Current Management of diagnosed cases of HCV Infection

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Management of HCV

- Screening
- Diagnosis
- Assessment
- Selection
- Clinical Record
- Treatment
- Follow up
Assessment

– Viral genotype
– Liver Biopsy
  • Stage
  • Additional diagnosis
– Compliance
– Psychiatric evaluation
– Co-morbid conditions
  • IHD
  • COPD
  • Alcohol
  • BMI
Management of HCV

Screening → Diagnosis → Assessment

Selection

Clinical Record → Treatment → Follow up
Selection

• Who makes the decision?
  – Patient
  – Specialist nurse
  – Doctor
  – D&A worker
  – Panel

• Selection criteria
  – Need for treatment
    • Patient views
    • Severity of liver disease
    • Absence of co-morbidity
    • Non-liver symptoms
  – Compliance
  – Likely response rates
  – Ability to tolerate treatment
Goals of Treatment

• Prevention of long term sequelae
• Reversal of liver damage
• Elimination of virus
• Resolution of symptoms
• Abolish source of infection
Side Effects of Therapy

- Interferon
  - Myalgia / Arthralgia
  - Fatigue
  - Alopecia
  - Autoimmune thyroiditis
  - Diabetes
  - Neutropaenia
  - Thrombocytopaenia
  - Depression

- Ribavirin
  - Anaemia
  - Teratogenicity
Management of HCV

Screening → Diagnosis → Assessment

Selection

Clinical Record

Treatment → Follow up
Principal Drugs

- Interferon α
  - 2a, 2b, consensus,
  - Pegylated
- Ribavirin
Actions of Interferons

- Interferon α
  - Antigen Presenting Cell
  - Infected Cell (HBV)
  - MHC CLASS I
  - Viral Peptides
  - NK CELL
  - CTL
  - IFNγ
  - TNFα

CD4
Ribavirin

• Nucleoside analogue
  – anti-viral
• Innosine monophosphate dehydrogenase inhibitor
  – reduces supply of GTP to virus
• Immunomodulator
  – induces Th1 immune responses
Pharmacokinetics of Interferon Thrice Weekly Injection

Interferon Levels

![Graph showing interferon levels over time with peaks at 0, 1, 2, 3, 4, 5, 6, 7, and 8.]
Pharmacokinetics of Interferon Once Weekly Pegylated IFNs

12 kD PEG IFNα2b

40 kD PEG IFNα2a
Response to treatment

Viral Load

Detection Limit

Pre-treatment  Treatment  End-treatment  Post-treatment
HCV Infection: Worldwide Genotype Distribution

Pegylated Interferons v Interferons & Ribavirin

Sustained Viral Response Rates

Alpha 2a

Alpha 2b

Pegylated
Non-pegylated
Pegylated Interferons v Interferons & Ribavirin

Genotype 1

Sustained Viral Response Rates

Alpha 2a
Alpha 2b

Pegylated
Non-pegylated
Pegylated Interferons v Interferons & Ribavirin

Genotype 2 / 3

Sustained Viral Response Rates

Alpha 2a

Alpha 2b

Pegylated
Non-pegylated
Effect of Ribavirin Dose

Pegylated Interferon + Ribavirin

- High Dose (1200 mg/d)
- Low Dose (800 mg/d)

Bar chart showing the comparison of Ribavirin dose effects between Genotype 1 and Genotype 2/3.
Protocol: HCV Gt 1

- Pegylated Ifn o.w. 48 weeks
  - Ifnα2a 180 μg
  - Ifnα2b 1.5 μg/kg
- Ribavirin daily 48 weeks
  - 1 – 1.2 g/d
  - >10.6 mg/kg/d
Protocol: HCV Gt 2/3

- Pegylated Ifn o.w. 24 weeks
  - Ifnα2a 180 µg
  - Ifnα2b 1.5 µg/kg
- Ribavirin daily 24 weeks
  - 1 – 1.2 g/d
  - >10.6 mg/kg/d
Predicting Treatment Failure

Genotype 1
- EVR + 80% → SVR + 60%
- EVR – 20% → SVR + 0.5 – 1.7%

Genotype 2/3
- EVR + 99% → SVR + 80%
- EVR – 1% →

Early Viral Response: PCR neg or 2-log reduction
Stopping Treatment Early

- Gt 2/3 – no point
- Gt 1
  - < 2 log drop or PCR pos at 12 weeks
    - 1.6% achieve SVR
  - PCR pos at 24 weeks
    - 0% achieve SVR
## Cytopaenias and Dose Reduction

<table>
<thead>
<tr>
<th>Cytopaenia</th>
<th>Dose Reduction</th>
<th>Ref</th>
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<tbody>
<tr>
<td>Anaemia</td>
<td>20 – 25%</td>
<td>Manns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fried</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>18 – 20%</td>
<td>Manns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fried</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3%</td>
<td>Sukowski</td>
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</table>
Depression

Peg-IFN & Ribavirin
N = 39

Depression
13 / 39 (33%)

Improved on Citalopram
11/13 (85%)

Hauser Mol Psychiatry 2002
Special Cases

• Acute HCV
• Transplants
• Cirrhosis grade B & C
• Renal patients
• Haemaglobinopathies
• Paediatric patients
• Advanced Cardiac Disease
• IVDU
• Treatment Failure on Interferon & Ribavirin
Acute HCV

