Overview of Current Developments in Treatment of Hepatitis C

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NIDDK, NIH, HHS
Known as non-A non-B hepatitis for 20 years

Discovered in 1989

Flaviviridae family

Positive single-stranded RNA genome

Six genotypes with up to 30% sequence variations

High mutational rates, quasipecies

High rate of chronicity

Silent disease progression

No vaccine

Treatment improving but not optimal
Case Presentation

• GR is a 45 yo WM business executive, incidentally noted to have elevated LFTs on routine PE and later diagnosed with hepatitis C

• Described brief experimentation with drugs during college years

• ALT 126, AST 117, Bili 1.0/0.4, Alb 3.6, PLT 89, HCV level 1.2 x 10^6 IU/mL, genotype 1a

• Liver biopsy: active inflammation with cirrhosis

• Treated with IFN and ribavirin
IFN 3 MU tiw
RBV 1200 mg
X 48 Weeks

ALT U/mL

Month

HCV RNA IU/mL

Patient GR
PegIFN 180 µg/wk
RBV 1200 mg
X 48 Weeks

Patient GR

IFN 3 MU tiw
RBV 1200 mg
X 48 Weeks

HCV RNA IU/mL

Month
Progress in Therapy of Hepatitis C

Sustained Virologic Response

- 1980: 6%
- 1990: 16%
- 2000: 39%
- 2010: 70%

IFN 6 m: 34%
IFN 12 m: 42%
IFN/R 6 m: 39%
IFN/R 12 m: 54%
PIFN 12m: 61%
PIFN/Rlo 12m: 61%
PIFN/R 12m: 61%
PIFN/R DAA: 70%

Ribavirin
PEG
Direct-Acting Antivirals
SVR and Rates of Liver Related Complications and HCC

Liver related complications

HCC

Progress in Therapy of Hepatitis C

Side Effects or Costs

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6m</th>
<th>IFN 12m</th>
<th>IFN/R 6m</th>
<th>IFN/R 12m</th>
<th>PIFN 12m</th>
<th>PIFN/R 12m</th>
<th>PIFN/R 12m</th>
<th>PIFN/R DAA</th>
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<td>1980</td>
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</table>

Direct-Acting Antivirals

PEG

Ribavirin
Therapy of Hepatitis C: Virological Responses

IFN-Based Therapy

Non-Response

Relapse

ETR

SVR

HCV RNA (Log IU/mL)

Weeks After Start of Therapy

Undetectable
Outcomes in Clinical Practice: Retrospective Studies in the US

Data from medical records review and included patients with genotype 1 HCV infection \(^{[1,2]}\)

- 2 centers in Dallas and Miami with 12-wk follow-up \(^{[1]}\)
- Exclusions: transplantation, dialysis, or HIV co-infected
- Of 498 patients identified
  - 18% began triple therapy
  - 21% discontinued triple therapy before wk 12

- Mount Sinai Medical Center and Montefiore with 12-wk follow-up \(^{[2]}\)
- Of 174 patients who initiated TVR-based triple therapy
  - 33% discontinued TVR prematurely
  - 21% discontinued treatment due to adverse events

Drug Therapy

Current and Future Therapies for Hepatitis C Virus Infection

T. Jake Liang, M.D., and Marc G. Ghany, M.D., M.H.Sc.
The Current Landscape of HCV Therapeutics

- PegIFN-α and other forms of IFNs
- Ribavirin and related compounds
- Direct acting antivirals
  - NS3 protease inhibitors
  - NS5B polymerase inhibitors (nuc and non-nuc)
  - NS5A
  - Other targets: p7 (BIT225), NS4B (clemizole)
Direct Acting Antiviral: Mechanism of Action

**NS3:** telaprevir (TVR), boceprevir (BOC)
**NS5a:** daclatasvir
**NS5b:** NI and NNI
Direct Acting Antiviral: Mechanism of Action

BIT 225
Clemizole
First-Generation DAA Regimens: Genotype 1 Patients

• Treatment-naïve and -experienced patients have better SVR from triple therapy than PIFN/Rbv
• Half to two-thirds of treatment-naïve patients given BOC and TVR can have reduced treatment duration
• Among treatment-experienced patients, relapsers have the best response and null responders have ~30% SVR
• Certain populations, like cirrhotics and AA, have lower SVR, and response-guided therapy (RGT) not recommended
• BOC and TVR have substantial side effects
First-Generation DAA Regimens: Important Management Issues

