

Changing the Game in Hepatitis C Virus Infection

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February 13, 2012

Viral Hepatitis

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (Delta)	Hepatitis E
Virus Family	picornavirus	hepadnavirus	flavivirus	unclassified	calicivirus-like
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Envelope	Unenveloped	Enveloped	Enveloped	Enveloped	Unenveloped
Transmission type	fecal-oral	Sexual, parenteral	parenteral	parenteral	fecal-oral
Reservoir	Human	Human	Human	Human	Human, Pig, Chicken, Rat
Vaccine Available?	Yes, Havrix (1995) Vaqta (1996)	Yes, Recombivax (1986) Engerix-B (1989)	No	No	No

▶ NNII, 2012 D/Pro, 2011

Hepatitis C Epidemiology

	Hepatitis C
Year	2007
Incidence (US)	17,000**
Prevalence (US)	3.2 million
Prevalence (global)	180 million
Deaths (US)	10,000
Annual Costs	\$1 billion

- ▶ 75% of infected people may not be identified
- ▶ 20- to 30-year disease progression
 - ▶ 200,000 patients infected per year in the late 1980s
- ▶ Asymptomatic disease

▶ McHutchinson, 2005

CDC: <http://www.cdc.gov/hepatitis/HCV/>
WHO: http://www.who.int/immunization/topics/hepatitis_c/en/

Routes of transmission

High Risk (>10%)

- ▶ IV drug use
- ▶ Hemophiliacs

Moderate Risk (5-10%)

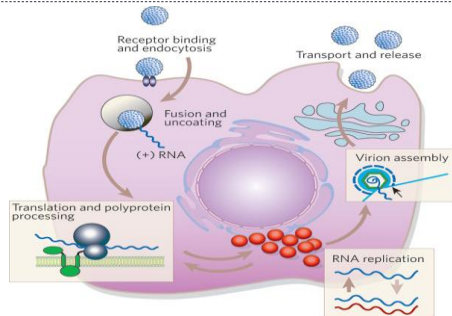
- ▶ Blood transfusions or transplants (before 1992)
- ▶ Peripartum transmission

Low Risk (1-5%)

- ▶ Iatrogenic
- ▶ Transmission via sharing personal items
- ▶ Sexual transmission

▶ MMWR, 1998

HCV Life Cycle

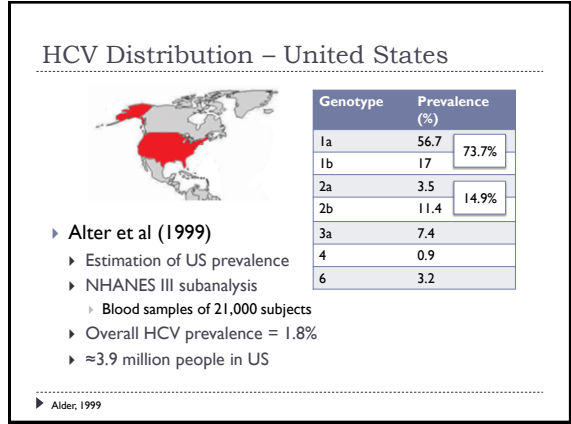
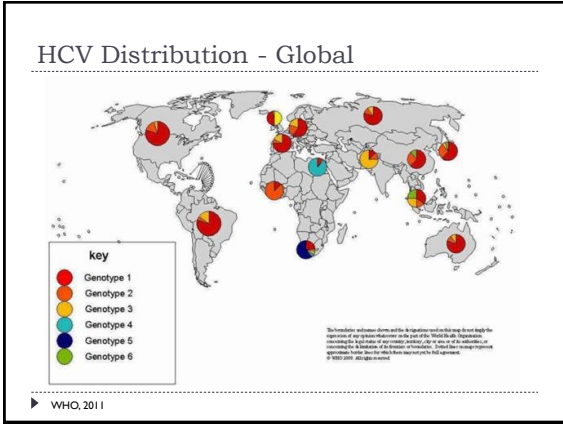


