HEPATITIS C
Past, Present and Future

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I have the following relationships to disclose:

- Merck: Advisory, Speaking, Research Support, Honoraria
- Gilead: Advisory, Speaking, Research Support, Honoraria
- Vertex: Advisory, Speaking, Research Support, Honoraria
- Tibotec: Research Support
- Bayer: Advisory, Speaking, Honoraria
- Abbott Labs: Research Support
- Inhibitex: Research Support
- Genentech: Advisory, Research Support
- Mochida: Research Support
- BMS: Advisory, Speaking, Research Support, Honoraria

I will be discussing off label experimental agents in the treatment of Hepatitis C without mentioning them by name.
VIRAL HEPATITIS
AN HISTORICAL PERSPECTIVE
VIRAL HEPATITIS
AN HISTORICAL PERSPECTIVE

• An “epidemic of yellow jaundice” was first described by Hippocrates over 2,400 years ago.
• The word “hepatitis” comes from the Greek word for liver “hepar” and the Greek suffix “itis” meaning “oy, I don’t feel so good” ¹
• Nothing much happened for the next 2,350 years except for occasional described outbreaks (e.g. in 1885 an outbreak from contaminated smallpox vaccine, possibly the 1st described “serum hepatitis” outbreak²)
• World War II resulted in outbreaks of “infectious hepatitis” and “serum hepatitis” in military personnel which started the modern era of hepatitis research

2. Lurman A, Beri Klin Wochenschr 1885;2: 20-23
VIRAL HEPATITIS
AN HISTORICAL PERSPECTIVE

• 1950’s and 1960’s 2 types of hepatitis identified\(^1\)-infectious or short incubation (hepatitis A)\(^2\) and long incubation or serum (hepatitis B)\(^3\)

• It became apparent that most cases of parenterally transmitted hepatitis were not due to Hepatitis A or B (non-A, non–B)\(^4\)

• Non-A, non-B hepatitis was shown to frequently progress to cirrhosis\(^5\), occurred in 10% of blood transfusion recipients in the U.S.\(^6\) as well as frequently seen in the community in the absence of transfusion\(^7\)

IDENTIFICATION OF HEPATITIS C VIRUS

• It took almost a decade before Michael Houghton and colleagues working in a private company laboratory (Chiron) in association with collaborators at the NIH were able to isolate a cDNA clone derived from the non A, non B viral hepatitis genome.¹
• This clone (5-1-1) was derived from RNA found only in NANBH infected chimpanzee plasma
• Clone 5-1-1 encodes a protein that binds antibodies found only in the plasma of patients with NANBH
• This led to the coining of the term Hepatitis C (HCV)

VIRAL HEPATITIS
AN HISTORICAL PERSPECTIVE

• The availability of recombinant Hepatitis C virus antigen led to the development of an enzyme immunoassay for antibody to hepatitis C.
• This test demonstrated that HCV was the commonest cause of parenterally transmitted NANB hepatitis world wide\(^1\) and could identify most infectious blood donors.\(^2\)

HEPATITIS C
VIROLOGY
HEPATITIS C
VIROLOGY

• Hepatitis C is an RNA virus.¹
• HCV is in its own genus (hepacivirus) in the flaviviridae family.¹
• The HCV genome is a 9.6 kb positive-strand RNA.¹,²
• It comprises a single long open reading frame (flanked by non coding regions) which encodes for a single polyprotein of 3,000 amino acids²
• This polyprotein is processed by cellular and viral proteases to produce structural and non structural viral proteins³
• The virus life is approximately 2.7 hours and 10^{12} virions produced per day⁴

3. Davis G et al, Semin Liver Dis 1999 (suppl 1): 103-112
HCV Life Cycle

Binding → Membrane fusion → Uncoating → Translation and polyprotein processing → RNA replication → -strands

Endocytosis

Virion assembly and maturation → Vesicle fusion and virion release

HCV STRUCTURE

GENETIC DIVERSITY OF HCV

• HCV replication is error prone without polymerase proof reading resulting in a heterogeneous viral population (quasispecies)
• There are 6 major genotypes of HCV and numerous subtypes ¹
• There are geographic differences in the prevalence of the different genotypes.
• The most prevalent genotype is 1.²,³
• The different genotypes exhibit different response rates to therapy.

