Universal HCV treatment: Strategies for simplification

PARIS
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CONFERENCE

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Disclosures

• Employee of Paris Public University Hospitals (AP-HP, Beaujon’s Hospital) and University of Paris

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  • Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, Roche.

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The goal of this lecture will be to understand direct-acting antivirals (DAAs) revolution and to propose a rational approach to simplify therapy, to achieve HCV elimination.
Universal HCV treatment: Strategies for simplification

✓ Direct-acting antivirals (DAAs)

✓ Treatment simplification

✓ Universal treatment

✓ Take home messages
Direct-acting antivirals: a Revolution

Asselah et al. Liver Int 2016; 36; S1:47-57.

Capsid
Metalloprotease
Serine protease
RNA helicase
Envelope glycoproteins
C
E1
E2
NS1
NS2
NS3
NS4A
NS4B
NS5A
NS5B
5’NTR
Structural proteins
Nonstructural proteins
3’NTR

Protease Inhibitors « ...previr »
Telaprevir
Boceprevir
Simeprevir
Paritaprevir
Glecaprevir
Grazoprevir
Voxilaprevir
Sovaprevir
ACH-2684

NS5A Inhibitors « ....asvir »
Daclatasvir
Ledipasvir
Velpatasvir (GS-5816)
Ombitasvir
Pibrentasvir
Elbasvir
MK-8408
Samatasvir
Odalasvir (ACH-3102)

Polymerase Inhibitors « .....buvir »
Nucs
Sofosbuvir
MK 3682
ACH-3422
ALS-335
Non-Nucs
Dasabuvir
GS-9669
MK-8876

Cofactors
RNA polymerase

Telaprevir
Boceprevir
Simeprevir
Paritaprevir
Glecaprevir
Grazoprevir
Voxilaprevir
Sovaprevir
ACH-2684
Daclatasvir
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Samatasvir
Odalasvir (ACH-3102)
Sofosbuvir
MK 3682
ACH-3422
ALS-335
Dasabuvir
GS-9669
MK-8876
Goals obtained by achieving
Sustained Virological Response (SVR) ≈ cure

• Eradicate the virus (HCV clearance)
• Reduce necroinflammation
• Stop fibrosis progression

Goals obtained by achieving Sustained Virological Response (SVR) ≈ cure

- Eradicate the virus (HCV clearance)
- Reduce necroinflammation
- Stop fibrosis progression
- Prevent cirrhosis & complications
- Prevent hepatocellular carcinoma
- Reduce extra-hepatic manifestations
- Increase survival

ANRS CO22 HEPATHER: Outcomes in patients treated with DAAs

2156 patients (63% with cirrhosis at baseline) were followed-up for a median of 18 months

Outcome incidence rates over the first 24 months after initiating DAA therapy*

Carrat F, et al. EASL 2016; Poster #LBP505
ANRS CO22 HEPATHER: Outcomes in patients treated with DAAs

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Outcome incidence rates over the first 24 months after initiating DAA therapy*

**Hepatocellular Carcinoma (HCC)**

<table>
<thead>
<tr>
<th>Period</th>
<th>Rate 1000 per 6-month period</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>36</td>
<td>0.0256</td>
</tr>
<tr>
<td>6–12</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>12–18</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

** Decompensation of cirrhosis (DC)**

<table>
<thead>
<tr>
<th>Period</th>
<th>Rate 1000 per 6-month period</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>33</td>
<td>0.0004</td>
</tr>
<tr>
<td>6–12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12–18</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>18–24</td>
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</tr>
</tbody>
</table>

HCC incidence rates decreased by 43% after 12 months from initiation of therapy (P=0.0256)

DC incidence rates decreased by 77% after 6 months from initiation of therapy (P=0.0004)

*SOF + RBV (n=283); SOF + PEG-IFN + RBV (n=228); SOF + DCV ± RBV (n=1048) or SOF + SMV ± RBV (n=597); †Number of events per period

Carrat F, et al. EASL 2016; Poster #LBP505
ANRS CO22 HEPATHER: Outcomes in patients treated with DAAs

2156 patients (63% with cirrhosis at baseline) were followed-up for a median of 18 months

