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REVIEW

The human pegivirus: A new name for an "ancient" virus. Can transfusion medicine come up with something new?

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Summary. – Human pegivirus (HPgV, formerly called GB virus C/hepatitis G virus) is a poorly understood RNA virus of the *Flaviviridae* family. The HPgV infection is common worldwide and the virus is likely transmitted by blood products. At this time, no causal association between HPgV and human diseases has been identified. While waiting for new findings to better understand the *Pegivirus* genus, the aim of our narrative review is to discuss the currently available information on HPgV focusing on its prevalence in blood donors and its potential threat to transfusion safety.

Keywords: GB virus type C; hepatitis G virus; human pegivirus; Flaviviridae; hepatitis; blood transfusion

Contents:

1. Introduction

In 2013, the International Committee on Taxonomy of Viruses (ICTV) ratified the creation of a new genus in the family *Flaviviridae*, the *Pegivirus* genus (Stapleton *et al.*, 2011). In the 1960s, in the progression of isolating and identifying the etiologic agent(s) responsible for non-A, non-B hepatitis, a transmission of viral hepatitis from humans to non-human primates (*Saguinus labiatus*) was achieved by Deinhardt and colleagues (Deinhardt *et al.*, 1967) starting from the serum from a subject with acute hepatitis (whose initials were G.B.). In 1995, the GB virus A and B (GBV-A, GBV-B), two viruses closely related to hepatitis C virus (HCV), were identified, but up to now they have not been found in humans (Schaluder *et al.*, 1995). A third virus was identified and named GBV-C using degenerate oligonucleotides to amplify related viral sequences in human serum samples (Simons *et al.*, 1995). Concomitantly, another research group identified novel RNA virus sequences in the serum of humans with hepatitis, and called this virus hepatitis G virus (HGV) (Linnen *et al.*, 1996). Following analysis of the genome sequences of HGV and GBV-C revealed that they were minor variants of the same virus species, while GBV-A and GBV-B were distinct (Stapleton *et al.*, 2011). Pegivirus A has been designated as the type species of this new genus and it has been found in primate host species (humans, chimpanzees and several New World

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Abbreviations: HPgV/HGV/GBV-C = human pegivirus; HGV = hepatitis G virus; HCV = hepatitis C virus; PBMCs = peripheral blood mononuclear cells; ALT = alanine aminotransferase

monkey species) unlike the pegivirus B which was found only in fruit bats (Epstein *et al.*, 2010). On the other hand, HGV/GBV-C, currently called human pegivirus (HPgV), is commonly detected in healthy blood donors at the time of donation, however it has limited pathogenicity and it is not clearly associated with any human disease (Bhattarai and Stapleton, 2012; Chivero *et al.*, 2014). Recently, two independent reports described the discovery of a novel human pegivirus that has been temporarily designated as human hepegivirus 1 (HHpgV-1) (Kapoor *et al.*, 2015) or as human pegivirus 2 (HPgV-2) (Berg *et al.*, 2015). Available data suggest that it is a highly divergent, blood borne virus, and seems to exhibit a low prevalence of viraemia in populations with parenteral exposure risk (Kapoor *et al.*, 2015; Berg *et al.*, 2015).

The aim of this narrative review article is to discuss the currently available information on this virus focusing on its potential threat to transfusion safety.

2. Search methods

We analysed the medical literature for published randomized controlled trials (RCTs), observational studies, and reviews concerning the prevalence of HPgV in blood donors. The PubMed/Medline electronic database was searched without temporal limits using the English and French language as a restriction. The Medical Subject Heading and key words used were: "human pegivirus", "hepatitis G virus", "blood donors", and "blood transfusion". We also screened the reference lists of the most relevant articles for additional studies not selected in our initial literature search.

3. The virus

In the last years, several novel pegiviruses have been found in a wide range of mammalian hosts, including bats, primates, rodents, dogs, cows and horses (Thézé *et al.*, 2015). These new discoveries have radically changed our knowledge of the various pegiviruses and their vast range of hosts. The potential for the different species of animal hosts to act as reservoirs of viral infection and sources of cross-species transmission is well known (Thézé *et al.*, 2015); it has been estimated that they are responsible for a quarter of all recently-emerged human pathogens (Woolhouse *et al.*, 2012).

