THE NATURAL AND UNNATURAL HISTORY OF HEPATITIS C VIRUS INFECTION

Harvey J. Alter, MD

NIH
FINANCIAL DISCLOSURE

At NIH, we can name our own salaries......

I have named mine.....Fred
FINANCIAL DISCLOSURE

I do not currently have any financial interests to disclose

However, if you each put $5 into the plate that will be passed around during my lecture, I will add another disclosure slide later.
Worldwide Burden of Chronic Viral Hepatitis

World population: 7 billion

HBV: 350 million chronically infected

HCV: 170 million chronically infected

75%-85% of HCV infections become persistent vs. 5% HBV

5 million in US
Rising Mortality Associated with HCV in the United States from 2003 - 2013

Other nationally notifiable infectious conditions

Hepatitis C

Number of deaths


CDC
RISK FACTORS FOR HCV INFECTION IN VOLUNTEER BLOOD DONORS: SIGNIFICANT RISKS IN LOGISTIC REGRESSION MODEL
HCV STATUS OF HETEROSEXUAL PARTNERS OF HCV-INFECTED BLOOD DONORS

HCV Negative 86%  
N=116

HCV Positive 14%

All 16 HCV+ partners had been transfused or used IV drugs

Sommer Lectures
CAUSES OF ACUTE CLINICAL HEPATITIS IN THE U.S.  
CDC ANALYSIS OF RELATIVE FREQUENCIES

Source: Sentinel Counties
ETIOLOGY OF NEWLY-DIAGNOSED CHRONIC LIVER DISEASE; REFERRED PATIENTS; 1999-2001 N=725

- HCV 42%
- HCV + alcohol 22%
- Alcohol 8%
- NAFLD 10%
- Other 8%
- Insufficient data 6%
- HBV 4%

CDC

Sommer Lectures
HCV VIREMIA DURING EARLY INFECTION

- **HCV RNA**
  - ramp-up phase: DT = 13-17 hrs
  - plateau phase viremia: $10^5$-$10^8$ gEq/mL

- **ALT**

- **anti-HCV EIAs**
  - 1st gen: 150 d
  - 2nd gen: 80 d
  - 3rd gen: 70 d

- **viral set-point**: $10^2$-$10^7$ gEq/mL
Quasispecies Nature of HCV, Strain H77
Analysis of HVR1 Region from 105 Clones
EVOLUTION OF HCV QUASISPECIES IN A PATIENT WITH RAPIDLY PROGRESSIVE CHRONIC HEPATITIS C
Hepatitis C in Chimpanzee 1494 Following Transfection with cDNA Clone, H77C (Genotype 1a)
Hepatitis C in Chimpanzee 1530 Following Transfection with cDNA Clone, H77C (Genotype 1a)
EX-VIVO T-CELL RESPONSE TO PEPTIDE POOLS SPANNING THE ENTIRE NS-3 REGION PULSED INTO AUTOLOGOUS APCs

<table>
<thead>
<tr>
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<th>CD8</th>
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<tr>
<td><strong>recovered</strong> (N=10)</td>
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<tr>
<td>100%</td>
<td>0%</td>
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<tr>
<td><strong>chronic</strong> (N=7)</td>
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<tr>
<td>0%</td>
<td>0%</td>
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<tr>
<td><strong>normal</strong> (N=8)</td>
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<tr>
<td>0%</td>
<td>0%</td>
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Wertheimer, AM; Hepatology 2003
THE NATURAL HISTORY OF VIRUS HOST INTERACTION

Evolving Quasispecies

Inhibitory Viral Proteins
- NS3
- NS4
- NS5
- C

Adaptive Immunity
- B cells
- T cells
- Perforins
- FAS-L
- IgG

Innate Immunity
- dsDNA
- dsRNA
- TRIF
- RIG-1
- MAVS

Induction
- NF-kB
- IRF3

Recovery
- 15-25%

Persistence
- 75-85%

Early Viremia
- $10^5 - 10^8$ gEq/mL
- $10^{13}$ particles per day
- DT = 13-17 hrs
Is life worth living?
That depends on the liver
Acute hepatitis

