www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.25 NO.9 September 2020

Hepatology

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

SmofKabiven®

THE MIX FOR LIFE

NEW AND IMPROVED LABEL

blue for CENTRAL ADMINISTRATION

black for PERIPHERAL ADMINISTRATION

ω-3 enriched PN – proven to improve clinical outcomes with excellent safety profile[1]:

- Significantly reduced length of hospital stay overall by **3 days**.
- Significantly reduced infection rate by **39%**

- Available in different bag sizes (Central: 493/986/1477/1970 ml, Peripheral: 1206/1448/1904 ml)
- Extensive compatibility data with micronutrients

Complete parenteral nutrition therapy with micronutrients

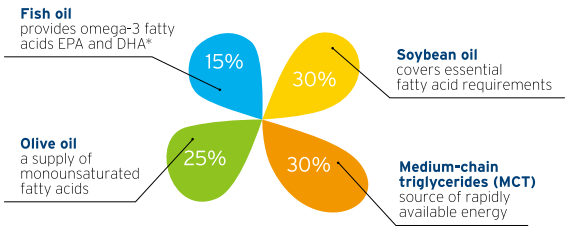
- All PN prescriptions should include a daily dose of multi-vitamins and trace elements[2-3]
- After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis[3]

Approved for children ≥ 2 years

References :
1. L. Pradelli et al. /Clinical Nutrition 33 (2014) 785-7 92
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
3. Braga et al. (2009) ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition, 28: 378-386
4. Biesalski HK. Gastroenterology 2009;137(5):92-104
http://www.espen.org/espenguidelines.html

SmofKabiven® contains unique **SMOFlipid®**

SMOFlipid® – A 4-oil mix with a well-balanced fatty acid pattern containing purified natural fish oil



*EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid

+ additional vitamin E
(approx. 200 mg α-tocopherol/liter) to counteract lipid peroxidation and oxidative stress[4]

Dipeptiven® 20% Glutamine

FRESENIUS KABI

caring for life

Fresenius Kabi Hong Kong Ltd.
Room 5001-5027, 50/F, Sun Hung Kai Centre,
30 Harbour Road, Wanchai, Hong Kong
Tel : (852) 2152 1330 Fax : (852) 2119 0815
www.fresenius-kabi.com

HK-DA-023-2020

Contents

Editorial

- **Hepatology in Hong Kong - How to Move Forward?** 2
  Dr George LAU

Medical Bulletin

- **Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need?** 5 CME
  Dr Gregory CHENG
- **MCHK CME Programme Self-assessment Questions** 10
- **Practice of Clinical Hepatology During COVID-19 Pandemic -the APASL, EASL and AASLD Recommendations, Which Ones to Follow?** 12
  Dr George LAU & Dr John W. WARD
- **NAFLD in Chinese - Growing Concern and Management Strategy** 16
  Dr Jian-gao FAN & Dr Jing ZENG
- **A Coalition Advancing Progress Toward Global Hepatitis Elimination: Achievements, Challenges and Opportunities** 18
  Dr John W. WARD
- **HBV Reactivation During Direct-acting Antiviral Therapy in Patients with HBV/HCV Coinfection** 24
  Dr Dong JI, Dr Cheng WANG, Dr Jinlin HOU & Dr Guofeng CHEN
- **Liver Transplantation in China: Development and Perspective** 28
  Dr Xiaofeng ZHANG, Dr Dali ZHANG & Dr Zhenwen LIU

Dermatology Quiz

- **Dermatology Quiz** 8
  Dr Lai-yin CHONG

Medical Diary of September 30

Calendar of Events 31

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

Disclaimer

The Cover Shot

Shall rainbows motivate Hong Kong to continue and endure through dark times!

In Hong Kong, we have suffered a decade of despair in Hepatology. Our 10-year average age-adjusted standardised reduction rate for liver cancer was around 2.0-2.8%, far short of the target of 10 % reduction over five years (2015-2020) set by the World Health organization. The mortality-incidence ratio remains high and static at 0.75 to 0.8, reflecting a failure of liver cancer surveillance. The progress of liver transplantation service has come to a halt, and no innovative algorithm was made available for better management of our fellow citizens with liver diseases. Let's disentangle the obstacles with science (facts) and humanity.

Move on! The bigger the storm, the brighter the rainbow!

Dr George LAU
MBBS(HK), MD(HK), FHKCP, MRCP(UK), FRCP(Edin), FRCP(Lond), FHKAM(Medicine)

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Hepatology in Hong Kong - How to Move Forward?

Dr George LAU

MBBS(HK), MD(HK), FHKCP, MRCP(UK), FRCP(Edin), FRCP(Lond), FHKAM(Medicine)
Chairman and Senior Consultant in Gastroenterology and Hepatology, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China
Chair Professor in Clinical Hepatology, The 5th Medical Centre of Chinese PLA General Hospital - Hong Kong Humanity & Health Medical Group, Beijing, China
Honorary Professor, Institute of Hepatology, 111 Coldharbour Lane, London SE5 9NT, United Kingdom

Editor

Dr George LAU

This year, 2020, represents the most challenging year for the practice of Hepatology. With the COVID-19 pandemic, all of us are having a difficult time. Due to the lack of effective vaccine and therapy for COVID-19, one needs to implement social distancing and quarantine, and this has made all walks of life, especially those in the lower social class, intolerable. Schools need to be closed, our flagship airline Cathy Pacific needs to ground most its flights, conferences change shape and become webinars. All restaurants need to be closed, and all retail shops are suffering from heavy loss. It is a real challenge for one to navigate through various financial and operational challenges imposed by the coronavirus while promptly addressing the needs of our patients with liver diseases. To this end, all three authoritative regional liver societies (American Association for the Study of Liver Diseases, European Association for the Study of the Liver and The Asian-Pacific Association for the Study of the Liver) have issued clinical practice guidelines to facilitate the practice of Hepatology during this COVID-19 pandemic.[1]

In parallel, there have been exciting new data on the use of systemic therapy, in terms of immune checkpoint inhibitor and targeted therapy, for hepatocellular carcinoma,[2] raising the hope of inducing complete remission in patients with inoperable HCC with an otherwise dismal prognosis.

In Mainland China, since 2015, over 4,000 cadaveric liver transplantation are being performed annually, with one-year overall survival rate above 90%. This has served not only our fellow citizens in mainland China but also all Chinese in Hong Kong SAR and Macau SAR, China.[3]

Hepatitis B virus (HBV) reactivation remains one of the main causes of acute on chronic liver diseases and our Beijing 302-HK Humanity and Health hepatitis C Liver centre was among the first medical team globally to report HBV reactivation in HCV-HBV coinfected patients treated with pan-oral direct acting antiviral agents (DAAs).[4] Based on this work and subsequent studies, preemptive use of nucleos(t)ide analogues is now being recommended for those HCV-HBV coinfected patients planned for treatment with DAAs.

In the near future, Hong Kong will be facing a new challenge to continue her role as an eminent international liver centre while staying as a key player in the greater Bay Area development in China. To face this daunting task, Hong Kong needs to remain as a coordinating centre for the elimination of viral hepatitis B and C in the Asia-Pacific region.[5]

Along with the marked economic growth in China, a practising hepatologist will be expected to see more patients with fatty liver. So far, the development of pharmacotherapies remains unsatisfactory. This is at least partly due to the heterogeneous pathogenesis of metabolic fatty liver diseases and inaccuracies in terminology and definitions. Based on a recent international consortium of experts in the field, consensus has recently been reached to adopt new nomenclature to replace the old term “non-alcoholic fatty liver disease (NAFLD)”, a

term which does not reflect current knowledge, by the new term "metabolic dysfunction-associated fatty liver disease (MAFLD)". This opens the door for efforts from the research community to update the nomenclature and subphenotype the disease and to accelerate the translational path to new treatments.[6]

Last but not least, in July 2020, it is so sad to have the loss of two of our beloved colleagues and teachers in Hepatology. Dr Roger Stanley Williams (CBE, FRCS, FRCO, FRCPE, FRACP, FMedSci) is highly regarded as "Father of Modern Hepatology". Dr Williams was born on August 28, 1931, and died peacefully on July 26, 2020, aged 88 years old. Over the past six decades, Dr Williams and his team have made a momentous contribution to the modernisation of Clinical Hepatology. In 1968, he initiated with Sir Roy Calne in Cambridge to perform the first liver transplantation in the United Kingdom. Till the very last week of his brilliant academic career, Dr Williams was working as full-time Director and Professor at the Institute of Hepatology, London and of the Foundation for Liver Research, King's College Hospital, Denmark Hill, London. Dr Williams had established, over a period of 60 years, the world renowned Institute of Liver Studies at King's College Hospital, a training hub for hundreds of hepatologists worldwide. Dr Williams also had a great heart to nurture youngsters and to maintain international collaboration with Asian countries, like China. Indeed, he had recently established a Sino-British fellowship programme with the Cheng Si-yuan (China-international) Hepatology Foundation (a Hong Kong-based charitable foundation) to propagate the well established research discipline in Hepatology in China. Dr Williams had published more than 3,000 research articles. In the last few years, he founded the Lancet commission on liver disease with Richard Horton as editor of the Lancet. Dr Williams's determination to improve the services for people suffering from liver disease was a vital factor in the success of the Lancet commission.

Fig. 1. Dr Roger Williams giving a state-of-the-art lecture on Acute liver failure at the 3rd China-international Liver conference, 2016 Beijing, China. (Photo from personal collection)

Locally, the abrupt departure of Dr Nancy Wai-yee Leung (1951-2020) is saddening! Trained in the United Kingdom, she was a dedicated hepatologist, and had been actively involved in public service and education related to liver diseases in Hong Kong as well as in the Asia-Pacific region. Indeed, more than two decades ago, she and Dr Ching-lung LAI pioneered the use of lamivudine for the treatment for chronic hepatitis B infection, rendering Hong Kong the leading centre worldwide.[7]

Fig. 2. Nancy with us at a liver symposium in Hong Kong, 2016. (Photo from personal collection)

We will miss both Dr Roger Willams and Dr Nancy Leung, and will remember their relentless efforts to improve the lives of so many patients with liver diseases. Our thoughts go to their loved ones.

References

1. Lau G and Ward JW. Practice of Clinical Hepatology during COVID-19 Pandemic - the APASL, EASL and AASLD Recommendations, Which Ones to Follow? The Hong Kong Medical Diary 2020; 25 (9):12-14.
2. Cheng G. Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need? The Hong Kong Medical Diary 2020; 25 (9):5-8.
3. Zhang X, Zhang D, Liu Z. Liver Transplantation in China: Development and Perspective. The Hong Kong Medical Diary 2020; 25 (9):28-29.
4. Ji D, Wang A, Hou JL, Chen GF. HBV Reactivation During Direct-acting Antiviral Therapy in Patients with HBV/HCV Coinfection. The Hong Kong Medical Diary 2020; 25 (9):24-26.
5. Ward JW. A Coalition Advancing Progress Toward Global Hepatitis Elimination: Challenges and Opportunities. The Hong Kong Medical Diary 2020; 25 (9):18-23.
6. Fan JG and Zeng J. NAFLD in Chinese - Growing Concern and Management Strategy. The Hong Kong Medical Diary 2020; 25 (9):16-17.
7. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med. 1998; 9;339(2):61-8.

NOW APPROVED

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

THE **SECOND-LINE TKI** WITH PROVEN EFFICACY FOR A BROAD AND CLINICALLY RELEVANT **HCC** PATIENT POPULATION

CABOMETYX® efficacy in HCC is proven in:

- Majority of 2L patients (71%)[1]
- Patients tolerable/intolerable to prior sorafenib[1]
- Patients with any AFP levels[2]

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor

References
1. Abou-Alfa GK, et al. N Engl J Med 2018;379:54–63. **2.** Kelley RK et al. Clin Cancer Res. Published online January 1, 2020.

CABOMETYX® Hong Kong Abridged Prescribing Information (Refer to Summary of Product Characteristics (SmPC) before prescribing)
Trade Name: CABOMETYX 20 / 40 / 60 mg film-coated tablets **INN:** Cabozantinib **Presentations:** Film-coated tablets, HDPE bottle with a polypropylene child-resistant closure and three silica gel dessicant canisters. Each bottle contains 30 film-coated tablets. **Indications:** Treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk; or adults following prior vascular endothelial growth factor (VEGF)-targeted therapy; or treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. **Posology & Administration:** Treatment should be initiated by a physician experienced in the administration of anticancer medicinal product. CABOMETYX tablets and COMETRIQ capsules are not bioequivalent and should not be used interchangeably. The recommended dose is 60 mg one daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of CABOMETYX therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose. Oral use: tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking the drug. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings & Precautions:** Physicians should evaluate closely the patient during the first 8 weeks of treatment to determine if dose modifications are warranted (in case of hypocalceamia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodisaesthesia syndrome (PPES), proteinuria and gastrointestinal events). Warnings: hepatic effects, hepatic encephalopathy, perforations and fistulas, thromboembolic events, gastrointestinal disorders, heamorrhage, thrombocytopenia, wound complications, hypertension, PPES, proteinuria, reversible posterior leukoencephalopathy syndrome, prolongation of QT interval, biochemical laboratory test abnormalities, CYP3A4 inducers and inhibitors, P-glycoprotein substrates, MRP2 inhibitors, excipient related warnings. **Interactions:** CYP3A4 inducers and inhibitors, P-glycoproteins substrates, MRP2 inhibitors, gastric pH modifying agents, bile salt-sequestering agents. **Pregnancy & Lactation & Fertility:** Pregnancy should be avoided while on cabozantinib, or while the partner is taking cabozantinib; an effective method of contraception should be used by both partners during treatment and for at least 4 months after completing therapy, along with a barrier method. Mothers should discontinue breast-feeding during the treatment. Male and Female fertility may be compromised by treatment with cabozantinib. **Ability to Drive & Use Machines:** Caution should be recommended when driving or operating machines while on cabozantinib. **Undesirable Effects:** RCC: diarrhoea, hypertension, dehydration, hyponatraemia, nausea, decreased appetite, embolism, fatigue, hypomagnesaemia, PPES. HCC: hepatic encephalopathy, PPES, asthenia, diarrhoea. **Date of preparation: 15/10/2019**

IPSEN
Innovation for patient care

IPSEN Pharma (Hong Kong)
Level 15, East Exchange Tower, 38-40 Leighton Road, Causeway Bay, Hong Kong
Tel: 2637 8898 Fax: 2637 3987 http://www.ipsen.com

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

CMX-HK-000071 August 2020

Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need?

Dr Gregory CHENG

MD(U of Toronto), PhD (Biological Science)

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong SAR, China
Faculty of Health Science, University of Macau, Macau SAR, China

Dr Gregory CHENG

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 September 2020.

Liver cancer is currently the second most common cause of cancer-related death worldwide, and hepatocellular carcinoma (HCC) accounts for more than 90% of liver cancers.[1,2] According to the report from the Hong Kong Cancer Registry 2014, liver cancer ranks as the fourth most common cancer and the third most common cause of cancer death in Hong Kong.[3]

The single largest risk factor for the development of HCC is cirrhosis of any aetiology. Chronic HBV is the major cause of HCC in Hong Kong, accounting for nearly 80% cases while HCV-related HCC accounted for 6.3%.[4] Recent studies showed that obesity, insulin resistance and non-alcoholic fatty liver disease (NAFLD) are emerging risk factors for HCC.[5-7] Effective strategies to reduce HCC-related health burden and mortality include correction of risk factors and regular surveillance to detect HCC in the early curative stage.

