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REVIEW ARTICLE

Is SEN Virus a Major Concern in Hemodialysis and Liver Transplantation?

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Although hepatotropic viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-identified viral agents for the development of hepatitis, infection with some other viruses may lead to varying degrees of liver injury. Moreover, the hepatic pathogenicity of a few viral agents still remains to be determined. In recent years, viral agents such as TTV and SEN virus with possible hepatic pathogenicity have been introduced. SEN virus has been reported with different rates of prevalence in high-risk groups such as dialysis patients, and low-risk groups such as blood donors. Identification of the SEN virus as a possible etiological agent of parenteral transmission hepatitis led to a major concern about the possibility of its role in liver diseases in hemodialysis patients as well as in renal transplant recipients. This manuscript provides an updated integrative review on SEN virus from virological aspect as well as epidemiologic and diagnostic medicine. Moreover, its role in liver diseases considering the co-infection with other hepatotropic viruses has also been reviewed.

Keywords: **SEN Virus, Hepatitis, Renal Dialysis, Liver Transplantation**

Introduction

Recently, a novel DNA virus has been detected in human blood, which is called SEN virus (SEN-V). The nomenclature of the virus comes from the initials of the first patient who was an intravenous drug user co-infected with HIV [1, 2]. Identification of SEN-V in Italy in 1999 provoked a series of researches on the clinical significance of this new virus. In addition, discovery of SEN-V increased the motivation to identify new viruses that can cause non -A- to -E hepatitis. Following the introduction of probable etiologic role of GBV-C (so called hepatitis G virus) as well as TTV (transfusion transmitted virus) in the development of non- A- to -E hepatitis, SEN-V has been suggested to play an etiologic role [2, 3]. However, until recently, there are multiple reports that demonstrated evidences for and against the effects of all these three viruses on liver function and histology. This review provides the most current information on the virological, epidemiological and clinical aspects as well as diagnostic assays of SEN-V as a new viral agent. In this manuscript, we have eventually focused on SEN-V infection in hemodialysis patients.

Virology

SEN-V was initially described as a single-stranded non-enveloped, circular DNA virus with a size of 26

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nm. The mean genome length consists of 3,900 nucleotides and at least three open reading frames (ORF) have been identified [4, 5]. Recently, SEN-V has been subgrouped into 9 genotypes [5]: A through I, differing by at least 25% in nucleotide sequences [6]. It has been suggested that genotypes SEN-V;C and H as well as SEN-V-D and- F could be combined due to similarities in ORF 1. The ORF1 with Arg/Lys-rich domains is the largest ORF with hydrophilic characteristic [7]. The role of ORF2 remains to be determined. The ORF3 translation results in the formation of a protein with a homology with a DNA topoisomerase I; therefore ORF3 seems to play a significant role in the replication of the virus [8]. Interestingly, SEN-V with a high mutation rate (7.32*10-4 per site per year) is more similar to RNA viruses rather than DNA viruses and this typical feature provides SEN-V the ability of persistence [9].

Study on the genome structure of SEN-V suggested similarities with the genome structure of the chicken anemia virus in the genus Gyrovirus as well as the TT virus [10]. For this reason, the phylogenetic analysis classified 9 strains of SEN-V as members of the Circoviridae family (TTV-related family of viruses) - a group of small, single stranded, non-enveloped circular DNA viruses. Considering TTV prototype, SEN-V shows homology less than 55% and 37% in sequence and amino acid, respectively [11]. Figure 1 demonstrates phylogenic tree of SEN-V by neighbouring-joining method. Recently, SEN-V has been clustered into a subgroup of Anellovirus: unclassified Anellovirus. The genus Anellovirus is officially approved by the international committee on taxonomy of viruses in 2005 [12]. It initially included the type species TTV, Torque teno mimi virus and unclassified animal viruses. The genus Anellovirus now has six members: Anellovirus PRA1, Anellovirus PRA4, SEN-V, Small Anellovirus, Torque teno mimi virus, TTV-like mimi virus.

