

## Current treatment of chronic hepatitis C in China: Dilemma and potential problems

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### Abstract

Major advances have been made in the treatment of chronic hepatitis C virus (HCV) infection with the advent of direct-acting antiviral agents (DAAs). China has the most cases of HCV infection worldwide, but

none of the DAAs has been approved in mainland China so far, and interferon (IFN)- $\alpha$ -based treatment remains the standard of care. HCV patients without response or with contraindications to IFN-based therapy have no alternative options. However, many patients buy DAAs, especially the generic forms of sofosbuvir, from other countries or areas. Under these circumstances, the use of these drugs may cause many predictable and unpredictable problems in ethics, law and medical practice. Given the obstacles of legal accessibility to DAAs and the potential problems of obtaining and using DAAs in China, the early launching of the DAAs in China or the legalization of buying drugs from areas outside China and using these drugs in China is an urgent issue and needs to be dealt with as soon as possible, in the interest of the patients.

**Key words:** Hepatitis C virus infection; Treatment; Direct-acting antiviral agent; Generics; China

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**Core tip:** This article describes the current treatment situation of chronic hepatitis C virus infection in China and discusses the potential problems pertinent to the access and the use of direct-acting antiviral agents (DAAs), especially the use of generic DAAs from various sources.

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### INTRODUCTION

Infection with hepatitis C virus (HCV) is a leading

cause of liver disease. Worldwide, an estimated 130-170 million people have HCV infection, and China has the most cases of HCV infection worldwide, with an estimated 29.8 million people<sup>[1]</sup>. A high proportion of people with HCV infection have developed advanced chronic liver diseases, including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC).

The primary goal of treating chronic HCV infection is to achieve a sustained virologic response (SVR), which is defined as the absence of serum HCV RNA 12-24 wk after cessation of treatment. Patients achieving an SVR are considered cured in that 99% of patients who achieve an SVR remain undetectable for virus during long-term follow-up<sup>[2]</sup>. Achievement of SVR is associated with improved clinical outcomes. Pegylated interferon (Peg-IFN)- $\alpha$  2a or 2b in combination with ribavirin (RBV) has been the standard of care for chronic HCV infection. However, treatment with Peg-IFN- $\alpha$  and RBV has limited efficacy. For instance, 48 wk of Peg-IFN and RBV therapy may achieve SVR in only 40% of patients with HCV genotype 1 infection<sup>[3]</sup>. Significant adverse events may accompany the duration of treatment<sup>[3-5]</sup>, resulting in poor adherence and premature treatment discontinuation. Moreover, patients with decompensated liver disease, patients with HIV/HCV co-infection, patients who have comorbidity such as heart disease or chronic kidney diseases, patients who have had renal failure and renal transplantation, and patients who have undergone liver transplantation for HCV-associated liver disease may be contraindicated to or ineligible for the regimen of IFN and RBV. Patients who have a null or low response to the regimen of IFN and RBV and patients who are unwilling to take the drugs have no alternative effective treatments. Therefore, novel treatments that have more potent antiviral activity and fewer adverse effects and are eligible and compatible for patients with complex comorbidity in real life settings are urgently required.

Fortunately, major advances have been made in the treatment of chronic HCV infection, with the advent of direct-acting antiviral agents (DAAs) in recent years. Many regimens free of IFN or free of both IFN and RBV have been devised based on combination of new DAAs. These new regimens provide excellent efficacy with higher SVR rates and good safety profile with fewer side effects, and are of shorter duration of treatment. The patients also have a better treatment experience, higher adherence to treatment, and substantial improvement of health-related quality of life during treatment<sup>[6]</sup>. DAA combination regimens also provide high SVR rates in patients with various HCV genotypes, disease conditions and treatment experiences, including cirrhosis associated with HCV genotype 1<sup>[7,8]</sup>, liver and kidney transplant recipients<sup>[9]</sup>, HCV-genotype-1-infected patients with compensated cirrhosis who had not achieved SVR after successive treatments with Peg-IFN and protease-inhibitor regimens<sup>[10]</sup>, and treatment-naïve and treatment-experienced patients co-infected with HIV and HCV

genotypes 1-4<sup>[11]</sup>.

