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Hepatology today and the future

Patrick Marcellin

These proceedings of the PHC 2019 reflect the remarkable recent advances in all fields of hepatology that are covered during this conference.

Thirty years after the discovering the hepatitis C virus, we can tell our patients that they have a 100% chance of cure with pangenotypic DAAs. The rare patients who relapse with resistance-associated substitutions after DAAs therapy are cured with appropriate retreatment. Cure means eradication of HCV infection with improved quality of life and outcome. Although the WHO HCV program, which seeks the elimination of hepatitis C by 2030 may be difficult to achieve, it is accompanied by active national programs worldwide.

We can tell our patients with hepatitis B that they have a 100% chance of viral suppression. Long term studies of patients receiving last generation NUCs demonstrate sustained remission without resistance, regression of liver lesions and improved outcome. WHO has set priorities to achieve global goals including more effective vaccination and easy access to therapy programs. The next objective is a cure. This objective is now realistic with the development of effective drugs of different viral targets. Future treatment will certainly include combinations that are adapted to the different phases of hepatitis B.

Patients with hepatitis delta can be told that new treatments are on the way. Ongoing phase 3 trials of Myrcludex and Lonafarnib should confirm their efficacy, which are synergistic in combination with interferon.

Patients with NAFLD must be receiving counselling. However, in this emerging liver disease, which affects 25% of the population, life style counselling is only effective in a minority of patients. The key issue is differentiating NASH from simple steatosis. As we learned from NANB hepatitis before discovering the virus, our lack of knowledge explains the problems we now face with NAFLD. We must determine the red line between fatty liver and NASH. There is still a long way to go to understand the physiopathology and natural history of the disease, to develop appropriate markers and effective treatments targeting oxidative stress and apoptosis, antifibrotics, inflammation and metabolic disturbances.

Significant progress has been in less common liver diseases such as autoimmune and chlolestatic diseases, if their unknown aetiology is a major field of research.

There are new possible effective treatments in patients with HCC. With improvements in diagnosis and characterization, treatment can be more effectively personalized. Furthermore, the results are promising with new drugs and others are on the way. Four agents have been added to sorafenib as systemic therapeutic options based on positive randomized trials : lenvatinib, regorafenib, cabozantinib and ramucirumab. Effective combinations may be expected soon.

Mortality and morbidity have been considerably improved in transplanted patients. The indications for transplantation have markedly changed in the last decade with increasing rates of transplantation in HCC, alcoholic disease and NASH and decreasing rates in HCV and HBV. The indications and the management of pre-transplantation patients have been refined and allow transplantation in better selected patients with a better outcome.

Hepatology is in a very active and promising phase of development in all fields and there is no doubt that the use of new digital technologies and artificial intelligence will revolutionize this speciality. We have entered a new era of precision hepatology and more efficient personalized management of patients with liver disease.

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HEPATITIS C

HCV: Is DAAs treatment failure still an issue?

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Key points

- Cirrhosis, virological factors, genotypes 1a and 3, and resistance associated substitutions (RASs) may favor the failure of direct acting antivirals (DAAs).
- Several DAAs combinations in patients with genotypes 1 or 4 infection can easily rescue failure following DAAs combinations without NS5A inhibitors.
- New triple combinations can easily rescue failures occurring after DAAs combinations containing NS5A inhibitors.
- NS5A RASs have no impact on the SVR rate with triple combinations after DAAs failure.

Despite the high overall success rate of the new direct acting antivirals (DAAs) a small proportion of treated patients do not achieve an SVR, mainly due to relapse and rarely to viral breakthrough under treatment[1]. Several factors may favor the failure of first generation DAAs, such as cirrhosis, virological factors, genotypes 1a and 3 and resistance associated substitutions (RASs), either pre-existing as a natural polymorphism, or induced by a previous DAAs regimen. A recent study using the HCV disease burden model (HEP-SIM) suggested that according to the number of patients treated with DAAs between 2014 and 2020 in five European countries (France, Germany, Italy, Spain and United Kingdom), there would be an expected 47,000 DAAs failures during this period and nearly all patients treated since 2015 will be NS5A-failures [2]. Guidelines proposed several retreatment options according to genotype [3].

Existing salvage regimens for failures after NS5A inhibitors-containing DAAs

Four options were available to patients with genotypes 1 or 4 who fail DAAs regimens containing NS5A inhibitors. The first option includes sofosbuvir (SOF) with paritaprevir boosted with ritonavir/ombitasvir plus dasabuvir (PrOD) for genotype 1 or PrO plus ribavirin (RBV) for genotype 4, for either 12 weeks in patients with mild fibrosis or 24 weeks in patients with subtype1a and in patients with severe fibrosis or compensated cirrhosis. This option achieves a SVR rate of 95% [4]. The second option combined SOF with grazoprevir/elbasvir (GZR/EBR) plus RBV for 12 weeks in patients with mild fibrosis or for 24 weeks in patients with subtype 1a and in those with severe fibrosis or compensated cirrhosis. This combination was found to be highly effective in achieving an SVR in all patients with mild disease treated for 12 weeks and in all patients with NS5A RASs treated for 16 weeks in a few studies [5, 6]. The third option combined SOF with daclatasvir (DCV) and simeprevir (SMV) plus RBV for 12 weeks in patients with mild fibrosis or for 24 weeks

in patients with subtype 1a and in those with severe fibrosis or compensated cirrhosis. This option was not endorsed by all real-life data [7]. There was a high rate of adverse, even fatal, events, and a low rate of response with this combination in DAAs failures, including some patients with advanced compensated cirrhosis, [8]. The last option was the association of glecaprevir/pibrentasvir (GLE/PIB) plus RBV for 12 or 16 weeks. One study showed a high SVR rate of 96% or more in patients treated either for 12 weeks in those with a NS3 RASs at baseline or for 16 weeks in those with NS5A RASs at baseline. The SVR rate in patients with both NS3 and NS5A RASs at baseline was suboptimal [9]. Therefore, this combination is not recommended in these cases at least in the EMEA label and in the last EASL guidelines[10].

The recommended retreatment option in patients with genotypes 2, 3, 5 and 6 who failed a DAAs combination with NS5A inhibitors, is the combination of sofosbuvir/velpatasvir (SOF/VEL) with RBV for 24 weeks[3]. This recommendation is supported by a small multicenter trial in which sixty-nine patients with genotypes 1, 2 or 3, who previously failed a NS5A containing DAAs regimen, were retreated with SOF/VEL and RBV for 24 weeks. The SVR rate was 97% in genotype 1 and 93% in genotype 2 patients regardless of NS5A RASs, but only 78% in patients with genotype 3 [11]. Therefore, there is an urgent need for a pangenotypic rescue regimen in patients who failed previous NS5A-containing DAAs regimens.

New salvage regimens for DAAs failures

The POLARIS 1 and 4 studies assessed the efficacy of 12 weeks of treatment with the triple fixed-dose combination (FDC) sofosbuvir/velpatasvir/voxilaprevir (SOL/VEL/VOX) in HCV DAAs treatment–experienced patients with or without compensated cirrhosis [12].

The POLARIS-1 study enrolled patients, infected with all HCV genotypes, who previously failed a NS5A-inhibitor containing regimen. Genotype 1 patients were randomly assigned in a 1:1 ratio to receive either the triple FDC or matching placebo once a day for 12 weeks. Patients who were infected with other genotypes were enrolled in the triple FDC once a day for 12 weeks. Forty-six percent of patients had compensated cirrhosis. Thirty-nine percent of patients had been previously treated with at least 2 HCV treatment regimens. The SVR rate was 96% compared to 0% with placebo. Overall the SVR rate was 99% in patients without cirrhosis and 93% in patients with cirrhosis. Baseline RASs were present in 83% of patients and 79% harbored NS5A RASs. The SVR rate was similar in patients with and without baseline RASs (96% and 99%, respectively). Six patients with cirrhosis had a relapse (one genotype 1a, 4 genotype 3 and one genotype 4). One patient with genotype 4 had treatment-emergent RASs.

Patients with genotype 1 who received placebo were subsequently treated with triple FDC once a day for 12 weeks [13]. One third of patients had cirrhosis. The overall SVR rate was 97%. Patients with and without cirrhosis had SVR rates of 98% and 97%, respectively. Four patients with genotype 1a infection and one with cirrhosis experienced a relapse. All patients had baseline RASs and two developed treatment–emergent RASs. The overall SVR rate of the primary and sub study of POLARIS-1 was 97%

The POLARIS-4 study enrolled patients who had previously failed a DAA regimen without an NS5A inhibitor. HCV genotype 1, 2 and 3 patients were randomly assigned in a 1:1 ratio to receive triple FDC or dual FDC (SOF/VEL) for 12 weeks. Genotype 4 patients

were also enrolled in the triple FDC regimen for 12 weeks [12]. Forty-six percent of patients had compensated cirrhosis. Thirty-nine percent of patients had previously received 2 or more HCV treatments. The overall rate of SVR was 98% in patients receiving triple FDC and 90% in those receiving dual FDC. The SVR rate in patients without cirrhosis was 98% in those receiving triple FDC and 94% in those receiving dual FDC compared to 98% and 86%, respectively in patients with cirrhosis. Forty-nine percent of enrolled patients had baseline RASs to NS3 or NS5A inhibitors. Only one of the patients treated with triple FDC relapsed compared to fourteen patients treated with dual FDC. The patient who failed triple FDC had no baseline RASs and no treatment-emergent RAS. The safety profile in POLARIS-1 and 4 studies was good. A recent combined analysis of the POLARIS program showed that baseline RASs did not influence the virological response to triple FDC, and that selection of viral resistances in patients who relapse after triple FDC are uncommon [14].

Another option is the combination SOF plus GLE/PIB ± RBV for 12-16 weeks based on two small studies involving patients who had failed previous DAAs regimens including GLE/PIB regimen [15 16]. The SVR rate was 96% [15].

Regulatory issues and guidelines recommendations

The US Federal Drug Administration (FDA) and European Medicines Agency (EMA) approved various treatment regimens based on the results of the phase III studies.

On July 18, 2017, the US FDA approved SOF/VEL/VOX FDC for 12 weeks in adult HCV patients of all genotypes with or without compensated cirrhosis (Child Pugh A) that have previously failed a HCV regimen containing an NS5A inhibitor. This regimen was also approved in patients with genotypes 1a or 3 with or without compensated cirrhosis who had previously failed an HCV regimen containing SOF without an NS5A inhibitor [17]. These approvals were included in the recent American Association for the study of Liver Diseases guidelines.

On July 27, 2017, the EMA approved SOF/VEL/VOX FDC with wider indications: 8 weeks of FDC, in treatment-naïve patients without cirrhosis of all genotypes and in patients with genotype 3 with cirrhosis. Twelve weeks of FDC, in treatment-naïve patients with cirrhosis of all genotypes and 12 weeks FDC, all genotypes, in treatment-experienced patients with DAAs failures with or without compensated cirrhosis.

The most recent EASL guidelines have included a few of these recently approved regimens. FDC is recommended for 12 weeks in treatment–naïve or experienced genotype 3 patients with cirrhosis. FDC is recommended for 12 weeks as first line treatment in patients with or without compensated cirrhosis who have failed a previous regimen with DAAs, either protease inhibitors and/or NS5A inhibitors.

An alternative option is the combination of SOF plus GLE/PIB ± RBV for 12-16 weeks. Moreover, triple FDC is recommended either in combination with weight-based dose RBV and/or to extend treatment to 16 or 14 weeks in very difficult-to-cure patients with NS5A RASs who have failed to achieve SVR twice after several DAAs regimens including protease and/or N5A inhibitors.

Summary

In conclusion, the single pill triple FDC SOF/VEL/VOX for 12 weeks or the triple combination SOF plus GLE/PIB with or without ribavirin for 12 weeks achieves a 96% SVR rate in the few patients who fail DAAs combinations, even the most recent pangenotypic regimens. Therefore, with the current available rescue regimens, DAAs treatment failure is no longer significant issue.

References

1. Buti M, Riveiro-Barciela M and Esteban R. Management of direct-acting antiviral agent failures. *J Hepatol*. 2015; 63: 1511-22.
2. Chhatwal J, Chen Q, Ayer T, et al. Hepatitis C virus re-treatment in the era of direct-acting antivirals: projections in the USA. *Aliment Pharmacol Ther*. 2018; 47: 1023-31.
3. European Association for the Study of the Liver. Electronic address eee. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol*. 2017; 66: 153-94.
4. Poordad F, Bennett M, Sepe TE, et al. Ombitasvir/paritaprevir/R, dasabuvir and sofosbuvir treatment of patients with HCV genotype 1infection who failed a prior course of DAA therapy: The QUARTZ-1 study; (Abstract). *J Hepatol*. 2016; 64: S767-S8.
5. Lawitz E, Poordad F, Gutierrez JA, et al. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. *Hepatology*. 2017; 65: 439-50.
6. de Ledinghen V, Laforest C, Hezode C, et al. Retreatment With Sofosbuvir Plus Grazoprevir/Elbasvir Plus Ribavirin of Patients With Hepatitis C Virus Genotype 1 or 4 Who Previously Failed an NS5A- or NS3-Containing Regimen: The ANRS HC34 REVENGE Study. *Clin Infect Dis*. 2018; 66: 1013-8.
7. Abdel-Moneim A, Aboud A, Abdel-Gabbar M, Zanaty MI and Ramadan M. A sofosbuvir-based quadruple regimen is highly effective in HCV type 4-infected Egyptian patients with DAA treatment failure. *J Hepatol*. 2018; 68: 1313-5.
8. Hezode C, Fourati S, Chevaliez S, et al. Sofosbuvir-Daclatasvir-Simeprevir Plus Ribavirin in Direct-Acting Antiviral-Experienced Patients With Hepatitis C. *Clin Infect Dis*. 2017; 64: 1615-8.
9. Poordad F, Pol S, Asatryan A, et al. Glecaprevir/Pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. *Hepatology*. 2018; 67: 1253-60.
10. European Association for the Study of the Liver. Electronic address eee and European Association for the Study of the L. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol*. 2018.
11. Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen. *Hepatology*. 2017; 66: 1083-9.
12. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *The New England journal of medicine*. 2017; 376: 2134-46.

13. Bourliere M, Gordon SC, Schiff ER, et al. Sofosbuvir-Velpatasvir-Voxilaprevir after blinded placebo in NS5A-inhibitor-experienced patients with chronic Hepatitis C in the Phase 3 POLARIS-1 study. *Lancet Gastroenterol Hepatol*. 2018; 3: 559-565.
14. Sarrazin C, Cooper CL, Manns MP, et al. No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12weeks in HCV DAA-experienced patients. *J Hepatol*. 2018; 69: 1221-30.
15. Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C infection. (Abstract). *J Hepatol*. 2018; 68: S23-S4.
16. De Ledinghen V, Varaut A, Bedoya JU, et al. Sofosbuvir plus glecaprevir/pibrentasvir in patients with difficult to treat HCV infection. Final resuts of the French Compassionate use. (Abstract). *J Hepatol*. 2018; 68: S529.
17. Struble K, Chan-Tack K, Qi K, Naeger LK and Birnkrant D. Benefit-risk assessment for sofosbuvir/velpatasvir/voxilaprevir based on patient population and hepatitis C virus genotype: U. S. Food and Drug Administration's evaluation. *Hepatology*. 2017, doi: 10.1002/hep.29601. [Epub ahead of print]

HCV treatment: are there still difficult to treat patients?

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Key points

- With pangenotypic direct acting antivirals there are no longer any so-called « difficult-to-treat patients ».
- The intrinsic toxicities of antiviral drugs and drug-drug interactions should be taken into account for the choice of therapy.
- Adherence may be a limitation to cure and require therapeutic education.
- The screening of HCV infection and access to care are now the main limitations to the WHO 2030 elimination plan, which is not restricted to « specific » populations.

With the almost absolute antiviral potency of pangenotypic direct acting antivirals (DAAs) there are no longer any so-called difficult-to-treat patients.

When interferon was the standard of care, fibrosis, genotype 1 infection, high viral load, metabolic syndrome, HIV coinfection and non CC IL28B genotypes were negative predictors of a sustained virological response (SVR) (1). Most of these negative predictors were no longer pertinent with first generation DAAs (2). Genotype 3 treatment-experienced patients with cirrhosis, patients with stage 3-5 chronic kidney disease (CKD) with genotypes other than 1 or 4, which prevented the use of sofosbuvir (3) or DAAs failure were the remaining difficult-to treat-patients until the last generation of DAAs became available. Even in those patients, pangenotypic DAAs now result in a SVR rate >97% in both clinical trials and in real life. The glecaprevir/pibrentasvir combination in patients with stage 3-5 CKD (4) or sofosbuvir/velpatasvir/voxilaprevir in DAA failures cure almost all patients (5). Even in most prior difficult to treat patients, therapy may be reduced to 8 weeks (6-7): in genotype 5-6 or patients with cirrhosis (Expedition 8, AASLD 2018) whatever the genotype with the glecaprevir/pibrentasvir combination or in genotype 3 (EASL 2018) with the sofosbuvir/velpatasvir combination.

The main limitations for the use of DAAs are :

The intrinsic toxicities of the drugs and the drug-drug interactions (DDI); adherence; and access to care for specific populations, including patients with active intravenous drug use, migrants, prisonners and those representing « hidden » epidemics.

1. Intrinsic toxicities of DAAs and drug-drug interactions.

Decompensated cirrhosis contraindicates the use of protease inhibitors which can cause liver damage and decompensation. In this case a protease inhibitor-free combination (sofosbuvir/velpatasvir) should be used for 12 weeks in combination with ribavirin. Severe hepatotoxicity has indeed been reported in 5-10% of HIV-infected patients receiving highly active antiretroviral therapy (8), and the main risk factors were hepatitis co-infection, advanced liver disease, and elevated liver transaminases at the start of therapy. Antiretroviral drugs associated with an increased risk of severe hepatotoxicity were stavudine, didanosine, nevirapine, and the protease inhibitors (full-dose) ritonavir and tipranavir (8). In the CUPIC

study including interferon-experienced patients with HCV genotype 1 infection and cirrhosis who were re-treated with telaprevir or boceprevir, we reported relatively high percentages of side effects (49.9%) including liver decompensation (10.4%) and death (2%). Baseline levels of albumin (<35 g/L) and platelet counts (<100.000/mm3), or the severity of the underlying liver disease, were the predictors of severe side effects or death (2).

Sofosbuvir is metabolized in the kidney and is not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/mn while protease inhibitors or NS5A inhibitors are mainly metabolized by the liver and do not require eGFR dose-adjustment and are good candidates for the treatment of patients with stage 4 and 5 CKD. The glecaprevir/pibrentasvir combination, whatever the genotype, or the grazoprevir/elbasvir combination for genotypes 1 (or 4), should be preferred. Patients with decompensated cirrhosis and CKD appear to be the last difficult to treat cases at present.

Drug-drug interactions remain an issue in HIV coinfected patients but also in patients treated with antiarythmic drugs (amiodarone) for sofosbuvir-containing regimens, as well as antiepileptic drugs, anticoagulants or anticancer drugs. The choice of the DAAs should be targeting in relation to the DDI and sometimes (HIV for example) the usual therapy should be modified during the 8 to 12 weeks of the DAA regimen. www.hep-druginteractions.org is an important source of support in daily practice and the need for pharmacological drug monitoring is rare. The coformulation of antivirals is rarely a limitation given the DDI.

2. Adherence

Although adherence has not been extensively evaluated it appears to be more frequently involved in the failure of DAAs than resistance-associated substitutions (Sarpel D et al. AASLD 2016). Even for the short duration of treatment, therapeutic education could help patients understand that adherence is of key importance for successful therapy.

3. Access to care

Access to care in specific populations, including patients with active intravenous drug use, migrants, prisonners and those representing « hidden » epidemics remains the main challenge for the future.

Only an estimated 34–48% of HCV chronic carriers are referred for assessment to a liver specialist. Moreover, less than 37% of patients receive treatment for hepatitis C in northern countries while the corresponding figure is less than 1% in low income countries (9). Therefore, developing models of care that could overcome barriers and improve access to care is a critical goal to modify the epidemiology of HCV to reach the WHO goal (90% reduction in the prevalence of hepatitis and 60% reduction in hepatitis-related mortality by 2030). To achieve the target of "HCV Elimination", all efforts should be made to increase awareness: education programs targeting at-risk populations, medical practitioners and other healthcare workers with a simple guide for the prescription of DAAs. Considering the systemic manifestations of hepatitis C infection, the approach must be multidisciplinary. "Micro-elimination" programs should be implemented in targeted populations (10).

Finally, lowering of the price of DAAs will increase access to treatment and access to low-cost generic drugs should be discussed with payers and the pharmaceutical industry. Patent sharing of these drugs has already made 14 drugs available and an estimated 3 million of the 4 million treated patients worldwide have been given generic drugs.

References

1. Mchutchison JG, Lawitz, EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatement of hepatitis C infection. *N Engl J Med*. **361**, 580-593 (2009).
2. Hezode,Ch., et al.Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol*. **59 (3)**:434-41 (2013).
3. Saxena, V., et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCV-target. *J Hepatol.* **62**, S267 (2015).
4. Gane, E., et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. *N Engl J Med.* **377**,1448-1455 (2017).
5. Bourliere, M., et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med.* **376,** 2134-2146 (2017).
6. Zeuzem, S., et al. Glecaprevir–Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *New Engl J Med.* **378**, 354–369 (2018).
7. Jacobson, I.M., et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. *Gastroenterology* **153**,113-122 (2017).
8. Vogel, M., Rockstroh, J.K. Hepatotoxicity and liver disease in the context of HIV therapy. *Curr Opin HIV AIDS* **2,** 306-313 (2007).
9. Razavi, H., et al. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. *Lancet Gastroenterol Hepatol.* **2,** 325-336 (2017).
10. Lazarus, J.V., et al. Micro-elimination - A path to global elimination of hepatitis C. *J Hepatol.* **67**,665-666 (2017).

Treatment of HCV decompensated cirrhosis

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Key points

- Chronic hepatitis C virus (HCV) can be effectively treated in patients with decompensated cirrhosis.
- The sustained viral response (SVR) rate that can be achieved in patients with decompensated cirrhosis is somewhat lower than in patients with stable compensated cirrhosis.
- The highest SVR rates are observed when ribavirin is used with sofosbuvir and an NS5A inhibitor.
- Regimens containing a protease inhibitor should not be used in patients with decompensated cirrhosis.
- Successful treatment of patients with HCV and decompensated cirrhosis appears to reduce the risk of hepatocellular carcinoma, improve the MELD score and may allow some patients to be removed from the liver transplant waiting list.

Patients with chronic HCV and decompensated cirrhosis are the most challenging to manage. The SVR rate in patients with decompensated Child class B and C cirrhosis is only in the 85-95% range compared to over 95% in patients with stable Child class A cirrhosis.

Should all patients with decompensated cirrhosis and chronic HCV be treated?

Achieving a SVR in patients with decompensated cirrhosis has been shown to improve the Child and MELD scores and may allow up to 33% of these patients to be removed from the liver transplant waiting list. However, treatment of HCV in all patients with decompensated cirrhosis may not be a good thing. Many patients with decompensated cirrhosis are highly symptomatic and suffer from one or more of the complications of portal hypertension including hepatic encephalopathy, ascites, chronic gastrointestinal blood loss, chronic kidney disease and severe fatigue. Achieving a SVR may not improve these symptoms and trap the patient into a state referred to as a "MELD purgatory", where they are too symptomatic to function normally, but with a MELD score that is too low to receive a liver transplant.

It is therefore essential to consider the pros and cons of HCV treatment in patients with decompensated cirrhosis. This should include the age of the patient, whether or not they are a liver transplant candidate, the Child score, MELD score and their current quality of life. In patients with medical contraindications, advanced age, or other reasons that prevent liver transplantation, treatment of HCV and achieving a SVR may improve quality of life, survival and be cost effective. In patients with an acceptable quality of life, despite hepatic decompensation, treatment of HCV to try to avoid liver transplantation may also be acceptable. Patients with a MELD score of more than 20 should probably not be treated for HCV until after they undergo a liver transplant.

Patients with decompensated cirrhosis who achieve a SVR are at risk of developing additional complications of cirrhosis including hepatocellular carcinoma (HCC). It is therefore imperative that all patients with cirrhosis continue to be monitored on a regular basis after they achieve a SVR and not be dismissed from follow-up. Patients who develop progressive liver failure or HCC despite SVR should be considered for liver transplantation.

Treating HCV in patients with decompensated cirrhosis is challenging. These patients may develop additional complications of cirrhosis during treatment and this could lead to hospitalization. Hospitalization of a patient receiving HCV treatment could affect compliance since direct-acting anti-viral agents (DAAs) are not available in hospital pharmacies and treatment may be interrupted if the patient did not bring their medication with them to the hospital or they are too ill to continue treatment.

Although several DAAs combinations are currently available to treat HCV, therapies which include a protease inhibitor cannot be used in patients with decompensated cirrhosis. Protease inhibitors are exclusively metabolized by the liver and have been shown to cause hepatotoxicity in patients with advanced cirrhosis. Only DAA combinations that used sofosbuvir and an NS5A inhibitor, either ledipasvir, valpatasvir or declatasvir should be used in patients with decompensated cirrhosis.

Use of Ribavirin:

The combination of sofosbuvir-velpatisvir and ribavirin (RBV) 600 mg daily for 12 weeks has been shown to achieve a higher SVR rate than either sofosbuvir-velpatasvir for 12 or 24 weeks (94% versus 83% and 86% SVR respectively) in patients with Child class B cirrhosis and a Child-Turcotte-Pugh (CTP) score of 7-9. The combination of ledipasvir-sofosbuvir and weight-based ribavirin (1000-1200 mg daily) for 12 or 24 weeks of treatment was shown to have an SVR rate of 87-89% in patients with Child class B and C cirrhosis. The SVR with ledipasvir-sofosbuvir and a lower dose of ribavirin, 600 mg daily, was 85% after 12 weeks and 90% after 24 weeks of treatment. In both studies the SVR rate was somewhat higher in patients with Child class B than class C cirrhosis. RBV is associated with an increased risk of adverse events which leads some patients to stop therapy early, especially with the higher weight-based dosing regimen. The lower 600 mg dose appears to result in a better balance between efficacy and tolerability.

Although RBV does appear to increase the SVR rate, it is not appropriate for use in all patients. Whether to use RBV depends on the patient's baseline hemoglobin and whether they are experiencing chronic gastrointestinal blood loss from portal hypertension and can tolerate another assault on their hemoglobin.

Treatment of HCV after liver transplantation:

Many patients with decompensated cirrhosis, especially those with a MELD score over 20, may be better off being treated for HCV after undergoing liver transplantation. Treatment of HCV after liver transplantation has been shown to have a SVR rate of 98% with many different regimens, including those containing a protease inhibitor.

Treatment of patients with HCC:

Several years ago it was suggested that treatment of HCV in patients with decompensated cirrhosis could increase the risk and aggressiveness of de novo or recurrent HCC following successful treatment. These initial studies were uncontrolled and mostly observational. Since then, several well controlled studies have demonstrated that successful

HCV treatment and achieving a SVR are associated with a reduction in the risk of both de novo and recurrent HCC. The risk of HCC is increased in patients with HCV and decompensated cirrhosis and in patients with thrombocytopenia.

HCV treatment has been shown to be effective in patients with HCC; although the SVR rate appears to be reduced compared to those without HCC (74% vs 94%). It remains unclear if treatment of HCV in patients with HCC who are not candidates for liver transplantation actually improves long term survival as this is probably related to HCC recurrence and the natural history of HCC rather than the presence of HCV. Long term follow-up studies of patients with HCC who have achieved SVR are required.

Case presentation

The patient was found to have chronic HCV in 2001, when he was 54 years of age. Risk factors for acquiring HCV was a blood transfusion he received at the age of 16 years following a motorcycle accident. A liver biopsy demonstrated stage 2 bridging fibrosis. Liver function was normal. The platelet count was 175,000, HCV genotype was 1A and HCV RNA Log_{10} 6.2 IU/ml. He was treated with peginterferon-alfa-2a once weekly and ribavirin 1200 mg daily. He developed anemia and treatment was stopped after 12 weeks for null response. He stopped consuming all alcohol.

The patient moved out of the area and had no further follow-up until 2016 when at age 69 years he developed variceal hemorrhage. He was hospitalized, underwent banding, developed edema, ascites and hepatic encephalopathy. He had a paracentesis and was treated with step 1 diuretics and lactulose twice a day.