HCV GENOTYPES

HEPATITIS C
DISEASE BURDEN AND EPIDEMIOLOGY
WORLDWIDE PREVALENCE OF HCV INFECTION

180 MILLION WITH HCV INFECTION

Prevalence of Infection

- >10%
- 2.5%-10%
- 1%-5%
- N/A

HCV INFECTION IN THE UNITED STATES

• NHANES: ~3.2 million persons chronically infected\(^1\)
  – Underestimate since survey did not account for incarcerated or homeless persons (The actual number is probably over 4 million)

ANNUAL ADJUSTED HCV MORTALITY RATES IN THE UNITED STATES

SUBSTANTIAL INCREASE IN US HCV MORTALITY

CDC Data Reveal 123% Increase in HCV Mortality

People with HCV infection have a 3-fold increased risk of overall mortality compared with uninfected individuals.

Increasing mortality rates among ages 45 to 64 years in part reflect the growing proportion of persons in the high HCV-prevalence birth cohort.

*Those born between 1945 and 1964.
CONTINUED INCREASE IN HCV MORTALITY AND MORBIDITY EXPECTED

Results of a Markov Model Based on HCV Natural History Studies*

- HCC: 81%
- Cirrhosis: 82%
- Decompensation: 106%
- Liver-Related Deaths: 181%

*Assumes no HCV treatment.
HCC=hepatocellular carcinoma.
HCV LEADING CAUSE OF LIVER TRANSPLANTS IN THE US

- Chronic HCV infection most common indication for liver transplantation in the US\(^1\)
- Up to 45% on liver transplant wait list have HCV\(^1,2\)
- Long-term survival in liver transplant recipients:\(^1\)
  - 5-year survival HCV negative=76%
  - 5-year survival HCV positive=68%

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HCV LEADING RISK FACTOR ASSOCIATED WITH HEPATOCELLULAR CARCINOMA (HCC) IN THE US

These data are from a large US, multicenter, cross-sectional study examining risk factors for HCC (N=691)\textsuperscript{1,2}

HBV=hepatitis B virus.
AGE-ADJUSTED INCIDENCE RATES FOR HCC (1976-2002)

NHANES (1999-2002):
ESTIMATED PREVALENCE OF HCV

Prevalence to Antibody to HCV

- **General Population**: 1.6% (1.3-1.9)
- **IDU**: 57.5% (44.1-69.9)
- **Blood Transfusion (<1992)**: 5.8% (3.7-9.0)
- **HIV**: 13.8% (5.3-31.3)
- **Dialysis**: 7.8%
- **Number of Sex Partners**
  - 1: 0.5% (0.2-1.4)
  - 2: 1.1% (0.5-2.1)
  - 3: 2.6% (1.5-4.6)
  - 4: 7.5% (5.3-10.6)
  - 5: 12.0% (8.5-16.7)

Prevalence of HCV in Select Populations

- **Incarcerated**: ~330,000 to 860,000 (16–41%)\(^1\)
- **IDU**: ~300,000 (80% to 90%)\(^2,3\)
- **Alcoholics**: ~240,000 (11% to 36%)\(^5\)
- **Homeless**: ~175,000 (22%)\(^7\)
- **Veterans**: ~280,000 (8%)\(^9\)
- **Children (6 to 18 years old)**: ~100,000 (0.1%)\(^9\)
- **HIV-infected**: ~300,000 (30%)\(^4\)
- **Living below poverty level**: ~940,000 (2.4%)\(^6\)

Female (37%)
Male (63%)

Adapted From the following:

\(^1\)CDC. MMWR. 2003;52(RR-1):1-33; \(^2\)Edlin B. Hepatology. 2002;36(5 suppl 1):S210-219; \(^3\)NHSDA Report 2003;
Prevalence of HCV in Racial/Ethnic Populations

*P < 0.005 for comparison with reference group (Non-Hispanic White)

In 2005, it was estimated that over 41 million Latinos lived in the United States. The Latino population is a diverse population. US census data show that the Latino population consists of nearly 64% Mexican Americans.

