



Hepatitis C

THE SILENT EPIDEMIC

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Objectives:

- 1) Basic understanding of the Epidemiology, Virology, Clinical aspects for Hepatitis C.
- 2) Simplified Work up of Hepatitis C.
- 3) Treatment Consideration with the Focus on Ribavirin / Interferon Therapy / Protease Inhibitors

Hepatitis C

Lecture Outline

- Viral History
- Epidemiology
 - Statistics
 - Transmission risk
 - Vertical Transmission
 - Health Care worker Risk
- Virus
 - Virus
 - Quasispecies
- Clinical
 - Infection outcomes (Chronic Disease)
 - Pathophysiology
 - Predictive Factors for Progressive Disease
 - Persons at risk
 - Extra Hepatic Disease Manifestations
- Diagnosis
 - Serology
 - Liver Biopsy
 - Diagnostic Studies
- Treatment
 - Interferon / Ribavirin (combination)
 - Ribavirin
 - Interferon History
 - Definition
 - Biologic Activity
 - Pegylated Interferons
 - Interferon Uses
 - Interferon Side Effects
 - Genotypic variability
 - Who to treat / Who not to
 - Therapeutic Monitoring
 - Genotypic Response Variations
 - Protease Inhibitors
- Summary

Hepatitis C

History

Mid 1970s:

Harvey J. Alter, research team demonstrated that most post-transfusion hepatitis cases were not due to hepatitis A or B viruses.

Despite this discovery, international research effort to identify the virus, initially called *non-A, non-B hepatitis* (NANBH), failed for the next decade.

1987: **Michael Houghton, Qui-Lim Choo, and George Kuo** at Chiron Corporation, collaborating with D.W. Bradley from CDC

1988: Virus was confirmed by ALTER by verifying its presence in a panel of Non A - Non B specimens.

1989: Discovery of the virus, re-named “**Hepatitis C virus**” (HCV), was published in two articles in the journal *Science*.

- *Science* Hepatitis C http://en.wikipedia.org/wiki/Hepatitis_C (Accessed 4/14/2008)

- 2000 Albert Lasker Award for Clinical Medical Research, The Lasker Foundation. (Accessed 20 February 2008)

- Choo Q, Kuo G, Weiner A, Overby L, Bradley D, Houghton M (1989). "Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome.". *Science* **244** (4902): 359-62. PMID 2523562 Kuo G, Choo Q, Alter H, Gitnick G, Redeker A, Purcell R, Miyamura T, Dienstag J, Alter M, Stevens C (1989).

"An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis.". *Science* **244** (4902): 362-4. PMID 2496467

Hepatitis C

History

*FDA Guidelines for Blood donation:

- **1990:** HCV EIA screening of all blood donations by 1st generation test.
- **1992:** Second generation HCV antibody Screening Tests.
- **1999:** HCV Nucleic Acid.

Epidemiology

Statistics

Transmission risk

Vertical Transmission

Health Care Worker Risk

Question #1

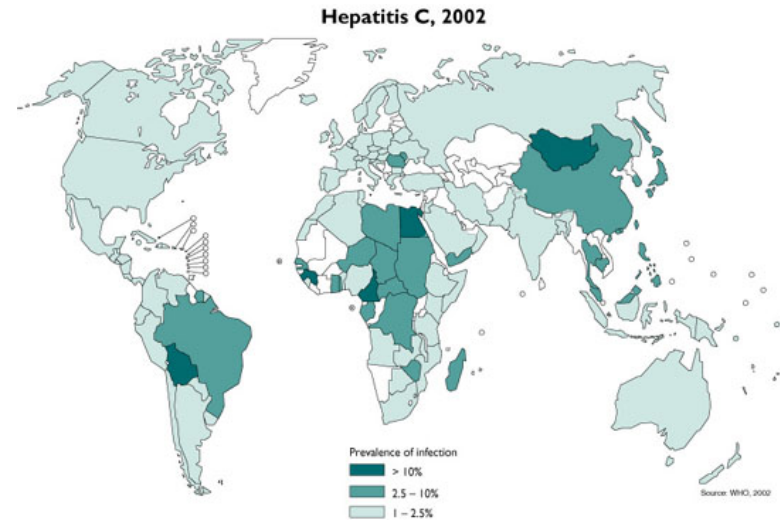
Regarding transmission of Hepatitis C all are true except:

- A) Casual household contact; and contact with the saliva of infected persons also appear to be *very inefficient* modes of transmission.
- B) Nosocomial transmission has been documented, such as from patient to patient by a colonoscopy, during dialysis, and during surgery.
- C) For needle “stick” exposure the relative risk of “hollow” needle stick transmission is Hepatitis B (30%), Hepatitis C (3%), and HIV (0.3%).
- D) When Hepatitis C testing became (available after 1994), most newly diagnosed cases are attributed to blood or blood product transfusions.

HEPATITIS C

Statistics

- 170 MILLION INFECTED WORLD WIDE
- 230,000 NEW CASES YEARLY
- PRIMARILY : 30 - 49 YEAR OLD

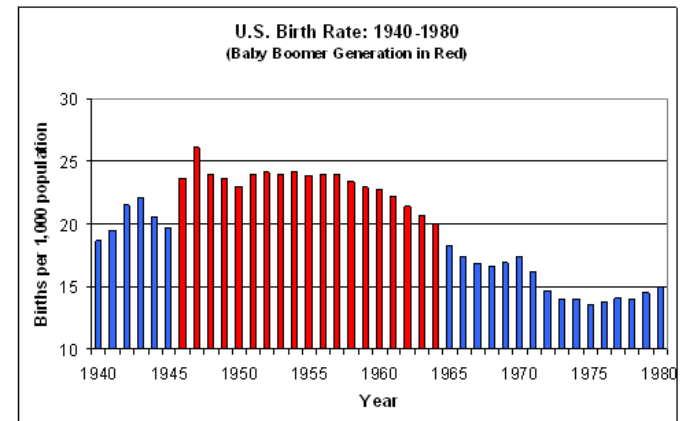


NORTHERN EGYPT	38%
USA (3.9 MILLION)	1.8%
SCANDANAVIA	0.15%

Hepatitis C

United States*

Clinical condition	Outcome
Chronic Infection	75-80%
Chronic Liver Disease	60-70%
Hepatic Cirrhosis (20-30 years)	5-20%



Hepatitis C :

- ❖ Approximately 3.2 million persons have chronic HCV infection.
- ❖ Infection is most prevalent among those born during 1945–1965.
- ❖ Majority of whom were likely infected during the 1970s and 1980s when rates were highest.
- ❖ 10,000 Yearly deaths from liver disease (1.5%)
- ❖ 1,000 Liver transplants per year.
- ❖ 350,000 HIV (35%) are co-infected with Hepatitis C.