Two weeks following the hospitalization his physical examination was significant for a few spider angioma on his chest, no obvious ascites, no edema, some mild forgetfulness but no asterixis. Laboratory values demonstrated total bilirubin 2.5 mg/dl, albumin 3.3 gm/dl, INR 1.5, sodium 136 mEq/L, creatinine 1.2 mg/dL, hemoglobin 10 g/L, serum ammonia 60 μmol/L and a platelet count of 85,000. α-fetoprotein (AFP) was 5.7 ng/mL with 12% AFP-L3. Ultrasound demonstrated an echogenic liver, no liver mass, a patent portal vein and a small amount of ascites. The Child score was 9, MELD score 17. He was treated with sofosbuvir-velpatasvir for 12 weeks but failed to achieve SVR.

He was evaluated and placed on the liver transplant waiting list with a MELD score of 17. He agreed to accept an HCV positive donor. He was monitored every 3 months. He underwent repeat esophagogastroduodenoscopy with banding of esophageal varices to obliteration.

In 2017 at the age of 70 years he was found to have a 3 cm mass on routine ultrasound. AFP had increased to 121 ng/mL with 33% AFP-L3. A dynamic MRI demonstrated a 3.2 cm mass with washout and rim enhancement in the right lobe, segment 6.

He was treated with transarterial chemoembolization, but 3 months later had some residual enhancement on MRI with no new lesions. He was treated with microwave ablation. An MRI 3 months later showed an ablation cavity with no enhancement and no new lesions.

In 2018, he was 71 years and had developed some mild muscle wasting. He was on step 2 diuretics and taking both lactulose and xifaxan. Laboratory values demonstrated total bilirubin 3.3 mg/dL, albumin 3.0 g/dL, INR 1.7, sodium 133 mEq/L, creatinine 1.4 mg/dL, hemoglobin 12 g/L, serum ammonia 55 μmol/L and a platelet count of 85,000. AFP was 5.7 ng/mL with 12% AFP-L3. Ultrasound demonstrated an echogenic liver, no liver mass, a patent portal vein

and a small amount of ascites. The Child score was 10, MELD score 23. He was treated with sofosbuvir-velpatasvir and ribavirin 300 mg twice a day for 12 weeks and achieved a SVR.

It is now 2019. He has not had recurrence of HCC, his performance status has improved, his most recent Child score is 7 and MELD is 18. He continues to be monitored for recurrence of HCC.

References

1. Bourliere M, Bronowicki J, de Ledinghen V, et al.. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomized, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15:397-404.
2. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterol. 2015;149:649 - 659.
3. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in patients with Decompensated cirrhosis. N Engl J Med. 2015;373:2618-2628.
4. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomized, phase 2 trial. Lancet Infect Dis. 2016;16:685-697.
5. Foster GR, Irving WL, Cheung MCM, et al. Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016; 65:741-747.
6. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. HCV-TARGET Study Group. Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients with Hepatitis C Virus Infection and Factors Associated with Sustained Virologic Response. Gastroenterol. 2016; 151:1131-1140.
7. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016; 63:1493-1505.
8. Belli LS, Berenguer M, Cortesi PA, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol. 2016; 65:524 - 531.
9. Ahmed A, Gonzalez SA, Cholankeril G, et al. Treatment of patients waitlisted for liver transplant with all-oral direct-acting antivirals is a cost-effective treatment strategy in the United States. Hepatology. 2017; 66:46-56.
10. Younossi ZM, Stepanova M, Charlton M, et al. Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial. Lancet Gastroenterol Hepatol. 2016; 1:122-132.
11. Tapper EB, Hughes MS, Buti M, et al. The Optimal Timing of Hepatitis C Therapy in Transplant Eligible Patients With Child B and C Cirrhosis: A Cost-Effectiveness Analysis. Transplantation. 2017; 101:987-995.

12. Beste LA, Green PK, Berry K, et al. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. J Hepatol. 2017; 67:32-39.
13. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol. 2018; 68:25-32.
14. Lleo A, et al. SVR is the strongest predictor of occurrence and recurrence of hepatocellular carcinoma in HCV cirrhotic patients after treatment with DAAs: a prospective multi-centric Italian study. J Hepatol. PS-154 (abstract).

Is the risk of HCC favorably or unfavorably influenced by HCV therapy with DAAs?

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Key points

- Cirrhosis is the strongest risk factor for hepatocellular carcinoma (HCC). Hepatitis C virus (HCV) is a major risk factor in the Western world and Japan.
- Direct Acting Antivirals (DAAs) have revolutionized the treatment of HCV infection, achieving high rates of sustained virological response (SVR), in both compensated and decompensated cirrhosis, with high compliance to therapy and a good safety profile.
- Despite conflicting reports, use of DAAs improves outcome in patients with HCV-related cirrhosis with or without HCC.
- There is an urgent need for high quality studies to evaluate the benefit of HCV eradication on clinically relevant outcomes in patients with intermediate or advanced HCC on compensated cirrhosis.

Direct acting antivirals (DAAs) stabilize or improve liver function in most patients with hepatitis C related cirrhosis, at all functional stages, with high rates of sustained virological response (SVR) and a good safety profile. Early reports originating from retrospective uncontrolled field-practice studies, linked DAA therapy to a high risk of occurrence or recurrence of hepatocellular carcinoma (HCC) in some cases. Since then, a substantial amount of data has confirmed that DAA-induced HCV clearance is associated with a reduced risk of waiting list dropout due to tumor progression or death, a lower rate of occurrence and recurrence of HCC and better long term preservation of liver function, leading to a longer survival.

Hepatocellular carcinoma is a major health care problem with an increasing incidence worldwide and a poor prognosis, and is the leading cause of mortality in patients with cirrhosis worldwide (1). Cirrhosis is the strongest risk factor for HCC, with hepatitis C virus (HCV) being a major risk factor in the Western world and Japan (2). The prognosis of patients with cirrhosis due to HCV is influenced by the progression towards hepatic decompensation and HCC and the latter is the leading cause of mortality in patients with compensated cirrhosis. In the past few years, several studies in patients treated with interferon-based therapy have clearly shown that the risk of HCC is markedly lower in patients who achieve a sustained virological response (SVR) than in those who do not (3).

HCC occurrence after DAAs treatment

The development of new direct-acting antivirals (DAAs) has revolutionized the treatment of HCV infection, with very high SVR rates (>90%), very few contraindications and a low rate of adverse events (4). There are no data from randomized controlled trials (RCTs) on the effect of HCV eradication by DAAs in patients with advanced or decompensated liver disease (with or without HCC), or in patients who have been successfully treated for HCC.

Thus, the available data on HCC in these patients is based on post-marketing surveillance and mostly concerns the occurrence (i.e., "de novo") or recurrence (relapse of previously cured) of HCC during and after DAA treatment in patients with HCV cirrhosis.

This lack of RCT data is especially important because of certain reports of a potentially increased risk of early HCC recurrence in patients who are successfully treated with DAAs, and an increased risk of HCC with more aggressive tumor behavior after DAA treatment (5,6).

Hypothetically, the mechanisms involved in the higher risk of HCC after DAA therapy include a loss of immune control due to the clearance of HCV-specific T cells from the liver. Some researchers have suggested that a rapid decrease in antigenic load upon HCV eradication can promote a hypo-responsive state in memory-helper T cells, a new condition which could play a role in the emergence of cancer events (7). A recent study has suggested that a DAA-mediated increase in vascular endothelial growth factor (VEGF) favors HCC recurrence/occurrence in susceptible patients who already have abnormal activation of neo-angiogenetic pathways in the liver tissue (8). On the other hand, since DAA therapy is now the accepted standard of care in patients with HCV infection (mainly due to a higher rate of SVR and the worldwide-accepted effect on clinical outcomes), RCTs comparing DAA to placebo are unethical and unfeasible.

The study by Conti et al. (6) reported a high incidence (3.17% after 24 weeks of follow-up) of HCC after viral clearance. Conversely, in a large retrospective cohort study including 22,500 HCV patients treated with DAAs Kanwal et al. (9) demonstrated an overall annual HCC incidence of 1.18% (95% CI, 1.04–1.32). It is interesting, to note that the annual HCC incidence was markedly higher in patients who did not achieve SVR (3.45%; 95% CI, 2.73–4.18) compared to those who did (0.90%; 95% CI, 0.77–1.03).

Moreover, Calvaruso et al. (10) collected data from a prospective study of 2,249 consecutive patients with HCV–associated cirrhosis (90.5% with Child-Pugh class A and 9.5% with Child- Pugh class B) treated with DAAs. One year after exposure to DAAs, HCC developed in 2.1% of patients with Child-Pugh class A with a SVR and 6.6% of patients with no SVR and in 7.8% of patients with Child-Pugh class B with a SVR and 12.4% of patients with no SVR ($P < .001$ by log-rank test).

It is important to consider that the reported *de novo* occurrence rate of HCC after DAA therapy may be mainly explained by the fact that patients with more advanced stages of cirrhosis, who are at an intrinsically higher risk of cancer, now have access to curative treatment. Conversely, when interferon/ribavirin was the only therapeutic option, treatment could be only attempted in well compensated patients with cirrhosis often without clinically significant portal hypertension, who are at lower risk of HCC.

Finally, the large metaanalysis performed by Waziry et al. (11) including 26 different studies (19 prospective, 5 retrospective and 2 retrospective-prospective cohorts) reported similar results for the occurrence of HCC following SVR: 1.14/199 per year [py] (95% CI 0.86-1.52) and 2.96/100 py (95% CI 5-29.58) in the interferon and DAAs group respectively. Meta-regression adjusting for study follow-up and age showed that DAA therapy was not associated with a higher occurrence of HCC (RR 0.68; 95 % CI 0.18-2.55; p=0.55).

HCC recurrence after DAAs treatment in successfully treated HCC

Although recent data from large retrospective and prospective cohort studies have clearly confirmed the reduced risk of incident HCC following a SVR with DAA, and that

cirrhosis is the main driver of the residual risk of HCC following SVR (9,10), there is some doubt about the risk of recurrent HCC in successfully treated HCC, mainly due to the methodological limitations of the studies. The clinical impact of DAAs on the recurrence of HCC is controversial based on limited and contrasting evidence. First, as mentioned, RCTs evaluating the efficacy of DAAs in patients successfully treated for HCC are lacking. Second, data from clinical practice are characterized by numerous methodological weaknesses, intrinsically linked to this complex context.

A retrospective analysis of 58 patients receiving DAAs, with prior HCC and a complete response after resection, ablation or transarterial chemoembolization (TACE), showed radiological tumor recurrence in 27.6% after a median follow-up of 5.7 months. No control group was included in this study (5). Another study by Conti et al (6) evaluated recurrent HCC after DAA therapy in 59 patients with cirrhosis, without a control group. HCC recurrence was found in 17 (28.8%) patients during the 24-week follow-up. On the other hand, data from 3 cohort studies including patients with chronic hepatitis C who were previously treated for HCC (HEPATHER study with 189 patients treated with DAA and 78 untreated patients; CirVir study with 13 patients treated with DAA and 66 untreated patients; and CUPILT study with 314 liver transplant recipients for HCC who were subsequently treated with DAA), showed no increase in the recurrence of HCC after DAA therapy compared to DAA-untreated patients (12).

Interestingly, recent studies (13,14) have identified a prior history of HCC recurrence as an independent predictor of recurrence. These results are particularly relevant because they show the wide heterogeneity of the populations included in many studies. Because of the absence of RCTs with an untreated control arm (which would be ethically unacceptable), a recently published meta-analysis of actuarial HCC survival and recurrence probabilities in patients with successfully treated HCC and compensated cirrhosis, without a prior history of HCC recurrence, untreated for HCV (15), represents the benchmark reference control. This meta-analysis of eleven studies (701 patients) showed that the pooled estimates of 6-month, 1-year and 2-year recurrence probabilities were 7.4% (95% CI, 4.0-10.0%), 20% (95% CI, 12.7-27.4%), and 47% (95% CI, 39.5-54.4%), respectively, while pooled estimates of 3-year and 5-year survival actuarial probabilities were 79.8% (95% CI, 74.2-85.8%), and 58.6% (95% CI, 51.1-67.1%).

So, how can the question of a possibly higher risk of HCC recurrence after DAA therapy be clearly answered? First, future cohort studies comparing DAA-untreated patients successfully treated for HCC and DAA-treated patients with no history of recurrence should be performed. Second, a meta-analysis of individual patient data is needed to better explore and explain the heterogeneity of patients included in published studies.

Another relevant point involves patients with viable HCC listed for liver transplant. In fact, there is some evidence (16,17) that DAA treatment could also improve liver function, reduce the risk of decompensation and reduce waiting list dropout due to HCC progression or death in patients with decompensated cirrhosis and HCC.

For the moment there is no evidence to prevent DAA treatment in patients: 1) without a history of HCC; 2) successfully treated for HCC; and 3) listed for liver transplant (with or without HCC).

There is an urgent need for high quality studies to evaluate the benefit of HCV eradication (risk of decompensation, HCC progression, and mortality) on clinically relevant outcomes in patients with intermediate or advanced HCC on compensated cirrhosis.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182-236.
2 Torres HA, Shigle TL, Hammoudi N, Link JT, Samaniego F, Kaseb A, Mallet V. The oncologic burden of hepatitis C virus infection: A clinical perspective. CA Cancer J Clin. 2017 Sep;67(5):411-431.
3 Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013 Mar 5;158(5 Pt 1):329-37.
4 AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015 Sep;62(3):932-54. s
5 Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016 Oct;65(4):719-726.
6 Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016 Oct;65(4):727-733.
7 Dalai SK, Khoruzhenko S, Drake CG, Jie CC, Sadegh-Nasseri S. Resolution of infection promotes a state of dormancy and long survival of CD4 memory T cells. Immunol Cell Biol. 2011 Nov;89(8):870-81.
8 Faillaci F, Marzi L, Critelli R, Milosa F, Schepis F, Turola E, et al. Liver Angiopoietin-2 Is a Key Predictor of De Novo or Recurrent Hepatocellular Cancer After Hepatitis C Virus Direct-Acting Antivirals. Hepatology. 2018 Sep;68(3):1010-1024.
9 Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterology. 2017 Oct;153(4):996-1005.e1.
10 Calvaruso V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, et al.; Rete Sicilia Selezione Terapia–HCV (RESIST-HCV). Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Gastroenterology. 2018 Aug;155(2):411-421.e4.
11 Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, George J, Dore GJ. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol. 2017 Dec;67(6):1204-1212.
12 ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect

of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016 Oct;65(4):734-740.

13 Virlogeux V, Pradat P, Hartig-Lavie K, Bailly F, Maynard M, et al. Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C. Liver Int. 2017 Aug;37(8):1122-1127.

14 Cabibbo G, Petta S, Calvaruso V, Cacciola I, Cannavò MR, Madonia S, et al.; Rete Sicilia Selezione Terapia - HCV (RESIST-HCV). Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. Aliment Pharmacol Ther. 2017 Oct;46(7):688-695.

15 Cabibbo G, Petta S, Barbàra M, Missale G, Virdone R, Caturelli E, et al; ITA.LI.CA study group. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int. 2017 Aug;37(8):1157-1166.

16 Huang AC, Mehta N, Dodge JL, Yao FY, Terrault NA. Direct-acting antivirals do not increase the risk of hepatocellular carcinoma recurrence after local-regional therapy or liver transplant waitlist dropout. Hepatology. 2018 Aug;68(2):449-461.

17 Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al.; European Liver and Intestine Association (ELITA). Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol. 2016 Sep;65(3):524-31.

How to treat HCV-HBV coinfection

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Key points

- The risk of drug-to-drug interactions between regimens to cure HCV and suppress HBV infection is very low.
- The risk of HBV reactivation during treatment with direct acting antivirals (DAAs) is similar to that observed with interferon-based therapy.
- All patients scheduled for anti-HCV treatment should be tested for HBsAg, and additional anti-HBc testing should be performed in immunocompromised patients.
- HBsAg positive patients with undetectable HBV DNA during DAAs therapy should be monitored for ALT activity. If ALT is elevated, HBV DNA should be measured and if detectable, nucleoside or nucleotide analogues (NUCs) administered.
- Patients with detectable HBV DNA prior to scheduled HCV treatment should receive NUCs at least one month before DAAs.

In general antiviral therapy can be administered in the same manner in patients with HBV-HCV coinfection as in monoinfected patients. However, there are certain limitations that should be mentioned. First, there is a risk of drug-to-drug interactions (DDI) between regimens administered to cure HCV and suppress HBV infection. Reactivation of HBV is also possible during or shortly after treatment with direct acting antivirals (DAAs) for HCV infection.

In HBV-HCV coinfected patients who are already receiving long-term treatment with nucleoside or nucleotide analogues (NUCs) for HBV suppression, optimal anti-HCV therapies must be chosen to avoid DDI. This is easy using the well known ”HEP drug interactions” website as a reference [1]. Co-administration of all medications for HBV and HCV is possible. Certain potential interactions may occur with the co-administration of ribavirin and tenofovir or lamivudine. However, this is theoretical and based on HCV/HIV coinfected patients treated with a combination of pegylated interferon alpha and ribavirin, so it does not have practical value. Tenofovir blood concentrations can be increased when administered with sofosbuvir-containing regimens, so patients on tenofovir disoproxil, should be monitored, especially those with kidney diseases and if possible an alternative DAA regimen should be selected. Other tenofovir-associated adverse reactions are unlikely due to the short course of DAA treatment in most patients.

There is no risk of interactions with DAA in patients treated with pegylated interferon alpha for HBV infection, except for possible decompensation in patients with cirrhosis, related to the mode of action of protease inhibitors and interferon. However, because of the possible risk of a life-threatening increase in HBV replication during DAAs treatment, potent NUCs should be used instead of pegylated interferon alpha in coinfected patients.

As mentioned, the second major risk of treatment in patients with HBV/HCV coinfection is life-threatening HBV reactivation during DAAs treatment. The problem was identified by the FDA in 2016 based on 29 cases, mainly from Asia. Unfortunately, details showed that almost half of these patients were not tested for HBsAg and only six were tested for anti-HBc antibodies before the start of DAAs therapy [2]. Further analysis clearly showed that the risk of HBV reactivation with DAAs was not significantly different than in previous interferon regimens [3]. Results of prospective studies in HBsAg positive patients and in those with isolated anti-HBc showed that HBV reactivation was usually not associated with significant clinical or laboratory signs of liver injury and that the increase in HBV DNA was transient [4, 5]. However, the major question was whether the risk of reactivation is only found in HBsAg positive patients or also includes those with isolated presence of anti-HBc. The FDA reported three cases of HBV reactivation in patients with isolated anti-HBc, but with unknown immune status [2]. However, several studies and our own observation in a large real world cohort of immunocompetent patients, clearly showed that there was no risk of HBV reactivation in HBsAg negative, anti-HBc positive patients treated with DAAs [6-9]. On the other hand, it has been shown that HBV reactivation can occur in patients with an isolated presence of anti-HBc during immunosupressive therapy [5, 10, 11]

EASL guidelines recommend that patients scheduled for anti-HCV therapy always be tested for HBsAg, anti-HBc and anti-HBs [12]. However, current knowledge suggests that testing these patients for HBsAg is enough, while anti-HBc should be recommended in immunocompromised patients only. Individuals with HBsAg or immunocompromised patients who are positive for anti-HBc should be tested for HBV DNA before beginning treatment. In those patients found to be HBsAg positive, ALT activity should be monitored during therapy in the following manner:

a) HBV DNA must be measured in the presence of any ALT elevation during DAAs therapy in patients with undetectable HBV DNA and normal ALT activity at baseline and potent NUCs (entecavir or tenofovir) must be administered in combination with DAAs therapy as soon as possible, even without waiting for HBV DNA testing results;
b) in patients with undetectable HBV DNA and elevated ALT activity that does not decrease in the first 4 weeks of DAAs treatment, HBV DNA testing should be repeated until the end of HCV therapy, and if results are positive, potent NUCs should be administered;
c) in patients with detectable HBV DNA prior to scheduled HCV treatment, NUCs therapy should be initiated at least one month before DAAs, optimally when the HBV viral load is undetectable;
d) patients who have been successfully treated with NUCs for a long period before the initiation of HCV therapy should continue this regimen along with DAAs treatment;
e) patients who do not achieve HBV suppression should be switched to an alternative, more efficient NUCs or, if this is impossible, carefully monitored during DAAs therapy.

Most reported HBV reactivations occurred after 4 to 12 weeks of DAAs therapy, but may also be observed after treatment has been terminated. Thus, patients who are at risk of HBV reactivation should continue NUC for at least 12 weeks after anti-HCV therapy is terminated.

References

1. https://www.hep-druginteractions.org/checker
2. Bersoff-Matcha S et al. Ann Intern Med 2017;166:792-798.
3. Butt AA et al. Aliment Pharmacol Ther 2018;47:412–420.
4. Liu CJ et al. Gastroenterology 2018;154:989–997.
5. Ogawa E et al. Liver International 2018;38:76–83.
6. Mucke VV et al. Aliment Pharmacol Ther 2017;46:432-439.
7. Yanny BT et al. J Clin Gastroenterol 2018;52:908-912.
8. Wang C et al. Clin Gastroenterol Hepatol 2017;15:132-136.
9. Sulkowski M et al. Clin Infect Dis 2016;63:1202-1204.
10. Vionnet J et al. Hepatology 2018;67:791-793.
11. Tamari A et al. J Viral Hepat 2017;24:672-678.
12. EASL Recommendations on Treatment of Hepatitis C 2018 Journal of Hepatology 2018;69:461-511.

Autoimmune hepatitis: challenges in diagnosis and management

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Key points

- Autoimmune hepatitis is a disease of unknown etiology.
- Environmental agents may trigger a self-perpetuating disease process towards autologous liver tissue in genetically susceptible individuals.
- Predniso(lo)ne alone or in combination with azathioprine is the standard-of-care (SOC). Normal ALT and AST levels as well as normal serum IgG and the relief of symptoms are the goals of therapy, which may be obtained in at least 30% of patients.
- The topical steroid budesonide can also be used instead of predniso(lo)ne in patients without cirrhosis to avoid steroid-specific side effects.
- In patients who do not respond or are intolerant to the SOC, alternative drugs such as cyclosporin A, tacrolimus, mycophenolate/MMF or biologicals such as anti TNF and anti CD 20 antibodies can be used. None of these second line therapies have been approved.

Autoimmune Hepatitis (AIH) is a disease of unknown etiology. However, a loss of tolerance against the patient's own liver is considered to be the main pathogenetic mechanism. One major pathogenetic hypothesis is that environmental agents, such as viruses and toxins, trigger the self-perpetuating autoimmune process in genetically susceptible individuals. Genes of the MHC locus are responsible for approximately 50% of the genetic risk. Other non-MHC genes include CTLA-4, the vitamin D receptor, but not the AIRE gene. Drugs and infectious agents such as hepatitis A, C and more recently E virus and Parvovirus B19 are among the environmental candidates triggering AIH.

The lack of hallmarks for AIH makes the diagnostic process challenging. Typical findings are high autoantibody titers, polyclonal hypergammaglobulinemia and histological findings of lympho-plasmacellular infiltrates with interface hepatitis. The low specificity of common autoantibodies such as ANA and SMA, and the very low sensitivity of AIH-specific autoantibodies such as SLA and LKM, emphasize the need to improve the clinical diagnostic work-up of patients with chronic hepatitis. After excluding the more common causes of hepatitis, e.g. viral infections and metabolic causes, a liver biopsy should be performed to confirm or exclude AIH or identify other causes of liver disease. Three scoring systems have recently become available to help clinicians make the diagnosis of AIH.

Immunosuppressive therapy prolongs survival in patients with severe AIH. Two phases of therapy must be distinguished. The first goal in newly diagnosed autoimmune hepatitis is the induction of remission. Remission is defined as the normalization of aminotransferases (ALT, AST) and immunoglobulins G (IgG) in serum. Most patients usually respond to therapy within six to twelve months. Improvement in clinical symptoms is followed by improvement in the

biochemical parameters of disease activity and then by improvement in histology. A significant reduction in aminotransferase levels is achieved after a few weeks of therapy. Predniso(lo)ne alone or in combination with azathioprine has been shown to induce remission in most patients and is regarded as the standard-of-care (SOC). The topical steroid budesonide, in combination with azathioprine, is an alternative to prednis(ol)one in patients without cirrhosis. Budesonide has been shown to induce disease remission in combination with azathioprine with fewer steroid-specific side effects (SSSE) compared to prednisone. In addition, budesonide can maintain remission previously induced by prednisone in combination with azathioprine. Once remission is achieved patients should be kept in remission (normal ALT, AST and IgG) with the lowest dose of immunosuppression possible. Careful evaluation of individual patients should help decide whether predni(sol)sone, budesonide, azathioprine or a combination of one of these steroids with azathioprine is used to maintain remission.

Patients treated with budesonide should not have cirrhosis, since the benefit of budesonide with a 90% first pass effect in the liver is lost if the patient has already developed portosystemic shunting. There are also safety concerns for budesonide use in patients with cirrhosis.

Around 20 – 40% of patients do not achieve remission. Individual alternative therapies should be evaluated for each of these patients. None of the second line therapies for AIH used in clinical practice have been approved. There are no prospective controlled trials with large numbers of patients in this population, but the first randomized controlled trial (RCT) in difficult-to-treat patients with a B cell-depleting antibody against the B-cell activating factor receptor (BAFF) receptor is ongoing. Mofetil/mycophenolate (MMF) at a dose of 2 x 1 g daily results in remission in a significant proportion of patients as second line therapy, in particular those intolerant to SOC. Alternative drugs include cyclosporin A, tacrolimus, cyclophosphamide, and others. Thus, tacrolimus combined with steroids seems to be the most potent second line therapy in patients with an incomplete response to the SOC. Women in particular suffer from SSSE including weight gain, moon face, diabetes, glaucoma and bone disease. A minority of AIH patients do not respond to first or second line therapies. In patients who fail to respond to the first and second line treatments mentioned above, biologicals such as monoclonal anti-TNF (e.g. Infliximab) or anti-B-cell antibodies such as anti-CD20 (Rituximab) are being explored as third line therapies. Furthermore, innovative cellular therapies are under experimental and clinical development including application of regulatory T cells (Tregs). Finally, low dose IL 2 is known to induce Tregs and may become a novel therapeutic strategy for AIH. Hopefully our insights into the pathogenesis of autoimmune hepatitis will improve to identify new therapeutic targets and obtain more specific and better tolerated treatments for AIH. At present 4% of all liver transplantations in Europe and North America are still due to AIH. If a correct diagnosis is obtained and appropriate therapy is chosen, liver transplantation should be avoidable in these patients.

References

1. Williams R, Ashton K, Aspinall R, Bellis MA, Bosanquet J, Cramp ME, et al. Implementation of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2015 Nov 21;386(10008):2098-111. PubMed PMID: 26700394.
2. European Association for the Study of the L. EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of hepatology. 2015 Oct;63(4):971-1004. PubMed PMID: 26341719.
3. Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. Journal of hepatology. 2014 Mar;60(3):612-7. PubMed PMID: 24326217.
4. Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis--Update 2015. Journal of hepatology. 2015 Apr;62(1 Suppl):S100-11. PubMed PMID: 25920079.
5. Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010 Oct;139(4):1198-206. PubMed PMID: 20600032.
6. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut. 1980 Jan;21(1):78-83. PubMed PMID: 6988304. Pubmed Central PMCID: PMC1419564.
7. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010 Jun;51(6):2193-213. PubMed PMID: 20513004.
8. Liberal R, de Boer YS, Andrade RJ, Bouma G, Dalekos GN, Floreani A, et al. Expert clinical management of autoimmune hepatitis in the real world. Alimentary pharmacology & therapeutics. 2017 Mar;45(5):723-32. PubMed PMID: 28004405.
9. De Lemos-Bonotto M, Valle-Tovo C, Costabeber AM, Mattos AA, Azeredo-da-Silva ALF. A systematic review and meta-analysis of second-line immunosuppressants for autoimmune hepatitis treatment. European journal of gastroenterology & hepatology. 2018 Feb;30(2):212-6. PubMed PMID: 29227329.
10. Efe C, Hagstrom H, Ytting H, Bhanji RA, Muller NF, Wang Q, et al. Efficacy and Safety of Mycophenolate Mofetil and Tacrolimus as Second-line Therapy for Patients With Autoimmune Hepatitis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2017 Dec;15(12):1950-6 e1. PubMed PMID: 28603052.
11. Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, Lohse AW, Montano-Loza AJ. Autoimmune hepatitis. Nat Rev Dis Primers. 2018 Apr 12;4:18017. doi: 10.1038/nrdp.2018.17.
12. Taubert R, Diestelhorst J, Junge N, Kirstein MM, Pischke S, Vogel A, Bantel H, Baumann U, Manns MP, Wedemeyer H, Jaeckel E. Increased seroprevalence of HAV and parvovirus B19 in children and of HEV in adults at diagnosis of autoimmune hepatitis. Sci Rep 2018; DOI: 10.1038/s41598-018-35882-7.

