Take-home messages
from Monday 13th January 2020

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Hôpital Saint Joseph

13th PHC Paris

ry 2020
Hepatitis B: first session
therapy of hepatitis B today: HBV suppression

Who to treat? A critical review of the international guidelines?
New endpoints and biomarkers for treatment of CHB?
Optimal management of CHB patients under NUC?
## Who to treat: critical review of international guidelines

<table>
<thead>
<tr>
<th></th>
<th>HBeAg +</th>
<th></th>
<th>HBeAg -</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA</td>
<td>ALT</td>
<td>Liver Biopsy</td>
<td>HBV DNA</td>
</tr>
<tr>
<td></td>
<td>UI/mL</td>
<td>≥ 2x ULN</td>
<td>Or Fibrosis</td>
<td>UI/ml</td>
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<td></td>
<td></td>
<td>(NIM)</td>
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<tr>
<td>AASLD 2018</td>
<td>&gt;20.000</td>
<td>≥ 2x ULN</td>
<td>≥ 2000</td>
<td>≥ 2x ULN</td>
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<tr>
<td>APASL 2016</td>
<td>&gt;20.000</td>
<td>&gt;2x ULN</td>
<td>&gt;2000</td>
<td>&gt;2x ULN</td>
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<tr>
<td>EASL 2017</td>
<td>&gt;2000</td>
<td>&gt;ULN</td>
<td>&gt;A1 and/or &gt;F1</td>
<td>&gt;2000</td>
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<tr>
<td></td>
<td>&gt;20.000</td>
<td>&gt;2x ULN</td>
<td>&gt;20.000</td>
<td>&gt;2xULN</td>
</tr>
<tr>
<td>WHO</td>
<td>&gt;20.000</td>
<td>&gt;ULN</td>
<td>(&gt;30yo)</td>
<td>&gt;20.000</td>
</tr>
</tbody>
</table>

* All cirrhotic patients regardless HBV DNA or ALT should be treated

NIM: non invasive methods

Terrault NA et al. Hepatology 2018 67; 1560-1599
Who to treat: critical review of international guidelines

• The development of Guidelines is now a structured process with the global standard being GRADE, relying on systematic reviews to provide the highest quality of evidence
• The WHO and AASLD have structured scoping questions and systematic reviews in their guidelines
• Although there are some differences between AASLD, EASL, APASL and WHO guidelines, in general they are in agreement
• In the future, use of Risk Calculators may simplify selection of patients suitable for therapy
• The goal of current guidelines is to reduce disease progression and mortality, as the likelihood of cure is low but this may change with treatments that can achieve functional cure
# New endpoints and biomarkers for treatment of CHB

**Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference**

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Sterilizing ‘cure’</th>
<th>Idealistic functional ‘cure’</th>
<th>Realistic functional ‘cure’</th>
<th>Attainable Partial functional ‘cure’</th>
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<tr>
<td><strong>Clinical scenario</strong></td>
<td><strong>Never infected</strong></td>
<td><strong>Recovery after acute HBV</strong></td>
<td><strong>Chronic HBV with HBsAg loss</strong></td>
<td><strong>Inactive carrier off treatment</strong></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>Anti-HBs</td>
<td>Negative/Positive</td>
<td>Positive</td>
<td>Positive/negative</td>
<td>Negative</td>
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<td>HBeAg</td>
<td>Negative</td>
<td>Negative</td>
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<td>Negative</td>
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<tr>
<td>Serum HBV DNA</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Low level or not detected</td>
</tr>
<tr>
<td>Hepatic cccDNA, transcription</td>
<td>Not detected</td>
<td>Detected</td>
<td>Detected</td>
<td>Detected</td>
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<tr>
<td>Integrated HBV DNA</td>
<td>Not detected</td>
<td>Detected?</td>
<td>Detected</td>
<td>Low level</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None</td>
<td>None</td>
<td>Inactive, fibrosis regresses over time</td>
<td>Inactive</td>
</tr>
<tr>
<td>Risk of HCC</td>
<td>Not increased</td>
<td>Not increased</td>
<td>Declines with time</td>
<td>Risk lower vs. active hepatitis</td>
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Cornberg M et al. J Hepatol 2019, epub
New endpoints and biomarkers for treatment of CHB

