Treatment of HCV Infection: Past, Present and Future

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HCV is an easy-to-cure virus
Curing HCV Infection
Curing HCV Infection

Treatment

HCV RNA level

LLD
Curing HCV Infection

Treatment

HCV RNA level

LLD
Curing HCV Infection

HCV RNA level

Treatment

LLD
Curing HCV Infection

HCV RNA level vs. Treatment

LLD
Curing HCV Infection

Treatment

Potency

HCV RNA level

LLD
Curing HCV Infection

- Treatment
  - Potency
  - High barrier to resistance

Graph showing HCV RNA level decreasing with treatment.
Anti-HCV Drugs
The “Old“ Drugs

Pegylated IFN-α

Ribavirin
HCV Lifecycle

Inhibition of polyprotein processing
NS3 Protease Inhibitors

NS3/4A Protease Inhibitors

1\textsuperscript{st}-wave, 1\textsuperscript{st}-generation
Telaprevir (Janssen)
Boceprevir (Merck)

2\textsuperscript{nd}-wave, 1\textsuperscript{st}-generation
Simeprevir (Janssen)
Faldaprevir (BI)
ABT-450/r (Abbvie)
Asunaprevir (BMS)
Danoprevir (Roche)
Sovaprevir (Achillion)
Vedroprevir (Gilead)
IDX320 (Idenix)
Vaniprevir (Merck, Japan)

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IDX320 (Idenix)
Vaniprevir (Merck, Japan)

2\textsuperscript{nd}-generation
MK-5172 (Merck)
ACH-2684 (Achillion)

Narrow genotypic activity
Low barrier to resistance

Pangenotypic (~)
Higher barrier to resistance

All genotypes except 3
Low barrier to resistance
HCV Lifecycle

Inhibition of HCV replication
Nucleoside/Nucleotide Analogue Inhibitors of HCV RdRp

Catalytic Site
Nucleotide Analogues Act as Chain Terminator

Primer strand

5’ G C C C A SOF

RNA chain cannot be elongated

3’ C G G U A G C G

Template strand
Nucleoside/Nucleotide Analogue Inhibitors of HCV RdRp

Sofosbuvir (Gilead)

Pangenotypic
High barrier to resistance
Non-Nucleoside Inhibitors (NNI)
Non-Nucleoside Inhibitors (NNI)

Thumb-1 inhibitors
- BMS-791325 (BMS)
- TMC647055 (Janssen)

Genotype 1 only
Low barrier to resistance

Thumb-2 inhibitors
- Lomibuvir (Vertex)
- GS-9669 (Gilead)

Genotype 1 only
Low barrier to resistance

Palm-1 inhibitors
- ABT-333 (Abbvie)
- ABT-072 (Abbvie)
- Setroobuvir (Roche)

Genotype 1 only
Low barrier to resistance
HCV Lifecycle

- Inhibition of HCV replication
- Inhibition of HCV assembly and release
- Receptor binding and endocytosis
- Fusion and uncoating
- Translation and polyprotein processing
- Membranous web
- RNA replication
- ER lumen
- Virion assembly
- LD
NS5A Inhibitors

NS5A Dimer

Domain III

Domain II

Domain I

Cytosol

ER membrane

ER lumen
NS5A Inhibitors

1st-generation
Daclatasvir (BMS)
Ledipasvir (Gilead)
ABT-267 (Abbvie)
PPI-461 (Presidio)
PPI-668 (Presidio)
ACH-2928 (Achillion)
GSK2336805 (GSK)
BMS824393
Samatasvir (Idenix)

Genotypes 1 and 4, other genotypes variable
Low barrier to resistance

2nd-generation
MK-8742 (Merck)
ACH-3102 (Achillion)
GS-5816 (Gilead)

Pangenotypic
Slightly higher barrier to resistance
II

HCV Treatment
Past, Present and Future
Before 2011
Our Good Old Friends

Pegylated IFN-α

Ribavirin
Virological Monitoring

PegIFNα-ribavirin

0 4 8 12 24 36 48 60 72

Weeks of treatment
On-Treatment Virologic Responses

Baseline  Week 4  Week 8  Week 12

-2 log

LLOD
On-Treatment Virologic Responses

Baseline | Week 4 | Week 8 | Week 12

-2 log

Null response
Stop treatment

LLOD
On-Treatment Virologic Responses

-2 log

RVR 24 weeks

Baseline  Week 4  Week 8  Week 12

LLOD
On-Treatment Virologic Responses

Baseline Week 4 Week 8 Week 12

-2 log

RVR 24 weeks

EVR 48 weeks

LLOD
On-Treatment Virologic Responses

-2 log

Baseline | Week 4 | Week 8 | Week 12
---|---|---|---
RVR 24 weeks | EVR 48 weeks | Slow VR 72 weeks | LLOD
Since 2011
New Standard-of-Care for HCV Genotype 1