13. Taubert R, Hupa-Breier KL, Jaeckel E, Manns MP. Novel therapeutic targets in autoimmune hepatitis. J Autoimmun. 2018 Nov 3. pii: S0896-8411(18)30601-2. doi: 10.1016/j.jaut.2018.10.022
14. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL *et al.* International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. Journal of hepatology, 1999;31**:**929-38.
15. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL *et al.* Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology, 2008;48**:**169-76.
16. Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, Fischler B, Gupte G, Hierro L, Indolfi G, Jahnel J, Smets F, Verkade HJ, Hadzic N. Diagnosis and Management of Paediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement. J Pediatr Gastroenterol Nutr. 2017 Nov 3. doi:

NAFLD/NASH

How to characterize NASH?

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Key points

- Nonalcoholic fatty liver disease (NAFLD) affects an estimated 25% of the general population worldwide.
- One of the key issues in NAFLD patients is the differentiation of NASH (Nonalcoholic steatohepatitis) from simple steatosis and the identification of advanced hepatic fibrosis.
- Sequential strategies combining serum biomarkers as a first step followed by measurement of liver stiffness as a second step have been proposed to identify patients with advanced fibrosis at risk of developing complications.

Nonalcoholic fatty liver disease (NAFLD) affects an estimated 25% of the general population worldwide. In a subset of NAFLD patients, who have the progressive form of NAFLD called nonalcoholic steatohepatitis (NASH), it can progress to advanced fibrosis, cirrhosis, hepatocellular carcinoma and liver-related morbidity and mortality.

Thus, key issues in NAFLD patients are the differentiation of NASH from simple steatosis and the identification of advanced hepatic fibrosis.

Until now, liver biopsy has been the gold standard for identifying these two critical endpoints but has well known limitations including invasiveness, rare but potentially life-threatening complications, poor acceptability, sampling variability and cost. Furthermore, given the magnitude of the NAFLD epidemic worldwide, liver biopsy evaluation is impractical and a non-invasive assessment for the diagnosis of NASH and advanced fibrosis is needed.

Sequential strategies combining widely available simple serum biomarkers as a first step followed by measurement of liver stiffness, using transient elastography, as a second step have been proposed to identify patients with advanced fibrosis at risk of developing complications.

References

1. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.
2. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.
3. Ferraioli G, Wong VW, Castera L, et al. Liver Ultrasound Elastography: An Update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. Ultrasound Med Biol 2018.
4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.

5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
6. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018;69:896-904.
7. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017;65:1557-65.
8. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65:570-8.
9. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology 2017;66:1486-501.
10. Kwok R, Choi KC, Wong GL, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016;65:1359-68.
11. Gines P, Graupera I, Lammert F, et al. Screening for liver fibrosis in the general population: a call for action. Lancet Gastroenterol Hepatol 2016;1:256-60.
12. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with NAFLD. Gastroenterology 2019:in press.

Is change of life style counselling efficient in patients with NAFLD/NASH?

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Key points

- Weight loss is a highly important strategy in NAFLD management. However, it is rarely systematically pursued in individual patients using the most effective behavioral techniques and thus remains ineffective in a many cases.
- An intense approach to lifestyle changes can achieve the recommended threshold of loss of 7%-10% of initial body weight. The latter is associated with both reduced liver fat and the disappearance of nonalcoholic steatohepatitis (NASH) as well as a significant reduction in fibrosis.
- A Mediterranean-type diet seems to be a reasonable suggestion in patients with NAFLD, particularly considering its beneficial role in cardiovascular and all-cause mortality.

The main environmental factors of obesity and its related non-communicable diseases, including NAFLD, are excess calorie intake, unhealthy diet, reduced physical activity and increased sedentarity, modulated by gene/behavior interaction. The contribution of excess calories is central, although the composition of the diet is also important. Indeed, the relative proportion of fat and carbohydrates and the specific dietary sources have become the subject of much research. Diets rich in saturated fatty acids (SFAs) are associated with increased liver fat, while those rich in monounsaturated fatty acids (MUFAs) or n-6 polyunsaturated fatty acids (n-6 PUFAs) tend to reduce liver fat (1). SFAs, MUFAs, and PUFAs may differently regulate adipose tissue inflammation and de novo lipogenesis (2). Foods rich in fructose, such as beverages and processed foods that are enriched with high fructose corn syrup, are the best example of an unhealthy diet. An excess of soft drink consumption is associated with a higher risk for NAFLD, NASH and fibrosis (3), through different mechanisms including increased de novo lipogenesis, generation of tissue advanced glycation end-products, ROS production, hepatic stellate cell activation and increased intestinal bacterial overgrowth and intestinal permeability.

Effects of dietary restriction

Dietary restriction is the most effective way to reduce liver fat. A 5% reduction in the body mass index is accompanied by a 25% reduction in liver fat on MRI measurements (4). Accordingly, weight loss is considered to be the cornerstone of therapy in all national and international guidelines on the clinical management of NAFLD. However, the clinical significance of hepatic fat clearance is uncertain, considering that fibrosis, not steatosis, regulates the progression of liver disease and determines the final outcome (5). Although several studies have tested the effectiveness of lifestyle modifications in NAFLD, only a few are based on solid behavioral strategies. Thus, NAFLD patients should be encouraged to initiate and maintain lifestyle modifications aimed at weight loss based on three main components: dietary recommendations, physical activity recommendations and cognitive-behavioral therapy

to address weight loss and weight maintenance obstacles (6). In the largest trial to date, 293 patients with biopsy-proven NASH were assigned to a low-fat hypocaloric diet 750 kcal/day less than the daily energy requirement (7). Macronutrient composition included 64% carbohydrates, 22% fat with <10% of total calories as saturated fats and 14% dietary protein. In addition, patients were encouraged to walk at least 200 min per week, to record habitual physical activity and to attend individual behavioral sessions to promote adherence. Following the 52-week intervent, at second biopsy, 25% had resolved histological steatohepatitis, and 19% had a regression of liver fibrosis. It is important to note that the extent of histological improvement mirrored the extent of weight loss. A higher proportion of subjects with ≥ 5% weight loss were found to have NASH resolution than subjects who lost less than this amount of weight. NASH resolution occurred in 90% of the patients who lost ≥10% of weight, while fibrosis regressed in 45%. However, only 10% of patients achieved the target of ≥ 10% or more of weight loss at one year. Similar results were reported in an earlier randomized controlled study in which patients with biopsy-proven NASH were assigned 2:1 to either lifestyle intervention or structured education (8).

Modification of diet composition

The optimal composition of the diet has been the subject of an intense search, and both low-fat and low-carbohydrate diets have been proposed. A recent meta-analysis of carbohydrate vs. fat for weight loss suggests that in hypocaloric diets, both high-fat, low-carbohydrate and low-fat, high-carbohydrate diets are equally effective in reducing liver lipid (9). Possibly, food choices based on the Mediterranean diet might be of additional help, considering the beneficial effect of this diet on cardiovascular outcomes (9). This diet, consumed by people living around the Mediterranea, includes higher proportions of monounsaturated fatty acids (MUFAs), lower carbohydrates and more low-Glycemic Index carbohydrates, minimal saturated fats, as well as increased dietary fibre and polyphenols. Typical food sources therefore include vegetables, unrefined cereals, legumes, olive oil, nuts and fish.

Lifestyle changes

It should be emphasized that lifestyle changes can improve several important outcomes independent of weight change, including the prevention of diabetes, adverse cardiovascular (CV) events and all-cause mortality including CV related mortality (10). This additional data is particularly significant as most patients with NASH will die from cardiovascular disease and the complications of type 2 diabetes. In particular, there can be significant benefits extending beyond the duration of the study, including reduction in the development of diabetes as well as all-cause and cardiovascular mortality (10). Unfortunately, similar long-term outcome studies have not been undertaken after defined interventions in NAFLD patients.

Although weight loss is a highly important strategy in NAFLD management, it is rarely systematically pursued using the most effective behavioral techniques and thus remains ineffective in a certain proportion of cases. In an ancillary part of the Look AHEAD (Action for Health in Diabetes) Study (11), the participants randomly assigned to an intensive lifestyle intervention lost significantly more weight, had greater reduction in steatosis, and a reduced likelihood of developing NAFLD than subjects receiving standard diabetes support and education. However, the Look AHEAD study has been stopped because of failure to reach the desired targets of a weight loss-induced reduction of cardiovascular mortality, casting doubts on the feasibility of behavioral treatment of overweight/obesity in the community.

References

1. Nguyen V, George J. Nonalcoholic Fatty Liver Disease Management: Dietary and Lifestyle Modifications. Semin Liver Dis. 2015;35(3):318-37.
2. Rosqvist F, Iggman D, Kullberg J, Cedernaes J, Johansson HE, Larsson A, et al. Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. Diabetes 2014;63:2356-2368.
3. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, Diehl AM. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology 2010;51:1961-1971.
4. Patel NS, Doycheva I, Peterson MR, Hooker J, Kisselva T, Schnabl B, et al. Effect of weight loss on magnetic resonance imaging estimation of liver fat and volume in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2015;13:561-568.
5. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-1554.
6. Marchesini G, Petta S, Dalle Grave R. Diet, weight loss, and liver health in nonalcoholic fatty liver disease: Pathophysiology, evidence, and practice. Hepatology. 2016;63(6):2032-43.
7. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367-378.
8. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–129.
9. Yki-Jarvinen H. Nutritional modulation of non-alcoholic fatty liver disease and insulin resistance. Nutrients 2015;7:9127–9138.
10. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014;2:474–480.
11. Lazo M, Solga SF, Horska A, Bonekamp S, Diehl AM, Brancati FL, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. Diabetes Care 2010;33:2156-2163.

Emerging therapeutics for nonalcoholic steatohepatitis

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Key points

- The number of individuals with cirrhosis and end stage liver disease is expected to triple over the course of the next 2 decades if the current pandemic of NAFLD is not brought into check.
- The focus of therapy is to improve disease activity and/or stage in the short term. In the long term, the goal is the prevent cirrhosis for those who have not developed cirrhosis.
- Treatment targets oxidative stress and apoptosis, antifibrotics, inflammation and metabolic disturbances.

Nonalcoholic steatohepatitis (NASH) is a major cause of liver related disease in the community. This has spurred a global effort to develop effective therapeutics for NASH. This review summarizes the state of the art in terms of drugs under development and emerging approaches for the treatment of NASH. This is a field that is evolving and this review is intended to provide a snapshot of the pharmacological development for the treatment of NASH.

There is intense research with numerous clinical trials for NASH and over 200 trials registered in clinical trials.gov. The current landscape may be considered in the context of the mechanism of action of the drugs being used.

1. Therapies that target metabolic derangements:

Multiple agents have targeted insulin resistance as the key cause of NASH. The earliest studies used pioglitazone and rosiglitazone [1,2]. Interestingly, pioglitazone has better effects on NASH that rosiglitazone, which has a purer peroxisome proliferator-activated receptor (PPAR)-γ profile. The PIVENS trial demonstrated that pioglitazone (30 mg/day) did indeed improve the resolution of steatohepatitis and meta-analyses of existing trials even indicate improvement in fibrosis [3,4]. A recent single center study confirms these results and shows a beneficial effect on fibrosis [5] However, these results are limited by weight gain and a risk of fractures in older women. The potential risks of bladder cancer have been largely debunked and the fears of PPAR-γ agonists causing increased mortality have not been confirmed [6]. Many of the effects of pioglitazone are mediated by mitochondrial pyruvate channels also known as mitochondrial targets of thiazolidinediones (mTOTs) and are in phase 2B trials. Enantiomers of pioglitazone, which have the metabolic benefits of pioglitazone without the associated weight gain, are also under development.

Elafibrinor is a PPAR α/δ agonist. The alpha component increases lipid oxidation and reduces steatosis and fatty acid overload, while the delta component reduces inflammatory signaling in macrophages. Although the GOLDEN trial missed the a priori primary endpoint, a post hoc analysis of subjects with NASH, NAS $\geq$ 4 and a fibrosis stage above 2 showed a therapeutic benefit [7]. A large pivotal trial (RESOLVE-IT) is currently under way and will read out in 2020. Numerous other PPAR agonists are in early development including a pan-PPAR agonist, lanifibrinor and a PPAR α/γ agonist, saroglitazar.

Another major target for therapy is the orphan nuclear receptor, farnesoid X receptor (FXR). This is the cognate receptor for bile acids, which mediates numerous metabolic functions. NASH is associated with an increase in bile acids derived from the cytosolic pathway and a decrease in mitochondrial bile acids resulting in a profile that has poor FXR activity [8]. The pharmacological activation of FXR results in increased glucose disposal in those with type 2 diabetes [9]. It has subsequently been demonstrated that obeticholic acid, a prototypic FXR agonist, further improves all of the histological features of NASH including steatosis, inflammation, hepatocellular ballooning and fibrosis[10]. These were the basis of the REGENERATE trial, which is a pivotal trial for approval by regulatory agencies and is expected to read out in 2019. Obeticholic acid is limited by the development of pruritus in up to 20% of subjects and is also associated with 10-20 mg/dl increase in LDL-cholesterol, which is responsive to statin therapy. These limitations have led to the use of a lower dose (10 mg) in one of the arms of the REGENERATE trial while the original studies used 25 mg. There are also several second generation FXR agonists that have been developed to mitigate the pruritus and LDL signals associated with obeticholic acid. One such molecule is currently under study by Gilead, while Tropifexor is another compound developed by Novartis. Both molecules have demonstrated decreased steatosis and liver enzymes in phase 2A trials and are undergoing evaluation in phase 2B trials.

There is controversy whether the effects of obeticholic acid are directly due to liver actions of the molecule or its effects on FXR activation in the intestine with release of FGF-19, which also has FXR mimetic effects. A recombinant form of FGF-19 that has not been found to be tumorogenic in animal models is currently in clinical trials. A phase 2A/2B trial has demonstrated a robust effect on the clearance of hepatic steatosis and improvement in liver enzymes, which was reflected by reduced steatohepatitis and even fibrosis [11]. Unfortunately, there were no control populations in the histology arms. A more rigorous phase 2B and 3 program is expected to follow. The key limitations of this agent is that it also causes some GI side effects and increases LDL-cholesterol. Like obeticholic acid, this can be managed with statins.

Another bile acid based approach is the conjugation of a fatty acid to a bile acid resulting in a fatty acid bile acid conjugate (FABAC) also known as Aramchol. Aramchol is an inhibitor of steroyl CoA desaturase, a key enzyme in lipogenesis. In a phase 2A trial, Aramchol produced a dose dependent improvement in hepatic steatosis [12]. Subsequently a phase 2B trial, not yet published in full form, demonstrated that it improved resolution of steatohepatitis and the individual features of NASH. However, a significant effect on fibrosis was not noted, although those with resolution of NASH experienced improved fibrosis.

FGF21 is a non-mitogenic cytokine associated with increased insulin sensitivity and direct antifibrotic effects. A phase 2A trial of FGF21 demonstrated evidence of decreased hepatic steatosis and liver enzymes. This was accompanied by improved liver stiffness, LDL-cholesterol and triglycerides. This agent is injectable and there are pegylated versions under development that can be used weekly or even monthly. Two major phase 2B trials (FALCON 1 and 2) are ongoing.

Another major development in the field is the use of thyroxine β receptor agonists, which specifically target the liver and avoid the cardiovascular effects of thyroxine α receptors. A recent phase 2A/2B trial from Madrigal, not yet published in full form, demonstrated

remarkable clearance of hepatic steatosis and improvement in liver enzymes accompanied by increased resolution of steatohepatitis. A pivotal trial using this compound is ongoing. Another recent trial with another thyroxine β receptor mimetic from Viking Pharmaceuticals confirmed these findings. There are a number of additional targets that are currently being studied such as cannabinoid receptor antagonists, miRNA based therapeutics, citrate lyase inhibitors etc.

2. Therapeutics targeting oxidative stress and apoptosis

Vitamin E was one of the earliest agents to be studied for NASH [13]. A large phase 2B trial demonstrated that it clearly reduces steatosis, ballooning, and inflammation but did not have a significant effect on the regression of fibrosis [3]. However, there have been fears that this dose of vitamin E could contribute to a general all cause mortality risk and prostate cancer. The prostate cancer risk has not been confirmed in metaanalyses, with Odds ratios from 1.03 to 0.98 in nonsmokers and smokers respectively [14].

Selonsertib is an apoptosis signaling kinase-1 (ASK1) inhibitor. ASK1 is involved in several pathways connecting cell stress to inflammation and apoptosis including oxidative stress and unfolded protein response. It has been shown to reduce hepatic fibrosis in a phase 2A/B trial [15]. These have led to two pivotal programs (STELLAR 3 and STELLAR 4) targeting NASH with bridging fibrosis and with cirrhosis, respectively. These are expected to read out in 2019.

Emricasan is a caspase inhibitor that blocks apoptosis. A phase 2B trial targeting NASH with cirrhosis with the hepatic venous pressure gradient as the primary endpoint, is now fully enrolled and should read out in the next few months.

3. Drugs targeting inflammation

Cenicrivoric is a C-C chemokine receptor 2 and 5 (CCR2-CCR5) antagonist. These chemokine receptors are also the receptor for MCP-1, a key inflammatory cytokine in NASH. A rigorously performed clinical trial in those with NASH, significant activity and fibrosis showed that this compound produced a statistically significant and sustained reduction in fibrosis [16]. Given that this target is downstream from the metabolic and cell stress drivers of disease, it does not affect steatohepatitis, steatosis, inflammation or ballooning. A pivotal trial (AURORA) is underway to evaluate the ability of this compound to prevent cirrhosis.

Several other anti-inflammatory molecules are under development including inflammasome inhibitors, TLR antagonists etc. However, a study using a toll like receptor (TLR4) antagonist was negative and another study using a bovine colostrum targeting endotoxin also lacked efficacy against NASH. These trials have been presented at international meetings and have not yet been published.

4. Anti-fibrotics

Several attempts to use pure anti-fibrotics are currently ongoing. Two major trials using a monoclonal antibody directed against lysl oxidase failed to demonstrate any clinical benefit [17]. A trial of Galectin also failed to meet its primary endpoint, although in a post hoc analysis a subgroup with moderate portal hypertension appears to have benefited. These data must be confirmed in future trials. Other approaches such as the use of integrin inhibitors and molecules targeting heat shock protein (HSP47) are under development.

5. Combination therapeutics

Patients with high activity and fibrosis are expected to require combination therapies. Several trials, including the ATLAS trial by Gilead are evaluating the clinical benefit of multiple combinations.

In summary, there is a lot of activity in the development of therapeutics for NASH. While there has been progress and the first wave of pivotal trials will read out in 2019, much remains to be done. Future trials are anticipated to integrate cardiovascular and liver endpoints.

References

1. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. The New England journal of medicine 2006;355:2297-307.
2. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. Hepatology 2003;38:1008-17.
3. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. The New England journal of medicine 2010;362:1675-85.
4. Mahady SE, Webster AC, Walker S, Sanyal A, George J. The role of thiazolidinediones in non-alcoholic steatohepatitis - a systematic review and meta analysis. Journal of hepatology 2011;55:1383-90.
5. Cusi K. Pioglitazone for the treatment of NASH in patients with prediabetes or type 2 diabetes mellitus. Gut 2017.
6. Davidson MB, Pan D. An updated meta-analysis of pioglitazone exposure and bladder cancer and comparison to the drug's effect on cardiovascular disease and non-alcoholic steatohepatitis. Diabetes research and clinical practice 2018;135:102-10.
7. Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-alpha and -delta, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology 2016;150:1147-59 e5.
8. Puri P, Daita K, Joyce A, et al. The presence and severity of nonalcoholic steatohepatitis is associated with specific changes in circulating bile acids. Hepatology 2017.
9. Mudaliar S, Henry RR, Sanyal AJ, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574-82 e1.
10. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956-65.
11. Harrison SA, Rinella ME, Abdelmalek MF, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391:1174-85.
12. Safadi R, Konikoff FM, Mahamid M, et al. The fatty acid-bile acid conjugate Aramchol reduces liver fat content in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2014;12:2085-91 e1.
13. Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. The Journal of pediatrics 2000;136:734-8.

14. Kim Y, Wei J, Citronberg J, Hartman T, Fedirko V, Goodman M. Relation of Vitamin E and Selenium Exposure to Prostate Cancer Risk by Smoking Status: A Review and Meta-Analysis. Anticancer research 2015;35:4983-96.
15. Loomba R, Lawitz E, Mantry PS, et al. The ASK1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: A randomized, phase 2 trial. Hepatology 2017.
16. Friedman SL, Ratziu V, Harrison SA, et al. A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis with Fibrosis. Hepatology 2017.
17. Harrison SA, Abdelmalek MF, Caldwell S, et al. Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis. Gastroenterology 2018;155:1140-53.

CROSS PATHS LIVER / METABOLISM

Cross paths liver/metabolism: the point of view of the hepatologist

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Key points

- Epidemiological and clinical studies have shown that NAFLD/NASH is highly prevalent in at risk populations and is under-recognized in the primary care setting.
- Screening for NAFLD/NASH in at risk populations is a major challenge. The most accurate of the simple non-invasive fibrosis markers is the FIB-4, which is based on age, ALT, AST and platelet count.
- Management of NAFLD requires a multidisciplinary approach including an endocrinological and cardiological assessment.
- Knowledge of guidelines on statin use in NAFLD must be improved in primary care physicians.
- Diet, bariatric surgery and pharmacological agents may be useful in NASH patients with diabetes.

Collaboration between hepatologists and endocrinologists and an integrative and synergistic approach is of major importance for the screening and management of NAFLD patients.

Epidemiological and clinical studies have shown that NAFLD/NASH is highly prevalent in at risk populations such as obese patients or those with type 2 diabetes. In the French Constances cohort, screening of patients by non-invasive tests has shown that the prevalence of NAFLD in patients with type 2 diabetes is 63%, while the prevalence of NASH with advanced fibrosis is 7.6%.

NAFLD is a condition that remains under-recognized in the primary care setting as recently shown in a series of NAFLD patients, in which only 21.5% had NAFLD mentioned as a possible diagnosis in their medical records, while only 10.4% were referred to a specialist. In a practice survey performed among 100 Australian specialists including endocrinologists, most believed that NAFLD was uncommon in their own patients and 71% reported that they did not make referrals to a hepatology unit.

Screening of NAFLD/NASH

Screening for NAFLD/NASH in at risk populations is a major challenge. Because there is no accurate marker of NASH, non-invasive markers of fibrosis, which have the best predictive value to determine morbi-mortality in NAFLD patients, have been proposed to screen this population. The most accurate, simple, non-invasive fibrosis marker is the FIB-4, which is based on age, ALT, AST and platelet count. Because of its high negative predictive value (>90%), FIB-4 can exclude patients with advanced fibrosis, especially in populations with a low prevalence of fibrosis. In the primary care setting, it has been reported that screening with FIB-4 can exclude most patients (70%) with a low risk of advanced fibrosis in patients

with suspected NAFLD. The stepwise combination of non-invasive fibrosis tests increases the diagnostic accuracy in NAFLD patients. The second screening step should be based on more accurate non-invasive methods such as fibroscan, to select patients with NASH and a high risk of advanced fibrosis. Moreover, fibroscan is now coupled with the Controlled Attenuated Parameter (CAP), which can assess the grade of liver steatosis.

Management of comorbidities

In a practice survey performed in 352 French gastroenterologists, most of them used a multidisciplinary approach in the management of NAFLD patients. Eighty seven percent of them referred NAFLD patients for an endocrinological and cardiological assessment of potential comorbidities. Moreover, 84% referred the patient to a dietician directly and did not leave this up to the endocrinologist. Sixty-nine percent of the participants felt that managing overweight patients was not within their field of competence and therefore referred them to endocrinologists or general practitioners. The use of statins in patients with NAFLD and dyslipidemia was investigated through a review of medical records in a Veterans Administration (VA) facility. This study showed that patients whose primary care physicians detected NAFLD were less likely to receive appropriate statin care than those with undetected NAFLD (OR = 0.34, 95% CI 0.18-0.64). This emphasizes the need to improve the knowledge of guidelines on statin use in NAFLD in the population of primary care physicians.

Treatment of NASH in diabetic patients

Besides lifestyle changes, there are no approved drugs for the treatment of NAFLD/NASH. Significant died-induced weight loss, (> 10%), has been shown to improve liver injury in NASH patients, including fibrosis. The results of bariatric surgery have also been impressive in morbidly obese patients. While there is no approved drug for treatment of NAFLD/NASH, several pharmacological agents that are used in the treatment of type 2 diabetes have shown some degree of efficacy in NASH. Glitazones such as pioglitazone and rosiglitazone were the first antidiabetic agents shown to improve liver injury in clinical trials in NASH patients. However, because of their potential toxicity, they are no longer prescribed in several countries such as in France. Liraglutide, a glucagon like peptide-1 (GLP-1) agonist, and sitagliptine, a dipeptidyl peptidase-4 (DPP-4) inhibitor, have shown promising results and should be used as first line therapy in patients with type 2 diabetes and NASH.

References

1. Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther 2016; 43: 83-95.
2. Nabi, O, Lacombe K, Boursier J, et al. Epidemiology of NAFLD and advanced fibrosis in the French general population: a population-based cohort study in 118,664 subjects (NASH-CO study). Hepatology 2018; 68 (S1).
3. Blais P, Husain N, Kramer JR, et al. Nonalcoholic fatty liver disease is under recognized in the primary care setting. Am J Gastroenterol 2015; 110:10–14.
4. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009; 7: 1104-1112.
5. Wong VW, Vergniol J, Wong GL, et al. Liver stiffness measurement using XL probe in

patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2012; 107: 1862-71.
6. Ratziu V, Cadranel JF, Serfaty L, et al. A survey of patterns of practice and perception of NAFLD in a large sample of practicing gastroenterologists in France. J Hepatol. 2012;57:376-383.
7. Blais P, Lin M, Kramer JR, et al. Statins are underutilized in patients with nonalcoholic fatty liver disease and dyslipidemia. *Dig Dis Sci*. 2016;61:1714-1720.
8. Cholankeril R, Patel V, Perumpail BJ, et al. Anti-Diabetic Medications for the Pharmacologic Management of NAFLD. Diseases. 2018 ; 6(4), pii: E93. doi: 10.3390/diseases6040093.
9. Yan J, Yao B, Kuang H, et al . Liraglutide, sitagliptin and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and NAFLD. Hepatology 2018 (in press)

Cross Paths Liver/Metabolism

NASH and type 2 diabetes mellitus: from epidemiology to pathophysiology

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Key points

- NAFLD and type 2 diabetes mellitus (T2DM) are closely associated because they share the same pathogenic context, i.e. obesity and insulin-resistance.
- T2DM patients have increased risk of death from liver-related complications and cancer.
- Advanced liver fibrosis should be screened for in T2DM patients. This requires close collaboration between hepatologists and diabetologists.

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the manifestation in the liver of the metabolic syndrome. The prevalence of NAFLD is following the pandemic of obesity and has reached 25% in the general population (1). NAFLD is now the leading cause of chronic liver disease and cirrhosis (2, 3) and is expected to become the main cause of liver transplantation within a few years (4). Longitudinal retrospective studies have shown that, among all the liver lesions observed in NAFLD, fibrosis is the main determinant of patient prognosis (5).

NAFLD and type 2 diabetes mellitus (T2DM) are closely associated because they share the same pathogenic context, i.e. obesity and insulin-resistance. The relationship between NAFLD and T2DM is complex since it is bidirectional. Some observational data suggest that NAFLD promotes hepatic insulin resistance and new-onset T2DM while other studies suggest that T2DM alone accelerates the progression of NAFLD to NASH. T2DM patients have an increased risk of death from liver-related complications and cancer (6). In the general population, T2DM is an independent risk factor of liver fibrosis (7). Models developed for the non-invasive diagnosis of liver fibrosis have all shown an independent and strong association between the presence of T2DM and advanced fibrosis in the liver (8-10). For all these reasons, it appears highly relevant to screen advanced liver fibrosis in T2DM patients and this requires close collaboration between hepatologists and diabetologists.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
2. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011;9:524-530.
3. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology 2016;64:1969-1977.

4. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. Gastroenterology 2017;152:1090-1099
5. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017;65:1557-1565.
6. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829-841.
7. Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. Hepatology 2016;63:138-147.
8. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-854.
9. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008;57:1441-1447.
10. Cales P, Laine F, Boursier J, Deugnier Y, Moal V, Oberti F, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J Hepatol 2009;50:165-173.