The HPgV (formerly called GB virus C/hepatitis G virus) is an enveloped, spherical virus about 50 nm in diameter. The HPgV genome is represented by a single-chain RNA (~9.4 kb) with positive polarity. It is similar to the HCV RNA in its organization, i.e. the structural genes are located at the genomic 5' region (containing an internal ribosomal entry site (IRES) directing translation of a polyprotein of approximately 3,000 amino acids) and non-structural genes at the 3' end (Thézé *et al.*, 2015). Phylogenetic data, compiled from various parts of the world, revealed the presence of seven distinct HPgV genotypes (Thézé *et al.*, 2015). The virus is efficiently transmitted by parenteral route (sexually, vertically from mother to child, intra-familiarly, intravenous drug use, and through exposure to infected blood and blood components) (Chivero and Stapleton, 2015). Sexual transmission appears to be more efficient than for HCV, probably due to lymphotropism and higher serum virus concentrations (Stapleton *et al.*, 2011).

The E-protein is an important molecule of HPgV (involved in the virus adhesion and fusion with the host cells) and it is the target for the production of the anti-HPgV antibodies. The viral proteins are not usually detected during active infection, but antibodies against the envelope glycoprotein E2 appear following viral clearance and appear to provide partial protection against reinfection (Chivero and Stapleton, 2015). Therefore, antibodies to E2 represent a marker of prior infection, although antibody levels may decrease and become undetectable over time (Chivero and Stapleton, 2015; Grassi *et al.*, 2000). Unlike HCV infection, simultaneous detection of viral RNA and antibodies to E2 or other viral proteins is not common (Bhattarai and Stapleton, 2012).

Diagnosis of HPgV is usually performed through the reverse transcription PCR (RT-PCR) and ELISA. The two above-mentioned diagnostic assays are based on the detection of different viral markers in biological samples: RT-PCR detects HPgV RNA molecules in the patient samples and ELISA detects antibodies to E2-proteins (Schaluder *et al.*, 1995; Chivero and Stapleton, 2015). At the moment, no licensed blood donor screening tests for HPgV exist.

4. Clinical relevance of HPgV infection

Since its discovery, the primary site(s) of replication and cellular receptors for HPgV has (have) not been identified and a correlation with non-A/non-E hepatitis remains a controversial issue even though HPgV RNA has been detected more frequently in patients with acute and chronic non-A/non-E hepatitis than in healthy subjects. Early studies indicated that the virus was hepatotropic (Grassi *et al.*, 2000; Hollingsworth *et al.*, 1998; Guilera *et al.*, 1998), although numerous studies carried out since the late 1990s, have shown that HPgV is not hepatotropic or only barely detectable in the liver of infected individuals (Pessoa *et al.*, 1998; Chivero *et al.*, 2014). The virus can persist for at least one month in culture in peripheral blood mononuclear cells (PBMCs) from infected individuals (Thézé *et al.*, 2015; Chivero and Stapleton, 2015). Moreover, in serum-derived from infected individuals, HPgV is capable of infecting PBMCs *in vitro* (Thézé *et al.*, 2015; Chivero and Stapleton,

