Journal of the Formosan Medical Association (2016) 115, 65–66

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PERSPECTIVES

Hepatitis C virus infection in Taiwan: Past, present, and future

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Received 17 June 2015; accepted 23 June 2015

Hepatitis C virus (HCV) infection is a global health problem, with 170 million people chronically infected with HCV worldwide. Chronic hepatitis C (CHC) is the leading cause of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[1] Therefore, prevention of HCV transmission and early intervention of HCV infection are urgently needed to reduce or halt the liver-related morbidity and mortality. The HCV viral genome was first discovered in 1989, and the complete nucleotide sequence of Taiwanese HCV genome was subsequently determined from a patient with post-transfusion hepatitis C in 1992.[2] Currently, seven major HCV genotypes and at least 60 subtypes have been identified, with varied geographical distribution. Among major genotypes, HCV genotype 1 is prevalent around the world. In Taiwan, HCV subtypes 1b and 2a are the major subtypes.[1]

The first clinical trial using combination of standard interferon (IFN) plus ribavirin (RBV) for the treatment of CHC was conducted in Taiwan,[2] and the combination of pegylated IFN (PEG-IFN) plus RBV therapy became the standard of care from 2004 to 2011, with an overall sustained virologic response (SVR) rate of 54–63% in western CHC patients.[1] A 48-week course of combination therapy was recommended to treat HCV genotype 1 infection in different parts of the world before the direct-acting antiviral (DAA) era. However, about 50–60% of CHC patients still do not respond to the combination therapy. In contrast, studies for Asian HCV genotype 1 patients showed a favorable treatment response to combination therapy.[3] With the introduction of early viral kinetics and response-guided therapy, HCV genotype 1 patients who have low baseline viral load and who achieve rapid virologic response, a truncated duration of therapy from 48 weeks to 24 weeks would have comparable SVR rates.[1] Recent large-scale follow-up studies indicated that CHC patients with SVR have improved hepatic and extrahepatic outcomes, including the reduction of HCC risk and better renal/circulatory consequences.[4]

Many pretreatment factors, including age, sex, body mass index, insulin resistance, hepatic steatosis/fibrosis, ethnicity, and viral load, are associated with SVR. Among them, single nucleotide polymorphisms near the interleukin 28B gene (rs8099917 and rs12979860) are found to be associated with spontaneous or treatment-induced viral clearance, and early viral kinetics to treatment in HCV genotype 1 patients.[5] In addition, microRNA-122 (miR-122) is shown to facilitate HCV replication *in vitro*, and serum miR-122 may be implicated as a biomarker for various liver diseases. A recent study suggested that serum miR-122 may serve as a surrogate of hepatic miR-122, and a higher pretreatment serum miR-122 level can help predict SVR to combination therapy.[6]

Although the treatment response to PEG-IFN and RBV in Taiwanese HCV genotype 1 patients is satisfactory, the ineligibility and treatment-related adverse events during

Conflicts of interest: The author has no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.06.012

Table 1 Current interferon-free direct-acting antiviral regimens for the treatment of chronic hepatitis C.

NS3/4A protease inhibitor	NS5A inhibitor	NS5B nucleotide analog	NS5B non-nucleotide analog	Ribavirin
Paritaprevir/ritonavir	Obmitasvir		Dasabuvir	± Ribavirin
Asunaprevir	Daclatasvir		± Beclabuvir	± Ribavirin
Grazoprevir	Elbasvir			± Ribavirin
	Ledipasvir	Sofosbuvir		± Ribavirin
	Daclatasvir	Sofosbuvir		± Ribavirin
Simeprevir		Sofosbuvir		± Ribavirin
		Sofosbuvir		Ribavirin

