Changing Trends in Hepatitis C Infection over the Past 50 Years in Japan

Hobyung Chung  Taisuke Ueda  Masatoshi Kudo
Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka-Sayama, Japan

Introduction
Hepatocellular carcinoma (HCC) is one of the most common causes of cancer death. The prevalence of HCC in Japan has increased over the past 50 years and more than 30,000 patients die because of HCC every year, accounting for rates of death of 36.3 and 17.5 per 100,000 males and females, respectively [1]. The main causes of HCC in Japan are hepatitis C virus (HCV) and hepatitis B virus (HBV); nearly 70% of HCC cases are caused by HCV [1]. This situation differs from that in other Asian countries where HBV-related HCC is more common, and the situation in Japan is more similar to that in Western countries [2, 3].

Japan has one of the highest endemic rates of HCV infection. The number of patients with HCV infection is estimated to be about 2,000,000 in Japan; 70% of patients are infected with HCV genotype 1b, the most prevalent subtype in Japan, started to spread in the 1930s among injecting drug users (IDUs) during and after World War II or through medical procedures such as blood transfusion and use of contaminated syringes. The prevalence of HCV infection is much lower in the current younger generation compared with that in the older generation, particularly those aged >55 years (0.1–0.2% vs. ≥ 2%). Therefore, the total number of patients with HCV infection is estimated to decrease, even though sporadic HCV transmission is mainly seen among young IDUs. Of note, HCV genotype 2 seems to be spreading among IDUs, but the response to antiviral therapy in these patients seems to be better than that in older patients, irrespective of the genotype. Although the number of patients who die because of HCC has steadily increased over the last 50 years, the incidence of HCC is now decreasing, mainly because of the decreased prevalence of HCV-related HCC.

Key Words
Chronic hepatitis • Hepatitis C virus • Hepatocellular carcinoma •Injecting drug user • Mortality rate • Post-transfusion hepatitis

Abstract
In Japan, hepatocellular carcinoma (HCC) is the fourth leading cause of death in males and the fifth in females. Hepatitis C virus (HCV) is a major cause of HCC in Japan, with 70% of cases being HCV related. HCV genotype 1b, the most prevalent subtype in Japan, started to spread in the 1930s among injecting drug users (IDUs) during and after World War II or through medical procedures such as blood transfusion and use of contaminated syringes. The prevalence of HCV infection is much lower in the current younger generation compared with that in the older generation, particularly those aged >55 years (0.1–0.2% vs. ≥ 2%). Therefore, the total number of patients with HCV infection is estimated to decrease, even though sporadic HCV transmission is mainly seen among young IDUs. Of note, HCV genotype 2 seems to be spreading among IDUs, but the response to antiviral therapy in these patients seems to be better than that in older patients, irrespective of the genotype. Although the number of patients who die because of HCC has steadily increased over the last 50 years, the incidence of HCC is now decreasing, mainly because of the decreased prevalence of HCV-related HCC.

Reference

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Published online: January 5, 2010

Masatoshi Kudo, MD, PhD
Department of Gastroenterology and Hepatology
Kinki University School of Medicine
377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511 (Japan)
Tel. +81 72 366 0221, Fax +81 72 367 2880, E-Mail m-kudo@med.kindai.ac.jp
When and How Did HCV First Spread in Japan?

Mizokami et al. [5] demonstrated based on molecular clock analysis that HCV genotype 1b, which is the most dominant genotype in Japan, started to spread in the 1930s. They also revealed that HCV genotype 1a started to spread in the United States in the 1960s, at least 30 years later than the spread of HCV genotype 1b in Japan. Furthermore, HCV infection is still increasing exponentially in the United States whereas it has been decreasing since approximately 1995 in Japan [5]. The main causes of HCV dissemination in Japan included intravenous stimulant drug (methamphetamine) abuse among the young generation during and after World War II, blood transfusion from paid blood donors, and injections using contaminated syringes and needles, particularly for the treatment of schistosomiasis japonica. Schistosomiasis japonica was previously an endemic disease in Japan before the introduction of intravenous antimony in 1921. Interestingly, HCV infection is more prevalent in south-western regions of Japan compared with north-eastern regions [4], and areas endemic for schistosomiasis japonica, such as Fukuoka and Hiroshima prefectures, are located in south-west Japan. It seems likely that the geographical distribution of schistosomiasis japonica is at least partly attributable to differences in the prevalence of HCV infection.

Resolution of HCV Transmission

Tanaka et al. [4] investigated the age-specific prevalence of HCV infection among first-time blood donors in Japan, and found that the prevalence of HCV infection is closely correlated with age. The number of HCV carriers increased with age and an exponential increase was seen in blood donors aged more than 55 years, irrespective of the area of Japan. On the other hand, the prevalence of HCV infection in blood donors younger than 30 years is quite low: 0.13% at 16–19 years and 0.21% at 20–29 years [4]. This suggests that the rate of HCV transmission has decreased significantly and that the total number of patients with HCV is likely to decrease [6–8].

