Future Direction in Hepatology

Session: Hepatology

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Paris-Sud, Paris Saclay University
Disclosures

Astellas
Abbvie
BMS
Intercept
Ipsen
Gilead
Novartis
Significant impact on patients’ care

(A) Age Standardized Death Rate per 100,000 inhabitants

(B) Age Standardized Death Rate Increase/Decrease (percentage)

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Ascione, A. Liver International. 2017
1. What changes could be expected regarding causes?
2. What treatments will revolutionize this field?
3. What tools could be implemented in a very next future?
Agenda

1. What changes could be expected regarding causes?
2. What treatments will revolutionize this field?
3. What tools could be implemented in a very next future?
Decline of viral hepatitis

HCV

HBV

Papatheodoridis, GV. J Viral Hepat. 2018

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Repercussion on waiting list for liver transplantation

Register study
2003 à 2015
47,591 WL patients

**FIG. 2.** ASIRs of LT WL per 100,000 U.S. population by etiology of liver disease and indication for WL. X-axis is the year of LT WL registration.

Flemming, JA. Hepatology. 2017
Hepatitis E: the neglected one

2 different zones and viruses

http://www.cdc.gov/
Kamar, Lancet 2012
Hepatitis E: the neglected one

Interhumaine transmission
Oro-fecal peril

70,000 deaths/y
50% of ALF
20% mortality rate during pregnancy

Hepatitis E: the neglected one

Interhumaine transmission
Oro-fecal peril

Zoonotic transmission
Ingestion of contaminated food

70,000 deaths/y
50% of ALF
20% mortality rate during pregnancy

Less severe
<5% of ALF

Rein Hepatology; The Global Prevalence of HEV. A Systematic Review. 2014
http://www.who.int/vaccines-documents/
One of the most frequent viral hepatitis in Western countries

- **Amérique du Nord**
  - Canada: 6%
  - USA: 19%

- **Asie**
  - Chine: 33%
  - Corée du Sud: 23%

- **Europe**
  - France: 22%
  - France (Sud Ouest): 52%
  - Pays Bas: 27%
  - Royaume Uni: 12%
  - Royaume Uni (Sud Ouest): 16%

Mansuy Hepatology 2016, Coilly Transplantation 2013
Clinical presentation

Symptomatic form
Patient type: Men 50-55 ans, comorbidities

Severe form
1. Chronic infection
2. Acute on chronic liver failure
   • Acute alcoholic hepatitis
3. Extra-hepatic manifestations
   • Neurological as Parsonage Turner Syndrome

IgM positivity

Asymptomatic

Chronic infection

- Described for genotypes 3 and 4 in immunocompromised individuals: transplanted, HIV, chemo and immunotherapies.
- Risk of chronic infection after acute infection: 2/3 in solid organ transplant recipients = Persistence of viral RNA > 3 months.

To look for any immunosuppressed person with cytolysis.
Can be rapidly fibrosing: Treat
Ribavirin low dose 3 months cure 80%
Raising of ASH and NASH

UNOS 2003 to 2015

% cirrdecompensated cirrhosis

% HCC

Goldberg. Gastroenterology. 2017
Do not forget alcohol…

Williams R et al. Lancet 2018
Alcohol impact mortality in patients with viral hepatitis

Schwarzinger, M. J Hepatol. 2017
The real burden is and will be hepatocellular carcinoma
In acute liver failure... Drug-Induced Liver Injury

<table>
<thead>
<tr>
<th>Countries</th>
<th>Study design</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Retrospective</td>
<td>2.4/100,000</td>
</tr>
<tr>
<td>Sweden</td>
<td>Retrospective</td>
<td>2.3/100,000</td>
</tr>
<tr>
<td>Islande</td>
<td>Prospective</td>
<td>19/100,000</td>
</tr>
<tr>
<td>France</td>
<td>Prospective</td>
<td>14/100,000</td>
</tr>
</tbody>
</table>

2015-2016 in France: 148 liver transplantation
- 42.6% acetaminophen toxicity
- 8.4% of DILI with other drug

Björnsson Semin Liver Dis 2014 34:115; EASL CPG DILI J Hepatol 2019; Larrey, J Hepatol 2019; 70Supp1:258
Agenda

1. What changes could be expected regarding causes?
2. What treatments will revolutionize this field?
3. What tools could be implemented in a very next future?
HCV therapy inspires the entire field…

Potent drugs, pangenotypic

>95% of sustained virological response

Even in most severe patients

Coilly, Femlee, *lancet infectious disease*, 2016
HBV cure will be another challenge...
Myrcludex to treat hepatitis D

Dual therapy with IFN and MYR allows 53% HDV virologic clearance and 27% loss of HBsAg

Bogomolov, P. J Hepatol. 2016
Cholestatic liver diseases: 2\textsuperscript{nd} line!