Hong Kong has already implemented universal hepatitis B vaccination for all newborns; the main task now is an effective antiviral treatment to prevent the development of cirrhosis and HCC in infected persons. Many studies have shown that antiviral treatment can decrease the incidence of HCC. Lamivudine therapy significantly reduced the risk of HCC in chronic hepatitis B patients with advanced fibrosis and cirrhosis when compared with placebo, 7.4% versus 3.9%.[8] A follow-up study showed that entecavir is more effective than lamivudine in the prevention of HCC with a 5-year cumulative incidence of HCC of 7% and 20% respectively.[9] In chronic HCV infection, patients who achieve sustained viral response (SVR) with antiviral therapy had a significantly lower risk of HCC compared with patients with suboptimal response.[10] However, suppression of viral replication in chronic hepatitis B and C patients could only reduce but not eliminate the risk of HCC, and regular surveillance is needed.

The relationship between diabetes mellitus (DM), obesity, metabolic syndrome, and HCC may be linked through the development of NAFLD. Obesity, insulin resistance, and the proinflammatory milieu of NAFLD may mediate carcinogenesis directly. With declining hepatitis B infection due to effective vaccination programme, the increasing prevalence of obesity, DM and NAFLD in Hong Kong will impact greatly on HCC incidence in HK in the foreseeable future unless considerable preventive measures are taken.[11] Major key preventive measures include a healthier diet and lifestyle modification. Regular walking and exercise are effective in the control of metabolic syndrome and NAFLD. Treatment with statins and metformin may also have beneficial effects on portal hypertension, complications of liver cirrhosis, and HCC prevention.[12]

HCC SURVEILLANCE

Ultrasonography (U/S) is the most widely used modality for HCC screening and surveillance, with reported sensitivity in the range of 40–81% and specificity of 80–100%.[13-15] B-mode U/S cannot demonstrate tumour vascularity, and colour Doppler imaging/power Doppler imaging carries low sensitivity for detecting the microflow in the nodules.[16] Contrast-enhanced U/S (CEUS) using microbubble contrast agents and low mechanical index contrast-specific imaging techniques carries a high sensitivity for the detection of the arterial hypervascularity, as well as rapid wash-out and late wash-out of tumour nodules that are characteristic of HCC.[17,18] CEUS also has the advantages of relative inexpensiveness, no nephrotoxicity of the contrast agents, and no ionising radiation as compared with dynamic CT and dynamic MRI. It is generally accepted that CEUS is a cost-effective second-line imaging modality for rapid diagnosis of HCC when focal lesion(s) is detected on U/S, although dynamic CT or dynamic MRI remains the gold standard for characterisation of small nodules in cirrhotic patients at high risk of HCC in some guidelines.[19,20] Typical HCC can be diagnosed by imaging, regardless of its size and AFP values, if a typical vascular pattern of arterial enhancement with portal venous wash-out is obtained on dynamic CT, dynamic MRI, or CEUS.[19]

Tumour markers for HCC are used in diagnosis, evaluation of treatment response and during post-treatment follow-up. AFP concentration higher than 500 ng/mL is diagnostic for HCC for tumour >5 cm detected on imaging, but not recommended as a confirmatory test for small HCC. The cut-off value of AFP should be set at 200 ng/mL when used in combination with the US in surveillance programs.[19] This AFP cut-off value can be set at a lower value in a population with hepatitis virus suppression or eradication.

Patients with liver cirrhosis and those with chronic HBV infection (even in the absence of cirrhosis) are candidates for HCC screening U/S and AFP every six months. Other high-risk groups include patients with NAFLD, chronic hepatitis C with fibrosis or hereditary hemochromatosis.[20]

HCC TREATMENT

Surgery

Liver resection (LR) is a first-line curative treatment for HCC among Child-Pugh A class patients and those with satisfactory liver reserves.[19] Liver transplantation provides the best curative treatment for all HCC patients from an oncologic point of view, and is recommended as a first-line treatment for HCC patients with Child-Pugh class B and C score if a liver graft is available. Resection of both isolated extrahepatic metastasis and the hepatic tumour may be considered in selected patients.[19,21]

Local Ablation

Image-guided percutaneous local ablation therapies with ethanol injection, microwave ablation (MWA), radiofrequency ablation (RFA), or irreversible electroporation (IRE) are a potentially curative treatment for patients with small HCC.[22-25] They are minimally invasive and easily repeatable for disease recurrence. They are mainly indicated for Child-Pugh class A or B HCC patients with three or fewer tumours and each ≤ 3 cm in diameter. Some non-randomised comparative studies reported that RFA had similar survival to resection,[26-28] while others found that resection was associated with higher survival.[19,29,30] Even in studies that reported that surgical resection was superior to RFA, there was no significant difference in overall survival in patients with HCC ≤ 3 cm in diameter.

Transarterial Chemoembolisation (TACE)

TACE is recommended as a first-line treatment of HCC for patients with unresectable, large/multifocal HCCs who do not have vascular invasion or extrahepatic spread. Selective TACE can be performed in patients with small tumours that are technically difficult to ablate with ethanol injection or RFA.[19,31]

Transarterial radioembolisation (TARE) involves the injection of implantable radioactive microspheres into tumour-feeding arteries. It exposes the tumour to a high dose of radiation while limiting radiation to the normal liver parenchyma. TARE using yttrium-90 (Y-90) is a promising regional therapy which can complement or replace TACE. Y-90 TARE can be used as a bridging therapy in patients with early HCC awaiting transplant, in intermediate HCC patients who have failed conventional TACE, or in advanced HCC with vascular invasion.[32]

Radiotherapy (RT)

Stereotactic body radiotherapy (SBRT) and proton beam radiation may be considered for patients who have failed other local therapies or those patients with symptomatic bony metastases.[33-36]

Systemic Therapy

Sorafenib is currently the standard first-line systemic treatment for HCC patients who are not suitable for surgery, locoregional therapy nor transarterial therapy.[37]

Regorafenib is an option for second-line treatment for patients who have developed progressive disease after sorafenib treatment.[38]

A recent phase III trial showed that Lenvatinib or Cabozantinib was non-inferior to sorafenib for overall survival, but showed statistically significant improvements in relapse-free survival, time to progression and overall response rate.[39,40]

Immunotherapy

Major breakthroughs have been achieved with agents targeting immune checkpoint proteins, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death-1 (PD-1), in patients with various types of cancer, including HCC.[19] Nivolumab, ipilimumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab had demonstrated activity alone or in combination with targeted therapy.[41-44]

THE ROLE OF THE GENERAL PRACTITIONER IN HCC MANAGEMENT

The general practitioner plays a crucial role in the prevention and surveillance of HCC.

1. Start patients with active hepatitis B or C infection on appropriate antiviral therapy according to current guidelines, aiming at hepatitis B DNA clearance or hepatitis C SVR and continue regular surveillance in these patients even after viral clearance.
2. Explain and promote healthy diets and lifestyle modifications to every individual who is at risk of or has been diagnosed with obesity, diabetes, metabolic syndrome or NAFLD. Start treatment with statins and metformin in indicated subjects.
3. Perform HCC screening with U/S and AFP every six months for patients with liver cirrhosis and those with chronic HBV infection (even in the absence of cirrhosis). Other high-risk groups include patients with NAFLD, chronic hepatitis C with fibrosis, and hereditary hemochromatosis.
4. Perform CEUS or dynamic CT or dynamic MRI when liver lesion(s) is detected on U/S.

Management of Confirmed HCC

1. Refer all patients with newly diagnosed HCC to hospitals with well-experienced hepatobiliary surgical teams or expertise in local ablative therapy.
2. Monitor and manage the side effects of patients receiving HCC treatment. Liver transplant recipients are immunocompromised and should be monitored closely for the development of fever and opportunistic infections. TACE is associated with the transient postembolisation syndrome, hepatic insufficiency, liver abscess, acute cholecystitis or gastrointestinal bleeding. TACE should be stopped when there is liver impairment or other serious complications or radiologic tumour progression despite adequate drug administration. The most

common acute side-effects of radiation therapy include transient fatigue, nausea, vomiting, and right upper quadrant pain. Possible long-term side-effects include worsening hepatic function with ascites, oedema, hepatomegaly, thrombocytopenia.[19] The most common adverse events of targeted therapy with sorafenib, regorafenib or Lenvatinib are diarrhoea, fatigue, hand-foot skin reaction. Diarrhoea greater than six times per day or skin desquamation may require stoppage of therapy. Severe adverse events with checkpoint inhibitors are uncommon (< 5%), but potentially severe immune-mediated pneumonitis, colitis, hepatitis or dermatitis may occur. Early recognition and prompt treatment with steroids are generally effective.

THE ROLE OF GENERAL PRACTITIONERS DURING IN HCC MANAGEMENT DURING COVID-19 PANDEMIC

The role will be even greater as many hospitals will cut down regular clinics, and general practitioners will manage patients at high risk of HCC or confirmed HCC. Continue HCC surveillance in high-risk subjects (cirrhosis, chronic hepatitis B) for HCC, adhering to the planned schedule if possible. A delay of two months is acceptable after discussing the risks and benefits of delaying surveillance with the patient. Patients with increased risk of HCC such as elevation of AFP or presence of liver nodule should be prioritised for HCC-surveillance.[45]

1. Immunosuppression doses should not be reduced in liver transplant patients in the absence of COVID-19 infection. Reduction of routine immunosuppression may increase risks of acute allograft rejection.
2. For HCC patients who are already on systemic treatment with kinase inhibitors therapy, treatment should be continued at the same dose. For HCC patients on immunotherapy, lengthening treatment intervals to every 4-6 weeks may be considered.

References

1. World Health Organaization. Cancer. http://www.who.int/mediacentre/factsheets/fs297/en/. Accessed 16 April 2020
2. Zhu RX, Seto WK, Lai CL, Yuen MF: Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut Liver 2016; 10: 332–339
3. Hong Kong Cancer Registry: Top Ten Cancers http://www3.ha.org.hk/cancereg/pdf/top10/ Accessed 16 June 2020
4. Tanaka M, Katayama F, Kato H, Tanaka H, Wang J, Qiao YL, et al. Hepatitis B and C virus infection and hepatocellular carcinoma in China: a review of epidemiology and control measures. J Epidemiol 2011; 21:401–416
5. Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Ito H, Wakai K, et al. Obesity and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2012; 42:212–221
6. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and metaanalysis. Diabetes Metab Res Rev 2012; 28:109–122
7. Scalera A, Tarantino G. Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease? World J Gastroenterol 2014; 20:9217–9228
8. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004; 351:1521–1531
9. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013; 58:98–107
10. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833–844
11. Traussnigg S, Kienbacher C, Halilbasic E, Rechling C, KazemiShirazi L, Hofer H, et al. Challenges and Management of Liver Cirrhosis: practical Issues in the Therapy of Patients with Cirrhosis due to NAFLD and NASH. Dig Dis 2015; 33:598–607 174.
12. DePeralta DK, Wei L, Ghoshal S, Schmidt B, Lauwers GY, Lanuti M, et al. Metformin prevents hepatocellular carcinoma development by suppressing hepatic progenitor cell activation in a rat model of cirrhosis. Cancer 2016; 122:1216–1227
13. Pocha C, Dieperink E, McMaken K, Knott A, Thuras P, Ho S. Surveillance for hepatocellular cancer with ultrasonography vs. Computed tomography–a randomised study. Aliment Pharmacol Ther 2013; 38:303–312
14. Yoon JH, Park JW, Lee JM. Noninvasive diagnosis of hepatocellular carcinoma: Elaboration on korean liver cancer study group-national cancer center Korea practice guidelines compared with other guidelines and remaining issues. Korean J Radiol 2016; 17:7–24
15. Khalili K, Menezes R, Kim TK, Kochak Yazdi L, Jang HJ, Sharma S, et al. The effectiveness of ultrasound surveillance for hepatocellular carcinoma in a Canadian centre and determinants of its success. Can J Gastroenterol Hepatol 2015; 29:267–273
16. Koito K, Namieno T, Morita K. Differential diagnosis of small hepatocellular carcinoma and adenomatous hyperplasia with power doppler sonography. AJR Am J Roentgenol 1998; 170:157–161
17. Kudo M. Defect reperfusion imaging with Sonazoid®: a breakthrough in hepatocellular carcinoma. Liver Cancer 2016; 5:1–7
18. Jang HJ, Kim TK, Burns PN, Wilson SR. CEUS: an essential component in a multimodality approach to small nodules in patients at high-risk for hepatocellular carcinoma. Eur J Radiol 2015; 84:1623–1635
19. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317-370. doi:10.1007/s12072-017-9799-9
20. Neri E, Bali MA, Ba-Ssalamah A, Boraschi P, Brancatelli G, Alves FC, et al. ESGAR consensus statement on liver MR imaging and clinical use of liver-specific contrast agents. Eur Radiol 2016; 26:921–931
21. Tateishi R, Yoshida H, Matsuyama Y, Mine N, Kondo Y, Omata M. Diagnostic accuracy of tumor markers for hepatocellular carcinoma: a systematic review. Hepatol Int 2008; 2:17–30
22. Poon RT, Cheung TT, Kwok PC, Lee AS, Li TW, Loke KL, et al. Hong Kong consensus recommendations on the management of hepatocellular carcinoma. Liver Cancer 2015; 4:51–69
23. Shiina S, Tateishi R, Imamura M, Teratani T, Koike Y, Sato S, et al. Percutaneous ethanol injection for HCC 20-year outcome and prognostic factors. Liver Int 2012; 32:1434–1442
24. Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012; 107:569–577
25. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. J Vasc Interv Radiol 2010;21: 192–203
26. Scheffer HJ, Nielsen K, de Jong MC, van Tilborg AA, Vieveen JM, Bouwman AR, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficay. J Vasc Interv Radiol 2014; 25:997–1011
27. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012; 57:794–802 484.
28. Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. J Gastroenterol Hepatol 2014; 29:193–200
29. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010; 252:903–912
30. Huang J, Hernandez-Alejandro R, Croome KP, Yan L, Wu H, Chen Z, et al. Radiofrequency ablation versus surgical resection for hepatocellular carcinoma in Childs A cirrhotics-a retrospective study of 1,061 cases. J Gastrointest Surg 2011; 15:311–320
31. Yun WK, Choi MS, Choi D, Rhim HC, Joh JW, Kim KH, et al. Superior long-term outcomes after surgery in child-pugh class A patients with single small hepatocellular carcinoma compared to radiofrequency ablation. Hepatol Int 2011; 5:722–729
32. Park JW, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, Han KH, Kudo M, Lee HC, Lee RC, Lesmana LA, Lim HY, Paik SW, Poon RT, Tan CK, Tanwandee T, Teng G, Cheng AL: Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). Liver Int 2013; 33: 327–337.

