New Treatments for Hepatitis B and C

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Hepatitis B

- In adults 90-95% of acute hepatitis B is cleared by the body
- 5-10% remain chronically infected
- Over 6 months of hepatitis B, chronic infection
- A small percentage of patients with Hepatitis B will clear without therapy
Natural History of Hepatitis B

Acute HBV infection
- 90% neonates
- 25–30% children
- <10% adults

~2%

Chronic infection
- 15–40%

Fulminant hepatic failure

Progressive chronic hepatitis

Inactive carrier state

Cirrhosis

 Decompensated cirrhosis

Death

HCC
Natural History of Hepatitis B

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- 90% neonates
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Progressive chronic hepatitis

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HCC

 Decompensated cirrhosis

Levels of HBV activity

- “Silent carrier” – have the virus, low activity, low virus titer
- “Chronic hepatitis” – have the virus, moderate to high activity, high virus titer
- “Cleared” – no detectable virus in the blood, no activity, undetectable virus titer
Goal of therapy with HBV

- Clear virus – not easy
- Suppress the virus - easier
- Minimize inflammation
- Slow progression of liver disease
- Reduce complications of cirrhosis
- Decrease risk of cancer
Prognostic importance of HBV DNA levels

• Cumulative incidence of HCC depends on HCV DNA level (Chen, et al; JAMA 2006), even in HBeAg-, normal ALT, non-cirrhotic patients

• Cumulative incidence of cirrhosis depends on HBV DNA level (Illoeje, et al; Gastroenterology 2006) and risks are similar between HBeAg- and Ag+ subsets
Goals of therapy with HBV

- Cure
- Treat
- Prevent complications
Treatment in 1982

- Nothing
Treatment 2007

- Interferon
- Pegylated interferon
- Lamivudine (3TC, Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Telbivudine (Tyzeka)
HBV Treatment 2007

Good
- One pill per day
- Decrease inflammation
- Decrease virus

Bad
- Expense
- Frequently long term treatment
- Often suppress but not cure
• Medications can clear or suppress virus
• Suppressing the virus can slow progression and reverse injury
• Suppressing the virus can reduce the complications of hepatitis
Hepatitis C

Over 3 Million Americans Are Infected With the Stealth Virus. Most Don’t Know It.
Treatment Hepatitis C

Sustained virological response (%)

- INTERFERON (24 weeks) 6%
- INTERFERON (48 weeks) 16%
- IFN + Ribavirin (24 weeks) 33%
- IFN + Ribavirin (48 weeks) 45%
- PEG-IFN + Ribavirin (48 weeks) 55%
Overall Response

**PEG-IFNs + RBV: SVR – Week 72**

- **IFN α-2b 3 MIU/RBV**: 47% (n = 505)
- **PEG-IFN α-2b 1.5 µg/kg/RBV**: 54% (n = 511)
- **IFN α-2b 3 MIU/RBV**: 44% (n = 444)
- **PEG-IFN α-2a 180 µg/RBV**: 56% (n = 453)

Results presented are from separate, independent trials with different control groups receiving standard IFN α-2b.


PEG-IFNs + RBV: SVR – Week 72

**Genotype 2/3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR Rate</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN α-2b 3 MIU/RBV</td>
<td>79%</td>
<td>146</td>
</tr>
<tr>
<td>PEG-IFN α-2b 1.5 µg/kg/RBV</td>
<td>82%</td>
<td>147</td>
</tr>
<tr>
<td>IFN α-2b 3 MIU/RBV</td>
<td>61%</td>
<td>145</td>
</tr>
<tr>
<td>PEG-IFN α-2a 180 µg/RBV</td>
<td>76%</td>
<td>140</td>
</tr>
</tbody>
</table>

*Results presented are from separate, independent trials with different control groups receiving standard IFN α-2b*

Pegylated Interferon and ribavirin nonresponders

- Mild disease – await better treatment
- Significant fibrosis
  - Crossover to other interferon? (limited data)
  - Break in therapy, prior compliance issues?
  - Daily Consensus interferon? Large trials underway
  - Maintenance Interferon? Large trials underway
Be in Charge