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New HBV biomarkers – for a more refined characterisation of the activity of the infection and risk for adverse outcomes
### New endpoints and biomarkers for treatment of CHB

**Classification of HBV-cure with new biomarkers**

<table>
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<tr>
<th>THERAPY</th>
<th>Partial cure</th>
<th>Functional cure</th>
<th>Complete cure</th>
<th>Sterilizing cure</th>
</tr>
</thead>
</table>

- **Partial cure**
  - HBcrAg -
  - HBV RNA -
  - HBV DNA -
  - Low HBsAg
  - LHBs/MHBs -
  - Low anti-HBc

- **Risk of reactivation**

- **LOD**
  - 2.5 U/mL
  - 0.05 IU/mL
  - 150 cp/mL
  - 5 IU/mL

- **Bloodstream biomarkers**

- **Intrahepatic biomarkers**

- **cccDNA**

- **Integrated HBV DNA**

Charre C et al. Antiviral Res 2019; 169: 104553
New endpoints and biomarkers for treatment of CHB

Chance for transition into a true functional or even complete cure stage after having achieved a partial cure?

Follow-up (1-> 10 yrs?)

- HBcrAg -
- HBV RNA -
- HBV DNA -
- Low HBsAg
- LHBs/MHBs -
- Low anti-HBc

Risk of reactivation

Modified according to Charre C et al. Antiviral Res 2019; 169: 104553
Optimal management of CHB under NUC

- **proper assessment** before starting therapy
- **selection of the most appropriate NUCs** for treatment, particularly in special populations
- switching to TAF when there are risk factors for TDF use
- **adequate HCC surveillance**, regardless of the type of NUC
- **Finite therapy duration**: further study investigating potential predictive factors of achieving HBsAg loss after stopping therapy
State of the art lecture

New EASL recommendations for the management of occupational liver disease
Take Home Message

- Collecting the occupational history is crucial. Patients must be assessed by a multidisciplinary team.

- Acute liver disease is rare compared to chronic liver injury. There are many sensitizing cofactors.

- Liver angiosarcoma is clearly associated with high exposure to vinyl chloride (in the past only), HCC is possible, cirrhosis is unlikely.

- Hepatitis and cholestasis are the dominant occupational lesions, often obscured by comorbidities such as alcohol and metabolic steatohepatitis.

- The unmet needs: availability of specific tests of toxicity.
Unmet Needs and Future Research

- A step forward in improving safety in the workplace is collecting cohort data from occupational exposure registries including clinical, biochemical and follow-up information in order to obtain incidence figures of hepatotoxicity and trends in re (emerging) OLD.

- The development and quantification of sensitive and specific biomarkers of liver damage caused by toxicants that may help in fine-tuning of differential diagnosis, without the need for histological examination of the liver. Could provide clues to prognosis.

- Advancements in the field of biomarkers would allow more effective risk stratification algorithms, while providing mechanistic insights that would help the development of safe and effective treatments.
Clinical case

Approach to the patient with CHB and decompensated cirrhosis
<table>
<thead>
<tr>
<th>HBV unknown</th>
<th>HBV known but not being treated</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Chronic progression of active HBV | HBV flair as a result of: • E-antigen seroconversion  
 • Treatment of HCV  
 • Cancer chemotherapy  
 • Treatment of immune disease  
   - High dose corticosteroids  
   - Calcineurin inhibitors  
   - Biologic agents | Start or restart oral HBV treatment  
 Stop inciting agent:  
 • Chemotherapy  
 • Immune suppressive agent  
 • PEGINF  
 Consider for transplant if liver function does not improve |
## HB DECOMPENSATED CIRRHOSIS NOT DUE TO HBV

