Global Elimination of Chronic Viral Hepatitis

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Abstract

Globally, chronic viral hepatitis is caused in the majority of cases by the Hepatitis B Virus (HBV), its associated defective Hepatitis Delta Virus (HDV) and the Hepatitis C Virus (HCV). Their structure and genetic organization as well as their global burden are known in great detail and have been successfully translated into important clinical applications, such as their sensitive and specific diagnosis, therapy and prevention of the associated liver diseases, including cirrhosis and hepatocellular carcinoma. In 2015, worldwide about 260 million individuals were infected with HBV and about 70 million by HCV. These infections are a leading cause of death with an estimated 1.34 million deaths per year or nearly 4,000 per day, similar to other infectious diseases, including HIV/AIDS, malaria and tuberculosis. While it is now possible to prevent hepatitis B and hepatitis D by vaccination against HBV and to cure hepatitis C by novel therapies with direct acting antiviral agents, the World Health Organization (WHO) goals of elimination of these infections by 2030 still pose a major challenge to the medical community as well as to the health care authorities and require their commitment to coordinated global interventions.

Keywords: Hepatitis B; Hepatitis D; Hepatitis C; Liver cirrhosis; Liver failure; Hepatocellular carcinoma; Preventive measures; Vaccination; Antiviral therapy

Introduction

Based on the specific and sensitive detection of hepatitis B, D and C virus infections (Figure 1), their epidemiology and natural course as well as their global burden have been studied in great detail. At the same time therapeutic and preventive strategies have been developed that should contribute to a reduced prevalence of these infections and their eventual elimination [1].

HBV Infection

HBV infection is a serious global public health problem (Figure 2a and 2b) with about 260 million people chronically infected [2]. It accounts for 500’000-1.2 million deaths per year and is the 10th leading cause of death worldwide. The prevalence of HBV infection varies markedly in different geographic and in different population subgroups. The area with the highest hepatitis B surface antigen (HBsAg) prevalence of >8% is Western sub-Saharan Africa, followed by Eastern sub-Saharan Africa, Central Asia, Southeast Asia, China and Oceania with a high intermediate prevalence of 5% to 7%, Latin America, Eastern Europe, North Africa, the Middle East, Turkey, Afghanistan, Pakistan, India and Australia with a low intermediate prevalence of 2% to 4% and the US and Canada, Central America, Brazil and Western Europe with a low prevalence of <2% [3]. From 1990 to 2005 the prevalence of chronic HBV infection decreased in most regions. This was most evident for Central sub-Saharan Africa, Tropical and Central Latin America, Southeast Asia and Central Europe. Despite the decreasing prevalence, the absolute number of HBsAg-positive individuals increased from 223 million in 1990 to 240 million in 2005. The decline of HBV infection prevalence may, at least in part, be related to expanded immunization, suggested by the strongest decline found in South East Asian children [3,4]. In the US, the HBsAg or anti-HBc prevalence in adults changed little during the period of 1999-2005 while it significantly decreased in children, reflecting the impact of global and domestic vaccination [5].

In the US, acute HBV infection has declined by 82% from 8.5 cases per 100,000 population in 1990 to 1.5 cases per 100,000 population in 2007, especially in children and adolescents [6,7]. Sexual exposure and injection drug are considered the major risk factors.

HDV Infection

HDV infection is traditionally endemic in central Africa, the Amazon Basin, Eastern and Mediterranean Europe, the Middle East and parts of Asia. HDV is a defective RNA virus and occurs only in association with HBV. Data regarding the global burden of HDV infection are somewhat
limited, however [8]. There are 8 HDV genotypes; their geographic distribution and the worldwide prevalence of HDV infection are well established [9]. Longitudinal studies have shown a decrease in HDV prevalence in some endemic regions, such as Italy where in HDV infected individuals the prevalence of HDV infection has decreased from about 25% in 1983 to 8% in 1997 [10]. Similar trends were observed in Spain, Turkey and Taiwan, for example. On the other hand, while epidemiological studies showed that HDV prevalence in HBV infected individuals remains in general <10% it is as high as 70% in some developing countries/areas such as Nigeria, Gabon, Iran, Pakistan, India, Tajikistan and Mongolia as well as the western Brazilian Amazon [9]. Further, in northern Europe and the US HDV infection still is a health care problem. While HDV prevalence is stable in France, it increased in London/England from about 3% in the 1980s to about 9% in 2005 [11]. Also in Germany, after a decrease of anti-HDV prevalence from about 19% in 1992 to about 7% in 1997, since 1999 an increase to about 14% has been documented [12]. This increase is in part caused by migrants from regions with a high HDV prevalence or by still occurring clustered outbreaks, e.g., in Greenland [13] or Mongolia [14].

