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References: 1.Behm BW & Peura DA. Expert Rev Gastroenterol Hepatol 2011;5(4):439-445 2.Kukulka M et al., Clin Exp Gastroenterol 2011;4:213-20 3.Dexilant Package insert DEX01 0115(1) 4.Howden CW et al., Aliment Pharmacol Ther 2009;30:895-907
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The Cover Shot

Hong Kong Daily Life-Style

As an amateur photographer I enjoy documenting Hong Kong from a life-style perspective. I will provide one example here. There are many – small and large – boats sailing within the Hong Kong waters. Some are for container traffic and some for leisure. However, quite a few boats are not standing out as large nor luxury, but they are still a part of the daily life in Hong Kong, and they are important as they ensure that goods are transported locally and for instance that services at the outer Islands are not interrupted. Those "working boats" come in different shapes and colours, but each of them has its own character and charm as illustrated by the adjutant photographs all taken in Pok Fu Lam. They represent an important traditional life-style of Hong Kong.

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Editorial

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Editor

Dr George LAU

Globally, there is an increasing prevalence of hepatitis C virus (HCV) infection and the number of people infected has increased from 2.3% to 2.8% (>122 million to >185 million people) between 1990 and 2005. In Asian-Pacific countries, the estimated HCV infection rates in the general populations were 1.3, 0.9, 0.4–1.0, 14.7, 0.1–0.3, 0.9–1.9, 1.0–2.0, 5, 4.4–8.6 and 0.5–1.3 % in Australia, Bangladesh, China Mainland, Egypt, Hong Kong, India, Japan, Pakistan, Taiwan and Turkey, respectively. In the China Mainland, Hong Kong, Macau and Taiwan, there are an estimated 35 million Chinese infected with HCV.[1] The diagnosis of HCV infection relies heavily on molecular technology and this will be addressed by Dr Wing-cheong Yam et al.[2] Up to now, HCV is classified into seven recognised genotypes on the basis of sequence of the viral genome, each differing at 30%-35% of nucleotide sites and into 67 confirmed and 20 provisional subtypes, differing at < 15% of nucleotide sites. Genotyping of HCV is important as it affects the treatment regimen. In Asia, the main HCV genotypes (GT) are GT1, GT3, GT1b, GT4, GT1b, GT3, GT1b, GT3, GT1b and GT2, GT1 in Australia, Bangladesh, China Mainland, Egypt, Hong Kong, India, Japan, Pakistan, Taiwan and Turkey, respectively (GT1b and GT2) for Taiwan. In Chinese, the most common HCV genotype is GT1b (56.8%), followed in prevalence by GT2 (24.1 %), GT3 (9.1 %) and GT6 (6.3 %) with substantial regional variations. The greatest HCV genotypic diversity was observed in the southern and western regions of the Mainland, which had significantly lower proportions of GT1 (41.4 % in the south, 45.7 % in the west) and correspondingly higher proportions of GT3 (23.7 %) and GT6 (20.4 %) in the south and GT2 (27.2 %) and GT3 (11.6 %) in the west. HCV GT1a was rare, comprising only 1.4 % overall. Left untreated, up to one-fifth of the chronic hepatitis C (CHC) patients will develop cirrhosis and a quarter of them will progress to end-stage liver disease or hepatocellular carcinoma.[3]

Recently, treatment of HCV infections has entered a new era with the availability of direct-acting antiviral agents (DAAs). DAAs are well tolerated, safe, orally deliverable, and can cure almost all HCV patients within 8 to 24 weeks of treatment. This is a major breakthrough from the previous interferon-based therapy, which required a treatment duration of 24-48 weeks, with a lot of side effects and an efficacy of less than 50%. By 2016, the United Stated Food & Drug Administration (US FDA) had approved several DAAs: Simeprevir (NS3/4A protease inhibitor), Sofosbuvir (NS5B polymerase inhibitor), Ledipasvir/sofosbuvir (NS5A inhibitor and NS5B polymerase inhibitor), Paritaprevir/r/ombitasvir + dasabuvir (NS3/4A protease inhibitor, NS5A inhibitor, and NS5B non-nucleoside polymerase inhibitor), Paritaprevir/r/ombitasvir + ribavirin (NS3/4A protease inhibitor and NS5A inhibitor), Daclatasvir (NS5A inhibitor), Elbasvir/grazoprevir (NS5A inhibitor and NS3/4A protease inhibitor), Sofosbuvir/velpatasvir (NS5B polymerase inhibitor and NS5A inhibitor) for the treatment of HCV infections as part of combination regimens including interferon and ribavirin or as interferon-free pan-oral combination regimens, with a sustained virologic response (SVR) rate >95%. However the cost is onerous, at around US$1,000-1,200 per day

and this has limited the wide availability of DAAs to persons who suffer from CHC infection.[4] In order to circumvent this issue, a better understanding of virus and host factors in the pathogenesis of HCV infection is demanded so as to enable us to tailored made therapy in a response-guided manner and to shorten the duration of therapy. In this series, we have invited Dr Fu-sheng Wang to address this issue.[5] The use of pan-oral DAAs has also allowed us to expand the treatment paradigm to previous "mission impossible" clinical categories and these include patients with decompensated liver diseases, liver transplantation, poor renal function, renal transplantation and coinfected with human immunodeficiency virus. Dr Roger Williams, had provided a state-of-the-art view on HCV-related liver transplantation with the introduction of pan-oral DAAs.[6] On the other hand, the use of pan-oral DAAs has also posed a new clinical problem, namely severe hepatitis due to hepatitis B reactivation in CHC patients coinfected with hepatitis B virus (HBV), reported by our group and others. The severity of hepatitis ranged from HBV reactivation without hepatitis to fulminant hepatic failure, requiring liver transplantation. The occurrence of these events have recently prompted the American Association for the Study of Liver Diseases to issue a new guidance, recommending testing of HBV before starting DAAs for HCV. On 4th Oct 2016, the US Food & Drug Administration issued a box warning about the risk of HBV reactivation, to have the warning added to the drug labels of these DAAs, and to direct health care professionals to screen and monitor for HBV in all patients receiving DAA treatment. Thus, it is highly important to evaluate the HBV status (hepatitis B surface antigen and hepatitis B core antibody) before initiating pan-oral DAAs therapy, especially in HBV endemic areas.[4]

References

1. Omata M, Kanda T, Yokosuka O, et al. Features of hepatitis C virus infection, current therapies and ongoing clinical trials in ten Asian Pacific countries. Hepatol Int 2015; 9:486-507;
2. Yam WC, To WC. Management of HCV infections: role of molecular diagnostic assays. The Hong Kong Medical Diary 2016; 21: 19-20;
3. Omata M., et al. "APASL consensus statements and recommendation on treatment of hepatitis C." Hepatol Int. (2016).
4. Lau G. Treatment of chronic hepatitis C infection- 2017 and beyond. The Hong Kong Medical Diary 2016; 21: 5-8;
5. Wang FS, Shi JJ. Clinical virology and immunology of hepatitis C virus infection. The Hong Kong Medical Diary 2016; 21: 21-23;
6. Williams R. A new era for liver transplantation in HCV positive patients. The Hong Kong Medical Diary 2016; 21: 13-18;

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Treatment of chronic hepatitis C infection- 2017 and beyond

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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 31 December 2016.

Introduction

In 2017, treatment of chronic hepatitis C (CHC) infection has become simple, effective and safe. This is largely related to the discoveries and development of a cell-based replicon system which enables identification of direct-acting antiviral agents (DAAs), which are highly effective against the hepatitis C virus (HCV). HCV is a small, positive-stranded RNA-enveloped virus, with a highly variable genome and can be classified into seven distinct genotypic groups. As DAA treatments are significantly more effective on certain genotypes than others, it is important to know a patient's HCV genotype prior to initiating treatment. The distribution of HCV genotypes and sub-genotypes varies substantially in different parts of the world. HCV genotype 1 is the most common, accounting for 46.2% of all HCV infections followed by genotype 3 (30.1%). Genotype 1a is most commonly detected in the United States and Europe. Genotype 1b, principally transmitted via blood transfusions, is currently the most common genotype in Japan and the China Mainland (> 60%). Genotypes 2a and 2b, representing 10-30% of global HCV types, are common in North America, Europe and Japan, while genotype 2c is found in Northern Italy. Genotype 3 is most prominent in the Indian subcontinent as well as Southeast Asia and Indonesia. Genotype 4 appears to be prevalent in North Africa and the Middle East, while genotypes 5 and 6 are most frequently reported in South Africa and Hong Kong, respectively (Fig. 1). The diversity of genotypes also varies; the highest diversity is observed in the China Mainland and South- East Asia, while in some countries, such as Egypt and Mongolia, almost all HCV infections are due to a single genotype. Hence, genotyping may not be required in countries where the epidemiological profile shows the presence of only a single HCV genotype. In the near future, pan-genotypic DAA regimens could obviate the need for genotyping, which would help facilitate the expansion of HCV treatment.[1-3]

Current standard of care

In USA, EU and most of developed countries, treatment of HCV comprises interferon-free DAA regimens, including combinations of DAAs and fixed-dose combination pills (Table 1). A Sustained virologic response (SVR), defined as an undetectable level of HCV RNA 12 weeks after the end of therapy, is the virologic surrogate for clinical cure. The SVRs have improved to >95% for most populations across all HCV genotypes, and the safety of these regimens is comparable to placebo. Accordingly, treatment guidelines by major continental hepatology societies, such as AASLD, EASL, and APASL have all adopted pan-oral DAAs as the choice of therapy for all patients with CHC infections.[1-3]

In addition to markedly improve the SVRs with negligible safety concern, the use of pan-oral DAAs has also allowed one to deal with HCV infections in clinical settings, previously not manageable in the interferon era. These include HCV patients coinfected with the human immunodeficiency virus (HIV), patients with advanced liver disease, patients with renal impairment

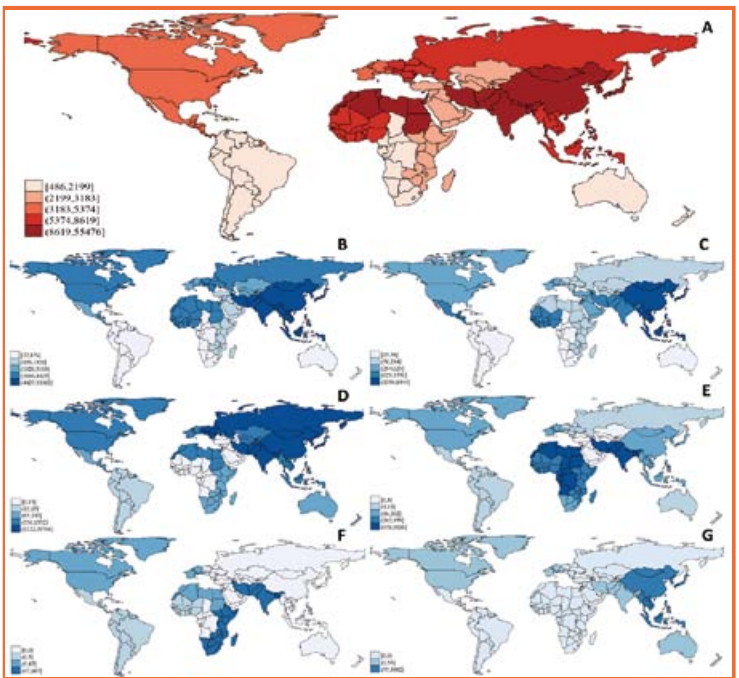

Fig. 1 Distribution of HCV seroprevalence (thousands) attributable to each genotype: (A) Seroprevalence total (B) Genotype 1 (C) Genotype 2 (D) Genotype 3 (E) Genotype 4 (F) Genotype 5 (G) Genotype 6

Table 1 Currently available HCV DAAs approved by FDA

Generic Name	Trade Name	FDA Approved Year	Mechanism of Action	SVR12 Rate for Treatment-naive HCV Subjects
Simeprevir	Olysio®	2013	NS3/4A protease inhibitor	GT 1–97%*
Sofosbuvir	Sovaldi®	2013	NS5B polymerase inhibitor	GT 1–89%
Ledipasvir/sofosbuvir	Harvoni®	2014	NS5A inhibitor and NS5B polymerase inhibitor	GT 1–99% GT 4–94% GT 5–93% GT 6–96%
Paritaprevir/r/ombitasvir + dasabuvir	Viekira Pak®	2014	NS3/4A protease inhibitor, NS5A inhibitor, and NS5B non-nucleoside polymerase inhibitor	GT 1–96%
Paritaprevir/r/ombitasvir	Technivie®	2015	NS3/4A protease inhibitor and NS5A inhibitor	GT 4–100%
Daclatasvir	Daklinza™	2015	NS5A inhibitor	GT 1–96%* GT 3–90%*
Elbasvir/grazoprevir	Zepatier™	2016	NS5A inhibitor and NS3/4A protease inhibitor	GT 1–95% GT 4–97%
Sofosbuvir/velpatasvir	Epclusa®	2016	NS5B polymerase inhibitor and NS5A inhibitor	GT 1–99% GT 2–100% GT 3–97%
				GT 4–100% GT 5–97% GT 6–100%

Abbreviations: FDA, US Food and Drug Administration; GT, genotype; r, ritonavir boosting; SVR12, sustained virologic response 12 weeks after end of treatment.
**SVR12 rates provided are for the oral combination of the DAA + sofosbuvir as per the label.*

and kidney transplant. Due to the accelerated disease pathogenesis and a poorer response to interferon-based therapies, advanced liver diseases account for one-tenth of the HIV-related morbidity and mortality. Pan-oral DAA combination therapies have been shown to be highly effective and safe in patients with HIV/HCV coinfection. The SVR rates were 96% with daclatasvir plus sofosbuvir, elbasvir/grazoprevir, or ledipasvir/sofosbuvir, and 95% with sofosbuvir/velpatasvir.[4-7]

