Natural history of HCV infection

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Disclosure

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Chronic HCV infection is leading cause of end-stage liver disease, HCC and liver related deaths in the Western world
Growing problem of HCV infection


HCV mortality increased
Reduced survival

In US people with chronic hepatitis B or C lived about 2 decades less on average than those who did not have these infections; chronic viral hepatitis was the 15th leading cause of death in the U.S. in 2010,

- During 2010 in USA there were a total of 18,473 deaths (0.7%) with hepatitis A, B, or C listed among the causes of death.
- 90% of these deaths listed hepatitis C.
- These deaths occurred mostly among people in the 45-64 age group (about three-quarters of such deaths).
- Among people who died of the same primary causes, decedents with hepatitis B or C listed as an additional cause died, on average, 22-23 years earlier than decedents who did not have these infections listed.

HCV characteristics

Family Flaviviridae
Enveloped
Positive-sense single-stranded RNA (9,6 kd)
3000-amino acid polyprotein
No RNA polymerase proofreading ability
Quasispecies
Half-life-2,7 hours
Daily production 10 trillion (10^{12}) virions

HCV life cycle
Worldwide prevalence of HCV- 180mln

Epidemiology HCV

- World - 180mln infected? In 2010 y. deaths from HCV related cirrhosis: 287400 and HCC: 195000

- In Europe seroprevalence of anti HCV
  - low (0.4%): Sweden, Netherlands, Germany
  - high (2-3%) Mediterranean countries

- Poland - 2013 y. (0.95 - 1.4%) - 700 000.
  - but only <40%
  - 200000-220000 are HCVRNA PCR positive
  - among them 40 000 women in procreation age
  - theoretically only 30% patients with progressive disease from this group should be treated (75 000)
  - decreasing incidence - 5.88/2013

HCV-list of the different genotypes

- 7 genotype (1-7) (differences 30-50%)
- > 50 subgenotype (np.1a,1b, itd.) (differences 15-30%)
- isolates (differences 5-15%)
- „quasispecies“ (1-5% nucleotide differences)

Western Europe USA – 1a, 1b, 2a, 3a
Eastern Europe – 1b
North Afrika – 4
Japan, China, Tajwan – 2
Hongkong, Makao – 6

POLAND: G1b-75%, G1a-5%, G3a-17%, G4c+d 1%
(differences between regions)

Each genotype is actually a mixture of closely-related viruses called quasi-species. These quasi-species have the ability to mutate very quickly and become immune to current treatments, which explains why chronic hepatitis C infection was so difficult to treat.

HCV genotype distribution


Genotypes
- G1
- G1a
- G1b
- G2
- G3
- G4
- G5
- G6
- Mixed or other

Prevalence of HCV infection
- <1.0%
- 1.0–1.9%
- 2.0–2.9%
- >2.9%
- Not studied
HCV infection: risk factors

- Current or former injection drug users, including those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987, when more advanced methods for manufacturing those products were developed
- Recipients of blood transfusions or solid organ transplants before July 1992, when better testing of blood donors became available
- Chronic hemodialysis patients
- Persons with known exposures to HCV, such as:
  - health care workers after needlesticks involving HCV-positive blood
  - recipients of blood or organs from a donor who tested HCV-positive
  - body piercing/scarring/tattooing etc

(HIV: 0.3%, HCV: 5-15%, HBV: > 60% (HBeAg +), < 30% (HBeAg -))

- Persons with HIV infection
- Children born to HCV-positive mothers
- Intranasal cocaine users
- Sex with multiple partners, particularly anal

Sexually Transmitted Diseases Treatment Guidelines MMWR 2010;59(RR-12)
HCV infection: risk factors

The mean volume of an accidental drop was 29 mcl (range 20-33 mcl).

At storage temperatures of 4° and 22° C, viable HCV was recovered from low titer spots after up to 6 weeks.

