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WJT World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2022 January 18; 12(1): 1-7

DOI: 10.5500/wjt.v12.i1.1

ISSN 2220-3230 (online)

OPINION REVIEW

Human pegivirus infection after transplant: Is there an impact?

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Author contributions: Mrzljak A made contributions to the concept and design the manuscript; Mrzljak A, Simunov B, Balen I, and Vilibic-Cavlek T were involved in writing the manuscript; Jurekovic Z critically revised the manuscript; and all authors approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Supported by the Croatian Science Foundation, Emerging and Neglected Hepatotropic Viruses after Solid Organ and Hematopoietic Stem Cell Transplantation, No. IP-2020-02-7407.

Country/Territory of origin: Croatia

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. In the transplantation setting, pegivirus infection does not seem to have a negative impact on the outcomes of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The possible immunomodulatory effect of pegivirus infections remains to be elucidated in further trials.

Key Words: Virome; Human pegivirus; Epidemiology; Solid-organ transplant; Hematopoietic stem cell transplantation

Core Tip: Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. Pegivirus infection does not seem to have a negative impact on the outcome of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals.

Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 31, 2021
Peer-review started: January 31, 2021
First decision: October 17, 2021
Revised: October 25, 2021
Accepted: January 6, 2022
Article in press: January 6, 2022
Published online: January 18, 2022

P-Reviewer: Chan WYK, Zhou S
S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

Citation: Mrzljak A, Simunov B, Balen I, Jurekovic Z, Vilibic-Cavlek T. Human pegivirus infection after transplant: Is there an impact? *World J Transplant* 2022; 12(1): 1-7
URL: https://www.wjgnet.com/2220-3230/full/v12/i1/1.htm
DOI: https://dx.doi.org/10.5500/wjt.v12.i1.1

INTRODUCTION

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Several studies have shown that the virome changes upon immunosuppression initiation[1,2]. Most notable is the increase in the anello-viruses but also in pegiviruses.

Pegiviruses are single-stranded positive-sense RNA viruses, most closely related to hepatitis C virus (HCV) in terms of genome organization with structural genes located at the 5' genomic region and non-structural genes at the 3' end[3]. The genome encodes a polyprotein that is co- and post-translationally cleaved into individual viral proteins. Structural proteins common to all pegiviruses are the envelope glycoproteins (E1 and E2), and non-structural proteins are NS2-NS5B[4]. Pegiviruses are classified into eleven species (pegivirus A-K) within the genus *Pegivirus* in the *Flaviviridae* family. Two pegiviruses are known to infect humans, the human pegivirus (HPgV) and the HPgV-2, but their pathogenicity is limited and no clear association with any human disease has been established[5].

HPgV was discovered in 1995 from the sera of patients with hepatitis by two independent investigator groups, who named it GB virus C and hepatitis G virus (HGV), respectively. The HPgV's E2 glycoprotein, involved in the adhesion and fusion with the host cells, targets the production of anti-HPgV antibodies, which appear after the viral clearance and provide partial protection against reinfection[6]. The virus is efficiently transmitted through sexual contact and intravenous substance use, vertically from mother to child, and through exposure to infected blood and blood components[7].

Available data suggest a high prevalence of HpgV viremia (> 40%) in populations with parenteral exposure risk[8]. Although early studies indicated that the HPgV is hepatotropic, numerous subsequent studies have shown that HPgV is rarely detectable in infected individuals' liver tissue. In addition, no evidence of a liver disease potentially linked to HPgV was observed during the follow-up of different patient categories[7].

HPgV-2 was isolated in 2015 from the plasma of HCV-infected patients with multiple blood-borne exposures in the United States[8]. A low prevalence of HPgV-2 viremia has been noted in the general population, but there is an increase in patients with HCV infection and injecting drug users co-infected with HCV[9]. Further studies indicated that HPgV-2 is a lymphotropic but not a hepatotropic virus, which may explain the lack of association with liver disease[10].

HPgVs are distributed globally, and viral RNA is present in roughly 750 million people[6], making it ubiquitous in human populations. The prevalence of HPgV viremia from cross-sectional studies of healthy blood donors in developed countries ranges between 1% and 5%. Nearly 200000 units of HPgVs-contaminated blood products are transfused each year in the United States[11]. In comparison, in developing countries, up to 20% of blood donors have an active infection[12]. Data suggest that approximately 1.5-2.5 billion people are currently infected or have evidence of prior HPgV infection[6].

Numerous studies examined the presence of HPgV in several countries. Generally, a high HPgV prevalence is observed among subjects with parenteral exposure, including those exposed to blood and blood products, those on hemodialysis, those with a history of intravenous substance use, and patients with chronic hepatitis C or human immunodeficiency virus (HIV) infection[13].