HEPATITIS C

TRANSMISSION

UNDEFINED (MOST COMMON)

TRANSFUSIONS

SHARING NEEDLES (IVDU)

INTRA FAMILY SPREAD (???)

NEEDLE STICKS

SEXUAL TRANSMISSION

PERINATAL SPREAD

NO INSECTS

TRANSFUSION:

PRE - SEROLOGY SCREENING (1980) 15 - 20%

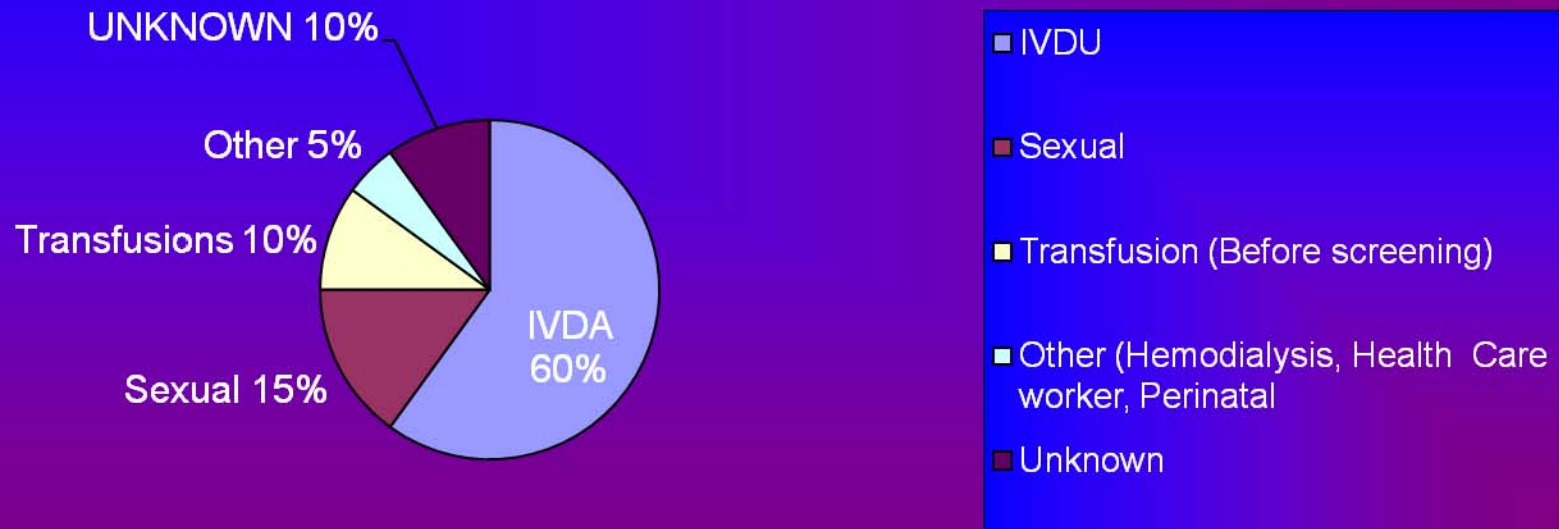
POST - SEROLOGY SCREENING (1994) 0.01%

Presently blood transfusion risk : 1 : 2,000,000 (Blood Screening)

HEPATITIS C

*TRANSMISSION

Sources of infection for Persons with Hepatitis C



* Adapted from CDC

Hepatitis C

Vertical transmission

“The transmission of a communicable disease from an infected mother to her child during the birth process”

- Mother-to-child transmission occurs relatively infrequently.
- Transmission occurs ONLY among women who are HCV RNA positive at the time of delivery :
6 out of 100. (6%)
- Women both HCV and HIV positive at the time of delivery, the risk is increased to approximately 25 out of 100. (25%)

Mother's Serostatus	Transmission risk of HCV
HCV RNA Positive	6%
HCV RNA and *HIV Positive	25%

* 25% risk HIV transmission (Untreated)

The risk of vertical transmission of HCV does not appear to be associated with method of delivery or breast feeding.

Hepatitis C

Comparative Risk of Health care worker Infection Risk

Virus	Needle stick: Relative Risk Acquiring from positive blood *
Hepatitis B	30%
Hepatitis C	3% **
HIV	0.3%

* These numbers are most likely influenced by the size of the inoculums, the size of the needle, and the depth of inoculation.

** After a needle-stick injury involving blood known to be infected ranged from 0 to 10 percent in various studies ^{1,2}

Hepatitis C

- ❖ Casual household contact and contact with the saliva of infected persons also appear to be very inefficient modes of transmission. ³
- ❖ Nosocomial transmission has been documented, such as from patient to patient by a colonoscopy, during dialysis, and during surgery. ³

1 Thomas DL, Factor SH, Kelen GD, Washington AS, Taylor E Jr, Quinn TC. Viral hepatitis in health care personnel at the Johns Hopkins Hospital: the seroprevalence of and risk factors for hepatitis B virus and hepatitis C virus infection. *Arch Intern Med* 1993;153:1705-1712.

2 Mitsui T, Iwano K, Masuko K, et al. Hepatitis C virus infection in medical personnel after needlestick accident. *Hepatology* 1992;16:1109-1114.

3 Lauer GM, Walker BD, Hepatitis C Virus Infection, *N Engl J Med* 2001;345:41-52

Virus

Virus

Quasispecies

Question #2

Regarding Hepatitis C virus all are true except:

- A) Serotypes 1 and 4 are less responsive to antiviral agents.
- B) Genotypic “QUASISPECIES” arise through naturally occurring mutations that result in chronic infections (RNA-dependent RNA polymerase that lacks a "proofreading" function).
- C) Predominant serotype in America is Type 1.
- D) Hepatitis C is a DNA virus that leads to chronic infection through chromosomal integration (As seen with the Herpes group).
- E) Serotype 1 seems more liver pathogenic than other Serotypes.

Single strand
RNA virus

Virology

Flaviviridae

Flaviviridae

Family of viruses that are primarily spread through arthropod vectors (Mainly ticks and mosquitoes).

