PATHOLOGY OF NAFLD

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• NAFLD: a chronic liver disease with a wide range of tissue lesions

• Liver biopsy allows an integrated evaluation of tissue damages related to various pathophysiological mechanisms

• Histology is central for disease definitions and prognosis in NAFLD

• Non invasive biomarkers are still unmet need
• CLASSIFICATIONS OF NAFLD:
  - INTEGRATED APPROACH (NASH CRN)
  - ANALYTICAL APPROACH (SAF)

• HISTOLOGY IN CLINICAL TRIALS
HISTORICAL LANDMARK

THE CLASSICAL VIEW: A DICHOTOMOUS CLASSIFICATION

Non Alcoholic Fatty Liver Diseases (NAFLD)

STEATOSIS (NAFL)

STEATOHEPATITIS (NASH)
THE NATURAL HISTORY OF NAFLD

STEATOSIS (NAFL)

STEATOHEPATITIS (NASH)

FIBROSIS

CIRRHOSIS

HCC
NASH: ASSOCIATION OF HISTOLOGICAL PATTERNS

STEATOSIS + BALLOONING + INFLAMMATION + Perisinusoidal fibrosis + Location in zone 3
THE LIMIT OF A DICHOTOMOUS CLASSIFICATION

STEATOSIS (NAFL)

BORDERLINE

STEATOHEPATITIS (NASH)
THE LIMIT OF A DICHOTOMOUS CLASSIFICATION

STEATOSIS (NAFL)

STEATOHEPATITIS (NASH)

BORDERLINE

(NE)
NAFLD Activity Score (NAS, 0-8)

STEATOSIS

+ BALLONING

+ INFLAMMATION

NASH CRN, Hepatology 2005
Correlation between NAS and histologic diagnosis of NASH

< 3: no NASH

3-4 : GREY ZONE

>5 : definitively NASH

NAS = Sum of lesions related to different mechanisms and with different clinical relevance (steatosis vs hepatocellular injury)

Ballooning (0-2) underweighted vs steatosis (0-3) or inflammation (0-3)

NAS has not been shown as a prognostic factor
• CLASSIFICATIONS OF NAFLD:
  – INTEGRATED APPROACH (NASH CRN)
  – ANALYTICAL APPROACH (SAF)

• HISTOLOGY IN CLINICAL TRIALS
UNDER THE LENS: THE 3 HISTOLOGICAL COMPONENTS OF NAFLD

FLIP consortium, Hepatology 2012, Hepatology 2014

STEATOSIS
THE MARKER

ACTIVITY
THE DRIVER

FIBROSIS
THE KILLER
The S.A.F. score
(Steatosis-Activity-Fibrosis)

- **S**teatosis (0-3) as for NASH CRN

- **A**CTIVITY (0-4) = BALLOONING (0-2) + LOBULAR INFLAMMATION (0-2)

- **F**ibrosis (0 – 4) as for NASH CRN

S0-3A0-4F0-4

Inflammation

Ballooning
HEPATOCELLULAR BALLOONING: THE HALLMARK OF NASH
SHAPE + COLOR + SIZE
The FLIP algorithm

REPRODUCIBILITY OF DIAGNOSIS OF NASH WITH FLIP ALGORITHM

Liver Pathologists (n=6)
- κ score: 0.54 (moderate) → 0.66 (substantial)
- Nbr of biopsies with agreement between all pathologists: 26/40 (65 %) → 34/40 (85 %)

General Pathologists (n=10)
- κ score: 0.35 (fair) → 0.70 (substantial)
- Nbr of biopsies with agreement between all pathologists: 18/40 (45 %) → 34/40 (85 %)

*The FLIP Pathology consortium, Hepatology 2014*

The definition of NASH by an association of 3 features and a clear definition of each of them make the diagnosis of NASH strongly reproducible
FIBROS IS THE KILLER
LIVER FIBROSIS: MAJOR PROGNOSTIC FACTOR

Overall survival according to stage of fibrosis in index biopsy

Liver Related Mortality

- Survival probability (%)
- Liver Related Mortality
- Log-rank test: p=0.0072
- Log-rank test: p=0.2109
- Log-rank test: p=4.6 x 10^6

Overall survival according to fibrosis stage and compared to control population

- Total number of deaths
- Log-rank test: p=0.001


Stage of Fibrosis (Kleiner et al, Hepatology 2005)
STAGE OF FIBROSIS: ROOM FOR IMPROVEMENT
STAGE OF FIBROSIS: ROOM FOR IMPROVEMENT

STAGE 3 / SEPTAL FIBROSIS
• CLASSIFICATION OF NAFLD:
  – INTEGRATED APPROACH
  – ANALYTICAL APPROACH

➢ HISTOLOGY IN CLINICAL TRIALS
  – Histology is a validated surrogate endpoint
MANY SHADES OF NAFLD
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ACTIVITY

FIBROSIS

A3F4
MANY SHADES OF NAFLD
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### Endpoint in Clinical Trials

#### Resolution of NASH Without Worsening of Fibrosis

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- **Curing the Disease**
- **Regression of Fibrosis Without Worsening of NASH**

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**Explanation:**

- **F0** indicates no fibrosis.
- **F1** indicates mild fibrosis.
- **F2** indicates moderate fibrosis.
- **F3** indicates severe fibrosis.
- **F4** indicates cirrhosis.

- **A0** indicates no steatosis.
- **A1** indicates mild steatosis.
- **A2** indicates moderate steatosis.
- **A3** indicates severe steatosis.
- **A4** indicates cirrhosis.

The matrix illustrates the progression of fibrosis and steatosis stages, with the goal of achieving resolution of NASH without worsening of fibrosis.
PATHOLOGY OF NAFLD
Take-home messages

• NAFLD is the combination of several features of variable intensity and of different prognostic values.

• The dichotomous classification NAFL vs NASH is an oversimplification which is no more relevant in clinical practice. New proposals have been formulated.

• NASH is defined by histological criteria. Therefore, biopsy is needed if diagnosis and evaluation of severity are required.

• Histology is the only accepted surrogate marker in clinical trials

• Non invasive markers are urgently needed
THANK YOU FOR YOUR ATTENTION!