J Gastroenterol (2018) 53:1168–1169
https://doi.org/10.1007/s00535-018-1493-8

The Japanese Society of Gastroenterology

EDITORIAL

The "real-world" efficacy and safety of DAAs for the treatment of HCV patients throughout Japan

Shinya Maekawa[1] · **Nobuyuki Enomoto**[1]

Received: 28 June 2018 / Accepted: 3 July 2018 / Published online: 6 July 2018

Hepatitis C virus (HCV) causes persistent infections in humans, leading in the long term to chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). An estimated 180 million individuals are infected worldwide, with around 1.5 million in Japan [1, 2]. Although viral eradication was difficult with conventional interferon-/ribavirin-based therapy, the recent development of novel, direct-acting antiviral agents (DAAs) has revolutionized the treatment of HCV infection. Among the DAAs for genotype-1 (Gt-1) HCV, the interferon-free regimen of ledipasvir and sofosbuvir therapy appears to be one of the most outstanding, because of its very high efficacy. Clinical trials using this regimen have achieved significant favorable responses all over the world and, in particular, the sustained viral response (SVR) rate of ledipasvir/sofosbuvir therapy reached 100% in a phase III clinical trial targeting Gt-1 patients conducted in Japan [3].

Opportunities to use the term "real-world" have been increasing recently, with respect to evaluating new drug efficacy. Specifically, clinical trials to evaluate new drugs involve limited patient populations because of the need to exclude noise and highlight the differences from previous drugs. However, when the drugs become widely available in clinical practice, they are administered to patients with various backgrounds and their efficacy may be somewhat lower than reported in clinical trials. In particular, in Japan, patients infected with HCV tend to be older, and older patients are more likely to have other diseases and to be prescribed various other medications. In this context, a major concern of physicians is to know the real-world efficacy, as well as the real-world safety, of these new DAAs.

In this issue of *Journal of Gastroenterology*, the Japanese Red Cross Liver Study Group report the real-world efficacy and safety of the ledipasvir/sofosbuvir regimen in 1461 interferon-free DAA-naïve patients with genotype 1 HCV infection [4]. As noted in their report, the Red Cross Hospital Group consists of core hospitals in large cities, as well as small hospitals in various provinces throughout Japan. Therefore, the data from this nationwide cohort might well reflect the current real-world situation in Japan, being derived from heterogeneous populations with varied clinical characteristics. Furthermore, 29.5% of the participants were aged 75 years or older.

In the study, 1452 (99.4%) of the 1461 patients completed the therapy and 1438 (99.0%) of those 1452 patients achieved SVR12 and SVR24. The SVR rate was not affected by age (98.8% in those under 75 years and 97.5% in those aged 75 years or older) or geographical location (98.5% in the east, and 98.4% in the west, of Japan). As to safety, adverse events were observed only in 2.9% ($n = 43$) overall and the adverse event rate did not increase with age (2.9% in those below 75 years and 3.0% in those aged 75 years or older). Grade III adverse events were observed in only 0.2% ($n = 3$). This result is truly astonishing because this high efficacy and high level of safety was observed throughout Japan, even in aged patients possibly complicated with other diseases and treated with various medications. In terms of factors influencing SVR, two independent factors, the NS5A–Y93H resistance-associated substitution (RAS) and the presence of cirrhosis, were found to influence the responses. However, 97.0% (363/

✉ Shinya Maekawa
maekawa@yamanashi.ac.jp

[1] First Department of Internal Medicine, Faculty of Medicine, University of Yamanashi, 1110, Shimokato, Chuo, Yamanashi 409-3898, Japan

374) achieved SVR, despite the presence of the NS5A–Y93H RAS, and 96.0% (333/347) achieved SVR, despite the presence of cirrhosis. Moreover, even with the concomitant presence of the NS5A–Y93H RAS and cirrhosis, 93.0% (120/129) achieved SVR, showing that even those patients with unfavorable factors have a very high likelihood of achieving SVR. From this study, we understand that ledipasvir/sofosbuvir is more than satisfactory in its efficacy and safety in the real-world. In my opinion, this result should be used as the new standard for anti-HCV therapy and the efficacy and safety of new DAA regimens should be evaluated in the light of these data.

However, difficult-to-treat patients were excluded from this analysis; the patients were all naïve to IFN-free DAA regimens and individuals with super-resistant RAS selected by previous DAA therapies were not included in the analysis. In addition, it is speculated that those patients with decompensated cirrhosis, renal failure or liver transplantation were also excluded. However, considering the efficacy and safety of the DAAs including newer DAA regimens, such as glecaprevir/pibrentasvir and sofosbuvir/velpatasvir(/ribavirin), and the high concordance between clinical trials and real-world data, viral clearance also may be achieved in these difficult-to-treat patients [5–8].

With these advanced DAA therapies, complete eradication of HCV throughout Japan is now becoming an achievable goal. Such a goal, however, becomes a political, rather than scientific problem. It has been reported that more than 500,000 anti-HCV-positive individuals in Japan remain untreated for a variety of reasons and, therefore, a policy encouraging patients to receive DAA therapy is needed [9]. On the other hand, although there may be various reasons for this failure to treat infected individuals, the major problem may be the lack of information regarding the latest HCV therapies among the public, as well as local physicians. In this sense, this magnificent real-world result is highly encouraging and should be communicated to potential patients, as well as local physicians.

In the near future, we feel confident that the complete eradication of HCV from Japan is no longer a mere dream.

References

1. Kim MN, Kim BK, Han K-H. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection in the Asia–Pacific region. J Gastroenterol. 2013;48:681–8.
2. Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med. 2013;19:850.
3. Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015;15:645–53.
4. Tsuji K, Kurosaki M, Itakura J, et al. Real-world efficacy and safety of ledipasvir and sofosbuvir in patients with hepatitis C virus genotype 1 infection: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. J Gastroenterol. 2018. https://doi.org/10.1007/s00535-018-1455-1
5. Jackson WE, Everson GT. Sofosbuvir and velpatasvir for the treatment of hepatitis C. Expert Rev Gastroenterol Hepatol. 2017;11:501–5.
6. Kumada H, Watanabe T, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in HCV-infected Japanese patients with prior DAA experience, severe renal impairment, or genotype 3 infection. J Gastroenterol. 2018;53:566–75.
7. Righi E, Londero A, Carnelutti A, Baccarani U, Bassetti M. Impact of new treatment options for hepatitis C virus infection in liver transplantation. World J Gastroenterol. 2015;21:10760.
8. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med. 2018;378:354–69.
9. http://www.mhlw.go.jp/file/05-Shingikai-10905750-Kenkoukyoku-Kanentaisakusuishinshitsu/0000090595.pdf. Accessed 25 Jan 2018