• 50% will progress to chronic
• 95% respond to interferon & ribavirin
Liver Transplants

- 98% re-infected
- 10% early graft loss
- Poor response to I + R
- Trials in transplant centres
Advanced Fibrosis / Cirrhosis

Heathcote EJ. NEJM 2000;343:1673-1680
Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis.
Cirrhosis B & C

- Poor tolerance of side effects
- High rates of decompensation

- HALT-C trial in US
- Similar Trial in UK
Renal Patients

- Often mild disease
- Poor tolerance of ribavirin
  - Anaemia
  - Pharmacokinetics
- Trials required
Paediatrics

• Low fibrosis stage and rate
• No RCTs
• If mild
  – Wait until old enough for full assessment
• If severe
  – Refer to paediatric unit
Continued Drug Use

- Trials suggest re-infection is rare
- Compliance required
- Link to needle exchange programme
- Cessation of IV use should be encouraged
Novel Rx

• Short Duration Therapy
  – Rapid viral responders
  – 3/12 HCV-Gt 2/3
  – 6/12 HCV Gt 1

• Direct anti-viral
  – Protease inhibitors
  – Polymerase inhibitors
  – Helicase inhibitors

• Ribavirin replacement
  – Viramidine

• Therapeutic Vaccination
Management of HCV

Screening → Diagnosis → Assessment → Selection

Clinical Record → Treatment → Follow up
Do we achieve our goals?

- Prevention of long term sequelae
- Reversal of liver damage
- Elimination of virus
- Resolution of symptoms
- Abolish source of infection
## Long Term Outcome of Treatment 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Resp</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Source</th>
<th>Genotype</th>
<th>RNA</th>
<th>ALT</th>
<th>HAI</th>
<th>RNA</th>
<th>ALT</th>
<th>HAI</th>
<th>Liver RNA</th>
<th>Follow-up (yr)</th>
<th>Clinical Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>SR</td>
<td>30</td>
<td>M</td>
<td>IDU</td>
<td>1a</td>
<td>+</td>
<td>376</td>
<td>11</td>
<td>&lt;100</td>
<td>20</td>
<td>3</td>
<td>–</td>
<td>11</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>SR</td>
<td>27</td>
<td>M</td>
<td>Tx</td>
<td>2a/2b</td>
<td>+</td>
<td>460</td>
<td>8</td>
<td>&lt;100</td>
<td>52</td>
<td>3</td>
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<td>10</td>
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<tr>
<td>3</td>
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<td>37</td>
<td>M</td>
<td>IDU</td>
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<td>+</td>
<td>306</td>
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<td>&lt;100</td>
<td>21</td>
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<tr>
<td>4</td>
<td>SR</td>
<td>40</td>
<td>M</td>
<td>Tx</td>
<td>3</td>
<td>+</td>
<td>272</td>
<td>11</td>
<td>&lt;100</td>
<td>35</td>
<td>2</td>
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<tr>
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<td>Tx</td>
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<td>+</td>
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<td>23</td>
<td>0</td>
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<tr>
<td>6</td>
<td>NR</td>
<td>51</td>
<td>M</td>
<td>IDU</td>
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<td>+</td>
<td>219</td>
<td>12</td>
<td>1500</td>
<td>23</td>
<td>11</td>
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<td>13</td>
<td>HCC/OLT</td>
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<tr>
<td>7</td>
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<td>41</td>
<td>M</td>
<td>Unknown</td>
<td>1b</td>
<td>+</td>
<td>419</td>
<td>14</td>
<td>1.18 × 10⁶</td>
<td>181</td>
<td>12</td>
<td>NA</td>
<td>6</td>
<td>Died/Stroke</td>
</tr>
<tr>
<td>8</td>
<td>NR</td>
<td>62</td>
<td>F</td>
<td>Tx</td>
<td>1b</td>
<td>+</td>
<td>200</td>
<td>8</td>
<td>0.049 × 10⁶</td>
<td>248</td>
<td>16</td>
<td>+</td>
<td>11</td>
<td>Symptoms</td>
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<tr>
<td>9</td>
<td>NR</td>
<td>38</td>
<td>M</td>
<td>Tx</td>
<td>1a</td>
<td>+</td>
<td>148</td>
<td>17</td>
<td>&gt;5 × 10⁶</td>
<td>102</td>
<td>15</td>
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<td>Symptoms</td>
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<tr>
<td>10</td>
<td>NR</td>
<td>46</td>
<td>M</td>
<td>Tx</td>
<td>1b</td>
<td>+</td>
<td>392</td>
<td>15</td>
<td>1.4 × 10⁶</td>
<td>326</td>
<td>12</td>
<td>NA</td>
<td>11</td>
<td>Symptoms</td>
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</tbody>
</table>
Follow-up for Untreated and Non-Responder Patients

- Untreated
  - Minimal fibrosis
    - Repeat biopsy every 5 years
  - Non-compliant
    - Address lifestyle or psychological issues

- Non-responders
  - Monitor
Management of HCV

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- Follow up
Summary

• Assessment and selection are essential
  – 30% of infected patients treated
• Compliance with therapy is essential
  – Full support team required
• Outcomes of therapy are poor
  – 50% of treated patients achieve SVR
Pegylated Interferon Trials

• Manns MP et al. Lancet 2001 22; 358: 958-65
  – Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial.

  – Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.

  – Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose.