HCV MEDICATIONS & THERAPEUTIC TRIALS

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DISCLOSURES
Active or Within 12 Months

• Research Support
  – Idenix
  – Roche
  – GSK
  – Schering
  – Vertex
  – Human Genome Sciences
  – SciClone

• Advisory Board
  – BMS
  – SciClone
  – Idenix
  – Vertex

• Speakers Bureau
  – SciClone

Agents and uses not approved by the FDA will be discussed
HEPATITIS C VIRUS

Genome

[Diagram showing the genome of the Hepatitis C Virus with structural and nonstructural proteins labeled.]
HCV DIVERSITY

- HCV replicates at high levels (>10 trillion virions/day)
- Lack of error correction leads to drift
- Drift is observed in two forms
  - Quasispecies
  - Genotypes
CURRENT TREATMENT
The Evolution of Efficacy With Interferon Based Therapy Over the Last 10 Years

- Interferon α-2b 24 weeks: 6%
- Interferon α-2b 48 weeks: 16%
- Interferon α-2b tiw + Ribavirin: 41%
- PEG-Interferon α-2b qw + Ribavirin: 24%–36%
- PEG-Interferon α-2a qw + Ribavirin: 54%–61%
HCV TREATMENT
Standard of Care 2007

Confirm HCV Present
Determine VL and Genotype
Evaluate Histology
Evaluate Contraindications to Rx

Genotype 1 or 4
Peg IFN alfa 2a or 2b + ribavirin
(wt. based) for 48 wks
EVR Evaluation → Early d/c
SVR 40-45%

Genotype 2 or 3
Peg IFN alfa 2a or 2b + ribavirin
800 mg/qd for 24 wks
SVR 70-85%

Pooled SVR 50-55%

Worse Outcomes
Poor Adherence
Obesity
Immunosuppressed
Cirrhosis
• Superiority should be required for first approval of small molecules
• Combination small molecule trials may be appropriate after Phase 2b evaluation of individual agents
• Prior to NDA studies MUST be initiated in special populations
  – HCV/HIV coinfection
  – Decompensated Liver Disease
  – Pediatric populations
• Appropriate representation of high prevalence minority groups is essential

Sherman et. al., HEPATOLOGY (in press)
HCV Life Cycle

- Binding
- Membrane fusion
- Endocytosis
- Virion assembly and maturation
- Uncoating
- Translation and polyprotein processing
- RNA replication (+ strands, - strands)
- Vesicle fusion and virion release

Agents That Block Entry

- Antibodies
- Entry Inhibitors
Agents That Block HCV Transport

- Antisense
- Ribozymes
- Small-interfering (si) RNA
mRNA

Antisense oligo

Translation arrest

Ribozyme

Endogenous ribonucleases destroy ineffective mRNA
Agents That Block Protease Function

• Protease Inhibitors
  – Blocks cleavage of structural proteins
  – Blocks cleavage of non-structural proteins from polyprotein
  – Blocks cleavage of non-structural proteins into individual proteins (NS3-NS4a serine protease inhibitors)
RNA

5' UTR region
Domains I-VI

9.6 kb

3' UTR region
5B-SL3 Poly U tail

IRES-mediated translation

Polyprotein

C E1 E2 NS2 NS3 A NS4 B A NS5 B

Polyprotein processing

C E1 E2 NS2 NS3 A NS4B NS5A NS5B

Core Envelope glycoproteins Protease Serine protease Helicase Serine protease cofactor Membr. web ? RNA-dependant RNA polymerase

Structural and non structural HCV proteins
Agents That Block Transcription

- Polymerase Inhibitors
  - Nucleoside Analog
  - Non-nucleoside Analog
- Cyclophilin B Inhibitors
- Helicase Inhibitors
Inhibition of Viral Assembly and/or Release

- Alpha-glucosidase inhibitors
- Release Inhibitors
Innate Immune Response Modifiers

- Therapeutic Vaccines
- Immunomodulatory Agents
  - TLR Agonists
  - Peptides
EXPERIMENTAL HCV AGENTS