Adapted from the following:
*PERSONS KNOWN TO BE AT INCREASED RISK FOR HCV INFECTION

- Injection drug use (past or current)
- Recipients of blood transfusions/blood products prior to 1992
- Patients receiving chronic hemodialysis
- Sexual partners of an HCV infected person
- HIV-infected persons
- Birth to an infected mother
- Persons with an elevated ALT
- Heath care workers suffering a needle stick injury

*Candidates for screening

BACKGROUND FOR NEW CDC SCREENING GUIDELINES

• Over 4 million Americans have HCV¹
• 75% have chronic disease²
• Most infected 20-40 years ago²
• Significant mortality rates especially those born between 1945 and 1965³,⁴
• These mortality rates are rising ⁵, ⁶
• We now have effective therapy which is cost effective⁷
• Newer, less toxic therapies are 3-5 years away⁸
• Only 25-50% of patients with chronic HCV are aware of their infection ⁹, ¹⁰, ¹¹

HCV, HBV, and HIV: Prevalence vs Undiagnosed Cases

* Extrapolated from small population study.

BIRTH COHORT SCREENING (1945-1965)

NEW CDC RECOMMENDATIONS

• The CDC is now recommending a one time screening test for HCV for all persons born between 1945 and 1965.¹ These recommendations are in addition to the previous risk based screening recommendations.

• It is estimated that this strategy will identify an additional 808,580 cases of HCV compared to the risk based screening strategy².

• The screening cost will be $2,874 per case identified².

• Birth cohort screening followed by dual therapy reduced deaths by 82,300 at a cost of $15,700 per QALY gained².

• Birth cohort screening followed by triple therapy reduced deaths by 121,000 at a cost of $35,700 per QALY gained².

• These figures are considered cost effective and comparable to other recommended procedures (e.g colorectal cancer screening, hypertension screening, cervical cancer screening etc.)³.

HEPATITIS C DIAGNOSIS
ACUTE HCV INFECTION: HCV MARKERS

CHRONIC HCV INFECTION: HCV MARKERS

Chevaliez S, et al, Liver Int. 2009;29(suppl 1):9-14
## CHRONIC HCV INFECTION: RECOMMENDED LABORATORY TESTS

<table>
<thead>
<tr>
<th>Test Application</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C antibody by enzyme immunoassay (EIA)</strong></td>
<td><em>Screening for past or present HCV infection (sensitive and inexpensive)</em></td>
</tr>
<tr>
<td><strong>PCR for HCV RNA</strong></td>
<td><em>Confirmation of positive EIA Medical evaluation and management</em></td>
</tr>
</tbody>
</table>

SEROLOGIC ASSAYS FOR HCV: ELISA SCREENING TESTS

- Detect circulating HCV antibodies
- Sensitivity (97% to 100%)
- Positive predictive value
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT (newer generation assays have less false negative rates)

<table>
<thead>
<tr>
<th>False Positives More Likely In</th>
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<tbody>
<tr>
<td>Patients with low risk of HCV infection</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>False Negatives More Likely In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severely immunocompromised patients</td>
</tr>
<tr>
<td>Transplant recipients</td>
</tr>
<tr>
<td>Patients with chronic renal failure on dialysis</td>
</tr>
<tr>
<td>HIV-positive patients</td>
</tr>
</tbody>
</table>