Epidemiology

The prevalence of 5 out of 9 SEN-V strains (A, B, H, C, D and E) as well as a consensus sequence as total SEN-V have been studied in various donor and patient populations. However, measuring total SEN-V was found not to be practical because the prevalence in donors was 13% and the rate in a transfused population exceeded 70% [11]. In addition, with the exception of SEN-V-D and- H, the other members do not seem to be related to non A to E hepatitis and clinical diseases. Therefore, most investigators have targeted -D and -H genotypes because of their frequent correlation with transfusion-associated non A to E hepatitis [11]. The prevalence of SEN-V-H is comparable to that of SEN-V-D in different subjects. There are some reports with different origins that show a higher prevalence of SEN-V-H in patients with hepatitis A [13], in mothers with injection drug abuse [5] and mothers with hepatitis C virus (HCV) genotype 1b [5, 14]. This discrepancy

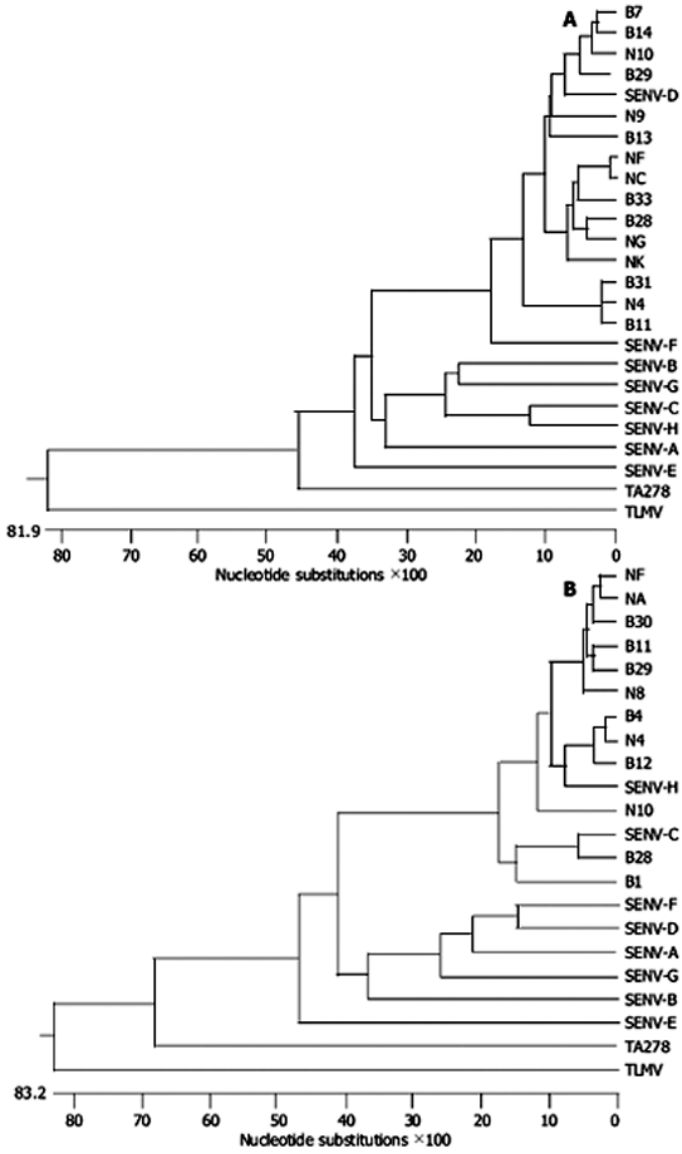

Figure 1. Phylogenic tree of SEN-V by neighbouring -joining method -adopted from Mu SJ, Du J, Zhan LS, *et al.* Prevalence of a newly identified SEN virus in China. *World J Gastroenterol* [13].

is postulated to be due to geographical distribution of SEN-V variants and differences between regions in the same country [15]. SEN-V is a common viral infection and active infection has been reported in both healthy blood donors and general population. However, this infection can be attributed to some of the SEN-V strains: SEN-V-B,-A and -E have been less frequently found among blood donors and do not appear to be related to non A-E hepatitis. On the other hand, genotypes D and H have been detected in 1% of blood donors but in more than 50% of non A to E hepatitis cases [16].