- Protease Inhibitors
  - BILN-2061
  - VX-950 (Telaprevir)
  - ITMN-191
  - TMC-114
  - SCH 503034 (Boceprevir)
  - ACH-806

- Polymerase Inhibitors
  - Nucleoside Analogues
    - NM-283 (Valopicitibine)
    - A-837093
    - R1626
  - Non-nucleoside
    - AG-021541
    - HCV-796
    - BIL-1941
    - R-7128
EXPERIMENTAL HCV AGENTS

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Experimental HCV Therapy
Other Classes

- Alpha-Glucosidase 1 Inhibitor
  - Celgosivir
- Ribavirin Substitutes
  - Taribavirin (Viramidine)
- Caspase Inhibitor
  - PF-03491390 (IDUN 6556)
- TLR Agonists
  - CPG 10101
- Cyclophilin Inhibitors
  - DEBIO-025
SCH 503034
Boceprevir

- Non-responder to PEG-IFN + riba pts.
- Phase IIa trial
  - SCH 503034, 200 mg TID or 400 mg TID, for 7 days
  - Peginterferon alfa-2b, 1.5 µg/kg QW, for 14 days
  - SCH 503034, 200 mg TID or 400 mg TID plus peginterferon alfa-2b, 1.5 µg/kg QW, for 14 days
- RESULTS
  - 40% taking SCH 503034 + PegIFN reached limit of detection (29 IU/ml)

Zeuzem et. al. HEPATOLOGY ABS #201 2006
**VX-950**
Telaprevir

- Phase 1b study in HCV-infected patients
- N=34
- Regimen
  - VX-950 450 mg q8h
  - VX-950 750 mg q8h
  - VS-950 1250 mg q12h
  - Placebo
- **RESULTS**
  - Well tolerated with HA most common AE

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Reesink et. al. HEPATOLOGY ABS#96 2006
VX-950
Telaprevir

- Viral mutation study
- N=16 Genotype 1 subjects
- Randomized
  - Telaprevir 750 mg q8h (VX-950) or
  - Telaprevir 750 mg q8h + peg-IFN
- HCV RNA mutations analyzed at Days 4, 8, 12, 14

Kieffer T et al. 2006 Hepatology Abs. 92
VX-950

- Median viral load decline
  - VX-950 = 4.4 log
  - VX-950 + Peg-IFN = 5.5 log
- VX-950 Mutation Rate = 50%
  - R155 and A156V/T appeared at Day 8
  - R155K/T and V36M/A predominant by Day 14
- No mutations on combo therapy
- All patients put on Peg + riba at day 15 and undetectable at 3 months

Kieffer T et al, 2006 Hepatology Abs. 92
VX-950
Telaprevir 12 Week Arm Results

• PROVE 1
• 250 subjects
• 3 groups (75 each) randomly assigned to telaprevir 750 mg every 8 hours, Pegasys 180 mcg/week, and ribavirin 1000-1200 mg/day for 12 weeks, followed by 0, 12, or 36 weeks of Pegasys plus ribavirin or Peg/riba control
• Analysis performed after 80 subjects reached week 12

• RESULTS
• 12 week HCV RNA –
  – Triple Drug: 70%
  – Control 39%
• Modified SVR (20 week)
  – Triple Drug 35%

McHutchison et. al. EASL 2007
ITMN-191
Polymerase Inhibitor

• Study in 2 replicon systems
• Mathematical analysis demonstrates synergistic effect between pegylated interferon alfa-2a and ITMN-191 in reduction of HCV replication

Tan et. al., HEPATOLOGY 2006, Abs 933
R1626
Polymerase Inhibitor

- Phase 1b
- N=41
- Randomization
  - 5 Arms including placebo with 4 doses in active treatment arms
  - Genotype 1 patients only
- Response
  - 3000 mg led to 2.64 log HCV RNA drop
  - 4000 mg led to 3.47 log HCV RNA drop
- Safety
  - Hematologic and other toxicities at highest dose (4500 mg)
- Phase II trial with Pegasys + riba in planning stage

