Take-home messages from Monday 14th January 2019

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Hôpital Saint Joseph
12th PHC
Paris
January 2018
Hepatitis C : first session

Is there still a role for personalized treatment ?
Is DAA treatment failure still an issue?
Are there still difficult to treat patients ?
Is there still a role for personalized treatment?

• Good medicine is ALWAYS personal

• Detailed pre-treatment assessment allows optimal therapy

BUT

• Pre-treatment assessment reduces access

Don’t let the perfect be the enemy of the good
Is DAA treatment failure still an issue?

- We have options for any DAA's failure in 2019

**DAA1 non NS5A**: SOF+PEG±RBV, SOF±RBV, SOF+SMV±RBV,
**DAA1 NS5A**: LDV/SOF±RBV, SOF+DCV±RBV, DCV+PEG±RBV, OBV/PTVr+DSV±RBV, OBV/PTVr±RBV, EBR/GZR±RBV, SOF/VEL.
**DAA2 NS5A**: SOF/VEL/VOX, glecaprevir/pibrentasvir, SOF+ glecaprevir/pibrentasvir

Marc Bourliere PHC 2019
Are there still difficult to treat patients?

• High & pangenotypic efficacy of the different regimens removed the « special » and almost the « difficult-to-treat » populations

• The 3 main remaining difficulties are mainly related to drug-drug interaction (including phytotherapy) and adherence

• Safety of DAAs is fair which does not exclude very rare and potentially severe adverse events nor their cautious prescription
State of the art lecture

Access to treatment and linkage to care
Access to treatment and linkage to care

- Barriers to HCV therapy still exist despite the availability of medications with near-universal efficacy.
- Barriers exist at multiple levels: Patient, provider, health system.
- While every country has unique challenges, some barriers are common across all countries.
- Goal of global elimination of HCV.
- May start with microelimination projects.
- Numerous examples of successful programs indicate that removing barriers and improving access to care is possible.
Patients with chronic HCV and decompensated cirrhosis are the most difficult to manage in the DAA era.

The SVR is lower – only 85-95%.

Achieving a SVR in a patient with advanced symptomatic cirrhosis may not improve quality of life.

- MELD purgatory
- Not appropriate for all patients
- Best for patients with:
  - Low MELD
  - Non-liver transplant candidates
Clinical case: Treatment of HCV decompensated cirrhosis

✓ Challenges of treating HCV:
  • Patients may decompensate further during treatment
  • Hospitalization may impact compliance
  • Agents containing a protease inhibitor cannot be used
  • High rate of AKI limits use of SOF containing agents
  • Although recommended it is difficult to use ribavirin

✓ Patients with cirrhosis who achieve SVR remain at increased to develop:
  • Hepatocellular carcinoma
  • Additional episodes of hepatic decompensation
Hepatitis C: second session

HCV therapies: the last challenges
How to treat HCV-HBV co-infections?
Do DAAs decrease the risk of HCC?
HCV therapies: the last challenges

• Several challenges remain in small populations. Most likely that these populations disappear faster than the challenges are solved
  – e.g. patients with decompensated cirrhosis
• Some challenges remain in large populations
  – e.g. HCC surveillance after SVR
• Some challenges are key to reduce the burden of disease in geographic regions and populations
  – Diagnosis rates, linkage to care, and access to DAAs
• One challenge to indeed eliminate HCV globally
  – Vaccine development
How to treat HCV-HBV co-infections?

• All patients scheduled for treatment of HCV infection should be tested for HBsAg.

• At least patients with confirmed or suspected immunodeficiency should be additionally tested for anti-HBc.

• Prophylaxis with potent nucleoside/nucleotide analogue should be administered at least 4 weeks before start of anti-HCV treatment in all HBsAg-positive and immunodeficient HBsAg-negative/anti-HBc-positive patients and continued at least until 12 weeks after HCV treatment termination.

• Immunocompetent HBsAg-negative/anti-HBc-positive patients probably do not need specific monitoring for possible HBV reactivation.
Do DAAs decrease the risk of HCC?

DAAs and cancer risk: Viral cure does not eliminate HCV-induced epigenetic changes

Cartoon modified from Zeisel et al., J. Hepatol. 2013

HCC occurrence after DAAs: the take-home message

Successful antiviral therapy reduces but does not eliminate, the risk of HCC development

Antonio Craxi, Massimo Levrero PHC 2019
Do DAAs decrease the risk of HCC?