▶ Lindenbach, 2005

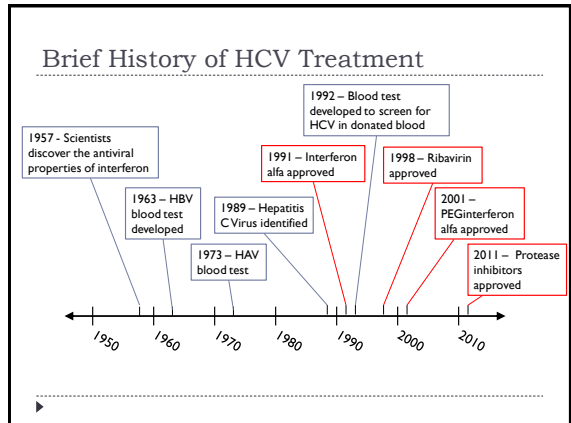
HCV Mutation and Variation

- ▶ Virus does not integrate into the host genome
 - ▶ Host eradication is possible
- ▶ Viral polymerase lacks "proofreading" ability
 - ▶ Enables frequent genome mutations
 - ▶ Drug resistance?
 - ▶ Immune evasion?
- ▶ Genotypes
 - ▶ Major type (1, 2, 3...)
 - ▶ 7 major types
 - ▶ 7a discovered in 2011
 - ▶ Subtypes (1a, 1b, 2a, 4c...)
 - ▶ 11 subtypes

▶ Nakano, 2012



HCV Clinical Disease and Treatment



Laboratory Testing

Test Type	Specific Assays	Purpose	Clinical Use
Serologic	• Enzyme Immunoassays (EIA, ELISA)	Detects anti-HCV antibody	Diagnosis
Molecular	• Polymerase Chain Reaction (PCR) • RT-PCR ("real time" PCR)	Quantifies viral nucleic acid	Measuring "viral load" and treatment response
Genotyping	• Gene sequencing	Identifies HCV gene sequence	Epidemiologic studies and selection of drug regimen

▶ D'Prez, 2011

- ### Acute versus Chronic HCV
- ▶ **Acute HCV**
 - ▶ Period from inoculation → seroconversion + eradication
 - ▶ <6 months
 - ▶ Presentation
 - ▶ RNA levels rise (>2 weeks)
 - ▶ Elevated serum ALT (4-12 weeks)
 - ▶ Non-specific symptoms (5-12 weeks)
 - ▶ Development of anti-HCV antibodies (~8 weeks)
 - ▶ **Chronic HCV**
 - ▶ Persistently detectable HCV RNA for 6 months or more
 - ▶ ± HCV antibodies
 - ▶ Clinical presentation
 - ▶ Variable, often asymptomatic
 - ▶ HCV RNA, ALT levels, hepatomegaly, and physical symptoms fluctuate

Predictors of Treatment Response

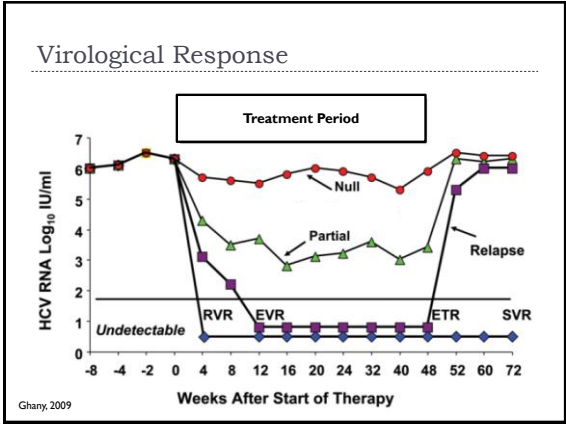
Major predictors

- ▶ Viral genotype
 - ▶ Non-type 1
- ▶ Pretreatment viral load
 - ▶ Viral load <600,000 IU/mL

Minor predictors

- ▶ High dose PegIFN
- ▶ High dose ribavirin (>10.6 mg/kg)
- ▶ Female gender
- ▶ Age <40 years
- ▶ Non-African-American race
- ▶ Body weight <75 kg
- ▶ Elevated ALT (<3x ULN)
- ▶ Absence of liver fibrosis or cirrhosis
- ▶ Absence of impaired fasting glucose

▶ Romero-Gomez, 2005 Hadziyannis, 2004



Virological Response

Response Type	Definition	Time Point
Rapid virological response (RVR)	HCV RNA negative	at treatment week 4
Early virological response (EVR)	Partial : >2 log reduction in HCV RNA level compared to baseline Complete: HCV RNA negative	at treatment week 12
End-of-treatment response (ETR)	HCV RNA negative	at the end of 24 or 48 weeks of treatment
Sustained virological response (SVR)	HCV RNA negative	24 weeks after cessation of treatment
Breakthrough	Reappearance of HCV RNA in serum	while still on therapy
Relapse	Reappearance of HCV RNA in serum	after therapy is discontinued
Non-response	Failure to clear HCV RNA from serum	after 24 weeks of therapy
Null response	Failure to decrease HCV RNA by >2 logs	after 24 week of therapy
Partial response	Two log decrease in HCV RNA but still HCV RNA positive	at week 24

