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Clinical Cases in Hepatitis: toward improving liver disease management in Australia

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Abstract

Clinical Cases in Hepatitis (CCH) 2018 was an interactive educational program for Australian physicians (gastroenterologists, hepatologists, infectious disease specialists) actively involved in the treatment of liver diseases including Hepatitis C Virus (HCV), Hepatitis B Virus (HBV) and non-alcoholic steatohepatitis (NASH). This educational program sponsored by Gilead Sciences took place on October 12–13 2018 and provided timely, informative case-based and practical education to Australian physicians. This report summarises keynote lectures from international leaders in the field of HCV, HBV and NASH, and practical clinical case studies designed to inform and educate Australian physicians on managing challenging patients.

Keywords:

Hepatitis C virus, hepatitis B virus, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease

Introduction

There has been significant progress toward eliminating Hepatitis C Virus (HCV) in Australia following the introduction of all oral direct-acting antiviral (DAA) therapies and new DAA regimens, with few patient populations remaining challenging to treat. For hepatitis B virus (HBV) and chronic hepatitis B (CHB) infection, nucleos(t)ide analogue (NA) therapies are effective in managing disease but these are lifelong treatments and challenges remain in finding an effective cure. Managing aging patients with multiple comorbidities is also a major clinical concern with lifelong treatment for CHB. While newer therapies on the distant horizon may support progress toward functional, complete or even sterilizing cure for CHB, current treatment strategies need to be adapted to the aging population. Non-alcoholic steatohepatitis (NASH) is now emerging as a national and global concern that parallels the obesity and diabetes epidemic. Diet and lifestyle modification are the cornerstone of managing NASH, with supportive pharmacotherapies in clinical development. In this rapidly changing environment, Clinical Cases in Hepatitis (CCH) 2018 was established as an interactive educational program for Australian physicians (gastroenterologists, hepatologists, infectious disease specialists) actively involved in the treatment of liver diseases including HCV, HBV and NASH. This educational program sponsored by Gilead Sciences took place on October 12–13 2018 and was attended by over 120 physicians. CCH provided timely, informative case-based and practical education to Australian physicians to update them on key developments and best practice to support their liver disease patients.

This report summarises keynote lectures from international leaders in the field of HCV, HBV and NASH, and practical clinical case studies designed to inform and educate Australian physicians on managing challenging patients.

HCV workshop

The Most Challenging HCV Patients Seen in Liver Clinics

Ed Gane, Auckland City Hospital, Auckland, New Zealand

Patients with renal failure

HCV infection is associated with markedly reduced survival in patients with end stage renal disease (ESRD).[1,2] However, Sustained Virologic Response (SVR) with interferon-based regimens was shown to improve survival in HCV-positive patients on dialysis in the global Dialysis Outcomes and Practice Outcomes Study (DOPPS) (Hazard Ratio [HR] for death 0.47 [95%CI 0.17-1.26]), emphasising the need to treat renally-impaired HCV patients.[3] The majority of direct-acting antivirals (DAAs) are cleared by the liver, making them safe to use in renal impairment, with the exception of nucleoside and nucleotide polymerase inhibitors, including sofosbuvir (SOF) and ribavirin (RBV), which are cleared by the kidney. DAAs approved in Australia for use in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) include elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/r + DSV)[*] and glecaprevir/pibrentasvir (GLE/PIB).[4-6] These agents have shown safety and efficacy in this population with high SVR rates reported that were similar to those of patients with normal renal function.[7-9] Consequently, HCV in ESRD should no longer be considered an unmet medical need.

Patients with decompensated cirrhosis

A recent consensus statement from the American Association for the Study of Liver Diseases (AASLD) on HCV management in liver transplantation concluded that all patients should be treated regardless of whether they are transplant candidates.[10] The only DAAs of concern in this population are those metabolised primarily by the liver – regimens containing non-nucleoside polymerase inhibitors or protease inhibitors, are not indicated for patients with moderate or severe hepatic impairments (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX], elbasvir/grazoprevir [ELB/GRZ], OBV/PTV/r + DSV, GLE/PIB). Both nucleoside and nucleotide polymerase inhibitors and NS5A inhibitors are safe in patients with hepatic impairment. Ledispavir/sofosbuvir (LDV/SOF) + RBV and sofosbuvir/velpatasvir (SOF/VEL) + RBV regimens have demonstrated high SVR rates in patients with Child-Turcotte-Pugh (CTP) B and C.[11-13] Furthermore, 84% of patients showed a reduction in model for end-stage liver disease (MELD) score to <15 from baseline. SVR rates post-transplant are high with all available DAA regimens

(95%–97%), with high tolerability reported.[12,14,15] Most centres globally have now eradicated recurrent HCV.

Patients with HCV-HCC

Questions to consider in relation to hepatocellular carcinoma (HCC) include whether there is an association between DAAs and the incidence of *de novo* HCC in patients with HCV cirrhosis, whether DAAs are associated with an increased risk of recurrent HCC in patients previously treated for HCC, and whether HCC progression is accelerated while on DAA therapy. These questions were considered in an interactive debate at CCH 2018 discussing the evidence for immediate versus deferred DAA treatment in patients with HCV-HCC. The debate concluded that there is a need for more prospective studies investigating HCC recurrence following DAA therapy. Although viral eradication has been shown to reduce the risk of HCC,[16] the heterogeneity of studies addressing these questions means that meta-analyses cannot currently confirm whether there is an increased risk of incident or recurrent HCC following DAA treatment.[17] Consequently, half of the delegates expressed that they would choose to defer treatment while the other half would treat immediately, due to the lack of evidence of an increased risk.