**Obeticholic acid**

**Bezafibrate**

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Corpechot, NEJM, 2018, Nevens, NEJM, 2017
Same pathways for NASH treatment

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Regenerate: the first study of a long list…

Target - 2400 patients
Randomization 1:1:1

Placebo (QD)
OCA 10 mg (QD)
OCA 25 mg (QD)

Month 18 Interim Analysis
Primary Endpoints

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
OR
NASH Resolution with No Worsening of Fibrosis

Study success was defined as achievement of one of these two primary endpoints.
Arm 25 mg: Pruritus 51%, treatment discontinuation for AE 13%, LDL 17%
New input in advanced HCC

Updated 5 October 2018

Lenvatinib (Lenvima®) - Eisai/MSD
- Phase III REFLECT
  - Global N: 954
  - Global Sites: 106
  - PE (non-inferior OS) met Jan 2017
  - EMA Final Jul 2017
  - EMA Approval Aug 2018

Nivolumab (Opdivo®) - BMS
- Phase III CheckMate-238
  - Global N: 350
  - Global Sites: 112
  - PE (OS) met Apr 2019
  - EMA approval Q3 2019 TBC

Durvalumab (Imfinzi®) + Tremelimumab - AstraZeneca
- Phase III HIMALAYA
  - Global N: 903
  - Global Sites: 344
  - PE Mar 2020

Bevacizumab (Avastin®) + Atezolizumab (Tecentriq®) - Roche
- Phase III AVT-201
  - Global N: 480
  - Global Sites: 113
  - PE May 2021
  - AstraZeneca data 2021 TBC

Pembrolizumab (Keytruda®) - MSD
- Phase III KEYNOTE-240
  - Global N: 408
  - Global Sites: 68
  - PE Feb 2019
  - Readout may be delayed to Q4'19/Q1'20 TBC

Tislelizumab (BGB-A317) - BeiGene/Celgene
- Phase III REACH-2
  - Global N: 383
  - Global Sites: 158
  - PE (OS) met Apr 2018
  - EMA filed Aug 2018
  - EMA approval Q1-Q2 19 (earliest Feb)

Ramucirumab (Cyramza®) - Eli Lilly
- Phase I/II CM-040
  - Global N: 338
  - Global Sites: 158
  - PE (OS) met Apr 2018
  - EMA Final Aug 2018
  - EMA approval Q1-Q2 19 (earliest Feb)

Pembrolizumab (Keytruda®) - MSD
- Phase III Keynote-240
  - Global N: 480
  - Global Sites: 113
  - PE Feb 2019
  - Readout may be delayed to Q4'19/Q1'20 TBC

Other Key Developments
- Phase III PHOCUS Pexa-Vec (oncolytic virus) + Sorafenib - ongoing monitoring, however competitive impact to be re-assessed
- Phase I Regorafenib + Pembrolizumab 1L Global (Eisai/MSD) - start June 18 (NCT03347292)
- Phase I Lenvatinib + Pembrolizumab 1L Global (Eisai/MSD) - as of Aug 2018, no. of patients and sites has increased (NCT03006926)
- New Phase II Tislelizumab 2L Global (BeiGene/Celgene) - first patient dosed Apr 2018 (NCT03419897)

No. of sites are regularly updated especially for newer trials.
Estimated Trial Readout Dates
* = Based on primary sources

Note: All timelines are subject to clinical trial results, regulatory reviews and/or reimbursement negotiations.

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### New input in advanced HCC