The prevalence of SEN-V increases in association with HIV-1 and hepatitis B and C viruses. This strongly supports the hypothesis that SEN-V is transmitted via blood. In a survey conducted with NIH (National Institute of Health) in post-cardiac surgery patients as well as in healthy blood donors with regard to SEN-V prevalence [11], the prevalence of SEN-V in a sample obtained from patients before surgery or transfusion was 2.8% which was not significantly different from what observed in blood donors (P=0.49). SEN-V was detected after surgery in 86 of 286 (30%) who were transfused compared with 3 of 97(3%) patients who were not transfused. Even after analysis of information for combined SEN-V-D and SEN-V-H infection or each one individually, the strong association between blood transfusion and SEN-V infection was observed. The risk of infection in transfused patients increased proportionally with the number of units of blood transfused, from 3% with no transfusion to 45.2% with >12 units transfused (P<0.0001). Association between blood donors and recipients has been reported in 68% of the cases.

In an investigation focused on the SEN-V infection among Baltimore injection drug users (IDUs), a high level of SEN-V infection (70.2%; 279/397) has been reported in the studied population. Serum level of SEN-V appeared to be a dynamic process that included both viral clearance and re-infection [1]. These findings suggest parenteral route as the most frequent route of transmission.

Few data are available on non-parenteral and other routes of infection such as mother- to -infant transmission, transmission via iatrogenic means in a hospital setting, fecal-oral and sexual-related routes. In a retrospective study on the stored blood samples obtained in 1982 from an Inuit population in the Northwest Territories, a remote and isolated population of Canada, the investigators found SEN-V infection in 36% of 160 subjects. SEN-V was also detected in 21% of 140 patients with liver disease. Thus, SEN-V seems to be a common infection in both healthy individuals as well as patients with chronic liver disease. The absence of injection drug use and the use of disposable needles for vaccination during past 60 years in the community studied strongly suggests the possibility of non- parenteral SEN-V transmission [17].

Mikuni *et al.* [6] found SEN-V infection with a high prevalence among blood donors and none had a history of serious illness or blood transfusion. In their study, the less considerable frequency of blood transfusion in subjects with non-B, non-C liver disease than in those with chronic HCV-related liver disease, suggests the existence of non-transfusion-related routes. There was no reported co-relation between SEN-V and folk medicine practices in Japan. Unlikely, HCV transmission was highly linked to folk medicine. This suggests that SEN-V uses a non-parenteral route that is not common with HCV infection [2]. The fact that the prevalence of SEN-V in patients with hepatitis A with fecal-oral transmission is higher than in healthy adults supports possible route of fecal-oral transmission [16]. In addition, TTV was detectable in stool from some cases. It can be concluded that the distant relationship between SEN-V and TTV can play a role in SEN-V fecal-oral transmission [16].

Little is known about mother to infant transmission of SEN-V. In Moriondo *et al.* study, 89 HCV-positive, HIV-1-negative mothers and their infants were studied for SEN-V infection [5]. Forty percent of mothers (36/89) were SEN-V infected and SEN-V-D was more frequent than SEN-V-H infection (94% *vs.* 14%). Both SEN-V-D and SEN-V-H can be transmitted vertically to the offspring with an overall rate of 47%. As a whole, 47% of babies born from SEN-V infected mothers were found to be SEN-V-positive. None of SEN-V-positive babies were born from SEN-V-negative mothers. SEN-V could not be detected from almost half of infected babies at birth. Thirty immunocompromised HIV-1-positve mothers and their offspring were observed in a study [18]. Fifteen out of 30 women were SEN-V-positive. Thirteen of their newborns were positive for at least one SEN-V strain. 3/15 were born from SEN-V -negative mothers while 10/15 were born from positive mothers. One newborn was positive at birth, eight became positive within 6 months of delivery, and 4 became positive in the following months. These results lead to two broad conclusions: first, low viral load at birth, and the latter, possible transmission via breast milk feeding and familial environment. To date, no data are available on mother-to-infant transmission of the SEN-V-D isolate.

Yoshida *et al.* have reported that there were no

significant differences in age, sex, liver function, history of blood transfusion, or amount of alcohol intake between SEN-V-negative and SEN-V-positive chronic liver disease and hepatocellular carcinoma (HCC) patients (19). To date, although not much scientific literature is available on SEN-V tendency to a specific age group or specific gender yet, results of many other studies support the data of Yoshida *et al.* [2, 6, 16, 17, 20].

