Take-home messages from Monday 15th January 2018

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11th PHC
Paris

PhC 2018 - www.aphc.info
Disclosures

- Board member for: MSD, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept
- Speaker for: MSD, Janssen, Gilead, BMS, Abbvie, Intercept
Hepatitis C : first session

Treatment of HCV: 100% cure?
Difficult to treat patients
Results in real life
Treatment of HCV: 100% cure?

- SOF + RBV 12–24 weeks
- SOF + SMV ± RBV 12–24 weeks
- SOF + DCV ± RBV 12–24 weeks
- SOF/LDV ± RBV 8–24 weeks
- SOF/VEL ± RBV 12 weeks
- SOF/LDV ± RBV ± DSV ± RBV 12–24 weeks
- SOF/VEL/V OX 12 weeks
- GRZ/EB ± DSV ± RBV 12–16 weeks
- GLE/PIB 8–12 weeks
- SOF/VEL/VOX 12 weeks

Asselah, Marcellin & Schinazi. Liver Int 2018, in press.
Treatment of HCV: 100% cure?

HCV elimination

PREVENTION
- Harm reduction
- Infection control
- Blood safety

TEST AND TREAT
- HCV screening (universal)
- Linkage to care: Treat with optimal DAAs

AWARENESS
- Increase awareness
- Fights barriers & stigma
- Advocacy
Difficult to treat patients

- Broad treatment indications in patients with HCV and (de)compensated cirrhosis, pre- and post-transplant

- Decompensated cirrhosis: Sofosbuvir +NS5A-inhibitor
  - Protease and non-nucleosidic polymerase inhibitors are contraindicated in patients with decompensated liver cirrhosis

- Safety of DAAs in these populations not yet fully defined – thorough surveillance during therapy

- Consider drug-drug interactions, in particular immunosuppressants in transplanted patients

- Timing of DAA treatment under discussion in patients with chronic hepatitis C and HCC treated with curative intention

- Patients with HCV-associated liver disease should disappear in the transplant setting
Results in real Life

- 92% HCV patients had co-morbidities
- 40% had 5 or more co-morbidities

DAAs combinations are highly effective and well tolerated in the real-world setting and globally, data from the real-life cohorts confirm those observed in clinical trials

- However, in some subgroups of patients it remains difficult to define optimal regimens (treatment duration, use of RBV,...) based on real-life cohorts

- In real-life, the majority of HCV patients has co-morbidities and multiple medications leading to potential DDIs

- Real-life cohorts are useful to highlight safety concerns (bradycardia with amiodarone or HBV reactivation)

Christophe Hezode PHC 2018
Clinical case: Management of patients with HCV related vasculitis

- Greater than 70% of mixed (II, III) cryoglobulinemic patients are associated with HCV RNA
- HCV triggers an immune response but most cases are asymptomatic
- Clinical relevant disease include neuropathies, cutaneous ulcers, arthropathies, renal failure, and vasculitis
- DAAs are highly likely to achieve SVR and restoration of immune system
- Advanced stages of the MC-vasculitis require additional pharmacotherapy, e.g. Rituximab, to achieve remission of the vasculitis in spite of SVR
Hepatitis C : second session

Cost benefit of treatment in F1 patients
Special population
The next waves of HCV : the epidemic of intravenous drug use
Cost-benefit of treatment in F1 patients

What happens if you don’t treat early HCV?

Age distribution of newly reported confirmed cases of hepatitis C virus infection --- Massachusetts, 2002 and 2009
Cost-benefit of treatment in F1 patients

Cost-benefits in mild disease

• Avoidance of liver complications PROVEN (and avoids long term follow up costs)

• Avoidance of non-liver complications PROVEN

• Prevention of transmission DATA SUPPORTED

Cost-benefits in mild disease

• Costs of therapy (drugs /admin) MINUS costs of follow up

• Costs vary by country but in ALL countries drug price should no longer be rate limiting
Treatment of « special populations »

- CKD
- HCV/HIV co-infection
- DAA failures
- Organ donor
- “Addict” patients
- Decompensated cirrhosis

Pangenotypic DAAs removed « Special populations »

- Safety of DAAs in those populations not yet fully defined – thorough surveillance during therapy
The next wave of HCV: the epidemic of intravenous drug use (USA)

Prevalence of HCV is changing:
Two waves of patients

<table>
<thead>
<tr>
<th></th>
<th>First Wave</th>
<th>Second Wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of persons</td>
<td>Millions</td>
<td>Thousands</td>
</tr>
<tr>
<td>Description</td>
<td>Baby Boomers</td>
<td>Millennials</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50-75</td>
<td>20-30s</td>
</tr>
<tr>
<td>Mode of infection</td>
<td>Medical care</td>
<td>Drug use</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>HCV testing</td>
<td>NA for decades</td>
<td>Readily available</td>
</tr>
<tr>
<td>Curative treatment</td>
<td>NA for decades</td>
<td>Readily available</td>
</tr>
<tr>
<td>At risk for cirrhosis</td>
<td>33-50%</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
Is Global elimination of HCV realistic?