2015). Several lines of evidence failed to identify an association between infection and acute or chronic hepatitis and suggested that it was characterized by marked lymphotropism (Chivero *et al.*, 2014). Earlier studies resulted in the detection of HPgV RNA in patients with non-A/non-E fulminant hepatitis, and consequently HPgV was implicated as its causative agent (Yoshiba *et al.*, 1994; Heringlake *et al.*, 1996; Saiz *et al.*, 1997; Sheng *et al.*, 1998; Anastassopoulou *et al.*, 2002). On the other hand, several other studies do not support the hypothesis that HPgV is capable of inducing fulminant hepatitis and suggest that the HPgV infection is coincidental and transmitted through transfusion of blood or blood products during the illness (Kanda *et al.*, 1996; Haydon *et al.*, 1997; Kapoor *et al.*, 2000; Kumar *et al.*, 2007). To date, HPgV has not been convincingly shown to cause any human disease (Kapoor *et al.*, 2015; Chivero and Stapleton, 2015). No clinical evidence of a liver disease potentially linked to HPgV infection was observed during a long follow-up of different categories of patients (Lefrère *et al.*, 1997). Linked to its capacity of replication in both T (CD4+ and CD8+) and B lymphocytes (Kapoor *et al.*, 2015) rather than in hepatocytes (Pessoa *et al.*, 1998), an association between HPgV viraemia and an increased risk of non-Hodgkin's lymphoma has been suggested (Chivero and Stapleton, 2015). Moreover, several studies have suggested a correlation of HPgV with other chronic diseases (e.g. aplastic anaemia, chronic renal failure) (Stapleton *et al.*, 2014; Chivero and Stapleton, 2015), but some of them were limited in sample size or were based on small numbers and most of them lacked controls. Interestingly, a beneficial effect of HPgV infection in human immunodeficiency virus (HIV) disease has been suggested and most studies and a meta-analysis found prolonged survival in HIV-infected individuals co-infected with HPgV compared with those without HPgV viraemia (Stapleton *et al.*, 2014). A study by Vahidnia and colleagues (Vahidnia *et al.*, 2012) on transfusion-related HPgV infection in HIV-infected individuals, confirmed a survival benefit in those subjects who acquire HPgV through blood transfusion. HPgV infection seems to have a protective role in HIV-infected individuals reducing immune activation and probably contributing to the detected improvement in HIV clinical outcomes (Chivero *et al.*, 2014; Schwarze-Zander *et al.*, 2012; Lanteri *et al.*, 2015). These findings are probably related to elective HPgV infection of naive T-cells that subsequently differentiate into effector or memory cells, or alternatively the infection of T-cells regardless of their differentiation state. Moreover, HPgV RNA was detected in T- and B-lymphocytes, NK-cells, and monocytes; it was present in all 14 study subjects' PBMCs, and in populations of T- and B-lymphocytes (Chivero *et al.*, 2014). In 2015, co-infection with HPgV in patients with Ebola virus disease appeared to be associated with improved survival (Lauck *et al.*, 2015).

5. Prevalence and distribution of HPgV

Worldwide, approximately 750 million people are actively infected (viraemic) and an estimated 0.75 to 1.5 billion people have evidence of prior HPgV infection (Chivero and Stapleton, 2015), but there is a large variation and difference in the spread of HPgV infection in different geographical regions. Actually, in the last three decades, many studies have examined the presence of HPgV/HGV/GBV-C in several countries, but most of them dealt with HPgV in adults or in selected groups of subjects or small communities in a vast territory. Generally, high HPgV prevalence is observed among subjects with the risk of parenteral exposures including those exposed to blood and blood products, those on haemodialysis, those with a history of intravenous drug use, and in subjects with chronic hepatitis C or HIV infection (Bhattarai and Stapleton, 2012). Taking into account the large variability reported in the evaluation of HPgV in the general population, further research could be justified to evaluate the real burden of the HPgV infection that, at the moment, appears significantly underestimated.

6. HPgV in blood donors

In the past, several studies from different countries investigated the molecular and/or serological HPgV prevalence in blood donor populations alone or compared with other selected clusters of subjects (e.g. healthy people, intravenous drug users, patients on haemodialysis, medical or surgical patients, subjects with chronic hepatitis or chronic diseases, etc.).

The article by Mohr and Stapleton in 2009 (Mohr and Stapleton, 2009) reported the HPgV/GBV-C prevalence rates in blood donors from various regions of the world. The prevalence among blood donors at the time of donation was summarised from the studies available at that time (50 studies, for a total of 11,391 blood donors). The authors stated that infection is common worldwide and is able to persist for decades. Although HPgV is not as efficient at establishing persistent infection as HCV, an estimated 25% of infections persist and in the other 75% viraemia clears within 2 years following infection in the majority of individuals infected by blood transfusion (Chivero and Stapleton, 2015). Moreover, the HPgV-RNA prevalence was higher in blood donors from developing countries (5%–18.9% in developing countries and 0.5%–5% in developed countries) (Mohr and Stapleton, 2009). In a study carried out among healthy voluntary blood donors in the Indian Armed Forces, Praharaj and colleagues showed that 13 out of 500 subjects (2.6%) tested where positive for HGV RNA (Praharaj *et al.*, 2005).