There is also not much information about the natural history, persistence and clearance of the SEN-V infection. Chronic infection of over 10-year duration has been observed in retrospectively tested samples of infected patients, but most of the patients cleared viremia during the first few months of exposure [16]. There has been reported clearance rates of 55%, 65%, 74% within first 6 months, 2 years and 5 years of exposure respectively [11]. Due to the lack of serological test for SEN-V [10, 16], it is difficult to assess accurate time of exposure [16].

Detection of SEN-V

SEN-V DNA can be detected by means of polymerase chain reaction assay (PCR). Briefly, SEN-V DNA is extracted from serum sample and is required to undergo two rounds of PCR each of which includes several cycles before further steps. The sensitivity and specificity of the PCR depend on the primers used in these two rounds. Positivity of samples is confirmed by duplicate retesting [2, 11]. Kojamo *et al.* developed two PCR assays; a general SEN-V screening and a genotype-specific assay [21]. By screening PCR, the specificity for all SEN-V genotypes and SEN-V related sequences was found to be 20/20 (100%). The specificity for SEN-V-D and SEN-V-H, with genotype-specific PCR, were 7/7 (100%) and 7/11 (64%), respectively. Hemi-nested PCR directed to N22 region can detect genotypes 1-6 TTVs, while by directing PCR to 5-non-translated region (Nested PCR), most of the genotypes could be detected and as a result, the population of TTV can be increased from 10-30% to >90% [8]. Nested PCR amplified with genotype-specific primers is indicated as a useful SEN-V screening assay. Moreover, because all components of the assay are readily available (specific antibodies are not required), viral testing can be performed in most laboratories that perform PCR [6, 13]. A rapid and sensitive molecular assay for the detection of four SEN-V strains (SEN-V-A,-C,-D,-H) is reported by Yasuhito Tanaka *et al.* [10]. Keeping in view the greater genetic diversity in SEN-V-C and-H than that within the other genotypes, they combined results for the SEN-V-H probe and the SEN-V-C/H probe to reduce the false negativity of the detection [10].

Considering the new classification of SEN-V into the genus Anellovirus, it is worth mentioning that rolling-circle amplification (RCA) and sequence-independent single primer amplification (SISPA) have been applied successfully to detect and clone Anellovirus. In a study by Biagini *et al.* [12] a combined RCA and SISPA approach was applied to four samples of human plasma and one sample of salvia from a cat. Nine Anelloviruses were detected by using this approach. In human plasma samples, two highly divergent sequences belonging to the species Torque teno mimi virus and in the cat´s salvia, two genomes that were separate by a genetic divergence of 46% were recognized. The authors concluded the potential role of RCA-SISPA for detecting circular (or circularized) target genomes. However, the studied approach showed few limitations. For example, the sensitivity of SISPA to detect viral sequences from blood samples was found relatively weak.

Detection of SEN-V in the liver

SEN-V is expected to be a hepatotrophic virus that may replicate via a ribonucleic acid (RNA) intermediate. To document whether SEN-V replicates in liver or not, liver tissues of 2 patients with hepatocellular carcinoma were examined. After extracting and destroying DNA with DNase, RNA was extracted. Half of RNA was reverse-transcribed to cDNA. Both RNA and cDNA were tested in a PCR reaction using SEN-V primers. As SEN-V is a DNA virus, amplification of cDNA and the lack of RNA amplification suggest that liver contained a SEN-V replicative intermediate. However, as the study conclusion was based on a single experiment, no statistical analysis was carried out [11].

Liver disease association

Whenever a novel agent is discovered and reported, the medical community soon attempts to discover its disease association. It would be difficult to approve causal role of the agent if the prevalence of the agent is high and the number of infected persons with prominent clinical manifestation is relatively low. Accordingly, the studies about SEN-V disease association have so far encountered with some uncertainties [11].