Options for NS5A failures

Resistance to NS5A inhibitors is an increasing challenge in Australia and New Zealand. There are two Therapeutic Goods Administration (TGA) registered salvage regimens in Australia: SOF/VEL/VOX for HCV Genotype (GT) 1-6 in patients who have previously received a DAA regimen containing a NS5A inhibitor; and GLE/PIB in patients with HCV GT1 who have been treated with a NS5A inhibitor or NS3/4A protease inhibitor, but not both classes of inhibitor. In an integrated analysis of four Phase II and Phase III studies of SOF/VEL/VOX in NS5A-experienced HCV GT1-6 patients (N=454), the SVR12 after 12 weeks was 97% overall, irrespective of previous DAA regimen or the DAA resistance profile.[18] This evidence suggests that SOF/VEL/VOX is a robust regimen for retreatment; this success has translated into the real world, with the TARGET study showing SVR rates of 100% over 12 weeks.[19]

*This regimen is no longer reimbursed under the Pharmaceutical Benefits Scheme in Australia.

Case study: Managing HCV GT 3 patients who fail previous DAAs

Ammar Majeed, Alfred Hospital, Melbourne

Case study

- 62-year-old male
- HCV GT3 infection acquired through previous short-term IV drug use
- Baseline characteristics
  - BMI: 30 kg/m^2
  - History of heavy alcohol use, COPD, GORD, T2DM, rheumatic fever
  - Stigmata of liver disease
  - Splenomegaly
  - No ascites
  - FibroScan®: 75 kPa
  - Ultrasound: cirrhosis and portal hypertension
  - Gastroscopy: grade 1 oesophageal varices
- SOF/DCV treatment was started for 24 weeks
  - At the start of treatment, viral load was 740,000 copies/mL
  - HCV PCR not detectable at the end of treatment
  - Three months after end of treatment, viral load was 3,100,000 copies/mL
    - ALT was elevated
    - Platelet count: 35
- Resistance Associated Substitution: Y93H
- Assessment at 12 months post-treatment
  - Continued abdominal pain
  - Ultrasound: two liver lesions, suggestive of HCC; progression to CTP B
  - Decision to retreat

ALT: alanine aminotransferase; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CTP: Child–Turcotte–Pugh; DCV: daclatasvir; GORD: gastro-oesophageal reflux disease; GT: genotype; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IV: intravenous; PCR: polymerase chain reaction; SOF: sofosbuvir; T2DM: type-2 diabetes mellitus.

Discussion around this case focused on key aspects of the patient's management at different stages of treatment. It was not surprising that this patient failed initial treatment as he had many risk factors for poor response (advanced fibrosis, obesity and other comorbidities, and GT3 infection). Age, gender, viral load, and cirrhosis status also impact on SVR rates with SOF-based regimens for GT3, especially with earlier generations of NS5A inhibitors.[13,20,21] As SVR improves outcomes, retreatment should be considered in patients at high risk of progression or

decompensation, particularly as resistance is less of an issue with newer generations of available DAAs. Given that the patient was well-compensated, waiting for new generation DAA regimens could be a viable management option. In GT3 HCV infection, a regimen containing a protease inhibitor may be necessary for patients with compensated cirrhosis who have failed previous treatment with NS5A-inhibitor based regimen. SOF/VEL/VOX is the only approved regimen for this indication in Australia.[22]

A triple-agent regimen (NS5A inhibitor, NS5B inhibitor and protease inhibitor) may be an effective approach in the present case, with close monitoring for decompensation. There was discussion around whether the patient should be considered for liver transplantation and it was agreed the overall prognosis for the next couple of years would inform that decision. In patients with high MELD scores, achieving SVR may increase their chances of being rescued from decompensated disease and improve long-term outcomes. In a study by Gane *et al.* SOF/VEL + RBV for 24 weeks resulted in SVR12 rates of 82% in GT3 patients with Y93H RAS at baseline.[23] Based on this evidence, the patient in this case received treatment with SOF/VEL + RBV for 24 weeks and subsequently achieved SVR. However, it is important to note that the TGA-registered treatment duration for this regimen is 12 weeks, which is also the treatment duration recommended by the most recent Australian consensus guidelines for management of HCV infection in patients with compensated liver disease who fail first-line DAA therapy.[24] Any retreatment strategies in such clinically challenging patients should consider the approval status of the regimens available. Treatment decisions should also be individualised to consider whether a longer treatment duration or addition of RBV are feasible options. It was agreed that in this case, stabilising the patient was crucial before considering transplantation and the best chance of achieving SVR may be in treating the patient post-transplant; SOF/VEL/VOX may be an option in that scenario.