33. Cheung TT, Kwok PC, Chan S, et al. Hong Kong Consensus Statements for the Management of Unresectable Hepatocellular Carcinoma. Liver Cancer. 2018;7(1):40-54. doi:10.1159/000485984
34. Lau WY, Teoh YL, Win KM, Lee RC, de Villa VH, Kim YH, Liang PC, Santos-Ocampo RS, Lo RH, Lim KB, Tai DW, Ng DC, Irani FG, Gogna A, Chow PK: Current role of selective internal radiation with yttrium-90 in liver tumors. Futur Oncol 2016; 12: 1193–1204
35. Keane FK, Wo JY, Zhu AX, Hong TS: Liver-directed radiotherapy for hepatocellular carcinoma. Liver Cancer 2016; 5: 198–209.
36. Weiner AA, Olsen J, Ma D, Dyk P, DeWees T, Myerson RJ, Parikh P: Stereotactic body radiotherapy for primary hepatic malignancies – report of a phase I/II institutional study. Radiother Oncol 2016; 121: 79–85.
37. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378–390.
38. R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 389: 56–66.
39. Kudo M, Finn R, Qin S, et al .Lenvatinib Versus Sorafenib in First-Line Treatment of Patients With Unresectable Hepatocellular Carcinoma: A Randomized Phase 3 Non-Inferiority Trial Lancet 2018 Mar 24;391(10126):1163-1173. doi:10.1016/S0140-6736(18)30207-1
40. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173. doi:10.1016/S0140-6736(18)30207-1
41. Sangro B, Gomez-Martin C, de la Mata M, Inarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013; 59:81–88 605.
42. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389 :2492–2502
43. Zhu AX, Finn RS, Edeline J et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label Phase II trial. Lancet Oncol. 19(7), 940–952 (2018)
44. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma.N Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745
45. APASL Covid-19 Task Force, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. Hepatol Int. 2020;14(4):415-428. doi:10.1007/s12072-020-10054-w

Dermatology Quiz

Dermatology Quiz

Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

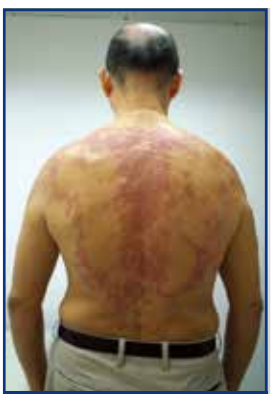


Fig.1: Extensive erythematous infiltrated plaques at the back

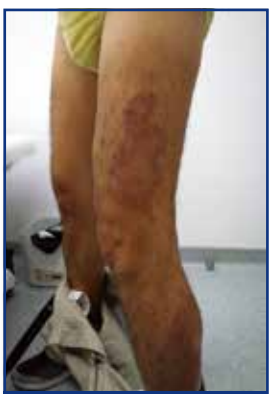


Fig.2: Polycyclic erythematous palpable edge of the plaque at the thigh

This 64-year-old man had a history of progressive non-itchy and painless erythematous infiltrated plaques at his back, thighs and legs for three months. There were no arthralgia and no systemic upset. He remained well apart from worsening of his skin lesions. He had a history of ischaemic heart disease and gout. A skin biopsy had been done for the diagnosis and exclusion of some important differential diagnoses. The histological diagnosis was interstitial granulomatous dermatitis (IGD). The Ziehl-Neelsen stain, Wate-Fite stain and fungal stain were all negative. There was no evidence of malignancy from the biopsy.

Questions

1. What are the differential diagnoses clinically?
2. Having established the pathological diagnosis of IGD, what laboratory tests would you order?
3. What are the reported systemic diseases associated with IGD?

(See P.32 for answers)

朗豪坊
LANGHAM PLACE

Premium Address for Medical Specialists

8 Argyle Street, Mongkok, Kowloon

Leasing Enquiry: 2879 2181 / 2879 2189 medical@langhamplace.com.hk

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need?" by Dr Gregory CHENG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 September 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Chronic HCV is the major cause of HCC in Hong Kong.**
2. **Non-alcoholic fatty liver disease (NAFLD) is an emerging risk factor for HCC in Hong Kong.**
3. **Antiviral (HCV/HBV) treatment can decrease the incidence of HCC.**
4. **Typical HCC can be diagnosed by imaging, regardless of its size and AFP values, if a typical vascular pattern of arterial enhancement with portal venous wash-out is obtained on dynamic CT, dynamic MRI, or CEUS.**
5. **HCC screening with U/S and AFP every six months is indicated for patients with hepatitis B and C infection only.**
6. **Liver transplantation provides the best curative treatment for all HCC patients from an oncologic point of view.**
7. **Resection of extrahepatic metastasis is never indicated in HCC patients.**
8. **Image-guided percutaneous local ablation therapies with ethanol injection, microwave ablation (MWA), radiofrequency ablation (RFA), or irreversible electroporation (IRE) are a potentially curative treatment for patients with small HCC.**
9. **Immunotherapy is not approved for the treatment of HCC.**
10. **Immunosuppression doses should not be reduced in liver transplant patients in the absence of COVID-19 infection.**

ANSWER SHEET FOR SEPTEMBER 2020

Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need?

Dr Gregory CHENG

MD(U of Toronto), PhD (Biological Science)

Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong SAR, China
Faculty of Health Science, University of Macau, Macau SAR, China

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to August 2020 Issue

Elimination of Hepatitis B and C in Hong Kong

1. T 2. F 3. F 4. F 5. T 6. T 7. T 8. F 9. T 10. T

KEYTRUDA®
(pembrolizumab)

Regardless of PD-L1 Expression Level[2]

THE ONLY ANTI-PD-1 FIRST-LINE COMBINATION TREATMENT FOR NONSQUAMOUS mNSCLC*

KEYTRUDA: **HELPING TO REDEFINE SURVIVAL EXPECTATIONS** FOR MORE PATIENTS WITH NONSQUAMOUS mNSCLC[1]

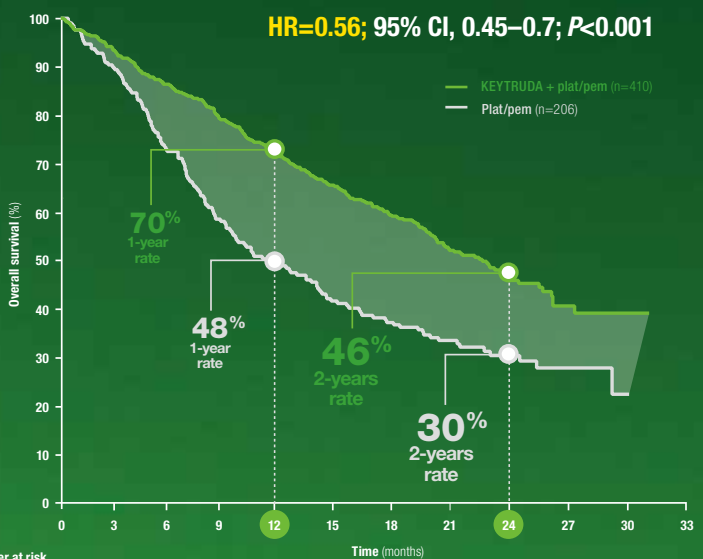
* **KEYTRUDA,** in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.[2]

22 MONTHS MEDIAN OS WITH KEYTRUDA + plat/pem[a] (95% CI, 19.5 - 25.2)
vs 10.7 months with plat/pem alone (95% CI, 8.7 - 13.6)

9 MONTHS MEDIAN PFS WITH KEYTRUDA + plat/pem[a] (95% CI, 8.1 - 9.9)
vs 4.9 months with plat/pem alone (95% CI, 4.7 - 5.5)

46% 2-YEAR OS RATE WITH KEYTRUDA + plat/pem[a]
vs 30% with plat/pem alone

Kaplan-Meier Estimates of OS in KEYNOTE-189 (ITT)[1,a,b]



Number at risk												
KEYTRUDA + plat/pem	410	377	346	316	283	256	234	144	79	28	2	0
Plat/pem	206	183	149	115	99	82	72	45	26	10	0	0

Adverse reaction profile for KEYTRUDA in combination with pemetrexed and platinum chemotherapy was consistent with that for each of the individual products.

[a] At data cutoff, median follow-up time was 23.1 months.[2] [b] HR based on the stratified Cox proportional hazard model; P value based on stratified log-rank test.[1]
mNSCLC = metastatic NSCLC; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase. Plat/pem = cisplatin or carboplatin + pemetrexed; OS = overall survival; HR = hazard ratio; CI = confidence interval.

Study Design: A Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in treatment-naïve patients with nonsquamous mNSCLC, including patients with no PD-L1 expression. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or patients who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking history, cisplatin vs carboplatin, objective response rate (ORR) and PD-L1 tumor expression (TPS <1% vs TPS ≥1%). Patients were randomized (2:1) to receive: KEYTRUDA 200 mg (n=410), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed Q3W for up to 24 months; or placebo (n=206), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by placebo and pemetrexed Q3W. Treatment continued until progression of disease or unacceptable toxicity. Primary efficacy outcome measures were OS and PFS as assessed by BICR per RECIST 1.1. Additional efficacy outcome measures were ORR and duration of response (DOR) as assessed by BICR per RECIST 1.1. Patients receiving placebo, platinum chemotherapy, and pemetrexed who experienced disease progression could cross over to receive KEYTRUDA as monotherapy.

Selected Safety Information for KEYTRUDA (pembrolizumab)
Indications: • Melanoma – KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma. • Non-Small Cell Lung Cancer – KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥50%) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. • Urothelial Carcinoma – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score (CPS) ≥10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • Classical Hodgkin Lymphoma – KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. **Dosage and administration:** • Patient Selection: Select patients for treatment of metastatic NSCLC with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression. • **Melanoma:** 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. • **NSCLC:** – In combination with pemetrexed and platinum chemotherapy or as a single agent for metastatic NSCLC patients that has not been previously treated with chemotherapy. 200mg. When administering KEYTRUDA in combination with chemotherapy, it should be administered prior to chemotherapy when given on the same day. - As a single agent for metastatic NSCLC patients that has been previously treated with chemotherapy. 2mg/kg. – KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. • **Urothelial Carcinoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. • **Classical Hodgkin Lymphoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. **Contraindications:** • None **Precautions:** • Immune-Mediated Pneumonitis • Immune-Mediated Colitis • Immune-Mediated Hepatitis • Immune-Mediated Endocrinopathies (hypophysitis; thyroid disorders - hyperthyroidism, hypothyroidism and thyroiditis, Type 1 diabetes) • Immune-Mediated Nephritis and Renal Dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) • Other Immune-Mediated Adverse Reactions • Infusion-Related Reactions (including hypersensitivity and anaphylaxis) • Complications of Allogeneic HSCT in Patients with Allogeneic HSCT prior to KEYTRUDA treatment • Increased Mortality in Patients with Multiple Myeloma • Embryofetal Toxicity • **For detailed precautions, please consult the full prescribing information. Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) when Keytruda was used as a single agent were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain; when Keytruda was used in combination with pemetrexed and platinum chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, and pyrexia. • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis • Immune-mediated endocrinopathies • Immune-mediated nephritis and renal dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) Other immune-mediated adverse reactions • Infusion-related reactions • As with all therapeutic proteins, there is the potential for immunogenicity. • **For detailed adverse events, please consult the full prescribing information.**

Before prescribing KEYTRUDA®, please consult the full prescribing information.

Reference:
1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018; 378(22):2078–2092. **2.** Hong Kong Product Circular (KEYTRUDA, MSD) **3.** Gadgeel S, et al. KEYNOTE 189: Updated Overall Survival and Progression After the Next Line of Therapy With Pembrolizumab plus Chemotherapy With Pemetrexed and Platinum vs Placebo plus Chemotherapy for Metastatic Nonsquamous Non-Small-Cell Lung Cancer. Poster Presented at the 2019 American Society of Clinical Oncology Annual Meeting; May 31 to June 4, 2019; Chicago, IL, USA

MSD
Merck Sharp & Dohme (Asia) Ltd.
27/F., Lee Garden Two, 28 Yun Ping Road, Causeway Bay, Hong Kong. Tel: (852) 3971 2800 Fax: (852) 2834 0756 Website: www.msd.com.hk

HK-KEY-00040 07/19

Practice of Clinical Hepatology During COVID-19 Pandemic -the APASL, EASL and AASLD Recommendations, Which Ones to Follow?

Dr George LAU

MBBS(HK), MD(HK), FHKCP, MRCP(UK), FRCP(Edin), FRCP(Lond), FHKAM(Medicine)

Chairman and Senior Consultant in Gastroenterology and Hepatology, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China
Chair Professor in Clinical Hepatology, The 5th Medical Centre of Chinese PLA General Hospital - Hong Kong Humanity & Health Medical Group, Beijing, China
Honorary Professor, Institute of Hepatology, 111 Coldharbour Lane, London SE5 9NT, United Kingdom

Dr John W. WARD

MD (Birm)

Coalition for Global Hepatitis Elimination, Task Force for Global Health, Decatur, GA, USA

Dr George LAU Dr John W. WARD

The Asian-Pacific Association for the Study of the Liver (APASL), American Association for the Study of Liver (AASLD), European Association for the Study of Liver (EASL), and US Centre of Disease Control (CDC) have all established guidelines for the practice in clinical Hepatology during the COVID-19 pandemics.[1-6] All of them emphasise the importance of social distancing in reducing exposure to SARS-CoV-2. To achieve this goal, the current practice in Hepatology may need to be adjusted. The adjustment must take into considerations regional practice, local resources, facilities and manpower. This article compares the APASL[1], AASLD[2] and EASL[3] recommendations for the management of chronic liver disease during COVID-19 pandemic and highlights the differences.

REDUCTION OF EXPOSURE AND SARS-CoV-2 TESTING

All the guidelines aim to prevent or reduce SARS-CoV-2 transmission between patients and healthcare personnel by physical distancing. All suggest reducing hospital visits by using telemedicine or phone visits to replace hospital visits in non-urgent situations. Blood tests should be performed in local laboratories and medicine dispensed by the local pharmacy as much as possible. AASLD recommends pre-clinic patients' temperature check and refusing entry of anyone with fever or COVID-19 symptoms into the liver clinic. Neither APSAL nor EASL specifically mention this strategy. AASLD recommends SARS-CoV-2 testing in patients with symptoms suggestive of COVID-19, but this may miss out a high number of asymptomatic but potentially infectious SARS-CoV-2 infected patients.[7] APASL recommends SARS-CoV-2 testing on patients with COVID-19 symptoms or those at high risk of exposure. EASL just recommends following the local hospital practice.

SARS-CoV-2 testing availability, cost and epidemiological factors must be considered. In Hong Kong, the test is quite expensive. Therefore, at times of high number of new COVID-19 cases daily, the APASL recommendation may be more appropriate. With low number of daily new cases, one may follow AASLD guidance.

AASLD and APSAL recommend a full set of personal protective equipment (PPE) including N95 masks and double gloves for an endoscopy procedure. EASL does not specify PPE requirements. *With adequate PPE supply, one may follow AASLD, or APSAL guidance and many procedures can be safely carried out. If PPE is in short supply, non-urgent endoscopy and biopsy procedures should be cancelled.*

MANAGEMENT OF LIVER TRANSPLANTATION DURING COVID-19

Liver Transplantation (LT) is the curative option for many liver diseases. However, with limited access to personal protective equipment (PPE) and other resources during the COVID-19 pandemic, and the potential risks of transmission between patients and healthcare workers, many governments have implemented restrictions on elective surgery including liver transplantation. All three guidelines recommend testing of liver transplant donors and recipients and prioritising patients with high Model for End-stage Liver Disease (MELD) scores, risk of decompensation, or tumour progression. There is controversy as to whether liver transplantation should be carried out in a COVID-19 recipient and whether liver should be harvested from a COVID-19 donor. AASLD does not recommend transplantation in SARS-CoV-2-positive recipients. APASL suggest careful evaluation of the risks of delaying transplantation and the risk of disease transmission and suggests that liver transplantation should only be performed in patients who have at least two negative SARS-CoV-2 results from sensitive nucleic acid amplification tests and perhaps the presence of neutralising antibodies. Finally, there is the issue of whether post-transplantation therapy should be adjusted during the COVID-19 pandemic as immunosuppression may potentially increase the risk of severe COVID-19. On the other hand, graft rejection may occur if post-transplant immunosuppression is reduced.

Without solid data on the increase risk of severe COVID-19 in immunosuppressed patients, all three guidelines recommend standard post-transplant immunosuppressive therapy in patients with mild COVID-19. In those COVID-19 LT patients with severe lymphopenia or worsening respiratory status, the dosage of azathioprine, mycophenolate and calcineurin inhibitor may be reduced but not discontinued. Both EASL and APASAL emphasise the importance of vaccination for Streptococcus pneumoniae and influenza in LT recipients and in patients with decompensated liver disease.

In Hong Kong, most hospitals have deferred LT during the COVID-19 pandemic. Liver should not be harvested from a

live donor with COVID-19. It is also highly unlikely that a deceased COVID-19 patient would be a suitable liver donor. If a non-infected cadaveric liver is available, one may follow the APASL guidance of performing LT in recipients who have at least two negative SARS-CoV-2 results from sensitive nucleic acid amplification tests as well as the presence of neutralising antibodies.

