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Highlights from the post-graduate course entitled "Elimination of viral hepatitis: are we ready?" held in Ljubljana, Slovenia, September 2019.

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Background

"Elimination of viral hepatitis: are we ready?" was the timely title of a post-graduate educational course sponsored by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) held in Ljubljana, Slovenia. The faculty included most key opinion leaders in the field with talks focusing mostly on hepatitis C and B, but extending to relatively neglected viruses such as HDV and HEV. Professors Mojca Matičič (SLO) and Mario Mondelli (I) were among the organizers of the course.

Q. Prof Mondelli, do you think that the target set by WHO for 2030 can realistically be met?

Viral Hepatitis is a major public health problem in need of an urgent response. This scenario prompted WHO to develop a strategic set of recommendations in an effort to achieve elimination in most countries by 2030. These include: i) achieving 90% coverage of three-dose HBV vaccination preventing 90% of mother to child transmission; ii) 100% screened blood donations and 90% implementation of reuse-prevention devices; iii) harm reduction interventions in at risk populations such as PWID; iv) high frequency of diagnosis and linkage to care for hepatitis C, to ensure a 90% reduction of incidence and 65% drop in mortality rate. These targets are indeed rather ambitious and probably achievable in a minority of virtuous countries that have implemented universal HBV vaccination and access to the highly efficacious direct acting antivirals for HCV cure, as well as "one health" [1] approaches to limit the risk of HAV and HEV infections. However, the 2020 interim milestones will not be met in most cases.

Q. How are we standing in terms of vaccine coverage?

Vaccine prophylaxis is available for hepatitis B and hepatitis A, but only HBV vaccination is recommended globally. We have witnessed a huge leap forward in HBV vaccine coverage globally from a mere 1% in 1990 to 81% in 2013 (WHO data on file). Still, there are a number of challenges. First, we should guarantee maximal coverage in neonates and infants, and guarantee timely birth dose administration, as per WHO recommendations. We must understand why some individuals are non-responders, particularly the elderly and immunosuppressed, and develop more immunogenic vaccines through translational research. In addition, we must understand what are the correlates of long-term protection and integrate hepatitis B vaccination in a control and elimination plan with therapy.

With respect to hepatitis A, implementation of global vaccination has met with perplexities over cost-effectiveness, since mortality in the general population is extremely low and HAV is invariably cleared after infection. Nonetheless countries like Israel are on the way to hepatitis A elimination thanks to a successful vaccination program in toddlers,[2] and Argentina showed that a single shot vaccination significantly reduced the incidence of infection. Another immunization strategy is to implement targeted immunization in high-risk individuals, including travelers from non-endemic to HAV endemic countries, food handlers, patients with chronic liver disease, immunosuppressed patients, family members and close contacts of individuals with acute hepatitis A, day care center staff and, last but not least, MSM, in whom a large epidemic of hepatitis A is still ongoing. The problem is further compounded by the limited availability of vaccine, with some European countries facing shortages. Passive immunization with normal human immunoglobulin is not indicated for protection since improved hygienic conditions reduced children exposure to HAV which is responsible for a large cohort of HAV-susceptible adults at present.[3]

Q. Are you confident that hepatitis C will eventually be eliminated in most countries?

The different national scenarios influence the outcomes of hepatitis C elimination efforts. Success will quite likely be achieved in small countries with clearly identifiable risk cohorts that have an elimination plan up and running as a result of politically-supported advocacy and screening programs. Implementation of the latter and linkage to care, as well as access to generic medicines are also key parameters to success. Increasing awareness, point-of-care testing, harm reduction policies, simplified treatment schedules and monitoring are additional important measures for hepatitis C elimination. There are already quite a few countries that are very close to elimination. Iceland is a remarkable example of an efficient elimination plan applied to a small country with a small HCV prevalence rate and a clearly identifiable risk cohort, i.e. PWID, MSM and incarcerated individuals. Of note, Iceland has witnessed a dramatic reduction in community viral load and HCV incidence in only 2 years. Indeed, between 2015 and 2017, there was a 55% reduction in incidence of total new HCV infections and a 73% reduction in hepatitis C viremic PWID.[4] This is a tremendously successful real-world example of treatment as prevention. Unfortunately, this will not work in most countries with a large number of HCV carriers and no specific risk cohort. One notable exception is Egypt that has aggressively pursued a capillary screening and linkage to care policy,[5] reaching HCV cure in about one half of the HCV-infected population estimated to total over 5 million.[6]

Q. Treatment as prevention: Will this be sufficient to eliminate hepatitis C ?

To be really effective, an infectious disease elimination program should include a vaccine that would ideally generate sterilizing immunity. With respect to HCV, early studies performed by Chiron Co. in chimpanzees clearly showed that vaccinated animals were by no means protected from infection, but they did not develop chronic infection compared to unvaccinated controls (Chiron, data on file). Researchers who were hoping for success of a hepatitis C vaccine, a chimpanzee-derived adenovirus vector AdCh3NSmut1 –MVANSMut carrying part of the HCV non-structural region to stimulate a hepatitis C specific T-cell response, were very disappointed when the phase I/II results were announced earlier this summer. The vaccine was tested in a double-blind, randomized, placebo-controlled clinical trial involving at-risk uninfected PWID volunteers followed for 18 months.