In patients with moderate hepatic impairment, ledipasvir/sofosbuvir with ribavirin 600 mg daily for 12 or 24 weeks (SOLAR study), daclatasvir plus sofosbuvir with low-dose ribavirin for 12 weeks (ALLY-1) and sofosbuvir/velapatasvir with or without ribavirin for 12 weeks and without ribavirin for 24 weeks (ASTRAL-4) have been reported to enable SVRs of 83–96%. However, in patients with decompensated liver diseases, the SVRs were much lower (56–87%). The current challenge is how to treat those CHC patients with hepatic decompensation. Firstly, in these patients, a lot of DAAs, such as simeprevir, elbasvir/grazoprevir, and paritaprevir/ritonavir/ombitasvir, due to the NS3/4A PI components of these regimens, are contraindicated due to toxicity. A second question is whether the liver can recover following virologic cure once portal hypertension has developed. Current data suggested that for patients with compensated cirrhosis and mild portal hypertension with MELD (Model for End-Stage Liver Disease) scores up to 15, DAA treatment could avoid the complications of portal hypertension and the need for liver transplantation. However, in patients with Child-Pugh class C disease, DAA therapy would not enhance recovery of liver function and portal hypertension and they are hence advised to proceed to transplantation. The "grey zone" is related to those with MELD scores in the 20s or with Child-Pugh class B cirrhosis. Should one initiate DAAs rather than to receive liver transplant and then DAA treatment? We will need to await future studies for more definitive answers.[8-11]

Not until recently, the majority of the ribavirin-free DAA regimens included sofosbuvir, is not recommended for use in patients with renal impairment (glomerular filtration rate <30 ml/min). The first DAA regimen approved by the FDA in patients with severe chronic kidney disease and end-stage renal disease was elbasvir/grazoprevir, a ribavirin-free, once-daily, fixed-dose combination pill. Elbasvir is a NS5A inhibitor and grazoprevir is a next-generation NS3/4A PI. Neither drug is renally excreted (<1%), so no change in the dosage is required in patients with renal dysfunction. The only registration trial of DAAs in patients with renal impairment to date reported an SVR of 94% with a 12-week course. This has also opened up the door to accept HCV-positive donor organs and postponing curative DAA therapy until after transplantation.[12]

HBV reactivation with pan-oral DAAs in HBV and HCV coinfected patients – a special concern in the Asian-Pacific region

Due to the shared modes of transmission, coinfection with both hepatitis B (HBV) and C virus (HCV), is not uncommon.[13] This is especially so in high-risk populations such as intravenous drug abusers, patients on haemodialysis or with organ transplantation, human immunodeficiency virus positive and β-thalassaemia patients.[14] In Chinese where HBV infection is endemic, HBV and HCV co-infection has been estimated to be as high as 8.4%.[15] Similar to hepatitis B reactivation in patients with CHB who were treated with immunosuppressive or chemotherapeutic agents, HBV reactivations in CHC patients with HBV coinfection treated with pan-oral DAAs, have recently been reported by our group and others.[16-21] The severity of hepatitis ranged from HBV reactivation without hepatitis[16] to fulminant hepatic failure, requiring liver transplantation.[17] The underlying mechanisms of HBV reactivation during pan-oral DAA therapy for

CHC remain speculative. Several previous reports have documented that de novo HCV superinfection in patients with CHB can result in HBeAg seroconversion and in some cases, clearance of HBsAg. This suggests that HCV infections can suppress HBV replication, but the detailed mechanism is not clear. New insights have been obtained from cell culture studies, where HBV and HCV were shown to replicate in the same hepatocyte without evidence of interference. This suggests that HCV suppresses HBV replication via an indirect immune mechanism. Like patients with occult hepatitis B virus infection (OBI) treated with intense immunosuppressive therapy, life-threatening fulminant hepatitis due to HBV reactivation has also been reported in CHC patients with OBI treated with NS3/4A protease inhibitor-containing regimens. So far, there are only very limited clinical trial data available for DAA treatment of HBV/HCV coinfected patients. This is because patients with coexisting hepatitis B surface antigen (HBsAg) are often excluded from clinical trials testing DAA treatment for HCV. Hence, not until recently, many treatment guidelines of HCV have not suggested any additional measure to be undertaken for HBV/HCV coinfected patients to be treated with DAAs as HCV monoinfected patients.[1-3] In addition, these events have recently prompted the US FDA to issue a box warning about the risk of HBV reactivation, to have the warning added to the drug labels of these DAAs, and to direct health care professionals to screen and monitor for HBV in all patients receiving DAA treatment. Thus, it is highly important to evaluate the HBV status (HBsAg and hepatitis B core antibody) before initiating pan-oral DAA therapy, especially in HBV endemic areas.[22]

Can we shorten the duration of DAA therapy?

Under current guidelines, the vast majority of patients are prescribed 12 weeks of DAA therapy, a treatment duration that has demonstrated high SVR rates across a variety of different viral and host characteristics. Reducing the treatment duration to less than 12 weeks would be desirable for increasing adherence and reducing the overall cost of treatment, factors that are essential to expand retention in the HCV care cascade across the globe. Many patients achieve SVRs with 8 weeks of therapy. In the ION-3 trial, among treatment-naïve, genotype 1 patients without cirrhosis who received 8 weeks of Ledipasvir/Sofosbuvir had an SVR rate of 94%,[23] and similar success has been observed in clinical practice, including 96% in the HCV-TARGET cohort.[24] Furthermore, in a trial among treatment-naive patients without cirrhosis who were infected with HCV genotype 1b, 8 weeks of treatment with the regimen of paritaprevir boosted with ritonavir, ombitasvir, and dasabuvir yielded an SVR of 98%.[25] These high SVR rates among selected groups of patients treated with currently licensed regimens suggest it may be possible to treat a broader range of patients for only 8 weeks and that treatment for even shorter durations may be feasible with more potent DAA regimens.

Although a reduction in the treatment duration below 8 weeks was not possible with the current DAAs, clinical trials have identified potential predictors of an SVR with shorter duration treatments. SYNERGY identified that a lower baseline HCV viral load, younger age, HCV genotype 1b, and absence of resistance-associated variants (RAVs) that confer greater than 20-fold resistance predict improved response to shorter duration therapies.[26] Similarly, C-SWIFT reported a low baseline HCV viral load, genotype, and absence of RAVs (NS5B);[27] while LEPTON recognised a low baseline HCV viral load and young age as favourable baseline characteristics.[28] While on treatment week 4 viral loads do not predict treatment outcomes,[29] preliminary viral measurements, as early as the first or second week of therapy, may have some utilities,[30] and modelling predicts that a more rapid second-phase viral decline would facilitate treatment durations of less than 8, with a carefully selected regimen.[31] According to Perelson et al., nucleoside analogue inhibitors, while powerful DAAs associated with improved treatment responses, do not alone produce a rapid second phase decline, but the addition of protease inhibitors improves this critical second phase of viral clearance.[32] Similarly, O'Brien et al. reported that patients' sex and IFNL4 rs12979860 genotype were associated with an SVR (per protocol) after 8 weeks of treatment with Ledipasvir/Sofosbuvir in the ION-3 study.[32] Having a predictive algorithm that provides an individualised estimate of SVR with a given DAA regimen and duration based on the baseline viral and host characteristics could streamline clinical decision-making in light of ultra-short DAA durations.

Recently, a response-guided trial by our group demonstrated patients treated with a three DAA-based treatment regimen (NS3/4 protease inhibitor and NS5A inhibitor-NS5B nucleotide analogue) who exhibit an ultra-rapid viral response (defined as a HCV RNA measured <500 IU/mL by the second day of therapy), may be effectively treated for just three weeks.[33] This small (N=18) proof-of-concept trial, which enrolled Chinese patients with HCV genotype 1b infection without cirrhosis, suggested that short duration therapies could be highly effective in a selective patient population and demonstrated that the duration of treatment needed to achieve an SVR was shorter than previously recognised, at least for some patients.[33] The role of response-guided therapy (RGT) has changed after standard DAA therapy is producing a high SVR > 90%. However, an individualised treatment duration using RGT is still beneficial for the objective of reducing the treatment duration and cost, preventing DAA side effects and limiting drug-drug interactions.[34] Further validation is needed for RGT with the objective of determining ultra-short treatment durations.

Shortening HCV therapy in targeted populations is possible and should be further explored. For the treatment of all hepatitis C patients, newer DAAs with increased potency and a longer half-life need to be developed. Factors that may predict SVR with ultra-short duration combination DAA therapy (e.g., HCV viral load, IFNL4 genotype, absence of RAVs, sex, and host cytokines) need to be explored further in large clinical trials. Coordinated global strategies exploring shorter duration therapies for hepatitis C are warranted and essential to reduce the cost of therapy and escalate the HCV care cascade across the globe.

Future development

In future, we need more effective pan-oral DAA regimens for HCV genotype 3 infections and to learn how to deal with DAAs' related antiviral resistance. In order to improve the accessibility of DAA therapy to CHC patients, one needs to reduce the cost of the therapy. This could be done by (1) shortening the duration of therapy (2) negotiating a reduced price with the pharmaceutical companies at the governmental level and (3) generic drug licensing via TRIPS (TRADE-RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS). In an attempt to shorten the duration of therapy, interest in response-guided therapy has been reinitiated. Future larger scale studies investigating shorter durations of therapy are warranted as this could markedly reduce the cost of DAA regimens by 60-75% and make curative treatment regimens more accessible and affordable and should also reduce the emergence of resistance and side effects. This could also help to curtail the massive use of counterfeiting medicine, which could be potentially harmful. Overall, these results suggest that further studies, including pharmacokinetic and immunological data should be undertaken to investigate the use of DAAs with high potency and non-overlapping resistance profiles tailored to specific characteristics of the subjects and viruses to significantly shorten the treatment duration without compromising efficacy.

References

1. AASLD IDSA HCV Guidance Panel (2016). "Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus." http://www.hcvguidelines.org
2. European Association for Study of Liver (2015). "EASL Recommendations on Treatment of Hepatitis C 2015." J Hepatol 63(1): 199-236.
3. Omata, M., et al. (2016). "APASL consensus statements and recommendation on treatment of hepatitis C." Hepatol Int.
4. Naggie S, Cooper C, Saag M, et al. 2015. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N. Engl. J. Med. 373(8):705–13
5. Wyles DL,Ruane PJ,Sulkowski MS,et al. 2015. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N. Engl. J. Med. 373(8):714–25
6. Rockstroh JK,Nelson M, Katlama C, et al. 2015. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non- randomised, open-label trial. Lancet HIV 2(8):e319–27
7. Wyles D, Brau N, Kottilil S, et al. 2016. Sofosbuvir/velpatasvir for 12 weeks in patients coinfected with HCV and HIV-1: the ASTRAL-5 Study. Presented at Int. Congr. Eur. Assoc. Stud. Liver Disease, Apr. 13–17, Barcelona, Spain
8. Charlton M, Everson GT, Flamm SL, et al. 2015. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 149(3):649–59
9. Manns M, Samuel D, Gane EJ, etal. 2016. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect. Disease. 16:685–97
10. Poordad F, Schiff ER, Vierling JM, et al. 2016. Daclatasvir with sofosbuvir and ribavirin for HCV infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology. 63:1493–505
11. Curry MP, O'Leary JG, Bzowej N, et al. 2015. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N. Engl. J. Med. 373(27):2618–28
12. Zepatier [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2016
13. Stanaway, J. D., et al. (2016). "The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013." Lancet 388(10049): 1081-1088
14. Reddy, G. A., et al. (2005). "Prevalence of HBV and HCV dual infection in patients on haemodialysis." Indian J Med Microbiol 23(1): 41-43
15. Yu G, Chi X, Wu R, et al. Replication Inhibition of Hepatitis B Virus and Hepatitis C Virus in Co-Infected Patients in Chinese Population. PLoS One 2015;10:e0139015
16. Collins JM, Raphael KL, Terry C, et al. Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir. Clin Infect Dis 2015;61:1302-1306
17. 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 Rep 2015;9:164
18. 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.
19. Takayama H, Sato T, Ikeda F, et al. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with HBV/HCV co-infection. Hepatol Res 2015. doi: 10.1111/hepr.12578.
20. Wang C, Ji D, Chen J, Shao Q, Li B, Liu 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. 2016 Jul 5. pii: S1542-3565(16)30370-6. doi: 10.1016/j.cgh.2016.06.023. [Epub ahead of print].
21. Ou P, Fang Z, Chen J. Hepatitis B reactivation in a chronic hepatitis C patient treated with ledipasvir and sofosbuvir: A case report." Clin Res Hepatol Gastroenterol. 2016 Sep 2. pii: S2210-7401(16)30106-1. doi: 10.1016/j.clinre.2016.08.001. [Epub ahead of print]
22. U.S. Food and Drug Administration (FDA). http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf
23. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med. 2014 May 15;370(20):1879–88.
24. Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients With Hepatitis C Virus Infection and Factors Associated of Sustained Virologic Response. Gastroenterology. 2016 Aug 24. pii: S0016-5085(16)34927-7. doi: 10.1053/j.gastro.2016.08.004. [Epub ahead of print]
25. Welzel T, Zeuzem S, Dumas E. GARNET: High SVR rates following eight-week treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir for patients with HCV genotype 1b infection. New Perspectives in Hepatitis C Virus Infection - The Roadmap for Cure. Paris; 2016 Sep. Report No.: Abstract 193.
26. Kohli A, Kattakuzhy S, Sidharthan S, Nelson A, McLaughlin M, Seamon C, et al. Four-Week Direct-Acting Antiviral Regimens in Noncirrhotic Patients With Hepatitis C Virus Genotype 1 InfectionAn Open-Label, Nonrandomized TrialAnti-HCV Regimens in Noncirrhotic Patients With Genotype 1 Infection. Ann Intern Med. 2015 Dec 15;163(12):899–907.
27. Poordad F, Lawitz E, Gutierrez J, Evans B, Howe A, Feng H, et al. C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection for durations of 4, 6 or 8 weeks and genotype 3 infection for duration of 8 or 12 weeks. EASL, 2015 Apr 22-26, Vienna, Austria.
28. Gane EJ, Schwabe C, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, et al. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-Naïve or Previously Treated Patients With Hepatitis C Virus Genotype 1 or 3 Infections. Gastroenterology. 2016 Sep;151(3):448–456.e1.
29. Sidharthan S, Kohli A, Sims Z, Nelson A, Osinusi A, Masur H, et al. Utility of Hepatitis C Viral Load Monitoring on Direct-Acting Antiviral Therapy. Clin Infect Dis. 2015 Mar 2;civ170.
30. Maasoumy B, Vermehren J, Welker M-W, Bremer B, Perner D, Höner zu Siederdissen C, et al. Clinical value of on-treatment HCV RNA levels during different sofosbuvir-based antiviral regimens. J Hepatol. 2016 Sep;65(3):473-82.
31. Perelson AS, Guedj J. Modelling hepatitis C therapy—predicting effects of treatment. Nat Rev Gastroenterol Hepatol. 2015 Aug;12(8):437–45.
32. O'Brien TR, Lang Kuhs KA, Pfeiffer RM. Subgroup Differences in Response to 8 Weeks of Ledipasvir/Sofosbuvir for Chronic Hepatitis C. Open Forum Infect Dis. 2014 Dec 13;1(3):ofu110.
33. Lau G, Benhamou Y, Chen G, Li J, Shao Q, Ji D, 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.
34. Maasoumy B, Vermehren J. Diagnostics in hepatitis C: The end of response-guided therapy? J Hepatol. 2016 Oct;65(1, Supplement):S67–81.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Treatment of chronic hepatitis C infection- 2017 and beyond" by Dr George LAU 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 31 December 2016. 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. Sofosbuvir is a NS5b nucleotide analogue with pan-genotypic anti-HCV activities
2. HCV Genotype 1a is the most common genotype in Chinese
3. For HCV-related liver cirrhosis, an MELD score >20 suggests "no return" with DAA treatment
4. Protease inhibitors, such as simeprevir, are contraindicated in decompensated liver cirrhosis
5. Hepatitis B due to hepatitis B reactivation after DAA treatment for HBV/HCV coinfected patients is related to the immune mechanism
6. The shortest duration of DAA treatment reported is 3 weeks
7. Treatment-experienced genotype 3 is the most difficult to treat genotype by DAAs
8. HCV Genotype 6 can be treated with daclatasvir and asunaprevir
9. Elbasvir/grazoprevir is the first combination DAAs approved for end-staged renal diseases
10. HCV genotyping affects treatment with DAAs