MANAGEMENT OF PATIENTS WITH CHRONIC LIVER DISEASE (CLD) DURING COVID-19

Elevation of serum transaminases is commonly observed in COVID-19 patients. This may be caused by SARS-CoV-2 infections, exacerbation of preexisting CLD or drug-induced liver toxicity. The care team must rule out flare-up of hepatitis B or C and drug toxicities.

HEPATITIS B AND C PATIENTS

There is no data to suggest that SARS-Cov-2 infection will lead to a flare-up of hepatitis B/C or patients with hepatitis B/C are at risk of severe COVID-19.

Both AASLD and APSAL recommend that hepatitis B/C patients already on anti-hepatitis treatment should have therapy continued. For hepatitis B/C patients not on anti-hepatitis therapy, therapy should be started if there is hepatitis flare-up.

Prophylactic treatment should be started in hepatitis B patients receiving immunosuppressive therapy for COVID-19, such as anti-IL6 therapy. In general, there is no need for prophylactic hepatitis C therapy.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

EASL mentions patients with non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) may suffer from metabolic comorbidities such as diabetes, hypertension and obesity, putting them at increased risk of severe COVID-19. APASL and AASLD suggest NAFLD is an independent prognostic factor for COVID-19 progression.

In Hong Kong, the prevalence of NAFLD is increasing, and NAFLD patients should be considered a high-risk group for severe COVID-19 and prioritised for investigational treatment according to APASL recommendations.

AUTOIMMUNE LIVER DISEASE

Immunosuppressive therapy recommendations are similar in all three guidelines and same as those for post-transplant patients.

COVID-19 THERAPY IN PATIENTS WITH CHRONIC LIVER DISEASE (CLD)

Most COVID-19 therapy may have hepatotoxicity, and the issue here is whether CLD patients with SARS-CoV-2 infections should receive investigational therapy.

So far, clinical data did not show any difference in liver enzymes abnormalities in COVID-19 patients with or without CLD. All three guidelines suggest careful monitoring of liver functions.

Currently, there are no proven therapies to prevent or treat COVID-19 infection, and many investigational or off-label therapeutics for COVID-19 carry hepatotoxicity. The results of lopinavir-ritonavir and hydroxychloroquine in randomised, controlled trials are disappointing. Close monitoring of liver functions is recommended for CLD COVID-19 patients on remdesivir.

MANAGEMENT OF HEPATOCELLULAR CARCINOMA (HCC) PATIENTS DURING COVID-19

All three guidelines suggest reducing patients' visits and a delay of 2 months in HCC ultrasound surveillance.

The debate here is whether treatment should be deferred in patients with newly diagnosed HCC if they have coexisting SARS-CoV-2 infection. For those HCC patients already on tyrosine kinase inhibitors (TKI) or checkpoint inhibitors, it is not certain whether they should continue treatment if they become infected with SARS-CoV-2. For newly diagnosed Child-Pugh class A HCC patients, liver resection provides the best chance of cure. Delaying liver resection in these patients may result in HCC progression to an unresectable stage. However, the risk of SARS-CoV-2 transmission to healthcare personnel during LR must be considered. For HCC patients already on or planning to start checkpoint inhibitor therapy, there is a potential risk that the therapy may cause cytokine storms and progression to severe COVID-19.

AASLD recommends proceeding with the indicated HCC treatments rather than deferring them.

EASL, on the other hand, recommends deferring locoregional therapies and temporarily withdrawing immune-checkpoint inhibitor therapy. HCC patients with non-severe COVID-19 may continue TKI on a case-by-case basis.

APSAL guidelines are in between, recommending proceeding with radiofrequency ablation, transcatheter-arterial chemoembolisation, TKI or immunotherapy while deferring LR and LT. Changing immunotherapy schedules to every 4-6 weeks may be considered to reduce hospital visits.

For patients with operable HCC, we suggest following the AASLD guidelines of proceeding with surgery under optimal PPE protection as this offers the best chance of long-term disease control. If LR/LT is not feasible, then APASL recommendations of radiofrequency ablation or TACE should be carried out. For unresectable cases, TKI will be preferred over checkpoint inhibitors. Patients already on TKIs should continue with standard dose unless there is COVID-19 progression.

CONDUCT OF CLINICAL TRIALS DURING COVID-19

Both APASL and AASLD have provided recommendations for the conduct of clinical trials during the COVID-19 pandemics. Both recommend the use of virtual visits, local laboratory testing/ imaging and home delivery of medications in the place of hospital visits to reduce SARS-CoV-2 exposure. APASL specifically recommends that all contingency measures during COVID-19 pandemic should have local regulators' approval, participants' consents and all deviations from the contingency measures must be clearly documented.

SUMMARY

All three guidelines recommend social distancing and reduction of exposure to SARS-CoV-2, but there are differences in the stringency of the measures. Individual institution should adopt the guidance according to local resources and epidemiological factors.

References

1. APASL Covid-19 Task Force, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. Hepatol Int. 2020 May 23:1–14. doi: 10.1007/s12072-020-10054-w
2. Fix OK, Hameed B, Fontana RJ. Insights for hepatology and liver transplant providers during the COVID-19 pandemic. AASLD Expert Panel Consensus Statement Hepatology. 16 April 2020 https://doi.org/10.1002/hep.31281
3. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID Position Paper. JHEP 2020; 2:100113.
4. World Health Organization. Guidance for health workers. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus2019/technical-guidance/health-workers. Accessed May 4, 2020.
5. Centres for Disease Control and Prevention. Infection control guidance for healthcare professionals about coronavirus (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-contr ol.html. Updated April 24, 2020. Accessed May 4, 2020.
6. World Health Organization. Coronavirus disease (COVID-19) technical guidance: patient management. https://www.who.int/emerg encies/diseases/novel-coronavirus-2019/technical-guidance/patientmanagement. Accessed May 4, 2020.
7. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility—King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep 2020; 69:377-381.

FOR TODAY FOR TOMORROW

DECLARE A BETTER TOMORROW

Forxiga® - Your Cardio-renal Guardian

START TODAY BETTER OUTCOME TOMORROW

DECLARE

Largest CVOT of SGLT2i with the **broadest** population from multiple risk factors to established ASCVD[1]

Reduction in cardiorenal events observed in T2DM patients[1]

↓17% CV death or hospitalisation for HF*

↓24% Cardiorenal composite endpoint†

↓47% Renal-specific composite endpoint†

Reassured safety profile of Forxiga®[1]

NEW LABEL AVAILABLE

* hHF alone was a separate, nominally significant exploratory endpoint in the DECLARE trial – the primary endpoint composite of CV death/hHF was driven by hHF.
† Nominally significant, prespecified exploratory outcome.

ASCVD=atherosclerotic cardiovascular disease. CV=cardiovascular. CVOT=cardiovascular outcome trial. hHF=hospitalisation for heart failure. HF=heart failure. SGLT2i=sodium-glucose cotransporter 2 inhibitors. T2DM=type 2 diabetes mellitus.

Reference: 1. Wiviott SD, et al. N Engl J Med 2019;380:347-57.

Abridged Prescribing Information (API)
FORXIGA® (dapagliflozin)
Composition: Dapagliflozin propanediol monohydrate film coated tablet, 5 mg or 10 mg. **Therapeutic Indications:** For the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance, or in addition to other medicinal products for the treatment of type 2 diabetes. **Dosage and Administration:** Recommended dose is 10 mg to be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. **Contraindications:** Hypersensitivity to the active substance or to any of its excipients. **Warnings and Precautions:** Renal function, risk of volume depletion and/or hypotension should be taken into account in patients. Dosage of insulin and sulphonylurea (SU) may need to be readjusted to reduce the risk of hypoglycaemia. May add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Use with caution in patients with increased risk of diabetic ketoacidosis; on anti-hypertensive therapy with a history of hypotension; elderly (≥ 65 years). Treatment should be temporarily interrupted when volume depleted; when treating pyelonephritis or urosepsis; in patients who are hospitalized for major surgical procedures or acute serious medical illnesses, until ketone values are normal. Should not be initiated in patients with a GFR < 60 ml/min; with type 1 diabetes; with hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption. Discontinue if GFR is persistently below 45 ml/min; if suspected or diagnosed diabetic ketoacidosis; if Fournier's gangrene is suspected; when pregnancy is detected; while breast-feeding. Limited or no data in cardiac failure; pregnancy; and paediatric population. **Adverse Reactions:** Very common: hypoglycaemia when used with SU or insulin. Common: vulvovaginitis, balanitis and related genital infections, urinary tract infection, dizziness, rash, back pain, dysuria, polyuria, dyslipidaemia, decreased creatinine renal clearance (during initial treatment), and increased haematocrit. Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal and genital pruritus, increased blood creatinine (during initial treatment), increased blood urea, and decreased weight. Rare: diabetic ketoacidosis. Very rare: necrotising fasciitis of the perineum (Fournier's gangrene), angioedema. Not known: acute kidney injury. **Drug interaction:** Coadministration with rifampicin may reduce dapagliflozin systemic exposure; coadministration with mefenamic acid may increase dapagliflozin systemic exposure. Monitoring glycaemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. **Storage:** Store below 30 °C. **Local prescribing information is available upon request. API.HK.FOR.0720**

Please contact HKPatientSafety@astrazeneca.com for reporting of Individual Case Safety Report (ICSR) to AstraZeneca Hong Kong Limited.

HK-41191 14/08/2020 4IC_1441A

AstraZeneca 阿斯利康

AstraZeneca Hong Kong Limited
Unit 1-3, 11/F, 18 King Wah Road, North Point, Hong Kong
Tel: (852) 2420 7388 Fax: (852) 2422 6788

forxiga dapagliflozin

NAFLD in Chinese : Growing Concern and Management Strategy

Dr Jian-gao FAN

Director, Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Children's Digestion and Nutrition, Shanghai 200092, China

Dr Jing ZENG

Consultant, Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

Dr Jian-gao FAN Dr Jing ZENG

INTRODUCTION

Along with the ageing population, the epidemics of obesity and the effective control of viral hepatitis, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the world, affecting about 1.7 billion people worldwide[1]. The spectrum of NAFLD includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and related cirrhosis, and hepatocellular carcinoma (HCC). Considering the close relationship of NAFLD with obesity, metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), NAFLD is currently proposed to be renamed as metabolic dysfunction associated fatty liver disease (MAFLD)[2]. In addition to causing serious complications of the liver, NAFLD is also a risk factor for MetS, T2DM, cardiovascular disease, chronic kidney disease, and various malignant tumours[3,4]. It is necessary to attach great importance to the prevention and control of the current epidemic of NAFLD. Therefore, the Chinese Fatty Liver and Alcoholic Liver Disease Study Group, established in 2001, have issued a series of consensus guidelines for the diagnosis and treatment of NAFLD[5], aiming to reduce the disease burden in China.

PREVALENCE, INCIDENCE AND NATURAL HISTORY OF NAFLD IN CHINA

Epidemiological investigations of fatty liver have been conducted in China since the 1990s. Due to the socio-economic changes, sedentary lifestyle and westernised diet in the past 30 years, NAFLD has become a public health issue in China. The prevalence of NAFLD in Shanghai adults has increased rapidly, from 3.9% in 1995, 14.0% in 2002, 17.3% in 2005, to 43.7% in 2015. Nationwide, the incidence of NAFLD in China has also increased from 4.2% between 2007 and 2010, 4.6% between 2011 and 2013, to 5.2% between 2014 and 2016[6]. NAFLD includes non-obese or lean NAFLD and NAFLD in children. NAFLD is now the most common chronic liver disease in China, accounting for nearly 50% of chronic liver diseases[6-11].

China is the largest country in Asia, with a land area of 9.6 million square kilometres, a population of 1.33 billion people and 56 nationalities. The different customs, dietary habit, and socio-economic levels have affected the epidemiology of NAFLD countrywide. A meta-analysis including 392 epidemiological surveys from 2008 to 2018 with a total of 2,054,554 people shows that the prevalence of NAFLD in China is now as high as 29.2% and is higher in middle age (younger than 45 years of age), males, northwestern region, Taiwan, per capita GDP greater than 100,000 yuan regions, and Uyghur and Hui ethnic groups[12].

The incidence of NAFLD also varies between regions, but related data are still limited.

According to reports, 20% to 40% of NAFLD patients will develop NASH or fibrosis, and even cirrhosis or HCC. The Gut and Obesity in Asia (GOASIA) Workgroup found that 58.9% and 46.1% of patients with NAFLD were diagnosed as NASH by biopsy, in mainland China and Hong Kong respectively[12, 13]. In China, there are more HBV-infected patients than in Western countries, and the status of NAFLD combined with viral hepatitis may greatly increase the risk of liver cirrhosis and HCC[5, 8].

As the prevalence and incidence of NAFLD have increased significantly and will continue to increase in view of the obesity and T2DM epidemics, doctors and the public must pay more attention to the harms of NAFLD.

DIAGNOSIS OF NAFLD IN CHINA

At present, more than 90% of NAFLD in China are diagnosed by ultrasound. But ultrasound is inaccurate if the liver fat content is less than 30%, and ultrasound cannot provide data on liver fibrosis and inflammation status. Although MRI / MRS and CT are more accurate methods for diagnosing hepatic steatosis than ultrasound, their clinical availability and examination prices have prevented them from being routinely adopted clinically. FibroScan and MRE can detect liver fibrosis, but these techniques are not commonly used in China clinical services, especially in community hospitals. Many serum biomarkers/test groups and algorithm models are currently being studied to facilitate the diagnosis and staging of NAFLD. However, the optimal cut-off values of these biomarkers for the diagnosis and staging of NAFLD still need to be established or verified in future studies.

MANAGEMENT STRATEGY OF NAFLD IN CHINA

In terms of treatment, there are no drugs specifically approved for the treatment of NAFLD. At present, the efficacy and safety of several promising drugs have not

been fully evaluated in the Asian population, especially for the Chinese population, as phase III clinical trials for the treatment of NASH with these new drugs are mainly conducted in Japan and South Korea. Related randomised controlled trials (RCT) that had been conducted in China included lifestyle interventions, traditional Chinese medicine (TCM), plant extracts, probiotics, and diabetes drugs, were of variable quality and inconclusive. In the future, it is necessary to improve the quality of NAFLD RCTs in China. Through careful trial design and expansion of sample size, and long-term follow-up, the quality of these researches, especially on Chinese medicine, will be improved.

Sufficient exercise had been shown to effectively reduce liver fat content, an important endpoint for the treatment of NAFLD in China and the elevated liver enzyme levels[14]. Intensive exercise programs or a combination of aerobic exercise and dietary adjustments can further reduce liver fat content. Dietary adjustments are more important as the unhealthy diets, such as sugar-sweetened beverages, make a greater impact on body metabolism and promote the occurrence of obesity, T2DM and NAFLD. However, it is concerning that not only the general population but also the government do not pay too much attention to exercise in China[15]. This situation needs to be changed.

If the blood pressure, and the blood glucose, lipids, transaminases, and other indicators of NAFLD patients have not returned to normal values after 3 to 6 months of lifestyle changes, the relevant drugs, such as anti-hypertensives, metformin or statin may be added. Many patients may need to use hepatoprotective drugs along with lifestyle changes and effective weight management.

CONCLUSION

The prevalence of NAFLD in China has increased rapidly in the past 20 years. At present, the prevalence of NAFLD in China has exceeded the global average. The prevalence of NAFLD continues to rise with the obesity and T2DM epidemics, resulting in various clinical complications, economic burden, and serious effects on the quality of life of NAFLD patients. However, the prevalence and harm of NAFLD have not yet received enough public attention. The screening of NAFLD and HCC in high-risk groups has not been effectively carried out, and many patients with NAFLD have not received the timely diagnosis and effective intervention. At present, the national epidemiological data of NAFLD in Chinese is still lacking, and there is no large sample size, long-term follow-up cohort study to explore the natural history of NAFLD. We need to develop better non-invasive detection methods for quantitative assessment of NAFLD and its associated inflammation and liver fibrosis. Although it may be possible to have effective drugs for the treatment of NAFLD in the future, we should also focus on the proper diet and lifestyle adjustments. We must understand the full financial burden of NAFLD and the economic impact of treatment effects. Finally, it is necessary to raise the awareness of the importance of NAFLD among ordinary people, relevant clinicians, medical insurance institutions, pharmaceutical companies, and policy departments to reduce the prevalence and disease burden of NAFLD effectively.