Case study: Managing cryoglobulinemia vasculitis in HCV

Paul Clark, Princess Alexandra Hospital, Brisbane

Case study:

- 49-year-old female
- HCV acquired between 1978–88 through IV drug use
- Presented with abdominal pain and fever, no prior symptoms of advanced liver disease
- Baseline characteristics
  - BMI: 31 kg/m^2
  - History of alcohol use, ex-smoker, hypertensive (on amlodipine)
  - Mild renal impairment (creatinine: 123 µmol/L)
  - No anaemia
  - No hepatic encephalopathy, small volume ascites
  - Negative chest x-ray, mid-stream urine tests, CT scans
- Diagnostic tap performed to test for presumptive SBP
  - Erythrocytes 3+, leucocytes 2+; specimen lysed
  - Received ceftriaxone
  - Creatinine normalised within 24 hours
  - Discharged after one week with diagnosis of HCV GT1 complicated by cirrhosis and portal hypertension
- Six months later, re-presented with pain and elevated creatinine (111 µmol/L)
  - Ascitic tap: no organisms or growth, biochemical improvement of ascites
  - Renal function continued to deteriorate
- Screening for renal diseases:
  - Low complement C3/C4 and cryoglobulins in the serum and plasma
  - Positive ANA
  - Renal biopsy revealed deposits typical of cryoglobulinemic vasculitis
- Patient received OBV/PTV/r + DSV* for 24 weeks
  - Subsequently achieved SVR with progressive improvement in renal function on therapy
  - Undetectable cryoglobulin in plasma or serum

*This regimen is no longer reimbursed under the Pharmaceutical Benefits Scheme in Australia.

ANA: anti-nuclear antibody; BMI: body mass index; CT: computed tomography; GT: genotype; HCV: hepatitis C virus; IV: intravenous; OBV/PTV/r + DSV: ombitasvir/paritaprevir/ritonavir + dasabuvir; SBP: spontaneous bacterial peritonitis; SVR: sustained virologic response.

This case highlighted that spontaneous bacterial peritonitis is a more common cause of acute kidney injury in cirrhosis than cryoglobulinaemic vasculitis. With recurrent presentations there is a strong case to manage with prophylactic antibiotics and repeat ascitic tap. Although the patient did improve on antibiotics, deterioration in renal function raised questions relating to other causes of glomerulonephritis in HCV patients. The presence of cryoglobulins, low C3/C4, rheumatoid factor positivity and biopsy should together inform a diagnosis of cryoglobulinaemic vasculitis. HCV infection is a major cause of mixed cryoglobulinaemic vasculitis, although this is an uncommon extra-hepatic manifestation of HCV infection, with overt CV observed in only 5-10% of cases.[25] The main features of HCV-related cryoglobulinaemic vasculitis include purpura and peripheral neuropathy (67%), arthralgia (58%) and glomerulonephritis (21%).[25] Renal manifestations of cryoglobulinaemic vasculitis are characterised by active urinary sediment and proteinuria, which should also prompt investigation into parenchymal renal injury after excluding other potential causes of acquired kidney injury. The patient received OBV/PTV/r + DSV for 24 weeks as this was the only DAA regimen approved for use in renally impaired patients at the time. She subsequently achieved SVR with progressive improvement in renal function on therapy. Antiviral treatment is generally associated with a good prognosis and other treatment options available for HCV-related cryoglobulinaemic vasculitis include SOF + RBV. In the open-label VASCUVALDIC study, 87.5% of patients receiving SOF + RBV achieved complete clinical response of cryoglobulinaemic vasculitis at 24 weeks; 74% of patients achieved SVR12 and low rates of serious AEs were reported.[25]

HBV workshop

Management of HBV in an aging patient population

Man-Fung Yuen, Queen Mary Hospital, Hong Kong

Challenges of managing an aging CHB population

The proportion of patients with chronic hepatitis B (CHB) aged >50 years in the US almost doubled between 2000-2005 and 2011-2015.[26] Consequently, the number of patients at risk of renal or bone impairment is likely to increase. A common comorbidity in CHB is renal impairment, and a substantial increase in chronic kidney disease (CKD) has been observed in CHB patients.[27] Furthermore, while it is known that the risk of fractures increases with age in the general population, the risk of osteoporosis is higher in patients with HBV than in those without HBV infection.[28] Other liver disease-related complications such as cirrhosis and HCC are also more likely to occur in an aging population. Asian patients aged ≥40 years have a higher risk of cirrhosis, and the relative risk of HCC increases from 3.6−5.4 to 8.3−17.7 in patients aged 40−49 years and >60 years, respectively, compared to those aged 30−39 years.[29,30]

Balancing the benefits and risks of first-line therapies

Currently recommended first-line therapies for CHB include the nucleos(t)ide analogues (NA) entecavir (ETV), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF), which provide effective long-term HBV DNA suppression in HBeAg-positive and HBeAg-negative patients, and they all have a high genetic barrier to resistance.[31-33] NA therapy for CHB is also associated with improved clinical outcomes including liver fibrosis regression, cirrhosis reversal and reduced HCC risk.[34-36] While these therapies have proved efficacious, the question remains whether they are appropriate for an aging population. In a large registry study of CHB patients in Hong Kong, the incidence of renal failure and fractures was shown to be similar between NA-treated patients and untreated patients, suggesting that there is no increase in the risk of renal or bone events with NA treatment. However, exposure to nucleotide analogues, compared with nucleoside analogues, was associated with an increased risk of hip fractures (HR 5.69; 95% CI 1.98–16.39; *P*=0.001) but not other events (HR 0.58–1.44; *P*=0.202–0.823).[37] A more recent propensity-score-matched cohort study of CHB patients in Hong Kong revealed a slight, yet statistically significant, increase in the 5-year risk of CKD progression in patients who received TDF compared with those receiving ETV treatment (5-year cumulative incidence of CKD [95%CI]: 47% [44-51%] and 49% [46-53%] for ETV and TDF, respectively; p =0.015).[38] Longer term data have supported the safety profile of TDF and have allowed patients who require

more careful management and monitoring to be identified. TDF should therefore only be used in patients with renal impairment if the benefits exceed the risks.[36]