Cross Paths Liver/Metabolism

NASH and type 2 diabetes: from epidemiology to pathophysiology

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Key points

- The AASLD guidelines recommend against population screening while EASL–EASD–EASO clinical practice guidelines recommend screening for NAFLD in people with type 2 diabetes.
- In EASL guidelines, surrogate markers of fibrosis (NAFLD Fibrosis Score, FIB-4, ELF or FibroTest) should be calculated for every NAFLD patient in order to rule out significant fibrosis
- Diabetes specialists refer too few screened patients to hepatologists.
- Non-invasive panels for the diagnosis of steatosis and fibrosis, developed in non-diabetic cohorts, underperform when applied to patients with type 2 diabetes.
- New clinical and/or biological biomarkers of steatosis and fibrosis should be specifically validated in people with type 2 diabetes.

Type 2 diabetes mellitus (T2DM) is associated with the presence of non alcoholic fatty liver disease (NAFLD) in about two-thirds of patients. Moreover, T2DM increases the risk of complications of NAFLD, more specifically, the risk of fibrosis, cirrhosis and hepatocellular carcinoma. Thus, it is necessary to perform steatosis screening in all people with T2DM. In the same way, an evaluation of the severity of NAFLD is indicated to prevent and diagnose the early complications of this disease. If significant fibrosis cannot be ruled out, diabetologists should refer diabetic patients to a hepatologist. The AASLD guidelines recommend against population screening, noting poor evidence for longer-term benefits and cost-effectiveness (1) while recent EASL–EASD–EASO clinical practice guidelines recommend screening for NAFLD in people with T2DM (2). In these recommendations, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since people with T2DM are at high risk of disease progression. In these new guidelines, surrogate markers of fibrosis (NAFLD Fibrosis Score, FIB-4, ELF or FibroTest) should be calculated for every NAFLD patient to rule out significant fibrosis.

There are currently no existing data about the clinical practices of diabetologists concerning NAFLD. However, the screening and evaluation of NAFLD in diabetes units does not seem to be highly effective. Diabetes specialists refer too few screened patients to hepatologists. The explanation for this is probably linked to the clinical practices of diabetologists as well as the tools they have at their disposal. Indeed, the prevalence and severity of NAFLD are underestimated among diabetes specialists (3). In a recent survey, less than 5% of diabetologists correctly assessed the prevalence and severity of advanced fibrotic non-alcoholic fatty liver disease in people with diabetes (3). Another difficulty involves the inadequacy of EASL–EASD–EASO clinical practice guidelines in individuals with T2DM. The application of EASL-

EASD-EASO guidelines results in a referral to a liver clinic of 34.6 to 84.9% people with T2DM, depending on the methods used for the diagnosis of steatosis and fibrosis (4). Strict application of these guidelines would lead to an excessive number of people with T2DM being referred to a liver clinic (4). It seems very difficult to apply these algorithms in routine clinical practice. A final difficulty is related to the validity of non-invasive steatosis and fibrosis scores in the diabetic population. Several studies have shown that non-invasive panels for the diagnosis of steatosis and fibrosis, which were developed in non-diabetic cohorts, underperformed when applied to patients with T2DM (5-7). We suggest that new clinical and/or biological biomarkers of steatosis and fibrosis should be specifically validated in people with type 2 diabetes. Lifestyle changes remain the cornerstone of therapy. A systematic review of studies assessing liver outcomes supported reduction of daily caloric intake in combination with 30 to 60 minutes of exercise 3 to 5 days per week (1). Regarding treatment for NAFLD, the AASLD advises pioglitazone in patients with biopsy-proven NASH with and without type 2 diabetes, and vitamin E in only patients without diabetes and with biopsy-proven NASH without cirrhosis (1).

References

1. Paul S, Davis AM. Diagnosis and Management of Nonalcoholic Liver Disease. JAMA. 2018 Nov 26. doi: 10.1001/jama.2018.17365.
2. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO) . EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64 : 1388–1402.
3. Marjot T, Sbardella E, Moolla A, Hazlehurst JM, Tan GD, Ainsworth M, Cobbold JFL, Tomlinson JW. Prevalence and severity of non-alcoholic fatty liver disease are underestimated in clinical practice: impact of a dedicated screening approach at a large university teaching hospital. Diabet Med. 2018 ;35:89-98.
4. Sberna AL, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, Duvillard L, Denimal D, Loffroy R, Vergès B, Hillon P, Petit JM. EASL, EASD and EASO clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. Diabet Med. 2018;35:368-375.
5. Guiu B, Crevisy-Girod E, Binquet C, Duvillard L, Masson D, Lepage C Hamza S, Krausé D, Verges B, Minello A, Cercueil JP, Hillon P, Petit JM. Prediction for steatosis in type-2 diabetes: clinico-biological markers versus 1H-MR spectroscopy. Eur Radiol 2012; 22:855-863.
6. Bril F, McPhaul MJ, Caulfield MP, Castille JM, Poynard T, Soldevila-Pico C, Clark VC, Firpi-Morell RJ, Lai J, Cusi K. Performance of the SteatoTest, ActiTest, NashTest and FibroTest in a multiethnic cohort of patients with type 2 diabetes mellitus. J Investig Med. 2018.
7. Bertot LC, Jeffrey GP, de Boer B, MacQuillan G, Garas G, Chin J, Huang Y, Adams LA. Diabetes impacts prediction of cirrhosis and prognosis by non-invasive fibrosis models in non-alcoholic fatty liver disease. Liver Int. 2018;38:1793-1802.

Copper and the liver

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Key points

- Copper is an essential micronutrient.
- Both copper overload and copper deficiency lead to liver disease.
- Wilson disease is the most common form of hereditary copper toxicity and is a treatable disease.
- Hepatic copper deficiency is associated with fatty liver including NASH.

Copper is incorporated into a variety of proteins and metalloenzymes (cytochrome C oxydase, superoxide dismutase, dopamine-ß hydroxylase, lysil-oxydase, tyrosinase) which perform essential metabolic functions. This micronutrient is necessary for the proper growth, development, and maintenance of liver, bone, connective tissue, brain, heart, and many other body organs. Both an excess and a deficiency in copper can lead to a variety of diseases, and can be either of genetic or non-genetic origin.

Copper overload

Wilson disease

Wilson disease (WD) is an autosomal recessive disorder caused by the *ATP7B* gene mutation. Dysfunction of the ATP7B protein leads to impaired biliary excretion of copper and thus to copper accumulation in the liver and extrahepatic tissues. The clinical picture is highly variable with hepatic and neurological diseases as the leading forms of presentation. The disease may become symptomatic at any age or may never become symptomatic. Typical clinical features such as extrapyramidal symptoms or Kayser-Fleischer rings are frequently absent in patients presenting with liver disease. The different phenotypic presentations of WD cannot be explained by the *ATP7B* mutation. There is a significant gender effect in index patients and a hepatic presentation is more common in females while a neurological presentation is found in males (1). The degree of liver disease increases with age but does not correlate with the genotype. About half of adult patients have cirrhosis at diagnosis while in non-cirrhotic patients steatosis is a common finding and may resemble non alcoholic steato-hepatitis (NASH) (2).

The methods used to diagnose/screen for WD include the measurement of copper parameters (serum copper, serum ceruloplasmin, urinary copper excretion, hepatic copper content) and molecular-genetic testing. No single test is specific per se and, thus, a range of tests must be performed. In many patients a combination of tests reflecting disturbed copper metabolism may be needed (3). Once the diagnosis is confirmed life-long treatment with copper-chelators (d-Penicillamine, Triethylenetetramin, Tetrathiomolybdate) or zinc is needed (4). For patients with acute WD or in patients with decompensated cirrhosis, liver transplantation is the only life-saving cure. The life expectancy in all other patients is normal with medical treatment (5).

"Indian" childhood cirrhosis

This rare condition, first described in India, causes cirrhosis in young children and is linked to exogenous copper exposure, with a genetic factor. Similar cases were described outside of India (Austria, Australia, Canada). In the North American form in native Cree-Ojibway Indians, a missense mutation (R565W) of the *CIRH1A* gene was detected on chromosome 16 (6). Some patients respond to treatment with copper chelators but advanced cases require liver transplantation.

Cholestasis

Hepatic copper content is markedly increased in any form of cholestatic disease. It is important to note that in the presence of cholestasis, hepatic copper cannot be used to diagnose WD. The copper content of the liver usually becomes normal if the cause of cholestasis is removed. In primary biliary cholangitis, chelation therapy with D-Penicillamine has not been found to be effective to improve the clinical outcome.

Copper deficiency

NAFLD/NASH

The role of hepatic copper content in non alcoholic fatty liver disease (NAFLD/NASH) is not clearly understood. Several studies in humans and in experimental animals have shown that hepatic copper levels were strongly and inversely correlated with the degree of steatosis. Restriction of dietary copper in Sprague-Dawley rats induced hepatic steatosis and insulin resistance (IR). Rats that remained on a copper-deficient diet had marked periportal macrovesicular steatosis without inflammation or fibrosis (7). Furthermore, they presented with higher surrogate markers of IR and higher total serum cholesterol, while triglyceride levels were decreased. Fructose feeding in rats led to impaired copper status and iron overload in the liver. Copper deficiency together with fructose feeding led to a significant increase in hepatic triglyceride and cholesterol content. (8,9) Dietary copper is mainly absorbed in the duodenum and the proximal jejunum by a copper specific transporter Ctr-1 in the apical membrane of the enterocytes. Ctr-1 expression is strongly increased in rats with copper deficiency but this effect was abolished with additional fructose feeding. Fructose also acts as an inhibitor of duodenal copper absorption thus boosting impaired oxidant defense and lipid peroxidation. It has been suggested that the reduced activity of fructose-metabolizing enzymes and their metabolites may be responsible for differences in the severity of copper deficiency associated with liver pathology. A gene-microarray differential analysis on the intestinal transcriptome of copper- and iron-deficient rats highlighted that copper deficiency downregulates the mitochondrial and peroxisomal beta-oxidation of fatty acids. Systemic copper deficiency in mice causes mitochondrial dysfunction and similar morphological alterations have been described in human NAFLD.

The mean hepatic copper content in patients with fatty liver was lower than in controls and the mean percentage of histologically lipid-containing hepatocytes was inversely correlated to hepatic copper content. Subgroup analysis showed that this inverse correlation was only significant in patients without the metabolic syndrome (10).

Malabsorption syndromes

Copper deficiency in patients with malabsorption syndromes, especially in celiac disease, is also associated with hepatic steatosis (11), but this has not been evaluated in systematic studies.

References

1. Ferenci P, Stremmel W, Członkowska A, et al. Age, sex, but not ATP7B genotype effectively influences the clinical phenotype of Wilson disease. Hepatology 2018 (in
2. press), DOI: 10.1002/hep.30280
3. Stättermayer AF, Traussnigg S, Dienes HP, et al. Hepatic steatosis in Wilson disease – role of copper and *PNPLA3* mutations. J.Hepatol 2015;63:156-63
4. European Association for the Study of the Liver: EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56:671-85.
   Beinhardt S, Leiss W, Stättermayer AF, et al. Long-term outcome of Wilson disease in a large Austrian cohort. Clin Gastroenterol Hepatol.2014;12:683-9
5. Chagnon P, Michaud J, Mitchell G, et al. A missense mutation (R565W) in cirhin (FLJ14728) in North American Indian childhood cirrhosis. Am J Hum Genet 2002;71: 1443–1449.
6. Tallino S, Duffy M, Ralle M, Cortés MP, Latorre M, Burkhead JL. Nutrigenomics analysis reveals that copper deficiency and dietary sucrose up-regulate inflammation, fibrosis and lipogenic pathways in a mature rat model of nonalcoholic fatty liver disease.
7. J Nutr Biochem. 2015;26:996-1006
8. Song M, Schuschke DA, Zhou Z, et al. High fructose feeding induces copper deficiency in Sprague-Dawley rats: a novel mechanism for obesity related fatty liver. J Hepatol. 2012;56:433-40
9. Heffern MC, Park HM, Au-Yeung HY, et al. In vivo bioluminescence imaging reveals copper deficiency in a murine model of nonalcoholic fatty liver disease. Proc Natl Acad Sci U S A. 2016;113:14219-14224
10. Stättermayer AF, Traussnigg S, Aigner E, et al. Low hepatic copper content and PNPLA3 polymorphism in non-alcoholic fatty liver disease in patients without metabolic syndrome. J Trace Elements in Medicine and Biology 2017;39:100-107
11. Tovoli F, Negrini G, Farì R, et al. Increased risk of nonalcoholic fatty liver disease in patients with coeliac disease on a gluten-free diet: beyond traditional metabolic factors. Aliment Pharmacol Ther. 2018;48:538-546.

HEPATITIS B

The impact of HBV therapy on public health

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Key points

- Chronic hepatitis B is a major burden on health care systems.
- The primary goal of treatment is to prevent severe outcomes of chronic hepatitis B.
- Barriers to expanding therapy for hepatitis B in resource-limited settings include limited infrastructural resources to perform appropriate diagnostic and monitoring assays.
- Scaling up treatment requires decentralization of healthcare and task shifting from highly trained specialists to community-based health workers in teams.
- Governments require the fundamental acceptance that viral hepatitis, which can be treated, leads to high numbers of deaths annually.
- WHO has set priorities for achieving global goals for HBV treatment

Introduction

Chronic hepatitis B (CHB) is a major burden on health care systems. The disease will persist as a cause of substantial morbidity and mortality for several decades, despite the progress of worldwide vaccination programs. Worldwide, there are an estimated 240 million chronically infected persons and chronic HBV remains an important cause of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [1-3] Age is a key factor in determining the risk of chronic infection as the consequences of disease increase with age. An estimated 650,000 people die each year from the complications caused by chronic hepatitis B infection, and overall, HBV accounts for around 45% of cases of HCC and 30% of cirrhosis worldwide, with much higher proportions in low and middle income countries (LMICs).[4]

Assessment of stage of disease

CHB-related liver disease can range from minimal fibrosis to cirrhosis, leading to a number of potentially life-threatening complications. Compensated cirrhosis may be clinically silent. To assess fibrosis and inflammatory changes requires a liver biopsy, but large-scale population based non-invasive testing and liver imaging can stage hepatic fibrosis. Simple non-invasive methods, for example fibroscan (transient elastography) or aspartate aminotransferase (AST)-to-platelet ratio index (APRI) scores or FIB-4 for estimating hepatic fibrosis (FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)) may be reliable in prevalent regions. The positive predictive value to determine cirrhosis is low for all non-invasive metrics, including APRI, and there has been limited assessment of these tests in Africa. [5-7].

Screening

Most international guidelines recommend screening in high-risk groups. These groups include household and sexual contacts of persons with CHB, HIV-infected individuals, people who inject drugs (PWID), men who have sex with men and sex workers. Those at risk who lack immunity must be offered hepatitis B vaccination. Other groups that may be considered

for screening include: indigenous peoples, the incarcerated, and transgender persons. Screening programs have been implemented in some countries. In New Zealand all Maori Pacific Islanders and Asians over the age of 15 are tested. Many countries offer routine antenatal screening to detect HBsAg and viremia in the mother. In China, screening includes children and adolescents, before admission to kindergarten, elementary, middle school and university. Most hospitalised patients in Singapore are screened. South Korea has screening programs linked to employment and national insurance.

Blood and organ donors should also be screened for HBsAg and other blood borne pathogens in accordance with WHO recommendations. As noted by the WHO consultation on HBV, surveillance for HBV varies widely in its methods and completeness. While chronic liver disease is an important health problem in high prevalent regions, no major efforts to identify persons with progressive disease are in progress except in some industrialised countries. [4] In the United States and Europe, population-based screening is also recommended for migrants from endemic countries but is not widespread. A systematic review undertaken by the US task force concluded that screening and antiviral treatment is associated with improved intermediate outcomes, but that research was required to better define the effects of screening and interventions on clinical outcomes and to identify an optimal strategy [8]. Screening for HIV and HCV in HBsAg-positive persons is mandatory.

Treatment

Timing and the need for treatment are important. A combined assessment, staging liver disease together with longitudinal concentrations of serum ALT and HBV DNA is required. Antiviral therapy should be targeted to the active phases of CHB when the risk of disease progression is highest. Several predictive factors (age, sex, genotype, family history of HCC) and co-factors (diabetes, HIV coinfection, alcohol) that may influence disease progression have been identified. Several national and international recommendations for treatment exist. The cost of antiviral treatments for hepatitis B has been reduced and has become affordable through generic production and subsidies. Most national guidelines suggest that persons with persistently abnormal ALT with a HBV DNA or > 2000 or > 20 000 IU/mL be treated irrespective of HBeAg status. However, in many countries where HBV infection is prevalent, health care costs are not met by the state but by individuals, and the ability to treat important chronic infectious diseases will still require non governmental or insurance programs for funding to treat those on low annual incomes. Minimal requirements for toxicity monitoring of tenofovir and entecavir favor their acceptability in LMICs. Moreover, tenofovir can be safely used in special categories such as pregnant women, in coinfected HIV/HBV and in persons with tuberculosis (TB) [9-12]. Tenofovir alafenamide (TAF) is dosed at 25mg and thus the toxicities of TAF are minimized [13]. Cost savings are realized via reduced generic manufacturing costs.

An estimated 5% to 15% of the 34 million HIV-infected persons worldwide are coinfected with HBV (59–62). These rates are highest in LMICs, particularly in South-East Asia and sub-Saharan Africa, South America, and in some populations, especially PWID. HIV coinfected persons require appropriate antiretroviral therapy to include tenofovir and emtricitabine or tenofovir plus lamivudine. It is vital to forestall resistance in in HIV-HBV co-infected patients receiving lamivudine.

Monitoring

An assessment of ALT, AST (for APRI), HBsAg, HBeAg and serum HBV DNA levels (where available and affordable), NITs and adherence considerations should be obtained at least once a year [7]. More frequent monitoring is recommended in some categories including persons with a more advanced disease and in persons not yet on treatment to identify a change in clinical status, which may indicate progression to active disease requiring treatment. Renal function should be measured at baseline [14]. Renal function requires annual monitoring in persons on long-term tenofovir or entecavir therapy, and growth should be monitored in children.

Barriers to expanding therapy

Barriers to expanding therapy for hepatitis B in resource-limited settings include a limited understanding of the prevalence of the disease and its distribution, limited data on treatment efficacy in low-income countries and limited infrastructural resources to perform appropriate diagnostic and monitoring assays. As HBV DNA testing remains limited in LMICs, treatment considerations are based on persistently abnormal ALT levels alone, regardless of HBeAg status. [4] Serum concentrations of HBV DNA are quantified by real-time polymerase chain reaction (PCR). Unfortunately, HBV DNA is not routinely tested in low-income countries. [15-17] However new advances in microfluidics and miniaturisation are being made.

Scaling up treatment

Many countries face significant challenges in implementing antiviral therapy for viral hepatitis. Treatment should be considered in the context of disease prevalence. There is an imperative need to identify individuals with advancing or advanced disease, and target treatment to prevent progression to liver failure. The impact of targeting treatment to patients with cirrhosis to prevent HCC is less certain.

A key barrier to HBV treatment in resource-limited settings is no longer the cost of medicines, but more often, the costs of diagnostic and monitoring facilities, and personnel. Drug costs are low: generic tenofovir is widely available from around US$ 50 per year of treatment. Generic entecavir has been introduced. In many national programs for HBV/HIV coinfected persons, generic tenofovir is available as first-line therapy in combination with other antiretrovirals. There is a critical need to make these diagnostics and drugs available at more affordable prices in resource limited settings [18].

The cost and complexity of treatment are no longer prohibitive. Treatment with NUCs for hepatitis B is relatively simple: one pill per day, although long-term maintenance therapy is necessary for most. Drug resistance is minimal with tenofovir and entecavir. However, the resources poured into AIDS have not been invested in chronic viral hepatitis (both B and C). Both policy makers and global health organisations need to overcome the short sighted view that because of the advent of hepatitis B vaccination this is not necessary or that it is not feasible to provide treatment for chronic hepatitis in rural settings. This false premise is costing lives.

New methodologies to expand treatment are needed. Much has been learned from the treatment of AIDS in many regions of the world. These systems will require decentralization of healthcare and task shifting from highly trained specialists to teams of community-based healthcare workers. Provisions that enable access to care in areas with few physicians have made an impact on mortality from AIDS without compromising care.[19]

Prevention

Vaccination is the most effective measure to reduce the global incidence of hepatitis B. Universal hepatitis B immunization programmes for infants, recommended by WHO in 1991, with the first dose at birth, have been highly effective in reducing the incidence and the prevalence of Hepatitis B in many countries. Many countries in the world administer hepatitis B vaccine starting at birth or in early childhood. However, vaccination, while a critical and laudable prevention strategy, will not have a large impact on the rates of end-stage liver disease or HCC for decades.

Conclusion

To make progress governments must clearly accept that viral hepatitis, which can be treated, leads to high numbers of deaths annually - despite the advent of HBV vaccination and effective treatments. The cost effectiveness of a screening and test and treat strategy has been evaluated. [20]

The WHO has set priorities for achieving global goals for HBV treatment, and there have been remarkable achievements: treatment structures for HIV now need to encompass treatment of hepatitis B (and C). An important first step would be to stop mother to child transmission with the use of nucleoside analogue treatment for highly viremic mothers, but prophylaxis would require a quantitative assessment of viremia in pregnant mothers. [21]

Potential cost savings can be achieved through economies of scale, synergy with other programmes and benefits of preventing the direct and indirect burden of end stage liver disease due to viral hepatitis. There may be additional benefits to cure and long term HBsAg loss prompting research in the area. [22, 23]

References

1. Wallace MC, Preen D, Jeffrey GP, et al. The evolving epidemiology of hepatocellular carcinoma: a global perspective. Expert Rev Gastroenterol Hepatol 2015:1-15.
2. Sherman M, Kim RW, Dziura J. Risk scores for hepatocellular carcinoma in chronic hepatitis B. Hepatology 2015.
3. Ott JJ, Stevens GA, Groeger J, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212-9.
4. WHO. WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. 2015.
5. Teshale E, Lu M, Rupp LB, et al. APRI and FIB-4 are good predictors of the stage of liver fibrosis in chronic hepatitis B: the Chronic Hepatitis Cohort Study (CHeCS). J Viral Hepat 2014;21:917-20.
6. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis

in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015;61:292-302.
7. Organization WH. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. 2015.
8. Chou R, Dana T, Bougatsos C, et al. Screening for hepatitis B virus infection in adolescents and adults: a systematic review to update the US Preventive Services Task Force recommendation. Annals of internal medicine 2014;161:31-45.
9. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. Gastroenterology. 2010;139:1934-1941.
10. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015.
11. Greenup AJ, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. J.Hepatol. 2014;61:502-507.
12. Rockstroh JK, Hardy WD. Antiretroviral therapy in coinfected patients: viral hepatitis and tuberculosis. Curr Opin HIV AIDS 2006;1:442-8.
13. Wyatt C, Baeten JM. Tenofovir alafenamide for HIV infection: is less more? The Lancet 2015.
14. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat 2011;2011:354908.
15. McMahon BJ. Chronic hepatitis B virus infection. Med Clin North Am 2014;98:39-54.
16. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012;142:1293-1302 e4.
17. Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. Alexandria, Virginia, 2009.
18. Afdhal NH, Bacon BR, Patel K, et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clin Gastroenterol Hepatol 2015;13:772-9 e1-3.
19. Farmer PE. Shattuck Lecture. Chronic infectious disease and the future of health care delivery. N Engl J Med 2013;369:2424-36.
20. Nayagam S, Conteh L, Sicuri E, et al. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. Lancet Glob Health 2016;4:e568-78.
21. Dusheiko G. Interruption of mother-to-infant transmission of hepatitis B: time to include selective antiviral prophylaxis? Lancet 2012;379:2019-21.
22. Yip TC, Wong GL, Chan HL, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. J Hepatol 2018.
23. Dusheiko G, Wang B, Carey I. HBsAg loss in chronic hepatitis B: pointers to the benefits of curative therapy. Hepatol Int 2016;10:727-9.

Long-term safety and efficacy of nucleos(t)ide analogues

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Key points

- Nucleos(t)ide analogues (NUCs) are the most common treatment of chronic hepatitis B (CHB).
- Current EASL guidelines recommend the most potent drugs with optimal resistance profiles. Entecavir (ETV), and tenofovir disoprovil disiproxil fumarate (TDF) or tenofovir alafenamide (TAF) are used as first-line monotherapies in CHB.
- ETV, TDF and TAF have been shown to have excellent safety profiles and are well tolerated by most patients including those with advanced and decompensated cirrhosis.
- TAF has a better renal and bone safety profile than TDF.
- Long-term studies have also shown that TEV or TDF have a beneficial effect on liver disease, including the regression of fibrosis and cirrhosis, and results in improved liver status in patients with hepatic decompensation.

Chronic hepatitis B virus (HBV) infection is a serious global health problem and one of the main causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma. An estimated 250 to 350 million individuals are positive to the hepatitis B surface antigen (HBsAg) for a worldwide prevalence of 3.6%, with marked geographic variabilities [1, 2].

Nucleos(t)ide analogues (NUCs) are the most common treatment of chronic hepatitis B (CHB). Current EASL guidelines recommend the most potent drugs with optimal resistance profiles. (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are used as first-line monotherapies in CHB (2). All NUCs must be administered for a long period to achieve durable viral suppression. These drugs have an excellent efficacy profile for suppressing viral replication, but slightly different safety profiles.

This review provides an overview of the long-term efficacy and safety data that have become available in the 10 years since ETV and TDF were first approved for the treatment of chronic hepatitis. New data on TAF, in particular in patients with CHB who switch from TDF to TAF, will also be presented.

Safety

ETV and TDF have been used for more than 10 years in the treatment of CHB, and are now generic drugs, while TAF was approved for this indication in 2016 and in some countries reimbursement is still pending. ETV and TDF have been shown to have excellent safety profiles and to be well tolerated by most patients including those with advanced and decompensated cirrhosis. ETV is a nucleoside analogue, and TDF and TAF are nucleotide analogues. All of these treatments are taken once a day at a fixed oral dose [2]. ETV and TDF being excreted mainly or fully by the kidneys, dose adjustment is required in patients with an estimated

glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2. However, dose adjustments are not required for TAF in patients ≥ 65 years old, with hepatic impairment, with renal impairment and eGFR ≥ 15 mL/min, or in patients receiving hemodialysis and with eGFR <15 mL/min. Data on the use of ETV in patients with eGFR < 30 mL/min/1.73 m^2 and those on dialysis are scarce. Dosing recommendations cannot be made for TAF in patients with eGFR < 15 mL/min who are not receiving hemodialysis.

Renal safety is an important factor when choosing appropriate NUCs for CHB because these drugs are eliminated by the kidneys unchanged, which is particularly important in patients who already have, or are at risk of, renal impairment [2]. The safety and efficacy of TAF has not yet been established in patients with HBV and decompensated liver disease, a Child Pugh Turcotte (CPT) score > 9 (CPT Class C), or in children younger than 12 years of age. There are ongoing studies in these populations.

The safety profile of ETV was evaluated in registration studies in 1051 patients with a median exposure to the drug of 3.5 years [3][12]. Fourteen (1%) patients discontinued the studies due to adverse events (AEs). Other AEs were rare, with the most common being myalgia (5%) and neuropathy-related AEs (4%). These data suggest that long-term administration of ETV is associated with low rates of serious AEs, discontinuations due to AEs, and ALT flares.

TDF was evaluated in a study including 641 patients treated for 8 to 10 years. Results showed that the drug was well tolerated with few discontinuations related to AEs, none related to the study medication (3%), and no new safety signals identified after 10 years. TDF was associated with worsening kidney function in 10 cases of renal impairment and in one case Fanconi syndrome was reported. Changes in bone mineral density were measured between years 4 and 8 of the study in 346 patients treated with TDF, and no clinically relevant bone loss was observed during this period [4].

In a meta-analysis of 11 studies comparing ETV and TDF in 1300 patients, no statistically significant differences were found for renal safety or hypophosphatemia between the two treatments over approximately 18 months of treatment [5]. TAF is being evaluated in 2 ongoing randomized, double-blind, phase 3 studies including 426 HBeAg(-) and 875 HBeAg(+) patients with CHB. Patients given TAF in both the HBeAg(+) and HBeAg (-)) cohorts had a significantly smaller decrease in bone mineral density in the hip and spine, as well as smaller mean increases in serum creatinine at weeks 48 and 98, showing that TAF has a better bone and renal safety profile. The most common adverse events overall were upper respiratory tract infections, with no differences between TAF and TDF. The most common grade 3 or 4 laboratory abnormalities were ALT elevations with 11% and 13% of patients receiving TAF and TDF, respectively [6-8].

At week 96, 540 patients were switched to open-label TAF including 284 (53%) with ≥ 1 TDF risk factor (RF) and 123 (23%) patients with ≥ 2 risk factors. At week 144, TDF patients who switched to TAF showed improvements in renal parameters with a greater percentage of patients showing improvement than worsening of chronic kidney disease stage. Improvements in hip and spine bone mineral density were found 1 year after switching [9].