- BOC and TVR should never be used as monotherapy
- Re-inforce adherence and compliance - regimens are complicated and pill burden high
- Full treatment duration necessary for patients with cirrhosis
- Review drug-drug interactions before initiating therapy: cytochrome p450 and P-glycoprotein transporter
- Rapid virologic response associated with high SVR
- Therapy can be tailored to on-treatment response (RGT)
- Futility rules can be established
First-Generation DAA Regimens: Important Management Issues

- Monitor for resistance
- Monitor for side effects: anemia, rash, anorectal burning, dysgeusia
- Adverse events can be managed but often a cause for stopping therapy
- Ribavirin dose reduction to manage anemia does not affect SVR
- Genetic (IL28 genotype) influence responsiveness because of the PegIFN/Rbv backbone
# Management Strategy for Genotype 1

<table>
<thead>
<tr>
<th>Status</th>
<th>SVR Rate</th>
<th>IL28B Testing</th>
<th>Liver Biopsy</th>
<th>Treatment Consideration</th>
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<tbody>
<tr>
<td>Naive</td>
<td>63–75%</td>
<td>Optional</td>
<td>Optional</td>
<td>Consider treatment; balance with disease severity and side effects; RGT</td>
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<tr>
<td>Relapsers</td>
<td>75–85%</td>
<td></td>
<td></td>
<td>Consider treatment; RGT</td>
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<tr>
<td>Partial Responder (&gt;2-log drop)</td>
<td>40-52%</td>
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<td></td>
<td>Consider treatment based on likelihood of disease progression and treatment response</td>
</tr>
<tr>
<td>Nonresponder (&lt;2-log drop)</td>
<td>29-38%</td>
<td></td>
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</tbody>
</table>

IL28B testing and liver biopsy are optional. Knowledge of fibrosis stage (liver biopsy or other means) is helpful. Treatment should be considered based on the likelihood of disease progression and treatment response.

*Liang & Ghany, NEJM 2013*
Management Strategy for Genotype Non-1

HCV Genotypes 2&3

- Naive
  - None
    - Consider treatment for all patients
    - 75-85% SVR

- Nonresponder
  - Wait for new therapy
  - ?? SVR

HCV Genotypes 4-6

- Naive
  - Insufficient data on the role of IL28B testing
    - Liver biopsy optional
    - Consider treatment for all patients
    - 50-70% SVR

- Nonresponder
  - Wait for new therapy
  - ?? SVR

Liang & Ghany, NEJM 2013
Combinations of DAAs with PegIFN/Rbv

- **Triple Regimens**
  - TMC-435 (PI)
  - Daclatasvir (NS5A)
  - Faldaprevir (PI)
  - ABT-450/ritonovir (PI)
  - Sofosbuvir (NI)

- **Quadruple Regimens**
  - Danoprevir (PI)/r + Mericitabine (NI)
  - Asunaprevir (PI) + Daclatasvir (NS5A)
  - Faldaprevir (PI) + BI 207127 (NNI)
  - VX-222 (NNI) + telaprevir (PI)
  - ABT-450/r (PI) + ABT-333 (NNI)
  - GS-9451 (PI) + GS-5885 (NS5A)

- All can achieve >90% SVR in phase 2/3 trials
- Once daily regimen
- Broader genotypic coverage
- Side effects seem less
- Fewer drug-drug interactions
Interferon-Free Regimens: Combinations of DAAs

- Combinations of DAAs studied
  - Danoprevir (PI) + RG7128 (NI)\textsuperscript{1}
  - GS-9256 (PI) + Tegobuvir (NNI)\textsuperscript{2, 3}
  - Asunaprevir (PI) + Daclatasvir (NS5A)\textsuperscript{4, 5}
  - Faldaprevir (PI) + Deleobuvir (NNI)\textsuperscript{6}
  - VX-222 (NNI) + Telaprevir (PI)\textsuperscript{7}
  - PSI-938 (NI) + PSI-7977 (NI)\textsuperscript{8}
  - ABT-450/ritonovir (PI) + ABT-333 (NNI)\textsuperscript{9}
  - Sofosbuvir (NI) + Ribavirin\textsuperscript{10} or Sofosbuvir + Daclatasvir (NS5A)\textsuperscript{11}

