Take-home messages from Monday 14th January 2019

Marc Bourliere , MD
Hôpital Saint Joseph

12th PHC
Paris
nuary 2018

France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

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

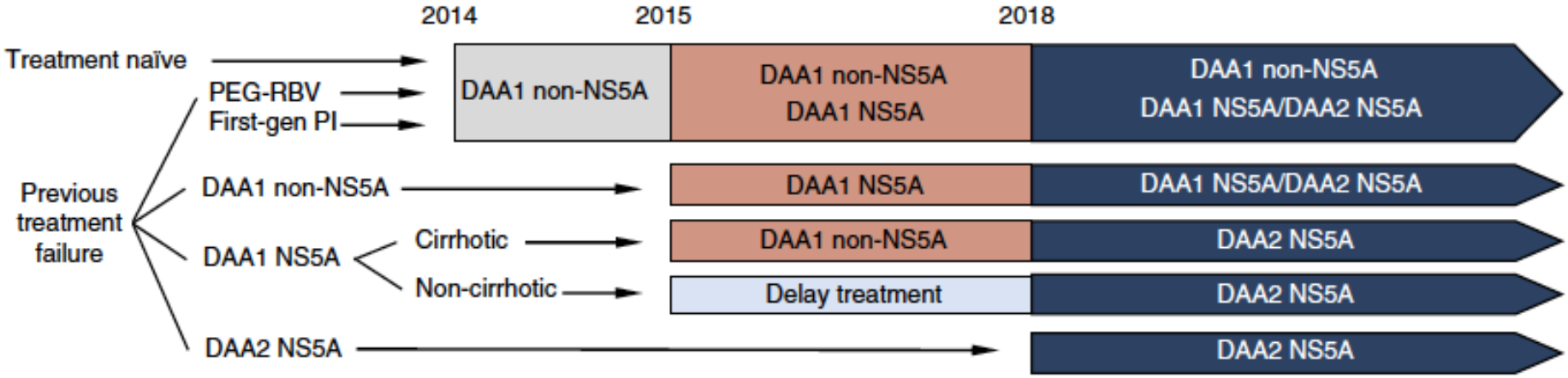
BUT

- 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 DAAs 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

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

Clinical case: Treatment of HCV decompensated cirrhosis

- ✓ 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

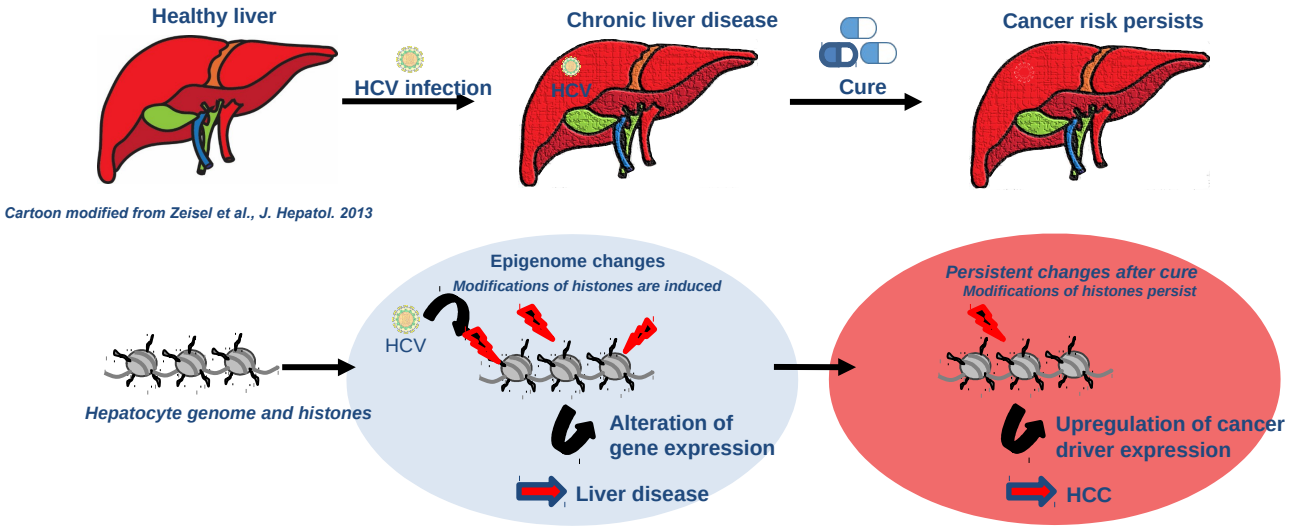
- Several challenges remain in small populations. Most likely that these populations disappear faster than the challenges are solved
  - e.g. patients with decompensated cirrhosis
- Some challenges remain in large populations
  - e.g. HCC surveillance after SVR
- Some challenges are key to reduce the 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 untill 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