References

1. Younossi Z, Tacke F, Arrese M, et al. Global Perspectives on Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. Hepatology 2019; 69(6): 2672-2682.
2. Eslam M, Sanyal AJ, George J; International Consensus Panel. NAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020; 158(7): 1999-2014.e1.
3. Kanwal F, Kramer JR, Li L, et al. Effect of Metabolic Traits on the Risk of Cirrhosis and Hepatocellular Cancer in Nonalcoholic Fatty Liver Disease. Hepatology 2020; 71(3): 808-819.
4. Younossi Z , Golabi P, Avila L, et al. The Global Epidemiology of NAFLD and NASH in Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis. J Hepatol 2019; 71(4): 793-801.
5. Fan JG, Wei L, Zhuang H. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4):163-173.
6. Zhou JH, Zhou F, Wang WX, et al. Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology 2020; 71(5): 1851-1864.
7. Wu YK, Zheng Q, Zou BY, et al. The Epidemiology of NAFLD in Mainland China With Analysis by Adjusted Gross Regional Domestic Product: A Meta-Analysis. Hepatol Int. 2020; 14(2): 259-269.
8. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017; 67(4): 862-873.
9. Eslam M, Fan JG, Mendez-Sanchez N. Non-alcoholic fatty liver disease in non-obese individuals: the impact of metabolic health. Lancet Gastroenterol Hepatol 2020; May 12:S2468-1253(20)30090-X.
10. Zhou J, Zhou F, Wang W, et al. Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology 2020; 71(5): 1851-1864.
11. Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019; 4(5): 389-398.
12. Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and MetaAnalysis. Hepatology 2019; 70(4):1119-1133.
13. Sheka AC, Adeyi O, Thompson J, et al. Nonalcoholic Steatohepatitis: A Review. JAMA 2020; 323(12): 1175-1183.
14. Asian Pacific Association for the Study of the Liver. Guidelines [Internet]. APASL. 2020 [cited 2020 Feb 26]. Available from:http://apasl.info/guidelines/.
15. Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2020; 5(2):167-228.

A Coalition Advancing Progress Toward Global Hepatitis Elimination: Achievements, Challenges and Opportunities

Dr John W. WARD

Dr John W. WARD

MD (Birm)

Coalition for Global Hepatitis Elimination, Task Force for Global Health, Decatur, GA, USA

Viral hepatitis is a large health problem globally now targeted for elimination. The two major forms of viral hepatitis, hepatitis B virus (HBV) and hepatitis C virus (HCV) cause over a million deaths per year from cirrhosis and liver cancer[1]. At least 325 million persons are living with HBV (257 million, 3.5% prevalence) and HCV (71 million, 1% prevalence) globally. Asian Pacific countries bear 45% of the global HBV burden[2]. China alone has a population of 80-110 million HBV infected persons, a quarter to a third of the global burden of HBV disease. The HBV infection prevalence, of ~7.0% in China are among the highest in the world[2,3].

Interventions are available to prevent, test and treat HBV and HCV infection. Hepatitis B vaccination of infants beginning at birth prevents over 95% of chronic HBV infections. Transmission of HBV and HCV, both blood-borne viruses, is effectively prevented by safe injection and other infection control procedures in health care and in the community, including among persons who inject drugs (PWID). HBV and HCV diagnosis and treatment prevents pre-mature mortality. In 2014, the first all-oral curative therapies for HCV were approved greatly improving patient outcomes. Indeed, clinical experience has confirmed 8-12-week regimens of HCV medications cure over 95% of HCV infected persons[1].

In 2015, reacting with concern to the hepatitis disease burden at a time of effective interventions, the United Nations called on the world to "combat hepatitis"[4]. In 2016, the WHO set goals for viral hepatitis elimination defined as a 90% decline in HBV and HCV incidence and a 65% reduction in HBV and HCV mortality by 2030[5]. The achievement of HBV and HCV elimination goals can avert over 26 million deaths, including over four million deaths from HBV and HCV infection by 2030[6].

To reach these HBV and HCV elimination targets, countries will need to scale up access to HepB vaccination and other interventions that prevent transmission, and testing and treatment to prevent mortality (Table 1). However, in many countries, access to HepB vaccination, and HBV and HCV care and treatment are poor. Recognising the challenges in implementing multiple interventions, advisory bodies recommended the development of a global coalition to build capacity and support for hepatitis elimination efforts worldwide[7,8]. In response, the Task Force for Global Health launched the Coalition for Global Hepatitis Elimination. This article describes the Hong Kong origins of the Coalition, the Coalition capacity building for hepatitis elimination aided by partnerships in Hong Kong, and Guangzhou, and opportunities for sharing strategies from successful hepatitis prevention programmes while learning how to overcome barriers to hepatitis elimination in China, Asia Pacific and globally.

COALITION FOR GLOBAL HEPATITIS ELIMINATION: ORIGINS IN HONG KONG

In 2011, ZeShan Foundation, a Hong Kong-based family foundation, launched a novel public-private partnership to aid mainland China in the prevention of mother-to-child transmission (PMTCT) of HBV. With the technical assistance of the US CDC, ZeShan Foundation donated resources to address the financial shortfalls threatening WHO assistance to the national HBV PMTCT programme in mainland China. The WHO programme was successfully completed with a formal evaluation confirming that the HepB vaccination programme achieved 85% HBV immunity among vaccinated children, and a 90% decrease in HBsAg prevalence (0.96%)[9]. With the mainland China programme as a model, ZeShan Foundation, in partnership with US CDC extended financial support for WHO to assist HBV PMTCT programmes in neighbouring Asian countries (10). With the experience of this successful public-private partnership, the CDC Foundation created a Viral Hepatitis Action Coalition to help the US CDC make meaningful advances in the prevention, screening, and treatment of viral hepatitis (https://www.cdcfoundation.org/vhac#). The Viral Hepatitis Action Coalition (VHAC) charter expired in 2016, CDC subsequently provided in-kind support for the Task Force for Global Health, to engage partners in the development of a coalition modelled after coalitions for other global disease elimination initiatives managed by the Task Force. VHAC partners moved to the Task Force for Global Health (TFGH) to continue support of global hepatitis elimination through the activities of the Coalition. ZeShan Foundation continues their support for eliminating hepatitis in developing countries.

HOW THE COALITION ASSISTS GLOBAL HEPATITIS ELIMINATION

Launched in July 2019, the mission of the Coalition is to strengthen the capacity of national and sub-national hepatitis elimination programmes through funding, advocacy, technical assistance, knowledge generation and dissemination among partners united in a community of practice. To advance progress toward hepatitis elimination, Coalition provides services in five strategic axes.

Table 1. WHO interim and final targets for implementation of interventions to achieve hepatitis elimination (Excerpted from Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. www.who.int accessed 8/03/2020)

Target areas	Baseline 2015	2020 target	2030 target
Service coverage			
Prevention			
Three-dose HBV for infants (coverage %)	84	90	90
Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)	39	50	90
Blood and injection safety			
Blood safety: donations screened with quality assurance (coverage %)	97	95	100
Injection safety: use of engineered devices[c] (coverage %)	5	50	90
Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])	20	200	300
Treatment			
Diagnosis of HBV and HCV (coverage %)	9-20	30	90
Treatment of HBV and HCV	7%-8%	5 million (HBV) and 3 million (HCV)	80% eligible treated
Impact leading to elimination			
Incidence of chronic HBV and HCV infections	6-10 million	30% reduction	90% reduction
Mortality from chronic HBV and HCV infections	1.34 million	10% reduction	65% reduction

[a]HBV: hepatitis B virus.
[b]HCV: hepatitis C virus.
[c]Although the service coverage target is about output (adoption of reuse prevention injection devices), the C.5 indicator focuses on outcome (provision of safe injections).

Convene a Community of Practice

The Coalition's community of practice for hepatitis elimination links partners with different financial resources, technical expertise and leadership responsibilities for hepatitis prevention, care and treatment. In the first year of operation, over 100 partners at the global, national and sub-national level are sharing financial resources, implementation tools and lessons learned on self-managed programme pages at www.globalhep.org.

Capacity Building Partnerships

No one individual, organisation or government can eliminate hepatitis. Coalition partners include government agencies, industry, professional associations, philanthropic and other civil society organisations. With the information shared by programmes, the Coalition develops collaboration among partners to address the challenges faced by specific programmes initiatives.

Data Dashboards for Over 190 Countries

For 191 countries, the Coalition complies data from strategic information partners to monitor trends in hepatitis burden, progress toward elimination goals and access to interventions (https://www.globalhep.org/country-profiles). Partners in the strategic information collaborative include WHO, the European CDC, CHAI, the University of Washington Global Burden of Disease project, Medicine Patent Pool, authors of systematic reviews and others. All information is linked to primary data sources, and the data files and graphics are freely downloadable. Together with the lessons learned by programmes, the Coalition provides a unique resource to check on progress toward elimination, learn of hepatitis elimination activities and promote collaborations across programmes[11].

Hepatitis Elimination Scorecards

Scorecards reveal strengths and gaps in hepatitis elimination programmes (Fig. 1, Fig. 2). In China, hepatitis B prevention is a national priority with HepB vaccination coverage among infants exceeding 95%. Globally, many countries have yet to develop hepatitis elimination plans, or set targets for HepB vaccination, and other prevention measures. Indeed, China and most other countries have not reduced HBV and HCV mortality by 10%, the WHO 2020 interim target (Fig. 1), revealing the need for improvements in HBV and HCV screening and linkage to care [1, 12-16].

Build a Trusted Dynamic Evidence Base for Hepatitis Elimination

To date, the Coalition has complied over 500 resources to guide programme planning with links to normative guidance, systematic reviews, and reports from WHO and other authoritative organisations. For example, the evidence base includes a synthesis of immunisation programme evaluations to guide the implementation of HepB birth dose vaccination. To guide national planning for hepatitis elimination, the Coalition assembled and reviewed almost 100 national and sub-national hepatitis action plans. With a checklist prepared with WHO, the Coalition highlights essential components of a hepatitis prevention plan including elimination targets, financing, implementation strategies, and partnerships to reach key populations (https://www.globalhep.org/evidence-base). The evidence base is dynamic with recent reports on the progress of the COVID-19 pandemic, the interaction between viral hepatitis and SARS-CoV-2 infection and recommendations for the management of patients with chronic liver disease during the COVID-19 pandemic.

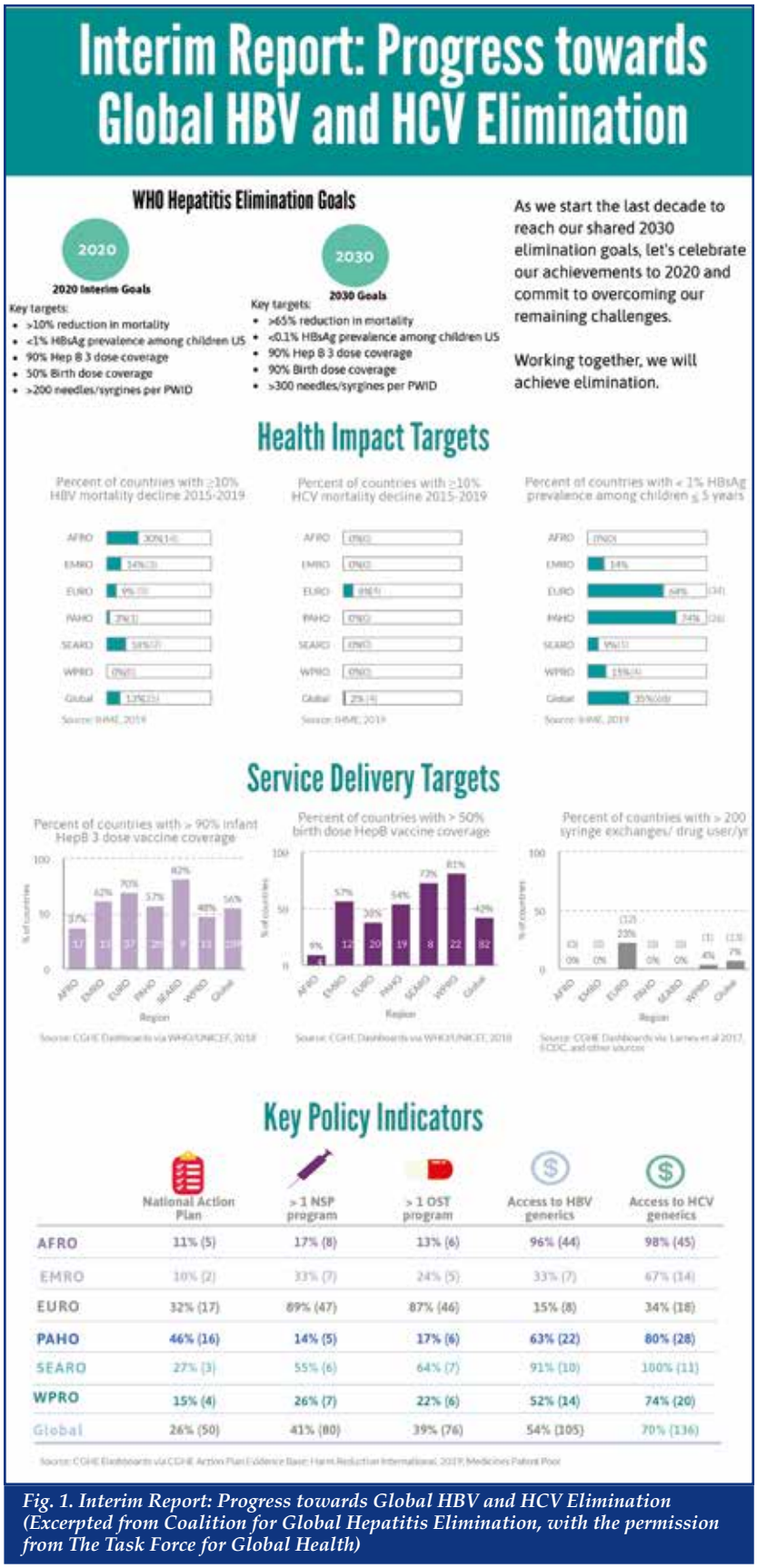


Fig. 1. Interim Report: Progress towards Global HBV and HCV Elimination (Excerpted from Coalition for Global Hepatitis Elimination, with the permission from The Task Force for Global Health)