INDICATIONS FOR HCV RNA TESTING

• Positive anti-HCV antibody test
• Considering antiviral treatment
  – Use sensitive quantitative assay (e.g. Taqman assay)
• Unexplained liver disease and negative anti-HCV antibody test and who are
  – Immunocompromised
  – Suspected of having acute HCV infection (prior to appearance of anti HCV)

# HCV ASSAYS:
## INTERPRETATION OF TESTING RESULTS

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Acute or chronic HCV depending on the clinical context</td>
</tr>
</tbody>
</table>
| +        | −       | Resolution of HCV  
|          |         | Acute HCV during period of low-level viremia* |
| −        | +       | Early acute HCV infection  
|          |         | Chronic HCV in setting of immunosuppressed state  
|          |         | False positive HCV RNA test* |
| −        | −       | Absence of HCV infection |

*extremely uncommon
HEPATITIS C
NATURAL HISTORY
**Acute HCV Infection**

- Spontaneous Resolution (15% to 45%)

**Chronic HCV Infection (55% to 85%)**

- *Stable (75% to 95%)*
- Cirrhosis (5% to 25%)
  
- *Stable (97% to 99%/year)*

**HCC or Decompensation (1% to 3%/year)**

- 20 to 30 Years Accelerated by Alcohol, HIV

*Often without symptoms*

** Usually subclinical
OUTCOME IN PERSONS WHO DEVELOP HEPATITIS C INFECTION

100

15% 

Resolve 15

85%

Chronic

Stable 68

Cirrhosis 17

75%

Mortality 4

20%

80%

25%

Courtesy of Seeff, LB and Alter, HJ.
FACTORS THAT MAY ACCELERATE HCV DISEASE PROGRESSION

• Age of acquisition of infection
• Male gender
• History of or current alcohol abuse Hepatic fibrosis stage
• Obesity
• Hepatic steatosis
• Metabolic syndrome/insulin resistance Diabetes mellitus
• Iron overload
• HIV coinfection
• Tobacco and cannabis use

FACTORS THAT MAY ACCELERATE HCV DISEASE PROGRESSION

Predicted Cumulative Rates of Cirrhosis by Age at HCV Infection

TREATMENT OF CHRONIC HCV INFECTION
CHRONIC HEPATITIS C
GOALS OF THERAPY

Primary Goal

- Eradicate HCV infection-
  Sustained viral response
  (SVR)-Cure

Secondary Goals

- Slow disease progression
- Improve histology
- Reduce risk of hepatocellular carcinoma
- Improve health-related quality of life
## APPROXIMATE RESPONSE RATES WITH IMPROVING THERAPIES

<table>
<thead>
<tr>
<th>YEAR</th>
<th>TREATMENT</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1990s</td>
<td>Interferon (24-48 weeks)</td>
<td>6-13</td>
</tr>
<tr>
<td>1998</td>
<td>Interferon plus Ribavirin</td>
<td>25</td>
</tr>
<tr>
<td>2001-2002</td>
<td>Pegylated Interferon plus Ribavirin</td>
<td>40</td>
</tr>
<tr>
<td>2011</td>
<td>Pegylated Interferon plus Ribavirin plus protease Inhibitor (genotype 1 only)</td>
<td>75</td>
</tr>
</tbody>
</table>

CHRONIC HEPATITIS C CURRENTLY APPROVED TREATMENTS

- Pegylated Interferon alfa 2b or 2a plus Ribavirin (Treat for 24 - 48 weeks)
- *Pegylated Interferon alfa 2b or 2a plus Ribavirin plus Bocepravir (Treat for 28-48 weeks)
- *Pegylated Interferon alfa 2b or 2a plus Ribavirin plus Telaprevir (Treat for 24-48 weeks)

* Genotype 1 only
INTERFERON ALFA AND THE HCV LIFECYCLE

- Interferon alfa promotes increased expression of proteins that interfere with viral replication
- Ribavirin enhances the antiviral effect of interferon; its precise mechanism of action is not certain