Improving safety outcomes with long-term NA therapy

Optimising the delivery of tenofovir while maintaining its efficacy and resistance profile has helped address existing challenges in patients with renal impairment. TAF is a targeted prodrug of tenofovir that provides improved delivery to hepatocytes. A higher proportion of patients achieved alanine aminotransferase (ALT) normalisation with TAF compared with TDF (50% and 40%, respectively, in HBeAg-negative patients [p=0.035]; 52% and 42%, respectively, in HBeAg-positive patients [p=0.003]).[39,40] Notably, the optimised delivery of tenofovir through TAF has resulted in improved safety outcomes. In patients who switched from TDF to TAF, markers of renal safety (creatinine clearance; Figure 1) and hip and spine bone mineral density (BMD) improved over 48 weeks.[41] Significant improvements in hip ($p<0.001$) and spine (p=0.042) BMD were also observed at Week 144 in patients who switched from TDF to TAF at Week 96.[41]

It is important to recognise that the aging CHB population is becoming the primary treatment group for CHB. With this comes several clinical challenges in providing long-term, efficacious antiviral therapy with minimal viral resistance while balancing the common comorbidities seen in these patients such as renal impairment and osteoporosis; both of which are closely linked. TAF supports improved ALT normalisation and renal/bone profiles compared with TDF; however, continuous safety monitoring is paramount for this aging CHB population and in patients with existing renal or bone issues. Any treatment strategy involving TAF in clinically challenging HBV patients with TDF-induced renal or bone disease should consider the approval status of the regimen.

Case study: Management and assessment of fibrosis/HCC risk in HBV and NASH

Miriam Levy, Liverpool Hospital, Sydney, NSW, Australia

Case study

- 41-year-old Asian male
- Baseline characteristics
  - Non-smoker, history of low-level alcohol consumption (10–20 g/day)
  - No regular medication, otherwise well
  - HBsAg positive, HBeAg negative, anti-HBe positive
  - HBV viral load: 28,000 IU/mL
  - Fluctuating ALT: 77 U/L and AST: 68 U/L
  - Other LFTs were normal
  - Platelet: 197
- Underwent non-invasive testing
  - APRI: 0.8
  - FibroScan®: 6.2 kPa
  - SWE: 6.4 kPa
  - Suggestive of F2 fibrosis
  - REACH-B score: 9 (0.5%, 1.2% and 3.2% risk of HCC over 3-, 5- and 10-years, respectively)
- Patient commenced treatment with TDF (300 mg daily)
  - Initial monitoring at 1 month, then every 3 months until HBV DNA was undetectable, then every 6 months
  - Following treatment, HBV became undetectable, ALT unchanged
- Other causes of liver disease were considered, including NASH (BMI 32 kg/m^2)
  - Considered stopping HBV treatment if NASH was the primary cause of liver disease
  - Modified PAGE-B score for Asian patients: patient's risk was lower on-treatment; patient continued HBV therapy
- Experienced weight gain, depression, loneliness

ALT: alanine aminotransferase; anti-HBe: hepatitis B e antibody; APRI: AST-to-platelet ratio; AST: aspartate aminotransferase; BMI: body mass index; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; LFT: liver function test; NASH: non-alcoholic steatohepatitis; REACH-B: Risk estimation for hepatocellular carcinoma in chronic hepatitis B.

This case may be initially considered a straightforward patient with CHB for whom management became progressively more challenging. Discussion raised the issue of whether he should receive treatment for HBV or if other underlying causes of ALT elevation be identified and managed appropriately (e.g. HCV, hepatitis D virus [HDV], NASH). Clinical practice guidelines would categorise this patient at moderate/severe risk of liver disease (HBeAg-positive, high HBV DNA and elevated ALT).[31] While the guidelines are clear in that these patients should receive treatment, there can be many grey areas that make decision-making challenging in the clinic.

Biopsy is used less often in practice now that there are other non-invasive tests available. Non-invasive markers such as transient elastography (TE) (e.g. with FibroScan®) can give a clearer picture of disease activity over time, particularly in distinguishing F2 fibrosis from cirrhosis.[42]

Because the patient was viraemic, delegates agreed that he should receive treatment regardless of whether he is HBeAg-positive or HBeAg-negative, because therapy is associated with a reduced risk of HCC. While the patient remains on treatment, there is a need to consider long-term impacts, especially renal and bone events. The patient's NASH should also be managed using available non-pharmacological and lifestyle approaches. Many of the patient's concerns related to ongoing weight gain and psychological issues, which should be the focus of patient care once a long-term treatment plan for CHB has been established.

Case study: Managing multiple coinfection in HBV and subsequent triggering of autoimmune hepatitis

Will Kemp, Alfred Hospital, Melbourne, VIC, Australia

Case study

- 55-year-old Egyptian male, lived in Australia since 2006
- Initial infection with hepatitis A (1985), experienced needlestick injury (1998), subsequently diagnosed with HBV (HBsAg positive)
- Commenced on lamivudine, followed by peginterferon-α-2a, 180 µg, for four months
- Positive for HCV in 2002: received Peginterferon-α 2a + ribavirin for nine months
    - SVR was achieved
    - F0 on biopsy
- LFTs increased between 2008–2010
    - Adefovir was added to lamivudine
- Assessment in 2011:
    - BMI: 28.8 kg/m^2
    - Hyperferritinaemia
    - SMA positive
    - Elevated IgG
    - Low caeruloplasmin
    - FibroScan®: 21.3 kPa
    - Ultrasound: irregular contour, diffusely coarse echotexture
    - HDV positive – treatment changed to TDF (July 2010)
    - Biopsy: suggestive of autoimmune hepatitis (AIH simplified score: 5; upgraded to probable AIH using revised original scoring system: 11)
- Patient continued to have ongoing hepatitis and immunosuppression with prednisolone
    - Switched to ETV, eventually ETV/BUD/azathioprine for four years
        - Developed T2DM, started oral hypoglycaemic treatment
    - LFTs remained elevated but stable
- Evaluation in 2017 revealed FibroScan® score of 45 kPa
    - Biopsy: progression to cirrhosis, ongoing necroinflammation
    - HBV viral replication undetectable
    - Persistent HDV (450,791 IU/mL)
    - Ongoing AIH
    - No evidence of NASH/drug toxicity
- From August 2017, LFTs progressively increased with ongoing necroinflammation and high-dose immunosuppression with 3 mg BUD, 500 mg MMF and 4mg TAC added
- By July 2018, ALT decreased to 121 U/L
- In August 2018, MMF was withdrawn (ETV/BUD/TAC continued)
    - LFTs revealed an ALT flare to 1,074 U/L
- Patient continues to have progressive liver disease to cirrhosis
- HAV and HCV have been cleared, HBV replication controlled, HDV remains untreated, poorly responsive AIH

AIH: autoimmune hepatitis; ALT: alanine aminotransferase; BMI: body mass index; BUD: budesonide; HBsAg: hepatitis B surface antigen; HAV: hepatitis A virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis D virus; LFT: liver function test; MMF: mycophenolate mofetil; NASH: non-alcoholic steatohepatitis; SMA: smooth muscle antibody; T2DM: type-2 diabetes mellitus; TDF: tenofovir disoproxil fumarate.

This complex case highlighted the challenges of managing multiple coinfections. Following initial HBV treatment with adefovir dipivoxil/lamivudine (ADV/LAM), liver screen revealed low HBV DNA and elevated ALT, raising suspicion of other causes of abnormal ALT. Many delegates suggested that at this stage they would test for hepatitis D virus (HDV), and in fact the patient was confirmed to be viraemic for HDV. Because ADV/LAM was not effective in completely suppressing HBV DNA, the patient was switched to TDF, which was considered the most appropriate long-term treatment at the time. The patient developed osteopenia of the hip and spine, leading delegates to suggest that they may be more likely to use TAF as a long-term antiviral if presented with a similar case now, as TAF has a more favourable bone safety profile than TDF.

There were questions around whether the patient should be treated with immunosuppressants for autoimmune hepatitis (AIH) or whether treatment should focus on managing HDV at this stage. Initiating steroid treatment in conjunction with TDF to target AIH was considered appropriate at the time and if ALT remained unchanged after a few months of treatment. Targeting HDV using interferon (IFN) may be another option. Bone toxicity is a concern with concomitant steroid/TDF therapy and should therefore be closely monitored. The patient's history and presentation are convoluted because of the different options – or lack of – available at the time. At present, the patient would have three options: 1. Treat with immunosuppression; 2. Treat with IFN; 3. Wait for other therapies to become available. Most delegates opted to watch and wait. A question remains over whether the intensive treatment course, particularly immunosuppression, over the past 10 years exacerbated the patient's condition. However, withdrawing immunosuppression may have precipitated the most recent ALT flare (>1,000 IU/L). While there was concern that this may reflect a fulminant presentation, in practice a single ALT reading of ≥1000 may not necessarily be reflective of fulminant disease but subsequent monitoring is warranted. Given that there are currently oral treatments for HDV in Phase III development, it may be an option to wait for clinical trials or treatments to become available. Further investigations to understand whether HDV is inducing the AIH

response may also be considered. This case illustrates that there is still much to learn about the complexity of coinfection and interactions with other disease processes.

NASH workshop

Advanced fibrosis in the NASH journey and non-invasive diagnostics

Vlad Ratziu, Hôpital La Pitié Salpêtrière, Paris, France

When to consider NASH

Metabolic risk factors are a major component of non-alcoholic fatty liver disease (NAFLD); patients with metabolic syndrome components should be investigated further for liver involvement. Screening for NAFLD should consider the presence of three factors: 1. Steatosis on ultrasound; 2. Metabolic risk factors and; 3. Abnormal Liver Function tests (LFTs). The presence of these three factors in the absence of other causes of chronic liver disease (including significant alcohol consumption) supports a diagnosis of 'primary' NAFLD. It should be noted however that not all patients with NAFLD have abnormal LFTs. If traditional metabolic risk factors (e.g. high Body Mass Index [BMI], diabetes, hypertension) are absent in the presence of other liver signs (elevated LFTs, steatosis), this may constitute a diagnosis of 'lean' NAFLD.[43] However, further investigation of 'lean' patients may reveal other more subtle metabolic risk factors (such as visceral adiposity) and the presence of insulin resistance. If metabolic factors are completely absent, there are rarer secondary causes of steatosis and abnormal LFTs, such as drug toxicity, or genetic diseases (such as abetalipoproteinemia, lysosomal acid lipase deficiency).