<table>
<thead>
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<th>HB in active</th>
<th>Intervention</th>
</tr>
</thead>
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<tr>
<td>HBV suppressed on treatment</td>
<td>Treat or continue treating HBV</td>
</tr>
<tr>
<td>Progression of another liver disease</td>
<td></td>
</tr>
<tr>
<td>Acute alcoholic hepatitis</td>
<td>Treat the inciting agent</td>
</tr>
<tr>
<td>Acute non-HBV hepatitis</td>
<td>Stop the inciting agent</td>
</tr>
<tr>
<td>Drug induced liver injury</td>
<td>Consider for transplant if liver function does not improve</td>
</tr>
<tr>
<td>• Cancer chemotherapy</td>
<td></td>
</tr>
<tr>
<td>• Check-point inhibitors</td>
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</table>
Hepatitis B: second session
therapy of hepatitis B tomorrow: HBV cure

Can we cure HBV with novel direct antivirals?
Boosting innate and adaptive immunity for HBV cure?
Will we need novel combinations to cure HBV infection?
Can we cure HBV with novel direct antivirals?

Cure of HBV infection with direct acting antivirals

- Curing infected hepatocytes
- With pre- and post- cccDNA targets
  - Accelerate the kinetics of cccDNA decay
  - Combination therapy likely required
  - Duration of treatment will depend on the rate of hepatocyte turn-over
  - Major issue: cccDNA half-life, number of infected cells, infected hepatocyte half-life?
- Direct targeting of cccDNA
  - Cytokine-mediated degradation
  - Nuclease-based gene editing
  - Small molecules
  - Still a long way to go: specificity, safety profile, delivery issues...
- Will this be sufficient or will we need combinations with immunomodulatory approaches?
Pathways to Achieving Functional Cure

**Inhibit Viral Replication**
- Virions (HBV DNA)
- +/- CpAM
- +/- RNAi
- +/- Entry inhibitor
- +/- cccDNA inhibitor

**Lower Viral Antigen Burden**
- HBeAg
- HBsAg
- Oligonucleotide
- Nucleic acid polymer
- +/- cccDNA inhibitor

**Boost Immune Response**
- NK cells
- T cells
- B cells
- Macrophages
- PD-1; PDL1
- Lymphotoxin B
- T Cell reprogramming
- Therapeutic vaccine

**NUC**
- siRNA

**TLR / RIG-I agonist**
Why Immune therapies didn’t (so far) work?

- CHB is characterized by defects in the intrahepatic innate immune responses, NK cells impaired in their anti-viral capacity, deeply dysfunctional HBV-specific T cells and the expansion of functionally defective HBsAg-specific atypical memory B cells

- Multiple approaches aimed to activate the intrahepatic innate immunity and to restore HBV specific adaptive immunity are actively pursued

IFN-alpha remains the only therapy that increases functional cure

Why Immune therapies didn’t (so far) work?

- Immune therapy could be an important asset for HBV cure but patients selection is crucial

- Immune therapies need to be personalized in relation to the immune profile of disease and not only to virological parameters
Will we need novel combinations to cure HBV?

Synergistic mechanisms need to incorporate a decrease in HBV transcription, loss of cccDNA or altered epigenetic regulation of cccDNA and immune modulation or immunologically stimulated hepatocyte cell turnover.

Nucleoside analogue suppressed patients being included in many current trials. Trials are progressing to combination therapy as additive or synergistic effects are sought.

These trials will provide important insights into the biology of HBV and perturbations of the immune response, required to effect HBsAg loss at different stages of the disease.
State of the art lecture

Hepatitis E: what is the real issue?
The issue of hepatitis E in 2020

- Incidence is high and rising
- Role of subtype (3f)
- There is a risk of transmission by transfusion
- Neurological disorders are frequent
- Treatment of acute hepatitis E with ribavirin in immunocompetent patients
- Second line treatment of chronically infected patients
Hepatitis Delta

New epidemiology of hepatitis delta?
How to optimize current therapy with PEG IFN?
New drugs for HDV?
Estimated prevalence of HDV infection with genotype distribution

New epidemiology of hepatitis delta?

- HDV infection: global health problem - increased liver related and overall mortality
- Global HDV prevalence: probably underestimated
- HDV: still endemic in many developing countries
- Illicit drug users, people with high-risk sexual behaviors and HIV co-infected: high-risk groups in the Western world
- Genuine decrease in HDV prevalence in developed countries in 1990’s - no further decline and perhaps a slight increase in the last decade due to migration from endemic countries
- Need for universal HBV vaccination and universal HDV screening for HBV+ patients
How to optimize current therapy with PEG IFN?