HCC recurrence after DAAs: the take-home message

• Patients with HCV cirrhosis and a previously cured HCC remain at risk of cancer recurrence after HCV eradication

• The risk of HCC recurrence is lower than in non-eradicated patients, and is proportional to previous HCC recurrence and tumor size

• Preliminary data in patients with previous cured HCC suggest that the response rate to DAAs is excellent and that survival may be higher in SVR patients despite HCC recurrence

• DAAs should not be withheld in these patients

Antonio Craxi, Massimo Levrero PHC 2019
State of the art lecture

Autoimmune hepatitis
Autoimmune hepatitis

- Female gender
- Extrahepatic autoimmune syndromes
- Hypergammaglobulinia (IgG)
- Autoantibodies: ANA, LKM-1, SMA, SLA/LP
- Genetics: HLA DR 3, DR 4, AIRE
- Histology

Immunosuppressive Therapy

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<tr>
<th>Feature/parameter</th>
<th>Discriminator</th>
<th>Score</th>
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<tbody>
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<td>Antibodies (max 2 points)</td>
<td>≥1:40</td>
<td>+1</td>
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<tr>
<td></td>
<td>≥1:80</td>
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<td>≥1:40</td>
<td>+2</td>
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<td>Any titre</td>
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<tr>
<td>IgG or γ-globulins level</td>
<td>&gt;ULN</td>
<td>+1</td>
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<tr>
<td></td>
<td>&gt;1.1x ULN</td>
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<tr>
<td>Liver histology</td>
<td>Compatible with AIH</td>
<td>+1</td>
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<tr>
<td>(evidence of hepatitis is required)</td>
<td>Typical of AIH</td>
<td>+2</td>
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<tr>
<td></td>
<td>Atypical</td>
<td>0</td>
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<td>Absence of viral hepatitis</td>
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<td>Yes</td>
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Score ≥7 = Definite AIH
Score ≥6 = Probable AIH
Autoimmune hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Prednisone (mg/day)</th>
<th>Prednison (mg/day)</th>
<th>Azathioprine USA (mg/day)</th>
<th>Azathioprine EU (mg/kg/day)</th>
<th>Cyclosporine A 3-5 mg/kg kg/qd</th>
<th>Tacrolimus 3 mg bid (5 – 7 ng/ml)</th>
<th>Mycophenolate Mofetil 750-1000 mg bid</th>
<th>Methotrexate 10 mg per week</th>
<th>Cyclophosphamide 1-1.5 mg/kg/day</th>
<th>Everolimus 0.75-1.5mg bid (3-6ng/ml)</th>
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<td>Week 1</td>
<td>60</td>
<td>30</td>
<td>50</td>
<td>1 - 2</td>
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<tr>
<td>Week 2</td>
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<td>20</td>
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<td>1 - 2</td>
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<td>Maintenance-Therapy</td>
<td>20 and less</td>
<td>10</td>
<td>50</td>
<td>1 - 2</td>
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**Reasons for Choice of Therapy**
- Cytopenia
- Thiopurinmethytransferase-Deficiency
- Pregnancy
- Tumors
- Therapy ≤6 Mo
- Postmenopausal
- Osteoporosis
- uncontrolled Diabetes, Hypertension, Obesity
- Acne
- Emotional Instability
- Cystitis, leucopenia
- Proteinuria, lipid disturbance, acne
- DIabetes, neuropathy
- Hypertension renal insufficiency

**Anti TNF**
- Anti CD 20 (Rituximab)
- Anti B cell and anti BAFF-R (VAY736)

- Anti CD 3
- Low dose IL-2
- Adoptive transfer of Tregs?
NASH

How to characterize NASH?
Is change of life style counseling efficient?
Therapeutic advances
How to characterize NASH?

- NASH is defined by histology which makes from liver biopsy a mandatory procedure if definite diagnosis is needed.

- Liver biopsy is a robust procedure that can assess all components of NAFLD if performed by trained physicians (hepatologists and pathologists).

- An analytical description that reports Activity and Fibrosis in a semi-linear fashion is more appropriate than a dichotomous classification (NASH vs No NASH).

- LB is obviously not a screening tool and biomarkers are strongly needed to select patients at high risk of severe disease and who will need a biopsy.
How to characterize NASH?

Patients with suspected NAFLD

1st line: GP / Diabetologist

Rule-out advanced fibrosis
FIB-4 or NAFLD Fibrosis Score

FIB-4 < 1.3
NFS < -1.455
Low risk

FIB-4 ≥ 1.3
NFS ≥ -1.455
Intermediate to high risk

Attempt lifestyle modifications and exercise

No further assessment
Repeat evaluation at 1 year?

Rule-out other causes of liver disease (OH, HBV, HCV)

2nd line: Hepatologist

Rule-in advanced fibrosis
Transient Elastography

LSM < 8 kPa
Low risk

LSM ≥ 8 kPa
Intermediate to high risk

Consider Liver Biopsy

Attempt lifestyle modifications and exercise

Consider repeat evaluation (1 year)

Failure (XL probe)
3.0 - 6.7%

MRE,
2D SWE or ARFI according to local availability

FIB-4 < 1.3
NFS < -1.455
Low risk

FIB-4 ≥ 1.3
NFS ≥ -1.455
Intermediate to high risk

Pierre Bedossa & Laurent Castera PHC 2019
How to characterize NASH?