Ribavirin (Rabetaol®, generic)

- ▶ **Mechanism poorly understood**
 - ▶ In vivo, phosphorylated to mono-, di-, and triphosphate metabolites
- ▶ **Proposed mechanism(s) of action**
 1. Inhibits inosine monophosphate dehydrogenase
 - ▶ Decreases cellular guanosine triphosphate (GTP)
 2. RNA virus mutagen
 - ▶ Increases rate of RNA virus mutation → "error catastrophe"
 3. Increases production of immunomodulators
 - ▶ Interleukin (IL)-2
 - ▶ Tumor necrosis factor-alpha (TNF-alpha)
 - ▶ Interferon-gamma (IFN γ)

Ribavirin

Inosine

▶ Phelps, 1995 Crozy, 2001 Tam, 1999

Ribavirin Dosing

- ▶ **Dosing Rules**
 - ▶ "Low" dose
 - ▶ 800 mg daily
 - ▶ Weight based dosing
 - ▶ 65-85 kg – 1,000 mg daily
 - ▶ 85-105 kg – 1,200 mg daily
 - ▶ >105 kg but <125 kg – 1,400 mg daily
- ▶ **Formulations**
 - ▶ Capsules (Rebetol®, Ribasphere®)
 - ▶ Tablets (Copegus®)
 - ▶ Take with food

▶ Rebetol, 2011

Interferon alfa

- ▶ **Endogenous protein**
 - ▶ Secreted by leukocytes upon viral infection
- ▶ **MOA**
 1. Encourages leukocyte cell differentiation
 2. Upregulates production of antiviral molecules
 - ▶ 2'-5'-oligoadenylate synthetase
 - ▶ Protein kinase
 3. Inhibits viral penetration and uncoating, viral assembly

▶ Taniguchi, 2001

Interferon alfa-2 Formulations

Peginterferon alfa-2b

- ▶ Peg-Intron®
- ▶ 12-kd linear polyethylene glycol (PEG)
 - ▶ Linked to IFN alfa-2b
- ▶ Weight-based dose
 - ▶ 1.5 mcg/kg/week SubQ + ribavirin

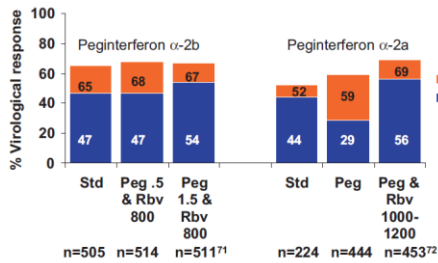
Peginterferon alfa-2a

- ▶ Pegasys®
- ▶ 40-kd branched PEG
 - ▶ Linked to IFN alfa-2a
- ▶ Fixed dose
 - ▶ 180 mcg/week SubQ + ribavirin

PegIFN alfa-2 Landmark Trials

	Manns et al. (2001)	Fried et al. (2002)
Drug	PegIFN alfa-2b (Peg-Intron)	PegIFN alfa-2a (Pegasys)
Design	Randomized, active comparator, open-label	Randomized, placebo-controlled, open-label
Subjects	1530 treatment-naïve subjects	1121 treatment-naïve subjects
Duration	48 weeks	48 weeks
Primary Endpoint	Sustained virologic response (SVR)	Sustained virologic response (SVR)
Assignment	Arm 1: IFN alfa-2b + ribavirin Arm 2: PegIFN alfa-2b 1.5 mcg/kg/week ribavirin Arm 3: PegIFN alfa-2b 1.5 mcg/kg/week for 4 weeks then 0.5 mcg/kg/week plus ribavirin	Arm 1: PegIFN alfa-2a 180 µg/week plus ribavirin Arm 2: PegIFN alfa-2a plus placebo Arm 3: IFN alfa-2b + ribavirin

