Research Assessment Exercise 2020
Impact Case Study

University: The University of Hong Kong (HKU)
Unit of Assessment (UoA): 03 - Clinical Medicine
Title of case study: Transforming the global health care management of chronic hepatitis B

(1) Summary of the impact

Through the first phase III clinical trial testing entecavir against hepatitis B infection, University of Hong Kong researchers have transformed the disease management globally. After approval by different national drug approving bodies, it was incorporated into European (2017) and American (2018) treatment guidelines and added to the WHO essential list of medicines in 2015. Indications for entecavir have been widened in different hepatitis B disease areas. These have led to decreasing incidence of end-staged liver disease worldwide. Economically, it brought a significant annual revenue generation in the patent holding company followed by the numerous drug manufacture and sales of generic formulations worldwide.

(2) Underpinning research

Key University of Hong Kong (HKU) Department of Medicine Researchers:
Professor Ching-Lung Lai (Chair Professor since 2003)
Professor Man-Fung Yuen (Chair Professor since 2013)
Dr Wai-Kay Seto (Associate Professor since 2016)

The first oral agent, lamivudine (nucleos(t)ide analogue) (NA) for hepatitis B virus (HBV) disease treatment was approved by Food and Health Administration (FDA) in 1998. The viral suppressive potency was only modest and the chance of development of viral resistance was high (14% at first year and step-wisely increased to 76% at 8 years). Because of these pitfalls, researchers in HKU continued to investigate a newer NA, entecavir. In the HKU-led, phase III, international, multicentre randomized control study run across 146 centres worldwide, it compared the viral suppressive potency, rate of drug resistance and clinical and laboratory safety between 296 patients treated with entecavir and 287 patients treated with lamivudine for 1 year (3.1). The study, published in 2006, demonstrated that entecavir was superior to lamivudine in terms of more potent viral suppression (greater median HBV DNA reduction: 5 vs. 4.5 log IU/mL and higher proportion of patients achieving undetectable serum HBV DNA: 90 vs 72% respectively) and lower rate of viral rebound resistance after (2 vs. 8% respectively). Viral mutations were identified in 20 out of 25 lamivudine-treated patients with viral rebound compared to none in entecavir-treated patients. The safety was comparable between two agents. The findings of this study resulted in the approval of entecavir for treatment of chronic hepatitis B (CHB) disease by FDA and European Medicines Agency (EMA) in 2005 and 2006 respectively.

HKU researchers continued to demonstrate by clinical studies that entecavir was also superior to the second approved NA (adefovir dipivoxil) (3.2). In particular, entecavir compared to adefovir had a greater for mean change from baseline in HBV DNA at week 12 (-6.23 versus -4.42 $\log_{10}$ copies/mL, respectively).

HKU researchers further studied the long term usage of entecavir and proved that it could continuously suppress the HBV (3.3). They also showed that this suppression led to reversing liver fibrosis and cirrhosis (3.4). They found that 5-year entecavir treatment was associated with regression of the liver fibrosis and also even reversion of liver cirrhosis demonstrated by the changes in the liver histology before and after the treatment. Prolonged use of entecavir was associated with a decrease incidence of cirrhosis-related complications and liver cancer (3.5). Monotherapy of entecavir could prevent of hepatitis B disease recurrence in HBV patients after liver transplantation. Entecavir was

also found to be able to prevent hepatitis flare which may cause mortality in patients receiving immunosuppressive therapies including long-term corticosteroid treatment, chemotherapy for malignant diseases, monoclonal antibody (e.g. rituximab) therapies (3.6).

(3) References to the research

3.1 Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colonno R, Fernandes L; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006; 354:1011-1020. DOI: 10.1056/NEJMoa051287

3.2 Leung N, Peng CY, Hann HW, Sollano J, Lao-Tan J, Hsu CW, Lesmana L, Yuen MF, Jeffers L, Sherman M, Min A, Mencarini K, Diva U, Cross A, Wilber R, Lopez Talavera J. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: A randomized international study of entecavir versus adefovir. Hepatology 2009;49(1):72-79. DOI: 10.1002/hep.22658

3.3 Yuen MF, Seto WK, Fung J, Wong DK, Yuen JC, Lai CL. Three years of continuous entecavir therapy in treatment-naïve chronic hepatitis B patients: VIRAL suppression, viral resistance, and clinical safety. Am J Gastroenterol. 2011;106:1264-1271. DOI: 10.1038/ajg.2011.45

3.4 Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, Lee SS, Halota W, Goodman Z, Chi YC, Zhang H, Hindes R, Iloeje U, Beebe S, Kreter B. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52(3):886-893. DOI: 10.1002/hep.23785

3.5 Seto WK, Lau EH, Wu JT, Hung IF, Leung WK, Cheung KS, Fung J, Lai CL, Yuen MF. Effects of nucleoside analogue prescription for hepatitis B on the incidence of liver cancer in Hong Kong: a territory-wide ecological study. Aliment Pharmacol Ther 2017;45(4):501-509. DOI: 10.1111/apt.13895

3.6 Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014;32(33):3736-3743. DOI: 10.1200/JCO.2014.56.7081

(4) Details of the impact

Impacts include: health and welfare, public policy and services, economy, commerce
Main Beneficiaries include: patients, WHO, healthcare providers, industry

It is estimated that CHB infection affects 257 million individuals and causes 880,000 liver-related deaths annually in the world.