Longer follow-up is needed to improve our understanding of the clinical impact of switching and to draft clinical recommendations. In the meantime, EASL guidelines recommend TAF rather than TDF in selected patients such as subjects > 60 years old, those with bone disease or at risk of bone problems (e.g. patients chronically receiving steroids or

other medications that worsen bone density), with a history of fragility fractures or osteoporosis, patients with abnormal renal function, defined as eGFR < 60 mL/min/1.73m, albuminuria, or low phosphate, and individuals on hemodialysis (2).

Efficacy

Current practice guidelines stress the importance of profound and durable suppression of HBV replication in CHB therapy [2]. Long-term studies have also shown that ETV and TDF have a beneficial effect on liver disease, including the regression of fibrosis and cirrhosis, and improve liver status in patients with hepatic decompensation [2]. Continued treatment for up to 10 years resulted in 96% to 98% of patients achieving undetectable serum HBV DNA (on-treatment analysis included some patients who added emtricitabine after week 72).

The resistance rates to ETV were very low in treatment naïve patients, even during long-term therapy. Resistance to ETV requires the accumulation of at least 3 mutations in the viral polymerase [2]. After 6 years of ETV treatment, only 1.2% of patients showed evidence of drug resistance [2]. No resistance has been observed with tenofovir after 10 years of therapy and no clear pattern of resistance-associated mutations has been identified in clinical trials or real-life studies. In addition, tenofovir has been shown to be active in patients who failed previous NUC therapies [2-4]. Rescue therapy with tenofovir has been found to be effective in patients with multidrug-resistant HBV, and also in those with a partial response to previous antiviral therapies [11].

The efficacy of TAF is being evaluated in 2 ongoing phase-3 studies in HBeAg(-) and HBeAg(+) CHB patients [6-8]. In the HBeAg(-)study, 426 patients were randomly assigned (2:1) to receive once-daily oral doses of TAF 25 mg (N=285) or TDF 300 mg (N=141) [15]. At week 48, HBV DNA < 29 IU/mL was achieved in 94% of patients in the TAF group and 93% in the TDF group (1.8%, 95% CI: -3.6% to 7.2%). A consistently higher percentage of patients achieved ALT normalization by central laboratory criteria within 48 weeks with TAF than with TDF (83.1% vs 75.2%, respectively, p=0.076). The percentage of patients with normalized ALT at week 48 was also higher in the TAF group (49.6%) using the most restrictive criteria (ULN ≤30 U/L for males and ≤19 U/L for females [6]), than in those receiving TDF (31.9%) (p<0.001). None of the patients in either treatment group experienced HBsAg loss by week 48.

In the HBeAg(+) study, 873 patients were randomly assigned (2:1) to receive either 25 mg TAF (N=581) or 300 mg TDF (N=292) [16]. At week 48 HBV DNA < 29 IU/mL was achieved in 371 (64%) patients receiving TAF and 195 (67%) receiving TDF, showing non-inferiority between the two treatments. Like in the HBeAg(-) study, a higher percentage of patients achieved ALT normalization at week 48 in the TAF group than in the TDF group according to central laboratory criteria (71.5% vs 66.8%; p=0.18) and AASLD criteria (ULN ≤ 30 U/L for men and ≤ 19 U/L for women: TAF 44.9%, TDF 36.2%; p=0.014) [6]. Seventy-eight (14%) and 34 (12%) patients in the TAF and TDF groups, respectively, experienced HBeAg loss, and 58 (10.3%) and 23 (8.1%) patients experienced seroconversion to anti-HBe at week 48. Only 4 patients (0.7%) in the TAF group and 1 (0.3%) in the TDF group experienced HBsAg loss. At week 96, the differences in the rates of viral suppression were similar in HBeAg-positive patients receiving TAF and TDF (73% vs. 75%, respectively, adjusted difference -2.2% (95% CI -8.3 to 3.9%; p ≤ 0.47), and in HBeAg-negative patients receiving TAF and TDF (90% vs. 91%, respectively, adjusted difference -0.6% (95% CI -7.0

to 5.8%; $p \leq 0.84$). In both studies the proportions of patients with alanine aminotransferase above the upper limit of normal at baseline, who had normal alanine aminotransferase at week 96 of treatment, were significantly higher in patients receiving TAF than in those receiving TDF (8)

No HBV pol/RT amino acid substitutions associated with resistance to tenofovir were detected in either treatment group after 96 weeks [8]. The study is ongoing and the virological response rates have been maintained at week 96.

Conclusion

In summary, in CHB patients, complete eradication of the virus is difficult, and long term treatment is often required. Entecavir, TDF and TAF are the most potent currently available NUCs for the treatment of CHB and are recommended as first-line monotherapy. ETV and TDF have been shown to have long-term efficacy and safety for up to 10 years in clinical studies, while TAF was recently approved for the treatment of HBV. Clinical studies have shown that prolonged suppression of HBV DNA with NUCs can stabilize the disease and lead to significant regression of fibrosis.

References

1) Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet (London, England) 2015; 386:1546-55
2) EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of hepatology 2017; 67:370-98.
3) Manns MP, Akarca US, Chang TT, et al. Long-term safety and tolerability of entecavir in patients with chronic hepatitis B in the rollover study ETV-901. Expert opinion on drug safety 2012; 11:361-8
4) Marcellin P, Gane EJ, Flisiak R, et al. Long Term Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Infection is Safe and Well Tolerated and Associated with Durable Virologic Response with no Detectable Resistance: 8 Year Results from Two Phase 3 Trials. Hepatology (Baltimore, Md) 2014; 60:313A-7A.
5) Zuo SR, Zuo XC, Wang CJ, et al. A meta-analysis comparing the efficacy of entecavir and tenofovir for the treatment of chronic hepatitis B infection. Journal of clinical pharmacology 2015; 55:288-97.
6) Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. The lancet Gastroenterology & hepatology 2016; 1:196-206.
7) Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. The lancet Gastroenterology & hepatology 2016; 1:185-95.

8) Agarwal K, Brunetto M, Seto WK et al 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection.J Hepatol. 2018 Apr;68(4):672-681.
9) Gane E Seto WK, Janseen H et al , Safety and efficacy at 1 year after switching from Tenofovir Disoproxil Fumurate to Tenofovir Alafenamide in chronic HBV patients with risk factors for TDF use EASL 2018 PS -156
10) Lim L, Thompson A, Patterson S, et al. Five-year efficacy and safety of tenofovir-based salvage therapy for patients with chronic hepatitis B who previously failed LAM/ADV therapy. Liver international : official journal of the International Association for the Study of the Liver 2017; 37:827-35.
11) Lim YS, Lee YS, Gwak GY, et al. Monotherapy with tenofovir disoproxil fumarate for multiple drug-resistant chronic hepatitis B: 3-year trial. Hepatology (Baltimore, Md) 2017; 66:772-83.
12) Marcellin P, Gane E, Buti, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study.Lancet. 2013 Feb 9;381(9865):468-75. doi: 10.1016/S0140-6736(12)61425-1.

HBV: The importance of NUCs-Peg IFN combination

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Key points

- Due to different mechanisms of action, the combination of pegylated-interferon (Peg-IFN) and nucleot(s)ide analogues (NUCs) may be an attractive approach to enhance the off-treatment rates of virological and serological response in chronic hepatitis B (CHB).
- The two drugs may be combined in different ways. A "de-novo combination" (the simultaneous initiation of Peg-IFN and NUCs) may be used in treatment-naïve patients. In patients with long-term effective virological remission with NUCs, Peg-IFN can be used in an "add-on" or "switch to" strategy.
- In a randomized clinical study, the "de-novo combination" of TDF and Peg-IFN accelerated HBsAg decline and increased HBsAg clearance rates.
- Promising results were achieved in patients with viral suppression receiving long-term NUCs. "Add-on" Peg-IFN in HBeAg-negative and "switch to" Peg-IFN in HBeAg-positive patients significantly accelerated the decline in HBsAg with a few patients clearing HBsAg.
- These strategies are not recommended in current clinical practice guidelines because of unproven long-term superior efficacy and should be carefully applied in each individual patient taking into consideration all the potential advantages and disadvantages.

The first-line drugs recommended in treatment-naïve patients with hepatitis B virus (HBV) infection are pegylated-interferon (Peg-IFN) and third generation nucleot(s)ide analogues (NUCs) such as entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Short-term treatment with Peg-IFN results in a sustained immune control of infection in nearly 30% of the patients leading to HBsAg seroclearance in approximately one third of responders. However, the widespread application of this strategy is limited by poor tolerability, side-effects profile and low effectiveness.

On the other hand, NUCs therapy results in virological suppression in almost all treated patients but there are low rates of HBsAg seroclearance. This results in the need for lifelong administration, with the hypothetical limitations of cost, resistance and safety. The above-mentioned limitations led researchers to develop new treatment strategies combining NUCs and Peg-IFN, to boost off-treatment virological and serological response, based on the assumption that the direct antiviral activity of NUCs could improve the immunomodulatory action of Peg-IFN and vice versa. Peg-IFN and NUCs can be combined in different ways: as a "de-novo combination" with the simultaneous initiation of both drugs in naïve patients, or as an "add-on" or "switch to" strategy in patients under long-term NUCs effective virological response Peg-IFN.

De novo Peg-IFN+NUCs combination

Studies in HBeAg-positive and -negative patients testing the combination of Peg-IFN with first or second generation NUCs did not confirm that the combination regimen was more effective than Peg-IFN monotherapy for virological and serological response (1). The combination of third generation NUCs, i.e. TDF, and PEG-IFN has been recently tested in a multicenter study including 740 treatment-naïve patients (58% HBeAg-positive, 75% Asians, 21% genotype D) who were randomized to receive a 48-week course of Peg-IFN+TDF (A), TDF+Peg-IFN for 16 weeks followed by TDF for 32 weeks (B), TDF alone (C) or 48 weeks of Peg-IFN alone (D) (2). Significantly higher rates of HBsAg loss at 72 weeks post-treatment were found with a 48-week course of Peg-IFN+TDF compared to monotherapy with either of these treatments. Secondary analysis showed that the only baseline factor associated with a response to therapy was genotype A. A decline in HBsAg at week 12 or 24 of treatment was associated with HBsAg loss at week 72, while a decrease in HBsAg >3.5 $\log_{10}$ IU/mL at week 24 identified HBsAg loss at week 72 in patients who completed a 48-week course of Peg-IFN+TDF (PPV=85% and NPV=99%) (3). Follow-up data at week 120 confirm the increased rate of HBsAg loss in patients treated with Peg-IFN+TDF compared to those receiving either monotherapy (10.4% vs 3.5% in group B and D vs 0% in group C) (4).

Add-on Peg-IFN in HBeAg positive CHB

A Chinese retrospective study was performed in 192 HBeAg-positive patients treated for at least two years with NUCs without achieving HBeAg loss or seroconversion. The results showed a higher rate of complete response (HBeAg loss with HBV DNA <2000 IU/mL: 60 vs 14%) and HBsAg loss (28 vs 0%) in those treated with a 48-week combination of Peg-IFN and the ongoing NUCs (n=83) than NUCs monotherapy (n=109) (5). In another study, 74 HBeAg-positive patients treated for 2.4 years with ETV or TDF with serum HBV DNA <2000 IU/mL were randomized to a 48-week add-on course of Peg-IFNα2b (n=36) or to continue NUCs monotherapy (n=38). HBeAg seroconversion with or without HBV DNA <200 IU/mL at week 48 was achieved in 17% of patients in the combination group compared to 5% of those treated with NUCs monotherapy (p=0.15). The add-on strategy resulted in a significantly greater HBsAg decline (0.59 vs 0.29 $\log_{10}$ IU/mL, p=0.021) and higher rates of HBsAg decline >1 $\log_{10}$ IU/mL (19% vs 0%, p=0.005) (6).

Add-on Peg-IFN in HBeAg negative CHB

Two recent European studies prospectively investigated the "add-on" Peg-IFN strategy in HBeAg-negative patients with HBV replication that was fully suppressed by long-term NUCs treatment.

An Italian open-label study of Peg-IFN alfa-2a 180 μg/week added to ongoing NUCs was performed in 70 HBeAg-negative genotype D-infected patients with HBV DNA <20 IU/mL. The results showed a ≥50% decline in serum HBsAg in 67% (29/43) at week 48 and 51% (28/55) of the patients at week 96 (7). Median serum HBsAg decreased throughout Peg-IFN treatment and was significantly lower than baseline at weeks 48, 72 and 96 (p<0.001). In a French randomised, controlled, open-label trial, 185 patients were randomized to receive a 48 week course of Peg-IFNalfa-2a 180 μg/ week in addition to NUCs or to continue to receive NUCs alone (8). At week 96, loss of HBsAg was reported in 7 (8%) out of 90 patients in the Peg-IFN+NUCs group vs 3 (3%) out of 93 in the NUCs-alone group. Overall, addition of a 48

week course of Peg-IFN to NUCs was poorly tolerated and did not result in a significant increase in HBsAg clearance.

Switch to Peg-IFN

This strategy was explored in 192 Chinese HBeAg-positive patients in the OSST trial (9). After 20 months (range 9-36) of ETV, patients with HBV DNA ≤1000 copies/ml and HBeAg levels <100 PEIU/mL were randomized 1:1 to either continue ETV or "switch to" Peg-IFNα2a 180 mg/week for 48 weeks. By week 48, while the proportion of patients with HBV DNA <1000 copies/mL and with normal ALT levels were significantly higher in the ETV group (98% vs 72%, p<0.0001 and 91% vs 58%, p<0.0001, respectively), serological response rates were significantly better in the Peg-IFN group (HBeAg seroconversion: 15% vs 6%, HBsAg loss: 8% vs 0% and HBsAg<10 IU/mL: 16% vs 0%). However, 40% of patients had viral rebound or virological breakthroughs and 8% required drug discontinuation due to adverse events. In patients who achieved HBsAg levels <200 IU/mL at week 12 of Peg-IFNα2a, 78% cleared HBsAg loss and 67% seroconverted to anti-HBe at week 48. One year after the end of therapy (EOT), virological and serological responses were sustained in most patients who switched from ETV to Peg-IFNα-2a: 73% had HBV DNA <1000 copies/mL; 64% and 60% had HBeAg loss and HBeAg seroconversion, respectively. Moreover, 86% of patients with HBsAg loss at EOT maintained this endpoint in the 48 weeks after EOT (10).

Recently, a Chinese randomized, multicenter, open-label study investigated the efficacy and safety of switching from NUCs to Peg-IFNα-2a in HBeAg-positive patients with a partial response, defined as HBV DNA <200 IU/mL and HBeAg loss after 1-3 years of NUCs therapy (11). Three-hundred patients were randomized 1:1 to Peg-IFN treatment for either 48 or 96 weeks (NUCs therapy was continued for the first 12 weeks) and followed-up for an additional 48 weeks after IFN discontinuation. Seventeen percent of the 271 patients who had completed the 48 weeks of treatment achieved HBsAg loss. HBsAg seroclearance was more frequently observed in patients with baseline HBsAg <1500 IU/mL than in those with HBsAg ≥1500 IU/mL (33% vs 4%, p<0.0001) as well as in those with HBsAg levels <200 IU/mL at week 24 than in those with HBsAg ≥200 IU/mL (48% vs 1%, p<0.0001). By combining baseline and week 24 HBsAg levels, the study suggests that only patients with baseline HBsAg <1500 IU/mL (n=124) should switch to Peg IFN and that Peg-IFN should only be continued for an additional 24 weeks (total 48 weeks) in the subset of patients (n=78) with HBsAg <200 IU/mL at week 24 of Peg-IFN. The positive predictive value (PPV) for HBsAg loss in this subset of patients is 51% while the negative predictive value (NPV) for the other groups is >95%.

Conclusions

The combination of NUCs and Peg-IFN either as a "de novo", "add-on" or "switch to" strategy has been attempted on the assumption that the direct antiviral action of NUCs could improve the immunomodulatory action of Peg-IFN leading to higher response rates and vice versa. The "de novo" or "add on" or "switch to" Peg-IFN with the effective NUCs treatment fosters HBsAg decline and increases The HBsAg loss rate. However, this approach is not currently recommended in clinical practice because the superior long-term efficacy has not been confirmed. This strategy should be carefully assessed in each individual patient taking into consideration all potential advantages and disadvantages. Studies of Peg-IFN and NUCs combinations are still ongoing in the large cohort of patients with a scheduled long-term follow-

up. This combination may be a future option to be considered when more robust data provides definitive evidence of efficacy and clinical benefits.

References

1. Viganò M, Invernizzi F, Grossi G, Lampertico P. Review article: the potential of interferon and nucleos(t)ide analogue combination therapy in chronic hepatitis B infection. Aliment Pharmacol Ther. 2016;44:653-61.
2. Marcellin P, Ahn SH, Ma X, et al. Combination of tenofovirdisoproxil fumarate and Peginterferonα-2a increases loss of hepatitis B surface antigen in patients with chronic hepatitis B. Gastroenterology 2016;150:134-44.
3. Marcellin P, Ahn SH, Chuang WL, et al. Predictors of response to tenofovir disoproxil fumarate plus peginterferon alfa-2a combination therapy for chronic hepatitis. Aliment Pharmacol Ther 2016;44:957-966
4. Ahn SH, Marcellin P, Ma X, et al. Hepatitis B surface antigen loss with Tenofovir Disoproxil Fumarate plus Peginterferon Alfa-2a: Week 120 Analysis. Dig Dis Sci. 2018 Aug 22. doi: 10.1007/s10620-018-5251-9. [Epub ahead of print]
5. Li G, Y.Yu, S. Chen, P. Fan, W. Zhang. Sequential combination therapy with NUC and Peg-IFN in HBeAg-positive CHB patients with prior long-term exposure to NUC. Antimicrob Agents Chemother 2015;59:4121-8.
6. Chi H, Hansen BE, Guo S, et al. Pegylated interferon Alfa-2b add-on treatment in hepatitis B virus envelope antigen-positive chronic hepatitis B patients treated with nucleos(t)ide analogue: a randomized controlled trial (PEGON). J Infect Dis 2017;215:1085-1093.
7. Lampertico P, Brunetto MR, Craxì A, et al. Add-on peginterferon alfa-2a to nucleos(t)ide analogue therapy for caucasian patients with hepatitis B 'e' antigen-negative chronic hepatitis B genotype D. J Viral Hepat 2018 Sep 5. doi: 10.1111/jvh.12999. [Epub ahead of print]
8. Bourlière M, Rabiega P, Ganne-Carrie N, et al. Effect on HBs antigen clearance of addition of pegylated interferon alfa-2a to nucleos(t)ide analogue therapy versus nucleos(t)ide analogue therapy alone in patients with HBe antigen-negative chronic hepatitis B and sustained undetectable plasma hepatitis B virus DNA: a randomised, controlled, open-label trial. Lancet Gastroenterol Hepatol 2017;2:177-188.
9. Ning Q, Han M, Sun Y, et al. Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: a randomised open-label trial (OSST trial). J Hepatol 2014;61:777-84.
10. Han M, Jiang J, Hou J, et al. Sustained immune control in HBeAg-positive patients who switched from entecavir therapy to pegylated interferon-α2a: 1 year follow-up of the OSST study. Antivir Ther 2016;21:337-44.
11. Hu P, Shang J, Zhang W, et al. HBsAg loss with Peg-interferon Alfa-2a in hepatitis B patients with partial response to nucleos(t)ide analog: New Switch Study. J Clin Transl Hepatol 2018;6:25-34.

HBV: to stop or not to stop NUCs

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Key points

- HBV chronic infected patients on nucleos(t)ide analogues NUCs only rarely achieve HBsAg loss.
- Attempts to discontinue NUCs have been made.
- Virological relapse is frequent after treatment discontinuation.
- A recent prospective randomized study demonstrated that unexpected side effects are not associated with NUCs discontinuation in non cirrhotic HBeAg-negative patients.

Nucleos(t)ide analogues (NUCs) therapy provides effective control of HBV replication in chronic HBV infected patients. Three first line regimens are currently recommended in EASL guidelines for the treatment of HBV chronic infection: tenofovir disoproxil fumarate (TDF), entecavir (ETV) and tenofovir alafenamide (TAF).

NUCs cannot eradicate the virus from the liver and only rarely achieve HBsAg (HBsAg) loss, considered the optimal treatment endpoint in all current guidelines. NUCs regimens are associated with slow HBsAg decline during therapy and require life-long administration in most chronic HBV infected patients. It has been calculated that one to several decades of NUCs therapy are required to achieve HBsAg clearance.

Although NUCs have an excellent safety profile, the need for long-term therapy may raise safety issues in the elderly, in patients with co-morbidities and in young patients who plan to have a family. For these reasons and in addition to monetary costs and poor adherence over time, many attempts have been made to discontinue NUCs treatment in the last few years. However, virological relapse after treatment discontinuation is frequent and whether NUCs treatment can safely be stopped before HBsAg loss remains the subject of debate.

Effects of stopping NUCs

The virological effects of stopping long-term NUCs therapy for hepatitis B e-antigen negative (HBe-negative) patients were investigated in a landmark study on NUCs treatment/discontinuation. It was performed in 33 patients in Greece receiving adefovir dipivoxil treatment. This study showed that the discontinuation of long term ADV therapy in HBeAg-negative patients, after 4 or 5 years, is safe and effective as it is associated with HBV immune-mediated elimination. Persistently undetectable or <2000 IU/ml HBV DNA levels combined with persistently normal ALT values 6 months post treatment were achieved in 55% of patients and HBsAg loss in 39%. FINITE, a prospective randomized controlled study was recently completed in Germany. The study evaluated the potential of finite tenofovir disoproxil fumarate therapy in HBeAg negative patients with chronic HBV hepatitis. Sixty-two percent of the patients who stopped TDF remained off-therapy to week 144. HBsAg loss or HBV DNA

<2000 UI/ml was observed in 43% of them. Four patients (19%) achieved HBsAg loss and three of them achieved HBsAg seroconversion. None of the patients experienced unexpected safety issues. These results support treatment discontinuation under strict surveillance in long-term HBV suppressed HBeAg negative patients.

Some more recent studies from Europe and Asia were performed to assess the risk of relapse and the decision and timing of re-treatment.

The risk of relapse

After NUCs discontinuation, HBV DNA can rapidly return with subsequent ALT flares, although a fraction of patients experience a functional cure. However, hepatic decompensation may be observed after discontinuation in patients with cirrhosis. Based on this evidence, a correct evaluation of the risks related to HBV treatment discontinuation is required to avoid liver failure associated with a severe biochemical relapse in patients with advanced liver disease.

EASL guidelines recommend discontinuing NUCs after confirmed HBsAg loss with or without the development of anti-HBsAg antibodies and suggest only discontinuing treatment in non-cirrhotic HBeAg-positive patients with chronic hepatitis after stable seroconversion from HBeAg to HBeAb and undetectable HBV DNA after 12 months of consolidation therapy. In addition, EASL suggests discontinuing treatment in HBeAg-negative patients without cirrhosis after at least three years of undetectable HBV DNA on-therapy. Close monitoring is warranted in patients who discontinue treatment.

On the other hand, in the Asian-Pacific region, where cost restrictions play a role in treatment discontinuation, NUCs treatment can be discontinued after at least 2 years in HBeAg-negative chronic HBV patients with undetectable serum HBV DNA on three occasions 6 months apart.

Relapses are observed in most HBeAg-negative chronic hepatitis B patients who discontinue treatment with NUCs. In patients with a significant increase in ALT, re-starting treatment should be considered. Although the relapse rate can vary across studies, most patients require re-treatment. After discontinuation, close follow-up of ALT and HBV DNA determinations are mandatory. Thus far, the identification of predictors of relapse remains difficult. The development of new biomarkers such as HBV RNA and HBcrAg may help clarify this issue.

Conclusions

In conclusion, there is now a body of evidence that has investigated when NUCs discontinuation is feasible and in which patients with chronic HBV infection and when to re-start treatment in those who experience a relapse after NUCs discontinuation.

References

1) Lampertico P, Maini M, Papatheodoridis G. optimal management of hepatitis B virus infection. EASL Special conference. J Hepatol 2015;63:1238-1253
2) Hadziyannis S, Sevastianos V, Rapti I et al Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop Long-term treatment with adefovir. Gastroenterology 2012;143:629-636
3) Berg T, Simon K-G, Mauss S, Schott E et al Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients FINITE study. J Hepatol 2017; 67:918-924
4) C.-H. Chen, Y.-C. Hsu, S.-N. Lu, C.-H. Hung, J.-H. Wang, C.-M. Lee and T.-H. Hu, The incidence and predictors of HBV relapse after cessation of tenofovir therapy in chronic hepatitis B patients, Journal of Viral Hepatitis, 2018; 25, 590-597.
5) Papatheodoridis G, Manolakopoulos S, Su T-H, Liu C-J et al Significance of definitions of relapse after discontinuation of oral antivirals in HBeAg-negative chronic hepatitis B. Hepatology 2018; 68: 415-424
6) Jeng W-J, Chen Yi-Cheng, Chien R-N et al Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen negative chronic hepatitis B. Hepatology 2018;68:425-434
7) Pietro Lampertico and Thomas Berg, Less can be more: A finite treatment approach for HBeAg-negative chronic hepatitis B, Hepatology, 2018; 68,397-400.
8) Flisiak R, Jaroszewicz J, Łucejko M, siRNA drug development against hepatitis B virus infection, Expert Opin Biol Ther, 2018;18:1-9.

When and how to use quantitative HBsAg

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Key points

- HBsAg is a direct viral product and serum levels are influenced by HBV genotypes. However, HBsAg can be a result of the transcription of HBV-DNA sequences integrated in the host's genome.
- HBsAg serum levels vary during the different phases of chronic HBV infection.
- The lowest levels are present in HBeAg negative infection.
- During antiviral therapy, HBsAg decreases faster in patients who respond to Peg-IFN therapy or Peg-IFN+ nucleos(t)ide analogues, (NUCs)] and slower in patients treated with NUCs.
- Combined quantitative serum HBsAg and viral load more accurately characterize the phase of HBV infection and the response to antiviral therapy in the single HBV carrier.

The clinical evidence that serum HBsAg loss is the virological event associated with significant improvement in clinical outcome and the availability of automated and standardized assays has prompted studies in the last 10 years to investigate the quantitative measurement of Hepatitis B surface antigen (qtHBsAg) as a potential new diagnostic tool for the management of HBV infected individuals [1]. HBsAg serum levels were shown to vary during the different phases of chronic HBV infection, with the lowest levels observed in carriers of HBeAg negative infection [2-3]. Furthermore, a progressive decrease in serum HBsAg levels was associated with effective Peg-Interferon (Peg-IFN) therapy and qtHBsAg was proposed as a potential marker to tailor therapy [4-5].

Factors influencing HBs Ag levels

However, for the appropriate use and correct interpretation of qtHBsAg all the potential factors influencing HBsAg serum levels, which may be considered a surrogate marker of virus/host interplay, must be taken into consideration. HBsAg is a direct viral product, therefore constitutive viral features may influence its production and secretion. Both *in vitro* and *in vivo* studies show that HBV genotypes influence HBsAg levels, the highest values are present in genotype A infected individuals [4,6] and HBsAg kinetics during Peg-IFN differ among genotypes [7]. Viral heterogeneity in the S gene (particularly in Pre-S1 and Pre-S2 domains) may affect HBsAg serum levels by modulating its secretion. Several reports suggest that a mutated S gene quasispecies is associated with low HBsAg serum levels, independently of the

phase of HBV infection [1]. On the other hand, recent studies show that HBsAg serum levels, particularly in HBeAg negative patients, may be a result, not only of the transcription of the specific mRNA originating from cccDNA, but also from the transcription of HBV-DNA sequences integrated in the host genome [1].

During the HBeAg positive phase of chronic infection, HBsAg serum levels are higher than in HBeAg negative chronic hepatitis B (4.5-5 vs 3.7-4.3 $\log_{10}$IU/ml). Lower HBsAg serum levels are associated with more advanced fibrosis, possibly because of the long lasting immune-elimination attempt that causes chronic necro-inflammation triggering fibrogenesis [1]. Spontaneous HBeAg seroconversion, which cannot be predicted by HBsAg serum levels, is usually followed by a very slow HBsAg decline. Therefore, soon after HBeAg seroconversion, HBsAg serum levels cannot be used to identify patients with transition to HBeAg negative infection from those with progression to HBeAg negative CHB [1]. On the other hand, in cohorts of HBeAg negative carriers, median HBsAg serum levels have been found to be significantly lower in HBeAg negative carriers without virus-induced liver disease than in those with HBeAg negative CHB. Moreover, the simultaneous presence of HBsAg <1,000IU/mL and HBV DNA ≤2,000IU/mL was associated with the identification of HBeAg negative carriers with a diagnostic accuracy ranging from 78% to 94.3% [1,8]. Therefore, the combined quantification of both serum HBsAg and HBV-DNA has been considered a useful approach in identifying carriers of HBeAg negative infection at a single point observation.