Efficacy Summary



▶ Ghany, 2009

Adverse Reactions

PegIFN alfa-2a

- ▶ Myelosuppression (17-20%)
 - ▶ Thrombocytopenia
 - ▶ Neutropenia
 - ▶ Anemia
- ▶ Depression (~30%)
- ▶ Immunomodulatory (30-50%)
 - ▶ Fatigue
 - ▶ Fever
 - ▶ Headache
 - ▶ Nausea
 - ▶ Anorexia
 - ▶ Rigors
 - ▶ Myalgia
 - ▶ Insomnia

Ribavirin

- ▶ Hemolytic anemia (10-20%)
 - ▶ Elevated bilirubin and uric acid
- ▶ Hepatic decompensation (1-4%)

▶ Clinical Pharmacology, 2012

PegIFN alfa-2a versus PegIFN alfa-2b

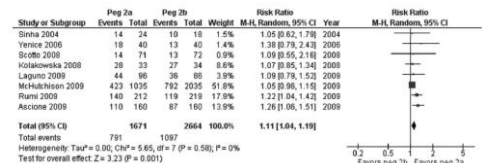
Peginterferon alpha-2a Is Associated with Higher Sustained Virological Response than Peginterferon alfa-2b in Chronic Hepatitis C: Systematic Review of Randomized Trials

Tahany Awad,¹ Kristian Thorland,¹ Goran Hanser,¹ Davor Simic,² Mahasen Mahrouk,² and Christian Glud²
 HEPATOLOGY, Vol. 51, No. 4, 2010

- ▶ Systematic review of head-to-head randomized trials
- ▶ 12 randomized trials
 - ▶ Efficacy/SVR (8 trials)
 - ▶ Mortality (1 trial)
 - ▶ Adverse reactions (11 trials)
- ▶ 5,008 patients

▶ Awad, 2010

PegIFN alfa-2a vs. alfa-2b – SVR



▶ PegIFN alfa-2b 41% vs. PegIFN alfa-2a 47%

▶ RRR = 1.11 (95% CI, 1.04-1.19)
 ▶ NNT = 16.2

▶ P < 0.04

PegIFN alfa-2a vs alfa-2b - Safety

Study or Subgroup	Peg 2a		Peg 2b		Risk Ratio		Year	Risk Ratio	
	Events	Total	Events	Total	M, Random, 95% CI	M, Random, 95% CI		N, Random, 95% CI	
Enzo 2004	0	10	0	10	Not estimable	2004			
Orin 2004	0	24	1	18	0.25 [0.01, 5.08]	2004			
Reval 2005	3	116	3	121	1.04 [0.21, 5.08]	2005			
Venice 2008	3	40	3	40	0.28 [0.01, 4.68]	2008			
Siva 2008	2	10	4	10	0.30 [0.02, 2.40]	2008			
Di Biase 2007	2	199	11	191	0.18 [0.04, 0.82]	2007			
Scott 2008	19	71	9	72	1.27 [0.53, 3.02]	2008			
McHutchison 2009	135	1035	227	2035	1.17 [0.86, 1.62]	2009			
Ramzi 2009	16	212	17	219	0.97 [0.62, 1.67]	2009			
Lapina 2009	12	86	7	86	1.04 [0.43, 2.12]	2009			
Aschone 2009	4	180	22	180	0.18 [0.06, 0.52]	2009			
Total (95% CI)	1971	2979	100.0%	2979	0.79 [0.51, 1.23]				
Total events	187	303							
Heterogeneity: Tau ² = 0.21; I ² = 19.7%; H ² = 8 (P = 0.02); P = 95%									
Test for overall effect: Z = 1.64 (P = 0.30)									

▶ **PegIFN alfa-2b 9.5%** vs. **PegIFN alfa-2a 10.2%**

▶ **RRR = 0.79 (95% CI, 0.51-1.23)**
▶ **NNT = 16.2**

▶ **P < 0.3**

PegIFN alfa-2a vs. alfa-2b - Summary

▶ Results

- ▶ PegIFN alfa-2a (Pegasys) had significant improvement in SVR
- ▶ PegIFN alfa-2b (Peg-Intron) had numeric improvement in safety

▶ Concerns/Weaknesses

- ▶ Multiple genotypes included
 - ▶ Genotype 1 (6 trials)
 - ▶ Genotype 2 and 3 (5 trials)
- ▶ Ribavirin dose varied across studies
- ▶ Heterogeneity of studies
- ▶ All adverse events deemed equivalent