\textsuperscript{1} Gane \textit{et al.} Lancet 2010;376:1467-1475; \textsuperscript{2} Zeuzem \textit{et al.} AASLD 2010; \textsuperscript{3} Foster \textit{et al.} EASL 2011; \textsuperscript{4} Lok \textit{et al.} NEJM 2012; \textsuperscript{5} Chayama \textit{et al.} Hepatology 2012; \textsuperscript{6} Zeuzem \textit{et al.} NEJM 2013; \textsuperscript{7} Di Bisceglie \textit{et al.} EASL 2011; \textsuperscript{8} Lawitz \textit{et al.} EASL 2011; \textsuperscript{9} Poordad \textit{et al.} NEJM 2013; \textsuperscript{10} Gane \textit{et al.} NEJM 2013, Lawitz \textit{et al} NEJM 2013, Jacobson \textit{et al}, NEJM 2013; \textsuperscript{11} Sulkowski \textit{et al}, EASL 2012
Summary

• IFN-free regimen possible
  – Genotype 1: suboptimal, better for Gt 1b
  – Genotypes 2 & 3: 90% for Gt 2 but only 56% for Gt 3 (sofosbuvir + ribavirin)

• Various combinations of DAAs

• Challenges remain: Gt 1a, cirrhosis, prior NRs

• May still need PegIFN and Rbv for optimal efficacy

• Non-DAA (host targeting) approach potentially useful
The Current Landscape of HCV Therapeutics

- PegIFN-α and other forms of IFNs
- Ribavirin and related compounds
- Direct acting antivirals
  - NS3 protease inhibitors
  - NS5B polymerase inhibitors (nuc and non-nuc)
  - NS5A
  - Other targets: p7 (BIT225), NS4B (clemizole)
- Host targeting antivirals
  - Cyclophilin A (alisporovir, SCY-635, NIM811)
  - MiRNA122 (miravirsen)
  - Viral entry: SRB1 (ITX 5061), EGFR, NPC1L1
  - Viral assembly/lipid metabolism (statins)
Direct Acting Antiviral: Mechanism of Action

Hepatocyte

CypA

Alisporovir, SCY-635, NIM 811

Miravirsen
Miravirsen in Genotype 1 Treatment-Naive Patients

Mean change in HCV RNA from baseline (Log_{10} IU/ml)

Dosing Period

Time - weeks

Janssen et al, NEJM 2013
Alisporovir + PIFN/Rbv vs. PIFN/Rbv
HCV GT1, Naive (ESSENTIAL-1 study, phase IIb)

Flisiak et al. EASL 2011
HCV Life Cycle

- **Entry**
  - ITX 5061
  - Erlotinib
  - Ezetimibe

- **Replication**
  - Statin
  - PPAR-γ agonist

- **Assembly**
  - Nucleus
  - Lipid droplet

- **Translation**
  - Endoplasmic Reticulum

- **Secretion**
  - Golgi

- **Trafficking**

- **Hepatocytes**

- **Tight junction**

- **Cell-Cell Transmission**

**Key Players**

- **HCV**
- **ITX 5061**
- **Erlotinib**
- **Ezetimibe**
- **Statin**
- **PPAR-γ agonist**

**Locations**

- **Liver Cell (Hepatocytes)**
- **Nucleus**
- **Golgi**
- **Lipid droplet**
- **Endoplasmic Reticulum**
- **Tight junction**
# Summary of DAAs in Development

<table>
<thead>
<tr>
<th>Drug Properties</th>
<th>NS3/4A Protease Inhibitor</th>
<th>NS5B Polymerase Inhibitor</th>
<th>NS5A Inhibitor</th>
<th>Cyclophilin A Inhibitor</th>
<th>miRNA122 Inhibitor</th>
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<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>Narrow (broader with 2nd-generation)</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Genotypic coverage</td>
<td>Nucleoside Analogue</td>
<td>Non-nucleoside Analogue</td>
<td>Efficacy</td>
<td>Drug-drug interactions</td>
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<td>Probability of drug resistance</td>
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Ideal Anti-HCV Therapy

- Interferon-free
- Close to 100% SVR
- All oral
- Once daily
- Few or no side effects
- One combination pill
- Short duration (12 weeks)
- Effective in all genotypes, cirrhosis, liver transplantation