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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.

Dr Johan KARLBERG
MD, PhD(Anatomy & Cell Biology), Bsc(Statistics & Education)
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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 States 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/ritonavir/ombitasvir + dasabuvir (NS3/4A protease inhibitor, NS5A inhibitor, and NS5B non-nucleoside polymerase inhibitor), Paritaprevir/ritonavir/ombitasvir + ribavirin (NS3/4A protease inhibitor and NS5A inhibitor), Daclatasvir (NS5A inhibitor), Elbasvir/grazoprevir (NS5A inhibitor and NS5A/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. 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 tailor 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. 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 coinfection 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. 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 coinfection 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.

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Treatment of chronic hepatitis C infection-2017 and beyond

Dr George LAU

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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 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
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.11-11

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/velpatasvir 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. First of all, in these patients, a lot of DAs, 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 DAs rather than to receive liver transplant and then DAA treatment? We will need to await future studies for more definitive answers.11-11

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 renal 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-orlal 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-orlal DAAs, have recently been reported by our group and others.14-21 The severity of hepatitis ranged from HBV reactivation without hepatitis16 to fulminant hepatic failure, requiring liver transplantation.17 The underlying mechanisms of HBV reactivation during pan-orlal DAA therapy for

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**Table 1 Currently available HCV DAAs approved by FDA**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA Approved Year</th>
<th>Mechanism of Action</th>
<th>SVR12 Rate for Treatment-naive HCV Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Olysio®</td>
<td>2013</td>
<td>NS3/4A protease inhibitor</td>
<td>GT 1–97%*</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi®</td>
<td>2013</td>
<td>NS5B polymerase inhibitor</td>
<td>GT 1–89%</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Harvoni®</td>
<td>2014</td>
<td>NS5A inhibitor and NS5B polymerase inhibitor</td>
<td>GT 1–96%</td>
</tr>
<tr>
<td>Paritaprevir/r/ombitasvir + dasabuvir</td>
<td>Viekira Pak®</td>
<td>2014</td>
<td>NS3/4A protease inhibitor, NS5A inhibitor, and NS5B non-nucleoside polymerase inhibitor</td>
<td>GT 1–90%</td>
</tr>
<tr>
<td>Paritaprevir/r/ombitasvir</td>
<td>Technivie®</td>
<td>2015</td>
<td>NS3/4A protease inhibitor and NS5A inhibitor</td>
<td>GT 4–100%</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>DaklinzaTM</td>
<td>2015</td>
<td>NS5A inhibitor</td>
<td>GT 1–96%<em>, GT 3–90%</em></td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>ZepatierTM</td>
<td>2016</td>
<td>NS5A inhibitor and NS3/4A protease inhibitor</td>
<td>GT 1–95%, GT 4–97%</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>Epclusa®</td>
<td>2016</td>
<td>NS5B polymerase inhibitor and NS5A inhibitor</td>
<td>GT 1–99%, GT 2–100%, GT 3–90%</td>
</tr>
</tbody>
</table>

*SVR12 rates provided are for the oral combination of the DAA + sofosbuvir as per the label.
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-naive, genotype 1 patients without cirrhosis who received 8 weeks of Ledipasvir/Sofosbuvir had an SVR rate of 94%, and similar success has been observed in clinical practice, including 96% in the HCV-TARGET cohort. 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%. 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 DAAAs, 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. Similarly, C-SWIFT reported a low baseline HCV viral load, genotype, and absence of RAVs (NS5B), while LEPTON recognised a low baseline HCV viral load and young age as favourable baseline characteristics. While on treatment week 4 viral loads do not predict treatment outcomes, preliminary viral measurements, as early as the first or second week of therapy, may have some utilities, and modelling predicts that a more rapid second-phase viral decline would facilitate treatment durations of less than 8, with a carefully selected regimen. According to Perelson et al., nucleoside analogue inhibitors, while powerful DAAAs 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. 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. 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 (NS5a protease inhibitor and NS5A inhibitor-N5SB 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. 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. 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. 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 DAAAs with increased potency and a longer half-life need to be developed. Factors that may impact 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 counterfeit 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


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 simprevir, 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

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Drug abuse in the acute medical setting

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 will 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. 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.