• Stay positive
• Minimize alcohol – best is zero
• Exercise
• Weight loss
• Increased scarring, less response to therapy with fatty liver + Hepatitis C
Promising treatments

- Optimizing the dose and duration of Pegylated interferon and ribavirin
- Suppress with “maintenance” therapy
- Inhibit fibrosis
- Test new antivirals
Agents with benefit in experimental models of fibrosis

- Pentoxiphylline
- Sirolimus
- ACE inhibitors
- Vitamin E
- Silymarin
New drug strategies

• Block HCV receptors (CD81, LDL)
• Disrupt HCV cell signaling
• Attack HCV directly
  – Antisense oligonucleotides
  – Small inhibitory RNAs
Treatment strategies

• Inhibit HCV enzymes needed to replicate
  • Nucleoside analogs
  • Non-nucleosides (other enzyme sites)
New medications

- ? efficacy as single agents
- ? development of resistance
- Combination with interferon, with or replacing ribavirin
SCH 503034 ± PEG-Intron 1.5 μg/kg QW in HCV-1, IFN Non-Responders

Relative HCV RNA Levels (log)

-3 -2.5 -2 -1.5 -1 -0.5 0

Days After the Start of Treatment

0 1 2 3 5 7 8 9 10 12 13

- Peg-Intron Alone (n=18)
- Peg-Intron + 200 mg TID SCH503034 (n=12)
- Peg-Intron + 400 mg TID SCH503034 (n=8)

Zeuzem AASLD 2005
US New Drug Development Process

Drug Discovery
Chemical Development
Animal Studies
Pre IND Meeting
IND Prep. & Submission
Human Studies Phase I-III
NDA Writing / Compilation
NDA Prep. & Submission
Use of Drug By Consumers

Time Required:
- Pre IND: 2-4 years
- IND: 2-3 mos.
- IND 30-Day Wait Period: 5 mos.
- Investigational Status: 1 month
- Pre NDA: ±7 years
- NDA: 5 mos.

Cost:
$330 - $800 million
# In the Pipeline

## Hepatitis C Trials

### Phase III

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Type</th>
<th>Drug Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abaferon</td>
<td>Interferon</td>
<td>Human Genome Sciences</td>
</tr>
<tr>
<td>Ribif (interferon beta-1a)</td>
<td>Interferon</td>
<td>Ares-Serono</td>
</tr>
</tbody>
</table>

### Phase II

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Type</th>
<th>Drug Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCH 503034</td>
<td>Protease Inhibitor</td>
<td>Schering</td>
</tr>
<tr>
<td>Telaprevir (VX-959)</td>
<td>Protease Inhibitor</td>
<td>Vertex</td>
</tr>
<tr>
<td>R1626</td>
<td>Polymerase Inhibitor</td>
<td>Roche</td>
</tr>
<tr>
<td>HCV-796</td>
<td>Polymerase Inhibitor</td>
<td>ViroPharma/Wyeth</td>
</tr>
<tr>
<td>Valopicitabine (NM283)</td>
<td>Polymerase Inhibitor</td>
<td>Idenix</td>
</tr>
<tr>
<td>IC41</td>
<td>Therapeutic Vaccine</td>
<td>InterCell</td>
</tr>
<tr>
<td>Suvas</td>
<td>Antiviral</td>
<td>Biovision</td>
</tr>
<tr>
<td>Celgosivir (MX-3253)</td>
<td>Gluconolactose Inhibitor</td>
<td>Mignex</td>
</tr>
<tr>
<td>VGX-410C</td>
<td>IRES (Viral Protein) Inhibitor</td>
<td>VGX Pharmaceuticals</td>
</tr>
<tr>
<td>ACH-0137/171</td>
<td>Replicase (Polymerase Enzyme) Inhibitor</td>
<td>Achillion</td>
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</tbody>
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### Phase I