<table>
<thead>
<tr>
<th>First-line setting</th>
<th>Drug(s)</th>
<th>Relative difference in overall survival</th>
<th>Absolute overall survival (mo)</th>
<th>Objective response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP&lt;sup&gt;6&lt;/sup&gt; (n = 602)</td>
<td>Sorafenib vs placebo</td>
<td>HR 0.69 (95% CI 0.55-0.87)</td>
<td>Sorafenib: 10.7&lt;br&gt;Placebo: 7.9</td>
<td>RECIST: 2% vs 1%</td>
</tr>
<tr>
<td>REFLECT&lt;sup&gt;10&lt;/sup&gt; (n = 954)</td>
<td>Lenvatinib vs sorafenib</td>
<td>HR 0.92 (95% CI 0.79-1.06)</td>
<td>Lenvatinib: 13.6&lt;br&gt;Sorafenib: 12.3</td>
<td>RECIST: 18.8% vs 6.5%&lt;br&gt;mRECIST: 40.6% vs 12.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line setting</th>
<th>Drug(s)</th>
<th>Relative difference in overall survival</th>
<th>Absolute overall survival (mo)</th>
<th>Objective response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESORCE&lt;sup&gt;32&lt;/sup&gt; (n = 573)</td>
<td>Regorafenib vs placebo</td>
<td>HR 0.63 (95% CI 0.50-0.79)</td>
<td>Regorafenib: 10.6&lt;br&gt;Placebo: 7.8</td>
<td>RECIST: 6.6% vs 2.6%&lt;br&gt;mRECIST: 10.6% vs 4.1%</td>
</tr>
<tr>
<td>CELESTIAL&lt;sup&gt;32&lt;/sup&gt; (n = 760)</td>
<td>Cabozantinib vs placebo</td>
<td>HR 0.76 (95% CI 0.63-0.92)</td>
<td>Cabozantinib: 10.2&lt;br&gt;Placebo: 8.0</td>
<td>RECIST: 4% vs 0.4%</td>
</tr>
<tr>
<td>REACH&lt;sup&gt;25&lt;/sup&gt; (n = 292)</td>
<td>Ramucirumab vs placebo</td>
<td>HR 0.71 (95% CI 0.53-0.95)</td>
<td>Ramucirumab: 8.5&lt;br&gt;Placebo: 7.3</td>
<td>RECIST: 4.6% vs 1.1%</td>
</tr>
<tr>
<td>Checkmate 040&lt;sup&gt;31,43&lt;/sup&gt; (n = 182)</td>
<td>Nivolumab single arm</td>
<td>Not applicable</td>
<td>Nivolumab: 15.6</td>
<td>RECIST: 14.5%&lt;br&gt;mRECIST: 18.6%</td>
</tr>
<tr>
<td>Checkmate-459 (n = 726)</td>
<td>Nivolumab vs Sorafenib</td>
<td>HR 0.85 (95% CI 0.72-1.02)</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Keynote 224&lt;sup&gt;32&lt;/sup&gt; (n = 104)</td>
<td>Pembrolizumab</td>
<td>Not applicable</td>
<td>Pembrolizumab: 12.9</td>
<td>RECIST: 17.3%</td>
</tr>
<tr>
<td>Keynote 240 (n = 413)</td>
<td>Pembrolizumab vs placebo</td>
<td>HR 0.78 (95% CI 0.61-0.99)</td>
<td>Pembrolizumab: 13.9&lt;br&gt;Placebo: 10.6</td>
<td>RECIST: 18.3% vs 4.4%</td>
</tr>
</tbody>
</table>
Several artificial and bioartificial liver devices are currently tested.
Next approaches to treat acute liver failure

Several artificial and bioartificial liver devices are currently tested

FULMAR Study

Results: Patient Survival (Primary Endpoint: 102 pts ITT analysis)
Saliba, Ann Int Med, 2013
Next approaches to treat acute liver failure

Several artificial and bioartificial liver devices are currently tested

- The ELAD system
- The Dialive system

Increased toxins and cytokines absorption
Next approaches to treat acute liver failure

HepaStem consists of liver-derived Mesenchymal Stem Cells that are obtained from ethically healthy donated organs and expanded in the lab.

Study HEP101*:
Multicenter Phase II Safety and Preliminary Efficacy Study of 2 dose regimens of HepaStem in Patients with Acute on Chronic Liver Failure (ACLF 0 and 1):
- Low dose
- High dose
Next approaches to treat chronic liver diseases

Bio-printing techniques

Zein, N. Liver Transplantation. 2013
Next approaches to treat chronic liver diseases

Devascularized scaffold
Next approaches to treat chronic liver diseases

Devascularized scaffold

Stem cell
Or neo cell
1. What changes could be expected regarding causes?
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Trends in steatosis measurement

Echo Scan/CT Scan

MRI-PDFF for grading hepatic steatosis
Trends in steatosis measurement

Echo Scan/CT Scan

MRI-PDFF for grading hepatic steatosis

Spectrophotometer to measure steatosis during harvesting

Golse, N, J Hepatol, 2019
Trends in fibrosis and portal staging

RMI for sur

Blood test

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Cales P, J Hepatol, 2017
« Machine learning », algorithm

![Diagram of machine learning algorithm with decision tree showing different groups based on various parameters such as albumin, aspartate aminotransferase (ASAT), total protein (TP), GGT, and platelet count.]

<table>
<thead>
<tr>
<th>Group</th>
<th>Size</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>547</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57</td>
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<td>3</td>
<td>590</td>
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<td>4</td>
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<td>6</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>397</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

| Age (Years) | 41 | 59 | 56 | 57 | 55 | 53 | 54 | 7 | 55 | 56 | 55 | 55 | 0 | 55 | 6 |

RVS: Pendant la période d'étude
p=0.001

ASAT: p=0.003
Genomic… in several issues

HASIPRO-cohort
70 patients
ALF of unknown cause

Coill A, Gille N, Carot V, Roque-Afonso AM, Work in progress 2019
In summary

Hepatology is a field perpetual renewal that leads to great improvement in patients’ care over few decades

• Great change in term of epidemiology is currently ongoing with the raising of NASH and the decease od infectious diseases
• New option treatments are already available for NASH and HCC… but change of paradigm is on-going: No control of symptoms only but control of the cause
• New tools will help … but we will have to be friendly with mathematical language
Acknowledgments