HCC ocurrence 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
- Immunsuppressive Therapy

Feature/parameter	Discriminator	Score
Antibodies (max 2 points)		(0–2 points total)
ANA or SMA+	≥1:40	+1
ANA or SMA+	≥1:80	+2
or LKM+	≥1:40	+2
or SLA/LP+	Any titre	+2
IgG or γ-globulins level	>ULN	+1
	>1.1x ULN	+2
Liver histology (evidence of hepatitis is required)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

Score ≥7 = Definite AIH
Score ≥6 = Probable AIH

Autoimmune hepatitis

	Prednisone	Prednisone	Azathioprine	
	(mg/ day)	(mg/ day)	USA (mg/ day)	EU (mg/ kg/ day)
Week 1	60	30	50	1 - 2
Week 2	40	20	50	1 - 2
Week 3	30	15	50	1 – 2
Week 4	30	15	50	1 – 2
Maintenance-Therapy	20 and less	10	50	1 - 2
Reasons for Choice of Therapy	Cytopenia Thiopurinmethyl-transferase-Deficiency Pregnancy Tumors Therapy ≤6 Mo	Postmenopausal Osteoporosis uncontrolled Diabetes, Hypertension, Obesity Acne Emotional Instability		

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 ?

Cyclosporine A	3-5 mg/kg kg/qd	hypertension renal insuffiency
Tacrolimus	3 mg bid (5 – 7 ng/ml)	hypertension renal insuffiency Diabetes, neuropathy
Mycophenolate Mofetil	750-1000 mg bid	Diarrhea, leucopenia
6-thioguanine	20 mg/day	
6-mercaptopurine	1.5 mg/kg/day	
Methotrexate	10 mg per week	
Cyclophosphamide	1-1.5 mg/kg/day	Cystitits, leucopenia
Everolimus	0.75-1.5mg bid (3-6ng/ml)	Proteinuria, lipid disturbance, ulcers

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 other causes of liver disease (OH, HBV, HCV)

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?

2nd line: Hepatologist

Rule-in advanced fibrosis
Transient Elastography

- LSM < 8 kPa → Low risk
- LSM ≥ 8 kPa → Intermediate to high risk → Consider Liver Biopsy

Failure (XL probe) 3.0- 6.7% MRE, 2D SWE or ARFI according to local availability

Attempt lifestyle modifications and exercise → Consider repeat evaluation (1 year)

Pierre Bedossa & Laurent Castera PHC 2019

How to characterize NASH ?