Algorithm for NASH screening

The AASLD guidelines do not currently recommend screening for NASH but the European Association for the Study of the Liver (EASL) has released management guidelines on strategies to identify people *at risk* of NASH. This algorithm is not designed as a screening tool for the general population but as a systematic approach to identify severe NASH in patients with existing metabolic risk factors (Figure 2).[44] If steatosis is present but LFTs are normal, serum fibrosis markers should be explored.

As NAFLD evolves, the focus shifts to differentiating steatosis in NAFLD from steatohepatitis, and then assessing the progression of fibrosis to more advanced disease. Fibrosis is the core determinant of prognosis and NASH is associated with more severe hepatic and systemic disease than steatosis. NASH drives fibrosis progression as a continuum from NAFLD, and liver-related mortality increases with increasing severity of fibrosis. A six-fold increase in cumulative

liver-related mortality due to NASH versus non-NASH on liver biopsy has been reported (NASH HR 6.28 [95%CI 1.90–20.76]).[45] Diagnosing NASH therefore has clear relevance in clinical practice.[46]

Detecting and monitoring fibrosis

Several simple non-invasive tools can be incorporated into clinical practice to assess fibrosis. Prof. Ratziu explained that in France, physicians rely on serum fibrosis markers and elastography. However, there is considerable discordance between the two assessment approaches, and also between different fibrosis markers and elastography methods. In a cross-sectional study of 452 NALFD patients, TE with Fibroscan® and the blood test Fibrometer^{V2G} were found to be the most accurate diagnostic tests for fibrosis among nine non-invasive tests evaluated.[47] These were also well-correlated with mortality, illustrating their practicality as prognostic tool in the clinical setting.[47] Furthermore, these tests have a high negative predictive value (>92%) for advanced fibrosis, emphasising their utility in excluding those at low risk.[48,49] However, Fibroscan® is limited by its high variability in short term measurements, particularly in patients with a baseline liver stiffness measurement (LSM) of >7kPa;[50] a second reading in patients with a baseline LSM of >7kPa is advisable.

The current approach to diagnosis will undoubtedly change with the arrival of new pharmaco-therapies indicated for patients with moderate fibrosis (F2) and active disease. Hence, future screening strategies will need to focus on identifying patients in need of therapy for which biomarker signatures are currently being investigated.

Case study: Monitoring fibrosis and dietary management of NASH

Marno Ryan, St Vincent's Hospital, Melbourne, VIC, Australia

Case study

- 51-year-old male
- Referred by rheumatologist with abnormal LFT
- History of presenting complaint:
    - Abnormal LFTs, asymptomatic
    - Recalls flu-like illness with elevated LFT in 1995
        - HIV/HCV/HBV/Ross River serology negative
        - Biopsy: "Fatty liver", told not to worry about it
- Medical/family history
    - T2DM managed with metformin, sitagliptin and dapagliflozin
        - Both parents and brother also had T2DM
    - Gout managed with allopurinol
    - Hypertension managed with perindopril/amlodipine (10 mg/5 mg)
    - Mixed dyslipidaemia managed with rosuvastatin (20 mg) and ezetimibe (10 mg)
    - Newly diagnosed psoriatic arthritis, commenced treatment with methotrexate but ceased when LFT found to be abnormal, currently considering a biologic
        - Recent MRI revealed bone erosions and synovitis involving MIP and PIP joints and skin on elbow
- Baseline characteristics (October 2017)
    - Non-smoker, 5–10 standard drinks/week, was active until knee injury 5 years ago, gaining 10 kg
    - Palmar erythema but no other stigmata CLD
    - Liver palpable 1 cm below costal margin
    - No splenomegaly
    - ANA/ASMA/AMA, ENAs and pANCA negative
    - Total IgG normal
    - HBsAg negative; HCV antibody negative
    - Haemochromatosis genotyping negative
    - ESR: 12; C-reactive protein: 4.9
    - FibroScan®: 23.4 kPa (IQR: 4, elastogram quality: good); CAP score: 240 dB/m
    - Biopsy: NASH, with features of cirrhosis; Metavir score A1F4
- Patient review (December 2017)
    - Commenced etanercept (TNF inhibitor) for PsA
    - Offered options for management of incipient cirrhosis (participation in NASH drug trial/weight loss)

Case study: Advanced Fibrosis in the Setting of NASH, *cont.*

Longitudinal test results

	10 October 17	23 May 18	Normal range
Weight	89.2	77.5	
BMI	**30.9**	**26.8**	20–25 kg/m^2
ARFI (Metavir Stage)	1.80 (F3–F4)	1.51 (F2)	
Blood tests			
Total protein	83	76	63 – 80 g/L
Albumin	43	41	34 – 45 g/L
ALP	72	64	35 – 110 U/L
GGT	**77**	25	5 – 50 U/L
ALT	**82**	28	5 – 40 U/L
AST	**70**	34	10 - 40 U/L
Bilirubin	18	8	4 – 20 µmol/L
Fasting glucose	**10.2**	5.2	<5.5 mmol/L
Total cholesterol	3.2	3.4	<5.6 mmol/L
Triglycerides	**4.5**	1.7	< 1.7 mmol/L
HDL-C	**0.80**	1.0	> 1.0 mmol/L
LDL-C	2.4	2.4	< 3.5 mmol/L
Ferritin	**622**	241	20 – 250 µg/L

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AMA: antimitochondrial antibody; ANA: anti-nuclear antibody; ARFI: acoustic radiation force impulse; ASMA: anti-smooth muscle antibody; AST: aspartate aminotransferase; BMI: body mass index; ENAs: extractable nuclear antigen antibodies; ESR: erythrocyte sedimentation rate; GGT: gamma glutamyltransferase; HBV: hepatitis B; HCV: hepatitis C; HDL-C: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; HBsAg: hepatitis B surface antigen; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; LFT: liver function test; MIP: p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; PIP: proximal interphalangeal joint; PsA: psoriatic arthritis; TNF: tumour necrosis factor.