Chronic hepatitis (80%)

Mild and stable

Cirrhosis

Severe and progressive

Decompensation

HCC

Death or OLT

10 – 40 years

60-70% 30-40%
Outcome of Chronic HCV Infection in Transfusion-Associated Hepatitis C

Stable or Slowly Progressive
- Cirrhosis in 15-40 years
- 60-70%

Severe and Progressive
- Cirrhosis in 5-10 years
- 20-30%

Rapidly Progressive
- Cirrhosis in < 5 years
- < 5%
NATURAL HISTORY OF FIBROSIS PROGRESSION IN CHRONIC HEPATITIS C

Fibrosis Stage (Metovir)

Stage 0  Stage 1  Stage 2  Stage 3  Stage 4

Fibrosis Unit = \frac{\text{Fibrosis Stage}}{\text{Duration of Infection}} = 0.133 \text{ FU/YR}

One Unit = One Stage

YEARS OF INFECTION

0  7.5  15  22.5  30  37.5

CIRRHOSIS

Poynard, T
LANCET 1997; 349: 825
FIBROSIS STAGE IN 490 VIREMIC WOMEN 25 YEARS AFTER EXPOSURE TO HCV1b CONTAMINATED Rh IMMUNE GLOBULIN

- none: 34%
- 1 - 2 mild portal: 55%
- 3 - 4 bridging: 9%
- 5 - 6 cirrhosis: 2%

Linear regression shows a significant trend over time.
OUTCOME OF HCV INFECTION AMONG LIVING SUBJECTS DURING TWO DECADES OF FOLLOW-UP

CIRCA 1974

ANTI-HCV+ N=103

77% 17% 7%

CIRCA 1997

ANTI-HCV+ HCV RNA+ N=79

ANTI-HCV+ HCV RNA- N=17

ANTI-HCV- HCV RNA- N=7

23-year outcome summary

viral persistence

ALT elevation

cirrhosis (estimated)

77% 50% 85%

23% 50% 15%

yes no

Seeff: NEJM 1992; 327:1906
HISTOLOGIC LESIONS IN 94 HCV RNA POSITIVE BLOOD DONORS

INFLAMMATION (HAI)
- Mild CH (1-7): 47%
- Mod CH (8-14): 53%
- Severe CH (15-18): 0%

FIBROSIS (HAI)
- None (0): 44%
- Mild (1): 41%
- Severe (3): 13%
- Cirrhosis (4): 2%

Mean duration of infection: 19.4 years
PROJECTED OUTCOMES IN CHRONIC HEPATITIS C VIRUS INFECTION
Slow vs. Rapid HCV Progressors: Viral Load

Slow progressors have increased levels of IFN-γ and MIP-1β in both acute and chronic infection.

Slow vs. Rapid HCV Progressors: Pro-Fibrogenic Cytokines

MCP-1 (Monocyte Chemotactic Protein; CCL2): Profibrogenic chemokine that both attracts and is produced by hepatic stellate cells

Excessive alcohol intake = > 40 g/day for women and > 60 g/day for men.

Alcohol Consumption Increases Risk of Cirrhosis in HCV-Infected Patients

*Excessive alcohol intake = > 40 g/day for women and > 60 g/day for men.

PROSPECTIVE STUDY COMPARING THE EFFECTS OF STEATOSIS AND NASH ON THE HISTOLOGIC OUTCOMES OF CHRONIC HEPATITIS C

Duration of Infection

- CHC Alone (N=160): 22 Years
- CHC + Steatosis (N=160): 24 Years
- CHC + NASH (N=160): 21 Years

Bedossa, P. Hepatology 2007; 46: 380
After A Brief Stay in America, David Returns to Florence
HCC Epidemiology

- HCC Infection
  - HCV Infection
    - Chronic Hepatitis
      - Cirrhosis
        - HCC
          - 1% (1-3%/yr)

- 100%
- 25-40 years
- 80%
- 20-30%
- 100%

Goodgame B, et al., Am J Gastroenterol 2003
ETIOLOGY OF HCC IN JAPAN BASED ON PCR OF PARAFFIN-EMBEDDED LIVER TISSUE

- HBV: 21%
- HCV: 63%
- HCV + HBV: 6%
- No viral marker: 10%

**78% genotype 1b**

Edamoto: Cancer 1996: 77:1787
PREVALENCE OF ANTI-HCV IN US AND JAPAN ACCORDING TO AGE

Adapted from Yoshizawa H: Oncology 2002
MOLECULAR CLOCK OF HCV GENOTYPE 1 EVOLUTION IN JAPAN AND THE USA

- Japan (genotype 1b)
- USA (genotype 1a)

HCC 8-10 X higher in Japan

30–40 yrs.

