

Pathway to Hepatitis Elimination and Control

Seng Gee Lim,^{1,2}*MBBS, FRACP, FRCP*, Guan Huei Lee,^{1,2}*MBBS, MRCP, PhD*

It has been 8 years since the World Health Assembly passed a resolution that viral hepatitis is indeed a major public health threat. Already, the World Health Organization (WHO) has set ambitious targets for 2030 to reduce new viral infections by 90%, diagnose 90% of infections and have 80% of eligible patients treated. For hepatitis C (HCV), as highly effective therapies to cure almost 100% of cases with 3 months of oral therapy have been achieved, the strategy has shifted to public health, resource allocation and utilisation, and policy and implementation.

In Singapore, formulation of a national strategy is slowly taking place, with a possible micro-elimination approach. However, the infrastructure to identify and deliver therapy needs to be put in place. For hepatitis B (HBV), while excellent agents to control the disease are available, the goal of functional cure—defined as loss of hepatitis B surface antigen (HBsAg) 6 months after stopping therapy—has yet to be achieved in significant numbers of patients. Efforts to address this requires understanding the pathogenesis of chronic hepatitis B (CHB) clearance—a key goal of the ‘Hepatitis B Translational Clinical Grant’—as well as identification of new targets and agents that are likely to lead to a functional cure. Thirty-six agents encompassing 10 classes of compounds are in preclinical and clinical testing, making this likely in the near future.

It is timely to see how far we have come, and how far we still have to go to address the spectre of viral hepatitis. It is a leading cause of mortality in the Asia Pacific and is estimated to cause over 1 million deaths per year according to the Global Health Survey¹ (the vast majority due to chronic CHB and the remainder due to chronic hepatitis C [CHC]). In Singapore, the impact of viral hepatitis is relatively smaller, in large part due to the foresight of early implementation of the HBV vaccination programme,² a strategy that has led to a considerable reduction in CHB. The overall prevalence of CHB was reduced to 3.6%² in 2010, from 5% to 6% in the 1980s.³ However, HBV-related liver disease is still a substantial problem.⁴ Hence, there should be no room for complacency as the patients who develop

these complications are generally above 50 years of age, while the oldest vaccinees are in their mid-20s. Does this mean that we have to wait another 2 to 3 decades before the benefits of vaccination are realised? Certainly not since much can be done to address the issue. First, however, we should take a page from the war against CHC to determine the strategic direction for CHB. HCV differs from HBV in that the virus is entirely cytoplasmic in its replication cycle,⁵ and has no nuclear lifecycle,⁶ nor does it integrate into the host genome.⁷ In the decade of 2000 to 2010, the standard of care was interferon therapy, with the addition of ribavirin and pegylation of interferon; treatment of HCV could be optimised no further with SVR rates of 40% to 70% at the cost of toxicity of antiviral therapy.⁸ Nonetheless, these SVR rates comprise a cure of HCV and are rates well above that achieved for HBV with existing therapies today. The eradication of HCV at that time was not even a consideration and many patients who were treatment failures or ineligible for therapy had no possibility of cure and either perished from advanced liver disease or liver cancer, with only a few fortunate patients being transplanted. With the advent of continually improving oral direct acting antiviral (DAA) therapy, we now have approved pan-genotypic oral DAA therapy with SVR rates close to 100%, representing an easy, safe cure strategy.^{9,10} At this time, we can contemplate HCV eradication—the WHO has set optimistic goals and timelines to achieve this.¹¹ This is a remarkable development for a condition that was unrecognised by the WHO only 8 years ago.¹²

Now, the war has moved to a different stage as the search for a cure is over. In a sense, the easy work has been done, and the search for HCV-positive patients takes on public health, financial, socioeconomic, policy and political overtones.¹³ The WHO has set the template, but each country has to make its own decisions on whether, and how to implement. For Singapore, the challenges are more straightforward since the prevalence rate is extremely low (approximately 0.1%)¹⁴ and likely to be archived in well characterised risk groups such as renal dialysis patients, blood transfusion

¹Division of Gastroenterology and Hepatology, National University Health System, Singapore

²Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Prof Lim Seng Gee, Division of Gastroenterology and Hepatology, National University Health System 1E Kent Ridge Road, Singapore 119228.