HCV Infection

HCV infection is endemic worldwide with about 71 million infected people [15]. It shows a significant geographic variability with the highest prevalence rates, based on anti-HCV positivity, in North Africa, the Middle East as well as Central and East Asia (>3.5%). Intermediate prevalences (1.5% to 3.5%) are found in Central and Southern Latin America, the Caribbean, Central, Eastern and Western Europe, sub-Saharan Africa, South and Southeast Asia as well as Australia. A low prevalence of HCV infection (<1.5%) has been documented in North America, Tropical Latin America and the Asia Pacific region [16].

Currently, the published data are inadequate to describe the true disease burden. Nevertheless, it appears that HCV infection is the most common form of viral hepatitis in the European Union. The HCV-related mortality in the US has significantly increased between 1999 and 2007 from about 3 to about 5 per 100,000 population with major risk factors being chronic liver disease, coinfection with HBV or HIV as well as alcohol-related conditions [17].

Global Burden of Chronic Viral Hepatitis Associated Liver Diseases

Due to chronic hepatitis, HBV, HDV and HCV infections are the cause of significant morbidity and mortality, depending on the global, regional and national prevalences of these infections and the incidences of their associated liver diseases. In a major concerted effort, the Global Disease Burden (GBD) was studied in a systematic analysis of global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010 [18] as well as of Disability-Adjusted Life Years (DALYs) in patients with 291 diseases and injuries in 21 geographic regions in 1990, 2005 and 2010 [19]. In these studies deaths from hepatitis B and C and the associated liver cirrhosis and HCC were considered. More recently, the Global Burden of Disease Study 2013 presented its findings on individuals with disability from 301 acute and chronic diseases and injuries in 188 countries between 1990 and 2013, including hepatitis B and C as well as the associated liver cirrhosis and HCC [20].

The global and regional mortality from hepatitis B and C as well as from HBV- and HCV-related liver cirrhosis and HCC showed a significant overall increase between 1990 and 2010 [18]. During the same time, the deaths from hepatitis B- or C-related liver cirrhosis decreased while deaths from HCCs were stable.

The study of Murray et al. [19] analyzed the GBD based on the DALYs. The data show that GBD shifted away from communicable to non-communicable diseases and from premature death to years lived with disability, except for sub-Saharan Africa where communicable, maternal, neonatal and nutritional disorders remain the major causes of diseases. While DALYs due to HBV- and HCV-associated liver cirrhosis remained constant between 1990 and 2010, there was an increase in HCC-related DALYs.

The GBD study 2013 [20] showed no major change of the prevalence of hepatitis B and C infection, respectively, between 1990 and 2013. By comparison, there was a significant increase of the incidence of HBV- or HCV-related liver cirrhosis and HCCs (Table 1). The dramatic increase of HCV-associated HCCs is likely due to the lack of efficient therapeutic strategies for patients with advanced liver fibrosis/cirrhosis in the era of interferon-based treatment regimens. With the availability of the novel Direct Acting Antiviral Agents (DAAs), it is to be expected that the incidence of HCV-associated HCCs will be effectively reduced.

Chronic HBV and HCV infection and their associated liver diseases, i.e., liver cirrhosis and HCCs [21], are responsible for the tremendous DALY rate worldwide, especially in Asia and to lesser degree in Europe (Figure 2) and for more than 1 million deaths worldwide each year (Figure 3) [22]. In fact, by 2040, the deaths from chronic hepatitis B and C are expected to exceed the combined mortality associated with HIV infection, tuberculosis and malaria [23].

Global Elimination of Chronic Viral Hepatitis B and C

While it is now possible to prevent hepatitis B and to cure hepatitis C the WHO goals are for HBV infection a decrease from

<table>
<thead>
<tr>
<th>Liver Diseases</th>
<th>2013 Prevalent Cases (x 1,000)</th>
<th>Change 1990-2013 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>331'037</td>
<td>-6</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>147'826</td>
<td>+1</td>
</tr>
<tr>
<td>HBV liver cirrhosis</td>
<td>869</td>
<td>+22</td>
</tr>
<tr>
<td>HCV liver cirrhosis</td>
<td>885</td>
<td>+61</td>
</tr>
<tr>
<td>Alcohol liver cirrhosis</td>
<td>802</td>
<td>+10</td>
</tr>
<tr>
<td>HBV HCC</td>
<td>451</td>
<td>+91</td>
</tr>
<tr>
<td>HCV HCC</td>
<td>512</td>
<td>+368</td>
</tr>
<tr>
<td>Alcohol HCC</td>
<td>197</td>
<td>+10</td>
</tr>
</tbody>
</table>
4.7 million new cases and 884,000 deaths in 2015 to 470,000 new cases and 309,000 deaths in 2030 and for HCV infection a decrease from 1.75 million new cases and 400,000 deaths in 2015 to 175,000 new cases and 140,000 deaths in 2030 and (Global Hepatitis Report. Geneva: World Health Organization, 2017) [1]. Viral elimination is defined as a 90% reduction of new infections and a 65% reduction of infection-associated deaths related to a 2015 baseline. Modeling studies for HBV and HCV infection, respectively, suggest that these goals can be achieved by 2030 [24,25].