FACTORS THAT PREDISPOSE TO LOWER SVR WITH PEGYLATED INTERFERON+RIBAVIRIN

**Disease Related**
- Genotype 1
- High HCV RNA levels
- Cirrhosis/bridging fibrosis
- Steatosis on liver biopsy

**Patient Related**
- Aged 40 years or older
- Male gender
- Heavier body weight
- African American ethnicity
- Metabolic syndrome/insulin resistance
- Diabetes
- Immunosuppression
- Alcohol abuse

**Treatment Related**
- Adherence
- Treatment duration and regimen
- Contraindications
- Dose reductions

GENOTYPE 1 PATIENTS WITH HIGH VIRAL LOAD HAVE LOWER SVR

PegIFN=pegylated interferon; RBV=ribavirin; SVR=sustained virologic response.

HCV LIFE CYCLE AND DAA* TARGETS


*Direct Acting anti-viral agents

*Role in HCV life cycle not well defined
SVR RATES WITH BOCEPREVIR AND TELAPRECVIR IN GT1 TREATMENT-NAIVE AND -EXPERIENCED PATIENTS

COMMON SIDE EFFECTS OF *INTERFERON AND **RIBAVIRIN

• Flu-like symptoms
• Neuro psychiatric symptoms
• Myalgias/arthralgias
• Fatigue
• Alopecia
• Thyroiditis
• Injection site reactions
• Neutropenia
• Anemia
• Thrombocytopenia
• Insomnia
• Tretogenicity

*Administered weekly as a subcutaneous injection
** Administered orally bid
ADDITIONAL FEATURES
TELAPREVIR* AND BOCEPREVIR*

- GI symptoms
- Dysgeusia
- Skin rash
- Anemia
- Ano rectal symptoms
- Complex regimens (Q 8 hours and must be taken with food)
- Drug-drug interactions
- Treatment length may be shorter in some patients

*Administered orally q 8 hours.
HCV TREATMENT
THE FUTURE
ONGOING STUDIES

• Over 40 new DAA compounds under study
• Newer DAAs are administered once a day or bid and are well tolerated. Many are pangenotypic. Many of these DAAs have a high barrier to development of resistance
HCV TREATMENT OPTIONS UNDER STUDY

• Triple therapy-PEG/Riba/DAA

• Quadruple therapy-PEG/Riba/ 2 DAA’s of different classes

• Interferon free regimens
  - Combination of 2 or more DAAs of different classes
HCV TREATMENT OPTIONS UNDER STUDY

• SVR rates in some of these studies are 80-100%
• A number of combinations are achieving SVR with as short as 12 weeks of therapy
• Ribavirin seems to be required even in the interferon free regimens
• BUT STUDIES ARE STILL VERY SMALL WITH HIGHLY SELECTED PATIENTS
SUMMARY OF THE FUTURE TREATMENT OF HCV

• All oral, interferon regimens will be available
• The ideal drug combination is yet to be found
• Treatment duration will vary according to patient groups (e.g. genotype, virus level, severity of liver pathology etc.)
• Large scale clinical trials are needed to establish reliable efficacy, durability and safety profile
TIME LINE FOR NEW TREATMENTS OF HCV

• The next generation DAAs will possibly be approved in 2013 or 2014

• Combination interferon free treatment regimens will possibly be available 2 years later
HEPATITIS C
SUMMARY

• The virus has been well characterized
• The life cycle of the virus is well known
• We know the natural history of HCV infection
• We know the number of cases with serious outcomes is increasing
• There are new screening strategies to identify more cases
• We have treatments which result in a cure in the majority of cases
• Treatments are still difficult to administer with complex regimens and many side effects
• We are on the verge of simpler, less toxic, all oral treatment regimens with the potential to cure the majority of cases with shorter courses of treatment
PARADIGM OF HCV DIAGNOSIS AND TREATMENT