The Natural History of HCV Infection

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Disclosures

• K.B. Kielland has given sponsored lectures for MSD and AbbVie
The natural history of hepatitis C

• Spontaneous clearance
• Progression of liver fibrosis
• All-cause and liver-related mortality
• Extrahepatic manifestations
• Disease progression in the era of direct-acting antivirals (DAA)

• Main focus will be on people who inject drugs (PWID)
Spontaneous clearance

- Spontaneous clearance is found between 15% and 40%, significant difference between studies.

- A meta-analysis of 31 studies with a total of 675 subjects with acute hepatitis C concluded with a weighted mean of 26% spontaneous clearance.

- Spontaneous clearance usually occurs the first 6 months, but retarded clearance may happen during some few years.

Micallef JM, Kaldor JM, Dore GJ. J Viral Hepat 2006; 13(1):34-41
# Spontaneous clearance

<table>
<thead>
<tr>
<th>Increased clearance</th>
<th>Reduced clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Male gender</td>
</tr>
<tr>
<td>Age &lt; 35 years</td>
<td>Age &gt;35 years</td>
</tr>
<tr>
<td>Symptomatic acute HCV infection</td>
<td>No acute symptoms</td>
</tr>
<tr>
<td>HBV co-infection</td>
<td>HIV co-infection</td>
</tr>
</tbody>
</table>

Complicated interaction between a long list of genetic factors

Micallef JM, Kaldor JM, Dore GJ. J Viral Hepat 2006; 13(1):34-41
Classification of the progression of liver fibrosis in hepatitis C

Biopsies: Metavir stages F0–F4

Normal liver
F0

Cirrhosis
F4

F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
(septal or bridging fibrosis)

Elastography

Amar Paul Dhillon, UCL Medical School Royal Free Campus, London

Shashidhar Venkatesh Murthy,
Mean duration of Metavir stages

A meta-analysis concluded with the following mean progression time through the Metavir stages

- F0–F1: 9 years
- F1–F2: 12 years
- F2–F3: 12 years
- F3–F4: 8 years
- F0–F4: 40 years

Conclusions:
- For probable more than half the patients the progression is very slow (“non-fibrosing”)
- For at least 1/3 it is much more rapid.

The natural course of liver disease in chronic hepatitis C

(age by exposure 20–25 years)

- **Anti-HCV+/HCV RNA−**: Spontaneous clearance 25–30%
- **HCV RNA+**: Chronic hepatitis C 70–75%

Acute hepatitis C

HCV exposure

Years since HCV exposure

ESLD, HCC, liver-tx, liver death
Factors which may increase or reduce fibrosis progression

<table>
<thead>
<tr>
<th>Host factors</th>
<th>External factors</th>
<th>Viral factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Alcohol</td>
<td>Genotype 3</td>
</tr>
<tr>
<td>High age at exposure</td>
<td>(Tobacco)</td>
<td>Genetic variability</td>
</tr>
<tr>
<td>Untreated co-infection HIV</td>
<td>(Cannabis)</td>
<td>HCV RNA quantity</td>
</tr>
<tr>
<td>Untreated co-infection HBV</td>
<td>Coffee (reduced fibrosis?)</td>
<td></td>
</tr>
<tr>
<td>Overweight/steatosis/NASH</td>
<td>Chocolate (reduced fibrosis?)</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metabolic syndrome/DM2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic and other factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Alanine aminotransferase (ALT)
- 2'-5'-oligoadenylate synthetase 1 (OAS 1)
- Factor V Leiden genotype (Arg560Gln)
- Ferritin
- Serum hepcidin
- IL-10 (-1082) AA genotype
- The ATA/ATA and ACC/ACC homozygous haplotypes
- IL-10 (-1082) GG genotype
- IL28B rs12979860 genotype CC
- IL28B SNP rs8099917 genotype TT
- MCP-1 (CCL-2)
- Homocysteine
- Methylene-tetrahydrofolate reductase (MTHFR) C677T polymorphism TT genotype
- Mixed cryoglobulinemia
- Non-organ-specific autoantibodies
Cirrhosis

