Current and Future Liver Treatment Options

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President of College of Hepatology of Portuguese Medical Association (2012-2015)
Editor-Chief of Acta Médica Portuguesa (2011-2016)
Vice-President of Portuguese Society of Gastroenterology (2013-2017)
President of Scientific Committee of SOS Hepatitis, patient NGO
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Infarmed – Coordinator of Consultive Panel for Hepatitis C (2014-2015)
Direção-Geral da Saúde – National Strategy for Viral Hepatitis
ACSS – referentiation group for digestive diseases

Pedagogic Committee of Medical School of Lisbon (2014-2017)
Scientific Committee of Masters in Palliative Care

Elected Member of General Assembly of United European Gastroenterology,
Advisory Member of Viral Hepatitis Prevention Board (WHO, CDC, ELPA, ECDC)
Fellowship of EBGH, American College of Gastroenterology, Sociedade Brasileira de Hepatologia
Conflict of Interests: Abbvie, BMS, MSD, Gilead, Janssen
A Cura da Hepatite C e um Fígado Saudável para 2008

Quem tem hepatite C deve manter a esperança já que as armas médicas contra esta doença são já muitas e eficazes.

4.ª Conferência Europeia sobre Doenças Raras

Lisboa 2007

A Associação Portuguesa dos Hemofílicos teve um papel preponderante na implementação da logística inerente à organização de um evento tão abrangente. Foi uma experiência inovadora com a qual adquirimos capacitação e conhecimentos.
“Core Business”

32% with cirrhosis
~52-63% with F3/F4
A person with 52 years

Data from National Registry for HCV treatment, Infarmed Portugal, 2016
Sustained Viral Response (SVR) = virological cure

HCV RNA negative 3 months after the end of therapy for ever and ever (>99%)
Cure hepatitis C (genotype 1)

Adapted from Hepatitis C, stigma and cure. Marinho RT, Barreira D, World Journal Gastroenterology 2013

- IFN SC 3Xw 24w
- IFN SC 3Xw + RBV 48w
- PEG-IFN SC 1Xw + RBV 48w
- PEG-IFN 1Xw + RBV 24-48w + Boceprevir / Telaprevir
- Oral DAAs 12w

↓ Risk of Hepatocellular Carcinoma
Eradication of Hepatitis C Virus Reduces the Risk of Hepatocellular Carcinoma in Patients with Compensated Cirrhosis

José Velosa · Fátima Serejo · Rui Marinho · Joana Nunes · Helena Glória
Risk of Death
Sustained Virologic Response and Clinical Outcomes in Patients with Chronic Hepatitis C and Advanced Fibrosis

Bart J. Veldt, MD; E. Jenny Heathcote, MD; Helner Wedemeyer, MD; Juerg Relichen, MD; W. Peter Hofmann, MD; Stefan Zeuzem, MD; Michael P. Mai

5-year occurrence
SVR: 4.4% (CI, 0.0%–12.9%)
No SVR: 12.9% (CI, 7.7%–18.0%)
P = 0.024 (log likelihood)

Liver-Related Death, %

Time, y

No SVR
At risk: 337
Events: 0

SVR
At risk: 142
Events: 0

No Response

SVR -Response
DAA – Direct-Acting Antiviral

Daclatasvir
Paritaprevir, Ombitasvir, Dasabuvir
Simeprevir
Sofosbuvir
Sofosbuvir/Ledipasvir
Clinical Trials = Real Life
Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Stefan Zeuzem, M.D., Ira M. Jacobson, M.D., Tolga Baykal, M.D., Rui T. Marinho, M.D., Ph.D., Fred Poordad, M.D., Marc Bourlière, M.D., Mark S. Sulkowski, M.D., Heiner Wedemeyer, M.D., Edward Tam, M.D., Paul Desmond, M.D., Donald M. Jensen, M.D., Adrian M. Di Bisceglie, M.D., Peter Varunok, M.D., Tarek Hassanein, M.D., Junyuan Xiong, M.D., Tami Pilot-Matias, Ph.D., Barbara DaSilva-Tillmann, M.D., Lois Larsen, M.D., Thomas Pockros, M.D., and Barry Bernstein, M.D.