NIT

Triage
in large
unselected
populations

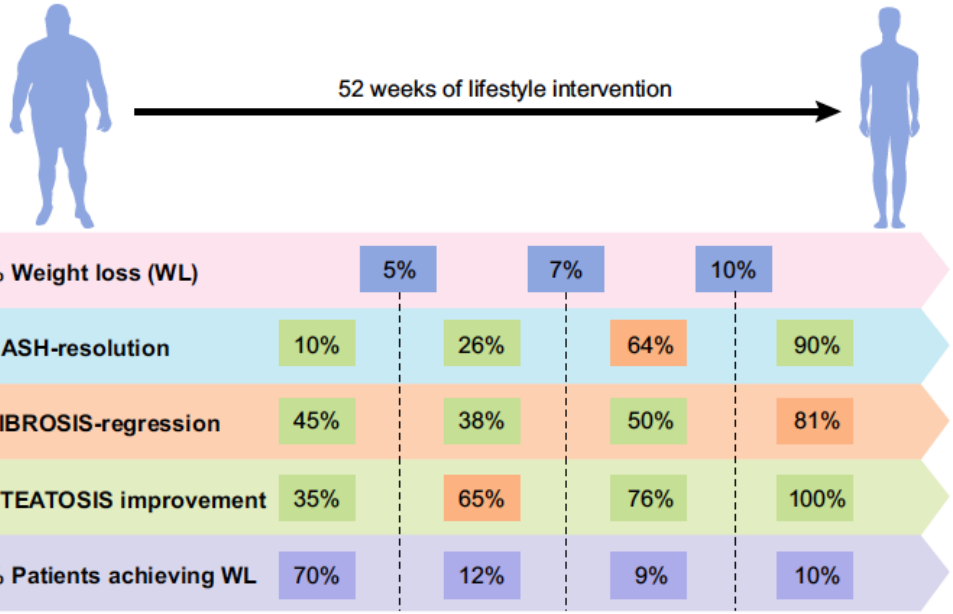
Liver biopsy

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**

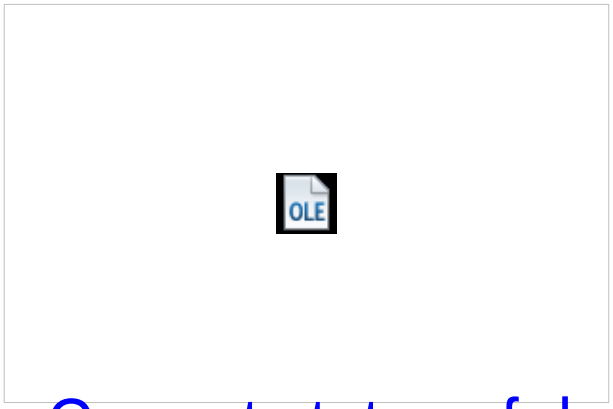
- ✓ **Three essential components**: Cognitive behavioural Therapy + dietary modifications + physical activity changes ➔ <u>ALL</u> required for successful outcomes

✓ **MULTIDISCIPLINARY, HOLISTIC, INDIVIDUALISED approach is key**
✓ Societal efforts to change an "**obesigenic environment**" is needed

Elisabetta Bugianesi PHC 2019

Therapeutic advances

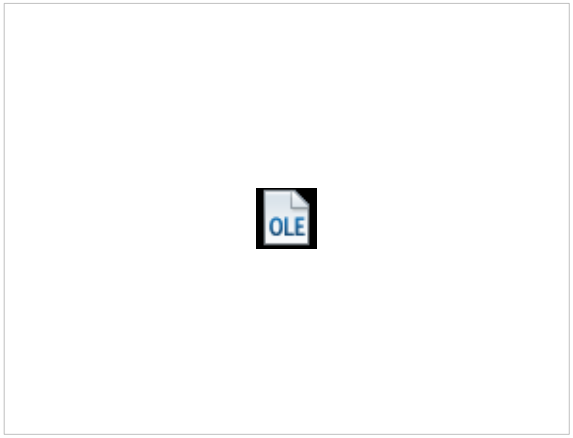
Bariatrics can improve liver histology

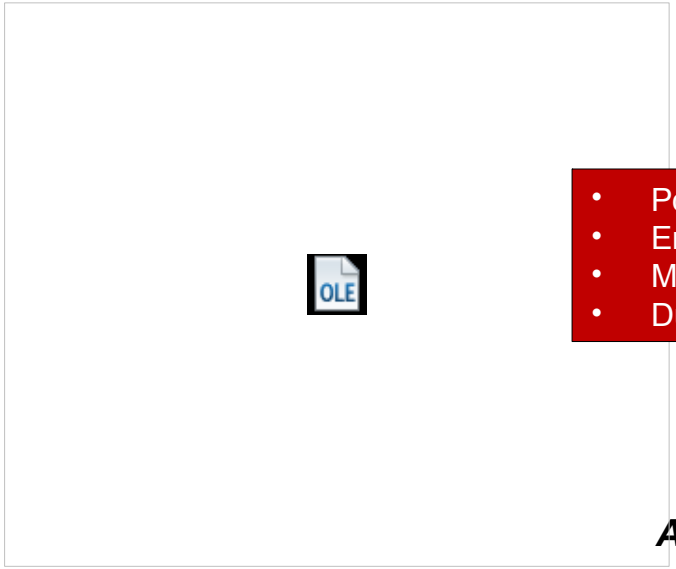


Histological resolution:

- 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



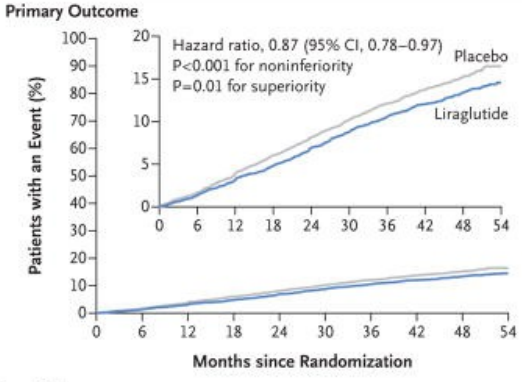


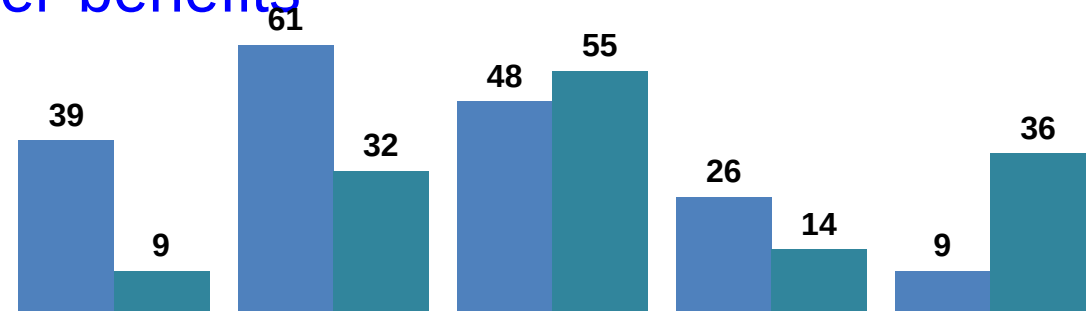
- Populations different
- Endpoint evolution
- Methods of assessment
- Duration of treatment