Based on the findings from the 71 selected studies published between 1996 and 2015 reported in Table 1, HPgV

showed seroprevalence of 1% (Ramezani *et al.*, 2008) to 31.9% (Sathar *et al.*, 1999) in healthy individuals and blood donors; this rate increases to 34% in HCV-infected deferred blood donors (Shev *et al.*, 1998). On the other hand, the viral RNA presence of HPgV ranges from between 0% (Arankalle *et al.*, 2001; Desai *et al.*, 2004; Kalkan *et al.*, 2005; Barusruk *et al.*, 2006; Ramezani *et al.*, 2008; Deshpande *et al.*, 2013) and 46.7% (Kar *et al.*, 2000) in healthy blood donors.

Following a more detailed analysis of HPgV seroprevalence reported in Table 1 for each continent and country, we noted that the serologic assay positivity ranges from 4.9% (Mastouri *et al.*, 2005) to 31.9% (Sathar *et al.*, 1999) and the molecular assay positivity ranges from 5% (Omar *et al.*, 2006) to 18.9% (Sathar *et al.*, 1999) in Africa; in the Americas, no data about seroprevalence is available (with the exception of the 7.3% reported in a Canadian study on identity unlinked and short-term deferred donors (Giulivi *et al.*, 2000)) and the molecular assay positivity ranges from 1.5% (Linnen *et al.*, 1996) to 10% (Lampe *et al.*, 1998); in Asia, the seroprevalence ranges from 1% (Ramezani *et al.*, 2008) to 11% (Xiao *et al.*, 2014) and the molecular assay positivity ranges from 0% (Arankalle *et al.*, 2001; Desai *et al.*, 2004; Kalkan *et al.*, 2005; Barusruk *et al.*, 2006; Ramezani *et al.*, 2008; Deshpande *et al.*, 2013) to 46.7% (Kar *et al.*, 2000); in European countries, the seroprevalence ranges from 9.5% (Mercier *et al.*, 1999) to 24.2% (Brojer *et al.*, 1999) and the molecular assay positivity ranges from 1% (Minton *et al.*, 1998) to 10% (Anastassopoulou *et al.*, 2000); the 10.8% (Moaven *et al.*, 1996) of seroprevalence rate was reported in healthy Australian blood donors and the molecular assay positivity ranges from 2.6% (Hyland *et al.*, 1998) to 4% (Moaven *et al.*, 1996) in the same population.

All in all, the data reported in Table 1 confirm the sharp contrast between different geographic areas (non-developed countries (endemic areas) vs. developed countries (non-endemic areas)). However, for most countries only one study on the prevalence of HPgV in blood donors was available. Furthermore, even when more than one study was carried out in the same country, they were concentrated in a limited period of time (usually in the late 1990s). For the above mentioned reason and for a general lack of data, it is very difficult to evaluate an infection rate trend in blood donors in the same country, except in a very few cases. A stable viral circulation was suggested in Polish (Brojer *et al.*, 1999; Grabarczyk *et al.*, 2006) and Taiwanese blood donors (Wang *et al.*, 1998; Yang *et al.*, 2006), while five studies showed an apparent decrease in the RNA positivity rate from 4% (Jain *et al.*, 1999; Kar *et al.*, 2000) to 0% (Arankalle *et al.*, 2001; Desai *et al.*, 2004; Deshpande *et al.*, 2013) over a period of 15 years in voluntary Indian blood donors. Strangely, a 5.8% HPgV seroprevalence reported in the Spanish general population in 2007 (López-Izquierdo *et al.*, 2007) is nearly three times less than that reported in a more selected population of blood donors in 1997 (Tacke *et al.*, 1997).