combination therapy would raise safety concerns, especially in older patients and those with various comorbidities.[7] With the introduction of novel DAAs targeting at the replication process of HCV, a paradigm shift of HCV treatment occurs. In early 2011, the first-generation protease inhibitors, telaprevir and boceprevir, achieved significantly higher SVR rates in HCV genotype 1 patients when they were used in combination with PEG-IFN and RBV. However, the use of telaprevir and boceprevir would increase pill burdens, and treatment-emergent adverse events. A little later, the newer protease inhibitors, simeprevir and sofosbuvir, showed even better SVR rates in treatment-naïve and -experienced HCV genotype 1 patients. However, the expected adverse events by PEG-IFN and RBV would last. In late 2013, the first all oral IFN-free regimens, sofosbuvir plus ribavirin, for 12—24 weeks was approved in HCV genotype 1—6 patients. The IFN-free therapy has the advantages of higher response rates, less frequent dosing and adverse events. Afterwards, novel IFN-free regimens further increase the overall SVR rates over 90% by using sofosbuvir plus ledipasvir, paritaprevir/ritonavir co-dosed with ombitasvir and dasabuvir, grazoprevir plus elbasvir, or daclatasvir co-dosed with asunaprevir and beclabuvir for 12 weeks (Table 1).[8] These novel DAA regimens are easy to use because of the low pill burden and short treatment duration, devoid of complex on-treatment monitoring, and few adverse predictors of responses. However, the prohibitive costs of these new regimens preclude their widespread use.

Over the past 25 years we have witnessed the miracle of hepatitis C, from discovery to cure. During this time period, three generations of Taiwanese hepatologists and scientists made tremendous contribution to its discovery, prevention, diagnosis, monitoring, and treatment.[2] Although IFN-free DAA regimens with SVR rates over 90% will come to Taiwan sooner or later, the major challenges still remain in terms of the prioritization and implementation of these new treatment strategies because the price of these agents is extremely high.

In summary, HCV cure through treatment is possible in Taiwan but raises major public health issues that need to be solved through the collaboration among the national health insurance system, pharmaceutical companies and medical societies. Thus Taiwanese people can expect a future without HCV infection.

Acknowledgments

The study was supported by grants from the National Taiwan University Hospital (NTUH.103-N2540), the Ministry of Health and Welfare (MOHW103-CDC-C-114-123105), and the Ministry of Science and Technology (MOST 103-2314-B-002-051-MY3), Executive Yuan, Taiwan.

References

1. Liu CH, Kao JH. Nanomedicines in the treatment of hepatitis C virus infection in Asian patients: optimizing use of peginterferon alfa. *Int J Nanomedicine* 2014;**9**:2051—67.
2. Chen DS. Fighting against viral hepatitis: lessons from Taiwan. *Hepatology* 2011;**54**:381—92.
3. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis* 2008;**47**:1260—9.
4. Hsu CS, Chao YC, Lin HH, Chen DS, Kao JH. Systematic review: impact of interferon-based therapy on HCV-related hepatocellular carcinoma. *Sci Rep* 2015;**5**:9954.
5. Hsu CS, Hsu SJ, Chen HC, Tseng TC, Liu CH, Niu WF, et al. Association of IL28B gene variations with mathematical modeling of viral kinetics in chronic hepatitis C patients with IFN plus ribavirin therapy. *Proc Natl Acad Sci U S A* 2011;**108**:3719—24.
6. Su TH, Liu CH, Liu CJ, Chen CL, Ting TT, Tseng TC, et al. Serum microRNA-122 level correlates with virologic responses to pegylated interferon therapy in chronic hepatitis C. *Proc Natl Acad Sci U S A* 2013;**110**:7844—9.
7. Lin JA, Chen YC, Cheng SN, Chen PJ, Chu HC, Hsieh TY, et al. Peginterferon alfa-2a plus ribavirin for hemophilic patients with chronic hepatitis C virus infection in Taiwan. *J Formos Med Assoc* 2014;**113**:727—33.
8. Hayes CN, Chayama K. Emerging treatments for chronic hepatitis C. *J Formos Med Assoc* 2015;**114**:204—15.