weeks is not an optimal course in the former group. Additionally, SOF+DCV is recognized only by the WHO as a first-line regimen in non-cirrhotic, GT3-infected patients.<sup>4</sup>

### Patients with compensated cirrhosis

Both SOF/VEL and GLE/PIB are recommended regimens for GT3-infected patients with compensated cirrhosis in the CMA, AASLD, EASL and WHO guidelines.<sup>1–4,29</sup> All the guidelines recommend an extended course (16 weeks) of GLE/PIB for treatment-experienced patients.<sup>1–4</sup> Co-administration of RBV with SOF/VEL can be considered irrespective of treatment experience according to the CMA guidelines,<sup>1</sup> while SOF/VEL+RBV is included only as an alternative for PegIFN+RBV-experienced patients in the AASLD guidelines.<sup>2</sup> According to EASL and AASLD, GT3-infected patients with compensated cirrhosis should receive RAS testing for Y93H before initiating treatment with SOF/VEL.<sup>2,29</sup> In the presence of Y93H, RBV should be co-administered or an alternative regimen should be used.<sup>2,29</sup> In contrast, the CMA does not recommend RAS testing at baseline in general and suggests considering RBV co-administration with SOF/VEL in cirrhotic, GT3-infected patients.<sup>1</sup> SOF/VEL/VOX is recommended for both treatment-naïve and treatment-experienced GT3-infected patients with compensated cirrhosis by the CMA and EASL guidelines, but only for those who are treatment-experienced in the AASLD guidelines.<sup>1–3</sup> Besides this, SOF+DCV is recommended only by the WHO

guidelines, for GT3-infected patients with compensated cirrhosis.<sup>4</sup>

### Patients with decompensated cirrhosis

Liver transplantation is the primary option for decompensated cirrhosis, whereas antiviral treatment may help prevent reinfection among liver recipients. Due to the safety concerns attributable to markedly increased drug exposure in patients with decompensated cirrhosis, protease inhibitor (PI)-containing regimens, such as GLE/PIB, SOF/VEL/VOX, and elbasvir/grazoprevir (EBR/GZR), are contraindicated in them.<sup>3</sup> The CMA, AASLD, and EASL guidelines recommend 12 weeks of SOF/VEL+RBV for GT3-infected patients with decompensated cirrhosis, and 24 weeks of SOF/VEL if RBV is contraindicated or not tolerated.<sup>1–3</sup> Additionally, 12 weeks of SOF+DCV+RBV or 24 weeks of SOF+DCV (when RBV is contraindicated or not tolerated) is also recommended for such patients in the CMA guidelines.<sup>1</sup> No treatment recommendations were provided by the WHO guidelines for patients with decompensated cirrhosis; although, the guidelines have noted the efficacy and safety of SOF/VEL and SOF+DCV in this patient population.<sup>4</sup>

Inappropriate use of PI-containing regimens in patients with decompensated cirrhosis could result in serious complications. In August 2019, the USA's Food and Drug Administration (known as the FDA) issued a warning on the risk of serious liver injury in patients with advanced liver disease receiving PI-containing regimens, following publication of several case reports.<sup>31</sup> Many of these cases should avoid PI-containing regimens, given the presence of signs and symptoms of decompensated cirrhosis or other serious liver problems.<sup>31</sup> The FDA thus recommends assessing liver disease severity at baseline, and close monitoring for worsening liver function when patients with compensated

cirrhosis receive PI-containing regimens.<sup>31</sup> The FDA also advises discontinuation upon the emergence of signs and symptoms of decompensation.<sup>31</sup> Therefore, a PI-free regimen like SOF/VEL would be more convenient for patients with compensated cirrhosis.

## Clinical data for DAAs in GT3-infected patients

### GT3a-infected patients

A large body of evidence has been generated in patients with GT3 infection from Western countries. Given the predominance of the GT3a subtype in GT3 infections, findings from Western GT3-infected patients in clinical trials could be largely regarded as those from GT3a-infected patients, although the distributions of GT3 subtypes were not always reported in studies. A smaller amount of data among GT3a-infected patients are also available from phase 3 clinical trials conducted in China. This section will review these two sets of efficacy data and discuss their implications and relevance for guiding the treatment of Chinese patients with GT3a infection.