When both serologic and molecular assays have been performed, the antibodies to E2-proteins have been found more frequently than viral RNA among healthy blood donors; nevertheless, similar HPgV prevalence rates detected by serologic and molecular assay (4.9% vs. 5.3%, respectively) have been reported in the study performed by Mastouri and colleagues (Mastouri *et al.*, 2005) with no positive donors for both viral markers and an overall HPgV prevalence in Tunisian donors more than 10%.

In order to evaluate a relationship between HPgV infection and alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) activity in HGV RNA-positive donors compared to a control group of healthy donors, several studies were performed in the late 1990s. Previous studies had shown a higher HPgV prevalence rate in blood donors with elevated ALT levels in comparison to those with normal ALT (Moaven *et al.*, 1996; Björkman *et al.*, 1998), but these differences were not statistically significant. Moreover, more recent findings suggest that there was no significant difference in the activity of liver enzymes in HGV/HPgV RNA-positive donors compared to a control group of healthy donors (Hitzler *et al.*, 2004; Xiao *et al.*, 2014). Similar findings were found in patients with documented post-transfusion HPgV-related hepatitis in whom the plasma ALT peak and the peak viral titers may be discordant, suggesting that HPgV may not be responsible for the rise in ALT levels (Uygun *et al.*, 2000; Lyra *et al.*, 2005; Stapleton *et al.*, 2014), especially in individuals without risk factors for acquiring parenterally transmitted agents (Feucht *et al.*, 1997). Therefore, increased ALT/AST levels are not to be considered valid surrogate markers for the presence of HPgV.

In our analysis, a certain degree of difference emerges from the comparison between non-remunerated and remunerated blood donors in terms of HPgV infection rate suggesting that it may be lower among voluntary blood donors. In fact, HPgV-RNA was detected from 0% (Arankalle *et al.*, 2001; Desai *et al.*, 2004; Kalkan *et al.*, 2005; Barusruk *et al.*, 2006; Ramezani *et al.*, 2008; Deshpande *et al.*, 2013) to 24.6% (Odeh *et al.*, 2010) in voluntary non-remunerated donors and from 4.3% (Ren *et al.*, 1998) to 46.7% (Kar *et al.*, 2000) in paid blood donors (Table 1).

Our study confirms the distribution of HPgV worldwide and its not negligible presence in healthy individuals like blood donors. Therefore, some limitations should be considered: i) some studies have a small sample size of enrolled blood donors; ii) different serological or molecular assays were used; iii) variability in the demographic and clinical features of the population, differences in host susceptibility or virulence of different viral strains; iv) finally, most of the studies were performed in the 1990s and describe

Table 1. Prevalence of hepatitis G virus (HGV)/GB virus type C (GBV-C)/human pegivirus (HPgV) in different geographical areas (from 1996 to 2015)