HPGV AFTER TRANSPLANTATION OF SOLID ORGANS AND NON-SOLID ORGANS

HPgVs have received much attention due to the possible beneficial immunomodulatory effects by reducing immune activation in patients with other viral diseases such as HIV infection, hepatitis B, and Ebola virus disease[14-17]. On the other hand, HPgV viremia has also been associated with the development of non-Hodgkin lymphoma (NHL). HPgV is a lymphotropic virus that may cause persistent infection in T and B lymphocytes, reduced Fas-mediated apoptosis, and impaired T cell and interleukin-2 receptor signaling[18]. HPgV infection anticipates the development of NHL by several years and resolved infection was not associated with NHL risk[19]. Pegiviruses have been studied both in hematopoietic stem cell transplantation (HSCT) and solid-organ transplant (SOT) recipients (Table 1).

Studies in HSCT recipients are limited. The prevalence of HPgV in HSCT patients ranges from 18.6%, as described in the study from Switzerland[20], to almost 30% in an earlier French study[21]. As in the general population, the risk of viremia rises with the number of received blood products[20,22]. No significant influence of pegiviruses on HSCT patient outcomes was found. On the other hand, no beneficial effect of pegivirus infections is currently proven; therefore, some studies warrant HPgV donor screening for blood products used in HSCT recipients until more conclusive studies are performed[22].

Early studies in SOT recipients were done mostly in liver transplant (LT) recipients, due to the presumed hepatotropic nature of the virus, all showing a high prevalence but no significant influence on patient outcomes[23-26]. The largest of the studies included in this review is the recent Japanese study on 313 LT recipients. This monocentric study showed an increased prevalence of HPgV in LT recipients compared to hepatectomy controls[27]. As in the earlier studies, there was no significant association between HPgV infection and LT outcomes. The study showed that HPgV infection induced the up-regulation of interferon-stimulated gene (ISG) expression in peripheral blood mononuclear cells[27].

HPgV is transmitted through parenteral, sexual, and perinatal routes[28]. Parenterally exposed individuals such as hemodialysis patients, therefore, have a higher risk of infection. An Indian study using univariate analysis showed that the prevalence of GB virus C/HGV RNA was significantly associated with ≥ 20 hemodialysis sessions[29]. After the transition from dialysis, the prevalence remains high in kidney transplant (KT) recipients, ranging from 12% to 47% in different countries[30-33]. A large Italian study in KT recipients (n = 155) showed an HGV RNA and anti-HGV prevalence of 24% and 17%, respectively[34]. None of the studies above, found any influence on patient outcomes, including kidney or liver function. On the other hand, the largest study in KT recipients (Germany, n = 221)[33] showed that a much higher proportion of KT recipients were exposed to HGV, than that suggested by HGV RNA detection alone. The prevalence of HGV RNA and anti-HGV in the study was 14% and 40%, respectively. Most infected individuals eliminate the virus over time. Unfortunately, the majority of other studies did not include serological analyses. Most of the studies on HPgV were done immediately after the discovery of the virus, focusing mostly on hepatic function or the function of the transplanted organ. Only the most recent study[1] tried to include other post-transplant complications in the analysis, *e.g.*, new-onset diabetes after transplantation or nephrotoxicity in LT recipients. The study highlighted a potential use of anellovirus infection as a proxy for determining the immunological status. At the moment there is no standard way to measure total immunosuppression, besides the widely available through levels of immunosuppressant drugs. In the same study, all of the HPgV positive participants were still alive 5 years after LT, indicating a protective role of HPgV in post-transplantation survival[1].

The paucity of other SOT recipient studies probably reflects the proportionately lower number of those transplants performed. We found no studies evaluating HPgV in simultaneous pancreas-kidney transplantations or lung transplant recipients. The studies in heart transplant recipients are concordant to those in other SOT, showing no adverse outcome but a high HPgV prevalence, up to 36%[35-42].

CONCLUSION

To conclude, pegivirus infection does not seem to have a negative impact on the outcome of transplant recipients. Nevertheless, studies are limited and lacking prospective data. What remains to be elucidated is the possible immunomodulatory effect of pegivirus infections. Also, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The subject deserves further research and evaluation.