I. Genus *Flavivirus*

- *Yellow fever virus*
- *West Nile virus*
- *Dengue Fever* — contains 67 identified human and animal viruses

II. Genus *Hepacivirus*

- *Hepatitis C virus* (Single member)

III. Genus *Pestivirus*

- *Bovine virus diarrhea*

Major diseases caused by the *Flaviviridae* family include:

- Dengue fever
- Japanese encephalitis
- Kyasanur Forest disease
- Murray Valley encephalitis
- St. Louis encephalitis
- Tick-borne encephalitis
- West Nile encephalitis
- Yellow fever
- Hepatitis C Virus Infection

1 <http://en.wikipedia.org/wiki/Flaviviridae> (Accessed 11/20/2011)

2 From MicrobeWiki, the student-edited microbiology resource <http://microbewiki.kenyon.edu/index.php/File:Flaviviridae.jpg> (Accessed 11/21/2011)

HEPATITIS C VIRUS

(1989) FLAVAVIRUS RNA

➤ **9,400 NUCLEOTIDES coding : 3,000 amino acids**

➤ **“HIGH” REPLICATIVE CAPACITY leads to:**

GENOTYPIC “QUASISPECIES”

Viral Replication occurs through an RNA-dependent RNA polymerase that lacks a "proofreading" function:

➤ **SERUM VIRAL LOADS (>500,000 viral copies /cc) common**

SIX “MAJOR” GENEOTYPES

HEPATITIS C

VIRUS Genotype/Quasispecies

Genotype	Factoid
Genotype 1	75% America
Genotype 2 or 3	20-25% America
Genotype 4	Africa
Genotype 5	Africa/South East Asia
Genotype 6	South East Asia

Patients with genotypes 2 and 3 are more than twice as likely as patients with genotype 1 to achieve a sustained virological response to therapy.

- Within all individuals, slightly different genetic versions of their genotype are present.
- Viral mutations occur spontaneously over time (in response to pressure from the host immune response) forming genetically distinct viral groups called “**quasispecies**”.

HEPATITIS C VIRUS

Quasispecies

CLINICAL IMPLICATIONS:

QUASISPECIES:

ESCAPE HOST IMMUNE RESPONSE (ANTIBODY)

QUASISPECIES:

“CONFOUND” LABORATORY TEST AND VACCINE DEVELOPMENT

“SEROTYPE ONE”

AND ASSOCIATED QUASISPECIES SEEM MORE LIVER PATHOGENIC

- ❖ SEROTYPE 1 and 4 ARE LESS RESPONSIVE TO “ANTIVIRAL” AGENTS
- ❖ SEROTYPE 2 and 3 ARE MORE RESPONSIVE TO TREATMENT

Clinical

- Infection out comes (Chronic Disease)
- Pathophysiology
- Predictive Factors for Progressive Disease
- Persons at risk
- Extra Hepatic Disease Manifestations

Chronic hepatitis C is defined as infection with the hepatitis C virus

.... persisting for more than six months.●

Question #3

Regarding Clinical Aspects of Hepatitis C all are true except:

- A) *80% Infections are asymptomatic and 75 - 85% result in "Life long" chronic infection ("QUASISPECIES").*
- B) 70% Chronic infection develop liver disease (Decades Later).
- C) Alcoholic beverage consumption accelerates HCV associated fibrosis and cirrhosis.
- D) Extra hepatic manifestations are related to antigen/antibody complexes (Porphyria Cutanea Tarda, Essential Mixed Cryoglobulinemia).
- E) "Spontaneous" resolution of chronic infection occurs 5 -25% of chronically infected persons per year.

HEPATITIS C VIRUS

Pathophysiology

- Detectable Viremia : 1 - 3 weeks
- Detectable Antibody : 3 - 12 weeks.
- *“Spontaneous viral clearance”*
 - Approximately 15 - 40% (Acute phase)
 - Normalization in liver function tests (ALT & AST)
 - Plasma clearance of HCV-RNA
- 60 - 85% patients develop Chronic hepatitis C
(Infection lasting more than 6 months)

Previous practice was to not treat acute infections to see if the person would spontaneously clear the virus.....

Recent studies have shown that treatment during the acute phase of Genotype 1 infections has a greater than 90% success rate with half the treatment time required for chronic infections

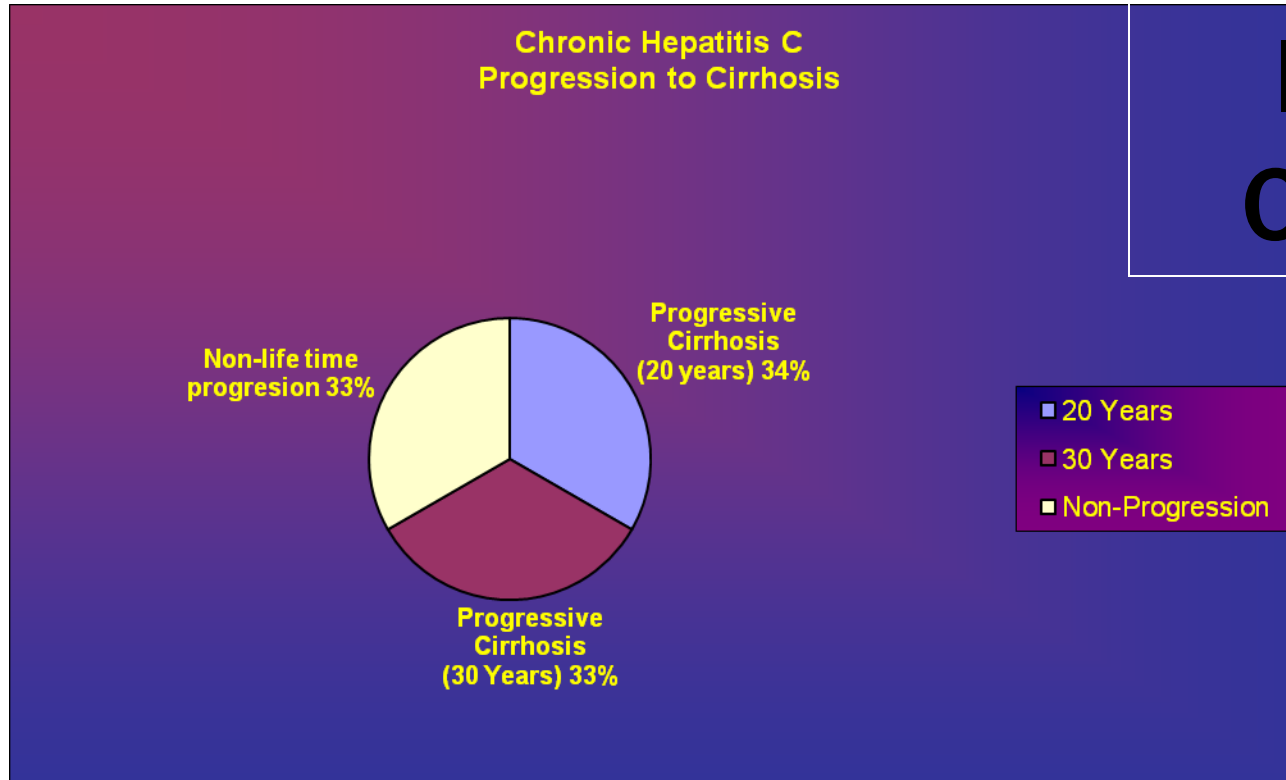
Hepatitis C

Infection outcomes

- **20%** **Clinical Jaundice (2 - 12 weeks)**
- **80%** ***Infections are asymptomatic!***
- **15 - 25%** **Resolve acute infection**
- **75 - 85%** **“Life long” chronic infection (“*QUASISPECIES*”)**
- **70%** **Chronic infection develop liver disease (Decades Later)**
- **1 - 4%** **Hepatocellular cancer**

“Spontaneous” resolution of chronic infection occurs (0.5 - 0.74% per year)

Hepatitis C Infection Outcomes



Virtually all people infected with HCV have evidence of inflammation on liver biopsy...