**Western GT3a-infected patients treated with SOF/VEL:** In ASTRAL-3, an international multicenter phase 3 clinical trial, the overall SVR12 rate in GT3-infected patients (with 96% [265/277] infected with GT3a) receiving 12-week SOF/VEL was 95% (264/277); of patients with GT3a infection, 95% (253/265) achieved SVR12.<sup>22</sup> Efficacy was independent of cirrhosis status, with the SVR12 rates in patients without and with compensated cirrhosis reported as 97% (191/197) and 91% (73/80), respectively (Supplementary Fig. 1).<sup>22</sup> An integrated analysis of five phase 3 clinical trials with 12 weeks of SOF/VEL, performed by Hezode *et al.*,<sup>32</sup> reported an SVR12 rate of 93% (53/57) in GT3-infected patients with baseline NS5A RASs from ASTRAL-3 and POLARIS-3. The analysis also found that 86% (19/22) of Y93H carriers, 96% (27/28) of A30K carriers, and all five of the A30K+L31M carriers achieved SVR12,<sup>32</sup> suggesting that the efficacy of SOF/VEL in GT3a-infected patients is largely unaffected by the A30K RAS. In another integrated analysis of six phase 2 and 3 clinical trials, Roberts *et al.*<sup>33</sup> found an SVR12 rate of 94% (316/337) in GT3-infected patients with compensated cirrhosis (with 97% [316/326] infected with GT3a among patients with available genotype data) after 12 weeks of SOF/VEL (Supplementary Fig. 1) but noted that A30K±L31M- and Y93H- carriers achieved SVR12 rates of 88% (22/25) and 60% (6/10), respectively.<sup>33</sup> These results suggest that Y93H-carrying, cirrhotic patients with GT3 infection may represent a particular patient population that do not respond optimally to 12-week SOF/VEL.<sup>33</sup> As a result, the AASLD and EASL guidelines now recommend 12 weeks of SOF/VEL for GT3-infected patients with compensated cirrhosis,<sup>2,3,29</sup> with co-administration of RBV in the presence of the Y93H RAS.<sup>2,29</sup> Likely due to the low prevalence (1.6%) of the Y93H RAS in Chinese GT3-infected patients,<sup>6,23</sup> the CMA guidelines do not recommend Y93H RAS testing in GT3-infected patients prior to treatment with SOF/VEL.

**Western GT3a-infected patients treated with GLE/PIB:** In an integrated analysis of five clinical trials of GLE/PIB including GT3-infected patients (with 99% [683/693] infected with GT3a), Flamm *et al.*<sup>34</sup> found that extending the treatment duration from 8 weeks to 12 weeks did not increase efficacy in treatment-naïve, non-cirrhotic patients, with the SVR12 rates at 95% (198/208 and 280/294) in both groups (Supplementary Fig. 1). Based on these findings, current guidelines generally recommend 8 weeks of GLE/PIB in such patients.<sup>1-4</sup> However, the treatment duration affected efficacy in treatment-experienced, non-cirrhotic patients. The rates of virological failure in those

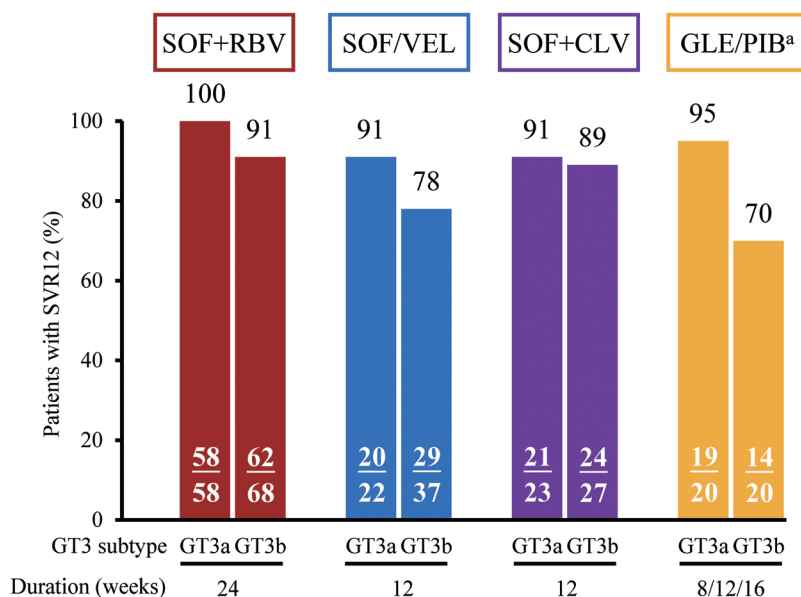
receiving 12 and 16 weeks of treatment were 10.2% (5/49) and 4.5% (1/22), respectively.<sup>34</sup> Currently, the EASL guidelines recommend 12 weeks of treatment in this group of patients,<sup>3</sup> while the CMA and WHO guidelines recommend 16 weeks.<sup>1,4</sup> Flamm *et al.*<sup>34</sup> also reported that 97% (67/69) of treatment-naïve patients with cirrhosis achieved SVR12 following 12 weeks of GLE/PIB, and 94% (48/51) of their treatment-experienced counterparts achieved SVR12 following 16 weeks of the regimen. Overall, GLE/PIB showed high efficacy among GT3a-infected patients. However, its treatment duration is dependent on treatment history and cirrhosis status, which may complicate clinical practice and affect its use in primary care settings.