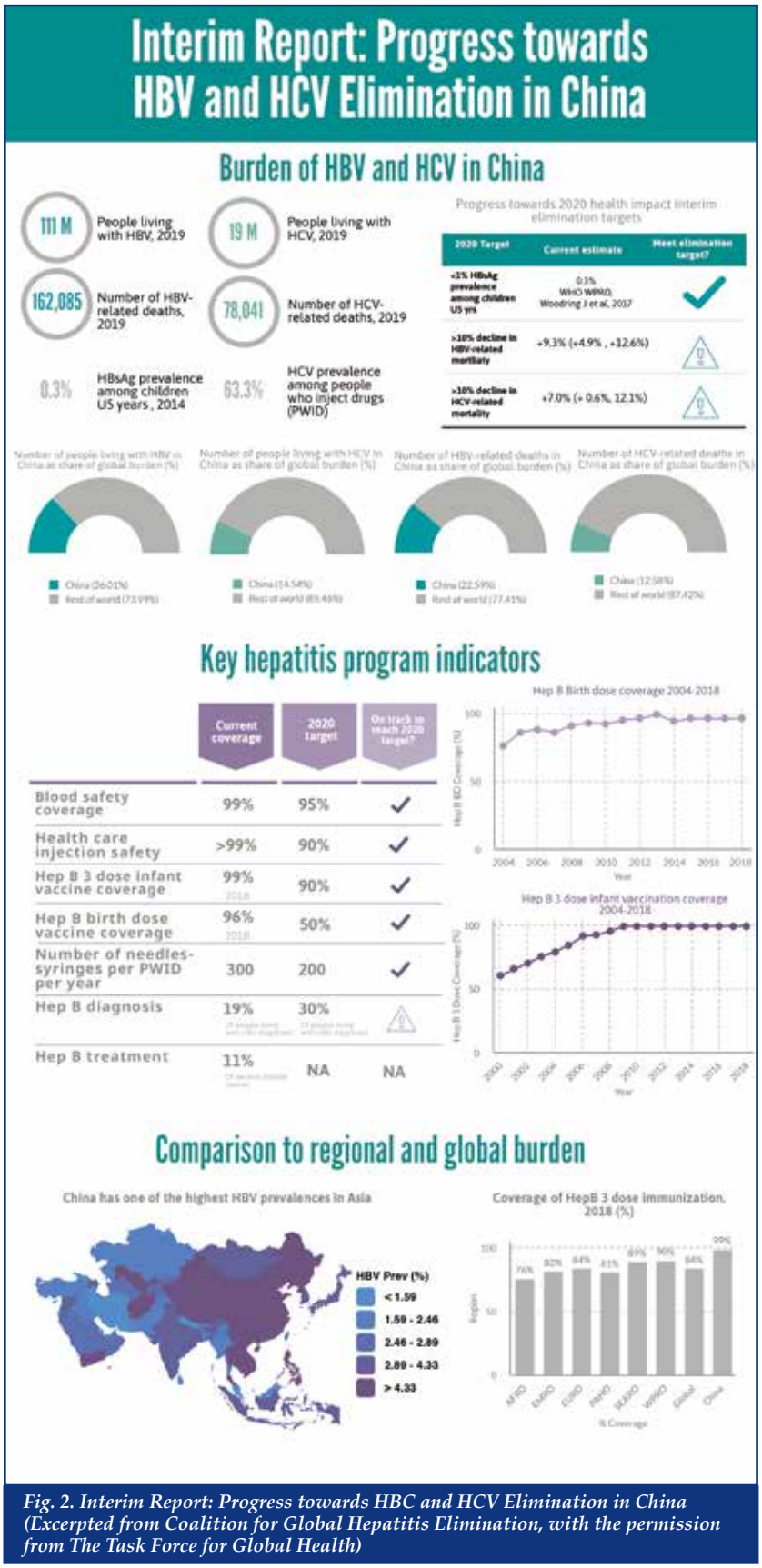


Fig. 2. Interim Report: Progress towards HBC and HCV Elimination in China (Excerpted from Coalition for Global Hepatitis Elimination, with the permission from The Task Force for Global Health)

Provide a Help Desk for Hepatitis Elimination

Guided by a Technical Advisory Board, the Coalition helps countries plan, implement and evaluate hepatitis elimination programmes. For example, the Coalition responds to inquiries regarding hepatitis B vaccination infection control and financing. The Coalition assists partners in Africa and Asia evaluate strategic information and the scale up HBV and HCV testing with linkage to care, the Coalition works with the Pan-American Health Organization to strengthen regional capacities accelerating progress toward hepatitis elimination in the Americas. To assist the dissemination of operational research, the Coalition launched *Innovations in Hepatitis Elimination* series in Clinical Liver Disease (https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/cld.988). To strengthen the evidence base from low/middle income countries and marginalised populations globally, the Coalition provides editorial assistance for authors with limited experience in scientific writing for peer-reviewed publications.

Identify Innovative Strategies and Technologies that Improve Hepatitis Prevention, Care and Treatment

With the input of partners in the community of practice and TAB guidance, CGHE coordinates operational research. Currently, CGHE partners are studying options of second line HCV therapies for retreatment of patients who fail initial HCV therapies in low and middle income countries where patented second line therapies are not available. Research priorities include HCV treatment as prevention strategies and HBV models of care that increase the number of persons diagnosed and treated for hepatitis B.

Support Global and Advocacy and Community Mobilisation

Through a global community of practice, the Coalition elevates the visibility of all partners increasing awareness of their work globally and in their home countries. Locally, the Coalition helps partners form coalitions of stakeholders for national or sub-national (i.e. "micro") elimination programmes. The Coalition honours the extraordinary work of Hepatitis Elimination Champions who through their passion, perseverance and ingenuity achieve remarkable advances toward hepatitis elimination often in resource constrained settings (https://www.globalhep.org/champions).

COALITION ACTIVITIES IN CHINA

Technical Assistance

Clinicians in Hong Kong and Guangzhou assist Coalition technical assistance and operational research activities. Dr Jinlin Hou, MD, Chairman and Professor of the Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou is a member of the Coalition Technical Advisory Board. Dr Hou advises responses to clinical questions, HBV PMTCT and operational research on HCV retreatment.

To inform the care of persons with viral hepatitis and other chronic liver diseases during the COVID-19 pandemic, Dr George Lau, Chairman of Humanity and Health Medical Group, Hong Kong and Chair Professor and Director of the 5th Medical Centre of Chinese PLA General Hospital - Hong Kong Humanity & Health Medical Group, Beijing, synthesised recommendations from three regional liver associations (APASL, AASLD, EASL) for the management of patients with chronic liver disease (https://www.globalhep.org/evidence-base/covid-19/clinical-liver-disease-covid-19-special-series).

Operational Research

The Coalition resources include China research findings. Study results guide the implementation of maternal antiviral prophylaxis for HBV EMTCT[17,18]. Investigations reveal new strategies efforts to simplify HCV therapy[19]. The Coalition community of practice provides new opportunities for collaborative research[20].

Elimination Champions

In 2019, the Coalition recognised Dr Ba Wensheng, of the Department of Immunisation, Qinghai Center for Diseases Prevention and Control, for his work to improve HepB vaccination among children in agricultural and high altitude areas of western China. In 2020, Linda Zhang manager of Stanford Center at Peking University in Beijing was honoured for her successful efforts to convince the Mayor of Suzhou to ban discriminatory practices in the workplace and in schools in improving economic and educational opportunities for an estimated 600,000 persons living with Hepatitis B (https://www.globalhep.org/champions).

Community of Practice

As partners in the Coalition community of practice, individuals and organisations can contribute financial support and join teams advancing progress in a particular country, the Asia Pacific and globally. Clinicians, civil society organisations and public health officials in China can share clinical know-how, successful public health strategies and contribute research findings. The Coalition data dashboard reveals China's HBV and HCV burden of disease, strengths and challenges for hepatitis elimination (Fig. 2). China and other countries can share technical expertise in HBV PMTCT, including moving to a triple elimination framework for HIV, syphilis and HBV.

In return, the experience learned from Coalition partners can help scale-up HBV care in China and meet other challenges to hepatitis elimination. One concern is the over 80% of PWID who have been infected with HCV[19]. New strategies for HCV testing and treatment for PWID are needed.

CLOSING

We, as global citizens, have a rare opportunity to work together, reach goals for hepatitis elimination by 2030

and avert over four million deaths including over 40% of lives saved in China, and other Asia Pacific countries. Nations need help preventing HBV and HCV transmission and disease. From a start in Hong Kong with the first public-private partnerships for hepatitis elimination, the Coalition for Global Hepatitis Elimination, is now the community of practice building capacity for hepatitis elimination through funding, advocacy, technical assistance, and operational research. The Coalition looks forward to continued collaborations with partners in China and other Asia Pacific countries to reach hepatitis elimination goals.

Working together, we will eliminate hepatitis.

References

1. WHO. Global Hepatitis Report. World Health Organization, Geneva, http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ accessed 7/23/2020.
2. Shan A, Cui F, Jia J. How to control highly endemic hepatitis B in Asia Jia J, Liver Int 2018: 38: 122-125.
3. Liu KDH, Seto W-K, Lau EHY, et al. A territory wide prevalence study on blood-borne and enteric viral hepatitis in Hong Kong. J Infect Dis. 2019 May 24;219(12):1924-1933.
4. United Nations General Assembly resolution A/RES/70/1 – Transforming our world: the 2030 Agenda for Sustainable Development, http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E accessed 7/20/2020.
5. Global Health Sector Strategy on Viral Hepatitis 2016–2021: Towards Ending Viral Hepatitis WHO/HIV/2016.06 © World Health Organization 2016. https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ accessed 7/23/2020.
6. Tordrup, D, Hutin Y, Stenberg K, et al. Additional resource needs for viral hepatitis elimination through universal health coverage: projections in 67 low-income and middle-income countries, 2016–30. Lancet Global Health 2019; 7(9): E1180-E1188.
7. Ward JW, Wiktor SZ, Cooke GS. Launch of the coalition for global hepatitis elimination: a recommendation of the Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):8-10.
8. Meeting of the International Task Force for Disease Eradication, June 2017. Wkly Epidemiol Rec 2017; 92:537–562.
9. Yang W, Liang X, Cui F, et al. Key outcomes and addressing remaining challenges--perspectives from a final evaluation of the China GAVI project. Vaccine. 2013 Dec 27;31 Suppl 9:J73-8.
10. Woodring J, Pastore R, Brink A, Ishikawa N, Takashima Y, Tohme RA. Progress toward hepatitis B control and elimination of mother-to-child transmission of hepatitis B virus - Western Pacific Region, 2005-2017. MMWR 2019 Mar 1;68(8):195-200.
11. WHO. Report of the WHO global partners meeting on hepatitis elimination (Geneva, SZ, 27–28 Februrary2019. https://www.who.int/ Accessed on July 20, 2020.
12. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017. https://www.who.int/ Accessed on July 20, 2020.
13. Chen S, Mao W, Guo L, Zhang J, Tang S, Combating hepatitis B and C by 2030: achievements, gaps, and options for actions in China BMJ Glob Health 2020 Jun;5(6):e002306.
14. Cox AL, El-Sayed MH, Kao JH, Lazarus JV, Lemoine M, Lok AS, Zoulim F. Progress towards elimination goals for viral hepatitis. Nat Rev Gastroenterol Hepatol . 2020 Jul 23;1-10.
15. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol . 2019 Feb;4(2):135-184.
16. Ward JW, Hinman AR. What Is needed to eliminate hepatitis B virus and hepatitis C virus as global health threats. Gastroenterology . 2019 Jan;156(2):297-310.
17. Yin X, Han G, Zhang H, et al. A real-world prospective study of mother-to-child transmission of HBV in China using a mobile health application (Shield 01). J Clin Transl Hepatol . 2020 Mar 28;8(1):1-8.
18. Fan R, Yin X, Liu Z, Liu Z, Lau G, Hou J. A hepatitis B-free generation in China: from dream to reality. Lancet Infect Dis. . 2016 Oct;16(10):1103-1105.
19. Lau G, Benhamou Y, Chen G, et al. Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study. Lancet Gastroenterol Hepatol . 2016 Oct;1(2):97-104.
20. Bao,Y, Larney S, Peacock A, et al. Prevalence of HIV, HCV and HBV infection and sociodemographic characteristics of people who inject drugs in China: a systematic review and meta-analysis. Int J Drug Policy. 2019 Aug; 70: 87–93.

HBV Reactivation During Direct-acting Antiviral Therapy in Patients with HBV/HCV Coinfection

Dr Dong JI
Second Liver Cirrhosis Diagnosis and Treatment Center, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Dr Cheng WANG
State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China

Dr Jinlin HOU
State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China

Dr Guofeng CHEN
Second Liver Cirrhosis Diagnosis and Treatment Center, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Dr Dong JI | Dr Cheng WANG | Dr Jinlin HOU | Dr Guofeng CHEN

Mono-infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) represents one of the major causes of liver diseases globally. Because of the similar mode of transmission, coinfection with HBV and HCV is common in HBV endemic areas and associated with substantial morbidity and mortality worldwide.[1,2] Recently, the use of direct-acting antivirals (DAAs) has revolutionised the care of HCV-infected patients with a very high rate of sustained virologic response. However, in the DAA era, the reactivation of HBV in patients treated for HCV is also often observed, resulting in either overt or occult HBV infection (negative hepatitis B surface antigen, but detectable liver and/or serum HBV DNA). This short review summarises the prevalence of HBV reactivation (HBVr) after HCV eradication in patients with HBV-HCV coinfection, and the management of HBVr.

EPIDEMIOLOGY OF HBV–HCV COINFECTION

Studies from Egypt and Turkey showed a rather low prevalence of HBV/HCV coinfection, 0.7 and 2.6% respectively.[3,4] On the contrary, data from China, Japan, Taiwan, India, Spain, Italy, and Iran showed that 10-16% of patients with chronic HBV infection are also infected with HCV.[5-12] The rate of HBV/HCV dual infection in HCV chronic carriers were 1.4% and 5.8% in two large surveys performed in the U.S.A.[13,14] Younger age, drug abuse, HIV coinfection, male sex and comorbidities requiring the transfusion of blood or blood products are independent risk factors associated with HBV/HCVcoinfection.[13] In an Italian survey, the rate of HBV/HCV coinfection in patients with HCV-related chronic liver disease was 1.3%.[15]

HBV REACTIVATION

Patients with chronic (hepatitis B surface antigen [HBsAg]-positive) or resolved (HBsAg-negative but HBcAb-positive) HBV infection are at risk of HBVr during or even after immunosuppressive therapy.[16,17] Manifestation of HBVr ranges from asymptomatic elevations of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to severe hepatitis accompanied by severe liver dysfunction, and even death.

Although HBV replication is usually suppressed in the presence of HCV coinfection, an overall HBVr rate of 14.5% was reported from patients following interferon-induced HCV eradication.[18] With the introduction of direct-acting antivirals (DAAs) for the treatment of HCV infection, HCV can be cleared in the majority of patients with chronic HCV infection. Although patients with HBV and HCV coinfection were excluded from most DAA approval studies, real-life reports suggested that HBVr might also occur following DAA-induced HCV clearance. De Monte et al.[19] reported a case of HBVr in an HCV-positive individual treated with the DAAs ledipasvir and sofosbuvir. Others have reported HBVr in HCV-positive individuals with inactive HBV treated with ledipasvir, daclatasvir and asunaprevir, after triple therapy with pegylated interferon (PEG-IFN)/ribavirin/simeprevir, or sofosbuvir/simeprevir/ribavirin or sofosbuvir/ledipasvir.[20-24] Based on these events, the United States Food and Drug Administration (FDA) has issued warnings regarding the risk of HBVr in coinfected patients receiving DAA.[25]

The mechanism of HBVr remains largely unknown. Up to now, loss of HBV immune control is the key initial event in HBVr, resulting in an increase in HBV DNA replication. Although both HBV and HCV primarily infect hepatocytes, the mechanism of liver injury caused by their infections is different.[26] HBV has a partially double-stranded DNA genome, which is transported into the nucleus to form covalently closed circular DNA (cccDNA) which is then transcribed by RNA polymerase II into pgRNA HBV replication then occurs in the cytoplasm of infected cells via reverse transcription of pgRNA.[26] During its propagation, the innate immunity of hepatocytes does not efficiently detect the virus, leading to a significantly muted interferon (IFN) response and downregulated IFN-stimulated gene (ISG) expression in the infected liver despite high levels of viral replication.[26] In contrast, HCV is an RNA virus that replicates exclusively in the cytoplasm. Unlike the stealth nature of HBV, HCV is recognised by host pattern-recognition receptors (PRRs) upon infection, resulting in a brisk IFN response and upregulation of hundreds of ISGs.[26,27] Cheng X et al. showed that HBV replication was suppressed by HCV coinfection both in cell culture and humanised mice. In vitro, HBV suppression was attenuated when interferon (IFN) signalling was blocked.[26] In vivo, HBV viremia which was initially suppressed by HCV superinfection, rebounded following HCV clearance by DAA treatment and the accompanied reduced hepatic IFN response.