Continent	Country	Prevalence		References
		Serologic assay (%)	Molecular assay (%)	
AFRICA	Burkina Faso	N.A.	7.4	Tao *et al.*, 2013
	Democratic Republic of the Congo	N.A.	12.7	Iles *et al.*, 2013
	Egypt	23.1 asymptomatic persons	N.A.	Darwish *et al.*, 1998
		N.A.	5	Omar *et al.*, 2006
		N.A.	12.2	El-Zayadi *et al.*, 1999
	South Africa	31.9	18.9	Sathar *et al.*, 1999
		N.A.	11.1	Casteling *et al.*, 1998
	Tunisia	4.9	5.3	Mastouri *et al.*, 2005
THE AMERICAS	Brazil	N.A.	9.7	Levi *et al.*, 2003
		N.A.	9	Bassit *et al.*, 1998
		N.A.	7.1	Oliveira *et al.*, 2002
		N.A.	10	Lampe *et al.*, 1998
		N.A.	8.6	Goubau *et al.*, 1999
	Canada	7.3 [identity unlinked (IU) and shortterm temporarily deferred (STTD)]	1.1 [identity unlinked (IU) and short-term temporarily deferred (STTD)]	Giulivi *et al.*, 2000
	Honduras	N.A.	2 healthy Honduran university students	Lara *et al.*, 1998
	USA	N.A.	1.5	Linnen *et al.*, 1996
ASIA	Bangladesh	N.A.	2.2	Showkath *et al.*, 2014
	China	N.A	2.57	Li *et al.*, 2002
		N.A.	15.8	Yan *et al.*, 2001
		N.A.	2	Wu *et al.*, 1997
		N.A.	4.3 paid donors	Ren *et al.*, 1998
		IgG 11 IgM 10.6	0.13	Xiao *et al.*, 2014
	India	N.A.	0	Desai *et al.*, 2004
		N.A.	0	Deshpande *et al.*, 2013
		N.A.	4	Jain *et al.*, 1999
		N.A.	16.3 paid plasma donors	Arankalle *et al.*, 2001
			0 voluntary blood donors	
		N.A.	46.7 commercial blood donors	Kar *et al.*, 2000
			4.0 voluntary donors	
	Iran	1	0	Ramezani *et al.*, 2008
		N.A.	1	Amini *et al.*, 2005
		8.6	N.A.	Rezvan *et al.*, 2007
	Japan	N.A.	7.4 blood donors with anti-HCV and HCV RNA	Yoshikawa, 1997
		N.A.	1.2 healthy volunteers	Noguchi *et al.*, 1997
		N.A.	0.5	Orito *et al.*, 1996
		2.5	1.3	Saitoh *et al.*, 2002

Table 1 (continued)

Continent	Country	Prevalence		References
		Serologic assay (%)	Molecular assay (%)	
ASIA	Jordan	N.A.	9.8	Odeh *et al.*, 2010
	Kuwait	N.A.	24.6	Odeh *et al.*, 2010
	Saudi Arabia	4.3	N.A.	Alhetheel *et al.*, 2014
		N.A.	1	Mitwalli *et al.*, 2000
		N.A.	2	Al-Ahdal *et al.*, 2000
	South Korea	N.A.	1.8	Jeon *et al.*, 2003
	Qatar	N.A.	13.7	AbuOdeh *et al.*, 2015
	Thailand	N.A.	0	Barusruk *et al.*, 2006
	Taiwan	N.A.	2.1	Wang *et al.*, 1998
		10.2	3.4	Yang *et al.*, 2006
	Turkey	N.A.	0	Kalkan *et al.*, 2005
	United Arab Emirates	N.A.	11.1	Abu Odeh *et al.*, 2005
	Vietnam	N.A.	7.4	Brown *et al.*, 1997
EUROPE	France	9.5	3.4	Mercier *et al.*, 1999
		14.5 estimated	2.59	Cantaloube *et al.*, 1999
	Germany	N.A.	1.9	Feucht *et al.*, 1997
		N.A.	1.34 total donors 2.18 urban donors 0.78 rural donors	Roth *et al.*, 1997
		N.A.	2	Stark *et al.*, 1996
		N.A.	1.6 blood donations	Hitzler *et al.*, 2004
	Greece	N.A.	10 healthy individuals	Anastassopoulou *et al.*, 2000
	Hungary	28 healthy individuals older than 60 years	8 healthy individuals	Takács *et al.*, 2002
	Iceland	13.2	3.8	Löve *et al.*, 1999
	Italy	N.A.	3.7	Romanò *et al.*, 2000
		12.6	N.A.	Villari *et al.*, 2001
		N.A.	1.5	Prati *et al.*, 1997
	Norway	10.5	2.5	Nordbø *et al.*, 2000
	Poland	24.2	3.2	Brojer *et al.*, 1999
		23.6	3.2	Grabarczyk *et al.*, 2006
	Spain	N.A.	3	Forns *et al.*, 1997
		16	N.A.	Tacke *et al.*, 1997
	Sweden	34 HCV infected deferred blood donors	22 HCV infected deferred blood donors	Shev *et al.*, 1998
		N.A.	3.3 all donors 1.6 normal ALT 4.1 raised ALT	Björkman *et al.*, 1998
		N.A.	3 healthy swedish volunteers	Lara *et al.*, 1998
	United Kingdom	N.A.	1	Minton *et al.*, 1998
		N.A.	2.25	Blair *et al.*, 1998