This case generated many questions from delegates regarding practical approaches to dietary management and lifestyle modification in patients with NAFLD/NASH. The long-term persistently elevated ALT and multiple signs of metabolic syndrome would place this patient at risk of fibrosis. In this patient, the non-invasive NAFLD fibrosis score was initially used to calculate his fibrosis stage. Most delegates indicated that they use Fibroscan® to obtain a baseline reading prior to biopsy, particularly in patients with a BMI between 25 and 35. Approximately one-third of delegates suggested that they would also biopsy in this situation. Biopsy in this case revealed that F4 fibrosis had developed over 23 years from a baseline of F1, which is a relatively quick progression to cirrhosis. Typically, fibrosis would be expected to

progress by 1 stage per 7.7 years in patients with NASH; up to 20% of patients progress rapidly to cirrhosis over 10 years.[51] At this stage, most of the delegates indicated that they would refer to a dietitian to plan initial management of NAFLD/NASH.

Lifestyle modification and weight loss are the cornerstone of management in NASH, but it is important to preserve muscle mass if patients lose a significant amount of weight. Weight loss management with the aim of reducing fat content should be considered in combination with physical activity. There are no current guidelines on the prescription of physical activity, but high intensity interval and resistance or aerobic training in patients with NASH are increasingly used.

This particular case is a positive example of how weight loss and improvements in liver and metabolic parameters can be achieved in a motivated patient, although these patients need to be followed to avoid them regaining weight. It also illustrates that patients with NASH on liver biopsy need to be monitored closely especially if multiple risk factors for disease progression are present (older age, Type 2 diabetes Mellitus (T2DM), metabolic syndrome, obesity). It is important to recognise that cirrhosis can occur with normal LFTs. The declining Acoustic Radiation Force Impulse (ARFI) and Fibroscan® scores following weight loss in this patient suggests that steatosis contributes to the LSM.

Case study: Management of multiple comorbidities in NASH

Alex Hodge, Monash Health, Melbourne, VIC, Australia

Case study

- 48-year-old female Torres Strait Islander
- Referral from GP with abnormal LFT
- Baseline characteristics:
    - Non-smoker, does not drink alcohol
    - History of T2DM, hypertension, dyslipidaemia, reflux, class III morbid obesity, repeated attempts at weight loss
    - BMI: 46 kg/m^2; weight: 143 kg
    - Waist circumference: 113 cm
    - Family history of T2DM (mother and sister), obstructive sleep apnoea and ischaemic heart disease (father)
    - Ultrasound: hepatomegaly, normal sized spleen, normal PV, smooth liver contour, no lesions, increased echogenicity
    - LFT: elevated GGT (74 U/L) and ALT (47 U/L), ALP, albumin and ferritin normal
    - HbA1C: 8.8%, haemoglobin and platelets normal
    - Triglycerides 3.9 mmol/L, LDL 2.3 mmol/L, HDL 0.9 mmol/L
    - Medications: ibesartan (300 mg), hydrochlorothiazide (25 mg), pantoprazole (40 mg), atorvastatin (20 mg)
- Twelve months after initial review
    - Did not have further liver investigations
    - Managed in diabetes clinic
        - Transitioned to insulin (320 U/day)
    - Also seeing general physician and psychologist
    - Weight: 139 kg (lost 10 kg, regained 6 kg)
        - Tried duromine and topiramate, ceased due to cost
- Twenty-eight months after initial review
    - Visit to bariatric clinic
        - Decision for laparoscopic cholecystectomy
        - Bariatric surgery deferred
        - Gastroscopy to assess for Barrett's oesophagus
    - Blood tests:
        - HbA1c: 7.8%
        - LFT: elevated ALP (262 U/L), GGT (178 U/L) and ALT (60 U/L); albumin and bilirubin normal
        - Triglycerides: 1.4 mmol/L, LDL: 2.7 mmol/L, HDL: 1.0 mmol/L
        - Haemoglobin: 137, platelets: 131

Case study *cont.*

- At 30 months:
  - Laparoscopic cholecystectomy and liver biopsy
    - Gall bladder: acute on chronic cholecystitis
    - Liver: abnormal architecture, fibrosis stage 4, steatosis stage 2, ballooning, steatohepatitis with cirrhosis (NAS 5)
- At 39 months:
  - Bariatric clinic
    - Weight: 152 kg (BMI 49.6 kg/m^2)
    - Ceased all original diet changes
    - Started exenatide (GLP-1 analogue, off-label)
    - Reclassification of gastroscopy to Category 1 (from Category 2)
  - Ultrasound:
    - Liver: increased echogenicity, moderately heterogeneous, mildly irregular contour
    - Spleen volume 1,300 mL
- At 40 months:
  - Gastroscopy revealed three columns of Grade I oesophageal varices, portal hypertensive gastropathy and gastric antral vascular ectasia
  - Bariatric surgery cancelled due to high risk (portal hypertension)
  - Ongoing cirrhosis surveillance and weight loss management

ALP: alkaline phosphatase; ALT: alanine aminotransferase; BMI: body mass index; GGT: gamma glutamyltransferase; GLP-1: glucagon-like peptide 1; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LFT: liver function test; NAS: non-alcoholic fatty liver disease activity score; T2DM: type-2 diabetes mellitus.