To date, the relationship of SEN-V to liver disease

remains disputable [2, 6, 11, 13, 16]. The significance, pathogenicity and clinical manifestation of SEN-V have been investigated in different modes of studies. High levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP) and also the pathological findings in SEN-V-positive patients compared with SEN-V-negative individuals has been reported. However, these findings were not statistically significant [16, 17, 22]. Another claim against the probable causative role of SEN-V in liver disease is that the majority of patients with severe liver failure are SEN-V-negative [17]. The prevalence of SEN-V in patients with non A to E hepatitis is reported higher compared with blood donors and healthy population but this difference is not statistically considerable and does not prove the causality of SEN-V. In China, SEN-V-D and/or SEN-V-H were positive in 31% of Chinese healthy adults, 36% of patients with acute or chronic hepatitis A, 59% of patients with chronic hepatitis B, 85% of patients with chronic hepatitis C and 68% of patients with non A to E hepatitis [13]. Based on a study of the SEN-V effects on progression of non A to E hepatitis, there were no significant differences in SEN-V DNA positivity rates between patients with chronic hepatitis, cirrhosis, HCC and acute hepatitis. In addition, there were no significant differences in SEN-V DNA positivity rates between blood donors and patients with non A to E hepatitis. It seems unlikely that SEN-V solely play causative role in hepatitis [6]. In Japan, Shibata *et al.* [23] studied the prevalence of SEN-V in patients with fulminant, acute and chronic hepatitis, cirrhosis and the two forms of chronic autoimmune liver disease. A higher prevalence of SEN-V was found in all these groups of liver diseases than that of healthy blood donors (10%). Nevertheless, SEN-V positivity rates did not differ significantly between those with etiologically cryptogenic liver disease and those with marker positive viral hepatitis.

SEN-V infection is not counted as a responsible agent for liver disease in children, as in adults. Moirondo *et al.* [5] investigated on 89 HIV-1 negative, HCV-RNA positive women and their infants for SEN-V infection. As a whole, 47% of babies born to SEN-V-positive mothers were found to be SEN-V-infected. All the babies in the study had normal liver function test, normal growth parameters, as well as neurological development.

Among the nine genotypes, SEN-V-H and SEN-V-D are more prevalent and considered having association with non A to E hepatitis [2, 3, 11, 13, 17, 24]. Umemura *et al.* performed the NIH (National Institute of Health) study (one of the most notable studies on the co-relation of SEN-V and non A to E hepatitis) [11]. The most significant finding was the possible association between acute SEN-V infection and the occurrence of transfusion-associated non A to E hepatitis. Among patients with transfusion-associated non A to E hepatitis, 11 out of 12 patients (92%) became SEN-V positive exactly after transfusion whereas 55 of 225 (24%) identically followed transfusion recipients did not develop hepatitis.

SEN-V positivity was higher among patients with liver disease than among the blood donors with a weak association (OR=1.407). Despite this statistically insignificant OR, it seems to be weaker than that found for hepatitis B surface antigen (HBsAg), HCV RNA and history of heavy alcohol intake, and so the possibility of an association between SEN-V and non A to E liver disease could not be excluded [6].

SEN-V/HBV/HCV co-infection

Viral hepatitis has a high prevalence and is considered as a serious public health concern. In addition, it is the main cause of chronic hepatitis (CH), cirrhosis (CL) and HCC worldwide. One hundred and seventy million individuals are infected with HCV throughout the world [25].

HCV and hepatitis B virus (HBV) causative roles to CH, CL and HCC have been established. Although co-infection with HCV is considered a risk factor for SEN-V infection [25-27], the exact interaction of SEN-V with HCV and HBV is still unclear.

SEN-V infection is more common in patients with chronic HBV or HCV [2, 22, 23]. Co-infection with SEN-V has been frequently found in 22-67% and 20-76% of patients with chronic hepatitis B and C, respectively [23, 28]. The prevalence of SEN-V infection in HCV-positive, HIV-1-negative, non-immunocompromised women is significantly higher than the prevalence in Italian blood donors, even if it is not comparable to the highest rate found in HIV-1 infected patients [5, 26].

In a study by Kao *et al.*, patients with chronic HBV or HCV infection plus HCC had higher SEN-V positivity rates in comparison with control subjects without these diseases, bringing the idea of possible SEN-V effect on progression from HBV or HCV infection to HCC [28]. In another study on patients with type C chronic hepatitis and cirrhosis, histopathological features of the liver was affected by SEN-V co-infection but the outcome of these

patients did not change. In fact, the incidence of HCC did not show a considerable difference between SEN-V-positive and -negative subjects (6.6% in SEN-V-positive vs. 6.9% in the SEN-V-negatives) [22]. It does not seem that SEN-V worsens the course of hepatitis C or affects the severity of HCV infection or the prognosis of HCC [2, 6, 11]. However, because of the histopathological changes attributed to SEN-V in the liver of the above patients, it is likely that a difference will be detected in the incidence of HCC among these patients during longer term of observation [22].