Therapeutic advances

Fibrosis improvement with current agents

GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits



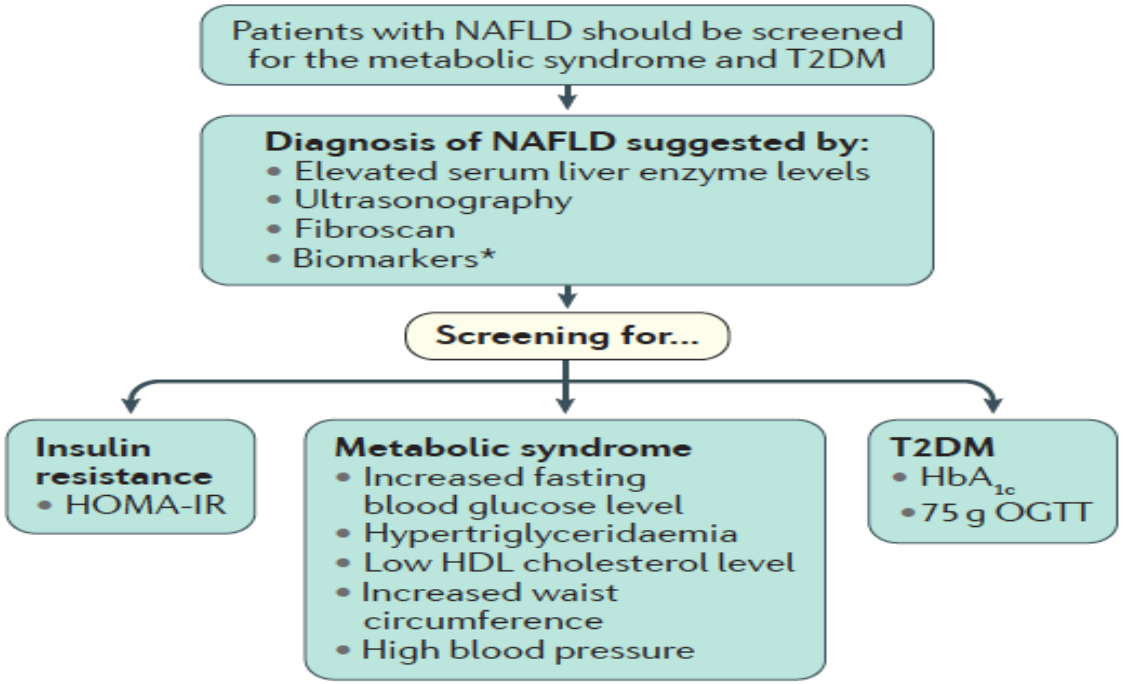


Arun Sanyal PHC 2019

Cross paths Liver/metabolism

Liver/Metabolism

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



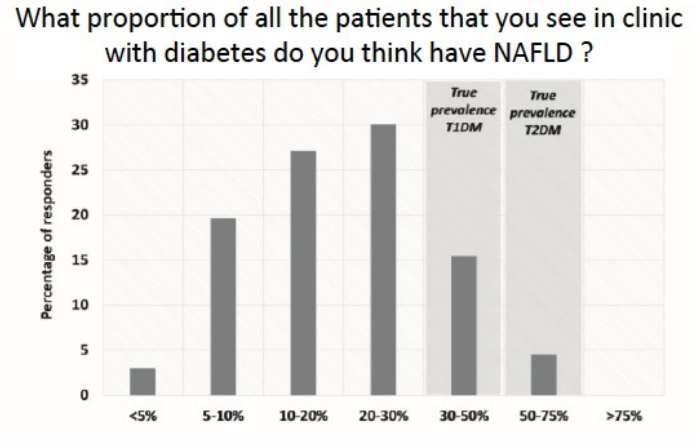
=> In clinical practice: FPG (> 125 mg/dL) & HbA1C (>6.4%)

Bertand Carriou, Jean Michel Petit, Lauwrence Serfaty PHC 2019

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



Less than 5 % of diabetogists give the right answer

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

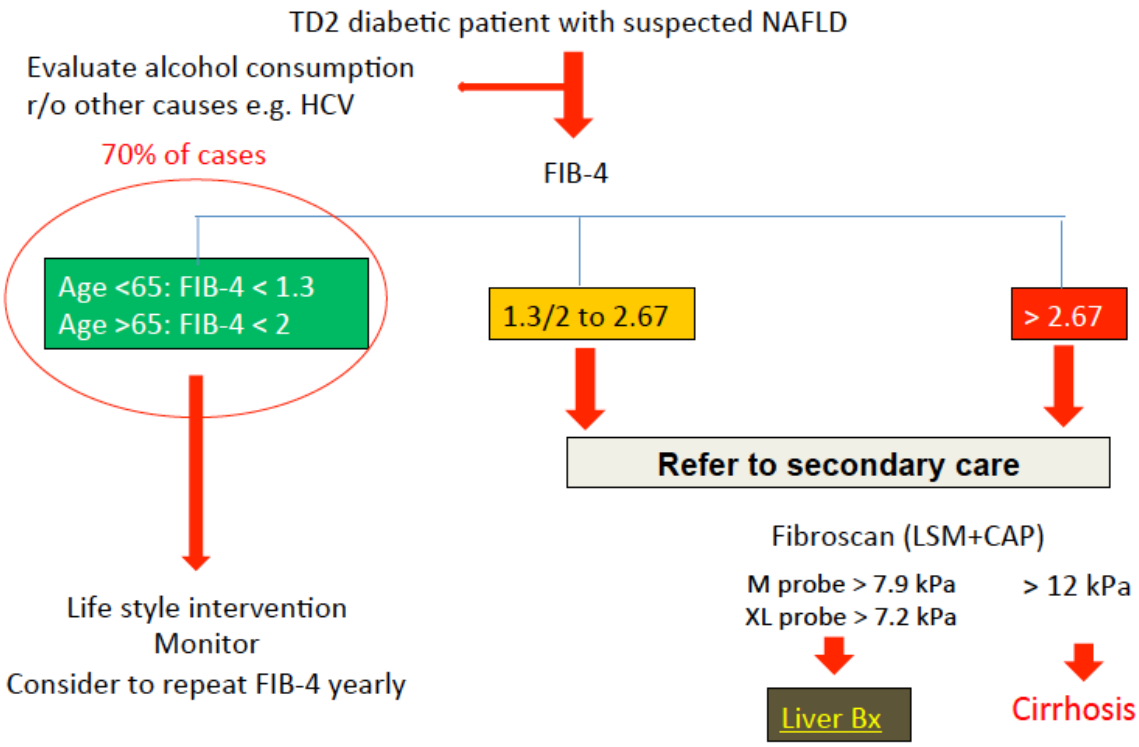
- FIB-4 should be the first line method to screen T2D patients for NASH
- Fibroscan as second line for detection of advanced fibrosis

Bertand Carriou, Jean Michel Petit, Lauwrence Serfaty PHC 2019

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 ?