These observations may explain why HCV is the so-called "dominant" virus in coinfection and HBVr is a result of diminished hepatic IFN response following HCV clearance.[28]

Clinically, many cross-sectional studies have evaluated the viral load of both viruses at a single checkpoint and reported a dominant role of HCV (high HCV-RNA and low or undetectable HBV-DNA levels) in most cases, whereas reciprocal interference or even a dominant effect of HBV was observed less frequently.[29,30] HBVr seems to occur more frequently in DAA-treated patients than in interferon-treated patients, and there are possible several explanations. First, HBVr typically occurs early during DAA therapy, whereas it occurs at the end of or even after interferon-based treatment. This could be explained by the rapid and profound reduction in HCV viral load in DAA-treated patients, resulting in an early loss of the viral interference that is mediated by innate or adaptive host immune responses in HCV/HBV coinfected subjects. Second, unlike DAAs which suppress only HCV replications, interferon also suppresses HBV replication and could lead to a sustained HBV response in a substantial proportion of patients.[31]

CLINICAL MANAGEMENT

Patients with high-risk factors such as repeated blood transfusion, hemodialysis therapy, intravenous drug use should be screened for HBV-HCV coinfection.

Treatment of HBV-HCV coinfected patients can be challenging because of potential HBVr. Once HCV is pharmacologically suppressed, its inhibitory effects on HBV replication may be weakened, resulting in possible HBVr. Interferon-based anti-HCV therapies have rarely led to HBVr due to their suppressive effect on both HBV and HCV replication. The introduction of DAA treatment has increased the risk of HBVr.

The European Association for the Study of the Liver (EASL) guidelines of HCV treatment recommends that HBsAg-positive HCV patients who fulfil the standard criteria for HBV treatment should receive nucleos(t)ide analogue (NA) treatment at the same time as DAA therapy. Those who do not fulfil the criteria should be treated prophylactically with NA during DAA treatment, and for 12 weeks following DAA discontinuation. For patients with liver cirrhosis, NA should be continued. For those patients with occult hepatitis B infection, there is no sufficient evidence to recommend prophylactic treatment. The HBsAg-negative patients at risk of occult HBV infection (anti-HBc-positive subjects) should be monitored for HBsAg every three months during DAA and for 12 weeks after stopping treatment. If HBVr occurs during or after DAA therapy, NA treatment should be initiated as soon as possible.[32] The American Association for the Study of Liver Diseases (AASLD) HCV Guidance suggests that HBV-HCV coinfected patients with low or undetectable HBV DNA levels should be either prophylactically treated with NA, or monitored at regular intervals during DAA treatment and treated as soon as HBVr occurs.[33] These recommendations, however, would have been suboptimal for the individuals with isolated HBcAb who are also at risk for HBV reactivation. These proposals also fail to include post DAA treatment follow-up, and HBV reactivation can occur some months after SVR.

SUMMARY

HBVr can occur during or after the eradication of HCV in patients previously exposed to hepatitis B. Outcomes of HBVr range from a mild hepatitis to severe liver failure or death. HBVr can be prevented with appropriate antiviral therapy. HBVr should not be ignored in clinical practice, and clinical decisions are a balance between risks and benefits. Empiric therapy for HBV is not appropriate, given that the risk of reactivation remains low. Thus, vigilant monitoring is vital and must continue for months post-SVR. Many unanswered questions remain about the appropriate care and management of chronic hepatitis C (CHC) patients at risk for HBVr, making this an area for further research.

References

1. Wang C, Ji D, Chen J, et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. Clin Gastroenterol Hepatol. 2017;15(1):132-136. doi:10.1016/j.cgh.2016.06.023
2. Abdelaal R, Yanny B, El Kabany M. HBV/HCV Coinfection in the Era of HCV-DAAs. Clin Liver Dis. 2019;23(3):463-472. doi:10.1016/j.cld.2019.04.003
3. Chakravarti A, Verma V, Jain M, Kar P. Characteristics of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. Trop Gastroenterol. 2005;26:183–187.
4. Mekky Ma, Nasr AM, Saleh MA, et al. Virologic and histologic characterisation of dual hepatitis B and C co-infection in Egyptian patients. Arab J Gastroenterol. 2013;14:143–147.
5. Senturk H, Tahan V, Canbakan B, et al. Clinicopathologic features of dual chronic hepatitis B and C infection: a comparison with single hepatitis B, C and delta infections. Ann Hepatol. 2008;7:52–58.
6. Crespo J, Lozano JL, de la CF, et al. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. Am J Gastroenterol. 1994;89:1147–1151.
7. Di Marco V, Lo Iacono O, Camma C, et al. The long term course of chronic hepatitis B. Hepatology. 1999;30:257–264.
8. Fattovich G, Tagger A, Brollo L, et al. Hepatitis C virus infection in chronic hepatitis B virus carriers. J Infect Dis. 1991;163:400–402.
9. Ohkawa K, Hayashi N, Yuki N, et al. Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients. J Hepatol. 1994;21:509–514.
10. Sato S, Fujiyama S, Tanaka M, et al. Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. J Hepatol. 1994;21:159–166.
11. Dai CY, Yu ML, Chuang WL, et al. Influence of hepatitis C virus on the profiles of patients with chronic hepatitis B virus infection. J Gastroenterol Hepatol. 2001;16:636–640.
12. Semnani S, Roshandel G, Abdolahi N, et al. Hepatitis B/C virus co-infection in Iran: a seroepidemiological study. Turk J Gastroenterol. 2007;18:20–21.
13. Bini EJ, Perumalswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. Hepatology. 2010;51:759–766.
14. Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, El-Serag HB. Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus infected patients. Hepatology. 2013;58:538–545.
15. Sagnelli E, Stroffolini T, Sagnelli C, et al. Epidemiological and clinical scenario of chronic liver diseases in Italy: Data from a multicenter nationwide survey. Dig Liver Dis. 2016;48(9):1066-71.
16. De Maria N, Colantoni A, Friedlander L, et al. The impact of previous HBV infection on the course of chronic hepatitis C. Am J Gastroenterol 2000; 95: 3529–36.
17. Mücke MM, Backus LI, Mücke VT, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2018;3(3):172-180. doi:10.1016/S2468-1253(18)30002-5
18. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: A systematic review and meta-analysis. Hepatology. 2017;66(1):13-26. doi:10.1002/hep.29109
19. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol. 2016;78:27–30. [PubMed: 26967675]

20. Takayama H, Sato T, Ikeda F, et al. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. Hepatol Res. 2016;46:489–491. [PubMed: 26297529]
21. Belperio PS, Shahoumian TA, Mole LA, et al. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. Hepatology. 2017;66:27–36.
22. Kimura H, Ohkawa K, Sakakibara M, et al. Sustained hepatitis C virus RNA clearance accompanied by elevation of hepatitis B virus DNA after short-term peginterferon-α, ribavirin and simeprevir therapy in a chronic hepatitis patient having dual infection with hepatitis B and C viruses. Kanzo. 2015;56:422–427.
23. Ende AR, Kim NH, Yeh MM, et al. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Reports. 2015;9:164.
24. Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of Ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected With HBV. Gastroenterology. 2018;154(4):989-997. doi:10.1053/j.gastro.2017.11.011
25. Suda T, Shimakami T, Shirasaki T, et al. Reactivation of hepatitis B virusu from an isolated anti-HBc positive patient after eradication of hepatitis C virus with direct-acting antiviral agents. J Hepatol. 2017;67:1108–1111. [PubMed: 28739112]
26. Cheng X, Uchida T, Xia Y, et al. Diminished hepatic IFN response following HCV clearance triggers HBV reactivation in coinfection. J Clin Invest. 2020;130(6):3205-3220. doi:10.1172/JCI135616
27. Pockros PJ. Black box warning for possible HBV reactivation during DAA therapy for chronic HCV infection. Gastroenterol Hepatol (NY). 2017;13(9):536–540.
28. Cheng X, Xia Y, Serti E, et al. Hepatitis B virus evades innate immunity of hepatocytes but activates cytokine production by macrophages. Hepatology. 2017;66(6):1779-1793. doi:10.1002/hep.29348
29. Nguyen LH, Ko S, Wong SS, et al. Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. Hepatology 2011; 53: 1839-1845
30. Sagnelli E, Sagnelli C, Macera M, Pisaturo M, Coppola N. An update on the treatment options for HBV/HCV coinfection. Expert Opin Pharmacother. 2017;18(16):1691-1702. doi:10.1080/14656566.2017.1398233
31. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352: 2682–95.
32. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J. Hepatol. 2018, 69, 461–511.
33. American Association for the Study of Liver Disease, Infectious Diseases Society of America. HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org Updated November 6, 2019.

可若夫醫療科技(香港)有限公司
Clovers
MEDICAL TECHNOLOGY (HONG KONG) LIMITED
Unit 3, 25/F Clifford Centre, 782 Cheung Sha Wan Road, Kowloon
Tel:+852 37068037 Fax: +852 37088480
www.cloversmedtech.com.hk

Liver Transplantation in China: Development and Perspective

Dr Xiaofeng ZHANG
Registrar, Liver Transplantation Center, the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Dr Dali ZHANG
Registrar, Liver Transplantation Center, the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China

Dr Zhenwen LIU
Director, Liver Transplantation Center, the Fifth Medical Center of Chinese PLA General Hospital, Beijing, China



Dr Xiaofeng ZHANG Dr Dali ZHANG Dr Zhenwen LIU

INTRODUCTION

Since Professor Thomas Starzl performed the first liver transplantation on a three-year-old patient with congenital biliary atresia in 1963, liver transplantation has become a curative option for many liver diseases. Along with the improvements in liver transplant surgical techniques, in recipient and donor preoperative assessments, in perioperative managements and in novel immunosuppression, liver transplantation is now recognised as an effective modality for end-stage liver disease.

HISTORY

The history of liver transplantation in China comprises 4 phases. The first phase is the "clinical trial stage". In the 1970s, Wuhan Tongji Hospital took the lead in carrying out canine orthotopic liver transplantation studies in China. On October 21, 1977, the Ruijin Hospital, which was affiliated to Shanghai Second Medical University, carried out the first domestic orthotopic liver transplantation[2]. From 1977 to 1983, a total of 57 liver transplantations were performed in China. Owing to various limitations, the longest survival time was only 264 days[3]. The second phase can be called the "stagnation stage". In the 1980s, owing to poor clinical outcome, high costs and donor shortage, liver transplantation was in a stagnation status in China[4].

The third phase is the "steady progress stage". In the 1990s, many outstanding scholars returned from abroad and promoted the development of liver transplantation. In the 21st century, China attained a lot of experience and achieved rapid development in liver transplantation technology. As a result, clinical efficacy was gradually approaching the international levels[5].

The fourth phase is "organ donation and liver transplantation stage". On March 21, 2007, the 171st Executive Meeting of the State Council adopted the "Regulations on Human Organ Transplantation" ordinance. From May 1, 2007, China's first "Regulations on Human Organ Transplantation" was officially implemented. To expand donor resources, China launched the pilot work of donation after cardiac death (DCD) in March 2010 and formulated the "Guide for Donation of Human Organs in China" in 2011. With reference to the international practice and with due considerations for China's current situation and previous experience, organ donations after death are divided into three categories: China Category I (CI), namely donation after brain death (DBD); China Category II (C-II), namely donation after cardiac death (DCD); and China Category III (C-III), donation after brain-heart double death (DBCD), which was special donation criteria during the transition period in China[6]. Since January 1, 2015, China has completely abolished using executed prisoner organs as the source of transplant donors. Voluntary organ donation after the death of citizen has become the only resource for organ transplantation, and a new era of transplantation has arrived.

DEVELOPMENT

Since 2015, China's organ donation and transplantation have developed rapidly. Up to now, there are 110 hospitals with qualifications for liver transplantation in China. According to the official website of the China Human Organ Donation Management Centre, up to June 3, 2020, there are 2,079,369 volunteer donor registrations in China, a total of 29,234 cases of DCD, and harvesting of 84,810 large organs such as liver, kidney, heart, lung and pancreas.

Although the liver donor pool has been expanded, it has not yet met the demand. China has a large number of hepatitis B carriers, who are not the ideal candidates for organ donation after death. Also, owing to traditional customs and cultural diversity, family members often oppose organ donations from many would-be donors after the latter's death. This has restricted the development of liver transplantation, and now there is still a shortage of donors. In 2017, the number of cadaveric organ donations in China exceeded 5,000, accounting for more than 15% of the global donation and in terms of the number of donations, it is currently ranked the second in the world[7]. However, China is a country with a large population, and the organ donation rate per million population is at a low level worldwide. In 2017, the organ donation rate of China mainland per million population was only 3.84[8]. Improving the rate of organ donation after death is the main direction of organ donation development. This is essential and is now carried out by Organ Procurement Organization (OPO)[9]. Increasing the number of qualified human organ donation coordinators, offering them professional training, inspiring their work enthusiasm, improving the organ donation process, and ensuring that every potential donor knows about the donation process will greatly increase the organ donation rate[10].

Since 2015, liver transplantation cases increased by more than 1,000 cases each year, and the total exceeded 6,000 cases in 2018. From January 1, 2015 to December

31, 2018, 17,330 cases of liver transplantation were performed in China, including 15,099 cases of DCD liver transplantation (87.1%) and 2,231 cases of live-donor liver transplantation (12.9%). Among them were 2,807 cases of childhood liver transplantation (16.2%). The one-, two- and three-year cumulative survival rates of liver transplant recipients were 84.2%, 79.0%, and 75.2% respectively. For adult hepatocellular carcinoma patients, the one-, two-, three-year cumulative survival rates for after liver transplantation were 76.7%, 67.2%, 59.4% respectively.

Since April 2005 when our centre started liver transplantation, we have completed a total of 904 live and cadaveric donor liver transplantation, with 100% successful operation rate and zero deaths during the perioperative period. The first liver transplant recipient in our centre has survived for 15 years. The one-, two- and three-year overall survival rates of transplant recipients were 91.3%, 82.4%, and 69.8% respectively, and those for adult hepatocellular carcinoma patients after liver transplantation were 89.9%, 76.4%, and 69.7% respectively, ranking top domestically. Our centre has established well-developed protocols for perioperative liver transplantation managements and has set up a liver transplant medicine unit and a liver transplant follow-up office led by experienced hepatologists and professional senior liver transplant coordinator respectively. In our centre, liver transplant patients are regularly followed up by hepatologists and surgeons. The management of short-term and long-term complications is discussed every week. Liver transplant follow-up rate is approaching 100%; liver transplant coordinators call up patients at follow-up time and document all clinical detals in medical records. The setting up of liver transplant surgery and medicine units and follow-up office provides guaranteed long-term follow-up and smooth recovery after transplantation, both of which greatly improve the long-term survival rates and quality of life after transplantation.

PERSPECTIVE

Liver transplantation in China has undergone rapid development. Promoting the donation of human organs can greatly promote the development of liver transplantation. At the time of the increased number of harvested organs, we must ensure the quality of harvested organs, improve donor assessment and maintain organ functions. Standardised organ acquisition technology and improved organ utilisation will improve the prognosis of liver transplant recipients and save more lives.[11]

Currently, liver transplant surgery is approaching international levels. However, the demand arising from increasing number of transplant patients has not been met by adequate provision of, liver transplantation medicine. A large number of liver transplant patients were under intermittent and non-systematic follow-up, which was the reason that long-term complications are not diagnosed and treated timely, which in turn lead to low long-term survival. Thus, along with the development of donation and transplant surgery, the development of transplantation medicine is much called for.

In summary, liver transplantation has had unprecedented opportunities and challenges in China. The future development of liver transplant surgery and medicine and donation remains promising.