SEN-V infection in terms of effects on HCV/HBV treatment response

It seems that multiple viral infection of liver turns out to be a resistant liver in terms of treatment response to the antiviral therapy. Predictably, dual infection with HBV, either HDV or HCV, could end up with an auspicious outcome of antiviral therapy in comparison with single HBV infection [29]. There are also some reports that have shown interference between HBV and HCV which is due to the suppressive roles of their replication processes on each other [29, 30]. It has been tried to find out the influence of SEN-V on clinical features and treatment response of chronic hepatitis B and C [31].

Umemura *et al.* reported no differences in response and clearance rate for HCV after interferon alpha (IFN-α) treatment between SEN-V-positive and SEN-V -negative cases [9]. Of the 16 SEV-V -positive patients with HCV co-infection, all but 1 patient responded to IFN-α monotherapy. SEN-V showed a prominent higher response rate (69%) than that of HCV (37%). This result can be explained by the fact that in the presence of HCV infection, IFN can give rise to higher levels of cytokines or other antiviral mediators that predominantly kill SEN-V. HCV and SEN-V responded to therapy independently. Interestingly, SEN-V-D was more responsive to IFN (with 73% sustained response rate) than SEN-V-H (33%) [9]. Similar results were found for SEN-V-D towards the combination therapy with a response rate of 88% for SEN-V-D versus 34% for SEN-V-H [32]. In Akita university school of medicine, Japan, 52 patients with chronic HCV infection underwent IFN therapy for a duration of 6 months [31]. Using PCR, 67% of those 52 patients were diagnosed with SEN-V of whom 42.3% were found to be SEN-V-D or SEN-V-H- positive by applying the C5s and D10s primers. SEN-V was sensitive to therapy but did not change the rate of HCV response to combination therapy [31, 32]. The post-treatment eradication rate of HCV RNA was 38.4% which was significantly lower than that of SEN-V DNA(77.1%). In this study, 50% of those with SEN-V-D or-H positives were eradicated of infection. SEN-V-D was susceptible to IFN comparably to SEN-V-H [33]. Ninety five patients with chronic hepatitis C were tested for SEN-V infection [31]. On the subject of chronic HCV response to the combination therapy with IFNα or Pegylated-interferon(PEG-IFN)α plus ribavirin, the results reflect no difference between patients with and without SEN-V co-infection(52% VS.50%). SEN-V is responsive to IFN but no strain took priority over the others in treatment response rates. Additional therapy with ribavirin does not enhance SEN-V response to IFN contrary to that of HCV. A higher pre-treatment SEN-V DNA level of 1.3 times was detected in SEN-V non-responder group, it represents that the SEN-V response rate is correlated with the SEN-V DNA level prior to treatment while there is no similar evidence for the treatment response of HCV.

Kao *et al.* and Rigas *et al.* carried out studies on the patients with chronic hepatic C who attended a combination course of therapy with 3million units IFN2α 3 times a week plus 1000-1200 mg ribavirin daily with the morning dose reduced to 400 mg for those weighing less than 72 kg, for 6 months [31]. Although Rigas *et al.* [34] achieved a negative effect of SEN-V on HCV response to the combination therapy, there was a higher response rate in patients with SEN-V co-infection rather than those without SEN-V in Kao *et al.* study [32]. Due to the statistically insignificant results of this finding, the sustained response rate of HCV to the combination therapy of IFN and ribavirin was compatible between SEN-V DNA-positive and -negative patients. No considerable differences were observed between the sustained response rate of SEN-V (35%) and HCV (40%) to combination therapy. The responsiveness of these two agents was not correlated.

The differences in the above studies can be attributed to patient selection and sample size.

To understand the impact which SEN-V co-infection has on the outcome of antiviral therapy in patients with hepatitis B, 45 HBV-positive patients were evaluated [29]. All of these patients treated with lamivudine 100 mg daily. The patients were tested for SEN-V DNA after a 12-month course of therapy. SEN-V DNA was detected in 5 of 45 patients. In terms of post-treatment ALT level and hepatitis B e antigen (HBeAg), there were no significant differences between patients with and

without SEN-V co-infection. On the contrary, the number of responders to lamivudine regarding HBV DNA level (as the criterion to define responders) was statistically higher in patients with HBV alone than those with SEN-V co-infection (30/40 vs.1/5). The results indicated that co-infection with SEN-V virus in chronic hepatitis B patients might adversely affect the outcome of lamivudine treatment [29].