However, the rate of progression of liver scarring (fibrosis) shows significant variability among individuals.

HEPATITIS C

Predictive factors for “Chronic Infection”

Older than 40 years at time of diagnosis

Longer duration of infection

Males

“Weakened” immune status

Co-infection with other hepatropic virus

Genotype I and its “Quasispecies”

Iron overload states, and alcoholics

HIV co-infection

Alcoholic beverage consumption
Accelerates HCV
associated fibrosis and cirrhosis,
and makes liver cancer more likely

HEPATITIS C
Persons at Risk

WHO TO SCREEN:

IVDU

Blood product transfusion (Before 1992)

Organ transplants (Before 1992)

All hemodialysis patients

Unexplained "ALT" elevations

Health care workers with percutaneous or

Mucus membrane exposure

Children born to HCV infected women

Hepatitis C

Extra Hepatic Manifestations

Primary Vasculitis

(High Viral Loads)

- **Essential Mixed Cryoglobulinemia**
- Purpura, Arthritis / Arthalgias,**
- **Cerebritis, Neuritis (Vasonervorum)**
- **Glomerulonephritis**

Dermal Manifestations:

- **Porphyria cutanea tarda**
- **Lichen planus**

Rarely:

**Aplastic anemia or
Non-Hodgkin's lymphoma**



Porphyria cutanea tarda

Can be inherited as a dominant trait or acquired due to liver disease. Sun exposed areas develop Blistering (vesicles and bullae), erosions and ulcerations, Fragile skin, pigmentary changes and scarring.

DIAGNOSIS

Serology

Liver Biopsy

Diagnostic Studies

Hepatitis C

Diagnosis

Advanced cirrhosis with mixed
**Macronodular and
Macronodular Patterns and
Moderate cholestasis**



- CT scan (Guided Biopsy)
- Ultra Sound
- CBC, Platelets
- Liver Transaminases

Liver biopsy (See bibliography)
DESMET Classification
Inflammation 0 - 4
Fibrosis 0 - 4

Test

- Elisa Screening
- RIBA confirmation (Not necessary)
- Viral quantation (PCR or bChain DNA)

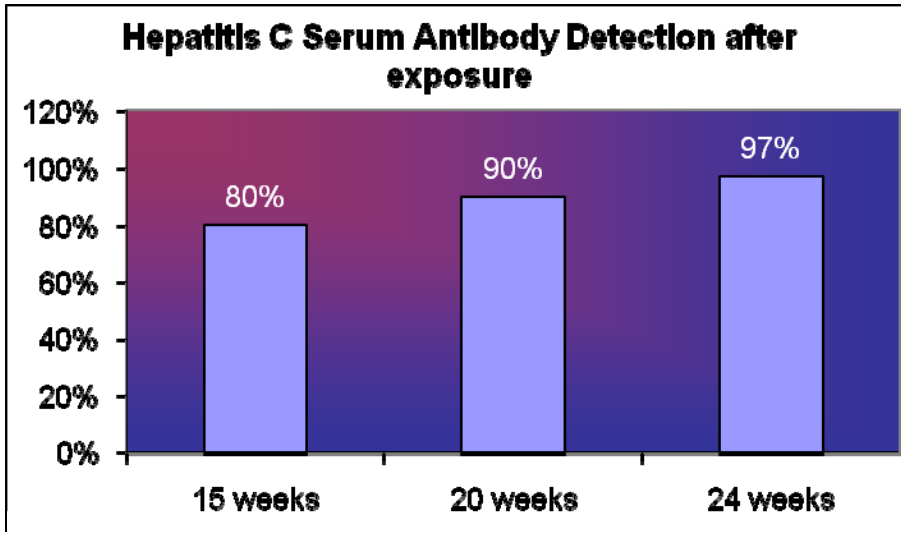
Factoid

- Third Generation
- With “low” pre-test suspicion
- Prognostic follow up

❖ **Viral genotyping (NOT NECESSARY):** (70 - 80% of USA strains are type I or I a)

Hepatitis C

Diagnosis



Feature	Factoid
LTA Elevation	Variable
LTA Elevation Correlation to disease	None
Viral Load Correlation to Liver injury	None
Radiographic findings	Not until Advanced disease
Liver biopsy	Best : Scarring / Inflammation

Treatment

Interferon / Ribavirin (combination)

Ribavirin

Interferon History

Definition

Biologic Activity

Pegylated Interferons

Interferon Uses

Interferon Side Effects

Genotypic variability

Who to treat / Who not to

Therapeutic Monitoring

Genotypic Response Variations

Protease Inhibitors

Summary

Question #4

Regarding treatment of Hepatitis C all are true except:

- A) Treatment is based on Antiviral agents (Nucleoside analogs, protease inhibitors) and Immune Modulating agents (Interferon)
- B) Therapy is usually well tolerated by most patients and is modestly expensive .
- C) “Double” drug therapy response rate is about 40%. “Triple” drug treatment regimens response is approximately 70%
- D) More severe treatment toxicities include severe patient Malaise; Psychiatric disturbances, Pancytopenias and Rashes.
- E) Best treatment patients (Response, Medication tolerance and reduced , morbidity) include: Advanced liver disease (Biopsy), Non - alcoholic , Females, Patients less than 40 years of age.