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<tr>
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<tbody>
<tr>
<td>EMZ702</td>
<td>Interferon Enhancer</td>
<td>Transition Therapeutics</td>
</tr>
<tr>
<td>Locetron (BLX-883)</td>
<td>Interferon</td>
<td>Biolex/OctoPlus</td>
</tr>
<tr>
<td>Omega Interferon</td>
<td>Interferon</td>
<td>Intas/Sanofi-ASTRA</td>
</tr>
<tr>
<td>Medrat Interferon</td>
<td>Interferon</td>
<td>Flame</td>
</tr>
<tr>
<td>Multiferon</td>
<td>Interferon</td>
<td>Viragen</td>
</tr>
<tr>
<td>Viramidine (taribavirin)</td>
<td>Ribavirin Prodrug</td>
<td>Valeant</td>
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## Hepatitis B Trials

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<tr>
<td>Entecavir (ETV)</td>
<td>Polymerase Inhibitor</td>
<td>Gilead</td>
</tr>
<tr>
<td>Clevudine (L-FMAU)</td>
<td>Polymerase Inhibitor</td>
<td>Gilead</td>
</tr>
<tr>
<td>Viread (tenofovir)</td>
<td>Polymerase Inhibitor</td>
<td>Gilead</td>
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<tr>
<td>Valdecoobine (monovalent)</td>
<td>Polymerase Inhibitor</td>
<td>Idenix</td>
</tr>
<tr>
<td>Amadovir (DAPD)</td>
<td>Polymerase Inhibitor</td>
<td>RPS Pharma</td>
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<tr>
<td>ANA 80</td>
<td>Polymerase Inhibitor</td>
<td>Analya</td>
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<tr>
<td>Fradefox</td>
<td>Polymerase Inhibitor</td>
<td>Metabasis Technologies</td>
</tr>
<tr>
<td>Racvir</td>
<td>Polymerase Inhibitor</td>
<td>Pharmasset</td>
</tr>
<tr>
<td>Alinia (nitroazomide)</td>
<td>Small Molecule Non-nucleoside</td>
<td>Romark</td>
</tr>
<tr>
<td>HI-8 HBV</td>
<td>Therapeutic Vaccine</td>
<td>Oxson</td>
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<tr>
<td>Hepavox B</td>
<td>Therapeutic Vaccine</td>
<td>Virexx</td>
</tr>
<tr>
<td>HBV Core Antigen Vaccine</td>
<td>Therapeutic Vaccine</td>
<td>Emergent Europe</td>
</tr>
<tr>
<td>SpeciFi-HepB</td>
<td>Immunomodulator</td>
<td>Chironos</td>
</tr>
</tbody>
</table>
New Hepatitis C therapies

• Phase III
  • 2 new Interferons
• Phase II
  • 10 inhibitors
  • 4 new interferons
  • 1 therapeutic vaccine
  • 1 interferon enhancer
  • 1 Ribavirin pro-drug
New Hepatitis C antivirals

- Phase I
  - 7 inhibitors
  - 2 therapeutic vaccines
  - 2 immunomodulators
  - 4 new interferons
Rising Incidence of Hepatocellular Carcinoma

Represents a 41% increase in mortality rate and a 46% increase in hospitalization

Hepatocellular Carcinoma

In HCV cirrhotic patients

- 7% in 5 years
- 14% in 10 years
- Screening – controversial
- AFP every 6-12 months
- US or CT every 12 months

Screening for Hepatocellular Carcinoma

- Hepatitis B: risk groups, non-cirrhosis, cirrhosis
- Hepatitis C: cirrhosis
- Alpha fetoprotein every 6 months
- Ultrasound, imaging every 6 months
Screening tests

- Imperfect tests
- Difficult to find a small tumor in a scarred, nodular liver
- Can allow for earlier detection of hepatocellular carcinoma
Treatment

Improvements in
• resection
• radiofrequency ablation
• chemoembolization
• transplantation
Hepatocellular Carcinoma in HCV

Cumulative incidence

N=2890

P<.001

Untreated
Interferon (possible effect)

Years

Conclusions

• Exciting advances in hepatitis B and C treatment
• Treatment does make a difference in progression and complication rate
• Lifestyle, Nutrition can make a difference
• New agents are promising in slowing or eradicating the virus