This case demonstrated the major issues surrounding management of several common systemic comorbidities in patients with NAFLD. Lifestyle modification and weight loss are the cornerstone of NAFLD management, and of the many metabolic comorbidities associated with NAFLD and NASH. Other management approaches, in the context of NAFLD, are outlined below.

NAFLD is intrinsically linked to the metabolic syndrome; for every feature of the metabolic syndrome, the prevalence of NAFLD increases.[52] Dyslipidaemia and low High Density Lipoprotein (HDL) are widely expected comorbidities in NAFLD. In the case of hypertriglyceridaemia, fish oil (high in Eicosapentaenoic acid (EPA) and Docosahexaenoic (DHA)), high dose statins and fibrate therapy are all proven approaches in reducing triglyceride levels by 30−50%. However, few delegates indicated that they would prescribe one or any of

these therapies to their patients with NAFLD. Consulting a dietitian initially was considered appropriate, and losing weight was agreed as the immediate initial approach to target dyslipidaemia.

Up to 75% of NAFLD patients have T2DM, and T2DM is associated with a 2–4 fold increase in NASH, fibrotic progression to cirrhosis, and HCC.[53] While there are currently no registered medications available for NAFLD or NASH, there are effective treatments for T2DM. Weight loss also has a positive impact on T2DM. Few delegates would modify a patient's T2DM medication; in some liver clinics, patients will not be seen unless their T2DM is well-managed. In future, gastroenterologists/hepatologists may be required to take a more active role in managing T2DM in their patients as NAFLD presentations increase.

Biopsy may be considered a risk in obese patients, so non-invasive approaches may provide an initial assessment. Appropriate management strategies can be discussed and implemented with other Health Care Professionals responsible for particular aspects of care (e.g. endocrinologists, cardiologists).

Practical approaches to dietary and lifestyle management of NAFLD/NASH

Throughout the NASH workshop, Dr Ingrid Hickman (Princess Alexandra Hospital, Brisbane) provided insights on the management of patients with NAFLD/NASH. Lifestyle modification and weight loss were reiterated as the cornerstone of management. While calorie restriction is a central goal, the quality of patients' diets is also important. Individualising patient approaches is paramount to ensure long-term adherence to lifestyle modification; practical advice included asking patients their current diet and exercise preferences. For example, understanding the level of control patients have on their dietary intake and the types of food they currently eat can provide the information physicians need to encourage them to modify their diet. In terms of exercise, gauging patients' motivation levels by learning more about their habits and preferences can help identify practical solutions to fit exercise into their daily routine. This can be a considerable challenge, particularly in patients who have never exercised or been physically active before. Aerobic exercise and resistance training can effectively reduce liver fat.[44] Emphasising the benefits of aerobic and anaerobic exercise in liver disease and in terms of general health[54] may support patient motivation.

Another practical insight to managing NAFLD/NASH patients was to examine their mental health. A BMI >40 should alert physicians to investigate psychosocial issues more closely. Depression is often highly prevalence in patients with NAFLD and mental health support should be incorporated into management plans. It should be noted that many pharmacotherapies

used for the treatment of mood disorders are associated with weight gain and metabolic syndrome.

Summary

While there has been much progress in improving outcomes in liver diseases, challenges still remain. Educational programs such as CCH provide a practical forum to help physicians to recognise difficult-to-manage patients and implement appropriate strategies in clinical practice.

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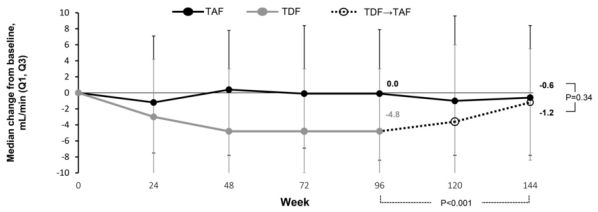
Figure legends

Figure 1.

Improvements in creatinine clearance in CHB patients 48 weeks after switching from TDF to TAF[41]

Figure 2.

EASL screening guidelines for NASH in individuals with metabolic risk factors.[44]



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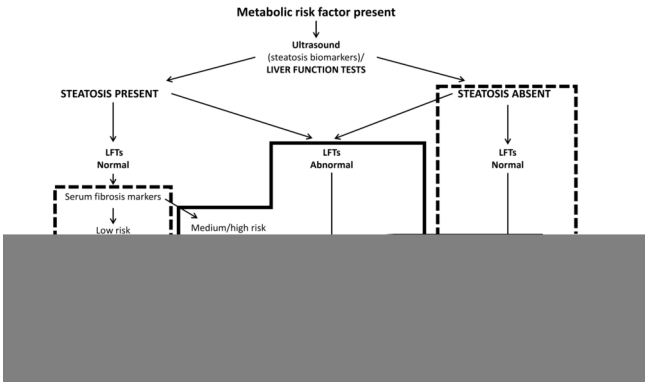

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