Flamm *et al.*<sup>34</sup> also explored the effect of RASs on the efficacy of GLE/PIB in GT3-infected patients that were treatment-naïve and non-cirrhotic. In patients receiving 8-week GLE/PIB, 100% (10/10) of Y93H carriers and 83% (15/18) of A30K carriers achieved SVR12 based on modified intention-to-treat (mITT) analysis.<sup>34</sup> Among those receiving 12-week GLE/PIB, Y93H carriers and A30K carriers achieved mITT SVR12 rates of 86% (12/14) and 93% (13/14), respectively;<sup>34</sup> whereas, a meta-analysis showed that both the A30K and Y93H RASs can reduce the efficacy of GLE/PIB in GT3-infected patients.<sup>35</sup> More real-world studies with larger samples are needed to verify this effect.

Although no head-to-head studies have been conducted between SOF/VEL and GLE/PIB, an analysis based on the American TRIO Network found that among cirrhotic, GT3-infected patients, GLE/PIB yielded a lower per-protocol SVR rate than SOF/VEL (88% [22/25] vs. 98% [57/58],  $p=0.044$ ).<sup>36</sup> This suggests a difference in efficacy between GLE/PIB and SOF/VEL in this patient population, but the reason for this remains to be investigated.

**Western GT3a-infected patients treated with SOF/VEL/VOX and EBR/GZR+SOF:** The phase 3 clinical trials POLARIS-2 and -3, both conducted in North America, Europe, and Oceania, found that 8 weeks of SOF/VEL/VOX achieved high SVR12 rates of 99% (91/92) and 96% (106/110) in GT3-infected patients without and with compensated cirrhosis, respectively (Supplementary Fig. 2).<sup>37</sup> Nevertheless, as experiences thus far indicate that GT3 is difficult-to-treat with DAAs, both the AASLD and EASL guidelines recommend a 12-week course for SOF/VEL/VOX for precautionary reasons.<sup>2,3</sup> The phase 2 study C-ISLE in the UK determined the use of EBR/GZR+SOF in GT3-infected patients with compensated cirrhosis (Supplementary Fig. 2).<sup>38</sup> In this trial, treatment-naïve patients receiving 8 weeks of EBR/GZR+SOF+RBV and 12 weeks of EBR/GZR+SOF achieved SVR12 rates of 91% (21/23) and 96% (23/24), respectively.<sup>38</sup> Treatment-experienced patients achieved an SVR12 rate of 100% (17/17) with 12 weeks of EBR/GZR+SOF, while addition of RBV or extension to a 16-week duration did not improve efficacy (with the SVR12 rates at 94% [17/18] for both).<sup>38</sup> Based on these findings, the AASLD recommends 12 weeks of EBR/GZR+SOF as an alternative for PegIFN+RBV-experienced, GT3-infected patients with compensated cirrhosis.<sup>2</sup>

**Western GT3a-infected patients treated with other DAA regimens:** In clinical trials for SOF+RBV, LDV/SOF+RBV, and SOF+DCV, cirrhotic and/or treatment-experienced GT3-infected patients emerged as difficult-to-treat patient populations (Supplementary Fig. 3) and achieved lower SVR12 rates compared with their counterparts in clinical trials for SOF/VEL and GLE/PIB.<sup>22,34</sup> For GT3-infected patients in the European phase 3 clinical trial VALANCE, while 24-week SOF+RBV treatment achieved an SVR12 rate of 91% (172/190) in non-cirrhotic patients, the SVR12 rates were 68% (41/60) in those with compensated cirrhosis and 62% (29/47) in treatment-experienced patients with compensated cirrhosis.<sup>39</sup> These observations align with the findings from the SOF+RBV arm in the ASTRAL-3