However, 10 to 30% of HBeAg negative infection carriers may have HBsAg serum levels above 1000 IU/ml and an accurate identification can require one year of follow-up with repeated HBV-DNA measurements. These carriers are usually under the age of 40 and infected with HBV genotypes other than B, C and D [9]. On the other hand, HBsAg serum levels were frequently reported to be lower (eventually <3 $\log_{10}$ IU/ml) in patients with cirrhosis than in those with chronic hepatitis. However, in these patients, viral load is usually >2000 IU/ml [8]. Therefore, in the HBeAg negative phase of HBV infection quantitative measurement of HBsAg optimizes the accuracy of characterization of low viremic carriers.

HBsAg during antiviral therapy

During antiviral therapy HBsAg serum kinetics appear to be significantly different depending on the type of drug [Peg-IFN or nucleos(t)ide analogues, (NUCs)] used and the response to treatment. In Peg-IFN treated patients, HBsAg serum levels decrease during the first 3-6 months of therapy differentiating responders from non responders [4-5,10]. On the other hand, in most NUCs treated patients HBsAg serum levels show a much slower decrease despite effective viremia suppression [1]. This can be explained by the different mechanisms of action of the 2 therapeutic strategies. Peg-IFN inhibits cccDNA activity directly, reducing the transcription of both HBV pre-genome and HBsAg mRNAs. In addition, by modulating the immune response, Peg-IFN may foster more effective immune control of HBV infection. NUCs do not act on cccDNA directly, but they inhibit viral polymerase, blocking the production of infective virions.

The HBsAg decline observed in NUCs treated patients can be explained by a combination of several mechanisms: reduction of circulating infective virions; progressive decline in infected hepatocyte burden (due to the reduction of new infections) and progressive effective immune-control of HBV infection (responsible for reduction of transcriptional active cccDNA).

These mechanisms may prevail differently in the early and late phases of NUCs treatment and their relevance may vary in the HBeAg positive and negative phase. At present, qtHBsAg monitoring is used for the early identification of non responders to Peg-IFN. In HBeAg positive patients, the probability of a response is minimal (Negative Predictive Value, NPV, 98%) when HBsAg serum levels are >20000 IU/ml at week 24, independently of HBV genotype. An earlier prediction (week 12) is HBV genotype-dependent because a lack of HBsAg decline in genotypes A (NPV 88%) or D (NPV 98%) infected individuals and HBsAg serum levels >20000 IU/ml in genotypes B (NPV 92%) or C (NPV 99%) [1,10].

In HBeAg negative CHB patients, the prediction of a non response to therapy requires the combination of both HBV-DNA (<2 $\log_{10}$ decline at week 12) and HBsAg (no decline). This algorithm was developed and validated in 2 different cohorts of 258 patients, most of whom (172 (66.6%)) were infected with genotype D. The NPV in the training cohort was 100% and it was 95% in the validation cohort. The only patient who achieved a response in spite of fulfilling the stopping rules was a Caucasian patient with genotype A infection [11]. This stopping rule requires further validation in genotypes B and C infected patients because they represented only 20% of the study population. Finally, a functional cure of HBeAg negative CHB (HBsAg loss 3 years after the end of therapy (EOT)) was achieved in 42% of patients with a 2 $\log_{10}$ HBsAg decrease during therapy and in 52% of patients with HBsAg serum levels < 10 IU/ml at EOT [4].

One major unmet need in the management of NUCs patients is the availability of markers to identify those at risk of relapse after NUCs discontinuation. The achievement of low HBsAg serum levels (< 100-200 IU/ml) during NUCs appears to be associated with a low probability (7-22%) of recurrence of florid viral replication (HBV-DNA > 200 or 2000 IU/ml) [12]. Furthermore, HBsAg loss (functional cure) has been recently shown to occur more frequently in HBeAg negative carriers with HBsAg serum levels < 100 IU/ml at the time of NUCs discontinuation [HR 20.6 (5.04-84), P<0.001]. However, only a few patients achieve very low serum HBsAg levels during NUCs, whereas about 50% of patients who discontinue NUCs require re-treatment.

Thus, future studies should investigate whether other, possibly HBV genotype specific, HBsAg thresholds in combination with other parameters, could increase the accuracy in the identification of patients who can safely stop NUCs.

Conclusion

In conclusion, the combined quantitative measurement of serum HBsAg and viral load helps more accurately characterize the phase of HBV infection or the response to antiviral therapy in the single HBV carrier provided that all variables interfering with HBsAg production are carefully considered.

References

1. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HL, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017;66:398-411.
2. Nguyen T, Thompson AJV, Bowden S, Croagh C, Bell S, Desmond PV et al. Hepatitis B Surface Antigen levels during the natural history of Chronic Hepatitis B: A perspective on Asia. J Hepatol 2010; 52:508-13

3. Jaroszewicz J, Serrano BC, Wursthorn K, Deterding K, Schlue J, Raupach R et al. Hepatitis B Surface Antigen levels during the natural history of Chronic Hepatitis B: A European perspective. J Hepatol 2010; 52:514-22
4. Brunetto MR, Moriconi F, Bonino F, Lau GK, Farci P, Yurdaydin C, et al. Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. Hepatology 2009;49:1141-1150.
5. Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peignoux M, et al. Early serum HBsAg drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. Hepatology 2009;49:1151-1157.
6. Sugiyama M, Tanaka Y, Kato T, Orito E, Ito K, Acharya SK et al. Influence of hepatitis B virus genotypes on the intrahepatic and extracellular expression of viral DNA and antigens. Hepatology 2006;44:915-924.
7. Brunetto MR, Marcellin P, Cherubini B, Yurdaydin C, Farci P, Hadziyannis SJ, Rothe V, Regep L, Bonino F. Response to peginterferon alfa-2a (40KD) in HBeAg-negative CHB: on-treatment kinetics of HBsAg serum levels vary by HBV genotype. J Hepatol. 2013;59:1153-9.
8. Brunetto MR, Oliveri F, Colombatto P, Moriconi F, Ciccorossi P, Coco B et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. Gastroenterology 2010;139:483-490
9. Oliveri F, Surace L, Cavallone D, Colombatto P, Ricco G, Salvati N, Coco B, Romagnoli V, Gattai R, Salvati A, Moriconi F, Yuan Q, Bonino F, Brunetto MR. Long-term outcome of inactive and active, low viraemic HBeAg-negative-hepatitis B virus infection: Benign course towards HBsAg clearance. Liver Int. 2017;37:1622-1631
10. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology 2013; 58:872-80
11. Rijckborst V, Hansen BE, Ferenci P, Brunetto MR, Tabak F, Cakaloglu Y, Lanza AG, Messina V, Iannacone C, Massetto B, Regep L, Colombo M, Janssen HL, Lampertico P. Validation of a stopping rule at week 12 using HBsAg and HBV DNA for HBeAg-negative patients treated with peginterferon alfa-2a. J Hepatol. 2012;56:1006-11.
12. Chang M-L, Liaw Y-F & Hadziyannis SJ Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen negative chronic hepatitis B Aliment Pharmacol Ther 2015; 42: 243–257
13. Marcellin P, Buti M, Krastev Z, de Man RA, Zeuzem S, Lou L, Gaggar A, Flaherty JF, Massetto B, Lin L, Dinh P, Subramanian GM, McHutchison JG, Flisiak R, Gurel S, Dusheiko GM, Heathcote EJ. Kinetics of hepatitis B surface antigen loss in patients with HBeAg-positive chronic hepatitis B treated with tenofovir disoproxil fumarate. J Hepatol. 2014 Dec;61(6):1228-37. doi: 10.1016/j.jhep.2014.07.019
14. Martinot-Peignoux M, Marcellin P. Virological and serological tools to optimize the management of patients with chronic hepatitis B.Liver Int. 2016 Jan;36 Suppl 1:78-84. doi: 10.1111/liv.12998.

Treatment of HBV in Pregnancy

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Key points

- HBV vaccination has been successful in reducing mother to child transmission (MTCT) by 90-95%, and subsequent chronic hepatitis B.
- However, Hepatitis B immunoglobulin (HBIG) MTCT may occur in 9.66% of mothers who are HBeAg positive or who have high viral loads, despite HBV vaccination.
- Antiviral therapy in the third trimester can significantly reduce MTCT and is recommended by all major guidelines.
- Stopping antiviral therapy is also recommended after delivery.

Chronic hepatitis B is a major global health problem and is a substantial burden to health systems, resulting in 887 000 deaths in 2015 (1), mostly from complications (including cirrhosis and hepatocellular carcinoma). In 2016 the estimated global prevalence of HBsAg was 3.9% (257 million people). The high prevalence of HBV is due to the rate of transmission by two modalities: perinatal transmission, responsible for most cases, and horizontal transmission from contaminated instruments that pierce the skin or contaminated blood products. The prevalence of maternal HBV infection ranges from 0.7-0.9% in the USA, (2) to 10.47% in China (3).

Since the 1980s HBV vaccination has reduced HBV carriage in children under 5 from 4.7% to 1.3%, and HBV birth dose coverage increased to 84% globally in 2015. In Taiwan, vaccination has been 78%-87% effective in reducing HBsAg seroprevalence in children, with a significant reduction in the incidence of childhood HCC per 100,000, from 0.54 to 0.20 (Risk Ratio = 0.36) (4) .

Thus, the management of maternal HBV remains one of the most important issues in chronic hepatitis B. There are two important considerations, first, the risk of HBV in the mother, and second, the risk of transmission to the neonate also known as mother-to-child-transmission (MTCT).

Risks to the health of the mother of HBV infection

A systematic review and meta-analysis (5) of more than 6 141 146 pregnant women showed that chronic HBV infection is associated with a significantly higher risk (28%) of preterm labor and a 16% higher risk of preterm birth in HBsAg+/HBeAg− women compared to uninfected women. There is also a 21% higher risk of preterm birth in HBsAg+/ HBeAg+ women compared to uninfected women. A meta-analysis of HBV pregnant women also found an increased risk of gestational diabetes (adjusted OR 1.47, 1.22 to 1.76) (6). There was no significant association with fetal abnormalities or the HBV status of the mother.

Risk of acute HBV flare

Pregnancy and the postpartum period are associated with unique changes that allow the mother to tolerate paternally derived fetal antigens and at the same time maintain humoral immunity. This affects systemic immune responses to infection and inflammation. Giles (7) found that HBV flares occurred in 2% of women during pregnancy and 25% post-partum. Although these flares are often self-resolving, all flares should be closely monitored and antiviral therapy can be started on a case by case basis. Decompensation was reported in 2%.

CHB cirrhosis and pregnancy

In a population based study (8), women with cirrhosis from hepatitis (n=339) had a two-fold risk of maternal complications such as antepartum and postpartum uterovaginal hemorrhage, blood transfusion, placental abruption and gestational hypertension. There was also a 2% mortality compared to none in controls. Features of decompensation occurred in 15%. Infants of patients with cirrhosis have an overall odds ratio of 3.66 for fetal complications compared to those without. Another population-based study from the USA (9) found that HBV cirrhosis confers a statistically significant increased risk of pre-eclampsia (13.5% versus 3.0%; $p<0.001$), preterm delivery (28.6% versus 8.9%; $p=0.001$), cesarean section in multiparous women (27.8% versus 10.1%; $p=0.029$), low birth weight (18.9% versus 4.5%; $p=0.001$), and neonatal death (2.7% versus 0.1%; $p=0.040$). It is very clear that pregnancy in HBV cirrhosis is associated with increased maternal and fetal complications.

Risks in pregnancy to baby/newborn

Vertical transmission accounts for 30-50% of cases of chronic HBV in high endemic areas, and 10-20% in intermediate and low endemic areas. Vertical transmission can occur in utero, during delivery or after delivery. Vertical transmission leads to chronicity in 90% of cases. This is in comparison to a risk of 50% in toddlers and young children and only 5% in adults acquired through a horizontal transmission.

Intrauterine transmission

The reported rates of intrauterine transmission vary from 5-40%. In a cohort prospective study performed in Taiwan in 1133 women with chronic HBV, the rate of neonates with positive serum in HBV PCR collected prior to administration of Hepatitis B immune globulin (HBIG) and vaccination was 8.9% (10). Amniocentesis was only found to increase the risk of MTCT if the viral load of the mother was high>7 $\log_{10}$ copies/ml (11).

During delivery

Most vertical HBV contamination occurs during delivery, either by blood mixture during labor, or by the child contacting infected bodily fluids. Before combined immunoprophylaxis was available, the risk of transmission increased from 10-30% in mothers with undetectable HBV DNA to 60-100% in mothers with detectable HBV DNA and 100% in mothers with a high viral load >700,000 copies/ml (12). A systematic review shows that after caesarian section, the rate of MTCT decreased from 9.31% to 4.37%, (RR=0.51; 95%CI: 0.44-0.60, $p < 0.001$) (13). There was also a relationship between the use of HBIG and a reduction in MTCT, but there was no effect in HBeAg status.

Breast feeding

Breast milk is potentially infectious because HBV has been detected in breast milk. However, a meta analysis has conclusively shown that breast feeding does not result in an increased risk of MTCT (14) .

Management of the pregnant mother to reduce MTCT

The first step to decrease MTCT is screening all pregnant women for HBV. Major guidelines recommend routine antenatal screening (15) (16) (17) . Screening should include HBsAg and HBsAb. If the mother is negative for HBsAb and HbsAg, then a vaccination can be administered during pregnancy, as it has been shown to be safe and effective. It can also be given in an accelerated schedule to high risk pregnant women. If HBsAg is positive, then HBV DNA, HBeAg and liver enzymes should be performed.

Combined immunoprophylaxis

The combination of HBIG and vaccination has been found to be effective in the prevention of HBV since 1982. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) both recommend giving a combination of HBIG and vaccination within 12 hours after birth (17) (15). One meta-analysis has shown that despite the use of vaccination and HBIG, the failure rate in mothers with a high viral load who are HBeAg positive is as high as 9.66% (18). When maternal HBV DNA levels are above the threshold of 1,000,000 copies/ml, there is a linear association between maternal HBV DNA levels and MTCT rates.

Antiviral therapy in pregnant women

A meta analysis has shown a significant reduction in MTCT of HBsAg with nucleos(t)ide analogues with a RR=0.51, 95% CI 0.45 - 0.57 (19). This is now recommended in all guidelines. The use of antiviral therapy in these patients (HBeAg+ women with viral load>200,000IU/ml or >1million copies/ml or HBsAg > $4\log_{10}$ IU/ml) is recommended by EASL (17), AASLD (15) and The Asia Pacific Association for the Study of the Liver (APASL) (16). This is expected to reduce MTCT to 0-5% in association with combined immunoprophylaxis at birth.

Which antivirals?

A meta-anlysis (19) comparing lamivudine, telbivudine and tenofovir did not show any statistically significant difference in the three antivirals. Telbivudine and tenofovir are currently rated pregnancy category B, and lamivudine pregnancy category C, by the US Food and Drug Administration based primarily on animal data, with no clear evidence of harm in sparse human data. The AASLD and EASL recommend tenofovir while the APASL recommends either telbivudine or tenofovir.

When to start?

Antivirals should be started in the third trimester to give enough time to decrease viral load. EASL recommends beginning treatment at 24-28 weeks of gestation and APASL at 28-32 weeks. HBV DNA levels should be brought to below 4 $\log_{10}$ IU/ml before delivery.

When to stop antivirals?

The duration of post-partum treatment varies between 0–3 months. While APASL recommends stopping antiviral therapy at delivery, AASLD suggests stopping up to 4 weeks after delivery, and EASL up to 3 months post delivery. Discontinuation of therapy at any point during or after pregnancy requires monitoring because of a potential HBV flare upon withdrawal of antiviral therapy in the subsequent 6 months. Extending third trimester antiviral therapy from 2 to 12 weeks postpartum did not protect against postpartum flares in one study.

Conclusions

Chronic hepatitis B is a global health problem and MTCT is the most common cause of transmission worldwide. Although HBV vaccination is the cornerstone of HBV elimination, implementation is still challenging in some countries. For mothers, there is an increased risk of HBV flares during and after pregnancy and an increased risk of complications during childbirth. MTCT is related to HBeAg status and high viral load, and measures taken to reduce this include caesarian section, immunoprophylaxis with HBV vaccination and HBIG, and antiviral therapy in the third trimester. Guidelines for the management of chronic hepatitis B in pregnancy are generally in agreement and are useful for clinicians to follow.

References

1. Organisation WH. WHO Factsheet: Hepatitis B: World Health Organisation; 2018.
2. Society for Maternal-Fetal M, Dionne-Odom J, Tita AT, Silverman NS. #38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. Am J Obstet Gynecol 2016;214:6-14.
3. Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, Yan D, et al. Prevalence of HBsAg/HBeAg amongst 1 936 801 couples preparing for pregnancy in rural China: An observational study. J Viral Hepat 2017;24:679-686.
4. Chang MH, Chen TH, Hsu HM, Wu TC, Kong MS, Liang DC, Ni YH, et al. Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: the effect and problems. Clinical cancer research : an official journal of the American Association for Cancer Research 2005;11:7953-7957.
5. Ma X, Sun D, Li C, Ying J, Yan Y. Chronic hepatitis B virus infection and preterm labor(birth) in pregnant women-an updated systematic review and meta-analysis. J Med Virol 2018;90:93-100.
6. Tan J, Mao X, Zhang G, Wang W, Pan T, Liu X, Sun X. Hepatitis B surface antigen positivity during pregnancy and risk of gestational diabetes mellitus: A systematic review and meta-analysis. J Viral Hepat 2018;25:1372-1383.
7. Giles M, Visvanathan K, Lewin S, Bowden S, Locarnini S, Spelman T, Sasadeusz J. Clinical and virological predictors of hepatic flares in pregnant women with chronic hepatitis B. Gut 2015;64:1810-1815.
8. Shaheen AA, Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. Liver Int 2010;30:275-283.
9. Puljic A, Salati J, Doss A, Caughey AB. Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices. J Matern Fetal Neonatal Med 2016;29:506-509.
10. Guo Z, Shi XH, Feng YL, Wang B, Feng LP, Wang SP, Zhang YW. Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women. J Viral Hepat 2013;20:317-321.
11. Yi W, Pan CQ, Hao J, Hu Y, Liu M, Li L, Liang D. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol 2014;60:523-529.
12. Pol S, Corouge M, Fontaine H. Hepatitis B virus infection and pregnancy. Clin Res Hepatol Gastroenterol 2011;35:618-622.

13. Yang M, Qin Q, Fang Q, Jiang L, Nie S. Cesarean section to prevent mother-to-child transmission of hepatitis B virus in China: A meta-analysis. BMC Pregnancy Childbirth 2017;17:303.
14. Zheng Y, Lu Y, Ye Q, Xia Y, Zhou Y, Yao Q, Wei S. Should chronic hepatitis B mothers breastfeed? a meta analysis. BMC Public Health 2011;11:502.
15. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, American Association for the Study of Liver D. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.
16. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
17. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.
18. Lin X, Guo Y, Zhou A, Zhang Y, Cao J, Yang M, Xiao F, et al. Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. Pediatr Infect Dis J 2014;33:897-903.
19. Song J, Yang F, Wang S, Tikande S, Deng Y, Tang W, Cao G. Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: a meta-analysis. J Viral Hepat 2018.

Treatment of Delta Hepatitis, what is new?

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Key points

- Myrcludex B and Lonafarnib in combination with Peg-IFN clearly reduce serum HDV-RNA and normalize ALT. However, they have no or minimal impact on serum HBsAg.
- These agents require long-term administration and safety /tolerance may become an issue.
- The combination of Peg IFN with REP 2139 appears to provide the best treatment for chronic hepatitis D. Larger randomized trials are needed to confirm the benefit of this therapy.
- The better tolerated Peg-IFN lambda may represent an alternative to Peg-IFN alfa in the long-term treatment of chronic hepatitis D.

Introduction

New therapeutic strategies against the Hepatitis D Virus (HDV) are being explored to interfere with the steps of the HDV cycle. Options under clinical evaluation include blocking HDV entry into hepatocytes by the synthetic peptide Myrcludex B, disruption of farnesylation of the large HD-antigen required for virion morphogenesis by Lonafarnib, and inhibition of the export of HDV by nucleic acid polymers (NAPs) through interference with the synthesis of subviral HBsAg particles.

Myrcludex B

The first blocking agent to enter clinical studies in chronic hepatitis D (CHD) is Myrcludex B (Myr), a synthetic myristoylated peptide made up of the 2-48 aminoacids in the preS1 region. This agent was developed based on evidence that the binding of the HBsAg to the Sodium Taurocholate Cotransporting Polypeptide (NTCP) requires the integrity of the homologous myristoylated preS segment of the large HBsAg protein. Myr competes with the HBsAg, inhibiting entry of HBsAg-coated HDV virions into liver cells (1). The rationale is that blocking the entry of HBsAg by Myr should protect uninfected liver cells from de-novo HDV infection, ultimately leading to a cure of HDV by recolonization of the liver by HDV-free hepatocytes.

Blank et al. (2) found that the concentration of Myr that blocks HDV entry is 100 times lower than that inhibiting bile acid transport. The drug is well tolerated with no dose limiting toxicity. Although modest and transient increases of amylase and lipase occur, they are clinically uneventful and spontaneously resolved. Bogomolov et al. (2) treated seven patients with Myr at a dose of 2 mg daily subcutaneously for 24 weeks. Therapy was accompanied by more than a 1 $\log_{10}$ reduction in serum HDV RNA in four patients and by its clearance in two. This led to the normalization of alanine aminotransferases (ALT) in six patients. A subsequent study investigated the efficacy of Myr in combination with tenofovir in 120 patients (3). Tenofovir at a dose of 245mg daily was first administered alone to each patient for 12 weeks, then the patients were randomized into four groups, who received tenofovir alone for 4 weeks or tenofovir with Myr given at 2 mg, 5 mg or 10 mg daily. The combination treatment

significantly decreased serum HDV RNA in each group (up to - 2.70 $\log_{10}$ in the 10 mg group) compared to tenofovir alone. The decrease in serum HDV RNA was associated with a reduction in intrahepatic HDV RNA in liver biopsies taken before and 24 weeks after terminating Myr (4). Almost half of all the patients in the Myr arms normalized ALT versus less than 7% of those receiving tenofovir alone. However, HBsAg was not modified by treatment and after treatment HDV serum RNA levels returned to baseline levels.

In a recently reported study (4), Myr was given in combination with pegylated interferon alfa (Peg IFN) at the standard dose of 180 μg weekly. Sixty patients were included and divided into four groups of 15 patients each, who received for 48 weeks 1) Peg-IFN monotherapy weekly (control); 2) Peg-IFN with 2 mg Myr; 3) Peg-IFN with 5 mg Myr daily; 4) 2 mg Myr monotherapy daily. The combination of Myr/Peg IFN consistently diminished serum HDV RNA levels (up to -5.33 $\log_{10}$ in the 5 mg combination group) compared to -1.95 $\log_{10}$ in the Peg-IFN alone group. HDV RNA became undetectable in 10/15 and in 8/14 of the patients who received the 2 mg and 5 mg Myr combination, respectively. Surprisingly, ALT normalization was more pronounced in patients treated with Myr alone (10/14) than in those treated in the two Myr/Peg arms. A decline in HBsAg levels by > 1 $\log_{10}$ was also seen in 7/15 patients in the 2 mg Myr B plus Peg-IFNα group and in 3/14 patients in the 5 mg Myr B plus Peg-IFNα group. No serious adverse events were reported during the 48-week treatment period.

Myr appears to be a HBsAg entry inhibitor with a good safety profile, that blocks the uptake of HDV into hepatocytes. However, it has no effect on cells already harboring replicating HBV, thus its clinical effect must await depletion by natural turn-over of the HDV-infected hepatocytes, a process that requires many months and influences the long duration of therapy. Peg IFN appears to play a synergistic role, accelerating the elimination of infected hepatocytes through an immune mechanism.

Lonafarnib

Farnesylation of the large HDV-antigen (L-HD-Ag) by the hepatocyte is critical to HDV morphogenesis. This step is necessary to promote the interaction of L-HD-Ag with the HBsAg for virion assembly, and its disruption by farnesyl-transferase inhibitors provides the basis for a new therapeutic strategy (6). Lonafarnib (LNF), a tricyclic derivate of carboxamide, was developed as a prototype inhibitor for clinical studies in CHD.

In an initial study (6), LNF diminished serum HDV RNA in a dose dependent manner (-0.73 $\log_{10}$ and -1.54 $\log_{10}$ from baseline in patients given for 28 days 100 mg. and 200 mg. of the drug, respectively). However, tolerance was poor. The highest and most effective dose was associated with important gastrointestinal side effects. Four subsequent studies, called LOWR HDV-1 to LOWR HDV-4, were performed to improve the efficacy and reduce adverse effects. Since LNF is metabolized by the cytochrome P450–3A4, in the LOWR 1 study (7) the CPY-3A4 inhibitor Ritonavir (RTV) was added to LNF to diminish side effects but retain the advantage of high dosing by greater drug exposure with lower delivery. This combination has improved the antiviral effect with better tolerability. 100 mg LNF BID together with RTV 100 mg reduced HDV RNA by 2.4 $\log_{10}$ and 3.2 $\log_{10}$ from baseline at weeks 4 and 8 of therapy, respectively. A similar improvement in efficacy was obtained using LNF 100 mg BID in combination with PEG-IFN.

The LOWR HDV-2 to LOWR HDV-4 studies (8-10) were designed to establish effective but less harmful dosing of LNF, based on the optimal combination of LNF with RTV +/- Peg-

IFN. Results indicate that the best regimens are 25 mg LNF with RTV 100 mg/ twice daily orally, plus PEG IFN, or 50mg LNF with Ritonavir 100 mg/twice daily orally. Overall, 50% of the patients treated with low dose LNF + RTV had a decline in viral load of more than 2 $\log_{10}$ or below the limit of quantitation. This rate increased to 89% with the addition of Peg IFN. ALT normalized in most patients in both regimens.

LNF is effective in reducing HDV-RNA, and with the addition of RTV its antiviral effect can be maintained while tolerability is improved. The addition of Peg IFN further increases the antiviral response.

REP 2139

A further follow up of the first REP 2139 study has been reported. In the original pilot study, 12 patients with CHD were given weekly intravenous REP 2139-Ca (500 mg) for 15 weeks, followed by 15 weeks of REP 2139-Ca (250 mg) combined with Peg IFN, and then Peg IFN monotherapy for 33 weeks more (11). Treated patients were found to have significant reductions in serum HDV RNA during therapy and HDV RNA became undetectable at the end of therapy in 9 of them. Eight patients had a decrease in HBsAg of >2 $\log_{10}$ during monotherapy and 5 patients were HBsAg negative at the end of treatment.

The follow-up data 2 years after stopping therapy confirmed that functional control of HBsAg (<LLOQ) and HDV RNA (target not detected) was maintained in 4 out of 11 and 7 out of 11 patients, respectively (12). Treatment induced transient flares of serum ALT and a stable reduction in platelets and white cell counts.

The mechanism of the therapeutic benefit of REP 2139 remains poorly understood in CHD. New evidence indicates that a variety of NAPs inhibit the entry of HDV in human hepatoma cells by preventing attachment of the virus to cell surface glycosaminoglycans. However, this is not a property of REP 2139, which failed to block the entry of both HDV and HBV (13)

Conclusions

New drugs targeting the HDV will probably lead to a better control of hepatitis D in the next years. Results with REP 2139/Peg IFN are the most promising. If confirmed in larger randomized trials, this combination will be a breakthrough in CHD treatment.

Myr and LNF combined with Peg-IFN consistently control HDV replication and normalize ALT. Time is needed to determine whether they will eradicate HDV with long-term treatments and/ or whether they may be adjusted to a functional cure, i.e. to maintain latent, clinically inactive HDV infections with continued therapy.

Prolonged treatments will raise the problem of tolerance and safety, in particular in association with the poorly tolerated Peg IFN alfa. Lambda IFN might be an alternative, as this cytokine has been found to induce fewer side effects that IFN and may be more suitable for long term treatments (6).