Outcome incidence rates over the first 24 months after initiating DAA therapy*

- Hepatocellular Carcinoma (HCC)
  - HCC incidence rates decreased by 43% after 12 months from initiation of therapy ($P=0.0256$)
- Decompensation of cirrhosis (DC)
  - DC incidence rates decreased by 77% after 6 months from initiation of therapy ($P=0.0004$)
- Liver-related Death
  - Major HCV-related outcomes decreased after DAA-based therapy

*SOF + RBV (n=283); SOF + PEG-IFN + RBV (n=228); SOF + DCV ± RBV (n=1048) or SOF + SMV ± RBV (n=597); †Number of events per period

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Top Priorities for Direct-Acting Antiviral Agents

- Potency (SVR)
- Genotype Coverage
- Resistance Barrier
- Safety/Tolerability

Top Priorities for Direct-Acting Antiviral Agents

- Potency (SVR)
- Genotype Coverage
- Resistance Barrier
- Safety/Tolerability
- Treatment Duration
- Half life & Pills burden
- Drug-drug Interaction
- Access/Cost

Universal HCV treatment: Strategies for simplification

✓ Direct-acting antivirals (DAAs)

✓ Treatment simplification

✓ Universal treatment

✓ Take home messages
Treatment simplification

- ✔ No ribavirin
- ✔ Shorten treatment duration
- ✔ Pan-genotypic efficacy
- ✔ Reduce pill burden
Analysis of 2485 HCV GT 1 patients treated with LDV/SOF for 8 weeks or 12 weeks under real-world conditions

Virological response (per protocol)

Overall  | HIV co-infection  | Age >70  | Patients on OST
---|---|---|---
SVR12 (%) | 98/827 | 96/73 | 99/65 | 99/76
LDV/SOF 8 weeks  | 98/1289 | 98/158 | 97/138 | 97/92
LDV/SOF 12 weeks  | 98/1314 | 98/161 | 97/143 | 95/95

Buggisch P, et al. AASLD 2016; Poster #883
Garnet: 8 weeks 3D in GT1b non cirrhotic patients

**ITT:** tous les patients ayant reçu au moins une dose de traitement

**mITT-GT:** ITT modifiée: exclusion des 3 patients non G1b

**mITT-GT-VF:** mITT-GT exclusion des échecs non virologiques

Asselah et al. AFEF 2016
Available and future DAAs (high efficacy and good tolerance) provide a unique opportunity to establish a program for HCV elimination.
POLARIS: sofosbuvir/velpastasvir/voxilaprevir

**Experienced Patients (DAAs)**

- **POLARIS-1**
  - n = 415
  - En échec d'inhibiteurs NS5A
  - G1: 123456
- **POLARIS-4**
  - n = 333
  - En échec d'inhibiteurs Non NS5A
  - G1: 123456

**Naïve Patients (DAAs)**

- **POLARIS-2**
  - n = 941
  - G: 123456
- **POLARIS-3**
  - n = 219
  - Cirrhose
  - G: 123456

**SVR12**

- 12 weeks: 96%
- 12 weeks: 97%
- 8 weeks: 95%
- 8 weeks: 96%
- Placebo: 12 weeks: 90%
- 12 weeks: 98%
- 12 weeks: 96%

*Source: Bourlière et al, AASLD 2016, A194
Zeuzem et al, AASLD 2016, A109
Jacobson et al, AASLD 2016, LB-12
Foster et al, AASLD 2016, A258*
**Glecaprevir/Pibrentasvir: Program**

**ENDURANCE Trials**
- GT1 non-cirrhotic including HIV co-infection: 8 vs 12 weeks
- GT2 placebo-controlled: 12 weeks
- GT3 active comparator: 12 weeks
- GT4-6: 12 weeks

**MAGELLAN Trials**
- GT1, 4-6 prior DAA failures: 12 vs 16 weeks

**EXPEDITION Trials**
- GT1, 2, 4-6 cirrhotic
- GT1-6 all stages of renal impairment

**SURVEYOR Trials**
- GT2, 4-6 non-cirrhotic: 8 weeks
- GT3 cirrhotic: 12 vs 16 weeks
EBR/GZR: Efficacy in Different Patient Populations 1-6