At 37° C, infectious HCV was recovered only up to 7 days.

HCV infectivity declined rapidly during the first 2 weeks of storage, followed by a slower decline.

Bleach (1:10 dilution) was the most effective antiseptic tested, with 1 minute of exposure eliminating infectious HCV in 100% of spots, followed by the commercial medical disinfectant CaviCide (1:10 dilution; 94% of spots) and 70% ethanol (87% of spots).

HCV clinical manifestations-liver disease progression

HCV clinical manifestations –extra-hepatic

**Haematological**
- Mixed cryoglobulinemia
- Aplastic anaemia
- Thrombocytopenia
- Non-Hodgkin’s β-cell lymphoma

**Dermatological**
- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotising vasculitis

**Renal**
- Glomerulonephritis
- Nephrotic syndrome

**Endocrine**
- Anti-thyroid antibodies
- Diabetes mellitus

**Salivary**
- Sialadenitis

**Ocular**
- Corneal ulcer
- Uveitis

**Vascular**
- Necrotising vasculitis
- Polyarteritis nodosa

**Neuromuscular**
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

**Autoimmune Phenomena**
- CREST syndrome

HCV infection-basic facts

- The transition from acute to chronic hepatitis C is usually **sub-clinical**
- The acute illness is clinically mild and is typically **unrecognised and undiagnosed**
- Risk of chronicity variable: **18-34%**
- The natural history of chronic hepatitis C remains **incompletely defined**; generally this is the **slowly progressive disease**
- Risk of cirrhosis (without cofactors!!!) **10-20% within 30 years**
- Cirrhosis related mortality **1-5%/year**
- Incidence of HCC in patients with HCV cirrhosis **1-4%/year**

Moreover, the effects of chronic HCV infection extend beyond liver-related mortality and decreased the quality of life.
Clinical picture is influenced by
1. host-
2. viral-
3. environmental factors
Factors influencing natural history and accelerating progression of the HCV infection

- Route of transmission
- Infectious viral load dose
- Acute phase/asymptomatic infection
- Older age at time of infection >40 years
- Polymorphism of HLA-II (DQB1*0301, DRB1*01)
- Race
- Gender: m>f
- BMI
- Insuline resistance
- Previous NAFLD
- Previous hemosiderosis/hemochromatosis
- HIV(!), HBV(!), Herpesvirusy coinfection?
- Previous or concurrent alcohol consumption

- genotypes
- pseudotypyys
- mutants
- level of replication
- immune response
- immunosupression

Blackard, Hepatology, 2008,47,1,321-331
Marcelin P. Liv.Int., 2009,29 (s1) 1-8
Bugianesi E.,Salamone F,Negro F,. Hepatol.2012, suppl1, 56,S56-s65
Acute hepatitis C

In those persons who do develop symptoms, the average time period from exposure to symptom onset is 4–12 weeks (range: 2–24 weeks).

Persons with newly acquired HCV infection usually are asymptomatic or have mild symptoms that are unlikely to prompt a visit to a health care professional.

Approximately 20%–30% of those newly infected with HCV experience some symptoms; they can include:

- Fever
- Fatigue
- Dark urine
- Clay-colored stool
- Abdominal pain
- Loss of appetite
- Nausea
- Vomiting
- Joint pain
- Jaundice

Acute resolution of HCV is not associated with any long-term sequelae.
Acute hepatitis C

Estimates of World annual incidence indicate that 3-4 mln people are newly infected each year.

The CDC estimates approximately 29,718 cases occurred in 2013, after adjusting for asymptomatic infection and underreported.

The number of acute cases of hepatitis C reported in the US increased from 1,778 in 2012 to 2,138 in 2013.

Where are others acute cases?