SEN-V among patients on maintenance hemodialysis

Patients on hemodialysis served as a high risk group for being infected by blood-borne viruses such as hepatitis C virus, because the hemodialysis materials used in different centers are not completely disposable and also the fact that the therapeutic procedures are frequently associated with bleeding and blood transfusion [35, 36]. Separate dialysis machines are usually utilized to prevent nosocomial transmission of such viruses. It is unclear whether patients on hemodialysis are at risk for acquiring SEN-V infection [37]. Pirovano *et al.* [38] found that the patients who undergo hemodialysis can be at high risk of SEN-V transmission. They represented the possibility of intraunit transmission of specific SEN-V variants and other important routes of SEN-V transmission excluding blood transfusion in hemodialysis patients. seventy out of 171 hemodialysis patients were positive for at least one SEN-V variant. Although, SEN-V-B, -D and -H were highly represented in hemodialysis patients, only SEN-V-D was significantly more frequent in hemodialysis patients compared with healthy controls. On the whole, the prevalence of SEN-V infection was found higher than that of age-matched healthy donors (44/163). Likewise, the proportion of SEN-V-positive subjects was significantly higher than that of HCV- and HBV-positive individuals (P<0.001). No significant differences for sex, age, length of time on hemodialysis, transaminase levels, HCV and HBV detection and liver ultrasonography were found between SEN-V-DNA-positive and -negative patients.

Another study investigated 78 patients on maintenance hemodialysis for SEN-V-H viremia using PCR. Blood samples of 226 healthy blood donors were evaluated as controls. A prevalence of 38/226(16.8%) was reported for SEN-V-H among blood donors. The prevalence of SEN-V-H among hemodialysis patients was 10/78(12.8%). Statistical analysis revealed no significant difference between the prevalences in those two groups (P=0.35).

SEN-V viremic patients do not develop clinical or biochemical signs of liver disease. In addition, the severity of hepatitis is not increased by parallel infection with SEN-V-H among HCV infected patients. Therefore, it was not considered as a necessity to use separate machines to dialysis SEN-V-H viremic patients [37].

In Slovakia, sera of 426 adult persons were examined for SEN-V infection. The prevalence of SEN-V infection reported 125/426 which was similar to observations from other countries [39]. Regarding risk factors for parenteral infection and different liver diseases, patients were divided into 7 groups. A higher number of SEN-V-positive subjects was found in the group on hemodialysis (36/72) in comparison with the group with acute hepatitis B, health care workers and the control group (P<0.05). By evaluating the importance of various risk factors of parenteral transmission of SEN-V, three factors showed remarkable differences between SEN-V positive and SEN-V-negative patients: the average count of surgical procedures in anamnesis per patient, the number of transfusions received and the duration of hemodialysis. Laboratory findings do not show any differences between SEN-V-positive and-negative patients concerning bilirubin, AST and ALT. No influence of SEN-V was observed on the course of illnesses or worsening of laboratory findings in the control group. Therefore, no pathogenetic role of SEN-V in liver injury was confirmed among all studied groups.

Study on the prevalence of SEN-V among patients undergoing hemodialysis (HD) in Poland, as well as risk factors for the infection revealed that SEN-V-H viremia was prevalent in 40% of HD patients and in 2% of control subjects (P<0.0001) [40]. In HD patients, there was no significant association between SEN-V prevalence and age, gender, dialysis vintage, previous blood transfusion, seropositivity for HBsAg, hepatitis C virus antibody (HCVAb) or HCV RNA. Clinical or biochemical markers of liver disease were not affected by SEN-V-H status. Consequently, SEN-V was not found to be responsible for liver damage in maintenance HD patients.