TREATMENT

HEPATITIS C

Protease

Telaprevir
Boceprevir



Nucleoside

Ribavirin



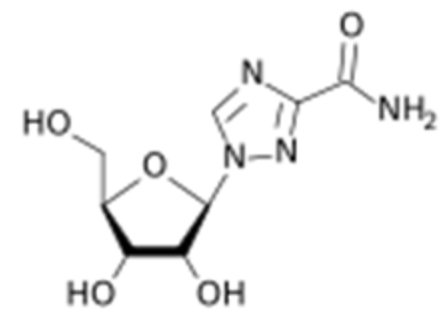
IMMUNE MODULATION

Peg Interferon

Ribavirin

Ribavirin

Rebetol[®]



- Anti-viral drug which is active against a number of DNA and RNA viruses.
- Nucleoside anti-metabolite
(Interfere with duplication of viral genetic material)

Activities:

- **Influenza**
- **Flavivirus (Hepatitis C)**
- **Viral hemorrhagic fevers:**
 - Lassa fever, Crimean-Congo hemorrhagic fever, and Hantavirus
- Smallpox
- Hepatitis B
- Polio
- Measles
- West Nile virus
- Dengue fever

Nucleoside drug resemble adenosine or guanosine,

- First synthesized in 1970
- Widely distributed in all tissues, including the CSF and brain
- Teratogenic
- Serious adverse side-effect of Ribavirin is hemolytic anemia,

Interferon

- 1954 Yasu-ichi Nagano, Yasuhiko Kojima
- 1957 Alick Isaacs, Jean Lindemann: Coined “Interferon”
- 1980 Recombinant DNA allows mass production

Interferons

Definition

Interferons

- Family of naturally-occurring proteins that are produced by cells of the immune system.
- Three classes of Interferons have been identified:
Alpha Beta Gamma
- Each class has different biological and physiological effects although their activities overlap.
- Together, the Interferons direct the immune system's attack on viruses, bacteria, tumors and other foreign agents.
- Interferons effects slow, block, or change the biologic growth or function of the agent (Organism).

Interferons

Biologic activity

Interferons

- **Produced by a wide variety of cells** in response to the presence of double-stranded RNA. (Key indicator of viral infection).
- **Interferons assist the immune response :**
 - Inhibiting viral replication
 - Activating natural killer cells/ macrophages
 - Increasing antigen presentation to lymphocytes
 - Inducing the resistance of host cells to viral infection.
- When the antigen is presented to matching T and B cells, those cells multiply and strategically and specifically wipe out the foreign substance.

Interferons

Pegylated interferon

Pegylated interferon

alfa-2b (Peg-Intron[®]) and alfa-2a (Pegasys[®])

Polyethylene Glycol (PEG) attached to interferon molecules.

- PEG causes the interferon to remain in the body longer, prolonging Half life and drug effectiveness.

Pegylated Interferon Advantage

Administered by subcutaneous or intramuscular injection.

Interferon Comparison	* Pegylated Alpha interferon Peg interferon alpha-2b (Peg-Intron® Schering-Plough) Peg interferon alpha-2a (Pegasys® Hoffmann-La Roche)	** Non Pegylated Interferon Alpha Interferon alfa-2a (Roferon-A® Hoffmann-La Roche) Interferon alpha-2b (Intron-A®; Schering-Plough) (interferon alfacon-1 (Infergen; Amgen))
Longer Half life	+++++	
Consistent blood levels	+++++	
Dosage interval	Once week	Three Times Week

* Peg interferon alpha-2b (1.5 mcg/kg) Once weekly
 Peg interferon alpha-2a (180 µg 1.0 mL) Once weekly

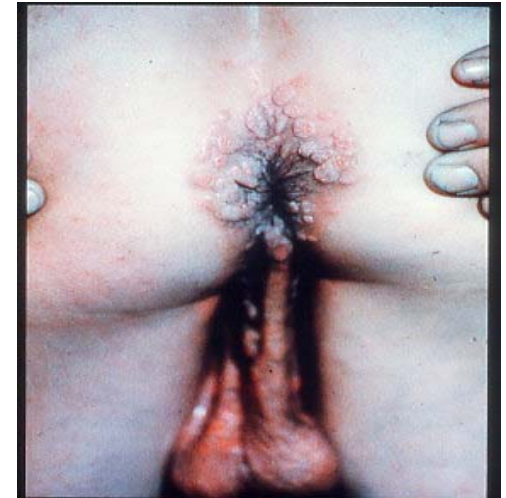
** alfa-2b AND alpha-2a : 3,000,000 units three times a week

Interferon Uses

- Hairy cell leukemia
- AIDS-related Kaposi's Sarcoma
- Chronic Myelogenous Leukemia
- Malignant Melanoma
- Condylomata Acuminata
- Chronic Hepatitis C
- Chronic Hepatitis B



Condyloma acuminata



Condyloma lata

Twenty year growth of “venereal warts” -Squamous cell cancer

- Both are contagious
- Condyloma lata (“Lotta syphilis organisms”)
- Each weighed 1.5 lbs
- Giant condylomata of Buschke- loenstein (HPV-6)

Interferon

Side effects

- Flu-like symptoms following each injection (Fever, Chills, Headache, Muscle aches and pains, Malaise); Alopecia
- These symptoms vary from mild to severe and occur in up to half of all patients.
- The symptoms tend to diminish with repeated injections

Management

- Analgesics : Acetaminophen (Tylenol)
- Antihistamines : Diphenhydramine (Benadryl).
- Interferon therapy causes (“Bone marrow”) Immunosuppression:
Neutropenia, Anemia, Thrombocytopenia

All known adverse effects are usually reversible and disappear a few days after the therapy has been finished.

* Psychiatric Side effects	Patients	Percent
	30	16.6%
Total	5	16.6%
Major Depression disorder	3	10%
Brief psychotic disorder	1	3.3%
Panic attacks	1	3.3%

Interferon
Side effects
 Depression and suicide

- Reported among patients receiving Interferons
- Unclear whether depression and suicidal thoughts are caused by the diseases being treated or the Interferons themselves.....

Therefore, all patients receiving treatment with an interferon should be observed for the development of depression and suicidal thoughts.

* Incidence of Psychiatric Side Effects During Pegylated Interferon- Alpha Retreatment in Non responder Hepatitis C Virus-Infected Patients
<http://www.medscape.com/viewarticle/564075> (Accessed 4/14/2008)
 - Medicine Net. Com <http://www.medicinenet.com/interferon/article.htm> (Accessed 4/14/2008)

Treatment of Hepatitis C

Who to treat:

- ❖ Advanced liver disease (Biopsy)
- ❖ Non - alcoholic
- ❖ Females, less than 40 :

Respond and tolerate therapy better

“Relative” contraindications to ponder:

Mental depression

Psych history

Unstable Cardiovascular status

Anemia

Autoimmune diseases

Diabetics

Alcoholics

PREGNANCY

Interferon

Therapeutic monitoring

Testing

RECOMENDATIONS

CBC and Chemistry evaluations

*2 weeks after initiation of treatment**

Pregnancy tests in women

Routinely

HCV RNA (Base line)

12 weeks** 24 weeks (Post treatment)***

** Erythropoietin Alfa and granulocyte colony stimulating factor (G-CSF) **may be** used to treat anemia and neutropenia, to maintain the patient on full medication doses.*

*** Patients who do not achieve virological suppression or a 2-log decrease in HCV RNA at 12 weeks, may have therapy discontinued.*

Although factors such as degree of fibrosis and tolerability of therapy should be considered.