Disease Eradication vs Elimination vs Control

- **DAAs providing 100% SVR**
  - No animal reservoir
  - Large carrier pool as reservoir
  - Therapy as cure and prevention
  - SVR near, but not, 100%

- **TREAT AND CURE 100% OF INFECTED**
  - Many HCV patients unknown to the health care system

- **PREVENT ALL NEW ACUTE AND CHRONIC INFECTIONS**
  - Reinfection likely in high risk groups
  - Without screenings and HCV vaccine HCV can be contained, maybe eliminated > 2030, but not eradicated

**HCV eradication achieved**
Is Global elimination of HCV realistic?

The 'Anna Karenina principle'

“All happy families look alike; each unhappy family is unhappy in its own way”

Patients with chronic HCV present patterns consistent with Anna Karenina effect

Treated or on treatment
They all showed willingness to be treated, link to care, adherence to treatments

Difficult-to-treat
Heterogeneous group, with poor willingness to be treated and difficult link to care
NASH

Worldwide epidemiology of NAFLD
Prognosis of NASH
Management of patients with NASH in real life
Future therapies in NASH
Non-alcoholic fatty liver disease NAFLD: a multi-system disease

• Hepatic
cirrhosis,
HCC
• Metabolic
Central obesity,
Insulin resistance,
Type 2 diabetes
• Cardiovascular
Dyslipidemia,
Hypertension
Cardiovascular Disease (CVD)

Extrahepatic complications of NAFLD

NAFLD is a chronic liver condition characterized by hepatic fat accumulation in the absence of ethanol abuse (<20g/day) & other identifiable causes
NAFLD is associated to insulin resistance
NAFLD is considered the hepatic manifestation of Metabolic Syndrome

Stefano Bellentani  PHC 2018
Global prevalence of NAFLD: 25%

Global prevalence of overweight and obesity: 39%

Obesity: 1 billion subjects overweight or obese around the world

Diabetes: over 380-milion cases, but 550 in 2030

Younossi et al., Hepatology 2016
**Are we ready to change from a negative definition (=NAFLD/ NASH) to a positive one?**

Moving to a positive definition of NASH: MAFL (Metabolic Associated Fatty Liver) and MASH (Metabolic Associated SteatoHepatitis) thus revising the old definition and classification

<table>
<thead>
<tr>
<th>Primary MAFL/MASH</th>
<th>Secondary MAFL/MASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy Obesity (MHO) (visceral obesity)</td>
<td>Associated with endocrine disorders:</td>
</tr>
<tr>
<td></td>
<td>- Polycystic Ovary Sindrome (POS)</td>
</tr>
<tr>
<td></td>
<td>- Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>- GH Deficiency</td>
</tr>
<tr>
<td>Metabolically Obesity Normal Weight (MONW) (Probably Genetic, too)</td>
<td>Environmental (High fructose diet; high fat diet)</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus (T2DM)</td>
<td>Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids..)</td>
</tr>
<tr>
<td>Genetic [PNPLA3 and TM6SF2 genes involved]</td>
<td>Jejunoileal bypass</td>
</tr>
<tr>
<td>Hypobetalipoprotein syndrome</td>
<td>Total Parenteral Nutrition (TPN), Starvation</td>
</tr>
<tr>
<td>Congenital Lipodistrophy</td>
<td>Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]</td>
</tr>
<tr>
<td>Lysosomal Acid Lypase Deficiency (LALD or Non-Obese Fatty Liver)</td>
<td></td>
</tr>
<tr>
<td>Unknown causes (Cryptogenic)</td>
<td></td>
</tr>
</tbody>
</table>

Stefano Bellentani  PHC 2018
Prognosis of NASH

• NAFLD patients have increased overall mortality compared to matched controls without NAFLD.

• The most common cause of death in NAFLD patients is cardiovascular disease followed by cancers.

• Fibrosis is associated with overall and liver-related mortality.