- Boceprevir
- Telaprevir
- Pegylated IFN-α
- Ribavirin

+
SVR According to Lead-in

**SPRINT-2, non-black**

- **BOC/RGT**
  - <1 log HCV RNA decrease: 29%
  - ≥1 log HCV RNA decrease: 82%

- **BOC/PR48**
  - <1 log HCV RNA decrease: 39%
  - ≥1 log HCV RNA decrease: 82%

# Rash Grading

<table>
<thead>
<tr>
<th>Mild rash</th>
<th>Moderate rash</th>
<th>Severe rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized skin eruption and/or a skin eruption with limited distribution (up to several isolated sites on the body)</td>
<td>Diffuse rash involving ≤50% of body surface area</td>
<td>Extent of rash &gt;50% of body surface area or with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Significant systemic symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mucous membrane ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Target lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Epidermal detachment</td>
</tr>
</tbody>
</table>

36.8% 13.8% 4.8%

*(Cacoub et al., J Hepatol 2012;56:455-63)*
Hb Shifts on Boceprevir

Li: Boceprevir triple therapy or placebo

Follow-up

Hemoglobin (g/dL) mean values

PR (N=547)
BOC/PR (N=1548)

(Sulkowski et al., EASL 2011)
Medicines that are Contraindicated with Boceprevir and Telaprevir

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Contraindicated with boceprevir</th>
<th>Contraindicated with telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoreceptor antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>EFV, all RTV-boosted PIs</td>
<td>DRV/RTV, FPV/RTV, LPV/RTV</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
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</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td><em>Hypericum perforatum</em> (St John’s wort)</td>
<td><em>Hypericum perforatum</em></td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drospirenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN</td>
<td>Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

*(Boceprevir package insert; Telaprevir package insert)*
Three DAAs Approved in 2014

- Sofosbuvir: Nucleotide, All genotypes
- Simeprevir: Protease, Gen 1, 4
- Daclatasvir: NS5A, Gen 1, 3, 4, 5, 6
Options in 2014

- **IFN-based regimens**
  - Sofosbuvir + Peg-IFNα + ribavirin (all genotypes)
  - Simeprevir + Peg-IFNα + ribavirin (genotypes 1, 4)
  - Daclatasvir + Peg-IFNα + ribavirin (genotypes 1, 3, 4-6)

- **IFN-free regimens**
  - Sofosbuvir + ribavirin (genotypes 2, 3)
  - Sofosbuvir + simeprevir (genotypes 1, 4)
  - Sofosbuvir + daclatasvir (genotypes 1, 3, 4-6)
P + R + Simeprevir-QUEST-1/2

Phase III, Treatment-naive, Gen 1

SVR24 rate (%)

- Simeprevir + PR (RGT 12+12)
- Placebo + PR

**QUEST-1**
- 80%
- N=264
- 50%
- N=130

**QUEST-2**
- 81%
- N=257
- 50%
- N=134

(Jacobson et al., EASL 2013; Manns et al., EASL 2013)
P + R + Sofosbuvir-NEUTRINO

Phase III, 12 weeks, Gen 1-4-5-6, Treatment-naive

SVR12 rate (%)

- **TOTAL**: 90% (N=327)
- **Genotype 1 (89%)**: 89% (N=292)
- **Genotype 4 (9%)**: 96% (N=28)
- **Genotype 5, 6 (2%)**: 100% (N=7)

(Lawitz et al., N Engl J Med 2013;368:1878-87)
Sofosbuvir + Simeprevir (PI) ± RBV
COSMOS, Gen 1, naive/null-responders, F3/4

(Jacobson et al., AASLD 2013)
Sofosbuvir + Daclatasvir ± RBV

Treatment-naive, Genotype 1

SVR24 rate (%)