Tanaka Y, et al, 2002
RISING INCIDENCE OF HCC IN THE UNITED STATES

Increase in HCV markers in HCC Patients 1993-1998

Age-Adjusted Incidence Rate per 100,000 patients

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<th>Time Period</th>
<th>1978-80</th>
<th>1996-98</th>
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<tr>
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Viral Markers

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<tr>
<td>HCV</td>
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<tr>
<td>HBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>p&lt;0.01</td>
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El-Serag, Gastroenterology, 2004
Assuming no changes in standard of care, the total number of patients with advanced liver disease in 20 yrs projected to be > 4-fold higher than in 2009.
HCV Life Cycle and DAA Targets

Receptor binding and endocytosis
Fusion and uncoating
Transport and release
(+) RNA
Translation and polyprotein processing
RNA replication
Virion assembly
Membranous web
ER lumen
LD
NS3/4 protease inhibitors
NS5B polymerase inhibitors
Nucleoside/nucleotide
Nonnucleoside

NS5A* inhibitors
*Role in HCV life cycle not well defined

Milestones in Therapy of Gt 1 HCV
COMBINATION THERAPY WITH SOFOSBUVIR (NS5B POLYMERASE) AND VELPATISVIR (NS5A) INHIBITORS FOR HCV GENOTYPES 1,2,4,5,6 INFECTION

624 Patients among whom 19% had cirrhosis and 32% were prior treatment failures

99% (CI: 98->99%) Sustained Virologic Response (SVR)

Feld, J, NEJM 2015;373:2599

In a related trial for genotype 3, 95% SVR (CI: 92-98%)

Foster GR, NEJM 2015;373:2608
With cure rates approaching 100%, from this time forward, once HCV infection is identified, no one should develop cirrhosis or die from hepatitis C.
THE GLASS IS HALF-EMPTY
HURDLES TO HEPATITS C ERADICATION

Identification of cases:
Estimated that 50% of HCV infections remain unidentified; >% in developing world; need for enhanced population screening beginning with those of known high risk

Access to Treatment:
With IFN-Based therapies, only 10% of eligible patients were treated; better with DAAs, but still <50% of known carriers get treated

High cost of Drugs:
The economic burden is preventing the cure of millions
HCV Economics 101

- 3-5 million HCV-infected in US; 150 million worldwide
- 12 week DAA regimen costs $50,000-$84,000
- While DAAs cost-effective in the long run, upfront costs are prohibitively high, being estimated at 150-200 billion to cure the US population
- Current Strategy: Treat the most severe cases first, but this adds cost by requiring biopsy or FS, leaves most patients untreated and allows fibrosis to silently progress in the untreated
- Big Pharma, insurance companies and the government need to find a sweet spot that assures reasonable profits while making these miracle drugs accessible to all in need
A PHILOSOPHIC PERSPECTIVE OF LIFE VERSUS AGE

Diagram showing the relationship between 'GIVE' and 'AGE' with a peak at 'ME'.
Sommer Lectures
Sommer Lectures
Sommer
Lectures
TEACHING LESSON: NEVER TELL ETHNIC JOKES

A French person says, “I’m tired and I’m thirsty…… I must have wine.”

A German person says, “I’m tired and I’m thirsty.......... I must have beer”

A Jewish person says, “I’m tired and I’m thirsty................ I must have diabetes
MORBIDITY AND MORTALITY IN 384 PATIENTS WITH COMPENSATED CIRRHOSIS TYPE C

Adjusted probability of survival equal in IFN treated and untreated

Fattovich, G
GASTRO 1997; 112: 463
CAN WE ERADICATE HCV IN THE DEVELOPED WORLD IN THE ABSENCE OF A VACCINE?