References

1. Starzl T E, Marchioro T L, Vonkaulla K N, et al. Homotransplantation of the Liver in Humans[J]. Surgery, gynecology & obstetrics, 1963, 117:659-676.
2. Suisheng Xia. The evolution and current situation of liver transplantation in China [J]. Chinese Journal of Organ Transplantation ,1995(1).
3. Suisheng Xia. Organ transplantation [M]. Shanghai, Shanghai Science and Technology Press,1995:1-5,174-185.
4. Wu J, Zheng S S . Liver transplantation in China: problems and their solutions[J]. Hepatobiliary & Pancreatic Diseases International, 2004, 3(2):170-174.
5. Ng, K.K. and C.M. Lo, Liver transplantation in Asia: past, present and future. Annals of the Academy of Medicine, Singapore, 2009. 38(4): 322-331.
6. National Health and Family Planning Commission of the People's Republic of China. Classification criteria for organ donations for cardiac death. [EB/OL]. http://www.nhc.gov.cn/yzygj/s3586q/201105/03ddc86c0d974c058832807f7414d596.shtml,2011-05-03.
7. Zhongyang Shen. Development and innovation of liver transplantation in China [J]. Journal of Clinical Hepatology,2019,35(11):2377-2385.
8. Zhonghua Chen. Organ transplantation 2019- Opportunities and Challenges [J]. Chinese Journal of Organ Transplantation,2019, 040(001):1-2.
9. Shunliang Yang, Jianming Tan. Organ acquisition and management [J]. Chinese Journal of Transplantation (e-edition, 2015, 009(001):1-5.
10. Jiye Zhu, Pengji Gao. Current status of organ donation and liver transplantation after the death of Chinese citizens [J]. Chinese Journal of Liver Surgery, 2016, 005(005):273-276.
11. Shusen Zheng, Jianhui Li. Scientific and standardized promotion of organ donation and transplantation in China [J]. Chinese Journal of Gastroenterology,2016, 015(005):417-420.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	* Certificate Course on Renal Medicine 2020 (Video Lectures) 3	* Certificate Course on Mental Health 2020 (Video Lectures) 4	5
6	7	* Facebook Live Treatments to Protect Patients with Hemorrhoidal Disease? 8	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –Strike a balance in coagulation * Certificate Course in Ophthalmology 2020 (Video Lectures) 9	* Facebook Live Importance of Timely & Regular Dosing for Effective Asthma Control * Certificate Course on Renal Medicine 2020 (Video Lectures) 10	* Facebook Live Back-to-school with Allergy: Controlling Allergic Rhinitis & Co-morbidities * Certificate Course on Mental Health 2020 (Video Lectures) 11	12
13	14	15	* Certificate Course in Ophthalmology 2020 (Video Lectures) 16	* Certificate Course on Renal Medicine 2020 (Video Lectures) 17	* Certificate Course on Mental Health 2020 (Video Lectures) 18	19
20	21	* Facebook Live Managing Heart Failure Patients in our Daily Practice 22	* Certificate Course in Ophthalmology 2020 (Video Lectures) 23	* Facebook Live Evaluation of Acute Pharyngitis in Adults * Certificate Course on Renal Medicine 2020 (Video Lectures) 24	* Facebook Live Update on the Management of Asthma * Certificate Course on Mental Health 2020 (Video Lectures) 25	26
27	28	29	* Facebook Live Strategic Treatment for Hypertension with Updated International * Certificate Course on Respiratory Medicine 2020 (Video Lectures) 30			

Date / Time	Function	Enquiry / Remarks
3 THU 7:00 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Desmond Yat-hin YAP, Dr Gensy Mei-wa TONG	Ms. Vienna LAM Tel: 2527 8898
4 FRI 7:00 PM	**Certificate Course on Mental Health 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Willy Chung-hin WONG	Ms. Vienna LAM Tel: 2527 8898
8 TUE 2:00 PM	**Facebook Live** **Treatments to Protect Patients with Hemorrhoidal Disease?** Organiser: HKMA Kowloon West Community Network; Speaker: Dr Daniel Chung-kei NG	Ms. Antonia LEE 2527 8285 1 CME Point
9 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Strike a balance in coagulation** Organiser: Hong Kong Neurosurgical Society; Speaker(s): Dr Ronald LI; Chairman: Dr Alberto Chi-ho CHU; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Name: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
7:00 PM	**Certificate Course in Ophthalmology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Wing-lau HO, Dr Jane Chun-chun YEUNG	Ms. Vienna LAM Tel: 2527 8898
10 THU 2:00 PM	**Facebook Live** **Importance of Timely & Regular Dosing for Effective Asthma Control** Organiser: HKMA Hong Kong East Community Network; Speaker: Dr KWONG Kwok-chu	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Chun-hay TAM, Ms Cherry Pui-yee LAW	Ms. Vienna LAM Tel: 2527 8898
11 FRI 2:00 PM	**Facebook Live** **Back-to-school with Allergy: Controlling Allergic Rhinitis & Co-morbidities** Organiser: HKMA Shatin Community Network; Speaker: Dr CHAN Hing-sang	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr John SO	Ms. Vienna LAM Tel: 2527 8898
16 WED 7:00 PM	**Certificate Course in Ophthalmology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Frank Hiu-ping LAI, Dr Fiona Oi-jing LUK	Ms. Vienna LAM Tel: 2527 8898
17 THU 7:00 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Sze-kit YUEN, Dr Elaine Tsz-ling HO	Ms. Vienna LAM Tel: 2527 8898
18 FRI 7:00 PM	**Certificate Course on Mental Health 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr WONG Hiu-mei	Ms. Vienna LAM Tel: 2527 8898
22 TUE 2:00 PM	**Facebook Live** **Managing Heart Failure Patients in our Daily Practice** Organiser: HKMA Kowloon West Community Network; Speaker: Dr LAU Chun-leung	Ms. Antonia LEE 2527 8285 1 CME Point
23 WED 7:00 PM	**Certificate Course in Ophthalmology 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Shaheeda MOHAMED, Dr Nancy Shi-yin YUEN	Ms. Vienna LAM Tel: 2527 8898
24 THU 2:00 PM	**Facebook Live** **Evaluation of Acute Pharyngitis in Adults** Organiser: HKMA Hong Kong East Community Network; Speaker: Dr LAM Sau-yee	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Maggie Kam-man MA, Dr Joseph Ho-sing WONG	Ms. Vienna LAM Tel: 2527 8898
25 FRI 2:00 PM	**Facebook Live** **Update on the Management of Asthma** Organiser: HKMA Shatin Community Network; Speaker: Dr WONG King-ying	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Venus Fung-ling TAM	Ms. Vienna LAM Tel: 2527 8898
30 WED 2:00 PM	**Facebook Live** **Strategic Treatment for Hypertension with Updated International Guidelines** Organiser: HKMA Shatin Community Network; Speaker: Dr Ray Chun-chung CHAN	Ms. Candice TONG 2527 8285 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Jones KWOK	Ms. Vienna LAM Tel: 2527 8898

Upcoming Event

17 - 18 October 2020	**Endocrinology, Diabetes & Metabolism Hong Kong (EDM HK) 3rd Annual Meeting** Venue: Hong Kong Convention and Exhibition Centre; Organiser: Department of Medicine, The University of Hong Kong, KK Leung Diabetes Centre and Osteoporosis Centre of Queen Mary Hospital; Co-chairmen: Dr Paul CH LEE and Dr Alan CH LEE; Speaker(s): Please refer to the website for scientific program (https://medic.hku.hk/en/Knowledge-Exchange/EDM-HK)	EDM HK 2020 Conference Secretariat c/o International Conference Consultants Ltd. (Email: edmhk2020@icc.com.hk / Tel: 2559 9973)

Answers to Dermatology Quiz

Answers:

1. Cutaneous T-cell lymphoma (such as mycosis fungoides), leukaemia cutis, granuloma annulare (generalised form), rheumatoid neutrophilic dermatosis, erythema elevatum diutinum, lichen planus, etc. should be considered from the clinical picture.

2. Screening tests for diabetes and autoimmune diseases should be done. Fasting blood glucose, antinuclear factor, rheumatoid factor, lactate dehydrogenase, liver and thyroid function tests were all normal. The only abnormal findings were elevated C-reactive protein: 16.4mg/L (Normal<0.3 mg/L) and leukopenia with white cell count: 2.5 x10^9/L. Peripheral blood smear did not reveal any atypical or malignant cells.

3. In the literature, diabetes, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, autoimmune thyroiditis and autoimmune hepatitis), haematologic malignancies (myelodysplastic syndrome, leukaemia, and lymphoma) and drug aetiology have been reported to be associated with IGD.

Discussion

Interstitial granulomatous dermatitis (IGD) is mainly a histological diagnosis. It is a rare skin disorder with a particular pattern of granulomatous inflammation. The classic original clinical description of IGD was of linear erythematous palpable cords on the lateral aspects of the trunk, called 'the rope sign', which was also shown in this patient. However clinical spectrum is heterogeneous, which vary from hyperpigmented, erythematous papules, plaques or nodules. The lesions are usually asymptomatic.

The treatment of choice of IGD is still not well established. Search for the associated systemic disease is mandatory. In this patient, he responded very well to a short course of oral steroid plus topical clobetasol ointment and then followed by hydroxychloroquine. He had also been referred to a haematologist for the leukopenia and possibility of haematologic malignancy. Initially, he was considered having chronic idiopathic leukopenia. However, the skin lesions recurred after a few months, together with pancytopenia. Bone marrow was done, and the diagnosis of acute myeloid leukaemia was established.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

IMPROVE-IT OUTCOMES RESULTS*

THINK BEYOND MONOTHERAPY

Atozet® (ezetimibe and atorvastatin) tablets

ACHIEVE TARGET LDL-C LEVELS WITH POWERFUL DUAL ACTION OF

ATOZET®

Abbreviation: LDL-C: low-density lipoprotein cholesterol
Reference: 1. Hong Kong Product Circular (Atozet, MSD)

Selected Safety Information on ATOZET

Indications: *Prevention of Cardiovascular Events* ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. ► *Hypercholesterolaemia* ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hypercholesterolaemia (Fredrickson Type IIa and IIb) where use of a combination product is appropriate •patients not appropriately controlled with a statin alone •patients already treated with a statin and ezetimibe. *Homozygous Familial Hypercholesterolaemia (HoFH)* ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g. low-density lipoprotein [LDL] apheresis). Contraindications: • Hypersensitivity to the active substances or to any of the excipients. • Therapy with ATOZET is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). Precautions: • Myopathy/Rhabdomyolysis ► In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. ► Also, ATOZET contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. ► A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. ► Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET. • Liver Enzymes ► Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended. • Hepatic Insufficiency ► Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended. • Interstitial lung disease ► If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued. • Diabetes mellitus ► Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI >30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. • Excipients ► ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. Adverse events: • Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. • In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. Please consult the full prescribing information for detailed adverse events.

Before prescribing, please consult the full prescribing information.

MSD

Merck Sharp & Dohme (Asia) Ltd.
30/F, Lee Garden Two, 99 Yun Ping Road, Causeway Bay, Hong Kong
Tel: (852) 3071 2800 · Fax: (852) 2424 0729 · www.msd.com.hk

HK-ATO-000339 11/19

TRESIBA®

insulin degludec [rDNA origin] injection

Once-daily TRESIBA®: Ultra-long duration of action[1,2]

WHEN IT IS TIME FOR BASAL INSULIN

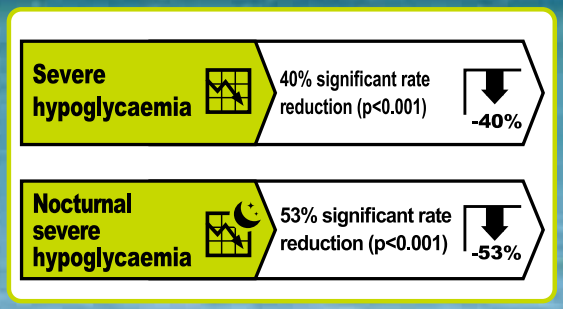
CHOOSE TRESIBA® FIRST

- **Successful reductions in HbA_{1c}**[3,4]
- **Lower risk of hypoglycaemia versus glargine U100** [5-7]
- **Flexibility in day-to-day dosing time when needed**
  ...delivered in a once-daily dose.[1]
- **Significantly lower day-to-day variability in glucose-lowering effect vs glargine U100 and U300** [8,9]
- **Approved for a broad range of patients**[1#]

DEVOTE Trial[5]

In **7,637** patients with type 2 diabetes at high risk of cardiovascular events[5]

At baseline: mean age was 65 years, diabetes duration was **16.4** years, HbA_{1C} was **8.4%**, and **83.9%** were on insulin therapy[5]



* Once daily (OD) plus additional antidiabetic treatments in accordance with standard of care.
\# Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year, elderly patients, renal and hepatic impairment patients.

Abbreviated prescribing information

Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch®) Consult Summary of Product Characteristics before prescribing.

Presentation: Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device or one cartridge contains 300 units of insulin degludec in 3 mL solution. Indications: Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. Posology and administration: Tresiba® is a basal insulin for once-daily subcutaneous administration any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In type 1 diabetes mellitus, Tresiba® must be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. The dose counter shows the number of units regardless of strength. No dose conversion should be done when transferring a patient to a new strength. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units followed by individual dosage adjustments. Transferring from other insulins: in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component, and when transferring from a twice daily regimen or from insulin glargine (300 units/ml) a dose reduction of 20% should be considered; in type 1 diabetes a dose reduction of 20% based on the previous insulin dose or basal component of a continuous subcutaneous insulin infusion should be considered with subsequent individual dosage adjustments. Doses and timing of concomitant treatment may require adjustment. Using Tresiba® in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus: when adding Tresiba® to GLP-1 receptor agonists, the recommended daily starting dose is 10 units; when adding GLP-1 receptor agonists to Tresiba®, it is recommended to reduce the dose of Tresiba® by 20% to minimize the risk of hypoglycaemia. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising basal insulin doses. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. In paediatric population, when changing basal insulin to Tresiba®, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia, Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine® needles. Contraindications: Hypersensitivity to the active substance or any of the excipients. Special warnings and precautions: Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In children care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimize the risk of hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under medical supervision and may result in a change in dosage. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. Pregnancy and lactation: There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding. Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. Undesirable effects: Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment. FlexTouch®, NovoFine®, Penfill®, and Tresiba® are registered trademarks of Novo Nordisk A/S.

References

1. Tresiba® Packing Insert. **2.** Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharmaceutical Research 2012;29(8):2104-14. **3.** Rodbard HW, Cariou B, Zinman B, Handelsman Y, Philis-Tsimikas A, Skjeth TV, Rana A, Mathieu C on behalf of the BEGIN Once Long Trial Investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. DIABETIC Medicine 2013;30(11):1298–304. **4.** Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L, Renard E,Russell Jones DL, Hansen CT, Rana A, Heller SR on behalf of the BEGIN® Basal–Bolus Type 1 Trial Investigators. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial. DIABETIC Medicine 2013;30(11):1293–297. **5.** Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr P-M, Lange M, Brown Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB for _the DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. New England Journal of Medicine 2017; 377:723–732. **6.** Wysham C,Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen L, Kvist K, Norwood P. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA 2017; 318(1):45–56. **7.** Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, Nielsen TSS, Warren M. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 2017; 318(1):33–44. **8.** Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes, Obesity and Metabolism 2012; 14:859–864. **9.** Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: lower day-to-day and within-day variability in pharmacodynamic response compared to insulin glargine 300 U/mL in type 1 diabetes. Diabetes, Obesity and Metabolism 2017; 19(7):1032–1039.

Further information is avaliable from
Novo Nordisk Hong Kong Ltd.
Unit 923A-928, 9/F, Trade Square, 681 Cheung Sha Wan Road, Kowloon, Hong Kong SAR, China Tel: (852) 2387 8555 Fax: (852) 2386 0800 www.novonordisk.com

TRE-D-20200302