**Fig. 1. SVR12 rates of SOF+RBV,<sup>45</sup> SOF/VEL,<sup>46</sup> SOF+CLV,<sup>44</sup> and GLE/PIB<sup>30</sup> in Chinese patients with GT3 infection.** <sup>a</sup>Treatment-naïve patients without or with compensated cirrhosis received 8 or 12 weeks of treatment, respectively, while treatment-experienced patients received a 16-week treatment regardless of cirrhosis status.

study.<sup>22</sup> The Canadian phase 2 trial study 1701 evaluated the efficacy of 12-week LDV/SOF+RBV in treatment-naïve, GT3-infected patients (with 95% [105/110] infected with GT3a) and found that those with compensated cirrhosis had a lower SVR12 rate than those without cirrhosis (79% [31/39] vs. 94% [68/72]).<sup>40</sup> As for 12-week SOF+DCV, the phase 3 study ALLY-3 conducted in the USA reported that among GT3-infected patients, the SVR12 rate was 96% (105/109) in non-cirrhotic patients, but was only 63% (20/32) in those with compensated cirrhosis.<sup>21</sup> The follow-up ALLY-3+ study investigated the efficacy of RBV co-administration with SOF+DCV in GT3-infected patients with compensated cirrhosis from the USA and found that despite co-administration with RBV, suboptimal SVR12 rates of 83% (15/18) and 89% (16/18) were achieved with 12-week and 16-week treatment, respectively.<sup>41</sup> Possibly for this reason, SOF+DCV is now not recommended by the CMA, AASLD, and EASL guidelines as a first-line regimen for GT3-infected patients.<sup>1-3</sup>

**Chinese GT3a-infected patients:** Among the seven DAA regimens that have been approved for GT3-infected patients in China, phase 3 clinical data in Chinese GT3-infected patients are only available for SOF/VEL (NCT02671500), SOF+RBV (NCT02021643), SOF+CLV (NCT03995485), and GLE/PIB (NCT03222583 and NCT03235349) (Figs. 1, 2).<sup>30,42-44</sup> It should be noted that no head-to-head clinical trials between these regimens have been conducted among Chinese GT3-infected patients.

In Chinese phase 3 clinical trials, the SVR12 rates in GT3a-infected patients receiving 12 weeks of SOF/VEL and 24 weeks of SOF+RBV were 91% (20/22) (89% [17/19] and 100% [3/3] in patients without and with compensated cirrhosis, respectively) and 100% (58/58), respectively,<sup>45,46</sup> similar to those reported among Western GT3-infected patients.<sup>22,39</sup> Since the prevalence of Y93H (the predominant NS5A RAS affecting the efficacy of SOF/VEL in GT3a-infected patients) is lower in China,<sup>6,23</sup> it is reasonable to anticipate SOF/VEL to have similar or better efficacy in Chinese GT3a-infected patients. Twelve weeks of SOF+CLV achieved an SVR12 rate of 91% (21/23) in GT3a-infected patients, being 90% (19/21) and 100% (2/2) in patients without and