Paid blood donation was commonly performed in Japan and post-transfusion hepatitis occurred in more than half of transfused cases until the beginning of the 1960s (fig. 1). After the introduction of voluntary blood donation in 1964 and HBsAg screening in 1972, the risk of post-transfusion hepatitis dramatically decreased (to around 10%). After the discovery of HCV RNA, screening tests for first- and second-generation HCV antibodies were started in 1989 and 1992, respectively. These screening tests further decreased the risk of post-transfusion hepatitis. Furthermore, nucleic acid amplification tests, introduced in 1999, almost eliminated the risk [8]. Although sporadic HCV transmission still occurs through other routes, such as intravenous drug abuse and accidental exposure in medical procedures (e.g. needlestick injury), measures to prevent post-transfusion hepatitis have significantly reduced the rate of HCV transmission.
Features of Recent HCV Transmission in Japan

As described above, HCV transmission through blood transfusion is now an extremely rare event. Instead, intravenous drug abuse has become the main cause of HCV transmission in developed areas such as Europe and the USA [9, 10]. The estimated prevalence of HCV infection among injecting drug users (IDUs) is between 30 and 80% [11–13]. The number of IDUs in Japan is steadily increasing, particularly among young people, according to the data published by the Ministry of Health, Labour and Welfare. Therefore, intravenous drug abuse has become an important route of HCV transmission among young people [8, 14]. Satoh et al. [15] investigated the HCV genotypes that are spreading among Japanese IDUs and found that non-1b genotypes of HCV, particularly genotype 2b, seemed to be most prevalent among IDUs. We also examined the HCV genotypes in 42 young (less than 40 years old) chronic hepatitis patients with HCV who were treated by peginterferon and ribavirin combination therapy at the Kinki University Hospital between 2006 and 2008. Twenty-one patients (50%) were infected with non-1 genotypes of HCV, 20 patients had genotype 2, and 1 patient had genotype 3. The proportion of non-1 genotypes in these patients is higher than that in the whole Japanese population with HCV infection, which is estimated to be about 30%. Possible transmission routes that were assessed by interviewing each patient were compared between those with genotype 1 and those with non-1 genotypes. As shown in figure 2, the major transmission routes appeared to be different between the 2 types: intravenous drug abuse was the major route of non-1 genotype HCV transmission, which is consistent with the results of previous reports [15, 16]. The sustained virological response rates in these patients, 72% for genotype 1 and 95% for non-1 genotype, are better than those in previous reports, probably due to the shorter duration of infection (associated with less advanced disease) and younger age, both of which are factors associated with favorable outcomes of IFN therapy [17, 18].

Accidental exposure to HCV during medical procedures is another important route of transmission, although the risk is believed to be very low (0.3–2.7%) [19–21]. These cases are usually monitored carefully after the accident and, even if they present with acute hepatitis, most cases can be cured by IFN therapy during the early phase of infection [22].

In summary, even though sporadic HCV infections are still occurring, particularly among young people, it seems that this population will not increase the total population of HCV infection in Japan.

Future Perspectives on HCV-Related Diseases and Mortality

In Japan, the number of HCC patients and their mortality rate remain extremely high in comparison with other developed countries [8]. Accordingly, a nationwide health screening program for viral hepatitis was launched to identify new patients with HCV or HBV infection who were unaware of their diseases. The target population of...
This program included citizens aged over 40 years, and the program was carried out between 2002 and 2006. A total of 6,280,111 people (26% of the target population) were tested in this program, and 99,950 patients with HCV infection were newly detected, and some of them have already been treated with IFN therapy. Therefore, this program will provide a significant contribution to decrease the number of patients who suffer from and die of HCV-related liver diseases.

Peginterferon and ribavirin combination therapy is the current standard treatment for chronic hepatitis C infection and improves the sustained virological response rate even in patients infected with HCV genotype 1 and who have high viral load [23]. In addition, several new-generation drugs, such as protease inhibitors and polymerase inhibitors, further enhance the efficacy of IFN therapy and will be available soon [24, 25]. The improved efficacy of antiviral therapy for HCV will inevitably contribute to decrease the HCV-related mortality rate.

Although the number of patients who die of HCC has steadily increased over the past 50 years, as shown in figure 3, the incidence of HCC has recently started to decrease in Japan, mainly because of the decrease in rates of HCV-related HCC [26, 27]. In addition, the age at diagnosis of HCC has increased in parallel with the increased proportion of older patients with HCV infection [27, 28]. These trends can be explained by an estimation of the decreased number of patients with HCV infection because of the extremely low prevalence of infection in the younger generation in conjunction with improved efficacy of antiviral therapy.

Conclusion

The spread of HCV infection in Japan started in the 1930s, and widespread dissemination of the virus has occurred since then. The risk of iatrogenic HCV transmission has been almost eliminated; however, sporadic HCV transmission still occurs. The prevalence of HCV infection in the younger generation is extremely low and the total number of HCV patients is expected to decrease. Although the number of patients who die of HCC has steadily increased because of the dissemination of HCV infection in the past, it is estimated to decrease in the near future because of the decrease in rates of HCV-related HCC.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

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