Overall mFASa SVR12 rates from the Phase 3 clinical trial program

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>-</th>
<th>Stage 4-5 CKD</th>
<th>OAT/PWI D ± HIV</th>
<th>IBLD ± HIV</th>
<th>HIV</th>
<th>± HIV</th>
<th>± HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>1,4,6</td>
<td>1</td>
<td>1,4,6</td>
<td>1,4</td>
<td>1,4,6</td>
<td>1,4,6</td>
<td>1,4,6</td>
</tr>
<tr>
<td>Treatment Experience</td>
<td>TN</td>
<td>TN/PR-PTF</td>
<td>TN</td>
<td>TN/PR-PTF</td>
<td>TN</td>
<td>PR-PTF</td>
<td></td>
</tr>
</tbody>
</table>

12 Weeks EBR/GZR Without RBV

16 Weeks EBR/GZR + RBV

amFAS excludes patients who failed for reasons unrelated to study medication.

EBR/GZR = elbasvir/grazoprevir; SVR12 = sustained virologic response 12 weeks after the cessation of treatment; CKD = chronic kidney disease; OAT = opioid agonist therapy; PWID = people who inject drugs; IBLD = inherited blood disorders; TN = treatment naive; HIV = human immunodeficiency virus; TE = treatment experienced; RBV = ribavirin; PR = peginterferon + ribavirin; PTF = prior-treatment failure; mFAS = modified full analysis set.

Current Therapies

With IFN

Sofosbuvir (G1,3,4,5,6)
Simeprevir (G1, 4)
Daclatasvir (G4)

IFN-free

G1,4
Simeprevir + Sofosbuvir
G1,2,3,4,5,6
Daclatasvir + Sofosbuvir
G2,3,4

2014
Jan–Jun
Jan–Jun
Jul–Dec
Jul–Dec

2015
Sofosbuvir + Ledipasvir

Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV
G1,4,5,6

RBV ±

Protease Inhibitors « …previr »
NS5A Inhibitors « ….asvir »
Polymerase Inhibitors « …..buvir »
Current and Future Therapies

Asselah et al. Liver Int 2016; 36; S1:47-57.
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Strategies for HCV elimination

Test & Treat

✓ Universal HCV screening
✓ Linkage to care: Treat all diagnosed with optimal DAAs

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Prevention
- Harm reduction
- Infection control
- Blood safety

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- Universal HCV screening
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Prevention
- Harm reduction
- Infection control
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Awareness
- Increase awareness
- Fights barriers and stigma
- Advocacy

HCV re-infection

Re-infection rate in total population and among PWID (Canada)

Spontaneous Clearance

- Population: 1.59
- PWID: 1.88

Cure after treatment (SVR)

- Population: 0.48
- PWID: 1.14

Islam et al. AASLD 2016, A60
DAAs therapies: Increase Prescribers

Prospective study ASCEND (USA): 600 patients treated with SOF/LDV by 6 Hepato-Gastroenterologists, 5 GP, 5 nurses after a SPECIFIC EDUCATION

Emmanuel et al, AASLD 2016, A22

SVR 12 (PP)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Nurses</th>
<th>GP</th>
<th>Specialists</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>93,6%</td>
<td>95,0%</td>
<td>94,5%</td>
<td>92,3%</td>
</tr>
<tr>
<td>Patients</td>
<td>548</td>
<td>135</td>
<td>142</td>
<td>240</td>
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</table>

SVR 12 patients with cirrhosis (PP)

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<tbody>
<tr>
<td></td>
<td>90,8%</td>
<td>86,7%</td>
<td>92,6%</td>
<td>92,3%</td>
</tr>
<tr>
<td>Patients</td>
<td>109</td>
<td>26</td>
<td>25</td>
<td>48</td>
</tr>
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Emmanuel et al, AASLD 2016, A22
Therapeutic Patient Education: a multidisciplinary team
Hepatitis plans for HCV elimination

National action plans and strategies:
http://apps.who.int/iris/bitstream/10665/183726/1/9789241509350_eng.pdf (all accessed January 2017)
Hepatitis plans for HCV elimination

France: universal access to HCV treatment

National action plans and strategies:
Universal HCV treatment: Strategies for simplification

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Universal HCV treatment: Strategies for simplification

Take Home Messages

HCV cure

- Combining DAAs results in high SVR (> 95%) and short duration (8-12 weeks).

HCV elimination requires improvement in:

- Screening (linkage to care)
- Prevention
- Access to treatment