Globally there are 20 heavily burdened countries that account for more than 75% of patients with viral hepatitis B and C, respectively. Key issues are affordable high-quality diagnostics and measures to improve access to vaccination and antiviral treatment as well as efforts to tackle stigma and discrimination. Indeed, progress has been made already in many countries throughout the world, demonstrating that sustained and coordinated efforts can be successful in achieving the WHO elimination goals by 2030 [1,26].

**Elimination of HBV/HDV and HCV infection: general measures**

Apart from testing and treatment of HBV- and HCV-infected individuals, to achieve these goals for HBV infection is the universal
realization of newborn immunization to prevent perinatal HBV transmission and for HCV infection the antiviral treatment of chronically infected individuals. For both infections, the safety of blood and blood products as well as the implementation of infection control programs are of paramount importance [26,27]. These include elimination of unsafe injection practices by avoiding reuse of unsterilized syringes or needles as the leading source of HCV infection [25,28]. Another important aspect is the better access to diagnostics, including non-hospital settings, vaccination and antiviral therapies.

**Vaccination: Key to elimination of HBV and HDV infection**

Therapeutic strategies for chronic hepatitis B include Pegylated Interferon (PegIFN) α-2a or 2b for 48 weeks or long-term oral treatment with a nucleos(t)ide analog, such as adefovir, entecavir, telaprevir, boceprevir, asunaprevir, faldaprevir, NSSA inhibitors (e.g., daclatasvir, ledipasvir), nucleosidic NS5B polymerase inhibitors (e.g., sofosbuvir, dasabuvir, deleobuvir, filibuvir, setrobuvir, tegobuvir). The antiviral efficacy of most DAAs is genotype-restricted while some are effective against all HCV genotypes (pangenotypic DAAs), e.g., Epclusa®, Vosevi®, Maviret®) direct acting antiviral agents.

While there are no prospects for a vaccine against HCV in the near future, after decades of IFN-based therapeutic strategies that were of limited efficacy and were associated with significant side effects (Figure 4), the availability of Direct Acting Antiviral Agents (DAAs) has revolutionized the therapy of chronic hepatitis C of any genotype with HCV elimination rates approaching 95% to 100% after on average a 12-week treatment course [29-31]. The DAAs (Figure 5) include protease inhibitors (e.g., simprevir, telaprevir, boceprevir, asunaprevir, faldaprevir), NSSA inhibitors (e.g., daclatasvir, ledipasvir), nucleosidic NS5B polymerase inhibitors (e.g., sofosbuvir, dasabuvir, deleobuvir, filibuvir, setrobuvir, tegobuvir). The antiviral efficacy of most DAAs is genotype-restricted while some are effective against all HCV genotypes (pangenotypic DAAs), e.g., Epclusa®, Vosevi®, Maviret® (Figure 6). Apart from their high efficacy in terms of reducing morbidity and mortality from liver cirrhosis and HCCs [29-31], the DAAs fortunately have an excellent safety profile and a low rate of side effects [26,27].

Affordability of DAAs has been documented as a key barrier to its widespread use in the richest and poorest health economies. Their cost is in some Western countries enormous and may limit their use in less privileged patients who potentially may benefit from these agents. A 12-week course with pangenotypic or genotype-restricted DAAs amounts to between 26,000 and 60,000 US in many Western countries that pose a significant financial problem to health care providers. These high cost are expected to significantly decrease in the near future. By comparison, the cost for a 12-week treatment in Egypt and India for example, is already now <105US$ [1]. Most importantly, in several countries with a high prevalence of HCV infection and/or low-income, e.g., in Egypt and other countries, DAAs are provided for free in the context of governmental treatment programs. However, low prices still can be a serious impediment because there may be no global donors subsidizing HCV treatment while other infections that WHO targeted for elimination by 2030 are being subsidized [26].

**Summary and Perspectives**

Overall, the worldwide prevalence of hepatitis B and C infection
is slowly decreasing. The coming years are expected to increase the detection rate and to improve our ability to prevent and to effectively treat viral hepatitis B and C, resulting in the control of these global infections by 2030 and the elimination of their associated morbidities and mortalities.

Next generation sequencing and bioinformatics hold the potential of human genomics for ‘precision medicine’. Pathogen genomics is being delivered for bacterial Foodborne illnesses, tuberculosis, parasitic diseases, the selection of seasonal influenza vaccine candidate strains, antimicrobial resistance and others. While many challenges need to be overcome, genomic data are increasingly translated into public health action [32].

References