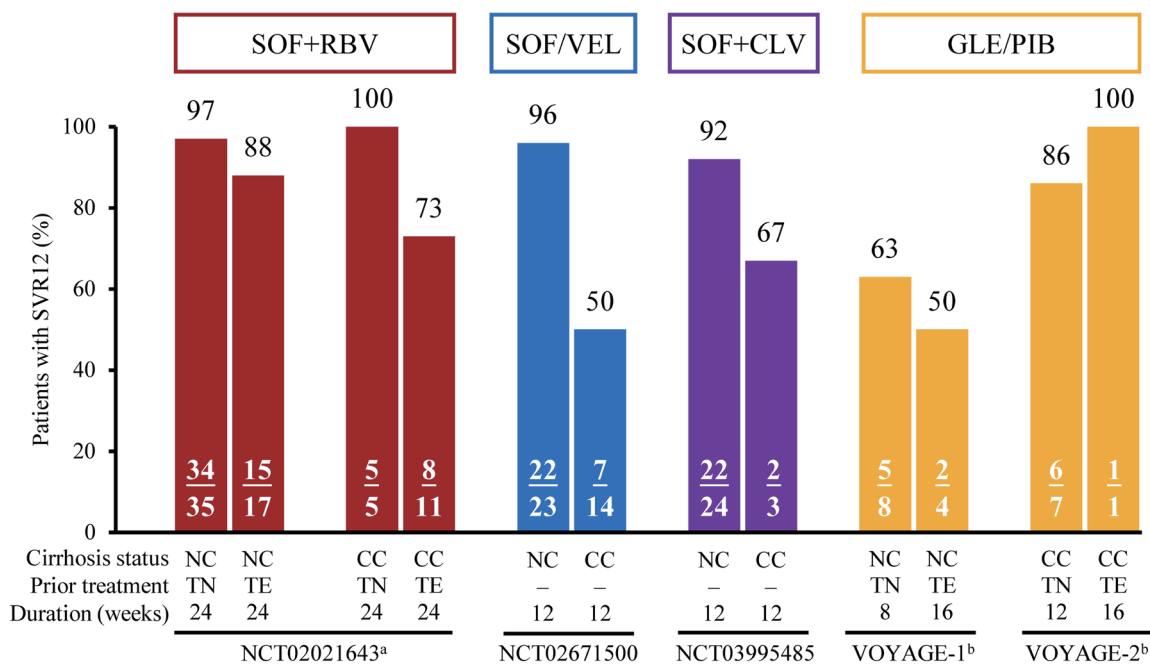
with compensated cirrhosis, respectively.<sup>44</sup> Thus, SOF+CLV and SOF/VEL appear to demonstrate comparable efficacy among Chinese patients with GT3a infection.

The two phase 3 studies VOYAGE-1 and -2 of GLE/PIB included Chinese GT3-infected patients without and with compensated cirrhosis, respectively.<sup>30</sup> In these two trials, treatment-naïve, GT3-infected patients without and with compensated cirrhosis received 8 or 12 weeks of treatment, respectively, while those who were GT3-infected and treatment-experienced were treated for 16 weeks regardless of cirrhosis status.<sup>30</sup> GLE/PIB achieved SVR12 rates of 93% (13/14) in non-cirrhotic, GT3a-infected patients in VOYAGE-1 and 100% (6/6) in GT3a-infected patients with compensated cirrhosis in VOYAGE-2.<sup>30</sup> The SVR12 rate in GT3a-infected patients across the two trials was 95% (19/20); similar to the efficacy of GLE/PIB in Western GT3-infected patients.<sup>34</sup> As such, recommendations that were largely based on clinical data from Western GT3-infected patients are most likely also applicable for GT3a-infected patients in China.

### GT3b-infected patients

Currently, limited data are available on the treatment of GT3b infection with DAAs. GT3b infection is under-represented in Western countries while in China only five phase 3 trials and a small number of real-world studies have reported on GT3b-infected patients treated with DAAs, revealing a gap in treatment needs that could not be sufficiently addressed based on Western experiences. More China-specific data are needed to inform guidelines for treating Chinese patients with GT3b infection and until then, preliminary strategies could be formulated for managing GT3 infection in the Chinese scenario, as discussed below.

**SOF-based regimens:** In pivotal trials of Chinese GT3b-infected patients, the SVR12 rates were 78% (29/37) for 12-week SOF/VEL, 89% (24/27) for 12-week SOF+CLV, and 91% (62/68) for 24-week SOF+RBV; these were all lower than their corresponding SVR12 rates in GT3a-infected patients in the same trials (Fig. 1).<sup>44-46</sup> The SVR12 rate for



**Fig. 2. SVR12 rates of SOF+RBV,<sup>45</sup> SOF/VEL,<sup>46</sup> SOF+CLV,<sup>44</sup> and GLE/PIB<sup>30,50</sup> in Chinese patients with GT3b infection.** <sup>a</sup>TE in this study was defined as prior treatment with IFN-based therapy. <sup>b</sup>TE in these two studies was defined as prior treatment with IFN with or without RBV, and/or SOF+RBV with or without IFN. CC, compensated cirrhosis; NC, no cirrhosis; TE, treatment-experienced; TN, treatment-naïve.