Table 1 Seroprevalence and RNA prevalence studies in different transplant populations

Type of transplant and period	Country/region	Patients (*n*)	RNA prevalence	Seroprevalence	Comment	Ref.
Liver transplant; 1997-2017	Japan	313	14.1%	/	No significant association between HPgV infection and liver transplant outcomes; HPgV infection induced the up-regulation of ISG expression in peripheral blood mononuclear cells	Izumi *et al*[27], 2019
Renal transplant; 1989-1996	Italy	155	24%	17%	Not associated with disease pathogenicity; Lower serum levels of HCV-RNA in HGV/HCV co-infected carriers compared to those infected with HCV only	De Filippi *et al* [34], 2001
Renal transplant; 2015-2016	Brazil	61	36.1%	/	Most common genotype 2 (80.9%), followed by G3 (9.5%), G1 (4.85), and G5 (4.8%); no significant impact on patient outcomes	Savassi-Ribas *et al*[31], 2020
Renal transplant	France	103 HCV positive RT recipients	28%	/	HGV infection has no detrimental effect on liver enzymes or liver histology in HCV-positive patients	Rostaing *et al* [37], 1999
Heart transplant; 1993-1998	Germany	51 transplant candidates	2.0%; 0	0; 6.0%	RNA persisted after transplant; anti-E2 antibodies persisted after transplant	Kallinowski *et al* [38], 2002
		Post-transplant	36.0% *de novo*	/	RNA persisted in 94% infected patients; No significant correlation between the number of blood transfusions and the infection; No impact on liver disease or patient outcome	
Liver transplant; 1993-1998	Germany	72 transplant candidates	11.%	/	RNA persisted in 88% of infected patients	Kallinowski *et al* [38], 2002
		Post-transplant	36% *de novo*	/	RNA persisted in 87% of infected patients; no significant correlation between the number of blood transfusions and the infection; no impact on liver disease or patient outcome	
Kidney transplant; 1997	Thailand	94	43%	/	Co-circulation of HGV and HCV RNA was detected in 12 patients (13%)	Raengsakulrach *et al*[30], 1997
Heart transplant; 1993-1996	Germany	243	24%	/	HGV infections are transfusion related; not related to the use of mechanical circulatory assist devices or immunosuppression	Wolff *et al*[36], 1996
Liver transplant; 1989-1996	Germany	98	Pre-tx 8.2%; post-tx 44%	/	None of the hepatitis B, hepatitis C, or fulminant hepatitis, were HGV-RNA positive preoperatively; HGV was frequently acquired after LT but had no impact on the short- and medium-term clinical course post-LT	Fischer *et al*[23], 1999
Liver transplant; 2007-2010	Iran	106	9.4%	/	Moderate prevalence of HGV infection in liver transplant recipients	Ebadi *et al*[39], 2011
Kidney transplant; 1986-1990	United States	93	12%	/	HGV infection does not adversely affect clinical outcome during early follow-up	Isaacson *et al*[32], 1999
Liver transplant; 1989-1996	Italy	136	Pre-tx 18.4%; post-tx 47.8%	Pre-tx 26.5%	Liver transplant patients are heavily exposed to HGV before and after transplantation; HGV does not induce liver disease; most infections are self-limited and induce a protective immunity (anti-E2 antibodies presence)	Silini *et al*[40], 1998
HSCT; 1985-1996	France	95	29.5%	/	Acute GVHD, chronic GVHD, or veno-occlusive disease are similar in HGV+ and HGV- recipients in early period after allogenic BMT	Corbi *et al*[21], 1997
Kidney transplant; 1997	Germany	221	14%	40%	The majority of infected individuals eliminate the virus over time	Stark *et al*[33], 1997
Kidney transplant; NA	Turkey	69	42%	/	Genotype 2 is the dominant type; subgroup 2a most common of the isolates	Erensoy *et al*[41], 2002

Liver transplant; 1993-1995	United Kingdom	47	47%	/	HGV does not cause significant liver disease after LT	Karayiannis *et al* [42], 1998
Liver transplant; 1979-1990	Netherlands	39	Pre-tx 15.4%; post-tx 43.6%	/	HGV infection is highly prevalent in liver transplant patients; in the absence of HBV or HCV co-infection with, no long-term negative influence on the graft	Haagsma *et al* [24], 1997
Kidney transplant; 1997-2000	India	70	52.9%	58.6%	GBV-C/HGV RNA significantly associated with ≥ 20 hemodialysis sessions	Abraham *et al* [29], 2003
Liver transplant; 1990-1994	United States	179	Pre-tx 15%; post-tx 50%	/	HGV infection not associated with poor outcome	Hoofnagle *et al* [26], 1997
HSCT; 2011-2017	China	188	18.6%	/	HPgV is highly prevalent in HSCT patients; blood transfusions significantly increase the risk of HPgV infection	Li *et al*[22], 2019
HSCT; 2014-2015	Switzerland	40	35%	/	HPgV is highly prevalent and persists for several months	Vu *et al*[20], 2019

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HGV: Hepatitis G virus; HSCT: Hematopoietic stem cell transplantation; HpgV: Human pegivirus; GBV-C: GB virus C; GVHD: Graft *versus* host disease; BMT: Bone marrow transplantation; ISG: Interferon-stimulated gene.

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