Hepatitis C treatment and care

Relevance to haemophilia

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Risk factors for HCV infection

- **Blood contamination**
  - Transfusion of blood products before 1990 [~70% haemophilia]
  - Injection drug use (now >90% of new infections)
  - Nosocomial spread (universal precautions)
  - Body piercing, tattooing
  - Medical spread (vaccinations, shistosomiasis eradication etc)

- **Sexual spread**

- **Birth in hyper-endemic country**
  - Egypt (genotype 4)
  - Vietnam/south China (genotype 6)
  - Italy – genotypes 1B and 2
HCV testing in people with haemophilia

- Meaning of positive anti-HCV test (with risk factor)
- PCR for HCV RNA to determine continuing infection:
  - Lower – age <2 yrs, infected after 1983, +HBV
- Genotype (1,2,3,4), viral load: relevance to therapy
- Exclude co-infections (HBV, HIV) and co-morbidity (FBG, lipids)
- Assess likely severity of liver disease
Outcomes of acute hepatitis C

- Most infections asymptomatic
- **Outcome:** 45-85% chronicity (15-55% resolution)
- **Better:** younger age, women, genotype 3 (vs 1), HBV co-infection, jaundice
- Resolution most likely in first 3 mo
- Altered by antiviral treatment
Antiviral therapy for acute hepatitis C

- Reduces chronicity [to 5-20%]
- Safe to wait 12 weeks
- Daily IFN (5 mU) has produced best results
- PEG-IFN seems equivalent [not on Section 100]
- 16 wk treatment for genotypes 2 and 3
- 24 wk treatment for genotype 1
- Ribavirin not needed
Co-morbidity in hepatitis C

relevance to natural history and patient care

- Alcohol
- Other toxins; iron
- **Metabolic** – central obesity, insulin resistance, obesity, diabetes, steatosis (fatty liver disease)
- Immune deficiency – HIV; transplantation
- Co-infections - other hepatitis viruses (HBV, HDV)
Alcohol worsens severity of chronic hepatitis C

- Threshold for fibrotic progression unclear
  - >80 g/day, at least 5 yr Khan M et al J G H 1998;13:419-26
  - >50 g/d Monto A et al Hepatology 2004;39:826-34
  - >20 g/d Colletta C et al Hepatology 2005;42:759-61

- Not “light” or “moderate”; not “binge”

- Lifetime alcohol increases rate of cirrhosis [Meta-analysis
Alcohol increases risk of HCC in hepatitis C (even after SVR)

*Iwasaki et al. Liver Int 2004;24:603-10*
Effects of alcohol on treatment outcome

- Management guidelines: *curb alcohol dependence before antiviral therapy, support during therapy*

- Exclusion of those with alcohol history recently challenged [Anand B et al Gastroenterol 2006;130:1606]

- Threshold unclear; compliance is the issue
Effects of other toxins on hepatitis C

- Iron – debated \((in \ vitro, \ Fe \ suppresses \ HCV \ replication)\)
  - 2 studies favour associations between HFE, increased hepatic Fe and worse fibrosis
  - 2 studies find no such effect
  - 1 study found phlebotomy beneficial; several others did not

- Cigarette smoking – worsens fibrosis

- Opiates – suboptimal treatment response
Drug deaths are more frequent than liver deaths in young people with HCV.

Metabolic factors and hepatitis C

- Obesity
- Central obesity
- Insulin resistance
- Type 2 diabetes
- Steatosis

What’s fat got to do with it?
Steatosis in hepatitis C

- Common
- Genotype-specific mechanisms
  - Genotype 2,3: direct viral effect
  - Genotype 1,4: principally host determinants (insulin resistance)
- Alcohol, central obesity, raised BMI
- Associated with more activity, more severe fibrosis
- Obesity reduces response to IFN-based treatment
Insulin resistance and hepatitis C

- Higher prevalence type 2 diabetes
- “Adjusted” incidence increased 11-fold
- Associated with portal activity
- More severe fibrosis
- Reduced response to IFN-based antivirals
Management of hepatitis C and metabolic syndrome

- Correct central obesity; monitor waist
- **Gradual** [0.5 - 1.0 kg/wk], **sustained** wt reduction
- Correct IR (exercise, low fat, low GI/high fibre diet)
- Treat obesity (appetite suppression, bariatric surgery)
- Control hyperglycaemia (anti-diabetics)
- Correct lipids (diet, statins, gemfibrozil)

*Does this increase chance of SVR to antiviral therapy?*
HBV co-infection and chronic hepatitis C