SOF/VEL in GT3b-infected patients was still as high as 96% (22/23) in those without cirrhosis, but decreased to 50% (7/14) in those with compensated cirrhosis (Fig. 2).<sup>46</sup> Similarly, post hoc analysis found that the SVR12 rates of 12-week SOF+CLV were 92% (22/24) and 67% (2/3) in GT3b-infected patients without and with compensated cirrhosis, respectively (Fig. 2).<sup>44</sup>

The Chinese GT3b-infected patients with available sequencing data in the phase 3 study of SOF/VEL all carried NS5A RASs, with the A30K+L31M double RASs present in 94% (33/35) of them.<sup>46</sup> It was thus suggested that A30K+L31M, when present concurrently with cirrhosis, could reduce the efficacy of SOF/VEL in GT3b-infected patients.<sup>47</sup> It is worth noting that the clinical trial of SOF/VEL in China included only 37 GT3b-infected patients, of whom 38% (14/37) were cirrhotic. This small sample might not be representative of the real-world GT3b-infected patient population in China.<sup>43</sup> Therefore, the effectiveness of SOF/VEL in this patient population awaits further elucidation.

The above pivotal trial identified cirrhotic, GT3b-infected patients (with pervasive key NS5A RASs) as a difficult-to-treat population, specifically in China. For such patients, Chinese data are not yet available on the effect of RBV co-administration with SOF/VEL. However, a meta-analysis of studies from Western countries showed that regardless of cirrhosis status, co-administering RBV can improve the efficacy of SOF/VEL in GT3-infected patients.<sup>48</sup> A Spanish randomized, open-label trial reported that 12 weeks of SOF/VEL without and with RBV achieved high SVR12 rates of 91% (92/101) and 96% (99/103), respectively, among GT3-infected patients with cirrhosis.<sup>49</sup> In patients carrying NS5A RASs, the addition of RBV resulted in a higher SVR12 rate (95% [21/22] vs. 84% [16/19]).<sup>49</sup> The SVR12 rate of 81% (13/16) achieved by 24 weeks of SOF+RBV in GT3b-infected patients with compensated cirrhosis also indicates the potential benefit from RBV co-administration.<sup>45</sup> These data, primarily from GT3a-infected patients, point to RBV co-administration as a possible strategy for improving the

efficacy of SOF/VEL in Chinese GT3b-infected patients, likely through reducing the risk of virological relapse. It will also be interesting to know whether the addition of PegIFN to SOF/VEL could increase its SVR rates among GT3b-infected patients with compensated cirrhosis, but this needs further investigation.

In this age of treatment pathway simplification for HCV management, cirrhotic, GT3-infected patients with baseline NS5A RASs remain a patient population with special treatment needs. Even for SOF/VEL, the regimen with the fixed treatment duration across HCV genotypes, cirrhotic status, and treatment history, the above patient population remains the only sub-group requiring treatment modification in the form of RBV co-administration.<sup>1,2,29</sup> Here, we propose a hierarchical pathway for identifying this specific patient population in the Chinese context, while avoiding excessive pre-treatment testing. Firstly, patients' cirrhosis status should be evaluated. Since clinical data support SOF/VEL's efficacy in non-cirrhotic European and Asian patients with various genotypes of HCV,<sup>22,43</sup> genotyping would not be necessary when initiating 12 weeks of SOF/VEL in non-cirrhotic patients. In patients with compensated cirrhosis, the transmission route could serve as a preliminary indicator of the need for genotyping. In China, given that GT3 is particularly common among HCV-infected PWID, genotyping would be necessary for cirrhotic PWID. Once a cirrhotic patient is identified with GT3 infection, the HCV subtype can direct the treatment decision, possibly without baseline RAS testing. As the Y93H RAS has a low prevalence in China, cirrhotic, GT3a-infected patients may consider an RBV-free regimen; in contrast, the near-universal presence of A30K+L31M in Chinese GT3b-infected patients warrants RBV co-administration for cirrhotic, GT3b-infected patients.