• Non-invasive markers of fibrosis predict mortality.
Management of patient with NASH in real life

- NAFLD /NASH remains under diagnosed in general and specialist practices
- Pattern of practice for the screening, diagnosis or therapeutic management of NAFLD /NASH are quite heterogeneous according to practitioners profile and country of origin, with poor adherence to guidelines
- This highlight the need for spreading NAFLD/NASH educational in the medical community and to promote the use of simple tools for patients screening.
Future Therapy in NASH

Who needs intervention

- Those at risk for progression:
  - multiple features of MetS (obesity + T2DM or HTN)
  - Elevated ALT
  - Steatohepatitis with some fibrosis
- Those who have progressed (bridging fibrosis or cirrhosis)
  - identified by non-invasive methods
  - further risk stratification with MELD or HVPG

Targets for NASH treatment

- Metabolism (steatosis)
  - PPARs
  - FXR
  - GLP-1
  - FABAC
  - FGF21

- Cell stress apoptosis
  - Vitamin E
  - ASK1

- Inflammation
  - CCR2-CCR5 (Cencrivioc blocks this target)

- Fibrogenic remodeling
  - Anti-fibrotics

IRRHOSIS

Arun Sanyal PHC 2018
Rational approach to therapeutics for NASH

Mainly anti-fibrotic

Targets:
- Metabolic
- Inflammation
- Fibrosis

Lifestyle
Metabolic targets

Mainly metabolic + Inflammatory

Disease activity (NAS) vs. Disease stage
Diagnosis of NASH

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

Pierre Bedossa & Laurent Castera PHC 2018
Around the world table: Access to therapy

Western countries
Others countries
## Access to HCV therapy in western countries

<table>
<thead>
<tr>
<th></th>
<th>Germany</th>
<th>Spain</th>
<th>Italy</th>
<th>France</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Plan</td>
<td>No</td>
<td>Yes</td>
<td>No (soon)</td>
<td>No</td>
<td>No (soon)</td>
</tr>
<tr>
<td>Screening program</td>
<td>No</td>
<td>Yes</td>
<td>Soon</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Program to improve access to Trt</td>
<td>No (local)</td>
<td>Yes (Prison, PWID)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Treatment restrictions</td>
<td>No</td>
<td>No (2017)</td>
<td>No</td>
<td>No (2017)</td>
<td>No</td>
</tr>
<tr>
<td>Nb HCV Patients</td>
<td>200,000</td>
<td>172-218,000</td>
<td>&gt;300,000</td>
<td>230,000</td>
<td>125,000</td>
</tr>
<tr>
<td>Nb patients treated so far with DAAs</td>
<td>55,000</td>
<td>81,643</td>
<td>109,408</td>
<td>91,764</td>
<td>25,000</td>
</tr>
<tr>
<td>Untreated Pts</td>
<td>110,000</td>
<td></td>
<td>114,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Thomas Berg & Maria Buti & Massimo Colombo & Victor de Ledinghen & Graham Foster PHC 2018*
## Access to HCV therapy in other countries

<table>
<thead>
<tr>
<th></th>
<th>Morocco</th>
<th>Egypt</th>
<th>Russia</th>
<th>Brazil</th>
<th>Poland</th>
<th>Romania</th>
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<tbody>
<tr>
<td>National Plan</td>
<td>Yes (2017)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (2018)</td>
</tr>
<tr>
<td>Screening program</td>
<td>No</td>
<td>Yes (2017)</td>
<td>Yes (PWID..)</td>
<td>Yes (2018)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Program to improve access to Trt</td>
<td>No</td>
<td>Yes</td>
<td>No (soon)</td>
<td>Yes (2018)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment restrictions</td>
<td>No (2017)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No(2015)</td>
<td>Yes</td>
</tr>
<tr>
<td>Nb HCV Patients</td>
<td>450,000</td>
<td>6,000,000</td>
<td>5,000,000</td>
<td>1-1,500,000</td>
<td>230,000</td>
<td>600,000</td>
</tr>
<tr>
<td>Nb patients treated so far with DAAs</td>
<td>11,000</td>
<td>1,344,496</td>
<td>35,000</td>
<td>112,114</td>
<td>25,300</td>
<td>6210</td>
</tr>
<tr>
<td>Nb patients treated in 2016/17</td>
<td>5,000</td>
<td>65,000</td>
<td>20,000</td>
<td>36,627 (2016)</td>
<td>12,000</td>
<td>12,000</td>
</tr>
</tbody>
</table>

Mustapha Benazzouz & Gamal Esmat & Vasily Isakov & Raymundo Parana & Robert Flisiak
Adriana Popescu  PHC 2018
Treating chronic viral hepatitis is not an easy task during war.

However Nabil and his college did their best to treat liver patients adequately.

Sanctions penalize the population and the patients and has no positive impact on the events or to bring peace back.

Nabil and his colleges ask us to put pressure on the leaders of our countries to lift the sanctions against Syrian population.
Conclusions of the day

- HCV Control: feasible
- HCV elimination: a goal
- HCV eradication: a dream that we need to fight hard in order to be achieved
Thank you for your attention

A great thanks to all speakers who provide me their presentation