- LI/SOF + DCV: 93% (N=15)
- SOF + DCV: 100% (N=14)
- SOF + DCV + RBV: 100% (N=15)

(Sulkowski et al., N Engl J Med 2014;370:211-21)
2015 and onwards
IFN-Free Combination Options

Option 1
- Protease inhibitor
- Nucleotide analogue
- Non-nucleoside inhibitor
- ± ribavirin

Option 2
- Protease inhibitor
- NS5A inhibitor
- Non-nucleoside inhibitor
- ± ribavirin

Option 3
- 2nd-gen protease inhibitor
- 2nd-gen NS5A inhibitor
- ± ribavirin

(Pawlotsky JM, Gastroenterology 2014; in press)
Sofosbuvir/Ledipasvir FDC ± RBV

ION-1-Phase III, Gen 1, Rx-naive, 16% cirrhosis

- SOF/LDV: 99% at 12 weeks, N=214
- SOF/LDV+RBV: 97% at 12 weeks, N=217
- SOF/LDV: 98% at 24 weeks, N=217
- SOF/LDV+RBV: 99% at 24 weeks, N=217

(Mangia et al., EASL 2014)
Sofosbuvir/Ledipasvir FDC ± RBV
ION-3-Phase III, Gen 1, Rx-naïve

94% 93% 95%
N=215 N=216 N=216
SOF/LDV 8 weeks SOF/LDV+RBV 8 weeks SOF/LDV 12 weeks

(Kowdley et al., EASL 2014)
SOF/LDV FDC ± GS-9669 or GS-9451 SYNERGY-Phase II, Gen 1, Rx-naïve

(SOF/LDV FDC ± GS-9669 or GS-9451)

100% 95% 100%

N=20 N=20 N=20

SOF/LDV 12 weeks SOF/LDV + GS-9669 6 weeks SOF/LDV + GS-9451 6 weeks

(Kohli et al., CROI 2014)
IFN-Free Combination Options

Option 1
- Protease inhibitor
- Nucleotide analogue
- Non-nucleoside inhibitor
- ± ribavirin

Option 2
- Protease inhibitor
- NS5A inhibitor
- Non-nucleoside inhibitor
- ± ribavirin

Option 3
- 2nd-gen protease inhibitor
- 2nd-gen NS5A inhibitor
- ± ribavirin

(Pawlotsky JM, Gastroenterology 2014; in press)
ABT-450/r (PI) ± ABT-267 (NS5A) ± ABT-333 (NNI) ± RBV
SAPPHIRE I - PEARL III – PEARL IV
Phase III, Genotype 1, Rx-naïve, 12 weeks

(SAPPHIRE-I (n=631) 96% 98% 97% 99% 99%)
(PEARL-IV (n=305) 95%  90%)
(PEARL-III (n=419)  99%)

(Feld et al., EASL 2014; Dieterich et al., EASL 2014)
IFN-Free Combination Options

Option 1

Protease inhibitor

Nucleotide analogue

Non-nucleoside inhibitor

± ribavirin

Option 2

Protease inhibitor

NS5A inhibitor

Non-nucleoside inhibitor

± ribavirin

Option 3

2nd-gen protease inhibitor

2nd-gen NS5A inhibitor

± ribavirin

(Pawlotsky JM, Gastroenterology 2014; in press)
MK-5172 (2nd-gen PI) + MK-8742 (2nd-gen NS5A)
C-WORTHY, Gen 1, Rx-naive, noncirrhotic, 12 wks

SVR12 rate (%)

<table>
<thead>
<tr>
<th>Dose Combination</th>
<th>N</th>
<th>SVR12 Rate</th>
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<tbody>
<tr>
<td>5172 + 8742 20 mg + RBV</td>
<td>24</td>
<td>96%</td>
</tr>
<tr>
<td>5172 + 8742 50 mg + RBV</td>
<td>27</td>
<td>89%</td>
</tr>
<tr>
<td>5172 + 8742 50 mg No RBV</td>
<td>12</td>
<td>100%</td>
</tr>
</tbody>
</table>

(Lawitz et al., EASL 2013)
Access Programs

- Gilead offers Egypt sofosbuvir at 99% discount (900$, >1 million treated)

- Gilead licensing sofosbuvir to 3-4 Indian manufacturers to allow sales at lower prices in 60 developing nations (most Subsaharan Africa)

(Gilead press releases, 2013-2014)