BACKGROUND
In this phase 3 trial we evaluated the efficacy and safety of the integrated combination of ABT-450 with ritonavir (ABT-450/r), ombitasvir (also known as ABT-267), dasabuvir (also known as ABT-333), and ribavirin for the retreatment of HCV in patients who were previously treated with peginterferon–ribavirin. 

This article was published on April 10, 2014, at NEJM.org.

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Figure 1. Sustained Virologic Response in the Entire Active-Regimen Group and According to Hepatitis C Virus (HCV) Genotype.
Hepatite C – Monitorização dos tratamentos

Data: 6 de junho de 2016

Tratamentos iniciados: 7676

Tratamentos finalizados (protocolo completo)
Informação recebida dos hospitais:
- Doentes curados: 2702
- Doentes não curados: 108

Resultados

SOF/LDV

SVR 96%
EMA 26th May 2016
Velpatasvir/Sofosbuvir
Grazoprevir/Elbasvir
**Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection**

**Table 2. Response during and after Treatment.**

<table>
<thead>
<tr>
<th>Response</th>
<th>Sofosbuvir-Velpatasvir (N=624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA &lt;15 IU/ml</td>
<td></td>
</tr>
<tr>
<td>During treatment period</td>
<td></td>
</tr>
<tr>
<td>At wk 2</td>
<td>355 (57)</td>
</tr>
<tr>
<td>At wk 4</td>
<td>564 (90)</td>
</tr>
<tr>
<td>At 12 wk after treatment period</td>
<td></td>
</tr>
<tr>
<td>Any genotype</td>
<td>618/624 (99)</td>
</tr>
<tr>
<td>1a</td>
<td>206/210 (98)</td>
</tr>
<tr>
<td>1b</td>
<td>117/118 (99)</td>
</tr>
<tr>
<td>2</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>4</td>
<td>116/116 (100)</td>
</tr>
<tr>
<td>5</td>
<td>34/35 (97)</td>
</tr>
<tr>
<td>6</td>
<td>41/41 (100)</td>
</tr>
</tbody>
</table>

**Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection**

**Figure 1. Sustained Virologic Response among Patients with HCV Genotype 3, According to Cirrhosis Status and Previous Treatment.**

**Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis**

**Table 2. Study Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sofosbuvir-Velpatasvir for 12 Wk (N=90)</th>
<th></th>
<th>Sofosbuvir-Velpatasvir for 12 Wk (N=87)</th>
<th>95% CI</th>
<th>Sofosbuvir-Velpatasvir for 24 Wk (N=90)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virologic response</td>
<td>75/90 (83)</td>
<td>74-90</td>
<td>82/87 (94)</td>
<td>87-98</td>
<td>77/90 (86)</td>
<td>77-93</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>44/50 (88)</td>
<td>76-96</td>
<td>51/54 (94)</td>
<td>85-99</td>
<td>51/55 (93)</td>
<td>82-98</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>16/18 (89)</td>
<td>65-99</td>
<td>14/14 (100)</td>
<td>77-100</td>
<td>14/16 (88)</td>
<td>62-98</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>4/4 (100)</td>
<td>40-100</td>
<td>3/3 (100)</td>
<td>33-67</td>
<td>3/4 (75)</td>
<td>19-99</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>7/14 (50)</td>
<td>77-83</td>
<td>11/13 (85)</td>
<td>55-98</td>
<td>6/12 (50)</td>
<td>21-79</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>4/4 (100)</td>
<td>40-100</td>
<td>2/2 (100)</td>
<td>16-100</td>
<td>2/2 (100)</td>
<td>16-100</td>
</tr>
</tbody>
</table>
Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial

Summary
Background There is a high medical need for an interferon-free, all-oral, short-duration therapy for hepatitis C virus (HCV) genotype 1 infection that is both effective versus diverse mutant genotypes, including patients with cirrhosis or previous null response.