• Cirrhosis:
  – Annual risk of liver cancer (HCC): 1–5%
  – Annual risk of hepatic failure (decompensation): 3–6% (variceal hemorrhage, ascites, encephalopathy)

• Decompensated cirrhosis:
  – Risk of death the following year 15–20%


Natural course of injecting drug use

Meta-analyses of mortality:

• People who inject drugs:
  ✓ Mortality rate: 2.3/100PY.
  ✓ Standard mortality rate: 15
  ✓ Main causes of deaths: Overdose and HIV

  Mathers. Bull World Health Organ 2013

• Dependent users of heroin/other opioids:
  ✓ Mortality rate: 2.1/100PY
  ✓ Standard mortality rate: 15
  ✓ Main cause of death: Overdose

  Degenhardt. Addiction 2011
Causes of death among PWID with chronic hepatitis C according to death age

- Substance dependence
- Suicide
- Violent
- HIV
- Liver disease
- Other disease

<table>
<thead>
<tr>
<th>Death age</th>
<th>&lt;30</th>
<th>30-39</th>
<th>40-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths</td>
<td>33</td>
<td>42</td>
<td>45</td>
<td>34</td>
</tr>
</tbody>
</table>

Kielland KB, unpublished information
Natural course of chronic hepatitis C
(age by exposure 20–25 years)

- Spontaneous clearance 25–30%
- Chronic hepatitis C 70–75%

Years since HCV exposure
HCV exposure

ESLD, HCC, liver-tx, liver death

F0–F1
F2
F3
F4
Natural course of chronic hepatitis C in PWID
(age by exposure 20–25 years)

- Spontaneous clearance: 25–30%
- Chronic hepatitis C: 70–75%
- Deaths by other causes than liver disease
- Liver deaths
- F0-F1
- F2
- F3
- F4
- ESLD, HCC, liver-tx
Estimated situation for anti-HCV positive PWID at age 50–60 years – about 30–35 years after HCV exposure

Among all HCV-exposed PWID

- Dead by other causes than liver disease: 45–50%
- Spontaneous clearance: 15%

Among surviving HCV-exposed PWID

- Spontaneous clearance: 25–30%
- F0–F1: 30–35%
- F2: 10%
- F3: 10%
- F4: 12%
- ESLD, HCC, liver-tx: 8%

May be fewer because of re-infections
May be strongly influenced by antiviral treatment
Extrahepatic manifestations

Certain associations with HCV:

– Cryoglobulinemia
  • >50% (mostly low levels without clinical consequences)
  • Prevalence increases with age, and in Europe higher in the south than in the north
  • Skin disease (<5%)
  • Kidney disease (glomerulonephritis)
  • Peripheral neuropathy

– Non-Hodgkin lymphoma, relative risk 2.0-2.5

Extrahepatic manifestations

Possibly or probably associated with HCV:

– Diabetes mellitus type 2
– Some autoimmune diseases
– Fatigue, depression secondary to the chronic inflammation
– Vascular disease?
– Brain affection directly associated with virus replication in the brain?
  • Impaired cognitive function? Depression? Fatigue?

Natural course of chronic hepatitis C in people who inject drugs in the late era of direct-acting anti-virals (DAAs)?

- Spontaneous clearance: 30%
- Deaths from other causes than liver disease
- Chronic hepatitis C
- Clearance (SVR) after treatment

Years since HCV exposure vs. %

- 0% to 100% over 30 years
- HCV exposure
Conclusions

• 30–40% of PWID with CHC will develop advanced liver fibrosis/cirrhosis within 25–40 years
• After age 40–50 years, liver disease becomes an increasingly important cause of death
• Among PWID under 40–50 years of age, other causes of death dominate
• Direct-acting antivirals may eliminate both the burden of liver disease and liver-related mortality