Gaeta GB et al J Hepatol 2006;44:S1-8-S13

• 5-10% HCV+ also HBsAg positive (higher with HIV)
• Usually HBeAg negative, HBV DNA <10^4 IU/mL
• Mechanisms of “viral interference” unclear
• Much higher rate of cirrhosis and HCC
• Treat “dominant” infection
  • Promising results with pegylated-interferon/ribavirin for HCV RNA positive cases
Outcomes of HCV infection

Acute hepatitis C
45 - 85% (age dependent)

Chronic HCV infection
70%

Chronic hepatitis C
1-4%/yr
2-10%

Cirrhosis
4 - 5%/yr

Decompensation

HCC

Time (yr)

10 20 30
Staging chronic hepatitis C
Fibrosis stages 1, 3, 4
Progression of liver disease in chronic hepatitis C

(Markov Modelling - Dore et al 2004)
Estimates and projections of Australians with HCV-related cirrhosis

*(Law et al 2004)*
Hepatocellular carcinoma complicates cirrhosis
Fibrotic progression rates for chronic hepatitis C

**Overall:** 0.12 fibrotic grades/yr
- *one stage worse every 8-10 yr*

**Age >50 yrs:** 0.33 /yr
- *one stage worse every 3-4 yr*

**Normal ALT:** 0.08 /yr
- *one stage worse every 12-15 yr*
Factors that influence fibrotic progression rate

- Age at infection
- ALT
- Lifetime alcohol history
- Central obesity/ insulin resistance
- Immunodeficiency
- Co-infections
Can we avoid liver biopsy?

**Fibrotic predictive indices** (at least 8 published; *Maor Y et al. Haemophilia 2007;13:1-8)

- **Age, AST, platelet count, alcohol history, total cholesterol, insulin resistance**, alpha-2 macroglobulin, apolipoprotein A1 and hyaluronan most useful variables

- FPI of above 5 variables: area under ROCs 0.84, 0.77 for test and validation cohorts (*Sud and Hui et al. Hepatol 2004;39:1239*)

- At score of ≥0.2, sensitivity 96% and NPV 93%
  - avoid liver biopsy 48% of cohort [67% *Maor et al 2007]*

- At ≥0.8, FPI was 94% specific and PPV of 87%
  - Identify most patients with severe fibrosis
Can we avoid liver biopsy?

- Pay attention to age* and duration of infection, hard liver edge/presence of spider naevi (not symptoms)
- Continued activity (ALT and AST)
- Lifetime alcohol history
- Central obesity
- Subtle (serial) changes in serum albumin, platelets
- Hepatic imaging (portal hypertension)
- Fibroscan (promising but not available in Australia)

* Recommended before children submitted to treatment
Liver biopsy with haemophilia

- Not contraindicated
- Pre-test, intra-test (6 hr after), post-test clotting factors
- Manage by haemophilia clinic (aim for 1 U/mL - 100% cover)
- Trans-jugular biopsy - experienced centres

Do we still need liver biopsy?

- Use liver biopsy when patient **MAY** have severe fibrosis, but not very keen on therapy (all children)
  - need evidence liver disease severe enough to warrant therapy
  - Or mild enough to allow no therapy (“therapeutic relief”)
- Do **NOT** use liver biopsy if informed patient keen to have therapy, irrespective of result! (PBS Section 100)
- ...or clinical, imaging and/or laboratory evidence suggests cirrhosis, and patient prepared to be treated
Treatment outcomes

- **Sustained viral response (SVR)** [PCR negative 6 mo post-treatment]
- End of treatment viral response with relapse
- **Nonresponse**
- **Intra-treatment responses**
  - 4 wk PCR negative = rapid virus response (RVR)
  - 12 wk viral response = >2 log reduction viral titre ("12 wk stopping rule")
Benefits of SVR

- Fibrotic regression
- Reduces HCC by 90%
- Decreases liver-related complications, need for liver transplantation, death
- Improves quality of life
Evolution of treatment for chronic hepatitis C*

Similar results reported for haemophilia
SVR genotypes 2,3

[Hadziyannis et al Ann Intern Med 2004]

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<tr>
<th>Treatment</th>
<th>24 weeks</th>
<th>48 weeks</th>
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<tbody>
<tr>
<td>PEG-IFNα2a RBV 800</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>PEG-IFNα2a RBV 1000/1200</td>
<td>78%</td>
<td>77%</td>
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<tr>
<td>n=106</td>
<td>n=162</td>
<td>n=111</td>
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<tr>
<td>n=165</td>
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SVR genotype 1

**high viral titre**

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<th>48 weeks</th>
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</thead>
<tbody>
<tr>
<td>PEG-IFNα2a RBV 800</td>
<td>16%</td>
<td></td>
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<tr>
<td>PEG-IFNα2a RBV 1000/1200</td>
<td>26%</td>
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<tr>
<td>PEG-IFNα2a RBV 800</td>
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<td>35%</td>
</tr>
<tr>
<td>PEG-IFNα2a RBV 1000/1200</td>
<td></td>
<td>46%</td>
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n=50 n=47 n=190 n=186
SVR genotype 1