Of these, 275 were given two doses of the vaccine, and 273 received two placebo doses. In each group, 14 participants developed chronic hepatitis C infection. Sadly, the vaccine made no difference. However, a new vaccine developed by Michael Houghton's group built upon earlier data[7] is currently being developed. The early prototype has been improved by better purifying the viral envelope antigen and by adding more conserved antigens which the virus will have a hard time evading from cellular immune responses. Finally, the new prototype contains a powerful adjuvant to power-up the immune response, boosting neutralizing antibody and cellular immune response to HCV. Let us hope that it will work. There is little doubt that hepatitis C elimination will not be completed in most countries without a vaccine. To this end, it may be worth citing Mike Houghton's words in a recent interview "If you want to control a global epidemic, you can't rely on diagnostics. You can't rely on antivirals. You need a vaccine. The history of infectious diseases has taught us that" (Medscape Medical News © 2019 Hepatitis C Vaccine Disappoints, Another in the Works - Medscape - Sep 09, 2019).

Q. What about hepatitis E? I understand that the received wisdom that describes it as a disease of little relevance in developed countries does not apply anymore.

Hepatitis E is a potentially life-threatening disease, with a mortality rate of about 3%. This is largely due to a disturbingly high (up to 25%) mortality in pregnant women in developing countries. The reasons for this are unclear. Intriguingly, HEV is the commonest cause of acute viral hepatitis in many European countries, so much so some countries (Ireland, UK, Germany, The Netherlands and Switzerland) have implemented universal donor screening. It is estimated that ≥2 million locally acquired HEV infections occur in Europe per year, mostly zoonotic in origin, with pigs as the primary host. Infections are locally acquired and travel history to exotic countries is irrelevant. HEV infections in the West are caused by genotype 3, affecting predominantly >60 year-old men, and usually responsible for self-limiting hepatitis. Deaths occur in patients with pre-existing chronic liver disease, whereas no deaths are described in pregnancy in developed countries. Genotype 3 infections are also responsible for chronic HEV infections in immunosuppressed patients. Luckily, HEV is sensitive to ribavirin; however, time of treatment and dosing are still undefined.[8] Potentially severe extra-hepatic complications include neurologic injury, i.e. Guillain–Barré syndrome, neuralgic amyotrophy, meningoencephalitis, myasthenia gravis, Bells Palsy, etc. To provide an idea of the HEV burden of disease in some geographical areas, between 2012 and 2017 there were 511 laboratory-confirmed hepatitis E cases in Scotland: 7% developed acute or acute-on-chronic liver failure, with 2 requiring emergency liver graft, 7% had neurologic complications and 50% of these developed long-term or permanent sequelae, 9% had (usually self-limiting) acute kidney injury, with a total mortality rate of 3.3% (H. Dalton, personal communication). The aforementioned calls for prompt attention to hepatitis E as a public health threat and a plea to develop a global vaccination program. Curiously, a highly effective vaccine has indeed been developed in the P.R. of China. The vaccine is based on a genotype 1 sequence but it is apparently protective also against genotype 3 HEV. Unfortunately, hepatitis E is still regarded as a neglected disease and a vaccine not worthy of industrial development.

Q. Finally, hepatitis delta: What is the magnitude of the problem and what is new in therapeutics?

HDV is a peculiar virus requiring the HBV envelope protein as coat of the fully developed virion. HDV is a single-stranded RNA virus similar to plant viroids/virusoids that is responsible for potentially severe chronic liver disease in HBV carriers (reviewed in[9]). The epidemiology of HDV does not necessarily follow that of HBV, e.g. areas that are highly endemic for HBV such as the P. R. of China have a low frequency of HDV infection. Hotspots are the Amazonas, some areas in Central Africa, Mongolia, Pakistan, Romania, and Turkey. The only licensed therapy is PEG-interferon alpha which has low sustained virological response and high relapse rates. Several new treatment approaches are being developed, the most interesting of which target the binding of HBsAg to the HBV receptor Na^+-taurocholate co-transporting polypeptide (NTCP), i.e. Myrcludex B, a synthetic N-acylated pre-S1 HBV envelope protein that can also dock to NTCP, blocking the virus entry mechanism. Myrcludex B has been shown to be a promising treatment for HDV by competing for binding to NTCP and resulting in a significant suppression of HDV replication in vivo. Inhibition of HDV replication may also be obtained by depletion of circulating HBsAg by administration of nucleic acid polymers.[10] Other approaches using prenylation inhibitors blocking virion assembly in vitro and in vivo have not met with major success.[11] Thus, the evidence so far suggests that preventing HBV envelope binding to NTCP or depleting HBV envelope polypeptides from the circulation are currently the most promising approaches in this setting. Combination treatments involving these molecules could be the answer to tackle this complex virus.

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