ANSWER SHEET FOR DECEMBER 2016

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2016 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Treatment of chronic hepatitis C infection- 2017 and beyond

Dr George LAU

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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.: _____ (for reference only)

Answers to November 2016 Issue

Drug abuse in the acute medical setting

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

Liver Stiffness Assessment in Chronic Hepatitis C

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Chronic hepatitis C (CHC) affects more than 120 million people globally and over 60% of them reside in Asia. Similar to many chronic liver diseases, the natural history of chronic hepatitis C is characterised by repeated liver injury and necroinflammation, development of fibrosis, progression to cirrhosis and liver decompensation. It is estimated that 10-15% of CHC patients would progress to cirrhosis in 20 years. Around 1-4% of cirrhotic patients would develop hepatocellular carcinoma (HCC) annually. In the new era of highly effective direct-acting antiviral agents (DAAs), the sustained virologic response (SVR) of antiviral treatment is often above 95%. Some of the newer generation of DAAs can even achieve an SVR approaching 100% and have pan-genotypic coverage. Therefore, CHC is now considered as a curable disease. Timely diagnosis of fibrosis or early cirrhosis in asymptomatic CHC patients to prioritise patients for antiviral treatment is important.

Liver biopsy is the traditional gold standard for the diagnosis of cirrhosis. Its small risk of potentially serious complications such as bleeding and nearby viscus injury has lowered patient acceptance. Besides, the risk of sampling error or inadequate sampling and lack of continuous evaluation on the dynamic change further limit its application. In recent years, the accuracy of non-invasive tests for liver stiffness assessment has been confirmed by numerous studies. The European Association for the Study of the Liver states that both physical liver stiffness measurement and biomarkers perform well as initial assessment of liver fibrosis in CHC patients. Liver biopsy is indicated in cases of indeterminate results, or when histology is required in cases of unknown or suspected mixed aetiologies.[1] In this article, various non-invasive modalities of liver stiffness assessment in CHC will be discussed.

Physical measurements of liver stiffness or elasticity

Transient elastography (TE; Fibroscan®; Echosens, Paris, France) is a one-dimension ultrasound measurement of the velocity of a low-frequency elastic shear wave propagated through the liver. The shear wave propagates faster when the liver tissue is stiffer. The two index prospective studies in 2005 by Castéra et al. and Ziol et al. demonstrated that TE is both sensitive and specific for diagnosing cirrhosis (METAVIR F4). The sensitivity and specificity were 87% and 91% respectively if the cutoff value was 12.5 kPa; 86% and 96% if the cutoff value was 14.6 kPa. TE is still highly specific in ruling out F2-4 liver fibrosis (with specificity of 89% and 91% in the two studies), yet its sensitivity falls to around 60% only. [2-3]

Acoustic radiation force impulse (ARFI; Siemens AG; Erlangen, Germany) uses shear acoustic waves induced by the radiation force of a focused ultrasonic beam. When compared with TE, ARFI allows visualisation of the liver parenchyma and sampling from many different areas. Another advantage is that ARFI can be performed successfully regardless of body mass index (BMI). Although the majority of studies did not reveal any significant difference between the diagnostic performance of TE and ARFI, Rizzo et al. recruited 139 CHC patients prospectively and reported that ARFI was more accurate than TE for the staging of significant and severe classes of liver fibrosis (P = 0.024 and P = 0.002, respectively), yet the difference was not seen in patients with cirrhosis. One point to note is that the performance of TE was lower than usual in the study (AUROC curve of around 0.8 for F3-4 fibrosis). [4]

Shave wave elastography (SWE; SuperSonic Imagine S.A., Aix-en-Provence, France) is a real-time two-dimensional estimate of liver stiffness by calculating the speed of a shear wave implemented on a diagnostic ultrasound system just like TE. Its potential advantages over TE include that it provides real-time B-mode imaging and can detect focal liver lesions, and it improves separation of fibrosis stages due to the use of shear waves with greater bandwidths. Moreover, both SWE and ARFI provide a real-time quantitative map of liver tissue stiffness. In a prospective study of 121 patients who received same day SWE, TE and ultrasound-guided liver biopsy, SWE was more accurate than TE and the AUROC curves for SWE were 0.92 (compare METAVIR F0-F1 versus F2-F4), 0.98 (compare F0-F2 versus F3-4), and 0.98 (compare F0-F3 versus F4) respectively. [5]

Magnetic resonance elastography (MRE) is another highly reliable non-invasive modality for assessment of liver stiffness. Previous studies of the conventional two-dimensional gradient-recalled echo (2D-GRE) with various serum fibrosis markers showed that the AUROC curves of MRE were higher than 0.95 in detecting all stages of liver fibrosis. The three-dimensional spin-echo echo planar imaging (3D-SE-EPI) further improves the accuracy than 2D-GRE by removing the unwanted longitudinal wave. In a prospective cohort of 179 patients with viral hepatitis (B or C), the diagnostic accuracy by EPI (86.7-91.3%, n=169) was higher compared with GRE (80.9-82.1%, n=158) after applying optimal cutoffs. [6] A major limitation of MRE is the high

cost involved, making it less readily available than ultrasound-based elastography.

Serum biomarkers

Many serum biomarkers have been studied and proposed for fibrosis staging in CHC patients.

The FibroTest®(Biopredictive, Paris, France, licensed as Fibrosure® in USA), was the first algorithm combining several serum parameters for fibrosis staging in CHC patients. It is a patented formula consisting of α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age and gender. This algorithm was derived from the results of a 2-year prospective cohort study (205 patients in first year, 134 patients in second year). [7] Blood samples were collected on the same day of liver biopsy and eleven serum markers were assessed. There was no difference (P = 0.44) in the AUROC curves in the first-year (0.836) and second-year groups (0.87) for significant fibrosis (defined as METAVIR F2-4 in this article). It also achieved a high negative predictive value (100% certainty of absence F2-4 with the scores ranging from zero to 0.10) and a high positive predictive value (> 90% certainty of presence of F2-4 with the scores ranging from 0.60 – 1.00).

The Fibrometer® (Echosens, Paris, France) is another patented formula serving the same purpose, which is combined of platelet count, prothrombin index, AST, α-2-macroglobulin, hyaluronate, urea and age. In its registration trial, the AUROC curves of the Fibrometer® were 0.88 in the exploratory population involving 478 patients with chronic liver disease (383 had viral hepatitis), and 0.89 in the validation population of 120 CHC patients. [8]

Other examples of patented formulas for fibrosis staging in CHC patients include Hepascore® (PathWest, University of Western Australia) consisting of bilirubin, γGT, hyaluronate, α-2-macroglobulin, age and gender; and FibroSpectII® (Promotheus Laboratory Inc, San Diego, USA) combining α-2-macroglobulin, hyaluronate and TIMP-I. The major limitations of these patented biomarkers are the cost issue and that they are not widely available in clinical practice and in Hong Kong.

The Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI) is the most widely used and validated non-patented biomakers. A meta-analysis analysed results from 6259 HCV patients from 33 studies and found that the mean AUROC values of APRI in diagnosis of significant fibrosis and cirrhosis were 0.77 and 0.83, respectively. [9] Up to date, The largest independent prospective study (913 of 1370 patients were HCV patients) which compared the widely used patented tests (FibroTest®, Fibrometer®, Hepascore®) with the non-patented test (APRI) showed that there was no significant differences between the tests.[10] Although some studies suggested that non-patented biomarkers might have lower diagnostic accuracy than the patented tests, they have the advantages that no additional costs are needed and they are easy to calculate. Therefore, they are more readily available.

Practical tips for staging liver fibrosis in CHC

The current EASL guideline recommendation on utilisations of non-invasive tests for fibrosis staging in CHC patients is to combine a serum biomarker to TE. However, the decision may depend on the availability of tests in different settings and the clinical presentation. If two tests are performed, the concordance between them can lead to more reliable interpretation of the results. In case of discordance, one should repeat the test and search for explanations. Liver biopsy may be indicated if discordance of results still persist. Both the American Association for the Study of Liver Diseases (AASLD) and EASL guidelines advocate early liver stiffness assessment in CHC patients. They recommend that CHC patients diagnosed with cirrhosis should then receive screening for portal hypertension and HCC. Therefore, all CHC patients should routinely receive fibrosis screening by non-invasive methods as part of the proper management.

Table 1: Comparisons of currently available non-invasive methods for liver fibrosis staging in chronic hepatitis C patients. (adopted from EASL-ALEH clinical practice guidelines) [1]

Non-invasive tests for liver stiffness assessment	Advantages	Disadvantages
Transient elastography (TE)	1) Most widely used and validated technique 2) User-friendly (performed at bedside; fast; easy to learn) 3) good reproducibility 4) High performance for cirrhosis (AUROC > 0.9)	1) Requires a dedicated device 2) Unable to discriminate between intermediate stages of fibrosis 3) False positive in situations e.g. elevated ALT and food intake
Acoustic radiation force impulse (ARFI)	1) Can be implemented on a regular ultrasound machine 2) Higher applicability than TE (ascites and obesity) 3) Performance equivalent to that of TE for significant fibrosis and cirrhosis 4) Region of interest small than TE but chosen by operator	1) Narrow range of values (0.5-4.4 m/sec) 2) Unable to discriminate between intermediate stages of fibrosis 3) Quality criteria not well defined
Shave wave elastography (SWE)	1) Can be implemented on a regular ultrasound machine 2) Region of interest chosen by operator in real-time 3) High range of values (2-150 kPa) 4) Higher performance for cirrhosis	1) Further validation needed 2) Unable to discriminate between intermediate stages of fibrosis 3) Quality criteria not well defined
Magnetic resonance elastography (MRE)	1) Can be implemented on a regular MRI machine 2) Examination of the whole liver 3) Higher applicability than TE (ascites and obesity) 4) Higher performance for cirrhosis	1) Further validation needed especially in comparison with TE 2) Time-consuming 3) Costly and requires MRI facility
Serum biomarkers	1) No cost and wide availability (non-patented) 2) Well validated 3) Can be performed in outpatient clinic	1) Non-specific of the liver 2) Unable to discriminate between intermediate stages of fibrosis 3) Performance not as good as TE for cirrhosis 4) Costly and limited availability (patented)

In conclusion, liver stiffness assessment in CHC patients can be done by various non-invasive methods. TE is currently the most commonly used modality in Hong Kong. The high diagnostic accuracy of TE with combination of serum markers allows timely fibrosis staging and largely replaces liver biopsy as the initial assessment for CHC patients.