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## CURRENT TREATMENT OF CHRONIC HCV INFECTION IN CHINA

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Because of the unavailability of the novel DAAs, IFN- $\alpha$  or Peg-IFN- $\alpha$  in combination with RBV remains the current standard of care for chronic HCV infection in mainland China. Under these circumstances, HCV patients, especially some important and difficult to treat HCV patients, such as nonresponders to IFN and RBV treatment and those with relapse; patients with renal failure or heart disease; patients intolerant to the adverse events of and with contraindications to IFN and RBV; patients with HCV-related cirrhosis and/or HCC; and patients with HIV/HCV co-infection have no other treatment options. In reality, however, the patients themselves are pragmatic. They try to seek help from other sources and find ways possible to obtain the drugs for the treatment of their disease. The high cost used to be one of the obstacles for some patients because of the unaffordability, but the cost is not an issue with the launching of generic drugs in some countries such as India. The price of the generic drugs is much lower than their brand-name counterparts. As a result, many HCV patients have bought or are going to buy DAAs, mainly sofosbuvir, a "blockbuster drug", from various regions or countries such as India and Bangladesh through different means, including through brokers, relatives and friends who have the opportunity to buy the drugs. The HCV patient population using DAAs, mainly sofosbuvir, from the above-mentioned sources is rapidly increasing in China.

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## DISCUSSION

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Undoubtedly, most patients may benefit from the use of these drugs. Ethically and responsibly, doctors would be pleased to see that the patients have access to effective medicines and the probable cure of their disease. However, some problems may be encountered.

First, none of the DAAs including sofosbuvir, whether generics or brand name, has been approved by the China Food and Drug Administration. In this respect, the use of these drugs appears to be illegal in China. There is a similar but not identical example. Lu Yong, a Chinese man, who was diagnosed with chronic myeloid leukemia when he was aged 34 years in 2002, was arrested, jailed and then released by the police authorities in China early this year because of purchasing the Indian generic drug imatinib mesylate for himself and other patients. Although he appeared to be accused of selling "fake drugs", he knows nothing about the reasons for either being arrested or being released<sup>[12]</sup>. It is suggested that there are some legal issues and gaps.

Second, physicians may feel frustrated and embarrassed when they are consulted by patients with chronic HCV infection regarding the treatment of the disease. The doctors may tell the patients that there are many new drugs that are effective and have fewer adverse effects and may be suitable for their condition when they advise patients who are unsuitable for IFN and RBV, but none of the drugs is lawfully available in China. Of course, the doctors can let the patients wait for the availability of these drugs. However, some of the patients, such as those with decompensated liver disease and those awaiting organ transplantation, cannot wait because of the rapid progress of their disease and its life-threatening potential. Another situation is that the patients consult doctors about using drugs that they have bought from other countries, mostly from illegal sources and by illegal means, and the drugs may thus be regarded as “fake drugs”. Additionally, the quality of the drugs may also not be guaranteed. In this situation, the doctors may place themselves at risk because they appear to guide their patients to use “fake drugs”.

Third, because of the lack of other DAAs for rational combination, most of the patients take sofosbuvir in combination with RBV and some patients even use sofosbuvir alone for the treatment of their HCV infection with various treatment durations, irrespective of the HCV genotypes involved, the underlying liver disease (hepatitis or cirrhosis) and comorbidity. In reality, the situation may be rather more complex than expected. HCV genotype 1 infection accounts for most cases of HCV infection in China, but there are also other genotypes in China, including 2, 3 and 6<sup>[13]</sup>.