Roberts S et. al., 2006 Abstract LB2
Valopicitabine
Polymerase Inhibitor

- NS5b polymerase inhibitor
  - Ribonucleoside
  - NM107-triphosphate competitively inhibits viral polymerase and is incorporated into viral RNA, causing chain termination

- Oral agent
  - Valyl ester pro-drug provides high oral bioavailability
  - Plasma half life (4-6 hrs) & intracellular half life (15 hrs) support once daily dosing

Valopicitabine (NM283)
2’-C-methylcytidine-3’-O-L-valine ester
**Valopicitabine Phase IIb Treatment Naïve Study**

Week 12 Efficacy Assessment

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<th>Week 1</th>
<th>Week 4</th>
<th>Week 48</th>
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<td>peg-IFNα + 800 mg NM283</td>
<td>Follow-up</td>
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<td>peg-IFNα + 200 mg NM283</td>
<td>Follow-up</td>
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<tr>
<td>E</td>
<td>peg-IFNα + 800 mg NM283</td>
<td>Follow-up</td>
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</tbody>
</table>

**Week 12 HCV RNA Response Criterion to Proceed:** ≥ 2 log drop

Lawitz et. al., HEPATOLOGY, 2006, Abs #93
Serum HCV RNA (Mean Log₁₀ Change From Baseline)

Greater HCV RNA reduction with same NM283 + pegIFN treatment in naïve pts

Study Week

Non-responders

C NM283 400→800 mg QD ramp (1st week)→ 800 mg QD + peg-IFN 180 µg QW (n=41)
D NM283 800 mg QD + peg-IFN 180 µg QW (n=41)

Treatment-naïve

B NM283 200 mg QD @ D1 + Peg-IFN 180 µg QW @ D8 (n=29)
C NM283 400→800 mg QD ramp (1st week)→ 800 mg QD + peg-IFN 180 µg QW (n=28)
D NM283 800 mg QD + peg-IFN 180 µg QW (n=28)

HCV RNA reductions to Week 16: NM283 trial in treatment-naïve pts (Dieterich, EASL 2006)

Sherman ISVHLD 2006
PF-03491390
Caspase Inhibitor

• Inhibitor of caspase which increases apoptosis of hepatocytes

• Design
  – N=204
  – Prior treatment non-responders
  – ALT > 1.5x ULN
  – Randomized to placebo or 3 dose regimens for 12 weeks

• Results
  – All active treatment arms significantly (p<0.001) reduced ALT and AST levels vs. Placebo arm
  – Non-significant dose response observed

Shiffman et. al., HEPATOLOGY, 2006 Abs 95
Celgosivir

- Phase II trial
- N=36
- Genotype 1 NR
- Peg-IFN alfa-2b + riba + celgosivir vs. Peg-IFN + riba
- 12 Week Response Reported

Kaita et. al., DDW 2007
LIMITATIONS OF SMALL MOLECULE BASED THERAPIES

• Safety
  – NM-283 (Valopicitibine) GI toxicity- No longer in development
  – BILN-2061 Animal cardiotoxicity- No longer in development
  – VX-950 (Telaprevir)- Rash
  – ACH861- Nephrotoxicity
  – HCV796- Hepatotoxicity

• Antiviral Activity
  – Genotype specific to varying degrees
  – Unknown whether wide quasispecies variation in population will limit therapy
  – Maximal SVR unknown for any agent

• RESISTANCE
  – Observed within 14 days with all protease inhibitors
  – Higher barrier of resistance to nucleoside analogues
Pre-existing mutation
HCV/HIV Coinfected Patients

• Comparison of signature mutations for NS3 protease inhibitor
• Design
  – 38 coinfected patients sequenced
  – 250 monoinfected sequences from GenBank analyzed
• A156G/T changes evaluated
• Results
  – Mutation found in 7.8% of coinfected vs. 0.8% of monoinfected (p<0.02
  – All changes in coinfected among those who received prior HIV protease inhibitors

Morsica et. al, HEPATOLOGY 2006 Abs 436
SUMMARY

• Many targets for directed HCV therapy are available
• Some agents show promise, but development is slow and should not delay treatment in individual patients now
• Expect need for Pegylated Interferon for the foreseeable future