References

1. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63:237-64.
2. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-50.
3. Ziol M, Handra-Luca A, Kettaneh A, Christidies C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.
4. Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasitve staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol. 2011;106:2112-20.
5. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56:2125-33.
6. Shi Y, Xia F, Li QJ, Li JH, Yu B, Li Y et al. Magnetic resonance elastrography for the evaluation of liver fibrosis in chronic hepatitis B and C by using both gradient-recalled echo and spin-echo echo planar imaging: a prospective study. Am J Gastroenterol. 2016;111:823-33.
7. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-75.
8. Calès P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konaté A et al. A novel panel of blood markers to assess the degree of liver fibrosis. Hepatology 2005;42:1373-81.
9. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011;53:726-36.
10. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H et al. Diagnostic accuracy of Fibroscan and comparison to liver fibrosis markers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol. 2010;53:1013-21.

Radiology Quiz

Radiology Quiz

Dr Christine LO

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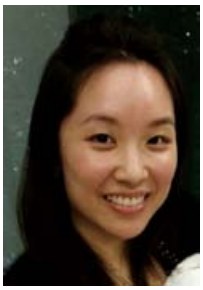
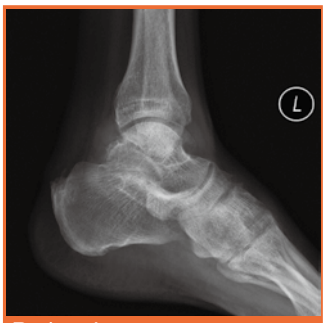
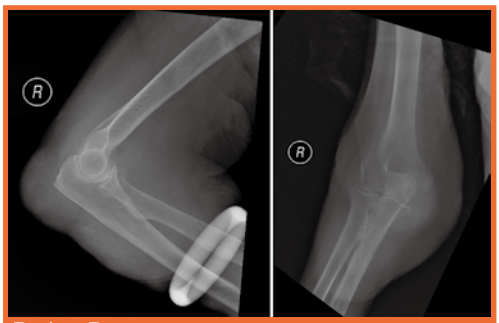


Dr Christine LO



Patient A



Patient B

Two afebrile adult patients (Patients A & B) presented with monoarticular joint pain. Please review their X-rays.

Questions

1. What are the major abnormalities in Patient A's left ankle and Patient B's right elbow?
2. What is your diagnosis?
3. What further investigations may be helpful?

(See P.29 for answers)

A new era for Liver Transplantation in HCV positive patients

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Dr Roger WILLIAMS

A new era it certainly is. What has been an intractable problem to date, namely, recurrence of Hepatitis C Virus (HCV) infection in the graft often leading to severe liver damage after an otherwise successful transplant, is now on the way to being solved. To give some background first, there are 170,000 million chronically infected subjects with HCV in the world and the number of liver transplants carried out each year is around 24,000. End-stage liver disease for chronic HCV infection is known to account for the greatest proportion of these transplants and it is relevant that a significant number – 20% to 30% of HCV positive cases listed for transplant in the West have consumed alcohol in excess.

Recurrence of HCV infection in the graft is almost universal when the patient has documented viraemia pre-transplant. Furthermore, the course of the chronic hepatitis that develops is accelerated as a consequence of immunosuppression. Twenty to 30% of transplanted cases have developed cirrhosis by 5 years with a significant reduction in long-term patient and graft survival. Earlier, patients can develop the dreaded complication of acute fibrosing cholestatic hepatitis. It is also known that the progression of recurrent disease in the graft is greater when the organ has come from a donor in the older age group. The decreased survival rates after 5 years as a result of disease recurrence has meant that many of these patients became candidates for re-transplantation. However, the use of this has been much questioned as the outcome is not as good as with the first transplant. As reported in a recent analysis from the States on serial measurements of the Model for End-stage Liver Disease (MELD), survival benefit for the patient having a re-transplant for HCV recurrent disease could only be demonstrated when the MELD score was greater than 24 compared with 15 for the first transplant. In other words, only patients with severe decompensation would benefit from a re-transplant. Results are affected to some extent by the quality of the donor graft and with a younger age donor, transplant benefit could be shown for those with a MELD of up to 21, as compared with 27 for a poorer quality graft.[1]

Not surprisingly, there have been many attempts at treating recurrent disease with antiviral drugs but until the very recent introduction of the new direct-acting antiviral agents (DAAs), results were disappointing. When given the previous standard regime of pegylated Interferon and Ribavirin, a sustained virologic response (SVR) is obtained in only 13% to 43% of cases. Addition of the first generation protease inhibitors – Telaprevir and Boceprevir, gave better SVR rates – up to 70% but the use of these agents was greatly limited by side effects, complexity of management and possible drug interactions with the immunosuppressive agents. The logical use of antiviral drugs pre-transplant to reduce viraemia in severely decompensated patients on the waiting list and thereby the risk of recurrent disease was rarely successful because of poor tolerance and poor efficacy.

The scenario for 2015 – 2016 with the new DAAs is much more encouraging. The course of treatment required is much shorter, i.e. 8, 12 or 24 weeks compared with 48 weeks and side effects are minimal. Furthermore, efficacy is pan genotypic. Numerous trials with various combinations of the new DAAs are being carried out with papers reaching publication reporting high SVR rates of 80% – 100% in cases with recurrent severe disease after transplantation. I picked out one recent study of Daclatasvir in combination with Sofosbuvir to make the point that when the recurrent disease is advanced, a significant number of cases (21%) will experience serious AE's with hepatic decompensation and even death.[2] Another study with Daclatasvir and Sofosbuvir also reported at the American Association for the Study of Liver Disease (AASLD) meeting in 2015 showed that nearly half of the patients had a slower virological clearance meaning that treatment had to be extended to 24 weeks.[3] The study of Charlton et al. of a large series of 3,337 patients with advanced HCV disease including 229 post-transplant cases also showed a high incidence of severe AE's and deaths with the new DAAs despite the efficacy in viral clearance. The percentage obtaining an SVR was reduced in the Child-Pugh C cases (Table 1).[4]

Table 1 – Ledipasvir & Sofosbuvir + Ribavirin in treatment of advanced liver disease

337patients including 229 post transplant

Child-Pugh	SVR%
A	96% – 98%
B	85% – 88%
C	60% – 75%
FCH	100%

77 (23%) of patients experienced severe AE – majority hepatic decompensation & 13 died

(Charlton M, et al. Gastroenterology. 2015; 149: 649-59)

*By intent-to-treat analysis, virologic response of HBeAg- patients (n=375) and HBeAg+ patients (n=266) are 75% and 58% respectively at week 384. Total 14 hepatocellular carcinomas were found during the study period. The incide
‡ HBV DNA <69 IU/mL ‡ Missing=excluded/addition of emtricitabine included CHB=chronic hepatitis B; HBeAg=hepatitis B e-antigen; HBV=hepatitis B virus

Reference: 1. Marcellin P, Gane E, Flisiak R, et al. Long Term Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Infection is Safe and Well Tolerated and Associated with Durable Virologic Response with no Detectable F

VIREAD Abbreviated Prescribing Information (Version: HK-OCT14-US-OCT13)
Presentation: Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). **Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment o without regard to food for patients ≥12 years of age and ≥35 kg. Elderly: Insufficient data to make dose recommendations for patients >65 years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine cl coadministration with products containing TDF or adefovir dipivoxil; patients coinfected with HIV-1 and HBV; decreases in bone mineral density; mineralization defects; fat redistribution; immune reconstitution syndrome; early virologi

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ence rate of serious drug-related adverse events was 1.2% (n=7) among patients (n=585) who entered the open-label phases.[1]

Resistance 8 Year Results from Two Phase 3 Trials (OR-229). The Liver Meeting 2014: American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11, 2014; Boston, MA, USA.

f HIV-1 infected adults and pediatric patients 12 years of age and older. **Dosage:** Adults: One tablet once daily taken orally, without regard to food. **Pediatric patients:** CHB: Not recommended; HIV-1: One tablet once daily taken orally, earance <50 mL/min. **Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; c failure. **Interactions & Side effects:** refer to Package Insert. **Before prescribing, please consult full prescribing information which is available upon request.**

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GLYPRESSIN Solution

Ready mixed, ready to go

MAP, mean arterial pressure; CBV, central blood volume; HR, heart rate

References: 1. Coelho FF, et al. Arq Bras Cir Dig 2014;27:138-144; 2. Levacher S, et al. 1995;346:865-68. ; 3. Söderlund C, et al. Scand J Gastroenterol. 1990;25:622-630; 4. Cavallin M, et al. Dig Dis 2015;33L548-554. ; 5. Mindikoglu AL, Weir MR. Am J Nephrol 2013; 38: 345-354; 6. MØller S, et al. Can J Gastroenterol 2001;15:94-106. ; 7. Baik SK, et al. Am J Gastroenterol 2005;100:631-5. ; 8. Escorsell A, et al. J Hepatol 1997;26:621-7.; 9. Kalambokis G, et al. J Gastroenterol Hepatol 2005;20:1075-81. ; 10. Kalambokis G, et al. Liver Int. 2010;30:1371-8.; 11. Escorsell A, et al. Gastroenterology 2001;120:161-9.; 12. Møller S, et al. J Hepatol 1997;26:1026-33. ; 13. Cirera I, et al. Hepatology 1995;22:106-11; 14. Sarin SK, Sharma P. Hepatology 2011;54:724-728. ; 15. Gluud LL, et al. Cochrane Database of Systematic Reviews 2012;9:CD005162. ; 16. Nadim MK, et al. J Hepatol 2016;64:717-735.

Abbreviated Prescribing Information of GLYPRESSIN

Indication: Treatment of bleeding oesophageal varices (BOV) and emergency treatment of type 1 hepatorenal syndrome (HRS). Dosage & Administration: GLYPRESSIN is administered intravenously. BOV: Initially 2 mg injection is given every 4 hours. Maintenance dose can be adjusted to 1 mg every 4 hours up to 24-48 hours. HRS: 3 to 4 mg of terlipressin acetate every 24 hours as 3 or 4 administrations. In the absence of any reduction of the serum creatinine after 3 days of treatment, cessation of GLYPRESSIN® treatment is advised. Contraindications: Pregnancy, hypersensitivity to terlipressin or any other excipients of the product. Undesirable effects: Headache, bradycardia, peripheral vasoconstriction, peripheral ischemia, facial pallor, hypertension, transient abdominal cramps and transient diarrhoea. Special Warnings: Blood pressure, heart rate and fluid balance should be monitored during treatment. Caution should be exercised in treating patients with hypertension, recognised heart disease, renal dysfunction, cerebral or peripheral vascular disease, asthma or respiratory failure. To avoid local necrosis at the injection site, the injection must be administered intravenously. In patients with septic shock with a low cardiac output terlipressin should not be used. Prior to use of terlipressin for hepatorenal syndrome, it must be ascertained that the patient has an acute functional renal failure and this functional renal failure does not respond to a suitable plasma expansion therapy.

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If patients are treated at an earlier stage of recurrent disease, AE's are mild as reported in several studies including the AbbVie combination regime of a Ritonavir boosted protease inhibitor (ABT-450) along with the NS5A inhibitor Ombitasvir (ABT-267) and NS5B polymerase inhibitor, Dasabuvir (ABT-333). The Ritonavir boosting of the protease inhibitor does interact with the metabolism of immunosuppressive drugs and the doses of Tacrolimus and Cyclosporine have to be reduced and their blood levels carefully monitored.[5] When Simeprevir is used in genotype 1a cases the Q80K resistant mutation can be an issue and has to be tested for.

I would draw attention to the special situation of a patient with HCV/HIV co-infection and how this can be transformed with use of the new DAAs. Poor graft survival for those co-infected patients has prompted concerns as to their suitability for a transplant. The two patient cases shown in Table 2 with evidence of severe hepatic decompensation, namely, ascites, hepatic encephalopathy (HE), or varices were treated several years after transplantation. In both instances, an SVR was obtained with definite improvement clinically and in biochemical tests as shown by a reduction in the Child Pugh score and increase in serum albumin concentration. In the future such cases are likely to be treated with the DAAs either before or after being accepted on the waiting list.[6]

Table 2 – Sofosbuvir, Simeprevir & Ribavirin for HIV/HCV-coinfected LT recipients

	Age (yrs)	Time post-LT	Child Pugh	Albumin
Case 1	48 ♀	4 yrs ascites/HE	10 → 5	2.3 → 3.6
Case 2	55 ♂	7 yrs ascites/varices	11 → 5	2.4 → 3.6

(Campos-Varela I, et al. Liver Transpl. 2015; 21(2): 272-4)

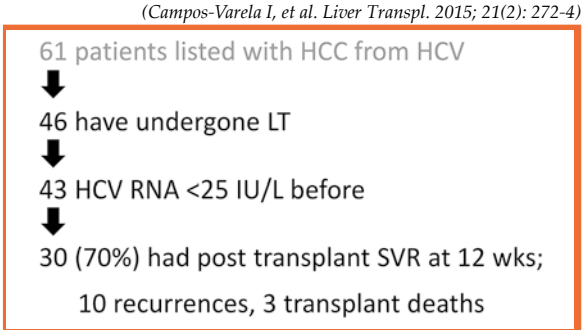

Fig. 1: Sofosbuvir plus Ribavirin before transplantation prevent HCV infection post-transplant in HCV cirrhosis & HCC

(Curry MP, et al. Gastroenterology. 2015; 148(1): 100-107.e1)

Using the new DAAs pre-transplant when the patient is on the waiting list to reduce HCV RNA load and likelihood of disease recurrence post-transplant is clearly the more attractive option. In the study illustrated in Fig. 1 the majority of those finally undergoing a transplant had obtained an SVR before transplantation and in 70% this was maintained at 12 weeks post-transplant; but there were a significant number of recurrences. The duration of undetectable HCV RNA before transplant was shown to predict lack of recurrence. Practical issues arise with the high cost of the new DAAs and the often prolonged time on the waiting list particularly as it seems that antiviral therapy has to be continued for a period after the transplant to avoid relapses.[7] The study of Yang et al. showed a lower risk of the MELD Score increasing whilst on the waiting list in addition to a lower risk of post-transplant HCC development.[8]

Clinical improvement with HCV clearance as a result of treatment with the new DAAs whilst on the waiting list could also be sufficient to allow delisting of the patient. In the very recently published European series of 103 consecutive listed patients with end-stage HCV cirrhosis but excluding complicating hepatocellular carcinoma (HCC), use of the new DAAs was able to reverse liver dysfunction and favoured the inactivation and delisting of about one patient out-of-three and one patient out-of-five in 60 weeks. Patients with lower MELD scores had higher chances of being delisted.[9]

In the future it is likely that most patients on the waiting list will have had a course of the new DAAs prior to listing and have either not shown sufficient clinical improvement or have not obtained an SVR. Whether in such cases further antiviral treatment when on the waiting list is worthwhile and whether viral load can be reduced prior to the transplant, requires further study.