- **NIT**
  - Triage in large unselected populations

- **Liver biopsy**
  - Assessment in selected populations or in clinical trials

Best used as an integrated system to allow more efficient evaluation of patients with NAFLD

*Pierre Bedossa & Laurent Castera PHC 2019*
Is change of life style counseling efficient?

Lifestyle change is an effective treatment modality for curing/controlling NAFLD/NASH. Traditional measure of success = weight loss, but other important endpoints independent of weight: diabetes incidence & complications, CVS events, mortality, and cancer.

Lifestyle change is difficult to achieve

Three essential components: Cognitive behavioural Therapy + dietary modifications + physical activity changes → ALL required for successful outcomes
Bariatrics can improve liver histology

Histological resolution:
- Steatosis resolution: 66%
- Lob Inflammation: 50%
- Ballooning: 76%
- Fibrosis: 40%
- 12% had worsening fibrosis
- Overall GRADE quality low

Current status of drug treatment- impact on NASH resolution

- Populations different
- Endpoint evolution
- Methods of assessment
- Duration of treatment
Therapeutic advances

Fibrosis improvement with current agents

GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits
Cross paths
Liver/metabolism
Liver/Metabolism

TAKE HOME MESSAGE 1:
The hepatologist should screen for T2D in patients with NAFLD

Patients with NAFLD should be screened for the metabolic syndrome and T2DM

Diagnosis of NAFLD suggested by:
- Elevated serum liver enzyme levels
- Ultrasonography
- Fibroscan
- Biomarkers*

Screening for...

- Insulin resistance
  - HOMA-IR
- Metabolic syndrome
  - Increased fasting blood glucose level
  - Hypertriglyceridaemia
  - Low HDL cholesterol level
  - Increased waist circumference
  - High blood pressure
- T2DM
  - HbA1c
  - 75 g OGTT

=> In clinical practice: FPG (> 125 mg/dL) & HbA1C (>6.4%)
Screening of NASH in patients with type 2 diabetes

- What is the knowledge of diabetes specialists regarding NAFLD in T2D patients?

- How to screen? : the performance of non-invasive methods in T2D patients

Less than 5% of diabetologists give the right answer

68% of diabetologists had not used non-invasive method for severity of LD

- FIB-4 should be the first line method to screen T2D patients for NASH

- Fibroscan as second line for detection of advanced fibrosis
Liver/Metabolism

Screening of NASH in patients with type 2 diabetes

- What is the knowledge of diabetes specialists regarding NAFLD in T2D patients?

- How to screen? : the performance of non-invasive methods in T2D patients

- Which patients to refer to a liver clinic?

TD2 diabetic patient with suspected NAFLD

Evaluate alcohol consumption r/o other causes e.g. HCV

70% of cases

Age <65: FIB-4 < 1.3
Age >65: FIB-4 < 2

1.3/2 to 2.67

> 2.67

Refer to secondary care

Fibroscan (LSM+CAP)
M probe > 7.9 kPa
XL probe > 7.2 kPa

Liver Bx

Cirrhosis

Life style intervention
Monitor
Consider to repeat FIB-4 yearly

Bertand Carriou, Jean Michel Petit, Lauwrence Serfaty  PHC 2019
• In patient with diabetes antidiabetic drugs should be adapted to the diagnosis and the severity of NAFLD
  - Pioglitazone is effective for long-term treatment of patients with NASH with type 2 diabetes
  - GLP1 analogues and SGLT2i have benefit against NAFLD in patients with type 2 diabetes, but it seems that this effect is mainly driven by weight loss

• the diagnosis of cirrhosis should lead to change the management of diabetes
  - HbA1c measurement is not accurate in patients with cirrhosis
  - protective effect of metformin
  - Caution to adverse effects of diabetes therapy
HCC today and the future

- Liver cancer is the 16th leading cause of death globally. Incident cases increased 114% from 471,000 in 1990 to 1,007,800 in 2016, causing 810,000 related deaths.
- 47% of increase
- The most pronounced increases were generally observed in countries with high socio-demographic index including the Netherlands, the UK, and the USA.