Reinfection after clearance of acute hepatitis C

-The risk of reinfection and superinfection remains a possibility after clearance of acute hepatitis C

-Particular risk groups:

- MSM
- PWID / IDU

Chronic hepatitis C

- Persistence > 6 months of positive HCVRNA
- Most persons with chronic HCV infection are asymptomatic
- However, many have chronic liver disease, which can range from mild to severe
- Chronic liver disease in HCV-infected persons is usually insidious, progressing slowly without any signs or symptoms for several decades
- Spontaneous resolution of chronic hepatitis C is relatively rare, but occur 0.5% year

Mauss S, Berg T., Rockstroh J., Sarrazin Ch., Wedemeyer H. Hepatology 2015, Flying Publisher
Probability of fibrosis progression to F4 according to age at infection

Rates of fibrosis progression is 0.1-0.2 per year;
In patients infected in age >70 \textit{300x fold higher} than in age <30

Adapted from Poynard et al. J Hepatol. 2001.
Liver cirrhosis and HCV

Wide range of:
- symptoms,
- signs
- and consequences
Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages

- **Stage 1**: No varices, No ascites
  - 1%

- **Stage 2**: Varices, No ascites
  - 4.4%
  - 3.4%

- **Stage 3**: Varices, Ascites +/-
  - 6.6%
  - 20%

- **Stage 4**: Variceal bleeding, +/- Ascites
  - 7.6%
  - 57%

**DEATH**

D’Amico G. Complication of portal hypertension. EASL Postgraduate Course, Milan, 2008, 10-15
HCC and HCV

- Chronic HCV infection is the leading cause of hepatocellular carcinoma (HCC) in the Western world.
- But RNA viral genome is not observed in HCC cells.
- >90% patients with HCC infected with HCV have had inductors/co-factors of carcinogenesis:
  - cirrhosis particularly active
  - alcohol consumption in past history
  - aflatoxinsy (B1)
  - "nonalcoholic steatohepatitis"
  - congenital metabolic disturbances

How can we change natural history of chronic HCV infection? Milestones of success

Early diagnosis

Proper treatment
Acute hepatitis C- therapy

- In the acute phase of the infection HCV is highly vulnerable to therapy with PEGIFNalfa. >90% of patients can be cured with IFN-alfa 6 months monotherapy -start time- after 12 weeks of disease

- Acute genotype 1 HCV infection in HIV infected men PEGIFNalfa/RBV/TVR v PR 12 weeks therapy 84% v.63%

- Resolution of HCV is not associated with any long-term sequela
**Chronic hepatitis, cirrhosis, HCC**
**HCV-therapy 2015**

**Nuc: nucleotide polymerase inhibitor; NS5A: hepatitis C virus non-structural protein 5a protease inhibitor**
I-free therapies

Following on from the recently available IFN-free combinations many more are expected in the near future

- SOF + LDV ± RBV
- SOF + other agents
- Abbvie combination ± RBV
- DCV + ASV
- MK-5172 + MK-8732 ± RBV

- SMV + SOF – OPTIMIST 1 and 2
- SMV + DCV + RBV – SATURN
- SMV + samatasvir – HELIX-1

- There is no clear direction with regard to the next tranche of standard of care
- The guidelines are rapidly changing
Overall SVR-HCVG1

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<td>90</td>
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<tr>
<td>2014*</td>
<td>94-99</td>
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</tbody>
</table>

*Please note that specific years are not arranged according to the scale.

Legend:
- IFN: 6 mo.
- IFN+RBV: 6 mo.
- IFN+RBV: 12 mo.
- PEG: 12 mo.
- PEG+RBV: 12 mo.
- PI+PEG: 6-12 mo.
- SMV+PEG: 6-12 mo.
- SOF+PEG: 3 mo.
- LDV/SOF: 3D Abbvie 2-3 mo.

References:
Achievement of SVR in any stage of HCV related diseases change natural history of HCV infection-reduce (but not fully eliminate) progression of liver cirrhosis, risk of HCC and lowers liver related mortality

Morgan TR.et al Hepatology 2010,52,833-844