Use of the new DAAs is likely to allow use of older grafts previously excluded because of the greater risk of developing severe recurrent disease.[10] Use of the new DAAs will also obliviate concerns over choice of immunosuppressive agents influencing the progression of post-transplant HCV recurrent disease. To date cyclosporine has been considered preferable to Tacrolimus as an immunosuppressive agent in HCV transplants because of its demonstrated anti-HCV viral effect. The recent data reported by Shaw et al. showed the benefit of switching from a Calcineurin drug regime to low dose monotherapy with Sirolimus.[11] The switch was at 15 months post-liver transplant. Follow-up over 10 to 15 years showed improved survival with slower progression to cirrhosis and of an extended time to the development of a primary HCC. The risk of developing diabetes post-transplant as a result of immunosuppression and/or Metabolic Syndrome is also likely to be reduced with HCV viral clearance.[12]

In conclusion and looking ahead:

Major improvements in 5 year and in the longer-term survival of end-stage HCV associated liver disease treated by transplantation are to be anticipated as a result of the introduction of the new DAAs with treatment regimes.

1. In patients who have developed recurrent HCV disease in the graft clinical improvement and viral clearance can be obtained with reduction in requirements for re-transplantation.
2. Pre-transplant treatment on the waiting list gives SVR rates above 70% but may need to be continued over the period of transplantation if recurrence of disease is to be uniformly prevented. The best timing and duration of DAAs in this situation requires evaluation because of the high cost implications.
3. An alternative and less costly approach is to delay DAAs to the first 6 to 12 months post-transplant and use them selectively in patients who are shown by HCV RNA, Liver Function Tests and liver histology to be progressing to a severe chronic hepatitis.

4. The good results obtainable with use of DAAs pre-transplant or in the early post-transplant period will obviate considerations of donor age and immunosuppressive drug regime previously important in determining graft outcome.
5. The new DAAs may enable some end-stage HCV patients to improve sufficiently to be removed from the transplant waiting list though probably not to the same extent as with chronic HBV infection. Most cases in the future are likely to have a trial of DAAs prior to being placed on the transplant list.
6. The increasing use of the DAAs, in the West as well as in the higher prevalence areas is likely to lead to a reduction in the number of end-stage HCV associated liver disease requiring transplantation over the next 15 to 20 years.

References

1. Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, Inadomi J, Terrault N, Rosen HR. Survival benefit of repeat liver transplantation in the United States: a serial MELD analysis by hepatitis C status and donor risk index. Am J Transplant. 2014; 14(11): 2588-94.
2. Herzer K, Welzel TM, Ferenci P, Petersen J, Gschwantler M, Cornberg M, Berg T, Spengler U, Weiland O, van der Valk M, Klinker H, Rockstroh JK, Schott E, Peck-Radosavljevic M, Zhao Y, Exposito MJ, Zeuzem S. Daclatasvir in combination with sofosbuvir with or without ribavirin is safe and efficacious in liver transplant recipients with HCV recurrence: Interim results of a muticenter compassionate use program. Hepatology 2015: 62(1) Suppl: 341A).
3. Herve C, Coilly A, Fougerou-Leurent C, de Ledinghen V, Pageaux G-P, Houssel-Derby P, Radenne S, Duvoux C, Di Martino V, Kamar N, d'Alteroche L, Canva V, Lebray P, Dumortier J, Silvain C, Besch C, Botta-Fridlund D, Tran A, Montialoux H, Rossignol E, Rohel A, Duclos-Vallee J-C, Leroy V. Determinants and impact of early viral kinetics in patients with HCV-recurrence after liver transplantation treated by sofosbuvir + daclatasvir: results from the ANRS CO23 CUPIT study. Hepatology 2015: 62 (1) Suppl: 209A).
4. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N; SOLAR-1 Investigators. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015; 149(3): 649-59.
5. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, Gordon F, Levitsky J, Terrault NA, Burton JR Jr, Xie W, Setze C, Badri P, Pilot-Matias T, Vilchez RA, Forns X. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014; 371(25): 2375-82.
6. Campos-Varela I, Straley S, Agudelo EZ, Carlson L, Terrault NA. Sofosbuvir, simeprevir, and ribavirin for the treatment of hepatitis C virus recurrence in human immunodeficiency virus/hepatitis C virus-coinfected liver transplant recipients. Liver Transpl. 2015; 21(2): 272-4.
7. Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology. 2015; 148(1): 100-107.e1.
8. Yang JD, Aqel BA, Watt KD, Vargas HE, Keaveny AP, Pungpapong S, Gores GJ, Roberts LR, Leise MD. Hepatitis C and HCC outcomes among patients listed for liver transplant with HCV-HCC who received direct acting antiviral therapy. Hepatology 2015: 62 (1) Suppl: 763-664A).
9. Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, Morelli C, Donato F, Volpes R, Pageaux GP, Coilly A, Fagiuoli S, Amaddeo G, Perricone G, Vinaixa C, Berlakovich G, Facchetti R, Polak W, Muiesan P, Duvoux C; European Liver and Intestine Association (ELITA). Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol. 2016; 65(3): 524-31.
10. Donato MF, Dondossola DE, Malinverno F, Monico S, Rigamonti C, Caccamo L, Aghemo A, Cavenago M, Lunghi G, Antonelli BB, Rossi G, Colombo M. Treating HCV patients on the LT waiting list with Sofosbuvir plus Ribavirin is associated with clinical benefits and allows for safe assignement of older grafts to LT recipients. Hepatology 2015: 62 (1) Suppl: 1058A).
11. Shaw M, Shankar A, Gee I, Nash K, Hoare M, Gibbs P, Davies, S, Alexander GJ. A retrospective 15-year review: survival advantage after switching to sirolimus in hepatitis C virus infected liver graft recipients. Aliment Pharmacol Ther, 2015; 41(4): 379-92.
12. Younossi Z, Stepanova M, Saab S, Trimble G, Mishra A, Henry L. The association of hepatitis C virus infection and post-liver transplant diabetes: data from 17 000 HCV-infected transplant recipients. Aliment Pharmacol Ther. 2015; 41(2): 209-17.

Management of HCV Infections: Role of Molecular Diagnostic Assays

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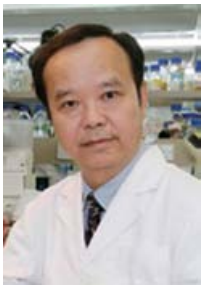

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Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and cirrhosis[1]. The long term impact of HCV infection is highly variable, ranging from minimal effects to chronic hepatitis, advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The development of detection assays for HCV has paralleled that of our understanding of the infection with introduction of increasingly effective therapies with progressively decreasing adverse effects. Serologic and molecular assays for HCV have played major roles in the identification of those with the viral infection, in determining the severity of the disease, and in the response to therapeutic interventions. An anti-HCV antibody test is recommended to screen for HCV infection (sensitivity of 95%, specificity of 99%, positive likelihood ratio of 95, and negative likelihood ratio of 0.05)[2]. If the anti-HCV antibody test result is positive, current infection should be con¬firmed with a qualitative measurement of HCV RNA. If the anti-HCV antibody test result is negative in a patient who may have been exposed to HCV within the previous six months, HCV RNA should be measured every four to eight weeks for at least six months or follow-up anti-HCV antibody testing should be performed in 12 weeks. Patients with a positive anti-HCV antibody test result but a negative HCV RNA test result are not considered to have HCV infection. Quantitative HCV RNA testing is recommended before initiating therapy to determine the baseline viral load, and testing for HCV genotype is recommended to help guide treatment decisions. In this article, the changing role of these molecular assays, particularly in light of recent advances in the mandate for HCV screening and the changing therapeutic landscape will be elaborated.

HCV viral load monitoring and genotyping

All patients with chronic HCV infection should be considered for treatment based on genotype, extent of fibrosis or cirrhosis, prior treatment, comorbidities, and poten¬tial adverse effects. The goal of therapy is to reduce all-cause mortality and liver-associated complications[2]. Monitoring of treatment effectiveness is assessed by repeated measurement of HCV RNA[3]. A sustained virologic response (SVR), defined by the absence of HCV RNA on polymerase chain reaction (PCR) testing 24 weeks after cessation of treatment, is associated with a 99% chance of being HCV RNA negative during long-term follow-up. SVR 12 weeks after treatment is a new primary end point in many recent drug trials. Quantitative HCV viral load is recommended at week 4 of treatment, and at 12 and 24 weeks after completion of therapy. Consequently, quantification assays with high accuracy and precision will have their significance for the upcoming years since only one single measurement is currently used to predict whether a patient is eligible for a shortened therapy and will or will not achieve an SVR. According to the European and American guidelines, real-time reverse transcription PCR is currently the method of reference for the quantification of HCV-RNA levels in clinical practice. As a result, more newly developed assays with improved sensitivity, accuracy, and reduced hands-on-time are available in the market. The European Association for the Study of the Liver (EASl) suggests the use of an assay with a lower limit of detection of ≤15 IU/ml.

Genotyping of HCV has also proven important due to the lower barrier to resistance of genotype 1a isolates compared to genotype 1b for multiple classes of direct-acting anti-viral agents (DAAs). The clinical significance of viral genetic diversity and subtype has been most extensively studied in pharmaceutical clinical trials focused on HCV genotype 1 infection. In Hong Kong, other than genotype 1b, genotype 6b was also highly prevalent among our patients[4]. More studies on the impact of genetic diversity in other genotypes may reveal similar nuances which may further improve clinical outcomes. A wide variety of genotyping

Table 1. Comparison of commercial quantitative HCV RNA assays from different manufacturers

Assay-specifications	Aptima HCV RNA	Artus HCV Q5-RGQ	COBAS HCV (6800/8800)	GeneXpert HCV	Real-time HCV	Veris DxN HCV	Versant kPCR
Manufacturer	Hologic	Qiagen	Roche	Cepheid	Abbott Molecular	Beckman Coulter	Siemens
Limit of detection (IU/mL)	4	21	10	4	12	12	15
Limit of Quantification (IU/mL)	10	35	15	10	12	12	15
Upper limit of quantification (IU/mL)	$1.0x10^8$	$1.8x10^7$	$1.0x10^8$	$1.0x10^8$	$1.0x10^8$	$1.0x10^8$	$1.0x10^8$
Batch wise	Continuously	Yes	Continuously	No	Yes	Yes	Yes
Hours to results	2.68	5-6	3.5	1.75	5.4-7.6	1.7	5-6

methods are used, including PCR amplification followed by strip-based reverse hybridisation, PCR followed by Sanger sequencing, and real-time PCR. These various genotyping methods offer certain benefits, but they also have their limitations. While sequencing can offer excellent resolution of HCV genotype, it can be time-consuming and labour-intensive, it requires skilled technologists and is costly, and results are not standardised. Real-time PCR methods offer workflow advantages, with a high degree of automation associated with reduced hands-on time, reduced technical expertise requirements, and reduced costs, and commercial methods which are approved for use in the United States (FDA) and Europe (CE) are now available.

Host genetic polymorphisms to predict therapeutic response

Conventional treatment for chronic HCV infection relies on the combination of pegylated-interferon and ribavirin (peg-IFN/RBV) therapy. Both interleukin-28B (IL-28B) polymorphisms and HCV genotypes serve as the strongest predictive values for therapeutic prognosis[5]. IL-28B genetic testing is widely used throughout the world for interferon based therapy prediction for HCV patients and is quite helpful not only for health care workers but also for the patients. There is a strong relationship between single nucleotide polymorphisms (SNPs) at or near the IL-28B gene and the SVR with peg-IFN/RBV treatment for chronic HCV infection. Recent studies identified two SNPs rs12979860 T/C and rs8099917 T/G that were located near IL-28B and acted as important baseline predictors for peg-IFN/RBV treatment responses. Strong association between favourable genotypes (C/C for rs12979860 and T/T for rs8099917) and high rates of SVR were observed in several genome wide association studies[6]. Both PCR and DNA sequencing protocols can be easily adopted for screening the IL28B polymorphisms among patients[7].