Cirrhosis

- SVR (%)
- n=78

All patients

- SVR (%)
- n=271

Treatment: PEG-IFNα2A + RBV 1000-1200 mg for 48 weeks
Treatment course for chronic hepatitis C

- GENOTYPEs 1 and 4: 48 wk full dose Peg-IFN and ribavirin (1000-1200 mg/day)
  - 12 wk “stopping rule”
  - Rapid viral response (RVR) – PCR neg at 4 wk, 24 wk treat

- GENOTYPES 2 and 3: RVR at 4 wk – consider 16 wk Peg-IFN/ R (1000 mg/day) [but relapse may be higher]

- If no RVR, continue for 24 weeks (at least) –

  *individualisation of therapy is now the state of the art!*
Who should be advised to have treatment?
Treatment decisions should be informed by ....

- **Natural history** - fibrotic stage, activity (ALT, biopsy), duration of infection
- Evidence of cirrhosis
- Age – 50 yrs a watershed!
- Chance of SVR (HCV genotype, viral load, obesity)
- Motivation and insights of affected person
- Symptoms vs co-morbidity, risks adverse effects

*NOT altered by concomitant haemophilia*
Adverse effects of Peg-IFN/ribavirin

- Pregnancy monitoring: double contraception
- Cough pharyngitis, GIT symptoms from ribavirin
- Pruritus, serious rash, worsening psoriasis
- Insomnia, *depression (liberal use of SSRIs)
- Thyroid (relatively common)
- Neuropathy, retinopathy, deafness

*22% one series [Posthouwer Haemophilia 2007;13:98-103]
Haematologic effects
Peg-IFN/ribavirin

- Hb drops ~30 g/L; from wk 1, nadir wk 4-6, then stable
- Concomitant rise in bilirubin, uric acid
- Effects on neutrophils, platelets more than for IFN
- Use of EPO and CSFs fashionable (~30% cases) in USA and Europe – evidence of efficacy equivocal
- Lower doses ribavirin; may lose therapeutic efficacy
- 80:80 dose: duration principle – some drug for longer is better!
Monitoring during antiviral treatment

- Before treatment, identify special risk of AE’s (depression, cardiac, haematological, autoimmune, thyroid)
- During therapy, monitor to prevent serious AE’s (FBC 4 wks, TSH 12 wks)
- Monitor ALT encourages compliance; don’t use alone
- PCR wks 4, 12, 24, 48; discontinue genotype 1, if fail to obtain drop of pretreatment viral titre ≥ 2 logs at 12 wks

With careful case selection, patient preparation and support/monitoring during treatment, dropout rates should be <10% for 6 mo and <15% for 12 mo treatment
Combination treatment: issues

- Case selection, contraindications
- Pre-treatment counselling
- Routine support and monitoring
- Special contexts: methadone, prisons
- Post-treatment monitoring

**Retreatment**
- Only when previous treatment suboptimal (IFN monotherapy)
- Good results, especially genotypes 2/3

**Other approaches to treatment**
- No treatment (or herbal medicines)

**Liver transplantation**
How long will PEG-IFN/ribavirin be standard of care?

- Protease inhibitors [telaprevir \{VX-950\}; valopicitabine \{NM283\}] - mutations 156V/T, 36/155 within 4 weeks
- Mutated variants sensitive to interferon *in vitro*
- Peg-interferon in combination therapy likely to remain
- Ribavirin substitutes generally disappointing
- However, combinations of PEG-IFN and protease inhibitors appear very promising
Immunosuppression and chronic HCV + HIV

- Hi proportion of HIV-infected also anti-HCV+ (29% France; 54% USA)
- Liver disease = AIDS as cause of death [HCV + HBV higher]
- Importance of CD4+ count [<200 /mL], high viral load
  - More rapid fibrotic progression: 25% cirrhosis in 15 yrs
  - Lower age of HCC
  - Lower SVR with IFN-based therapy (improved with PEG-IFN/ribavirin)
  - Increased rate of hepatic ADRs to HAART
Treatment of HCV co-infection in someone with HIV

- Treat HCV before HAART if CD4+ count >300 (particularly genotype 3)
- Avoid didanosine and AZT
- Apply 2 log stopping rules
- Improved responses with PEG-IFN/ribavirin
- Consider loading dose PEG-IFN and longer therapy
Self-care is best care

- Avoid excessive alcohol
- Avoid central obesity, diabetes – exercise!
- Stop smoking
- Vaccinate/avoid risk factors for other hepatitis viruses and HIV
- Understand course of hepatitis C, and what can be done to improve this if required
- Positive approach to health and life-style