**** Patients who achieve an end-of-treatment virological response should have HCV RNA testing performed 24 weeks after stopping treatment SVR. (“Sustained Virologic Response”)*

Genotypic Response Variations

Genotype *	Agents	Duration	Response
Chronic carriers (No Treatment)	—	—	(0.5 - 0.74% per year)
Genotype 2	Pegylated interferon alpha Ribavirin	24 weeks	75%
Genotype 3	Pegylated interferon alpha Ribavirin	24 weeks	75%
Genotype 4	Pegylated interferon alpha Ribavirin	48 weeks	65%
** Genotype 1	Pegylated interferon alpha Ribavirin	48 weeks	50%

- Those with low initial viral loads respond much better to treatment than those with higher viral loads (>2 million virions / ml).
- * If NO 2 - log viral reduction or complete clearance of RNA (termed *early virological response*) after 12 weeks, the chance of treatment success is less than 1%
- ** 80% of hepatitis C patients United States ARE Genotype 1
- Genotype 4 is more common in the Middle East and Africa.

Interferon / Ribavirin

“Pegylated interferon”

In summary:

- ❖ **The most experienced/ available current treatment for chronic Hepatitis C is peg interferon alpha plus Ribavirin.**
(Leads to an overall sustained response rate in over 50% of all patients).
- ❖ **The sustained response rates are even better for individuals infected with non-type 1 genotypes of the hepatitis C virus.**
(Unfortunately less the 20 - 30% US patients)

Interferon / Ribavirin

“Pegylated interferon”

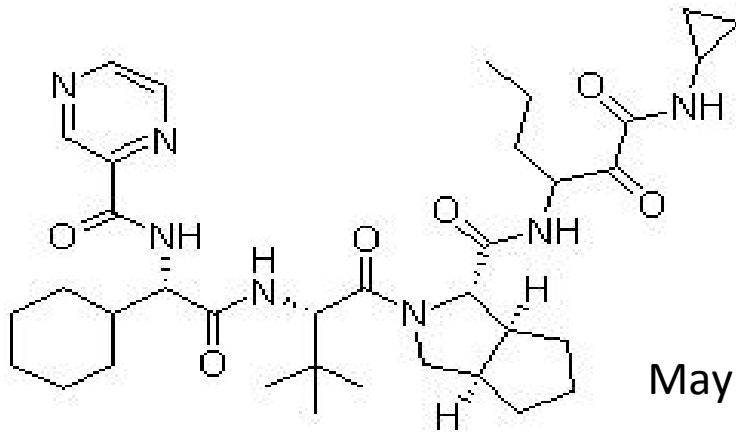
In summary

As the currently available interferon alpha-based treatments for chronic hepatitis C are associated with many side effects....

And effective in only about half of patients, more research is needed to develop safer, more effective and cheaper drugs.....

Hepatitis C

Treatment: Protease Inhibitors

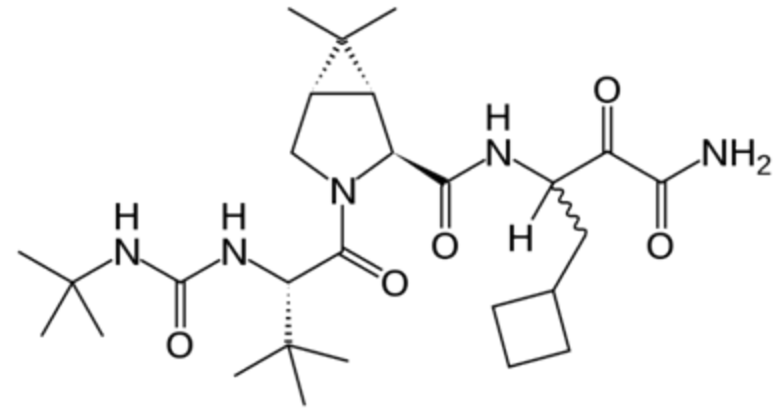


May 23, 2011

Telaprevir (VX-950)

May 23, 2011

INCIVEK[®]

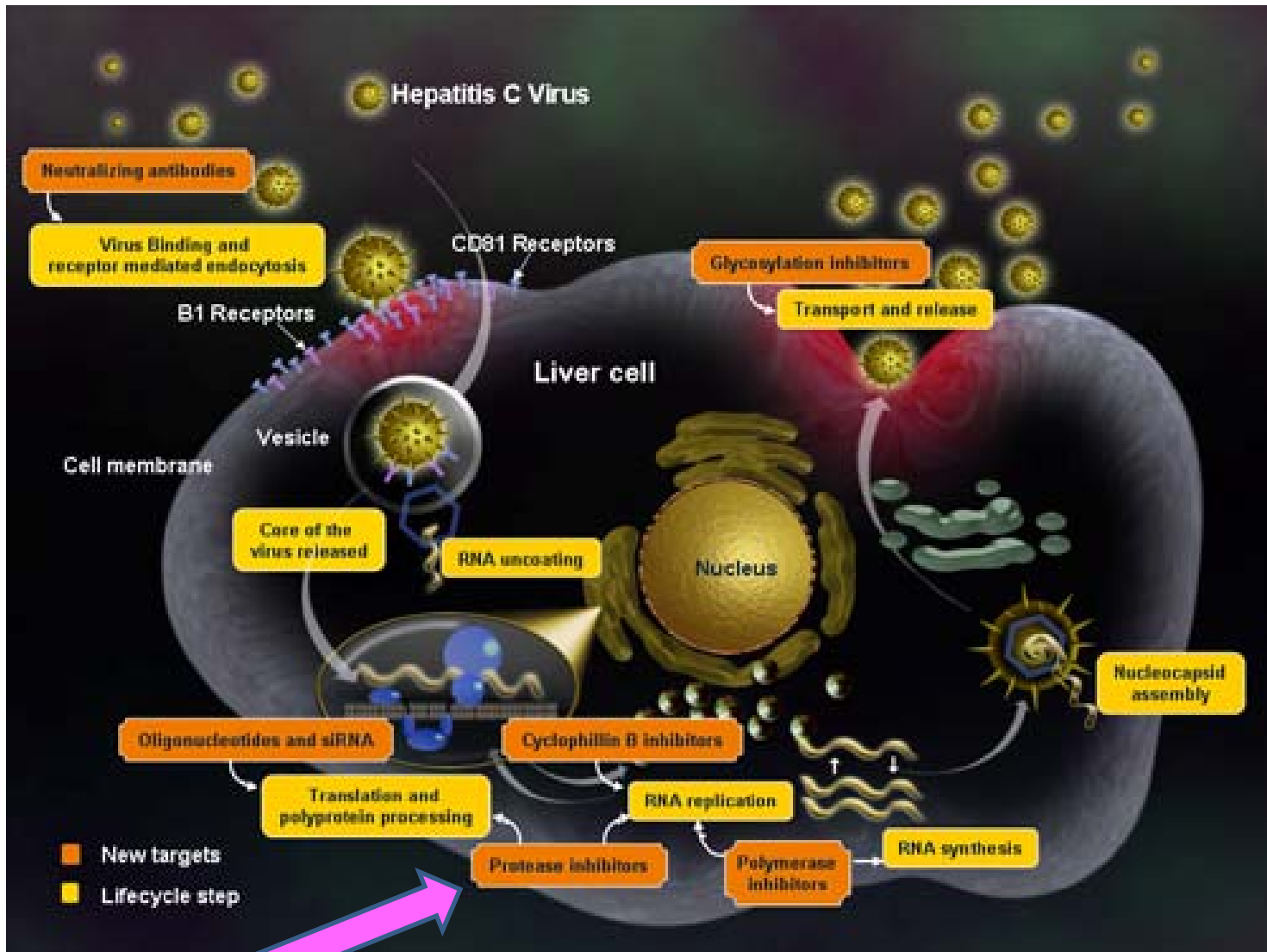


Boceprevir

May 13, 2011

VICTRELIS[®]

Class of antiviral drugs known as Viral
“Protease Inhibitors”



Hep C Life cycle.....More agents to come?

Hepatitis C

Treatment: Protease Inhibitors **TELAPREVIR**

ADVANCE (Telaprevir)

**1,088 untreated patients
(HCV genome 1)**

***Standard 48 week
(Alone)**

Standard

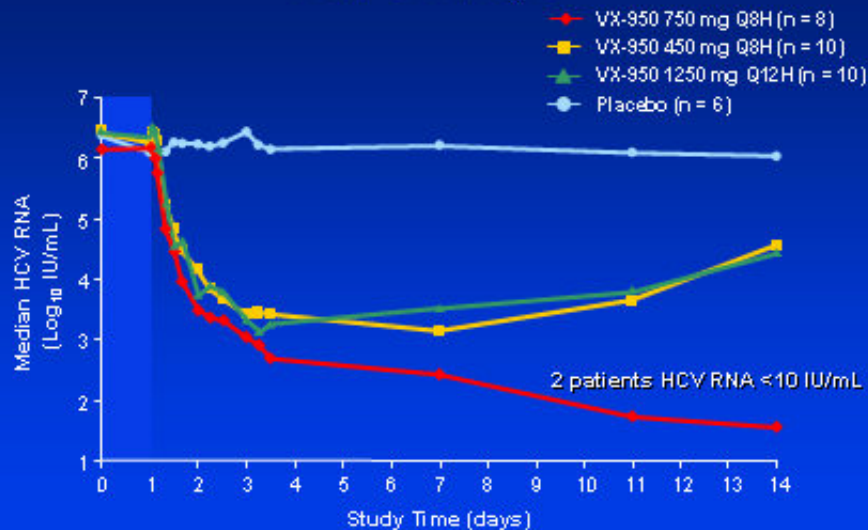
- With 8 or 12 weeks of Telaprevir
- Then 24 Or 48 weeks of follow up standard therapy

Response	44%	8 weeks 69%
		12 weeks 75%
African-Americans	25%	62%
Advance Liver cirrhosis	33%	62%

* Standard: Ribavirin / Peg Interferon

Protease Inhibitor Telaprevir (VX-950) Monotherapy

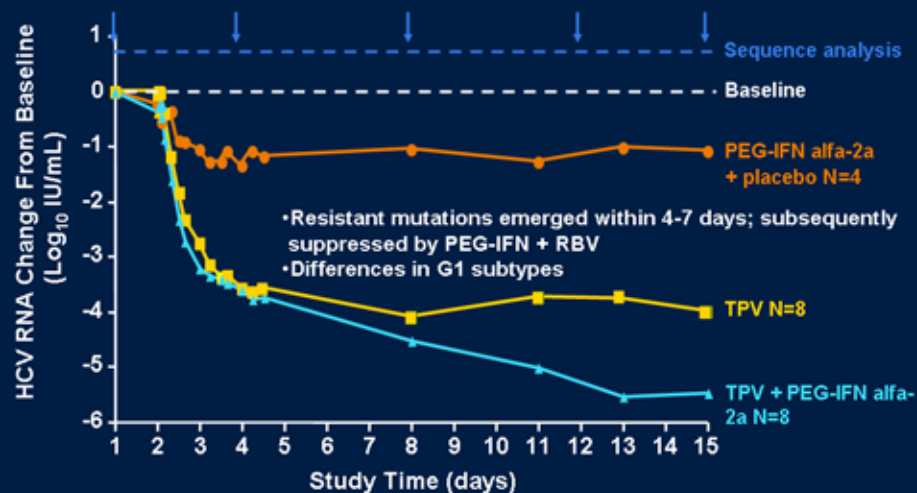
Proof of Principle



Reprinted from Reesink HW, et al. *Gastroenterology*. 2005;128:A-697, with permission from Elsevier.

