Advances in Hepatitis C Virus Therapeutics

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Current therapies
- Pegylated IFN and ribavirin (RCTs)
- HCV therapy among “difficult to treat” populations
- Impact of HCV therapy on projected liver disease burden

Future therapies
- Improved strategies with currently available therapy
- New agents (e.g. protease inhibitors)

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Hepatitis C notifications: 1990-2003

Source: NCHECR Annual Surveillance Report 2004

Estimates of people with hepatitis C by disease stage


Estimates of people with hepatitis C by disease stage


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Estimates of BBV prevalence in Australia

HCV HIV HBV

90,000 – 160,000

12,000

250,000

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Estimates of people with HCV-related cirrhosis: 1990-2020

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### Sustained Virological Response

- PEG-IFN-α2b+RBV 80/80/80 adherence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>24 weeks</th>
<th>48 weeks</th>
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</thead>
<tbody>
<tr>
<td>IFN-α2b</td>
<td>8%-12%</td>
<td>15%-22%</td>
</tr>
<tr>
<td>PEG-IFN-α2b+RBV</td>
<td>25%-29%</td>
<td>41%</td>
</tr>
<tr>
<td>PEG-IFN-α2b</td>
<td>6%-9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**IFN action**

**The dsRNA-Dependent Protein Kinase (PKR) Pathway**

- IFN induces Mx proteins
- PKR
- 2-5A synthetases
- ATP
- ppA2'p5'A2'p5'A (2-5A)
- 2-5A dependent RNase (RNase L)
- RNA cleavage
- ADP
- PKR-Pi
- GTP
- GDP+ Pi
- 3ATP
- 2Pi
- Viral dsRNA activates PKR-Pi
- SIGNAL TRANSDUCTION
- elF2α+ATP elF2α-Pi+ADP
- INHIBITION OF PROTEIN SYNTHESIS AND TRANSCRIPTIONAL CONTROL

**The Mx Pathway**

- IFN-α2b
- 48 weeks
- 15%-22%
- IFN-α2b+RBV
- 48 weeks
- 41%
- PEG-IFN-α2b
- 24 weeks
- 6%-9%
- PEG-IFN-α2b+RBV
- 24-48 weeks
- 61%-65%

**Rationale for Pegylation**

- Pegylation = binding of ethylene oxide polymers to drug molecule
- Decreases clearance – prolonged half life / sustained blood levels
- Decreases proteolysis and immunogenicity
- Less frequent dosing

**PEG-IFN serum concentrations**

- IFN-α 3 MIU 3x weekly
- PEG-IFN-α2b 1.5 mcg/kg SC weekly
- PEG-IFN-α2a 180 µg SC weekly

**Sustained virological response (PEG-IFN-α2a+RBV)**

- IFN-α2b + placebo: 29%
- IFN + RBV: 44%
- PEG-IFN-α2b + RBV: 65%

**Current therapies**

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**Future therapies**

- Improved strategies with currently available therapy
- New agents (e.g. protease inhibitors)
Factors associated with poorer SVR

- HCV genotype 1
- HCV viral load (genotype 1)
- Severe fibrosis – cirrhosis
- High body weight
- Age > 40 years
- African American ethnicity
- HIV coinfection
- < 80% adherence (RBV > PEG-IFN)
Access to Australian government funded HCV treatment requires:
- >= 18 years
- liver biopsy consistent with chronic HCV infection
- at least fibrosis (F) 1 with moderate inflammation or F2
- compensated liver disease
- naïve to HCV treatment

Current levels of HCV treatment in Australia are low ~1,500-2,000/year

HCV treatment scenarios assessed: 2,000 – 10,000/year
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Estimates of people with cirrhosis

- Without treatment
- Current treatment (maintenance of liver biopsy and treatment of abnormal ALT)
- Mid (maintenance of liver biopsy and treatment of abnormal ALT)
- Optimistic treatment (removal of liver biopsy and treatment of normal ALT)

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Estimates of people with liver failure

- Without treatment
- Current treatment (maintenance of liver biopsy and treatment of abnormal ALT)
- Mid (maintenance of liver biopsy and treatment of abnormal ALT)
- Optimistic treatment (removal of liver biopsy and treatment of normal ALT)

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Estimates of total QALYs lost

- Without treatment
- Current treatment (maintenance of liver biopsy and treatment of abnormal ALT)
- Mid (maintenance of liver biopsy and treatment of normal ALT)
- Optimistic treatment (removal of liver biopsy and treatment of normal ALT)

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Therapeutic strategies currently under investigation (I)
- High dose PEG-IFN induction for genotype 1 (CHARIOT)
- Longer duration of PEG/RBV (72 wks) for genotype 1
- Shorter duration of PEG/RBV (16 wks) for genotype 2/3
- High individualized RBV dosing
- Long-term low dose PEG-IFN in non-responders (HALT-C)

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Therapeutic strategies currently under investigation (II)
- Use of RBV pro-drug (Viramidine)
- G-CSF and EPO supplementation
- Prophylactic anti-depressant therapy
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**HCV Genome**

![HCV Genome Diagram]

**HCV enzymes are targets for new therapies**

![HCV Enzymes Diagram]

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**Challenges in drug development**

- High variation in HCV genome
- High mutational capacity - resistance
- Lack of conventional tissue culture system for in vitro studies
- Lack of small animal model
- Lack of understanding of HCV pathogenesis

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**Therapies in development**

![Therapies in Development Diagram]
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Protease Inhibitor – BILN 2061

- NS3/4A protease inhibitor
- First small molecule agent to demonstrate HCV antiviral activity
- Active in inhibiting HCV RNA replicons in cultured cells
- Phase I clinical trial (genotype 1)
  - 200mg bd for 2 days
  - 2-3 log reduction in HCV RNA within 48 hours
- Further toxicology (animals) at higher doses demonstrated cardiac toxicity
- ?? Resistance

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Strategies for increased access to HCV treatment

- Increasing awareness of improved treatment response
- Broadened base of practitioners involved in HCV care
- Multidisciplinary clinics
- Enhanced clinical trial infrastructure
- Research on most appropriate treatment delivery models
- Removal of liver biopsy requirement
- Advocacy