Viral Hepatitis Prevention Board

New hepatitis B treatments

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Objectives

To inform public health policy makers on what can be expected on hepatitis B treatment in the near future and evaluate their preparedness, by aiming to:

- give an overview of the various different new approaches and experimental treatment compounds being investigated, some of which are in the earliest stages of clinical trials;
- look at the public health needs to implement hepatitis B treatment protocols in European countries and the impact they may have on WHO's hepatitis elimination goals;
- explore the synergies with, competition and lessons learnt from hepatitis C treatment, all within a public health framework; and
- examine how hepatitis B treatment articulates with hepatitis B vaccination programmes.

Context

- Recently there has been much activity on hepatitis generally – summits, conferences, meetings, programmes and projects (ACHIEVE, INTEGRATE), and advocacy (e.g. World Hepatitis Day, hepatitis awareness months, and hepatitis testing days), and there is a forthcoming HBV Cure workshop (Paris, April 2018)
- Even so, many millions of people with chronic hepatitis B are still undiagnosed and untreated: one estimate shows that about 9% of about 257 million people living with HBV have been diagnosed and only about 1% (1.7 million) are being adequately treated; chronic HBV infection is one of the top 20 causes of mortality worldwide; hepatocellular carcinoma is the third leading cause of cancer death worldwide. In the WHO European Region, an estimated 15 million people are chronically infected with HBV, and in the European Union and European Economic Area about 5 million chronically HBV infected patients (0.9% prevalence), with about 25,000 newly diagnosed cases in 2015
- WHO's Global health sector strategy on viral hepatitis set the target of elimination of viral hepatitis as a public health threat by 2030; its strategic goals: prevent new infections, especially mother-to-child transmission of HBV, and clear HBV in chronic infections

Context (continued)

- HBV has a complex life cycle
- No *virological* ("sterilizing") cure is yet available for HBV – less than 5% of infected people are thought to clear the virus completely on current treatments; only *functional* cures are currently attainable (in which stable covalently closed circular (ccc) DNA and integrated HBV DNA remain), and life-long treatment is generally necessary
- Current treatment choice relies on six approved nucleos(t)ide analogues (NAs), three of which have high barriers to resistance; pegylated interferon may be considered for mild to moderate disease; combination therapies do not add much advantage
- Barriers to eradicating HBV are defective immune responses (T and B cells) and an inefficient innate immune system, integration of HBV DNA, and the formation of a reservoir of cccDNA with a long half-life in hepatocyte nuclei and which is not eliminated by current therapies (NAs and interferon); only a few copies of cccDNA can lead to full-blown infection

Context (continued)

- Good progress is being recorded towards vaccination coverage targets of the WHO's Global health sector strategy on viral hepatitis
- However, much better progress is needed to reach the targets for the prevention of mother-to-child transmission of HBV (50% timely birth dose vaccine by 2020 and 90% by 2030, from a baseline of 39% in 2015)
- Even though vaccination coverage rates in some countries may be high (e.g. 97% in Taiwan) infected subjects are still being seen
- Need to screen pregnant women to identify whom to treat
- Primary prevention is effective for pregnant women: namely, NA treatment in third trimester in women with a high viral load, timely birth vaccination, and administration of HBIg - but questions were raised about timing of treatment in pregnancy

Treatment and biomarkers

- There have been major advances over 10 years, from interferon to third-generation NAs with high barriers to resistance: better tolerated, ease of administration, cheap, effective, and studies show a reduction in risk of HCC by 50%
- NAs suppress viral replication but do not clear HBV; flares following cessation of treatment may stimulate reactivation of immune responses
- EASL's update in 2017 of its 2012 Clinical Practice Guidelines for the management of chronic HBV infection has been welcomed; it provides recommendations and advice for physicians
- The updated guidelines also introduced a new nomenclature for chronic HBV infection, dividing it into two different types based on the presence or absence of HBeAg and two different stages distinguishing between chronic infection and chronic disease
- The current end-point for treatment is long-term suppression of viral replication; HBV DNA as a marker of viral replication is important but not sufficient
- Other candidate markers are needed – e.g. quantitatively measured HBsAg, core-related antigen, HBV RNA – as well as correlates of infection and cure

