ZKBS
Zentrale Kommission
für die Biologische Sicherheit

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Recommendation by the ZKBS on the risk assessment of hepatitis D viruses as donor or recipient organisms according to § 5 para. 1 GenTSV

General Information

Eight different hepatitis D viruses (HDV 1 to 8) are currently known. Alternatively, these viruses are named hepatitis delta viruses. Taxonomically the viruses are each assigned to a separate species (*Deltavirus cameroonense*, *D. carense*, *D. italiense*, *D. japanense*, *D. peruense*, *D. senegalense*, *D. taiwanense*, *D. togense*) within the genus *Deltavirus*. Together with the so-called HDV-like viruses they form the family *Kolmioviridae*.

HDV have a circular, single-stranded RNA genome of negative polarity with a length of approximately 1700 nucleotides. This RNA is present in the viral particle as a nucleoprotein complex with the delta antigen, the sole protein encoded by HDV.

HDV are defective viruses. Their infectivity depends on a simultaneous infection with the hepatitis B virus (HBV), because the HBV surface proteins (HBsAg) also serve as envelope proteins for HDV [1]. However, more recent *in vitro* and *in vivo* experiments have proven that also envelope proteins of additional viruses, which are in part not related to HBV, may enable the infection with HDV including the subsequent release of HDV particles. These alternative envelope proteins originate from Hepadnaviruses of animals, the hepatitis C virus, dengue virus, West Nile virus and the human metapneumovirus [2, 3]. A relevance of a complementation by these alternative helper viruses for actual clinical cases, however, is currently not shown.

Humans are the natural hosts of HDV. Aside from them, the chimpanzee (*Pan troglodytes*) and the northern tree shrew (*Tupaia belangeri sinensis*) are susceptible for a co-infection with HDV and HBV. In addition, the groundhog (*Marmota monax*) and the domestic duck *(Anas platyrhynchos domestica)*, amongst others, may be infected experimentally, if HDV are complemented by alternative envelope proteins [2]. In general, the replication of the viral genome by the cellular RNA polymerase II may occur in the nucleus of different cell types. The viral replication during a natural infection of humans, however, is restricted to hepatocytes due to the tropism of the HBsAg [1, 3].

Co-infections with HDV can be seen globally in individuals infected with HBV. The prevalence varies by region. The highest prevalences are seen in southern Europe, the Middle East, eastern Africa and Asia. The lowest prevelences are recorded in northern Europe, North America and South Africa [1]. HDV infections are very rare in Germany. In the year 2020 only 41 infections were registered in Germany. Overall it is estimated that globally approximately 12 million individuals are infected with HDV. This correspond to about 4.5 % of the chronically

with HBV infected persons [4]. Of the eight HDV only HDV 1 is globally distributed. HDV 2 and 4 are predominantly present in Asia, HDV 3 in South America and HDV 5 to 8 in Africa [1].

The course of the disease depends on which point in time the HDV infection coincides with HBV infection. Co-infection with HBV and HDV usually results in an acute, self-limiting infection. Chronic infection develops in about 2 % of co-infected patients. A superinfection occurs when chronic HBV carriers are infected with HDV. In 90% of the cases, this results in severe, acute hepatitis and chronic progression of the HDV infection. Superinfection is often associated with a fulminant form of hepatitis. Chronic HDV infection leads to liver cirrhosis within 5 to 10 years in 50 % - 70 % of the patients. The likelihood of developing liver cirrhosis in HDV infected persons is thus three times higher than in patients chronically infected with HBV alone. The question whether hepatocellular carcinoma occur more often in HDV infected patients is not resolved. Addressing this issue, studies have been published describing an HDV infection as promoting factor, while others do not confirm an increased likelihood upon co-infection as compared to chronic HBV infection alone [5, 6]. HDV 1 seems to possess the greatest pathogenic potential of the eight HDV. However, HDV 5 to 8 are currently not well studied [1].

Like HBV, HDV is transmitted horizontally (parenterally or through sexual contact) and vertically (perinatally). It is not transmitted by the aerogenic route, food or water [4].

Therapeutic options to treat HDV are still limited. Treatment with interferon alpha has shown low success rates. Better results were achieved by treatment with pegylated interferon alpha [1]. In July 2020 Bulevirtid received conditional market approval in the EU, being the first active substance to specifically treat chronic HDV infection. The substance is an entry inhibitor which specifically binds to the HBV/HDV receptor NTCP on the surface of hepatocytes. Bulevirtid may be administered alone or as part of a combination therapy with active substances targeting the underlying HBV infection. As part of a combination therapy with the nucleotide analogue Tenofovir Bulevirtid reached an efficacy of approximately 54 % (end point at least 99 % reduction of HDV RNA in the blood) after a treatment duration of 24 weeks [7, 8]. Antiviral therapies against HBV, e. g. with nucleotide or nucleoside analogues, are ineffective against HDV [1]. However, the vaccination against HBV also protects against a co-infection with HDV. Yet, if an HBV infection is already present, a subsequent vaccination against HBV will not provide protection against a superinfection with HDV [9].

According to the TRBA 462 “classification of viruses into risk groups” (last updated on November 10th 2020) HDV are classified into **risk group 2**. As a donor and recipient organism for genetic engineering operations HBV, upon which an HDV infection depends, is classified into **risk group 2** in accordance with § 5 para. 1 GenTSV in conjunction with Annex 1.

Recommendation

According to § 5 para. 1 GenTSV in conjunction with the criteria in Annex 1 GenTSV the hepatitis D viruses are assigned to **risk group 2** as donor and recipient organisms for genetic engineering operations.

Reasoning

An effective HBV vaccine is available for the prevention of an HDV infection. A targeted therapy of a chronic HBV infection with a moderately efficacious antiviral agent is possible.

With proper handling by trained personnel, the risk of infection in a genetic engineering facility is assessed as low due to the possible routes of transmission of the virus. The infectivity of HDV depends on a simultaneous infection with HBV. HDV is not transmitted via the aerogenic route, by food or water. One possible source of infection is through injury while handling contaminated instruments. This should be avoided by implementing additional precautionary measures. For these reasons, level 2 safety measures provide adequate protection against infection and safeguard the goods and interests listed in § 1 of the German Genetic Engineering Act (GenTG).

Additional Recommendation

The ZKBS recommends persons that are infected with HBV not to perform genetic engineering operations with HDV. Furthermore, the ZKBS recommends the vaccination against HBV and the periodic monitoring of the immune status to all persons conducting genetic engineering operations with HDV.

Literatur

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