Although the combination of sofosbuvir and RBV is a pan-genotypic regimen and may be applied for HCV genotypes 1-6, and this regimen remains the standard of care for genotypes 2 and 3, its efficacy was suboptimal in patients with HCV genotype 1, with an SVR of 54% for genotype 1b treatment-naïve hepatitis and 60% for genotype 1 treatment-naïve cirrhosis after 24 wk of treatment<sup>[14]</sup>. In the United States, the regimen of sofosbuvir and RBV for 24 wk in patients with genotype 1 infection is not recommended because of the longer treatment duration and lower expected SVR rates compared with other regimens<sup>[15]</sup>. The efficacy of this regimen for treatment-experienced genotypes 2 and 3 infection, with or without cirrhosis, was also suboptimal, with an SVR of 72% for genotype 2 treatment-experienced cirrhosis after 12 wk of treatment, an SVR of 77% for genotype 3 treatment-experienced hepatitis after 24 wk of treatment, and an SVR of 60% for genotype 3 treatment-experienced cirrhosis after 24 wk of treatment<sup>[14]</sup>. Based on these data, it is indicated that a proportion of patients with HCV genotype 1 or genotypes 2 and 3 treatment-experienced hepatitis or cirrhosis is using a non-optimal regimen for treatment. Therefore, it is anticipated that higher non-response and relapse rates may result from the use of this regimen.

Another concern is the possibility of treatment-emergent variants that may confer resistance to the antiviral treatment, although sofosbuvir has high genetic barriers to resistance<sup>[14]</sup>. Of note, a DAA used as monotherapy is not recommended because of the strong likelihood of treatment failure and the potential to induce resistance<sup>[15]</sup>.

Moreover, the drug safety and drug-drug interactions pertinent to the use of sofosbuvir and RBV or sofosbuvir alone cannot be completely ignored. Sofosbuvir has a good safe profile and few drug-drug interactions. However, the safety of sofosbuvir in patients with some comorbidity, such as severe renal impairment (an estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>) or end-stage renal disease on dialysis, is not well established, in that the levels of sofosbuvir and its metabolite are substantially elevated in such patients<sup>[15]</sup>. In contrast, co-administration of P-glycoprotein inhibitors, including anticonvulsants such as phenobarbital, antimycobacterials such as rifampin, ritonavir-boosted tipranavir, and St John's wort can decrease sofosbuvir concentrations<sup>[16]</sup>. Additionally, although sofosbuvir is not supposed to have significant pharmacological interactions with tacrolimus or cyclosporine<sup>[17]</sup>, unexpected tacrolimus/cyclosporine reduction, which needs dosage adjustment, was observed in transplant recipients during sofosbuvir/RBV treatment for severe HCV infection recurrence. This raises the importance of awareness in the post-transplant HCV-recurrence setting when sofosbuvir is administered<sup>[18]</sup>. All these may place the patients with some comorbidity in unsafe conditions or bring new problems for the retreatment of patients if necessary.

## CONCLUSION

As doctors, we hope for early launching of the DAAs, not only sofosbuvir but also other agents that can be rationally combined with sofosbuvir, in China, and the legalization of buying drugs including generic drugs from areas outside China and using these drugs in China, without further delay, in the interest of the patients. Presently, regulations concerning the usage of drugs, including generic drugs from other areas and international routes, should be established by the health authorities in China to meet the urgent needs. In the long run, China's health authorities need to reform fully their drug import policy and distribution system to satisfy legitimately and sensibly the therapeutic requirement of patients. In particular, the authorities need to guarantee the timely availability of novel drugs, even if they may be generics, for the urgent need of severely ill patients to improve survival and quality of life. At the same time, doctors may become confident to advise the use of such drugs without fear of violating the law or regulations concerning the quality of the drugs. We wish for the early arrival of a time when patients can easily and legally have access to effective drugs, and doctors can lawfully and

unimpeachably play their role in the treatment of HCV infection.

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