The combination of Simeprevir (a HCV NS3/4A protease inhibitor) and Sofosbuvir (NS5B RNA-dependent RNA polymerase inhibitor) has recently been approved by the Food and Drug Administration in Nov 2014 for an all-oral, interferon- and ribavirin-free treatment option for chronic HCV infection. Furthermore, adding a DAA agent to peg-IFN/RBV dual therapy increases the success rate of SVR. The role of IL-28B polymorphisms on the DAAs regimens and viral decline prediction are unclear. Instead, a new dinucleotide frameshift variant in IFN-lamda-4 (IFNL4, ss469415590 TT/ΔG) seems to be a better marker than the IL-28B SNPs in predicting both peg-IFN/RBV and DAAs treatment responses. Individuals who carry the minor ΔG allele of the ss469415590 variant generate a novel IFNL4 protein, whereas those who carry the major TT allele causes to a frameshift and disrupt the open reading frame of IFNL4. The latter case facilitates HCV clearance and improves peg-IFN/RBV treatment outcome. In IFN-free DAA therapies, patients carrying IFNL4-ΔG are significantly associated with slower early viral clearance and decreased drug efficacy than patients carrying homozygous IFNL4 TT/TT[8]. The unfavourable rs12979860-T allele is somewhat in different degrees of linkage disequilibrium with ss46941590-ΔG allele depending on the racial background. The integration of IL-28B and IFNL4 polymorphisms is therefore possible to strengthen the clinicians' decisions on treatment regimens.

Resistance to DAAs in clinical practice

Among protease, nucleotide and non-nucleoside inhibitors in DAA, heterogeneity of viral genes within NS3, NS5A, and NS5B areas interacting with DAAs exist between HCV geno- and subtypes as well as HCV isolates of the same geno- and subtype and amino acid polymorphisms associated with suboptimal efficacy of DAAs are termed resistance associated variants (RAVs). RAVs may be associated with virologic treatment failures. However, virologic treatment failures typically occur only if other negative predictive host or viral factors are present in the same patient, susceptibility to additional antiviral agents is reduced or duration of treatment is suboptimal. Genotypic resistance analysis is based on DNA sequencing technologies. Below the detection limits of available assays, it is unknown whether certain variants exist and persist although due to the error prone replication of HCV. It is likely that all possible single and double variants are continuously generated[9]. Currently, there is no regulatory-agency approved assay for the determination of HCV antiviral drug resistance and testing is largely performed in specialised settings with self-validated, laboratory-developed, sequencing-based assays.

Future directions

As DAA therapies continue to increase in effectiveness with minimal side effects, will HCV treatment be implemented solely on the basis of the diagnostic test result for active HCV viraemia or will they require other tests (which may not be available as Point of Care Testing (POCT) such as for HCV genotype, alanine aminotransferase levels, platelet count, or degree of fibrosis (Fibroscan/Fibrotest)? Diagnostics have played an important role in numerous aspects of HCV, from its discovery to prevention of its transmission, treatment management, and, hopefully, eventual global eradication. Thoughtful, pragmatic, evidence-based approaches to identify the best way to roll out HCV therapies, including the necessary associated diagnostics, are needed.

References

1. Guidelines for the screening, care and treatment of persons with hepati¬tis C infection. Geneva, Switzerland: World Health Organization; 2014.
2. American Association for the Study of Liver Diseases; Infectious Dis¬eases Society of America. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/. Accessed March 1, 2015.
3. European Association for Study of Liver. EASL Clinical Practice Guide¬lines: management of hepatitis C virus infection [published correction appears in J Hepatol. 2014;61(1):183-4]. J Hepatol. 2014;60(2):392-420.
4. Lam TH, Cheng RS, Lai ST, Tsang TY, Cheng VC, Ho SL, Yam WC. Evaluation of in-house and commercial genotyping assays for molecular typing of hepatitis C virus in Hong Kong.Br J Biomed Sci. 2010;67(2):82-5.
5. Fathy MM, Abo Taleb ME, El Hawary MS, Nabih MI, Aref WM, Makhlouf MM. Assessment of interleukin 28B genotype as a predictor of response to combined therapy with pegylated interferon plus ribavirin in HCV infected Egyptian patients. Cytokine. 2015 Aug;74(2):268-72.
6. Tanaka Y, Nishida N, Sugiyama M (2009) Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 41(10): 1105-1109.
7. To SWC, Siu GKH, Wong KH, Chan KCW, Yuen KT, Ng HM, Yam WC. Utilization of a Duplex HybProbe Real-Time PCR to Detect and Estimate IL-28B Polymorphisms Prevalence among HIV/HCV Co-infected Patients in Hong Kong. J Med Microb Diagn 2015, 4:3
8. Riva E, Scagnolari C, Turriziani O and Antonelli G. Hepatitis C virus and interferon type III (interferon-λ3/interleukin-28B and interferon-λ4): genetic basis of susceptibility to infection and response to antiviral treatment. Clin Microbiol Infect 2014; 20:1237-1245
9. Rong L, Dahari H, Ribeiro RM, Perelson AS. Rapid emergence of protease inhibitor resistance in hepatitis C virus. Sci Transl Med 2010;2:30 ra32.

Clinical virology and immunology of hepatitis C virus infection

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Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide, and approximately 60–80% of them will become chronically infected. Multiple liver diseases including hepatic fibrosis, end-stage cirrhosis, and hepatocellular carcinoma(HCC) will develop over a period of 5-30 years in chronic HCV infection individuals[1]. Immune responses of the patients dominate the disease progression, and it is important to fully interpret the course of immunopathogenesis of HCV infection, consequently to exploit effective strategies to eliminate HCV. Here, we will review the current advances in HCV immunology that have contributed to our understanding of HCV infection.

1. Hepatitis C virus

HCV is a single-strand, positive-sense RNA virus identified in 1989, belonging to the Hepacivirus Genus of the Flaviviridae family. As the only hepatophilia virus of the Flaviviridae family, HCV has a restricted host range and only infects humans and chimpanzees. The HCV genome is approximately 9.6 kb in length, consisting of 5′ and 3′ untranslated regions (UTRs), an uninterrupted open reading frame(ORF) encoding a polyprotein precursor of approximately 3,000 amino acids. The polyprotein is cleaved by viral and cellular proteases into 10 different proteins, including three structural proteins (core, E1 and E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B). The nonstructural proteins do not constitute the viral particles, but mainly participate in the process of HCV replication and translation. Newly developed direct-acting antiviral agent (DAA) drugs greatly inhibit HCV replication, even cure chronic HCV infection by targeting NS3-4A, NS5A and NS5B. HCV mainly infects hepatocytes and multiple cellular factors are involved in this process, including CD81, scavenger receptor type B1 (SRB1), claudin-1 and occludin. Recently, the discovery of the central core of the E2 protein, E2core, may facilitate the understanding of the elusive hepatitis C virus fusion mechanism[2].

Based on the nucleotide sequence variations of the Core, E1 and NS5B, HCV is classified into seven genotypes (1–7) and 67 different subtypes, and the subtypes differ in their sequence by 20–25% within the genotypes. The different HCV genotypes show different characteristics in their geographical distribution, pathogenesis and response to therapy.

2. Immune characteristics of HCV infection

As the first line of the host's defence against viral infections, the innate immune system detects cytosolic HCV RNA. Subsequently interferons (IFNs) are secreted and then NK cells become activated, exerting the early suppression of HCV. Antigen presenting cells (APCs) (mainly Kupffer cells and DCs) that reside in the liver, uptake apoptotic bodies from destroyed HCV-infected hepatocytes and respectively present HCV-derived epitopes to both $CD4^+$ and $CD8^+$ T cells in the context of MHC class II and MHC class I, timely orchestrate virus-specific adaptive responses. Whether humoral immunity during HCV infection has an essential role in viral clearance has not yet been determined; cellular immune responses, especially efficient HCV-specific $CD8^+$ T cellular immunity, substantially drive disease progression, ultimately, the outcome of HCV infection. Vigorous, multi-specific and long-lasting HCV-specific $CD8^+$ T cell responses are exerted in patients or chimpanzees with a self-limited HCV infection; whereas, weak, or even without virus-specific $CD8^+$ T cell responses are induced in chronic infection. HLA-B27, HLA-B57 and HLA-A3 allotypes are suggested to be associated with spontaneous HCV clearance[3], revealing the crucial role of HCV-specific $CD8^+$ T cells in the outcome of acute HCV infection.

2.1 Characteristics of immune response in early HCV infection

HCV replicates rapidly after infection, and the virus RNA can be detectable in the peripheral blood of infected individuals within one week. The innate immune system senses the virus RNA, interferon stimulated genes(ISGs) appeared in the liver and NK cells are activated (increased expression of NKG2D and increased effector functions consisting of IFNγ production and cytotoxicity)[3]. Failure of the innate immune system to control early events of infection induces the development of an adaptive immune response against HCV, but T cell immune responses seemed delayed and HCV-specific $CD4^+$ and $CD8^+$ T cells can be detectable in the liver and peripheral blood approximately 6-8 weeks after initial HCV exposure. Subsequently, HCV-specific T cells expand without a rise in liver enzyme levels indicating the destruction of infected hepatocytes until 12 weeks. In this phase, most infected individuals achieve partial control of viraemia and show similar features of cellular immunity, irrespective of the clinical outcome. Patients with long-lasting roust HCV-specific T cell immune responses

are prone to spontaneously eliminate the virus within the first 6 months and a smaller portion may clear their infection in 12 months[4]. Then, HCV-specific T cell immune responses evolve to be contracted in parallel to increased expression of CD127, a marker of memory T cells. Whereas, 60-80% of infected individuals progress into persistent HCV infection, because of the collapse of virus-specific T cell immunity[4].

Previous studies and clinical observations revealed that the outcome of acute HCV infection is influenced by host immune and genetic factors mostly associated with the host's anti-viral immunity, including killer inhibitory receptors(KIRs), HLA molecules, ISGs, chemokines, cytokines, etc. For example, gene KIR2DL3 and its ligand HLA-C1 alleles, which are known to result in a lower threshold for NK cell activation, are more likely to clear HCV infection than individuals with other KIR2DL:HLA-C combinations[3]. Polymorphism in the IL28B(IFNl3) and /or IFNL4 gene not only influences immune responses and the capacity to spontaneously eliminate HCV, but also the response to IFN therapy, though the mechanism needs further elaboration[5].

2.2 Chronic HCV infection: Immune dysfunction

Deficiency of the host's anti-viral immunity, especially HCV-specific $CD8^+$ T cells exhaustion, is the remarkable specialty during persistent HCV infection. Despite ISGs inducing IFNs production, sustained activation of the immune system has detrimental effects on the surrounding tissues and the patients' ability to combat HCV infection. Chronic exposure to endogenous IFN-α induced phosphorylation of signal transducer and activation of transcription (STAT)1 in NK cells, which results in pSTAT1-dependent cytotoxicity dominant over pSTAT4-dependent IFN-γ production in intracellular signalling pathways[6]. As a consequence, NK cells displace a "functional dichotomy" characterised by enhanced cytotoxicity and expression of the apoptosis-inducing ligand TRAIL (also known as TNFSF10), a simultaneous deficiency to produce adequate amounts of IFN-γ and tumour necrosis factor (TNF)-α, with consequent failure to eradicate HCV[7].

HCV-specific $CD8^+$ T cell functional deficiency is the hallmark of chronic HCV infection, recognising epitopes no longer present due to viral mutation or T cell exhaustion with impaired proliferation, cytotoxicity and γ-interferon secretion when specific for epitopes that remain intact. T cell exhaustion is the primary explanation for T cell dysfunction in chronic HCV infection, characterised by the down-regulation of CD127, up-regulation of inhibitory receptors on T cells, including PD-1 (programmed cell death protein 1), CTLA4 (cytotoxic T lymphocyte antigen 4), TIM3, KLRG1 (killer cell lectin-like receptor G1), CD160 and 2B4 (also known as CD224) and T-bet deficiency, as well as high levels of expression of CD39[3]. The co-expression of multiple inhibitory receptors is detectable in intrahepatic HCV-specific $CD8^+$ T cells in chronic HCV infected patients. Blockade of the PD-1, CTLA-4, and/or Tim-3 pathways may reverse the exhaustion of $CD8^+$ T cells in vitro. However, in vivo blockade of the PD-1 pathway alone has limited efficacy suggesting the combinatorial blockade of inhibitory receptors seems to be required for the efficient restoration of exhausted HCV-specific $CD8^+$ T cell functions[5].

Continuous stimulation of virus antigens is the main cause for T cell exhaustion in chronic HCV infection[8]. HCV E2 protein and a short RNA fragment coded by E2 were found to respectively inhibit distal and proximal T-cell receptor-mediated signalling, likely aiding in establishing infection and contributing to viral persistence. Recently, prostaglandin E2 was reported as a novel inhibitory receptor that inhibited CTL survival and function in LCMV infection, and might exert similar influences in chronic HCV infection. Extensive regulatory T (Treg) cell expansion and cytokines like IL-10, TGF-ß expression can also seriously impair HCV-specific T cell responses.

In addition to the above mechanisms contributing to $CD8^+$ T cell dysfunctions, HCV-specific $CD4^+$ T cells immune deficiency is the primary cause for HCV-specific $CD8^+$ T cell functional exhaustion. In acute HCV infection, roust and broad HCV-specific $CD8^+$ T cell responses which are critical for virus spontaneous resolution, are helped and maintained by $CD4^+$ T cells, HCV- specific $CD4^+$ T cell responses diminished or even disappeared (e.g. during the late phase of acute HCV infection) , which impaired virus-specific $CD8^+$ T cell functions resulting in the establishment of persistent viraemia[4]. Fctors contributing to the collapse of $CD4^+$ T cell responses are uncertain. Several researches observed high expressions of inhibitory receptors (PD-1, CTLA4, etc.), and an imbalance between Th17 and Treg cells may lead to the failure of HCV-specific $CD4^+$ T cell help[9].

