New Investigational Treatments for Hepatitis C Infection

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San Mateo County Public Health
July 10, 2013
SMC Community Board Meeting
New Investigational Treatments for Hepatitis C Infection

• HCV Epidemiology and Natural History
• HCV Life Cycle and Structure
• Review Classes of HCV Therapeutic Agents
• Recent Data for New HCV Therapeutic Agents
HCV: How common is it in the US?

- Estimated 3.9 million people in the US have HCV infection. Recent figures that include populations at high risk indicate that this number may be as high as 5 to 7 million.

- HCV infection has now surpassed HIV as the leading cause of death among chronic viral diseases in the United States, and HIV/HCV coinfection is associated with an increased risk of cirrhosis and liver failure.

- Because modes of HIV and HCV transmission (through skin blood exposure and sexual intercourse) are shared, 20% to 30% of patients with HIV infection are coinfectected with HCV.
What’s the natural history of HCV?

• HCV progresses to chronic disease in 55% to 85% of cases

• Cirrhosis occurs in 20% of HCV only infected patients within 20 years of infection and is the leading cause of liver transplants in the US

• HIV co-infected patients have a > 2x increased risk of cirrhosis than HCV only patients
HCV genotypes: Why do they matter?

• HCV genotype 1 is responsible for 60- 70% of infections in the US, but treatment with peginterferon alfa and ribavirin is effective in only 40-50% of patients with HCV genotype 1 only infection.

• In HIV-positive patients with genotype 1 HCV infection and a high plasma HCV RNA level (> 800,000 IU/mL), cure (SVR) was achieved in only 20% of patients.
HCV Genome and Structure

(a) Model structure of HCV

- Envelope glycoprotein 1
- Envelope glycoprotein 2
- Envelope lipid
- RNA genome
- Capsid proteins

(b) Proteins encoded by the HCV genome

- HCV RNA
- Region encoding polyprotein precursor
- 5' NTR
- Region encoding polyprotein precursor
- 3' NTR

Structural proteins:
- p22
- gp35
- gp70
- p7
- p23

Nonstructural proteins:
- p20
- p8
- p27
- p56/58
- p68

- NS3
- NS4A
- NS5A
- NS5B

Nucleocapsid
- Transmembrane protein
- Cofactors

Source: Curr Opin Gastroenterol © 2013 Lippincott Williams & Wilkins
NS3/4A Protease Inhibitors

- High potency
- Low barrier to resistance
- First generation only active against Genotype 1 (Telaprevir, Boceprevir)
- Second generation active against multiple genotypes
- Use in combination therapy
NS5B Polymerase Inhibitors

- Moderate/high potency
- Higher barrier to resistance
- Active against multiple or all genotypes
- Use in Interferon-sparing/free regimens
NS5A Inhibitors

• Mechanism of action unknown
• Active against multiple or all genotypes
• Moderate potency
• Moderate barrier to resistance
• Use in Interferon-sparing/free regimens
HCV Drug Development in 2013

Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
Treatment Response in DAA Era

Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
Sofosbuvir – NS5B Polymerase Inhibitor

- Active against all genotypes
- No significant drug-drug interactions
- No concerning safety issues thus far
- Studied in over 2000 patients so far
- Submitted for FDA approval April 2013
<table>
<thead>
<tr>
<th>Response</th>
<th>NEUTRINO Study</th>
<th>FISSION Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF+PEG+RBV for 12 Wk (N = 327)</td>
<td>SOF+RBV for 12 Wk (N = 253)</td>
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<tr>
<td>HCV RNA &lt;25 IU/ml — no./total no. (%)</td>
<td></td>
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<tr>
<td>During treatment</td>
<td></td>
<td></td>
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<tr>
<td>At 2 wk</td>
<td>299/327 (91)</td>
<td>231/251 (92)</td>
</tr>
<tr>
<td>At 4 wk</td>
<td>321/325 (99)</td>
<td>249/250 (&gt;99)</td>
</tr>
<tr>
<td>At last observed measurement</td>
<td>326/327 (&gt;99)</td>
<td>249/253 (98)</td>
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<tr>
<td>After end of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>302/327 (92)</td>
<td>187/253 (74)</td>
</tr>
<tr>
<td>At 12 wk</td>
<td>295/327 (90)</td>
<td>170/253 (67)</td>
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<tr>
<td>Viral breakthrough during treatment — no. (%)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Relapse in patients with HCV RNA &lt;25 IU/ml at end of treatment — no./total no. (%)</td>
<td>25/320 (8)</td>
<td>71/242 (29)</td>
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<tr>
<td>Patients who completed treatment</td>
<td>25/320 (8)</td>
<td>71/242 (29)</td>
</tr>
<tr>
<td>Patients who did not complete treatment</td>
<td>3/6 (50)</td>
<td>3/7 (43)</td>
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</table>

NEUTRINO Study: Treatment-naive Genotypes 1, 4, 5, 6
FISSION Study: Treatment-naive Genotypes 2, 3

From Lawitz et al, NEJM 4/23/13
Simeprevir – 2\textsuperscript{nd} Generation NS3/4A Inhibitor

- Active against multiple genotypes
- Does have drug-drug interactions with some HIV antiretrovirals
- No concerning safety issues thus far
- Submitted for FDA approval April 2013
SMV + P/R x 12 wks followed by P/R x 12-36 wks

Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
COSMOS: SOF + SMV ± RBV
GT 1 Null Responders 12 vs 24 weeks

HCV RNA < LLOQ (25 IU/mL)

RVR

EOT

SVR8

Duke Clinical Research Institute
Lawitz et al. CROI 2013 Abstract 155

Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
Daclatasvir – NS5A Inhibitor

• Active against all genotypes
• Does have drug-drug interactions with HIV antiretrovirals
• No safety issues thus far
SOF + DCV ± RBV for 12 or 24 weeks
GT 1, 2, 3 Tx Naive

HCV RNA < LLOQ (25 IU/mL)

<table>
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<tr>
<th></th>
<th>W4</th>
<th>EOT</th>
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<th>SVR12/24</th>
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<tbody>
<tr>
<td>GT1-12+</td>
<td>95</td>
<td>85</td>
<td>88</td>
<td>93</td>
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<tr>
<td>G1-12-</td>
<td>100</td>
<td>100</td>
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<td>100</td>
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<tr>
<td>GT1-24+</td>
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<tr>
<td>GT2/3+</td>
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<tr>
<td>GT2/3-</td>
<td>100</td>
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Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
SOF + DCV ± RBV for 24 weeks
GT 1 Triple therapy failures

HCV RNA <LOQ (25 IU/mL)

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<thead>
<tr>
<th></th>
<th>W2</th>
<th>W4</th>
<th>EOT</th>
<th>SVR12</th>
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<tr>
<td>Triple</td>
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<tr>
<td>Dual</td>
<td>91</td>
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<tr>
<td></td>
<td>80</td>
<td>95</td>
<td>100</td>
<td>95*</td>
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Slide courtesy S Naggie, IAS HCV Review SSF 6/4/13
Key Points

• Multiple targets for HCV treatment with many new therapeutic agents in use and development

• Interferon-sparing and Interferon-free HCV treatment regimens potentially available soon for HCV-monoinfected patients

• Effectiveness of new regimens in HCV/HIV co-infected individuals being studied
Thank You!