Outcome from the HKU-led studies have had a major impact on international guidelines for the management of chronic hepatitis. The HKU investigators led studies on entecavir were adopted as scientific bases to support the recommendation of use of this drug in different areas of hepatitis B disease. These included the citations in the guidelines for the treatment of CHB of the European Association for the Study of the Liver (EASL) 2017 ([A] – page 377, 391; reference: 65, 222), the American Association for the Study of Liver Diseases (AASLD) 2018 ([B] – page 1561,1578; reference: 16 (3.1 above), 203 (3.6 above)] and the National Institute for Health and Care Excellence (NICE) ([C] – page 172, 290-292; reference 14 (3.4 above), 53 (3.1 above))

Entecavir (Baraclude^{TM}) was originally manufactured by Bristol-Meyers Squibb, approved by the FDA in 2005, and subsequently licensed for use in over 60 countries. In 2014, entecavir (Baraclude^{TM}) generated an annual revenue of USD 1.527 billion [D]. The patent of entecavir (Baraclude^{TM}) expired in 2014 and generics were subsequently manufactured in many countries, including China, India, Philippines and Vietnam.

In 2015, entecavir was added to the **World Health Organization (WHO) Essential List of Medicines** ([E], page 58), again based on our studies (3.3 and 3.4 above). These are medications to which all people globally should have access at all times in sufficient amounts at generally affordable prices, and is a reference for many governments when making decisions on health spending. The WHO Expert Committee recommended the inclusion of entecavir based on its potent efficacy, tolerability, high genetic barrier to resistance, license for use in children aged 2-11 years, and potential public health impact [E]. Entecavir was similarly included in the **China National Health Commission's List of Essential Medicines** (2016). Entecavir is currently fully reimbursed by the National Healthcare Insurance of Mainland China [Fi-ii]. Entecavir is also partially reimbursed in various national co-payment health care systems worldwide e.g. Australia [G].

Because of the recommendation from treatment guidelines mentioned above and hence with the availability of generic formulation, entecavir is cost-effective in the treatment of CHB. In Mainland China, Entecavir monotherapy was **the most cost-effectiveness strategy** in the management of treatment-naïve CHB, with the lowest incremental cost-effectiveness ratio of USD 6,112/quality adjusted life years. This was calculated based on the price of generic entecavir in 2014 which was then USD 1,381 per year [H]. With the centralization of drug procurement procedures throughout China, in 2019, the price of reimbursable generic entecavir has dropped to RMB 453 per year, or USD 66 per year (Manufacturer: Chia Tai-Tianqing Pharmaceutical Holdings Co. Ltd) [I], likely further increasing the drug's cost-effectiveness. If generic entecavir achieves a global prescription volume of 5 million individuals, the minimum estimate price of generic entecavir can be profitable at as low as USD 36 per year [J]. Entecavir was similarly found to be cost-effective in other regions worldwide.

Because of the availability of effective treatment with entecavir, it positively influences The WHO to set a **2030 target for eliminating viral hepatitis** as a global public health threat, with the aim of reducing liver-related mortality by 65%. This will require a 90% diagnostic uptake rate and an 80% treatment rate among eligible patients. Nonetheless, the Center of Disease Control estimated that in 2016, HBV-related diagnostic and treatment rates worldwide were only 10% and 5% respectively.

(5) Sources to corroborate the impact

[A] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398. DOI: 10.1016/j.jhep.2017.03.021

[B] Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018;67:1560-1599. DOI: 10.1002/hep.29800

[C] National Clinical Guideline Centre. Hepatitis B (chronic) Diagnosis and management of chronic hepatitis B in children, young people and adults (accessed 26 June 2019)

[D] 2014 Bristol-Myers Squibb Annual Report. Delivering Transformational Medicines to Patients. New York: Bristol-Myers Squibb Company; 2014.

[E] WHO. The selection and use of essential medicines: report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) 2015. (accessed 26 June 2019).

[Fi] Interpretation of the National Essential list of Medicine, PRC National Health Commission 国家基本药物目录（2018 年版）解读 (accessed June 26 2019)

[Fii] National Essential List of Medicines 2018 年版国家基本药物目录 (accessed June 26 2019) (P. 9, 110)

[G] Entecavir. The Pharmaceutical Benefits Scheme. Australian Government Department of Health. (accessed June 26 2019).

[H] Lai K, Zhang C, Ke W, et al. Cost-Effectiveness Comparison Between the Response-Guided Therapies and Monotherapies of Nucleos(t)ide Analogues for Chronic Hepatitis B Patients in China. Clin Drug Investig 2017; 37(3): 233-47. DOI: 10.1007/s40261-016-0486-8

[I] 深圳市卫生健康委员会文件 深卫健医管 [2019] 5 号-市卫生健康委关于做好国家组织药品集中采购中选药品临床配备使用工作的通知 (**附件一**, P.8) (not for open access)

[J] Hill A. Cost and prices of entecavir to treat hepatitis B. Generics and Biosimilars Initiative. 2016. (accessed 26 June 2019).