**GLE/PIB:** Across VOYAGE-1 and -2, SVR12 was achieved by GLE/PIB in 70% (14/20) of Chinese patients with GT3b infection (Fig. 1).<sup>30</sup> In VOYAGE-1, the SVR12 rate was 58% (7/12) in non-cirrhotic, GT3b-infected patients, with 63% (5/8) in treatment-naïve patients and 50% (2/4) in treat-

ment-experienced patients (Fig. 2).<sup>50</sup> These results are inferior to the SVR12 rates that GLE/PIB achieved in Western GT3-infected patients and Chinese GT3a-infected patients, as discussed above.<sup>30,34</sup> The findings from these two trials imply that the recommended 8-week course of GLE/PIB in treatment-naïve, non-cirrhotic patients with GT3 infection is not feasible in China.<sup>1-4</sup> An extended course might be a reasonable approach to improve the efficacy in those patients but would further complicate the treatment duration of GLE/PIB, which already depends on HCV genotype, cirrhosis status, and treatment history. In contrast, 12-week SOF/VEL achieved an SVR12 rate of 96% in non-cirrhotic, GT3b-infected patients,<sup>46</sup> and thus may be a better option for this patient population. In VOVAGE-2, the SVR12 rate was 88% (7/8) in GT3b-infected patients with compensated cirrhosis; specifically, 6 out of 7 treatment-naïve patients and 1 treatment-experienced patient achieved SVR12 (Fig. 2).<sup>50</sup> However, the efficacy of GLE/PIB in cirrhotic patients with GT3b infection should be considered inconclusive given the small sample size ( $n=8$ ) of such patients in the trial.<sup>30</sup> All six GT3b-infected patients experiencing virologic failure in VOYAGE-1 and -2 carried NS5A M31 polymorphism at baseline,<sup>30</sup> indicating that the efficacy of GLE/PIB in Chinese patients with GT3b infection may be affected by the presence of NS5A M31 polymorphism.<sup>6,23</sup>

There is a small amount of real-world data for using DAAs among Chinese GT3-infected patients. A retrospective study conducted in six hospitals across provinces investigated the efficacy of different DAAs in GT3-infected patients.<sup>51</sup> The study included 12 patients (5 GT3a, 7 GT3b) receiving 12 weeks of SOF+DCV and 10 patients (5 GT3a, 5 GT3b) receiving 12 weeks of SOF/VEL.<sup>51</sup> All patients receiving SOF/VEL achieved SVR12, but only 3 (60%) GT3a- and 4 (57%) GT3b-infected patients in the SOF+DCV group achieved SVR12.<sup>51</sup> In a cohort study conducted at a tertiary hospital of Sichuan Province in treatment-naïve, GT3-infected patients, SVR24 was achieved in 86% (49/57), 92% (22/24), and 100% (21/21) of patients receiving SOF+DCV, SOF+DCV+RBV, and SOF/VEL, respectively;<sup>52</sup> all 10 patients with virologic failure were in the SOF+DCV±RBV groups.<sup>52</sup> Taken together, these data suggest that for Chinese GT3-infected patients, SOF+DCV may be a suboptimal option due to higher failure rates, while SOF/VEL tends to have better efficacy. As GLE/PIB and SOF+CLV were only recently approved in China, their real-world efficacy in Chinese GT3-infected patients remains to be determined.

### Future directions

In order to achieve the WHO 2030 HCV elimination goal, China would need effective solutions to increase the diagnosis and treatment rates and to reduce the incidence of HCV infection. Studies have shown a low treatment rate of HCV infection in China. One retrospective study in a tertiary hospital in Chongqing, southwest China showed that from 2013 to 2015, only 46% of the HCV RNA-positive patients received antiviral treatment.<sup>53</sup> The low treatment rates before the availability of DAAs could be partly due to the tedious administration method, the various contraindications, and the prevalent side effects of PegIFN+RBV, which severely limited its use in HCV treatment.

By 2020, all the DAAs recommended in the international guidelines have been approved in China, as well as some domestically produced ones (Table 1). To increase the treatment rates of HCV infection and reduce the financial burden of HCV treatment for patients, the National Healthcare Security Administration (commonly known as the NHSA) have included four regimens (SOF/VEL and SOF+CLV for non-GT1b patients; LDV/SOF and EBR/GZR for GT1b patients)