Treatment and biomarker approaches

- A broad portfolio of new anti-viral compounds and various approaches was described
- There are two main classes of targets for new therapies: (1) antivirals and (2) immune restoration
- There are many potential targets in HBV life cycle, with different potential modes of action, including for antivirals:
  - inhibition of viral entry and replication, capsid assembly, and secretion
  - interference with cccDNA formation and with RNA

  and for immune restoration:
  - development of immunomodulatory approaches;
  - check-point inhibitors and toll-like receptors (TLR) agonists; and
  - therapeutic vaccines
- The conclusion is that there is a long way to go.

Treatment and biomarker approaches (continued)

- New drugs and treatments will need new diagnostic biomarkers
- HBV DNA, HBeAg and HBsAg will remain the most important diagnostic markers, but consideration may need to be given to ratios of large, middle and small HBs proteins (which are distinct markers for specific phases of infection) and to the potential value of HBV RNA and HBcrAg (core-related antigen)
- An issue surrounds distinguishing between HBsAg produced from integrated HBV DNA and that from episomal HBV cccDNA
- Another issue raised was when to start treatment in HBV-infected pregnant women; guidance in Germany is to start at 32 weeks of gestation but commencement in the first treatment (as in Italy) is more generally advised – there is a dichotomy between public health and clinical needs

Case finding and access to care

- There was agreement that hepatitis B is an invisible disease in invisible populations across Europe, and great efforts are needed to raise awareness among policy-makers, general practitioners and other health professionals (including obstetricians and gynaecologists), patients, specific communities and the general public, and to increase access to prevention and treatment.
- Although HBV prevalence rates are low in the general populations in most European countries, they are higher in some populations at risk such as refugees, migrants and other hard-to-reach groups such as people who inject drugs, in various countries in Europe – examples were given for Germany, Belgium and the UK
- The epidemiological situation varies across Europe, with some countries having large pockets of infected subjects in migrant populations and others having almost none; national plans will have to reflect domestic circumstances and epidemiology
- Widespread ignorance and misperceptions about hepatitis B (including the disease itself, screening and diagnosis, and treatment) need to be corrected, not just among hard-to-reach communities but also among clinicians (including obstetricians and gynaecologists), general practitioners, community leaders, the general public and policy makers; stigmatization and discrimination still need to be countered

Case finding and access to care (continued)

- In terms of access to prevention, care and treatment, language barriers were common and recognized, and the value of language support (from interpretation to translated materials) was underlined
- One study in the UK showed the value and the cost-effectiveness of case-finding interventions in migrants from countries with high or intermediate HBV prevalence rates (confirming a similar study in the Netherlands), with good response rates and onward referral to care
- There was recognition of political sensitivities about targeting and approaching migrants and other such communities, but the public health need and value were accepted; there was agreement about the applicability of broadening the approach
- Another, ongoing study in the UK is looking at the cost-effectiveness of routine screening for HBV and HCV in patients admitted to accident & emergency departments in the country; again the approach is well-received – results are due in autumn 2018

Recommendations from group discussion

- Besides prospective new treatments for hepatitis B in order to achieve WHO's elimination goals, there is a need for better screening and testing in order to identify infected subjects and to ensure that they enter the cascade of care in line with WHO's strategy, as well as a need to improve coverage and timeliness of vaccination
- Many European countries do not have national hepatitis plans; their governments should urgently draft national strategies and action plans (including budgetary aspects)
- Those European countries that do have national hepatitis plans should review them, taking into account existing gaps in their immunization programmes, diagnostic approaches, available treatments and the potential for new antiviral drugs and treatments
- Policy-makers need more evidence-based material in order to incorporate future new hepatitis B therapies into the treatment and care management policies