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).

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 ultrasonography-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.

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. 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) was the first algorithm combining several serum parameters for fibrosis staging in CHC patients. It is a patented formula consisting of α-2-macroglobulin, hyaluronate, 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). 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 METAIV 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 composed 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.

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


Radiology Quiz

Dr Christine LO

Department of Radiology
Queen Mary Hospital

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

Dr Roger WILLIAMS
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The Institute of Hepatology London, Foundation for Liver Research, London, and Faculty of Life Sciences & Medicine, King’s College London, London, UK

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

<table>
<thead>
<tr>
<th>Child-Pugh</th>
<th>SVR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>96% – 98%</td>
</tr>
<tr>
<td>B</td>
<td>85% – 88%</td>
</tr>
<tr>
<td>C</td>
<td>60% – 75%</td>
</tr>
<tr>
<td>FCH</td>
<td>100%</td>
</tr>
</tbody>
</table>

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

*By intent-to-treat analysis, virologic response of HBsAg- patients (n=375) and HBsAg+ patients (n=266) are 75% and 58% respectively at week 544. Total 14 hepatocellular carcinomas were found during the study period. The incidence of HCC was 0.5% at 544 weeks.

HBV DNA <49 IU/mL  * Missing=excluded/addition of emtricitabine included  CHB=chronic hepatitis B, HBsAg=hepatitis B e-antigen, HBV=hepatitis B virus

VIREAD® 8 years

Viread® has been clinically proven for its efficacy over 8-year treatment journey. After 8 years of continuous treatment with Viread®:

- 0% resistance was found
- ≥98% patients achieved virologic response regardless of HBeAg status in on-treatment analysis

Reference rate of serious drug-related adverse events was 1.2% (n=77) among patients (n=585) who entered the open-label phases.1

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

1 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, tolerance <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 package prescribing information which is available upon request.
At the ready
to save lives

Bleeding oesophageal varices (BOV)

- Proven to reduce mortality\(^1\)
- Early haemostasis verified by endoscopy\(^2,3\)
- Improves renal blood flow, relevant for pre-HRS patients\(^4,5\)
- Helps restore haemodynamics (↑MAP ↑CBV ↓HR)\(^6-13\)
- Allows bolus injection\(^14\)

Type 1 hepatorenal syndrome (HRS)

- Proven to reduce mortality\(^15\)
- Effectively reversed HRS\(^15\)
- Treatment of choice in HRS\(^16\)

NEW
GLYPRESSIN Solution
Ready mixed, ready to go

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


Acknowledged: Prescribing Information of GLYPRESSIN

Indication: Treatment of bleeding oesophageal varices (BOV) and emergency management of type 1 hepatorenal syndrome (HRS). Dosage & Administration: GLYPRESSIN is administered intravenously. BOV: Initially, 2 mg injection is given every 6 hours. Should be repeated up to 24 mg injection. HRS: 3 to 4 mg intravenous boli every 24 hours for 3 or 4 injections. In the absence of any resolution of ascites, readmission after 8 days of treatment, cessation of GLYPRESSIN treatment is advised. Contraindications: Pregnancy, hypersensitivity to terlipressin or any other excipients of the product, Undesirable effects: Headache, nausea, peripheral vasodilation, bowel colic, facial edema, hypertension, transient abdominal discomfort and transient diarrhea. Special Warnings: Blood pressure, heart rate and fluid balance should be monitored during treatment. Caution should be exercised in treating patients with hypernatremia, recognized heart disease, renal dysfunction, cardiac and peripheral vascular disease, ascites or respiratory failure. To avoid iatrogenic further events of the injection site, the injection must be administered intravenously. If patients with hepatic 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 result from a suitable chronic renal 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) alone with the NSSA inhibitor Ombitasvir (ABT-267) and NSSB 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. 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.

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

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Time post-LT</th>
<th>Child Pugh</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>48</td>
<td>4 yrs</td>
<td>10 → 5</td>
</tr>
<tr>
<td>Case 2</td>
<td>55</td>
<td>7 yrs</td>
<td>11 → 5</td>
</tr>
</tbody>
</table>


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. 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.