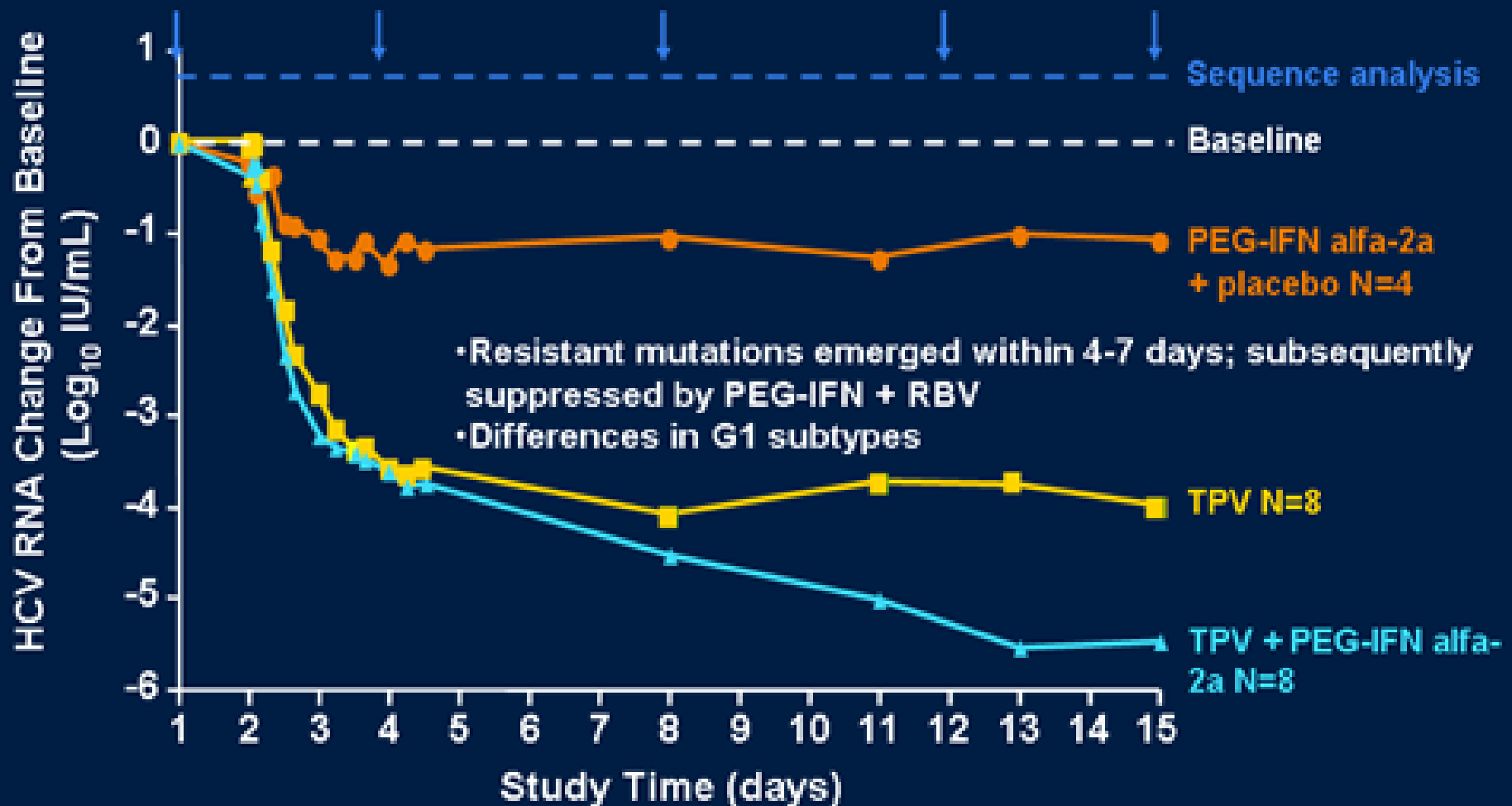
TELAPREVIR

Changes in HCV RNA in Patients Treated With Telaprevir (TPV) +/- PEG-IFN x 2 Wks



Kieffer TL, et al. *Hepatology*. 2007;46:631-639. Copyright © 2007 American Association for the Study of Liver Disease.

Changes in HCV RNA in Patients Treated With Telaprevir (TPV) +/- PEG-IFN x 2 Wks



Hepatitis C

Treatment: Protease Inhibitors : **BOCEPRIVIR**

Boceprivir	SPRINT 1	Sprint 2 Standard/Placebo controlled	Respond 2 Non responders to Standard treatment
Patients:	595	938 White/159 Black	403
Cirrhosis	6-9%		
High viral load	90%		
African-American	14-17%		
Sustained Viral Response	75%	40% Placebo 67% Treatment	21% Standard treatment 59% Response guided therapy 66% Fixed-duration therapy

Standard treatment/placebo = Ribavirin/Interferon
SVR = Sustained Viral Response

SPRINT-1 trial Phase II trial of Boceprivir in difficult-to-treat patients with HCV genotype 1

SPRINT-2 trial Double-blind study randomly assigned adults with untreated hepatitis C virus, genotype 1

RESPOND-2 trial Patients/ chronic hepatitis C genotype 1/ Who did not have a sustained response to therapy with peginterferon-ribavirin therapy

- Poordad, F, et al. (March 2011). "Boceprivir for Untreated Chronic HCV Genotype 1 Infection". *N Engl J Med.* **364** (13): 1195–206
- Jensen, D (March 2011). "A New Era of Hepatitis C Therapy Begins". *N Engl J Med.* **364** (13): 1272–1273
- Bacon, B, et al. (March 2011). "Boceprivir for Previously Treated Chronic HCV Genotype 1 Infection"*N Engl J Med.* **364** (13): 1207–17
- <http://en.wikipedia.org/wiki/Boceprevi>

Hepatitis C

Treatment: Protease Inhibitors : **DOSE**

Drug	Suggested dosage regimens
Telaprevir *	<ul style="list-style-type: none">➤ 12 week THREE DRUG Combination with both Interferon and Ribavirin➤ Then complete treatment (to 24-48 weeks total) with Ribavirin and Interferon
Boceprvir **	<ul style="list-style-type: none">➤ Initiate therapy with peg interferon Alfa and ribavirin for 4 weeks THEN:➤ Add Boceprvir 800 mg PO TID (i.e. Q 7-9hr) with food Treatment duration➤ Duration of treatment depends on HCV-RNA levels at treatment weeks 8,12, and 24

* Telaprevir <http://www.drugs.com/ppa/telaprevir.html> (Accessed 11/28/2011)

** Boceprvir <http://reference.medscape.com/drug/victrelis-boceprvir-999655> (Accessed 11/28/2011)

Hepatitis C

Treatment: Protease Inhibitors End points

Patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance quasispecies

Boceprivir

Treatment futility

- Discontinuation of therapy is recommended in all patients with either of the following circumstances:
 - HCV-RNA levels >1000 IU/mL at treatment weeks 4 or 12
- OR
- HCV-RNA levels detectable at treatment week 24

Telaprevir

Treatment futility

- Discontinuation of therapy is recommended in all patients with either of the following circumstances:
 - If HCV-RNA levels 100 IU/mL or greater at week 12, discontinue 3-medication regimen
- OR
- If confirmed, detectable HCV-RNA levels at week 24, discontinue 3-medication regimen

* Telaprevir <http://www.drugs.com/ppa/telaprevir.html> (Accessed 11/28/2011)

** Boceprivir <http://reference.medscape.com/drug/victrelis-boceprevir-999655> (Accessed 11/28/2011)

Hepatitis C

Treatment: Protease Inhibitors

Treatment costs

Drug combination	Estimated cost	Factoid
Peg Interferon/Ribavirin	\$18,000 – \$36,000	\$500 Peg interferon /week \$100 Ribavirin /week
Peg Interferon / Ribavirin With either: Telaprevir or Boceprevir	\$48,000 - \$85,000	\$1,100 /week more
Liver transplant	Estimated First-Year Charge: \$314,600	Annual Follow-up Charge: \$21,900

Hepatitis C

Treatment: Protease Inhibitors

“HCV protease inhibitors represent a major advance in our ability to treat chronic HCV infection.

Future therapy will be more complex, not easier, but the improvement in the rate of sustained virologic....have been eagerly awaited.

We will soon embark on a new era of successful HCV therapy.”

- Donald M Jensen, M.D.

“A New Era of Hepatitis C Therapy Begins”

N Engl J Med. 364 (13): 1272–1273

Questions?



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