A survey conducted in Japan tested 189 patients on maintenance hemodialysis for SEN-V as well as 60 healthy control subjects [41]. Of the 189, 154 were followed up for 2 years. Although SEN-V infection is almost frequent among Japanese general population, the prevalence in patients on maintenance hemodialysis (38%) was significantly higher than that of control group (22%). There was no significant correlation between SEN-V infection and blood transfusion history or duration of

hemodialysis. Serum levels of ALT was associated with HCV, but not with SEN-V viremia. Sixty three out of 154 patients who were followed up, remained negative. Thirty four out of 154 acquired SEN-V infection, SEN-V disappeared in 28/154 and 29 patients remained positive for SEN-V. Male patients tended to retain SEN-V viremia longer than females, whereas, it has not been reported that SEN-V infection differs by gender in healthy individuals or in patients with liver diseases. On the whole, SEN-V was not found to be as a causative agent for hepatitis in patients on hemodialysis.

In Taiwan, the prevalence and clinical importance of SEN-V-D and SEN-V-H were investigated in 99 patients on maintenance hemodialysis [42]. The overall prevalence of SEN-V-D/H was 61.6%. No association was found between positivity of SEN-V DNA and gender, the duration on hemodialysis, the history of blood transfusion or the presence of HBsAg or HCV. Mean serum ALT levels were significantly higher among the patients with anti-HCV (P= 0.003) and patients with SEN-V-D and -H concurrent infection (P=0.034). Therefore, the ALT level in patients on maintenance hemodialysis was associated with not only the anti-HCV positivity but also with the concomitant viremia of both SEN-V-H and SEN-V-D (as an independent factor of HCV infection).

SEN-V and liver transplantation

The prevalence of idiopathic post-liver transplant graft hepatitis with viral histological features has been reported to be up to 22% [3]. Liver transplant recipients are at high risk for acquiring previously undetected transfusion-associated viruses. On the one hand, this complication is due to unavoidable transfusion of passenger blood cells and transplanted allograft itself. Moreover, these patients underwent several blood products transfusions in the pre-transplantation care, during transplantation surgery and in the post-transplantation period. On the other hand, liver transplant recipients are significantly immunosuppressed and it is well accepted that recurrent HCV and hepatitis B virus post-transplantation are aggressive diseases associated with worse post-transplantation outcomes.

Fifty eight unselected liver transplant recipients tested for SEN-V in a cross-sectional study [4]. The aim of the study was to determine point prevalence of SEN-V in these patients and clarify the correlation between SEN-V infection and serum liver biochemistry. Of the 58 patients, 51.7% (30 patients) were positive for either SEN-V-C/H (2 genotypes that are highly homologous) and/or SEN-V-D. Subgroup analysis revealed no significant difference based on pre-transplantation liver disease. Patients underwent transplantation for HCV and developed evidence of post-transplantation HCV recurrence (14 of 21 patients) and were more likely to be SEN-V positive in comparison with those that underwent transplantation for other liver diseases (79% vs.40%, P=0.02). When SEN-V status was compared with liver biochemistry test results, no significant differences were found, although SEN-V-positive subjects showed a higher mean serum ALT and AST levels. This feature was attributable to the subgroup of SEN-V positive with HCV recurrence. Surprisingly, even the patients with HCV-graft recurrence who collectively had a higher mean serum ALT, did not show any significant differences based on SEN-V status. Therefore, despite high proportion of SEN-V-positive subjects among the liver transplant recipients and association with HCV recurrence, it was not documented that SEN-V was negatively affecting graft function.

Conclusions

SEN-V, like TTV, is a DNA virus and latest candidate virus to be investigated as a possible liver pathogen. In preliminary studies, SEN-V was reported to be associated with the same transmission risk factors as HCV and HBV, but other studies revealed the possibilities of other routes of transmission such as fecal-oral route. Nine subtypes of SEN-V are known so far. Only two genotypes of -D and-H seem to have correlation with transfusion-associated non A to E hepatitis. This acute hepatitis is self-limited. There is no convincing evidence to prove that SEN-V can cause chronic hepatitis, end-stage cirrhosis or be a risk factor for developing hepatocellular carcinoma.

The baseline prevalence of SEN-V in the healthy population may be quite high depending on the life style in a given society; however, this doesn't necessasitate screening the donor population for SEN-V as the causality is not established yet. However, at present, SEN-V has no established pathogenicity and it may have disease associations that have not been identified yet. On the other hand, it may serve as an organism that has some beneficial role in maintaining homeostasis in the host. It is certainly worthy of more attention from the scientific community, even in the absence of confirmed disease associations.

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