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.

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. Use of the new DAAs will also obviate 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. 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.

**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


Management of HCV Infections: Role of Molecular Diagnostic Assays

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Introduction
Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and cirrhosis. 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). If the anti-HCV antibody test result is positive, current infection should be confirmed 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. Monitoring of treatment effectiveness is assessed by repeated measurement of HCV RNA. 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. 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
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, if 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 prognosis1. 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 studies2. Both PCR and DNA sequencing protocols can be easily adopted for screening the IL28B polymorphisms among patients.

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-lambda-4 (IFNL4, ss496415590 TT/AG) 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 AG allele of the ss496415590 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-AG are significantly associated with slower early viral clearance and decreased drug efficacy than patients carrying homozygous IFNL4 TT/TT. The unfavourable rs12979860-T allele is somewhat in different degrees of linkage disequilibrium with ss49641590-∆G 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, heterogeneous 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 generated3. 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
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. 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.

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, 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). 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 rourst 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. 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.

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 KIR2DL3:HLA-C combinations. Polymorphism in the IL28B (IFN13) and/or IFN4 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.

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. 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.

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. The core-expression of multiple inhibitory receptors is detectable in intrahepatic HCV-specific CD8+ T cells in chronic HCV infected patients. Blockade of the PD-1, CTLA4, 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.

Continuous stimulation of virus antigens is the main cause for T cell exhaustion in chronic HCV infection. 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 which might exert similar influences in chronic HCV infection. Extensive regulatory T (Treg) cell expansion and cytokines like IL-10, TGF-β 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, robust 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. Factors 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.

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. 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. Additionally, virus-specific CD8+ and CD4+ T cell responses show a correlation with treatment outcome during IFN-α therapy. 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. 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. 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. 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. 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

Fraud in Medical Research – A life-Style?

Dr Johan KARLBERG

MD, PhD(Arthritis & Cell Biology), Bsc(Statistics & Education)
Director, Humanity & Health Research Centre, Hong Kong SAR, China; Member, Bioethics Advisory Panel, Pfizer, New York, NT, USA; Clinical Trial Magnifier, Editor

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 occurred in October and there were subsequent killings during a heavy Christmas snowstorm that paralysed infrastructures in Svanstrand, Österlen and Skåne. 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. 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.
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<td>Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax: 2965 4061 1.5 points College of Surgeons of Hong Kong</td>
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<td>Ms. Polly TAI / Ms. Cordy WONG Tel: 3949 3430 (Ms. TAI) / 3949 3087 (Ms. WONG) 1 CME Point</td>
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For more details, please contact:

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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. Increased opacity over the medial and posterior joint compartments.

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/

Dr Christine LO
Department of Radiology
Queen Mary Hospital
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Daklinza® + Sunvepra®
as a novel ALL-ORAL, IFN-FREE, RBV-FREE HCV therapy:
- Achieved SVR irrespective of patient characteristics
- Maximized outcome with pre-treatment NSSA L31/Y93 RAV testing
- Low pill burden (Daklinza® 60 mg QD + Sunvepra® 100 mg BD)
- Well-tolerated: Evidenced by lower overall AE & discontinuation rates

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

References:

Daklinza® and Sunvepra® are investigational therapies. Daklinza® and Sunvepra® are indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated cirrhosis (including cirrhosis due to chronic hepatitis B), who are infected with HCV genotype 1, 2, or 3, and who have previously been treated or have never before been treated with an HCV regimen that included a protease inhibitor, or who have not responded or have relapsed after previous treatment with an HCV regimen that included a protease inhibitor. Daklinza® and Sunvepra® are contraindicated in combination with other medicinal products that have not been approved for the treatment of chronic hepatitis C virus infection in adults with compensated cirrhosis (including cirrhosis due to chronic hepatitis B), who are infected with HCV genotype 1, 2, or 3, and who have previously been treated or have never before been treated with an HCV regimen that included a protease inhibitor, or who have not responded or have relapsed after previous treatment with an HCV regimen that included a protease inhibitor.

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Please refer to full prescribing information and brochures for full information. For full prescribing information, please visit www.daclatasvir.com or www.sunvepra.com.