Table 1 (continued)

Continent	Country	Prevalence		References
		Serologic assay (%)	Molecular assay (%)	
OCEANIA	Australia	N.A.	4 normal ALT 5 raised ALT	Moaven *et al.*, 1996
		10.8	2.6	Hyland *et al.*, 1998
VARIOUS COUNTRIES		Austria 15.3 Germany 10.9 Moldova 13.6 Spain 12.9 South Africa 20.3 Brazil 19.5 Bhutan 3.9 Malaysia 6.3 Philippines 2.7	N.A.	Ross *et al.*, 1998

N.A. = not applicable; HCV = hepatitis C virus; IgG = immunoglobulin G; IgM = immunoglobulin M; ALT = alanine aminotransferase.

a scenario that has probably changed, especially in the last 10–15 years.

7. Discussion

Although the discovery of HPgV goes back about 20 years, several lines of evidence suggest that it is an ancient virus that is well-adapted to growth in the human host. The capacity of adaptation and evolution of HPgV in humans (common in RNA viruses) seems to be confirmed by the geographical distribution of HPgV genotypes (Sharp *et al.*, 2011). Moreover, the low pathogenicity, the absence of a causal association with human diseases, or the slower progression of the infection could suggest that HPgV is a human symbiont or commensal (Kapoor *et al.*, 2015) These findings, related to better survival outcomes in HIV-infected individuals led to HPgV being nicknamed "Good Boy Virus" (Bhattarai and Stapleton, 2012). Moreover, respect to the past, recent epidemiological data provided by several studies report a lower frequency of HPgV infection markers in haemophilia patients treated with virucidally activated substances rather than non-inactivated blood products (Yamada-Osaki *et al.*, 1998; Kreuz *et al.*, 2002; Grabarczyk *et al.*, 2006). In fact, although the presence of viral RNA in plasma pools and in intravenous immunoglobulins have been shown, currently produced plasma-derived medicinal products are subject to effective inactivation and/or removal steps for viruses such as HPgV (Zhang *et al.*, 2016).

On the other hand, as it appears HPgV anti-inflammatory effects are favourable in selected subjects; its effects on the host immune system function could contribute to the observed association between HPgV and non-Hodgkin's lymphoma by reducing immune surveillance mechanisms (Chivero and Stapleton, 2015). An enigmatic aspect, which still requires further clarification, is the mechanisms by which HPgV infects different blood cell types and persists in humans. A better comprehension of the mechanisms of HPgV persistence and clearance in humans should be subject of further research. Considering that human pegiviruses are phylogenetically a close relative of HCV, GBV-B has been used as a surrogate model for HCV infection to understand pathogenesis, immunology, and the HCV persistence in humans as well as it has been used for the improvement of future development of novel vaccines and immunotherapies (Manickam and Reeves, 2014).

8. Conclusions

Due to the lack of studies on pathogenicity of HPgV, its unclear association with known acute disease and the preventive measures already recommended in order to guarantee the safety of blood and blood products, the World Health Organization (WHO), the European Directorate for the Quality of Medicines & HealthCare (EDQM), and the US Food and Drug Administration (FDA) have not developed recommendations about the risk of transfusion transmissible HPgV infection. As consequence, currently no country has made a decision to implement HPgV screening programmes in blood donors; this would seem to be the right decision considering that further studies are necessary to establish the real HPgV influence on human health as well as on transfusion medicine. Furthermore, as there is no action

justified at the moment in terms of blood safety a system should be implemented by the competent authorities to monitor further developments in this field. A continuous surveillance of this type seems more reasonable if we take into account that it is very likely, given the rapid progress in viral detection methods, that many other such 'orphan' viruses will be identified, also taking into account the recent discovery of new blood-borne viruses (Kapoor *et al.*, 2015; Berg *et al.*, 2015).

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