References

1) Urban S, Bartenschlager R, Kubitz R, Zoulim F. Strategies to inhibit entry of HBV and HDV into hepatocytes. Gastroenterology 2014; 147: 48–64.
2) Lempp F.A., Urban S. Hepatitis Delta Virus: Replication Strategy and Upcoming Therapeutic Options for a Neglected Human Pathogen. Viruses 2017; 9: 172.
3) Wedemeyer H, Bogomolov P, Blank A, et al. Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in

combination with Tenofovir in patients with chronic HBV/HDV co-infection. J Hepatol 2018; 68: S3, Abstract GS-005.
4) Allweiss L, Dettmer C, Volz T, et al. Strong intrahepatic decline of hepatitis D virus RNA and antigen after 24 weeks of treatment with Myrcludex B in combinationwith Tenofovir in chronic HBV/HDV infected patients: Interim results from a multicenter, open-label phase 2b clinical trial. JHepatol 2018; 68: S90, Abstract PS-162.
5) Wedemeyer H, Schöneweis K, Bogomolov PO, et al. Interim results of a multicentre, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of Myrcludex B in combination with Peg-Interferon Alpha 2a in patients with chronic HBV/HDV Infection. Hepatology 2018; 68(S1): 11A, Abstract 16.
6) Koh C, Heller T, Glenn JS. Pathogenesis of the New Therapies for Hepatitis D Gastroenterology. 2018 Oct 18. pii: S0016-5085(18)35162-X. doi: 10.1053/j.gastro.2018.09.058
7) Yurdaydyn C, Keskin O, Kalkan C, et al. Optimizing lonafarnib treatment for the management of chronic delta hepatitis: The LOWR HDV-1 study. Hepatology 2018; 67: 1224-36.
8) Yurdaydin C, Idilman R, Kalkan R, et al. A phase 2 dose-optimization study of lonafarnib with Ritonavir for the treatment of chronic delta hepatitis—end of treatment results from the LOWR HDV-2 study. J Hepatol 2017; 66: S33–4, Abstract GS-008.
9) Koh C, Surana P, Han T, et al. A phase 2 study exploring once daily dosing of ritonavir boosted lonafarnib for the treatment of chronic delta hepatitis – end of study results from the LOWR HDV-3study. J Hepatol 2017; 66: S101–2, Abstract LBP-519.
10) Wedemeyer H, Port K, Deterding K, et al. A phase2 dose-escalation study of lonafarnib plus ritonavir in patients with chronic hepatitis D: final results from the Lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) study. J Hepatol 2017; 66: S24, Abstract PS-039.
11) Vaillant A. REP 2139: antiviral mechanisms and applications in achieving functional control of HBV and HDV infection. ACS Infect Dis. 2018, Oct 5. doi: 10.1021/acs infec.dis.8b00156.
12) Bazinet M, Pantea V, Cebotarescu V, Cojuhari L, Jimbei P, Vaillant A. Establishment of persistent functional remission of HBV and HDV infection following REP 2139 and pegylated interferon alpha 2a therapy patients with chronic HBV/ HDV co-infection: 18 month follow-up results from the REP 301- LTF study. J Hepatol 2018; 68: S509, Abstract FRI-326.
13) Beilstein F, Blanchet M, Vaillant A, Sureau C. Nucleic Acid Polymers are active against Hepatitis Delta Virus infection in vitro. J Virol. 2018 Jan 30;92(4). pii: e01416-17. doi: 10.1128/JVI.01416-17. Print 2018 Feb 15

HEPATOCELLULAR CARCINOMA

HCC today and in the future

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Key points

- Hepatocellular carcinoma (HCC), the main cause of death in patients with compensated cirrhosis of all etiologies, is the second leading cause of death from cancer in men and the sixth in women, worldwide.
- The incidence of HCC is increasing in northern Europe, North America and English speaking Asia as a consequence of inappropriate life styles, including the metabolic syndrome epidemic, while it is declining in traditionally high risk countries following effective public health measures.
- In the developing world where most cases of HCC are found, the implementation of preventive strategies, including the elimination of viral hepatitis is the only realistic option to fight this disease.
- In the developed world, the strategy to fight HCC includes expanding both prevention and screening of patients at risk to foster access to potentially curative treatments.
- Liver transplantation is the only realistic hope for a cure, however, it is restricted to highly selected patients with small tumors confined to the liver and is limited by the shortage of liver donors. With the control of viral hepatitis and the decrease in the number of decompensated patients on the waiting list, effective down-staging procedures have led to expanded access to liver transplantation in patients beyond the Milan criteria, with significant gains in survival.
- While the control of viral hepatitis has led to improved outcome with non transplant therapeutic procedures, significant step forwards are also foreseen in the treatment of advanced cancer with the development of immune oncology based therapeutic regimens.

The extent of the problem

Hepatocellular carcinoma (HCC) is the most difficult to cure aspect of end-stage liver disease and the main cause of death in patients with compensated cirrhosis of all etiologies. In 2015, 810,000 people (521,000 men) died from HCC making it the fourth cause of death from cancer following lung, colorectal, and stomach cancers. In the last two decades, cases of incident liver cancer increased by 75%, 47% due to the changing structure of age in the population, and 35% due to population growth. According to the WHO database, HCC mortality is increasing in northern Europe, North America and English speaking Asia due to the epidemic of viral hepatitis that has spread from parenteral risk behaviors, expanded alcohol abuse, as well as the increase in the metabolic syndrome in which liver steatosis is detected in up to 25% of the world's population. The threat of HCC is only partially reduced by a decline

in this disease in traditionally high risk countries including Mediterranean European regions, Japan and Hong Kong as a result of effective measures such as screening of blood donors and mass vaccination of newborns against hepatitis B virus, which is still the main risk factor of HCC worldwide. We should also begin to perceive the benefits in the population from widespread access to antiviral therapy for hepatitis B and C infection as long as strategies of linkage to care are more vigorously applied. The WHO program to eliminate viral hepatitis by 2030, which could prevent 65% of HCC-related mortalities would, in fact, require a 7% annual decline in the global burden of hepatitis, a goal that has only been reached by a few countries so far.

The situation today

In the face of these perspectives, the real life issue today is the many patients who are identified with any stage of HCC, compared to the few who succeed in accessing potentially curative therapies. In fact, access to the latter is determined by the classification of disease stage, based on tumor burden, liver impairment and performance status. The application of these strict selection criteria inevitably results in a small minority of patients being eligible for curative therapies. This limitation is even more significant in resource poor, HCC endemic countries where surveillance programs for early diagnosis are not in place. In the developed areas of the world where early diagnosis of HCC is increasing, liver transplantation, surgical resection and local ablation have proven to be the most effective first line options and provide significant survival benefits to accurately selected patients with early stage tumors (Barcelona Clinic Liver Cancer [BCLC] 0/A). In these same regions, the many patients with a greater tumor burden confined to the liver (intermediate stage BCLC B), in whom radical treatments are not indicated, may still obtain marked benefits to survival from repeated local treatment with transarterial chemoembolization (TACE). Survival can still be markedly improved in patients with advanced stage tumors, ie symptomatic patients with extrahepatic or intravascular tumor spread, using oral treatment with systemic therapies. First-line therapy in such patients is now based on two tyrosine kinase inhibitors, while second line therapy relies on one tyrosine kinase inhibitors and two monoclonal antibodies, including check point inhibitors, which are now being tested in sequence or in combination to provide substantial increases in survival compared to tyrosine kinase inhibitors alone.

Remaining challenges

That said, there are many remaining challenges in both the developed and developing countries. Because HCC is a two world disease, it is not possible to predict whether advances in disease control will follow the "one-size-fits-all" paradigm. In the developing regions, control of HCC will requires massive public health interventions for the primary prevention of risk factors including eliminating viral hepatitis as a major public health threat by 2030, reducing the harmful use of alcohol and tobacco, and controlling diabetes and obesity.

Prevention of risk factors is also a priority in resource rich areas of the world, combined however, with efforts to improve detection of early stage cancer through screening of at risk populations and fostering linkage to care. Adherence to the therapeutic algorithms for HCC recommended by international societies is often compromised by the scarcity of liver donors, the strategic localization of early tumors and the presence of co-morbidities, which affect the risk-benefit ratio of both transplant and non transplant curative treatments, while showing the need for alternative therapeutic options outside the recommended standard of care.

For liver transplantation the future is already being implemented in most transplant centers with the increase in the number of patients listed with HCC beyond the Milan criteria, with benefits to survival following control of viral hepatitis and a maintained radiological response to bridge therapy for a reasonably long waiting time. The hepatitis B and C viruses can be effectively controlled with direct antivirals, thus making it possible to refine treatment criteria for the many patients with intermediate stage HCC using sequential interventions based on local ablative treatment and resection. Although there is little chance that patients with advanced HCC have comparable benefits to survival with sequential medical treatment, management of this difficult to treat population could be optimized once reliable serum biomarkers of response to therapy have been identified and immune oncological therapies become available.

While progress in the treatment of HCC takes many forms, extending access to donor organs remains strategically important because in Europe and the United States fewer than 5% of all HCC patients are treated with transplantation. The production of a bioengineered liver from human stem cells is a clear long term objective of regenerative medicine for the hepatology community and is also a strategy of the European Association for the Study of the Liver (EASL), which recently endorsed the creation of a consortium including the most prestigious research centers in Europe to foster research in regenerative medicine.

References

1) European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J. Hepatol 2018;69 :182–236.
2) Heimbach J, Kulik LM, Finn R, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology.2017 doi: 10.1002/hep.29086 .
3) Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma. JAMA Surg. 2016;151: 846-53.
4) Cucchetti A, Piscaglia F, Cescon M, Ercolani G, Pinna AD.Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. World J Gastroenterol. 2013;14: 4106-18.
5) Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology. 2005;234:954-60 .
6) Halazun KJ, Patzer RE, Rana AA, et al. Standing the test of time: outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. Hepatology. 2014;60:1957-62
7) Mazzaferro V. Squaring the circle of selection and allocation in liver transplantation for HCC: An adaptive approach. Hepatology.2016; 63:1707-17.
8) Bruix J, Merle P, Granito A, et al. Analysis of overall survival (OS) by pattern of progression of hepatocellular carcinoma (HCC) during prior sorafenib treatment in the randomized phase 3 RESORCE trial comparing regorafenib with placebo.

Presented at: 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China.

9) Mellero I, Sangro B, Yau T, et al. Safety and preliminary efficacy of nivolumab in patients with advanced hepatocellular carcinoma: interim analysis of the phase 1/2 CheckMate 040 study. Presented at: 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China.
10) Kim WR, Loomba R, Berg T, Aguilar Schall RE, Yee LJ, Dinh PV, Flaherty JF, Martins EB, Therneau TM, Jacobson I, Fung S, Gurel S, Buti M, Marcellin P. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B.
11) Cancer. 2015 Oct 15;121(20):3631-8. doi: 10.1002/cncr.29537.
12) Ganne-Carrié N, Layese R, Bourcier V, Cagnot C, Marcellin P et al; ANRS CO12 CirVir study group. Nomogram for individualized prediction of hepatocellular carcinoma occurrence in HCV-cirrhosis (ANRS CO12 CirVir).
13) Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, et al; Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. ANRS CO12 CirVir Group. Gastroenterology. 2018 Nov;155(5):1436-1450.e6. doi: 10.1053/j.gastro.2018.07.015. Epub 2018

Hepatocellular carcinoma and metabolic syndrome

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Key points

- NAFLD is an emerging risk factor for HCC.
- HCC related to NAFLD may develop in the absence of advanced fibrosis.
- The pathogenesis of HCC related to NAFLD is multifactorial.
- HCC related to NAFLD may display specific pathomolecular features.

Metabolic syndrome, mainly through the development of Non-Alcoholic Fatty Liver Disease (NAFLD), is emerging as a critical risk factor for hepatocellular carcinoma (HCC) worldwide (1,2). Accordingly, NASH (Non Alcoholic Steato-Hepatitis) is the fastest growing cause of HCC in patients listed for liver transplantation (3). In addition to the classical multistep process of liver carcinogenesis with HCC occurring in a cirrhotic background liver, HCC in patients with NAFLD may develop in the absence of advanced fibrosis [4–6], suggesting involvement of specific mechanisms of carcinogenesis. Among them, polymorphisms of patatin like phospholipase domain containing 3 (PNPLA3), the role of microbiota and the deregulation of adipokines have been described (7,8).

HCC that develops in the setting of NAFLD may present with specific pathomolecular characteristics: (i) displaying a steatohepatitic variant, (ii) belonging to a specific molecular subgroup with less vascular invasion and satellite nodules and/or (iii) showing specific chromosomal alterations (9–11).

Finally, the policy of HCC screening in patients with NAFLD and the antitumoral potential of common treatments used in this setting (metformin, statins,...) require further study.

References

(1) Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology 2011;54:463–71.
(2) Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014;60:110–7.
(3) Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol 2018. doi: 10.1016/j.cgh.2018.05.057
(4) Paradis V, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. Hepatology 2009;49:851–9.
(5) Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 2012;56:1384–91.

(6) Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans is Associated With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2016;14:124-31.
(7) Singal AG, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am J Gastroenterol 2014;109:325–34. doi:10.1038/ajg.2013.476.
(8) Dapito DH, Mencin A, Gwak G-Y, Pradere J-P, Jang M-K, Mederacke I, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell 2012;21:504–16. doi:10.1016/j.ccr.2012.02.007.
(9) Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitch JH, Moreira RK. The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol 2012;43:737–46. doi:10.1016/j.humpath.2011.07.005.
(10) Calderaro J, Couchy G, Imbeaud S, Amaddeo G, Letouzé E, Blanc J-F, et al. Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification. J Hepatol 2017;67:727–38. doi:10.1016/j.jhep.2017.05.014.
(11) Paradis V, Albuquerque M, Mebarki M, Hernandez L, Zalinski S, Quentin S, et al. Cullin7: a new gene involved in liver carcinogenesis related to metabolic syndrome. Gut 2013;62:911–9. doi:10.1136/gutjnl-2012-302091.

Discrepancies between EASL, AASLD and APASL guidelines on hepatocellular carcinoma management

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Key points

- Different guidelines on the management of HCC exist in different parts of the world.
- Despite significant conceptual differences, treatment recommendations are similar.
- In general, there is a more liberal approach to liver resection in Asian countries.
- Newly available systemic compounds need to be integrated in updated versions.

Hepatocellular carcinoma (HCC) shows a heterogeneous distribution throughout the world and different guidelines on the management of HCC have been developed in these different regions based on expert consensus recommendations. Since 2001, when the European Association for the Study of the Liver (EASL) issued their HCC guidelines, at least 20 guidelines have been published or updated, in particular from the American Association for the Study of Liver Diseases (AASLD) for the USA (1, 2), the Asian Pacific Association for the Study of the Liver (APASL) for the Asia-Pacific region (3), the European Association For The Study of the Liver (EASL) for Europe (4), and the Japan Society of Hepatology (JSH) for Japan (5, 6) as well as others.

Although the different guidelines on the therapeutic management of hepatocellular carcinoma from North America, Europe and Asia-Pacific have clear differences in general concept, the actual differences in recommended treatments are limited. The most important differences concern liver resection. While the AASLD/EASL guidelines recommend the presence of a single nodule and Child-Pugh A functional status, other guidelines accept multinodularity and a Child-Pugh B status in selected cases (7), an indication which is also discussed in the West (8).

One important element that has not yet been integrated into most international guidelines is the arrival of new kinase [lenvatinib (9) and regorafenib (10)] and checkpoint inhibitors [e.g. nivolumab (11) and pembrolizumab (12)]. These drugs are expected to be included in the next updates of these guidelines.

This presentation provides an updated comparison of the most recent versions of the EASL, AASLD and APASL guidelines.

References

1. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2.
2. Heimbach J, Kulik LM, Finn R, Sirlin CB, Abecassis M, Roberts LR, et al. Aasld guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2017.
3. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317-70.

4. European Association For The Study Of The Liver, European Organisation For Research and Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.
5. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis. 2011;29(3):339-64.
6. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014;3(3-4):458-68.
7. Francesco Tovoli, Giulia Negrini & Luigi Bolondi. Comparative analysis of current guidelines for the treatment of hepatocellular carcinoma. Hepat. Oncol. (2016) 3(2), 119–136.
8. Galle PR, Tovoli F, Foerster F, Worns MA, Cucchetti A, Bolondi L. The treatment of intermediate stage tumours beyond TACE: From surgery to systemic therapy. J Hepatol. 2017;67(1):173-83.
9. Cheng A-L, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). Journal of Clinical Oncology. 2017;35(15_suppl):4001-.
10. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2016.
11. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-502.
12. Finn RS, Chan SL, Zhu AX, Knox JJ, Cheng A-L, Siegel AB, et al. KEYNOTE-240: Randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma. Journal of Clinical Oncology. 2017;35(4_suppl):TPS503-TPS.

Therapeutic advances in HCC

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Key points

- Post-operative outcomes after liver resection can be improved by a thorough, careful evaluation of the extent of resection, functional liver reserve and portal hypertension.
- Percutaneous microwave or laser ablation, cryoablation or irreversible electroporation must be shown to provide a therapeutic benefit before the indications for percutaneous ablation are extended.
- Selective internal radiation therapy, alone or in combination with sorafenib, has failed to improve survival compared to sorafenib alone in patients with advanced tumors, despite a higher response rate, and should be explored in selected patient populations.
- The systemic therapy toolbox for advanced stage patients now includes two first-line drugs (sorafenib and lenvatinib) and four second-line drugs after sorafenib (regorafenib, cabozantinib, ramucirumab and nivolumab).
- Immune checkpoint inhibitors, alone and in combination with antiangiogenics or other immune checkpoint inhibitors, are being tested for different tumor stages.

The treatment of hepatocellular carcinoma (HCC) depends on the extent and distribution of tumor burden and the degree of liver dysfunction. Therapeutic advances have recently been made in different areas. Improvement in surgical techniques, in particular the development of laparoscopic liver resection, as well as a better understanding of the factors that lead to postoperative liver failure, are increasing the indications for resection. In patients without cirrhosis or with compensated cirrhosis, the risk of post-operative decompensation and overall survival depend upon the quantity and quality of the remnant liver and can be estimated based on the extent of resection, functional liver reserve, indocyanine green clearance and/or portal hypertension. Different algorithmms are now used to improve individual patient selection.

Thermal percutaneous ablation can result in complete tumor necrosis in tumors < 3 cm and can even be considered an alternative to resection. Total thermal ablation is unlikely in larger tumors or in those located near large vessels, and can result in significant toxicity when the tumors are close to large bile ducts or on the liver surface. New techniques and devices including microwave or laser ablation, cryoablation and irreversible electroporation have not yet been shown to be beneficial in these situations.

Intra-arterial therapies include transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT). TACE is the mainstay of treatment in early tumors not suitable for resection, transplantation or ablation, and multiple tumors that can be superselectively targeted. Conventional TACE using chemotherapeutic drugs mixed with lipiodol followed by gelatin foam or calibrated beads is the standard procedure worldwide. Although doxorubicin-eluting beads are not more effective, they provide a more standardized way to perform TACE. Although small randomized trials and large cohort series suggest that similar outcomes may be expected with SIRT, this option has not been compared to TACE in large randomized trials in good TACE candidates. On the other hand, SIRT can be safely administered to patients with large tumors or in the presence of portal vein thrombosis, where TACE is associated with a higher risk of complications. Despite a higher response rate, SIRT has failed to improve survival compared to sorafenib in patients with more advanced tumors. The combination of SIRT and sorafenib has also failed to improve survival compared to sorafenib alone in a similar population despite a higher response rate. In the latter clinical trial, post-hoc subgroup analysis has suggested a benefit in patients without cirrhosis but confirmation is needed.

The most important advances have occurred with systemic therapy and several drugs have recently become therapeutic options for HCC. No cytotoxic drugs, alone or in combination, have been shown to have significant activity. More than a decade ago, sorafenib was the first agent shown to prolong survival in patients with advanced stage disease or after progression. The activity of sorafenib seems to be limited to a population with fairly advanced tumors because it failed to increase the time to progression or overall survival when used in combination with TACE, after complete ablation or successful resection. A recent Japanese trial has shown an increase in progression-free survival in patients receiving sorafenib in combination with TACE versus TACE alone. However, in this trial progression-free survival was described as the time until death or a situation in which the continuation of TACE was not possible due to untreatable tumor progression, deterioration to Child-Pugh C or the development of vascular invasion or extrahepatic metastases. This innovative endpoint has not been validated and survival data have not yet been reported.

Four agents have been added as systemic therapeutic options based on positive randomized trials. Lenvatinib has been shown to be non-inferior to sorafenib in prolonging survival in patients who are naïve to systemic treatment. Regorafenib prolonged survival compared to placebo in patients with good tolerance to a relevant dose of sorafenib and with radiological progression. Cabozantinib has been shown to prolong survival in patients that are intolerant or have progressed to up to two lines of systemic therapy with sorafenib. Although ramucirumab initially failed to show a benefit in patients that were intolerant to sorafenib or had progressed, after a post-hoc analysis a subsequent trial showed that this intravenous drug prolonged survival in the subgroup of patients with serum α-fetoprotein > 400 UI/ml.

On the other hand, immunotherapy is a subject of intense research in the field of liver cancer, as in many other types of tumors. The antitumor cytotoxic activity of T lymphocytes can be enhanced by drugs that interfere with two key checkpoint signals, blocking cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1). Tremelimumab, a CTLA-4 blocker, and nivolumab and pembrolizumab have been tested in single-arm trials. Tremelimumab was initially tested in a small trial and showed an

overall response rate of 18%. Nivolumab and pembrolizumab have been tested in large trials and consistently produce long lasting objective remissions in around 15% of patients with extended overall survival compared to the expected outcome in similar placebo-treated patients. Nivolumab has been approved in several countries based on these data. The enthusiasm about immunotherapies requires confirmation. The results of two randomized trials comparing nivolumab to sorafenib as first-line therapy and pembrolizumab to placebo as second-line therapy after sorafenib are eagerly awaited. Immune checkpoint inhibitors, alone and in doublets, are also being tested in combination with TACE and in the adjuvant setting following resection or ablation in patients at high risk of recurrence. Combination therapies are now being tested. There is little overlap between the toxicity of multikinase inhibitors or antiangiogenics and immune checkpoints inhibitors. Pre-clinical evidence on synergistic activity is lacking, but an additive effect could improve the efficacy of systemic therapies. Early data are available in two of these combinations, lenvatinib combined with pembrolizumab and bevacizumab combined with the anti-PD-L1 inhibitor, atezolizumab. A 33% overall response rate according to RECIST 1.1 criteria has been reported for the latter.

The molecular derangements associated with HCC are increasingly well known. Molecular subgroups are defined by whole-genome based analysis of DNA aberrations or gene expression. Several activated oncogenic signaling routes have also been identified. Unfortunately, some of these cannot be targeted by available drugs and those that can seem to be less relevant or redundant. Nevertheless, agents targeting fibroblast growth factor and TGF-α are under investigation.

References

1. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
2. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358–80.
3. ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Supplement_4):iv238-iv255.
4. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Prim. 2016 Apr 14;2:16019.
5. Sangro B, Salem R. Transarterial chemoembolization and radioembolization. Semin Liver Dis. 2014 Nov;34(4):435-43.
6. Sangro B, Martínez-Urbistondo D, Bester L, Bilbao JI, Coldwell DM, Flamen P, et al. Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review. Hepatology. 2017 Sep;66(3):969-982.
7. Spreafico C, Sposito C, Vaiani M, Cascella T, Bhoori S, Morosi C, et al. Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. J Hepatol. 2018 Apr;68(4):724–32.
8. Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment

(RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 5;389(10064):56–66.
9. Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul 5;379(1):54–63.
10. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun;389(10088):2492–502.
11. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018 Jul;19(7):940–52.
12. Zucman-Rossi J, Villanueva A, Nault J-C, Llovet JM. Genetic Landscape and Biomarkers of Hepatocellular Carcinoma. Gastroenterology. 2015 Oct;149(5):1226–1239.e4.

END STAGE LIVER DISEASE AND TRANSPLANTATION

Liver Transplantation: shifting etiologies of cirrhosis bring new challenges

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Key points

1. Hepatitis C (HCV) has been the most frequent indication for liver transplantation (LT) for nearly two decades, but direct acting antiviral therapy has rapidly changed this. Fewer patients are being listed for LT and the survival of post-LT recipients with HCV is now similar to those without HCV. In 2019, alcohol-associated liver disease (ALD) and non-alcoholic steatohepatitis (NASH) are the most frequent indications for LT.
2. In the US, the rates of LT for ALD have increased in the past 5-7 years, reflecting increased use of LT for severe alcoholic hepatitis and for decompensated cirrhosis. Overall, survival is similar to non-ALD etiologies but post-LT challenges include higher rates of infections (especially in those with severe alcoholic hepatitis), de novo malignancies and, most importantly, relapse to alcohol use.
3. NASH as an indication for LT has increased significantly in the past decade, while HCC as an indication is rising even more rapidly. Five-year survival rates in NASH LT recipients are similar or better than non-NASH recipients, probably due to careful patient selection and the low short-term impact of recurrent NASH. Post-LT challenges include lower eligibility for LT in the severe and morbidly obese, higher rates of cardiac complications and a risk of recurrent NASH.

For nearly two decades, HCV infection has dominated the liver transplantation (LT) landscape. However, direct acting antivirals (DAAs) have produced dramatic results in LT candidates and recipients, resulting in a rapid reduction in the HCV-positive patients on the waiting list and improved post-LT survival. In 2019 and beyond, HCC is expected to be the primary indication for LT with fewer listed for decompensated cirrhosis, mirroring the pattern seen with hepatitis B since the availability of effective nucleoside analogue therapy. HCV will be a less frequent indication for LT in the coming years and ALD and NASH will predominate and bring new challenges.

Alcohol-associated Liver Disease (ALD)

ALD is still an important indication for LT because effective therapies to treat or reverse alcohol-associated injury are largely lacking. In the US and Europe, ALD is now the leading indication for LT. This is due, in part, to the decline in LT for HCV, and probably to a more flexible policy on abstinence and a willingness to consider LT in patients with severe alcoholic hepatitis. Moreover, population-based studies of overlapping etiologies of non-alcoholic fatty liver and ALD suggest that an increase in alcohol-associated liver disease may also be occurring. The survival of transplant recipients with ALD is similar to that of other etiologies of cirrhosis: 75-85% at 5 years and 60-75% at 10 years [1, 2].

The key challenges to optimize outcomes in transplant patients with ALD are:

- A higher risk of infectious complications, in part related to corticosteroid use in patients with concurrent alcoholic hepatitis. Other factors may include alcohol associated dysbiosis and altered gut mucosal barrier. Strategies to prevent infectious complications are limited to the avoidance of corticosteroids unless the benefit is clear. Future therapies may include manipulation of the microbiome.
- A higher risk of post-transplant malignancies, especially head, neck, esophagus and lung cancers. In part, this reflects higher rates of tobacco use among ALD patients. In a French study, LT recipients with history of ALD who continued to smoke post-LT had a cumulative incidence of tobacco-related cancers of 12.3%, 20.6%, 42.6% at 3, 5 and 10 years respectively [3]. De novo malignancies reduce overall survival. Intensive surveillance strategies aimed at early detection and treatment appear indicated, although smoking cessation is the most important measure.
- Relapse to alcohol use post-LT. Relapse of alcohol use occurs in 45% of ALD transplant recipients after follow-up periods of 3-5 years but relapse to harmful alcohol use occurs in up to 20% [4]. The latter is associated with recurrent ALD, cirrhosis and death [4, 5]. A French multicenter study found that ~5% of patients returned to heavy alcohol use and one-third developed recurrent ALD cirrhosis a median of 4.4 years after relapse, suggesting accelerated disease progression post-LT [5]. Younger age and early return to alcohol use after LT have been associated with more harmful patterns and a risk of recurrent ALD post-LT [5]. While the length of pre-LT abstinence is associated with the rates of post-LT relapse, there is less support for the "6-month" rule. Monitoring for use with serum/urine biomarkers may be helpful to identify those in need of active intervention. Centers that provide pre- and post-LT counseling or those which embed alcohol management into the routine post-LT follow-up, report significantly lower rates of relapse. Future studies should explore the use of medications to reduce cravings and novel therapies to reduce liver injury related to alcohol use.

Non-Alcoholic Fatty Liver Disease (NAFLD)

Trends in wait-listed patients and transplant recipients in Europe and the US highlight the increasing prevalence of NASH. In Europe, LT for NASH increased from 1.1% to 6.2% from 2007 to 2017 [6]. In the US, LT for NASH increased from 1.2% in 2001 to 9.7% in 2009 [7]. While NASH still represents a modest percentage of LTs in Europe and the US, the rates are growing steadily and given the global prevalence of NAFLD, it is expected to be the most common indication for LT in the next decade. It is interesting to note that the ratio of LT listings for HCC increased 10.4-fold from 2004 to 2015, in contrast to a 2.7-fold and 5.6-fold increase for alcohol and HCV [8]. Whether this is a reflection of a higher risk of HCC in patients with NAFLD or a LT selection bias requires further study. Importantly, survival rates after 5 years in NASH LT recipients are similar or better than other indications [7]. This may be related to the selection of patients with a lower prevalence of severe metabolic complications, including cardiovascular disease, or the lower frequency of recurrent disease post-LT. Because of the lack of long-term data in studies of 10 years or more, these results must be considered with caution.