- Off-label use of PegIFN (48 weeks) is currently the only recommended therapy by international guidelines.
- Indications: chronic hepatits and compensated cirrhosis.
- Virologic response: approx 20%-30% at week 24 post-treatment but high risk (50%?) of late relapse.
- Strategies to improve effectiveness: combo with NUC, extension to 96 weeks, lambda IFN.(no/limited evidence so far)
- Predictors of response: early on therapy decline of HBsAg and/or HDV-RNA (to be confirmed)
- Long-term outcome: improved in sustained responders.
- New anti-HDV therapies are urgently needed (with pegIFN?).
New drugs for HDV?

- Drugs in development include entry inhibitors (Bulevirtide), prenylation inhibitors (Lonafarnib), and HBsAg release inhibitors (NAP: REP 2139).
- There is a need for long-term robust end-points (HCC, cirrhosis decompensation).
- HBV cure program will also lead to HDV cure, but only in a long-term.
Awards PHC 2020

The future of autoimmune liver disease
The future of Autoimmune liver disease

- New biomarkers are needed to predict non-response to UDCA in PBC
- Obeticholic acid (OCA) and bezafibrate are used for non-response to UDCA in PBC, the combination of both and novel drugs like Selective peroxisome proliferator-activated receptor (PPAR) and fibroblast growth factor 19 (FGF19) agonists are under development.
- There is no existing treatment that alters the natural course of PSC apart from transplantation.
- Several medical therapies for PSC are under clinical development like Nor-UDCA, Fecal Microbiota Transplantation (FMT) and others.
- However, generally accepted treatment endpoints as well as biomarkers for the risk-stratification are still needed for the development of novel PSC therapies.
- Therapies for non-responders to standard-of-care are an unmet need for AIH patients.
- Promising AIH therapies under development are targeting B cells, cytokines like TNF and IL 2 and Tregs.
Hepatitis C: the elimination
The last difficult to treat patients
Macro elimination
Micro elimination
The last difficult to treat patients

• Several challenge:
  – Homeless people / PWID
  – DDI
  – Treatment of patients with CKD 4/5 patients and decompensated cirrhosis
  – Treatment of decompensated cirrhosis with or without LT options
  – Non responders to SOF/VEL/VOX HCV
  – treatments with HCC BCLC stage B/C
  – Pregnant women

• Several challenges remain in small populations. Most likely that these populations disappear faster than the challenges are solved
  – e.g. patients with decompensated cirrhosis

• Key challenges to reduce the burden of disease in geographic regions and populations:
  – Diagnosis rates
  – Linkage to care
  – Access to DAAs
HCV Macro-elimination

• WHO elimination goals to be reached 2030

• HCV diagnosis 90%, treatment coverage 80%, reduction of deaths 65%

• By 2017 only 12 countries on track to reach these goals

• Barriers for elimination still remain, awareness of the infection, economy for testing and treatment, linkage to care

• Reducing global burden depends on success of prevention, outreached screening and treatment and progress in key high-burden countries
HCV Macro-elimination

What is needed for HCV elimination and where are the patients?

84% of high income countries are not on track to meet the WHO´s 2030 targets
Collaboration between stakeholders is essential to achieve HCV elimination.
Micro-elimination

• At least three populations with increase complexity to reach:
  – Easy to screen patients
  – High risk of transmission patients
  – Difficult to reach patients

• Access to care even in easy to treat patients may be hard

• So be pragmatic and adopt policy at each situation
State of the art lecture

Vascular liver disease: new advance
Advance in vascular liver disease

• Diagnosis of congenital extrahepatic portosystemic shunt, and its closure, should be liberally considered.

• Slowing of portal blood flow parallels progression of cirrhosis and development of PVT. Still, no threshold of velocity triggering anticoagulation therapy has yet been established.

• Nonspecific beta-blockers may contribute to PVT. Direct evidence and exact mechanism still to be provided. No changes in current practice are yet warranted.

• Transient PVT is most common in cirrhosis. Its role as an indicator for subsequent extrahepatic extension or a factor for aggravating liver disease requires further studies.
Thank you for your attention

A great thanks to all speakers who provide me their presentation