HISTORY OF HCV IN JAPAN

Alan Franciscus, who is the editor in chief of the hepatitis C virus (HCV) Advocate website, introduced the history of HCV in Japan. Modern medicine and public health came early to Japan in the late 1800s. In the early 1900s, the discovery of the hypodermic needle and a drug to treat schistosomiasis would transmit hepatitis C throughout Japan. Schistosomiasis is a disease caused by a worm that lives in water snails. When people wade in water for agricultural work, the worm enters their body and lays eggs. The eggs hatch and travel to the liver. Schistosomiasis causes damage to the liver, the gastrointestinal system, kidneys, and genitals. It can, over time, cause death. In some parts of the world, it is considered as deadly as malaria. The first treatment developed to treat schistosomiasis consisted of multiple intravenous injections of antimony sodium tartrate. By the 1970s there were approximately 10 million intravenous injections given to people in Japan. The large-scale use came later during World War II, when it was prescribed as an oral and injectable stimulant for tired soldiers, pilots, and ammunition workers during the war. After the war methamphetamine was prescribed for general postwar trauma. In 1949, Japan banned the manufacture of methamphetamine, but illegal methamphetamine use continued as did the hepatitis C epidemic.

CURRENT STATUS OF HCV INFECTION IN JAPAN

Of all the industrialized countries of the world, Japan has the highest rate of hepatitis C. It also has 1 of the oldest and most varied histories of hepatitis C in the world among the industrialized modern nations. Hepatitis C and its complications are the leading cause of liver cancer in Japan. Japan has the highest rate of liver cancer among the industrialized countries. From 2004 to 2014, PegIFN/RBV treatment was the mainstream of hepatitis C treatment. In 2014, the first interferon-free therapy was approved in Japan. Subsequently, other interferon-free therapies have been approved. Hepatitis C virus infection in hepatitis C patients in Japan has become possible with a probability of 96% or more.
standard of care for treating HCV. Japan has a multilayered health care system. Many people can get health care insurance through their employer or the national health care system. The government system covers about 70% and the patient covers the remaining 30%.

PROGRESS AND FUTURE OF HEPATITIS C THERAPY IN JAPAN

From 2004 to 2014, PegIFN/RBV treatment was the mainstream of hepatitis C treatment. In 2014, the first interferon-free therapy was approved in Japan. Subsequently, other interferon-free therapies have been approved, which are listed below:

- September 2014 – Asunaprevir and Daclatasvir – HCV1
- May 2015 – SOVALDI® (sofosbuvir)/RBV – HCV2
- September 2015 – HARVONI – HCV1
- December 2015 – VIEKIRA PAK – HCV1

The HCV disinfection in hepatitis C patients in Japan has become possible with a probability of 96% or more.

DACLATASVIR AND ASUNAPREVIR COMBINATION THERAPY FOR HCV1 IN JAPAN

All oral combinations of direct-acting antivirals may improve the efficacy and safety outcomes for patients with HCV infection, particularly those who are poor candidates for interferon/ribavirin-based regimens.

In July 2014, the Japanese Ministry of Health, Labor and Welfare (MHLW) approved Daklinza® (daclatasvir), a potent, pan-genotypic NS5A replication complex inhibitor (in vitro), and Sunvepra® (asunaprevir), an NS3/4A protease inhibitor. The Daklinza + Sunvepra dual regimen is Japan's first all-oral, interferon- and ribavirin-free treatment regimen for patients with genotype 1 chronic HCV infection, including those with compensated cirrhosis.

In 2014, Kumada et al5 reported the results of a phase 3, open-label study to assess the efficacy and safety of an all-oral combination of the NS5B polymerase inhibitor sofosbuvir and RBV in patients with chronic genotype 2 HCV infection. They enrolled 90 treatment-naïve and 63 previously treated patients at 20 sites in Japan. All patients received sofosbuvir 400 mg plus RBV (weight-based dosing) for 12 weeks. The primary endpoint was sustained virologic response at 12 SVR12 weeks after therapy. Of the 153 patients enrolled and treated, 60% had HCV genotype 2a, 11% had cirrhosis, and 22% were 65 years or older. Overall, 148 patients (97%) achieved SVR12. Of the 90 treatment-naïve patients, 88 (98%) achieved SVR12, and of the 63 previously treated patients, 60 (95%) achieved SVR12. The rate of SVR12 was 94% in patients with cirrhosis and in those aged 65 and older. No patients discontinued study treatment due to adverse events. The most common adverse events were nasopharyngitis, anemia, and headache. They concluded that 12 weeks of sofosbuvir and RBV resulted in high rates of SVR12 in treatment-naïve and previously treated patients with chronic genotype 2 HCV infection. The treatment was safe and well tolerated by patients, including the elderly and those with cirrhosis.

In July 2015, the Japanese MHLW approved HARVONI® (ledipasvir 90 mg/sofosbuvir 400 mg), the first once-daily single-tablet regimen for the treatment of chronic hepatitis C genotype 1 infection in adults. Harvoni combines the
N55A inhibitor ledipasvir with the nucleotide analog polymerase inhibitor sofosbuvir, approved by the MHLW under the trade name Sovaldi. Harvoni is indicated for the suppression of viremia in patients with genotype 1 chronic hepatitis C virus (HCV) infection with or without compensated cirrhosis, with the treatment duration of 12 weeks.

Mizokami et al.7 reported the results of an open-label study to assess the efficacy and safety of Harvoni in patients with chronic genotype 1 HCV infection in Japan. In this randomized, open-label study, we enrolled patients from 19 clinical Japanese centers. Patients were randomly assigned (1:1) to receive either ledipasvir (90 mg) and sofosbuvir (400 mg) or ledipasvir, sofosbuvir, and RBV orally once daily for 12 weeks. A total of 341 patients were randomly assigned to treatment groups and received at least 1 dose of study treatment. Sustained virologic response12 was achieved in all 171 (100%) patients (83 of 83 treatment naive and 88 of 88 treatment experienced) receiving ledipasvir–sofosbuvir and 167 (98%) of 170 patients (80 of 83 treatment naive and 87 of 87 treatment experienced) receiving ledipasvir–sofosbuvir plus RBV. Of the 76 patients with baseline NS5A-resistant variants, 75 (99%) achieved SVR12. 2 (1.2%) of 170 patients in the ledipasvir–sofosbuvir plus RBV group discontinued treatment because of adverse events. The most common adverse events were nasopharyngitis (29.2%), headache (7.0%), and malaise (5.3%) in patients receiving ledipasvir–sofosbuvir, and nasopharyngitis (23.5%), anemia (13.5%), and headache in those receiving ledipasvir–sofosbuvir plus RBV (8.8%). They concluded that the efficacy, tolerability, and absence of drug–drug interactions of ledipasvir–sofosbuvir suggest that it could be an important option for the treatment of genotype 1 HCV in Japanese patients.

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