Key challenges to optimize outcomes in transplant patients with NASH are:

- Defining acceptable BMI limits for LT. Technically, LT in severely obese patients is more challenging, with more infectious and surgical complications. In a US study evaluating wait-listed patients based on BMI, 11% and 19% of centers did not list any severely (BMI 35-40) or morbidly obese (BMI 40-60) patients, respectively [9]. BMI is not a good predictor for wait-list and post-LT survival, suggesting that specific cut-offs should not be used to guide LT eligibility. The use of sleeve gastrectomy before or concurrently with LT, could help increase the number of obese NASH LT candidates [10, 11]. On the other hand, patients with prior roux-en-y gastric bypass have higher waiting list mortality, suggesting that patients with cirrhosis and malabsorptive bariatric surgery could be at a higher risk of malnutrition [12]. A supervised diet and exercise interventions designed to improve the eligibility for LT of obese NASH patients are needed.
- Although recurrent cirrhosis is infrequent after 5 years, recurrent NASH is common after LT and is therefore a risk for the progression of fibrosis [13]. Using transient elastography, 27% of patients were found to have advanced fibrosis and 5.4% had cirrhosis a mean 6.25 years post-LT [13]. In a biopsy-based study, NASH with fibrosis was present in 71% of those with recurrent NAFLD compared to 13% of those with de novo post-LT NAFLD [14]. This suggests that *recurrent* NAFLD is more likely to progress than *de novo* NAFLD, suggesting that a more aggressive approach to prevention/treatment may be needed. To date, no clinical trials of new therapies have been undertaken in LT recipients.
- Patients with NASH have a higher risk of cardiovascular events than non-NASH patients. Cardiovascular events within the first year (70% occurring perioperatively) after LT are associated with a 50% overall mortality [15]. Post-LT metabolic syndrome and its individual components are also higher raising concerns of worsening trajectories for the NASH patient post-LT. Ultimately, selection of LT candidates probably influences this risk as well as how aggressively the metabolic syndrome is managed post-LT.

References:

1. Dumortier J, Guillaud O, Adham M, et al. Negative impact of de novo malignancies rather than alcohol relapse on survival after liver transplantation for alcoholic cirrhosis: a retrospective analysis of 305 patients in a single center. Am J Gastro 2007;102:1032-41.
2. Singal AK, Bashar H, Anand BS, et al. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. Hepatology 2012;55:1398-405.
3. Renaud L, Hilleret MN, Thimonier E, et al. De novo malignancies screening after liver transplantation for alcoholic liver disease: a comparative opportunistic study. Liver Transpl 2018.
4. DiMartini A, Dew MA, Day N, et al. Trajectories of alcohol consumption following liver transplantation. Am J Transplant 2010;10:2305-12.
5. Dumortier J, Dharancy S, Cannesson A, et al. Recurrent alcoholic cirrhosis in severe alcoholic relapse after liver transplantation: a frequent and serious complication. Am J Gastroenterol 2015;110:1160-6; quiz 1167.

6. Belli LS, Perricone G, Adam R, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810-817.
7. Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology 2011;141:1249-53.
8. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States. Clin Gastroenterol Hepatol 2017;15:767-775 e3.
9. Segev DL, Thompson RE, Locke JE, et al. Prolonged waiting times for liver transplantation in obese patients. Ann Surg 2008;248:863-70.
10. Zamora-Valdes D, Watt KD, Kellogg TA, et al. Long-term outcomes of patients undergoing simultaneous liver transplantation and sleeve gastrectomy. Hepatology 2018;68:485-495.
11. Lin MY, Tavakol MM, Sarin A, et al. Safety and feasibility of sleeve gastrectomy in morbidly obese patients following liver transplantation. Surg Endosc 2013;27:81-5.
12. Idriss R, Hasse J, Wu T, et al. Impact of prior bariatric surgery on perioperative liver transplant outcomes. Liver Transpl 2018.
13. Bhati C, Idowu MO, Sanyal AJ, et al. Long-term Outcomes in Patients Undergoing Liver Transplantation for Nonalcoholic Steatohepatitis-Related Cirrhosis. Transplantation 2017;101:1867-1874.
14. Vallin M, Guillaud O, Boillot O, et al. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. Liver Transpl 2014;20:1064-71.
15. Vanwagner LB, Bhave M, Te HS, et al. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology 2012;56:1741-50.

Management of patients with decompensated cirrhosis

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Key points

- Decompensated hepatitis C virus (HCV) cirrhosis is now uncommon while the proportion of patients with cirrhosis related to non-alcoholic steatohepatitis (NASH) is increasing.
- Preventing infection is an important goal in patients with cirrhosis. The long term administration of antibiotics, in particular norfloxacin has been associated with lower mortality. Albumin has been recommended in association with antibiotics for spontaneous bacterial peritonitis for three decades.
- Acute on chronic liver failure is a syndrome with a high rate of early mortality. Early administration of large spectrum antibiotics is now recommended to treat infections.
- Acute kidney injury is also a common complication of advanced cirrhosis, and is predictive of a worse outcome. Terlipressin has been shown to be effective in reversing hepatorenal syndrome in at least 50% of patients.
- Non-selective beta blockers are used in the primary or secondary prophylaxis of variceal bleeding and Transjugular intrahepatic portosystemic shunts are an alternative to large volume paracentesis.
- Liver transplantation is the best option in patients with advanced cirrhosis.

The face of cirrhosis has changed since the introduction of direct antiviral agents (DAAs). Decompensated hepatitis C virus (HCV) cirrhosis is now uncommon while the proportion of patients with cirrhosis related to non-alcoholic steatohepatitis (NASH) is increasing. Patients with NASH-related cirrhosis tend to be older than those with HCV-related cirrhosis when decompensation occurs. They have more comorbidities that must be considered using a multidisciplinary approach. Alcoholic abuse still represents a significant source of decompensated cirrhosis in Western countries.

Patients with cirrhosis are at risk of developing bacterial infections due to various factors including bacterial translocation and immune dysfunction. Even though the prognosis has improved over time, mortality rates remain relatively high (about 20% for spontaneous bacterial peritonitis [SBP]) [1,13]. About 25-30% of patients develop infections during hospitalization. Thus, preventing infection is an important goal. Long term administration of antibiotics in patients with ascites and low ascitic fluid protein concentrations is a controversial issue. A recent randomized trial comparing the long term administration of norfloxacin to placebo has shown that norfloxacin was associated with lower mortality in patients with protein ascitic fluid concentration ≤15g/L [2]. It is interesting to note that norfloxacin did not increase the rate of multidrug resistant infections. Albumin has been recommended in association with antibiotics for the treatment of SBP for more than 3 decades. However, the role of albumin in the treatment of bacterial infections other than SBP has been controversial [3]. Recently, a large controlled

trial comparing intravenous albumin (40g twice weekly for two weeks and then 40g weekly for up to 18 months) was associated with a significant improvement in 18-month survival in patients with decompensated cirrhosis [4]. In this study, patients receiving albumin were less likely to develop SBP, infections other than SBP, severe encephalopathy and renal dysfunction. This study raises the issue of the systemic administration of albumin in patients with advanced cirrhosis. Even if albumin was associated with a better outcome, the difference in survival was modest compared to standard medical therapy.

Acute on chronic liver failure (ACLF) is a syndrome with a high rate of early mortality defined by the occurrence of organ failure(s) in patients with cirrhosis [5]. The higher the number of failed organs, the higher the mortality. Bacterial infections represent a frequent precipitating factor of ACLF. In a large European series of patients with ACLF, about 30% of those with culture positive infections were infected with multidrug resistant bacteria [6]. Antibiotic resistance was associated with a poor outcome. Depending on local epidemiology, early administration of large spectrum antibiotics is now recommended to treat infections, including community acquired infections, with de-escalation when possible.

Acute kidney injury (AKI) is also a common complication of advanced cirrhosis, and is predictive of a worse outcome. Early recognition of AKI and early identification of the phenotype of AKI are essential to initiate appropriate therapy at an early stage and to improve outcome. Patients with advanced cirrhosis have reduced muscle mass (especially women) and decreased creatine production. Thus, patients with serum creatinine within the normal range may have markedly impaired renal function. The definitions of AKI in cirrhosis have recently been revised to take into account these difficulties [7]. AKI in cirrhosis is now defined by an increase in serum creatinine $\geq$ 0.3 mg/dL (26.5 μmol/L) within 48 hours or a percentage increase of serum creatinine $\geq$ 50% from baseline which is known or presumed to have occurred within the prior 7 days. AKI is then categorized into 3 stages of increasing severity.

Hepatorenal syndrome (HRS) is considered to be one of the different phenotypes of AKI in cirrhosis, termed AKI-HRS. A distinction must be made between HRS and acute tubular necrosis (ATN) because vasoconstrictors such as terlipressin are only justified in the presence of HRS. Besides criteria for the clinical definition, urinary neutrophil gelatinase (NGAL) associated lipocalin, a biomarker of tubular damage, is significantly higher in patients with ATN compared to those with HRS. However, no clear cut off value differentiates HRS from AKI. Terlipressin has been shown to be effective in reversing HRS in at least 50% of patients. However, even in responders to terlipressin, life expectancy is limited in the absence of liver transplantation. The incidence of adverse events is significantly lower with a continuous infusion of terlipressin than with boluses, with a similar rate of responders [8].

Non-selective beta blockers (NSBBs) are extensively used in patients with cirrhosis in the primary or secondary prophylaxis of variceal bleeding. Interestingly, recent data suggest that NSBBs in patients with refractory ascites are associated with a worse outcome [9]. Patients with NSBBs are at higher risk of developing paracentesis-induced circulatory dysfunction. NSBBs may compromise the adaptative capacity of the heart in patients with important fluctuations in central volume and may precipitate AKI. NSBBs should be used with caution in patients with refractory ascites and large varices. However, not all the results of these studies showed a negative impact of NSBBs on survival in patients with refractory ascites.

Transjugular intrahepatic portosystemic shunts (TIPS) are an alternative to large volume paracentesis. A recent controlled trial in patients with recurrent ascites has shown a benefit to transplant-free survival with TIPS compared to standard medical therapy [10]. However, TIPS may be contraindicated in patients with advanced cirrhosis and/or patients with present or past encephalopathy. Another recent option is the insertion of an automated low flow pump that derives ascites from the peritoneal cavity to the bladder (Alfapump®). Ascites is then eliminated in the urine. A preliminary controlled trial in a relatively small number of patients has shown that Alfapump® reduces significantly the need for paracentesis and improves quality of life [11]. Larger studies are needed to evaluate changes in nutritional status with the Alfapump® and any possible impact on survival.

Liver transplantation is the best option in patients with advanced cirrhosis. Since the implementation of the MELD score-based allocation policy, priority for transplantation is given to the most severely ill patients. More patients with impaired renal function are listed and transplanted. The proportion of patients receiving combined liver and kidney transplantation has increased in several countries in Europe as well as in the United States. The upper limit in terms of disease severity that defined transplant futility (too low probability of survival to justify transplantation) is a matter of debate. In particular, which patients with cirrhosis in the ICU with organ failures should be transplanted and which patients should not is an important issue. Several recent series have shown that good results can be achieved in patients with ACLF, at the cost of higher morbidity and longer hospital stays. However, whether patients with grade 3 ACLF are good candidates for transplantation is still a subject of debate due to contrasting results in the literature [12]. A case by case selection is needed. In these patients with cirrhosis and organ failure, the CLIF SOFA score is a better prognostic tool than the MELD score.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460.
2. Moreau R, Elkrief L, Bureau C, Perarnau JM, Thevenot T, Saliba F, et al. Effects of Long-term Norfloxacin Therapy in Patients With Advanced Cirrhosis. Gastroenterology 2018. In press, uncorrected proof, Available online 23 August 2018
3. Guevara M, Terra C, Nazar A, Sola E, Fernandez J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol 2012;57:759-765.
4. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417-2429.
5. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-1437, 1437 e1421-1429.
6. Fernandez J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2018.

7. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968-974.
8. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology 2016;63:983-992.
9. Serste T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010;52:1017-1022.
10. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology 2017;152:157-163.
11. Bureau C, Adebayo D, Chalret de Rieu M, Elkrief L, Valla D, Peck-Radosavljevic M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: A multicenter randomized controlled study. J Hepatol 2017;67:940-949.
12. Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708-715.
13. Asselah T, Marcellin P, Schinazi RF Treatment of hepatitis C virus infection with direct acting antiviral agents: 100% cure ? Liver Int. 2018 Feb;38 Suppl 1:7-13. doi: 10.1111/liv.13673. Review.

Optimal management of portal hypertension

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Key points

- Transient elastography may be useful for the early identification of patients at risk of developing clinically significant portal hypertension.
- Etiological treatment of the underlying liver disease may reduce portal hypertension up to a certain level.
- Reduction of dose or discontinuation of NSBB can be considered in patients with refractory ascites who develop low blood pressure and impairment in renal function.
- In patients with variceal bleeding, antibiotic prophylaxis is mandatory and should be instituted from admission.
- Early TIPS placement improves the survival of high risk-patients with acute variceal bleeding (e.g. Child-Pugh class C <14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy. Criteria for high risk patients are being redefined.

Portal hypertension (PH) is a severe complication of chronic liver disease (CLD). Cirrhosis is the most frequent cause of PH and its complications, such as esophageal and gastric varices, variceal bleeding, ascites, spontaneous bacterial peritonitis and other infections, hepatorenal syndrome and portosystemic encephalopathy[1]. These complications represent the first cause of death and the main indication for liver transplantation in these patients.

Cirrhosis is a heterogeneous disease that is currently classified in two main stages: compensated and decompensated cirrhosis[2].

A new entity called compensated advanced chronic liver disease (cACLD) has been proposed to reflect that severe fibrosis and cirrhosis is a continuum in asymptomatic patients, and that distinguishing between the two stages is often clinically impossible[3]. Portal hypertension may occur before an established histological diagnosis of cirrhosis.

Hepatic venous pressure gradient (HVPG) measurement is the gold-standard method to assess the presence of PH.

To confirm cACLD, invasive methods include liver biopsy showing severe fibrosis or established cirrhosis, upper GI endoscopy showing gastroesophageal varices and/or HVPG measurement with values >5 mmHg indicating sinusoidal PH or >10 mmHg indicating clinically significant PH (CSPH).

The introduction of transient elastography (TE) into clinical practice has allowed the early identification of patients with CLD at risk of developing CSPH. Liver stiffness by TE is useful to suggest cACLD in asymptomatic subjects with known causes of CLD. Patients with a liver stiffness <20 kPa and with a platelet count >150.000 have a very low risk of having esophageal varices requiring treatment, and can avoid screening endoscopy[3].

Treatment of PH differs depending on the stages of cirrhosis, since the prognosis, mechanisms of disease and therapeutic targets are different.

The treatment of PH includes the prevention of first bleeding, the treatment of acute variceal bleeding and the prevention of recurrent bleeding.

Prevention of first bleeding

Etiological treatment of the underlying liver disease may reduce PH and prevents complications in patients with established cirrhosis.

In patients with no varices or small varices, there is no indication to use beta blockers to prevent the formation of varices[3].

Patients with small varices with red wale marks or Child-Pugh C class have an increased risk of bleeding and should be treated with non-selective beta blockers (NSBB). Patients with small varices without signs of increased risk may be treated with NSBB to prevent bleeding[3]. Patients with medium-large varices should be treated either with NSBB or endoscopic band ligation for the prevention of the first variceal bleeding[3,4]. The choice of treatment should be based on local resources and expertise, patient characteristics, contraindications and adverse events. Traditional NSBB (propranolol, nadolol) and carvedilol are valid first line treatments[4,5].

Measurement of HVPG offers additional relevant information on the response to therapy. A decrease in HVPG of at least 10% from baseline or to <12 mmHg after chronic treatment with NSBB is associated with a significant reduction in the risk of variceal bleeding[6]. However, the decision to treat with betablockers should be taken when indicated, independently of the possibility of measuring HVPG.

The use of statins to reduce portal pressure is one of the promising new strategies and should be evaluated in further studies since clinical evidence of a beneficial effect of statins on the complications of PH or survival is still lacking[7].

Cyanoacrylate injection appears to be more effective than beta blockers in preventing first bleeding in patients with large gastroesophageal varices type 2 or isolated gastric varices type 1. Further studies are needed to evaluate the risk/benefit of using cyanoacrylate in this setting.

The safety of NSBB in subgroups with end-stage disease (refractory ascites and/or spontaneous bacterial peritonitis) has been questioned[8]. Close monitoring is necessary in patients with refractory ascites, and a reduction in the dose or discontinuation can be considered in those who develop low blood pressure and impairment in renal function. If NSBB are stopped, endoscopic band ligation should be performed.

Treatment of acute bleeding

When an acute bleeding episode occurs in patients with cirrhosis and PH, Child-Pugh class C, the updated MELD score, and failure to achieve primary hemostasis are the variables most consistently found to predict six week mortality[3]. Patients with acute variceal bleeding should be considered for intensive care unit. The goal of resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore hemodynamic stability. Packed red blood cell transfusion should be done at a target hemoglobin level of between 7 and 8 g/dl. Antibiotic prophylaxis is mandatory and should be started at admission. Intravenous ceftriaxone (1g/24h) should be considered in patients with advanced cirrhosis, in settings with a high prevalence of quinolone-resistant bacterial infections and in patients on quinolone prophylaxis. Either lactulose or rifaximin may prevent hepatic encephalopathy. However, further studies are

needed to evaluate the risk/benefit and to identify high risk patients before formal recommendations can be made.

When variceal bleeding is suspected, vasoactive drugs should be started, ideally before endoscopy. Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy and continued for up to five days.

Endoscopy should be performed within 12h of presentation in patients with cirrhosis presenting with GI bleeding. In patients with altered consciousness, endoscopy should be performed and the airway should be protected. Ligation is the recommended form of endoscopic therapy for acute esophageal variceal bleeding. Endoscopic therapy with a tissue adhesive (e.g. N-butylcyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) and type 2 gastroesophageal varices (GOV2) that extend beyond the cardia. EVL or a tissue adhesive can be used in bleeding from type 1 gastroesophageal varices (GOV1)[3,8].

Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) placement with polytetrafluoroethylene (PTFE)-covered stents within 72h (ideally 24h) improves survival in high risk-patients with acute variceal bleeding[9]. This must be considered in patients bleeding from EV, GOV1 and GOV2 at high risk of treatment failure (e.g. Child-Pugh class C <14 points or Child-Pugh class B with active bleeding) after initial pharmacological and endoscopic therapy. The criteria for high risk patients are being redefined.

Because of the high incidence of severe adverse events, balloon tamponade should only be used in refractory variceal bleeding, as a temporary ‘‘bridge’’ (for a maximum of 24 h), until definitive treatment can be instituted[3].

Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by PTFE-covered TIPS. Rebleeding during the first five days may be managed by a second attempt at endoscopic therapy. If rebleeding is severe, PTFE-covered TIPS is probably the best option.

Prevention of recurrent bleeding

Prevention of recurrent variceal hemorrhage should be obtained with the combination of NSBB (propranolol or nadolol) + endoscopic band ligation[3,10]. Ligation should not be used as monotherapy unless there is intolerance/contraindications to NSBB. NSBB should be used as monotherapy in patients with cirrhosis who cannot be treated with band ligation. Covered TIPS is the treatment of choice in patients that fail first line therapy (NSBB + band ligation).

In patients with portal hypertensive gastropathy, NSBB are first line therapy in preventing recurrent bleeding[3]. TIPS may be considered in patients in whom NSBB and/or endoscopic therapies fail.

References

1. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: Rational basis, available treatments and future options. J Hepatol 2008;48 Suppl 1:S68-S92.
2. Garcia-Tsao G, Abraldes JG, Berzigotti A and Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2017;65:310-35

3. De Franchis R and Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
4. Lebrec D, Nouel O, Corbic M, Benhamou JP. Propranolol: A medical treatment for portal hypertension? Lancet 1980;2:180-2.
5. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009;50:825-33.
6. Bureau C, Peron JM, Alric L, Morales J, Sanchez J, Barange K, et al. "A la carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology 2002;36:1361-6.
7 Abraldes JG, Albillos A, Banares R, Turnes J, Gonzalez R, Garcia-Pagan JC, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009;136:1651-8.
8. Angeli P, Wong F, Ginés P, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968–74.
9. Garcia-Pagan JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362:2370-9.
10. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: A controlled study. N Engl J Med 1981;305:1371-4.

Liver transplantation for alcoholic hepatitis

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Key points

- In patients with severe alcoholic hepatitis the failure of medical therapy can be rapidly identified. Six-month survival is around 30% in these patients.
- Expert guidelines no longer recommend a fixed period of abstinence before transplantation.
- Early liver transplantation in these patients is an attractive but highly controversial option because it challenges the 6-month abstinence rule before liver transplantation.
- Two recent American studies have provided additional data supporting early liver transplantation as rescue therapy in patients with severe alcoholic hepatitis who fail to respond to medical therapy and confirmed low rates of alcohol use post-liver transplantation.

Does the 6-month rule limit access to liver transplantation for the most severely ill patients?

The optimal timing for liver transplantation in alcoholic patients differs markedly among transplant programs. Decisions on transplant eligibility should be made on an individual basis, with careful prediction of short-term survival. In the particular setting of non-responders to corticosteroids, strict application of a period of sobriety as a policy for transplant eligibility is unfair, because most of these patients will die before the end of the 6-month period of sobriety.

It is well established that doctors and the public do not share the same viewpoint on graft allocation. It is important to increase public awareness. In particular, most philosophers and ethicists feel that patients with self-inflicted diseases should have the same access to medical resources, and that personal responsibility should not influence the decision to transplant.

Early liver transplantation improves patient survival

Patients with severe alcoholic hepatitis who fail medical therapy can be identified early. They have a 6-month survival of around 30%. As most deaths occur within 2 months, early liver transplantation in these patients is an attractive but highly controversial option, because it challenges the 6-month abstinence rule before liver transplantation. The first study evaluating early liver transplantation in patients with severe alcoholic hepatitis undergoing their first episode of liver disease that failed medical therapy showed significant improvement in survival in patients who were transplanted early. Patients were carefully selected on the following criteria: full consensus of the paramedical and medical staff, no co-morbidities, social integration and supportive family members [1]. The results of this study support future

evaluation in highly selected patients with severe alcoholic hepatitis who fail medical therapy [2]. Early liver transplantation was associated with a low rate of recurrent alcohol use and good adherence to medical regimens in the absence of graft dysfunction. Two recent American studies have provided additional data supporting early liver transplantation as rescue therapy in patients with severe alcoholic hepatitis who fail to respond to medical therapy. They confirmed low rates of alcohol use post-liver translation [3, 4].

The fear that early liver transplantation may decrease organ donation is not supported by a survey showing that most potential donors were supportive or neutral about this new indication [5]. Only ethical principles recommending active treatment of patients without discrimination, and the best scientific knowledge should be applied in the evaluation of changes in clinical practices [6]. However, due to organ shortage, the selection process of patients with severe alcoholic hepatitis should remain stringent to limit transplant availability in this group. The use of a combination of baseline MELD score [7] and the Lille score at 7 days [8] seems to be the most effective approach to identify patients with the highest risk of short-term mortality and to limit the number of unnecessary procedures [9].

Unlike the recommendations from the past decade [12] expert guidelines no longer recommend a fixed period of abstinence prior to transplantation [10, 11] and they have stopped listing alcoholic hepatitis as an absolute contraindication [10] to liver transplantation.

References

1. Mathurin P Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallee JC. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011; 365: 1790-1800.
2. Brown RS. Transplantation for alcoholic hepatitis--time to rethink the 6-month "rule". N Engl J Med 2011; 365: 1836-1838.
3. Im GY Kim-Schluger L, Shenoy A, Schubert E, Goel A, Friedman SL, Florman S, Schiano TD. Early Liver Transplantation for Severe Alcoholic Hepatitis in the United States--A Single-Center Experience. Am J Transplant 2016; 16: 841-849.
4. Lee B. P.,Chen P. H.,Haugen C.,Hernaez R.,Gurakar A.,Philosophe B.,Dagher N.,Moore S. A.,Li Z.,Cameron A. M. Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis. Ann Surg 2017; 265: 20-29.
5. Stroh G.,Rosell T.,Dong F.,Forster J. Early liver transplantation for patients with acute alcoholic hepatitis: public views and the effects on organ donation. Am J Transplant 2015; 15: 1598-1604.
6. Donckier V Lucidi V, Gustot T, Moreno C. Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. J Hepatol 2014; 60: 866-871.
7. Kamath PS Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33: 464-470.
8. Louvet A Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin

P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007; 45: 1348-1354.

9. Louvet A.,Labreuche J.,Artru F.,Boursier J.,Kim D. J.,O'Grady J.,Trepo E.,Nahon P.,Ganne-Carrie N.,Naveau S.,Diaz E.,Gustot T.,Lassailly G.,Cannesson-Leroy A.,Canva-Delcambre V.,Dharancy S.,Park S. H.,Moreno C.,Morgan T. R.,Duhamel A.,Mathurin P. Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis. Gastroenterology 2015; 149: 398-406 e398; quiz e316-397.
10. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol 2018.
11. Singal A. K.,Bataller R.,Ahn J.,Kamath P. S.,Shah V. H. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol 2018.
12. Bathgate AJ. Recommendations for alcohol-related liver disease. Lancet 2006; 367: 2045-2046.

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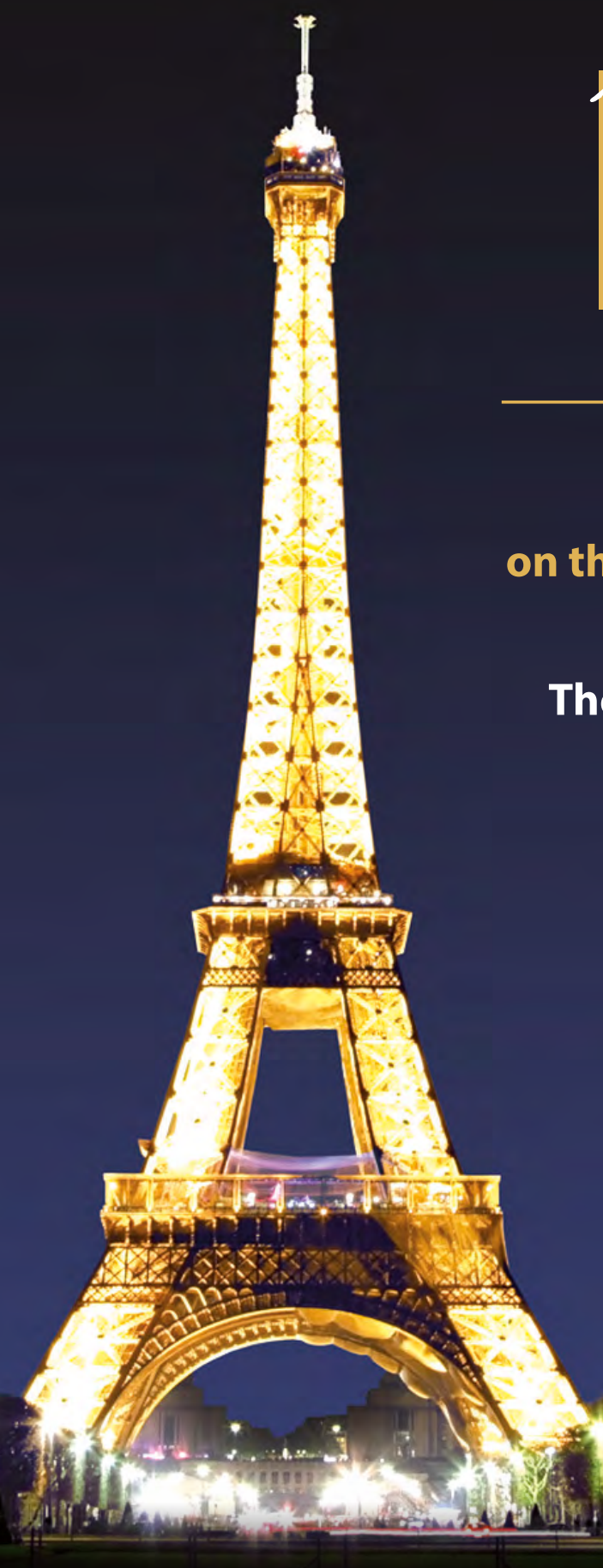

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