Bertand Carriou, Jean Michel Petit, Lauwrence Serfaty PHC 2019

Liver/Metabolism

- 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

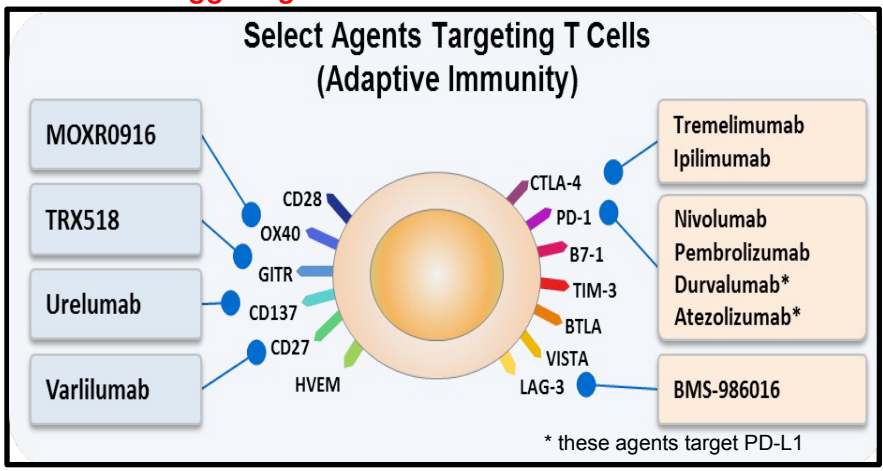
Bertand Carriou, Jean Michel Petit, Lauwrence Serfaty PHC 2019

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.

TREATMENT	BCLC	SURVIVAL
Resection/Transplantation/Ablation	Liver only disease Limited tumor burden	> 5 years
Chemoembolization	Liver only disease No vascular invasion PS 0 Selective approach	>2.5 years
Sorafenib / Lenvatinib	No tumor burden limit Preserved liver function PS 0-2	+/- 10 mo.
Rego / Cabo / Ramu (high AFP) Nivolumab	No tumor burden limit Preserved liver function PS 0-2	up to 16 mo.

The "Gold Rush" of Cancer Immunotherapy Trials Triggering a Reversal of T Cell Exhaustion



Stimulating Agents **Blocking Agen**

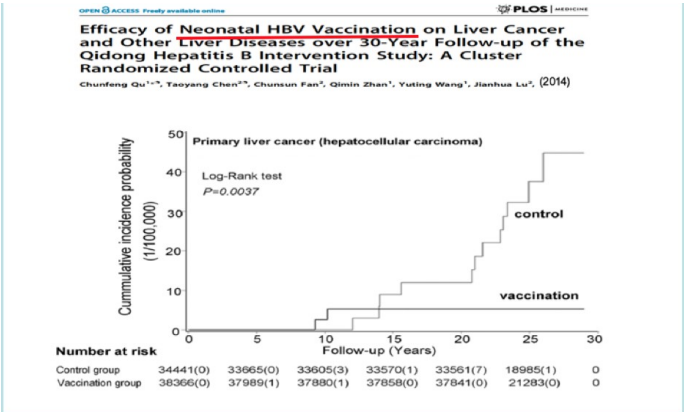
Massimo Colombo PHC 2019

HCC today and the future

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 .

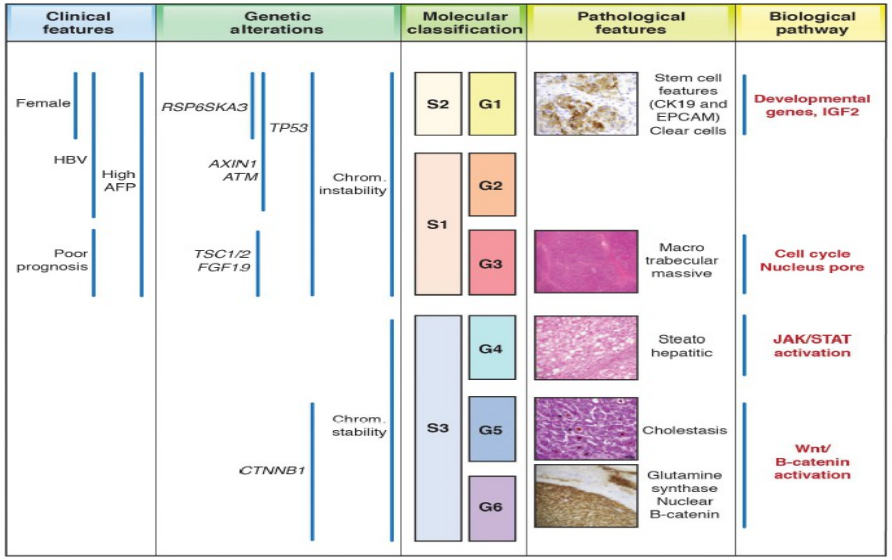
Hong-Kong no screening, OS of HCC was 17.8 months during the period 2003-2014.

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



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

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