<table>
<thead>
<tr>
<th>Treatment duration (weeks)</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin (arm B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously untreated patients with cirrhosis</td>
<td>90%</td>
<td>97%</td>
</tr>
<tr>
<td>PR null with or without cirrhosis</td>
<td>94%</td>
<td>97%</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin (arm B5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously untreated patients with cirrhosis</td>
<td>92%</td>
<td>90%</td>
</tr>
<tr>
<td>PR null with or without cirrhosis</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>No ribavirin (arm B5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously untreated patients with cirrhosis</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>PR null with or without cirrhosis</td>
<td>79%</td>
<td>95%</td>
</tr>
<tr>
<td>No ribavirin (arm B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously untreated patients with cirrhosis</td>
<td>78%</td>
<td>100%</td>
</tr>
<tr>
<td>PR null with or without cirrhosis</td>
<td>79%</td>
<td>89%</td>
</tr>
</tbody>
</table>

SVR12 (95% CI)
- 28/31, 90% (74-98)
- 28/29, 97% (82-100)
- 31/32, 97% (84-100)
- 29/31, 94% (79-99)
- 30/32, 94% (79-99)
- 30/33, 91% (89-100)
- 33/33, 100% (91-100)
- 33/33, 97% (84-100)
- 24/5 (9)

Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial

Summary
Background Both hepatitis C virus (HCV) mono-infected and HIV/HCV co-infected patients are in need of safe, effective, all-oral HCV regimens. In a phase 2 study we aimed to assess the efficacy and safety of grazoprevir (MK-5172), HCV NS5A (NS5A) protease inhibitor and two doses of elbasvir (MK-8742; HCV NS5A inhibitor) in patients with...

<table>
<thead>
<tr>
<th>Treatment duration (weeks)</th>
<th>8</th>
<th>12</th>
<th>12</th>
<th>12</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin (arm B1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV mono-infected</td>
<td>80%</td>
<td>93%</td>
<td>98%</td>
<td>98%</td>
<td>80%</td>
</tr>
<tr>
<td>HIV/HCV co-infected</td>
<td>78%</td>
<td>93%</td>
<td>98%</td>
<td>97%</td>
<td>80%</td>
</tr>
</tbody>
</table>

SVR12 (95% CI)
- 24/30, 80% (68-92)
- 79/85, 93% (90-95)
- 43/44, 98% (96-100)
- 28/29, 97% (93-100)
- 26/30, 80% (68-92)
Potential Reduction in HCV-Related Liver Deaths by Treatment Strategy based on Liver Fibrosis

Hepatitis C: The Curative Era

F2-F4: Stages of liver fibrosis including moderate (F2), severe (F3), and cirrhosis (F4)
Coffin, CID 2012 (modified for novel direct-acting agents)
Future >2016?

- New DAAs pangenotypic, decompensated cirrhosis
- Coformulation, some 8 weeks, no more RBV
- And the 5-10% that didn’t respond?
- Health Public Issue (€€, politicians, health professionals, pharmaceutical industry, patients, journalists, etc)
- 1st chronic oncogenic virus that man is able to cure
Future >2016?

Saving lives and Families

- New DAAs pangenotypic, decompensated cirrhosis
- Coformulation, some 8 weeks, no more RBV
- And the 5-10% that didn’t respond?
- Health Public Issue (€€, politicians, health professionals, pharmaceutical industry, patients, journalists, etc)
- 1st chronic oncogenic virus that man is able to cure
"Liver Circle"

- Acute Hepatitis
- Chronic Hepatitis
- Palliative Care
- Transplant
- Decompensated Cirrhosis
- Compensated Cirrhosis
- Death
- HCC

30-40%
Thank's a lot!!