2.3 Host immune responses to antiviral therapy in Chronic Hepatitis C patients

HCV-specific $CD8^+$ T cells are well recognised as a critical element to eliminate HCV infection, especially after the end of treatment to control HCV traces that may persist for several years in some sustained virologic response (SVR) patients with apparent clinical disease resolution[10]. Therefore, restoration of HCV-specific $CD8^+$ T cell responses determines the antiviral efficacy in chronic hepatitis C (CHC) patients.

α-Interferon (IFN-α), as the main regimen for HCV infection, has a direct antiviral activity by the induction of ISGs, as well as immunoregulation by affecting the innate and adaptive immune response via stimulation of $CD8^+$ T cells, NK cells and other immunocytes. But the role of IFN-α based therapy on HCV-specific T cell kinetics is still controversial. Several reports showed that there was virus-specific $CD8^+$ T cell restoration at least partially in SVR CHC patients treated with PEG-α-interferon/ribavirin characterised by increased frequency and number of HCV-specific $CD8^+$ T cells, enhanced cytotoxicity and induction of HCV-multispecific $CD4^+$ Th1 response[10]. Additionally, virus-specific $CD8^+$ and $CD4^+$ T cell responses show a correlation with treatment outcome during IFN-α therapy[10]. However, more researches have suggested that IFN-α has dichotomy effects on the host's immunity to either enhance immune cell activation or to exert negative immunoregulation[11]. During chronic viral infection, IFN-α signalling predominantly exerts detrimental effects on T cells, and blockade of IFN-α can reduce excessive immune activation and accompanying immune suppressive mechanisms, consequently to enhance T cell-dependent resolution of LCMV infection in vivo. Besides, IFN-α based

therapies have been suggested to accentuate the NK cell functional dichotomy with massive expansion of TRAIL-expressing NK cells, that may have the potential to delete virus-specific T cells. In fact, pegylated type I interferon (PegIFN) therapy mediated specific T cells immune restoration is rarely detected within chronic HCV infection although it was reported during acute infection, providing a consensus with the low efficacy of IFN-α based therapy to CHC patients.

The recently developed DAAs therapy has transformed HCV infection. Interestingly, responders to DAAs had a significant increase in the number and frequency of HCV-specific $CD8^+$ T cells, a restored HCV-specific proliferative capacity and functionality, as well as upregulation of CD127 expression and decreased PD-1 high-level expression in HCV-specific $CD8^+$ T cells[12]. In contrast to Peg IFN-based therapies, the combination use of DAAs may reverse the exhaustion of HCV-specific $CD8^+$ T cells in CHC patients. As an IFN-α free regimen, DAAs therapy was reported to restore innate immunity in chronic hepatitis C, with loss of intrahepatic immune activation by IFN-α, which is indicated by decreased levels of CXCL10 and CXCL11 and normalisation of NK cell phenotype and function[13]. However, more unknowns should be underscored, e.g. whether SVR patients with a therapy of DAAs were always accompanied by a restoration of HCV-specific immune response and how to use the extent of T cell reconstitution as a guide to personalise DAAs. Apart from T cells and NK cells, how DAAs will influence other immunocytes? All of that need more immune evidences and clinical observations.

3 Conclusion

The host's immune responses against HCV infection, particularly the kinetics of HCV-specific $CD8^+$ T cell responses, not only drive disease progression, but also have a significant influence on the efficacy of antiviral treatment in HCV-infected individuals(Fig.1). SVR patients treated by DAAs or IFN-α /RBV may achieve a partial restoration of impaired antiviral immune responses. More so, DAAs have been reported to rescue exhausted HCV-specific T cell responses and cure innate immunity, with high rates of SVR. But more DAA resistant mutants emergence makes an essential to further elaborate HCV immunology, and a cost-effective, prophylactic and therapeutic HCV vaccine is still urgently needed to fight HCV infection worldwide.

References

1. Heathcote EJ. Prevention of hepatitis C virus-related hepatocellular carcinoma. Gastroenterology (2004) 127: S294–302.
2. Khan AG, Whidby J, Miller MT, et al. Structure of the core ectodomain of the hepatitis C virus envelope glycoprotein 2. Nature (2014) 509(7500): 381–384.
3. Shin EC, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. Nat Rev Immunol (2016) 16(8):509-523.
4. Lauer GM. Immune Responses to Hepatitis C Virus (HCV) Infection and the Prospects for an EffectiveHCV Vaccine or Immunotherapies. J Infect Dis (2013) 207 Suppl 1: S7-S12.
5. Abdel-Hakeem MS, Shoukry NH. Protective immunity against hepatitis C : many shades of gray. Front Immunol (2014) 5:274.
6. Miyagi T, Takehara T, Nishio K, et al. Altered interferon-alpha signaling in natural killer cells from patients with chronic hepatitis C virus infection. J Hepatol (2010) 53: 424–430.
7. Mondelli MU. Direc t-Acting Antivirals Cure Innate Immunity in Chronic Hepatitis C. Gastroenterology (2015) 149(1): 25-28.
8. Douam F, Ding Q, Ploss A. Recent advances in understanding hepatitis C. F1000Res (2016) 3:5.
9. Kared H, Fabre T, Bedard N, et al. Galectin-9 and IL-21 mediatecross-regulation between Th17 and Treg cells during acute hepatitis C. PLoS Pathog (2013) 9(6):e1003422.
10. Larrubia JR, Moreno-Cubero E, Miquel J, et al. Hepatitis C virus-specific cytotoxic T cell response restoration after treatment-induced hepatitis C virus control. World J Gastroenterol (2015) 21(12): 3480-3491.
11. Odorizzi PM, Wherry EJ. Immunology. An interferon paradox. Science (2013) 340:155–156.
12. Martin B, Hennecke N, Lohmann V, et al. Restoration of HCV-specific CD8+ T cell function by interferon-free therapy. J Hepatol (2014) 61(3): 538-543.
13. Serti E, Chepa-Lotrea X, Kim YJ, et al. Successful Interferon-Free Therapy of Chronic Hepatitis C Virus Infection Normalizes Natural Killer Cell Function. Gastroenterology (2015) 149(1): 190-200.e2.

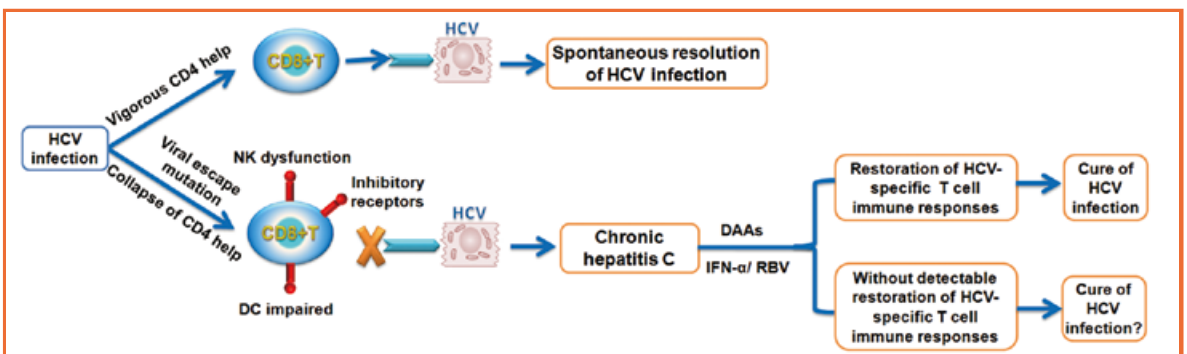

Fig. 1 Characteristics of HCV-specific immune response during chronic HCV infection.
In acute HCV infection, vigorous, broad and long-lasting virus-specific CD8+T cell responses are competent to eliminate HCV; Weak and narrow CD8+ T cell responses are prone to establish persistent infection. Restoration of impaired antiviral T cell responses will make a cure in patients with chronic HCV infection. DAA, direct-acting antiviral; IFN-α, interferon alpha; RBV, ribavirin.

Fraud in Medical Research – A life-Style?

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Research fraud in medical research exists as fraud exists in other parts of our society. For some persons, it may represent a way of living i.e. a life-style.

The following short text is taken from a directive story - Assassin in Svanstrand by Markus Swan alias Johan Karlberg. The full story is available as free download at http://www.clinicaltrialmagnifier.org/detective-story/.

Background: This is a fictional detective story about the unethical conduct of clinical trials and insider trading based on the trial results. The story took place in Svanstrand, a small Swedish fishing village and a summer holiday paradise for people escaping from the city. A murder occured in October and there were subsequent killings during a heavy Christmas snowstorm that paralysed infrastructures in Svanstrand, Österlen and Skane. Markus Swan and his wife Karin had recently renovated their summer house in Svanstrand on their return from Hong Kong, and were planning a traditional family Christmas there. Markus visited Svanstrand in October and witnessed two people fighting at the end of the old concrete pier.

From the book:

I was reading the interview with Mr Craft in the business supplement of NySydan. He had been attending a closed international meeting on 'Globalisation of Insider Trading: New Developments'. The participants represented experts from the major financial nations.

'A first question, Mr Craft. Why is your meeting taking place in a small village?'.

Craft replied, 'Because we have a local guest speaker tomorrow. He suggested this very nice but snowy part of the world. Professor Bertil Latas will give a presentation entitled 'Side-effects and termination of drug development of new pharmaceutical compounds'.

'How do you define insider trading?'.

'Insider trading is perceived as fraud. Fraud is defined as intended dishonesty made for personal gain or to harm another person. Fraud is seen as a criminal act. Fraud appears in many areas of society and a common reason for fraudulent behaviour is to collect money or other valuables from others. An excellent example of fraud is insider trading. Another good example is match-fixing in sport, which generally refers to fixing the final result. However, fraud can also be found in science when the results of research studies are falsified to gain prestige rather than immediate monetary gain. However, outstanding scientific research publication records will eventually lead to financial gains through promotions and so on. The use of performance-enhancing drugs is another area of fraud and it's mostly done to improve athletic performance. Any type of fraudulent behaviour is performed to gain an advantage over others and for personal gain by using prohibited methods'.

I wondered if I knew about any research fraud. Yes, of course. I personally know two clinical researchers that were caught for scientific fraud. They were punished by being sacked from the academic institution and the incidents were never made public. Their publications are therefore still in the public domain and readers are unaware that they might be useless and misleading. I also knew three colleagues had manipulated research data before their manuscript was sent for review by international journals.

I looked out through the window and saw that the snow had started melting on the roof, saving me another go with the shovel.

I continued thinking about scientific fraud. We could only guess the size of the problem. A recent study by the British Medical Journal including the response of 2,800 clinicians and academics showed that 13% had witnessed colleagues intentionally altering or fabricating research data and 6% were aware of possible research fraud at their institution that hadn't been properly examined. If those figures were true then we were facing scientific fraud on a large scale. There had also been many reports on pharmaceutical companies that had falsified publications simply to boost sales. The saga went on and on.

Fig. 1 Clinical Trial Magnifier Detective Story-Icy

Fig. 2. Clinical Trial Magnifier Detective Story-Post Storm

Fig. 3 Clinical Trial Magnifier Detective Story-SnowStorm

Fig. 4 Clinical Trial Magnifier Detective Story-Storm After

Fig. 5 Clinical Trial Magnifier Detective Story-Storm Entrance

Fig. 6 Clinical Trial Magnifier Detective Story-Storm NoWay

Photos by Dr Johan PE Karlberg, Copyright

Public talk on Muscle Loss

On 4 June 2016, a public talk on Muscle Loss was held in the Lecture Hall, FMSHK Office that had attracted 85 participants. Muscle loss is common as people age. The Federation was privileged to invite Dr YIP Wai-man, Specialist in Geriatric Medicine, who delivered a talk on the causes, symptoms and diagnosis of muscle loss. Dr Yip also suggested some simple exercises to test and enhance muscular strength. Another speaker, Ms Sally POON, Chairperson of the Hong Kong Practising Dietitians Union, delivered a talk on nutrition and suggested to the audience typical healthy diets for preventing muscle loss. Numerous questions in the Q&A session from the actively participating audience helped to complete a very successful and interactive seminar.