Difficult but possible because:

- 1) Neonatal transmission negligible; 2) sexual spread inefficient; 3) transfusion risk eliminated; 4) HCW spread minimal
- Risk is mostly restricted to a single population — IVDU; controlling shared needle use and curing infected IDUs would have major impact since every cured carrier reduces secondary spread
- Resources needed for a “Test and Treat” policy are considerable, but achievable
- Treatments with >90% cure rates can trend toward HCV eradication by eliminating the virus one host at a time.
- If an effective HCV vaccine were developed would it be recommended for universal use in industrialized countries?
Development of Hepatocellular Carcinoma Following Transfusion

- blood transfusion
- chronic active hepatitis
- chronic persistent hepatitis
- cirrhosis of liver
- acute icteric hepatitis
- positive for anti-HCV
- hepatoma

From: Kiyosawa, et al
Data suggest that malignant hepatocytes express or lack factors that regulate HCV entry or replication.
REMARKABLE ACHIEVEMENTS OVER FIVE DECADES OF HEPATITIS VIRUS RESEARCH

- Identification of HBV, HAV, HDV, HEV, NANB/HCV
- Established strong link between HBV, HDV, HCV and hepatocellular carcinoma
- Development of vaccines for HBV, HAV and HEV
- The virtual eradication of post-transfusion hepatitis
- Successful transplantation for HCC & end-stage LD
- Highly effective long-term suppression of HBV replication with oral nucleos(t)ide inhibitors
- Greater than 95% cure rates in chronic hepatitis C using oral direct acting anti-virals

Is it possible, or even likely, that hepatitis B & C can be eradicated over the next 3-5 decades?
TRANSFUSION ASSOCIATED NON-A, NON-B HEPATITIS MORTALITY 18 AND 23 YEARS AFTER TRANSFUSION

All Cause Mortality

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<tr>
<th>Year</th>
<th>Cases Percent</th>
<th>Controls Percent</th>
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<tbody>
<tr>
<td>18 Years</td>
<td>41.9%</td>
<td>42.7%</td>
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<tr>
<td>23 Years</td>
<td>58.4%</td>
<td>58.1%</td>
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Liver Related Mortality

<table>
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<tr>
<th>Year</th>
<th>Cases Percent</th>
<th>Controls Percent</th>
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</thead>
<tbody>
<tr>
<td>18 Years</td>
<td>2.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>23 Years</td>
<td>3.1%</td>
<td>1.3%</td>
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CCL2/MCP1 Is a Major Chemotactic Factor for Hepatic Stellate Cells (HSC)

Establishment of an autocrine loop by which HSC both produce and are attracted by CCL2

Modified from: Friedmann, J. Biol. Chem. 2000
Serum IFN-γ and MIP-1β Levels Remained Significantly Higher in Slow Progressors During the Course of HCV Disease
CAN WE ERADICATE HCV IN THE DEVELOPING WORLD IN THE ABSENCE OF A VACCINE?

- The vast majority of the 170+ million global carriers reside in developing nations.
- Modes of parenteral spread are different with health-care related exposures accounting for 2 million infections/year and 40% of the global burden.
- Requires major changes in health-care practice (disposable needles, fully sterilized instruments, universal precautions, fully tested blood supply, cessation of ritual and medicinal scarifications).
- These daunting and costly preventive strategies would be in addition to the massive costs of population screening and treatment of positives.
- Will WHO, Gates Foundation, and Western societies be motivated to take on HCV as they did HIV?
- For the 3rd world, vaccination is the answer, but is it achievable?
Kinetics of Virus Replication and HCV-Specific Adaptive Immune Responses in Primary HCV Infection

- HCV triggers an early and strong type-1 IFN response, but the virus is resistant to innate immune responses.
- Innate immune responses are similar in viral clearance vs. persistence (Bigger et al., J. Virol. 2004)

THE TOLERIZING EFFECT OF HCV PROTEASE AS A MECHANISM OF HCV PERSISTENCE