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>BCLC</th>
<th>SURVIVAL</th>
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<tbody>
<tr>
<td>Resection/Transplantation/Ablation</td>
<td>Liver only disease</td>
<td>&gt; 5 years</td>
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<tr>
<td></td>
<td>Limited tumor burden</td>
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<tr>
<td>Chemoembolization</td>
<td>Liver only disease</td>
<td>&gt; 2.5 years</td>
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<tr>
<td></td>
<td>No vascular invasion</td>
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<tr>
<td></td>
<td>PS 0</td>
<td></td>
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<tr>
<td></td>
<td>Selective approach</td>
<td></td>
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<tr>
<td>Sorafenib / Lenvatinib</td>
<td>No tumor burden limit</td>
<td>+/- 10 mo.</td>
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<tr>
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<td>Preserved liver function</td>
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<tr>
<td></td>
<td>PS 0-2</td>
<td></td>
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<tr>
<td>Rego / Cabo / Ramu (high AFP)</td>
<td>No tumor burden limit</td>
<td>up to 16 mo.</td>
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<tr>
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<td>Preserved liver function</td>
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<td>PS 0-2</td>
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<td>Nivolumab</td>
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The “Gold Rush” of Cancer Immunotherapy Trials Triggering a Reversal of T Cell Exhaustion
2018 EASL Recommendations
1. Public health policies to prevent, detect, and treat chronic liver disease
2. Appropriate cancer surveillance to detect HCC in a stage amenable to curative treatment

Prevention: HBV vaccination

Appropriate cancer surveillance

The lesson from Japan: Screening rose from 12.9% (1966-1979) to 77.6% (2000-2013) curative treatments from 3.3% to 62.8%. OS from 16.6 to 52 mo.

BUT

France < 25% of HCC are diagnosed in the context of cirrhosis surveillance <30% are amenable to curative treatment.

Hong-Kong no screening, OS of HCC was 17.8 months during the period 2003-2014.

USA HCC patients missing US surveillance: HCV 13%, ETOH 40%, NAFLD 50%. Meta-analysis by Singal (2012): 18.4% uptake of surveillance in cirrhotics.
HCC today and the future

2018 EASL Recommendations
3. Link molecular subclasses in clinical trials to therapeutic response and outcome

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Genetic alterations</th>
<th>Molecular classification</th>
<th>Pathological features</th>
<th>Biological pathway</th>
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<tbody>
<tr>
<td>Female</td>
<td>RSP8/RA23</td>
<td>S2</td>
<td>Stem cell features (CK19 and EPCAM) Clear cells</td>
<td>Developmental genes, IGF2</td>
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<td>HBV</td>
<td>AXIN2 ATM</td>
<td>G1</td>
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<td>High AFP</td>
<td>TK1</td>
<td>S1</td>
<td>Macrophage, massive</td>
<td>Cell cycle Nucleus pore</td>
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<tr>
<td>Poor prognosis</td>
<td>TSC1/2</td>
<td>G2</td>
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<td>EGFR</td>
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<td>CTNNB1</td>
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<td>JAK/STAT activation</td>
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<td>G5</td>
<td>Cholestasis</td>
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<td>G6</td>
<td>Glutamine synthetase, Nuclear β-catenin</td>
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**FUTURE DIRECTIONS**

**Liquid biopsy**
- **Use** : diagnosis, disease stratification and monitoring response to treatment.
- **Candidates** : extracellular vesicles, cell-free nucleic acids and tumor cells.

*Mann J et al Gut 2018;67:2204-2012*

**Personalized Medicine**
- Use HCC subclasses to select the optimal therapy for patients
- Biomarkers to identify the subsets of patients with highest rates of response to specific targeted therapies

*Dhanasekaran R et al Gastroenterology 2018*

Massimo Colombo PHC 2019
Metals and the liver

Copper and the liver
Iron and the liver
Copper and the Liver

Take home message Wilson disease

- Highly variable clinical presentation
- No clear cut evidence for a correlation genotype-phenotype
- Cofactors:
  - Genetic factors?
  - Environmental factors?
- Message for hepatologists: consider Wilson disease in any patient with unclear liver disease! IT IS TREATABLE!

NAFLD – copper connection

- Experimental:
  - Low copper diet leads to NAFLD
  - Low copper diet + high sucrose – highest degree of steatosis
  - High fat diet decreases hepatic copper content
- Patients:
  - Low hepatic copper content in (lean) NAFLD
  - Interaction with hepatic iron
Iron and the Liver

- The liver is the main storage site of iron but also the central regulator of body iron homeostasis as the main source of hepcidin, the iron hormone.
- Genetic loss of hepcidin or hepcidin-ancillary regulators, such as HFE, cause hereditary hemochromatosis, the paradigmatic human iron overload disease.
- Loss of hepcidin-producing liver mass may cause systemic non-hemochromatosis iron overload.
- Liver disease factors/mediators that modulate the capacity of the liver to produce hepcidin may cause hepatic iron overload and affect liver disease progression.
- Manipulating hepcidin synthesis activity or hepcidin hormone-replacing strategies represent the first etiologic cure for iron-related disorders.
Thank you for your attention

A great thanks to all speakers who provide me their presentation