Email: mdclimsg@nus.edu.sg

recipients, people who inject drugs and migrants from countries that harbour high rates of HCV. Once HCV-infected patients in these risk groups are identified, they can be progressively treated and cured (a strategy called micro-elimination).¹⁵ In Singapore, the low burden of disease is counterbalanced by the high cost of treatment, but the consequences of non-treatment may be even higher in increased morbidity and mortality and the even higher cost of managing complications.¹⁶ Notwithstanding the policy issues, there are infrastructure needs that can streamline the path to elimination. The WHO defines elimination as the complete cure of that disease in a defined geographical region.¹⁷ The first question is how do we know we have achieved this? This requires 2 components—the absence of new cases and the cure of all known cases. In Singapore, viral hepatitis is a notifiable disease,¹⁸ hence all cases should be captured by the Ministry of Health. In reality, only acute cases are reported. Consequently, the capture of data on cases is incomplete and bulk data is not available to determine disease burden or outcome. Countries that have the most successful programmes (such as Australia) have a comprehensive notification system that detects new cases of chronic HCV, track outbreaks, monitor treatment, and outcomes. Australia estimates that 75% of the disease burden has been diagnosed, and are on the path to treatment and cure.¹⁹ We can learn much from such infrastructure. Since viral hepatitis is already a notifiable disease in Singapore, setting up such a system could be possible. The benefits are potentially enormous, particularly in the detection of disease outbreaks, linkage to care and outcomes such as disease complications and mortality, and linkage to therapy. One big difference between Australia and Singapore is the much lower prevalence of HCV here—1.4%²⁰ compared to approximately 0.1%. A screening strategy for low prevalence countries needs to utilise a micro-elimination strategy¹⁵ targeting pockets of high-risk patients which include blood transfusion recipients before 1990, renal dialysis patients, patients with liver disease, individuals with frequent transfusions or blood products, people who inject drugs and migrants from countries with high prevalence rates. HCV antibody testing should be routinely added to multiphasic health screening in addition of HBsAg. Overall, a targeted testing strategy for such high-risk groups will allow for a more precise picture of the burden of disease—a necessity in planning healthcare budgets and health resources. Ultimately, an affordable treatment strategy is needed for elimination, and such a strategy is being evaluated in Singapore. What HCV has today that enables the public health approach is a highly effective cure that can be universally delivered to large groups of infected patients. This, unfortunately, is what is missing in HBV today.

Returning to CHB, we have highly effective oral antiviral agents that are able to control disease.²¹ A recent consensus workshop has proposed that loss of HBsAg can be called functional cure,²² and should be the objective of therapy. This is a substantial milestone in the approach of CHB which has been thought to be lifelong and “incurable.” However, there is increasing evidence of success in a functional cure, and Singapore has been one of the global centres taking a leading role in this field. The award of the Translational Clinical Research (TCR) Grant of \$25 million for the eradication of HBV has consolidated a national effort for a HBV cure. The investigators of the grant comprise a national translational group of 29 researchers and scientists who have been working collaboratively on the eradication of CHB through a comprehensive approach via 3 integrated themes of examining host/viral interactions, target discovery with validation, novel agents, and experimental therapeutics. The team has found and characterised immune cells in CHB infection, as well as important proteins used by the virus to replicate. A novel animal model is now being validated and 8 compounds have been found to be active against HBV and are now being tested. In order to optimise a functional cure of CHB with existing therapy, we conducted a clinical trial to test the combination of interferon and nucleoside analogues, and preliminary data suggests that this can lead to a functional cure of CHB in about 11% of patients. However, before we can address the issue of elimination of HBV, we need better treatments similar to HCV that are able to cure high proportions of patients with short-term therapy. The infrastructure laid down in the push for HCV elimination can then be seamlessly utilised to treat HBV. In the interim, there are 10 new classes of compounds and 36 new agents²³ in clinical or preclinical testing that raise expectations that a functional cure is not too far away.

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