Public talk on Osteoporosis

A public talk on Osteoporosis was held in the Federation Lecture Hall on 29 October 2016,. Again, it was our pleasure and privilege to invite Dr Wai-man YIP, Specialist in Geriatric Medicine, to deliver a talk on "How to keep bones strong and healthy?", and Ms Sally POON, Chairperson of the HK Practising Dietitians Union, to deliver a talk followed by a cooking demonstration. She taught the audience how to prepare simple healthy meals and suggested eating tips to promote bone health. Judging from the active questioning and involvement in the cooking demonstration, the participants greatly enjoyed this educational event.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				★ HKMA Hong Kong East Community Network - New Biological Treatment for Atopic Dermatitis ★ HKMA Kowloon East Community Network - Update on Biologics for Osteoporosis Treatment ★ HKMA New Territories West Community Network - Lecture Series on Clinical Oncology (Session 2): Immunotherapy - Recent Treatment for Cancers **1**	**2**	**3**
4	**5**	★ HKMA Yau Tsim Mong Community Network - Role of DPP IV Inhibitors in the Context of Latest Trials ★ HKMA Kowloon West Community Network - What's New in HIV Medicine 2016 ★ FMSHK Officers' Meeting ★ HKMA Council Meeting **6**	★ HKMA Central, Western & Southern Community Network - Update on COPD Exacerbations **7**	★ HKMA New Territories West Community Network - Advances in Chronic Heart Failure Treatment ★ HKMA Kowloon East Community Network - Asthma - What does Guideline Defined Approach Management Means to Primary Care Doctors? ★ HKMA Structured CME Programme with HKS&H Session 11: Non-surgical Management of Lung Cancer **8**	**9**	★ Refresher Course for Health Care Providers 2016/2017 **10**
11	**12**	**13**	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –Moyamoya Disease **14**	★ HKMA Hong Kong East Community Network - Update on Cancer Immunotherapy ★ HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2016 (Sessoin 6): Paediatric Immunisations Update ★ FMSHK Executive Committee Meeting **15**	**16**	**17**
18	**19**	★ HKMA Kowloon West Community Network - GERD Pathophysiology and Management **20**	**21**	**22**	**23**	**24**
25	**26**	**27**	**28**	**29**	**30**	★ HKMA Annual Ball 2016 **31**

Date / Time	Function	Enquiry / Remarks
1 THU 1:00 PM	**HKMA Hong Kong East Community Network - New Biological Treatment for Atopic Dermatitis** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. GOH Kim Yeow; Speaker: Dr. CHAN Yung; Venue: The Hong Kong Management Association (香港管理專業協會), Room 201, 2/F, Pico Tower, 66 Gloucester Road, Wan Chai, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - Update on Biologics for Osteoporosis Treatment** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. YIP Man Lung, Ronald; Venue: Lei Garden Restaurant (利苑酒家), Shop no. L5-8, APM, Kwun Tong, No. 418 Kwun Tong Road, Kwun Tong, Kowloon	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Lecture Series on Clinical Oncology (Session 2): Immunotherapy - Recent Treatment for Cancers** Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. TSE Yiu Cheong, Adrian; Venue: Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
6 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Role of DPP IV Inhibitors in the Context of Latest Trials** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHENG Kai Chi, Thomas; Speaker: Dr. CHAN Wing Bun; Venue: Jade Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon West Community Network - What's New in HIV Medicine 2016** Organiser: HKMA Kowloon West Community Network; Speaker: Dr. TSANG Kay Yan; Venue: Crystal Room IV-V, 3/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Ms. Christine WONG Tel: 2527 8285
7 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Update on COPD Exacerbations** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. TSANG Chun Au; Speaker: Dr. LO Ho Yin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
8 THU 1:00 PM	**HKMA New Territories West Community Network - Advances in Chronic Heart Failure Treatment** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHUNG Siu Kwan, Ivan; Speaker: Dr. YAN Chun Ting, Fergus; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - Asthma - What does Guideline Defined Approach Management Means to Primary Care Doctors?** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. MA Ping Kwan, Danny; Speaker: Dr. LO Chi Wai; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O (將軍澳唐德街3號香港九龍東智選假日酒店6樓彩雲軒)	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
2:00 PM	**HKMA Structured CME Programme with HKS&H Session 11: Non-surgical Management of Lung Cancer** Organiser: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. YAU Chun Chung; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
10 SAT 2:15 PM	**Refresher Course for Health Care Providers 2016/2017** Organiser: Hong Kong Medical Association & HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr. CHAN Tsz Mim, Jasmine; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
14 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Moyamoya Disease** Organizer: Hong Kong Neurosurgical Society; Chairman: Dr NG Yuen Ting, Rebecca; Speaker: Dr HUNG Cheung Yu; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax.: 2965 4061 1.5 points College of Surgeons of Hong Kong
15 THU 1:00 PM	**HKMA Hong Kong East Community Network - Update on Cancer Immunotherapy** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. LAM See Yui, Joseph; Speaker: Dr. CHOI Ho Keung; Venue: The Hong Kong Management Association (香港管理專業協會), Room 201, 2/F, Pico Tower, 66 Gloucester Road, Wan Chai, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2016 (Sessoin 6): Paediatric Immunisations Update** Organiser: HKMA Kowloon East Community Network & Hong Kong College of Family Physicians & United Christian Hospital; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. CHEUNG Chi Hung, Patrick; Venue: Conference Room, G/F, Block K,United Christian Hospital (UCH), 130 Hip Wo Street, Kwun Tong, Kowloon	Ms. Polly TAI / Ms. Cordy WONG Tel: 3949 3430 (Ms. TAI) / 3949 3087 (Ms. WONG) 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
20 TUE 1:00 PM	**HKMA Kowloon West Community Network - GERD Pathophysiology and Management** Organiser: HKMA Kowloon West Community Network; Speaker: Dr. LI, Ernest Han Fai; Venue: Crystal Room IV-V, 3/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
31 SAT 8:00 PM	**HKMA Annual Ball 2016** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHAN Yee Shing, Alvin & Dr. YEUNG Hip Wo, Victor; Venue: Conrad Hong Kong, One Pacific Place, 88 Queensway, Admiralty	Ms. Candy YUEN Miss Ellie FU Tel: 2527 8285

Answers to Radiology Quiz

Answer:

1. Findings

   Patient A:
   One lateral radiograph of the left ankle was given.
   Mild increased soft tissue density noted at the anterior and posterior left ankle joint. Bulging of the anterior fat line noted. Erosions noted at the posterior border of the talus. No bony destruction.

   Patient B:
   Two radiographs of the right elbow were given (anteroposterior and lateral).
   Gross right elbow swelling. Paraarticular erosions seen at the humeral condyles and olecranon. Increased opacity over the medial and posterior joint compartments.

2. Both patients have late stage gouty arthritis. Radiological findings in gout usually do not occur until 6-8 years later in the disease. Patient B also had olecranon bursitis. The feet, hands, wrists, elbows and knees are preferentially affected in gout. Chronic tophaceous gout involves both the soft tissue and joint. Associated intraarticular or juxtaarticular erosions are commonly seen in the late stage, as seen in both our patients.

3. Since both patients complained of monoarticular joint pain, a septic workup should be performed to exclude septic arthritis. A detailed history for purine rich foods, alcohol, diuretics or cyclosporin may be helpful to rule in gout.Uric acid level may be raised (~20) in gouty arthritis. Synovial fluid or tophi may be evaluated for monosodium urate crystals.

Reference:
1. http://radsource.us/gout/
2. J. Llauger, J. Palmer, N. Rosón, et al. Nonseptic monoarthritis: Imaging features with clinical and histopathologic correlation. Radiographics, 20 (2000 Oct)

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Department of Radiology
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AE = adverse event. BD = twice daily. HCV = hepatitis C virus. IFN = interferon. NS5A = nonstructural protein 5A. NS5A RAV = NS5A resistance-associated variant. QD = once daily. RBV = ribavirin. SVR = sustained virologic response.

References
1. Manns M, Pol S, Jacobson IM, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet 2014;384:1597-1605. 2. Data on file. 3. McPhee F, Suzuki Y, Toyota J, et al. High Sustained Virologic Response to Daclatasvir Plus Asunaprevir in Elderly and Cirrhotic Patients with Hepatitis C Virus Genotype 1b Without Baseline NS5A Polymorphisms. Adv Ther 2015;32:637-649 4. Daklinza® Tablets 60 mg prescribing information (Effective date : January 2016). 5. Sunvepra® Capsules 100 mg prescribing information (Effective date : January 2016).

DAKLINZA® tablets ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Each tablet contains 60 mg daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) or 30 mg daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride). **INDICATION(S):** DAKLINZA is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease (including cirrhosis). [see DOSAGE & ADMINISTRATION] **DOSAGE & ADMINISTRATION:** 60 mg once daily, taken orally, with or without food in combination with sofosbuvir (for HCV genotype 1 or 3 or SUNVEPRA® (for HCV genotype 1b). Recommended treatment duration is 12 or 24 weeks, depending on the HCV genotype and prior treatment. Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers. **CONTRAINDICATIONS:** • Patients with previously demonstrated hypersensitivity to daclatasvir or any component of the product. • Contraindications applicable to those medicinal products used in combination with DAKLINZA. • Combination of DAKLINZA with peginterferon alfa and ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant. • Combination with strong CYP3A4 inducer. Contraindicated drugs include, but are not limited to, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, dexamethasone and St John's wort (Hypericum perforatum). • Coadministration with moderate CYP3A4 inducers is contraindicated with regimens that include SUNVEPRA. **SPECIAL WARNINGS AND PRECAUTIONS:** • DAKLINZA must not be administered as monotherapy. • Drug-induced liver injury, in some cases severe, has been observed with SUNVEPRA containing regimens. • Severe bradycardia has been observed in patients receiving amiodarone with DAKLINZA and sofosbuvir. Close monitoring is recommended. **ADVERSE REACTIONS:** Headache, fatigue, diarrhoea, nasopharyngitis, nausea, pruritus, asthenia, influenza-like illness, insomnia, rash, anaemia, cough, dry skin, alopecia, irritability, pyrexia, myalgia, eosinophilia and increased AST. Refer to full prescribing information for other side effects. **PREGNANCY & LACTATION:** DAKLINZA should not be used during pregnancy or in women of childbearing potential not using contraception. Use of effective contraception should be continued for 5 weeks after completion of treatment. Mothers should be instructed not to breastfeed if they are taking DAKLINZA. See also the product information for ribavirin and peginterferon alfa. **INTERACTIONS:** Moderate or strong inducers of CYP3A4. Strong inhibitors of CYP3A4. Medicinal products that are substrates of P-gp, OATP1B1 or 1B3, or BCRP with a narrow therapeutic range. Consult the full prescribing information prior to and during treatment for potential drug interactions. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.** Prescribing information last revised: January 2016

SUNVEPRA® capsules ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Each soft gelatin capsule contains 100 mg of asunaprevir. **INDICATION(S):** SUNVEPRA is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) in adults with compensated liver disease (including cirrhosis). [See DOSAGE & ADMINISTRATION] **DOSAGE & ADMINISTRATION:** For patients with HCV Genotype 1b infection who are treatment-naive, failed peginterferon alfa/ribavirin: 100 mg twice daily, taken orally, with or without food. Recommended treatment duration is 24 weeks. SUNVEPRA must be administered in combination with DAKLINZA. Reduce dose to 100 mg once daily for patients with severe renal impairment [creatinine clearance (CrCl) < 30mL/min] who are not receiving hemodialysis. **CONTRAINDICATIONS:** • Patients with previously demonstrated hypersensitivity to asunaprevir or any component of the product. • Contraindications of medicinal products used in combination with DAKLINZA. • Combination of SUNVEPRA with DAKLINZA, peginterferon alfa, and ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant. • Patients with moderate or severe hepatic impairment (Child-Pugh B or C, score 7 or greater) and patients with decompensated liver disease. • SUNVEPRA is contraindicated in combination with: thioridazine, drugs that strongly or moderately induce CYP3A (phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, bosentan, dexamethasone, St John's wort (Hypericum perforatum), efavirenz, etravirine, nevirapine and modafinil), drugs that strongly or moderately inhibit CYP3A (itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole, clarithromycin, erythromycin, diltiazem, verapamil, atazanavir, darunavir/ritonavir, fosamprenavir, indinavir, lopinavir/ritonavir, ritonavir, saquinavir and cobicistat), and drugs that strongly inhibit organic anion transporting polypeptide (OATP) 1B1 (rifampicin, cyclosporine and gemfibrozil). **SPECIAL WARNINGS AND PRECAUTIONS:** • SUNVEPRA must not be administered as monotherapy. • **POTENTIAL FOR HEPATOTOXICITY:** For patients receiving SUNVEPRA-containing regimens, liver enzymes (ALT, AST) and bilirubin levels should be monitored at least once every 2 weeks for the initial 12 weeks of treatment, and every 4 weeks thereafter until completion of therapy. Any upward trend in ALT or AST levels warrants more frequent monitoring. Discontinue SUNVEPRA immediately and do not resume in patients who experience: on-treatment elevations in ALT levels 10 x ULN or greater, or on-treatment elevations in both AL T levels> 5 x ULN and total bilirubin> 2 x ULN. • For patients using oral contraception, a high-dose oral contraceptive (containing at least 30 mcg of ethinyl estradiol combined with norethindrone acetate/norethindrone) is recommended. **ADVERSE REACTIONS:** Headache, fatigue, diarrhoea, nasopharyngitis, nausea, pruritus, asthenia, influenza-like illness, insomnia, rash, anaemia, cough, dry skin, alopecia, irritability, pyrexia, myalgia, eosinophilia, and increase in AST. Refer to full prescribing information for other side effects. **PREGNANCY & LACTATION:** No adequate and well-controlled studies of SUNVEPRA in pregnant women. SUNVEPRA in combination with DAKLINZA should not be used during pregnancy or in women of childbearing potential not using contraception. Mothers should be instructed not to breastfeed if they are taking SUNVEPRA. See also the product information for DAKLINZA, ribavirin and peginterferon alfa. **INTERACTIONS:** Moderate or strong inducers of CYP3A. Moderate or strong inhibitors of CYP3A. Strong inhibitors of OATP-mediated transport. Use with caution and close clinical monitoring when administered with substrates of CYP2D6, OATP 1B1/1B3- and P-gp-mediated transport, and CYP3A. See also CONTRAINDICATIONS. Consult the full prescribing information prior to and during treatment for potential drug interactions. **PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.** Prescribing information last revised: January 2016

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Daklinza® (daclatasvir)

Sunvepra® (asunaprevir)