into the National Reimbursement Drug List. It should be noted that in the regimen of SOF+CLV, only CLV has been included in the list, but generic SOF is given to patients free of charge by the CLV manufacturer to form a complete regimen. The prices of the regimens included in the list have been reduced drastically as a result of drug pricing negotiations between NHSA and the manufacturers. For the treatment of GT3 infection, the total price paid by a patient and medical insurance is RMB13,104 (~\$2,019 USD) for a 12-week course of SOF/VEL and RMB10,038 (~\$1,547 USD) for a 12-week course of SOF+CLV. To fully capitalize on high efficacy and good tolerability of these versatile regimen options as well as the reduced prices, strategies should be devised to roll out DAA treatment on a large scale. These regimens would not only help existing HCV-infected patients achieve virological clearance and thereby slow down disease progression but also contribute to reducing the risk of further HCV transmission. As discussed above, data for cirrhotic, GT3b-infected patients are still insufficient to formulate treatment recommendations and thus clinical trials focusing on this subpopulation should be conducted in China to determine the optimal regimens.

In terms of HCV prevention, it is important to adopt interventions tailored to the epidemiological characteristics of HCV transmission, for different high-risk populations and in different geographical regions. Specifically, southwest China sees higher prevalence of GT3 and concentration of the GT3b subtype.<sup>9,11</sup> Considering that injection drug use is the main risk factor for contracting GT3 in China,<sup>52</sup> strategies targeting PWID, such as providing single-use injection supplies and opioid replacement rehabilitation therapy, would be critical for controlling HCV transmission in this region.<sup>54</sup> Recently, the number of patients contracting GT3 infection from unprotected sex has been rising in China.<sup>11</sup> As GT3 infection is also starting to spread beyond southwest China,<sup>13</sup> changes in the epidemiological pattern of HCV transmission may necessitate adjustments to regional or local HCV prevention strategies. Another HCV high-risk population in China are patients undergoing hemodialysis (HD), with a meta-analysis from 2009 revealing an HCV prevalence of 41.1% in this group.<sup>55</sup> With more stringent hygiene practices in hospitals in recent years, the prevalence of HCV in HD patients has decreased dramatically. Nevertheless, a 2011 cross-sectional study in Beijing showed that the prevalence of HCV antibody positivity in patients on HD was still as high as 6.1%, and HCV RNA positivity was 4.6%, with GT3a and GT3b each taking up 1.1% of these HCV-infected patients.<sup>56</sup> The national sentinel surveillance for HCV also reported that the rate of HCV antibody positivity among Chinese patients on HD was 4.5% in 2016 and 4.4% in 2017.<sup>57</sup> These findings suggest that standard operation procedures and management guidelines in HD centers should be strictly enforced to further reduce the HCV transmission in this patient population.<sup>58</sup> Overall, the considerable geographical variation across the expanse of China calls for more systematic, region-specific investigations into the epidemiology of HCV in high-risk populations, so that treatment and intervention strategies can cater to local needs.

### Conclusions

GT3a and GT3b subtypes each account for around half of the GT3 infections in China, with the A30K and L31M double RASs universally present in GT3b-infected patients. Phase 3 clinical trials in Chinese GT3-infected patients have supported the efficacy of SOF/VEL, SOF+RBV, SOF+CLV, and GLE/PIB in GT3a-infected patients with high SVR12 rates. SOF/VEL for 12 weeks has proven to be highly efficacious in non-cirrhotic, GT3b-infected patients but achieved a

lower SVR12 rate in GT3b-infected patients with cirrhosis; hence, RBV might need to be co-administered for this latter group to improve SVR12. The clinical data of SOF+CLV in GT3b-infected patients are scarce but appear similar to those of SOF/VEL. GLE/PIB for 8 weeks produced a suboptimal SVR12 rate in treatment-naïve, non-cirrhotic patients with GT3b infection, and its efficacy is still inconclusive in cirrhotic, GT3b-infected patients. For the Chinese population, treatment strategies for GT3a-infected patients can be formulated based on recommendations in international guidelines and current clinical data, but there are insufficient data to make recommendations for GT3b-infected patients. More clinical trials with larger sample sizes are thus needed to evaluate various regimens and then to determine the optimal ones in this group. Additionally, considering the increasing number of GT3-infected patients in recent years, China needs to adopt active intervention strategies to minimize HCV transmission.

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## Conflict of interest

XW reports consulting fees for MSD and speaker fees for Gilead Sciences and GlaxoSmithKline. The other author has no conflict of interests related to this publication.

## Author contributions

Study concept and design (XW, LW), drafting of the manuscript (XW, LW), and critical revision of the manuscript (XW, LW).

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