Summary of 2009 AASLD Guidelines

- ▶ **PegIFN alfa-2 + ribavirin >> IFN alfa-2 + ribavirin**
 - ▶ **EVR = 63-69%**
 - ▶ **SVR = ~55%**
- ▶ **No preference of PegIFN alfa-2a versus PegIFN alfa-2b**
 - ▶ Meta-analysis from 2010 shows SVR benefit of PegIFN alfa-2a
 - ▶ No mortality benefit of either agent*
- ▶ **Doses and duration of therapy based upon genotype**

▶ Ghany, 2009

*McHutchison, 2009

Summary of 2009 AASLD Guidelines

- ▶ **Genotype 1**
 - ▶ PegIFN alfa-2a/b
 - ▶ Weight-based ribavirin (1000-1200 mg daily)
- ▶ **Genotype 2/3**
 - ▶ PegIFN alfa-2a/b
 - ▶ Fixed-dose ribavirin (800 mg daily)
 - ▶ Duration: 24 weeks
- ▶ **Genotype 4**
 - ▶ PegIFN alfa-2a/b
 - ▶ Weight-based ribavirin
 - ▶ Duration: 48 weeks
- ▶ **Genotype 5/6**
 - ▶ Poor level of evidence to support dosing recommendations

▶ Ghany, 2009

Khuroo, 2004

Case Study - Part 2

- ▶ **HC starts treatment (November 2009)**
 - ▶ PegIFN alfa-2a (Pegasys®) 180 mcg/week
 - ▶ Ribavirin 400 mg twice daily (fixed dose)
- ▶ **Treatment course**
 - ▶ Partial response at week 12
 - ▶ HCV RNA: 1,783,028 (baseline) → 20,345 (~3 log decrease)
 - ▶ Complete response by week 16
 - ▶ Sustained through week 48
 - ▶ Significant adverse reactions on weeks 32-48
 - ▶ Malaise
 - ▶ Depression
 - Fluoxetine 20 mg daily
- ▶ **Treatment complete (October 2010)**
 - ▶ Relapse 10 weeks after treatment (January 2011)

Case Study - Part 2

- ▶ **Did HC receive appropriate therapy?**
 - ▶ Medications?
 - ▶ Length of therapy?
- ▶ **Did HC attain:**
 - ▶ Rapid virological response (RVR)?
 - ▶ Early virological response (EVR)?
 - ▶ End of treatment response (ETR)?
 - ▶ Sustained virological response?

ADVANCE – Adverse Events

- ▶ **Common ADRs**
 - ▶ Nausea, diarrhea, pruritus, and rash were >10% higher rates of rash for telaprevir groups
 - ▶ 5-7% of the subjects taking telaprevir discontinued treatment due to rash
- ▶ **Hematologic**
 - ▶ Any grade anemia
 - ▶ 37-39% in telaprevir group versus 19% in placebo group
 - ▶ Use of ESAs not reported

ADVANCE - Conclusions

- ▶ Telaprevir-containing regimens compared to PegIFN + ribavirin alone showed significant increase in SVR rates
 - ▶ Telaprevir regimens were statistically significant
 - ▶ Numerically improved SVR rates for patients treated with telaprevir for 12 weeks versus 8 weeks
- ▶ Common adverse events included nausea, diarrhea, pruritus, rash, and anemia

Boceprevir – SPRINT-2 Trial

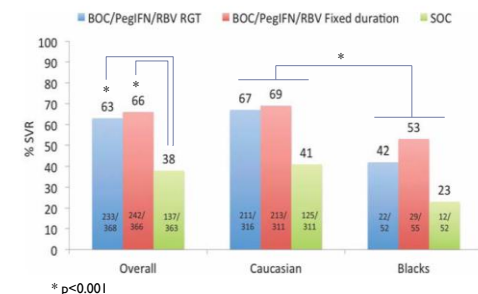


Boceprevir for Untreated Chronic HCV Genotype 1 Infection

Fred Poordad, M.D.; Jonathan McCone, Jr., M.D.; Bruce S. Brozon, M.D.; Steven Brant, M.D.; Michael P. Mann, M.D.; Mark S. Sulkowski, M.D.; Ira M. Jacobson, M.D.; K. Rajender Reddy, M.D.; Zachary D. Conrad, M.D.; Ph.D.; Randolph Shuper, M.D.; Mark J. Lofgren, M.D.; Steven Sanderson, M.D.

Study design	Randomized, double-blind, placebo-controlled trial
Subjects	938 nonblack and 159 black treatment-naïve subjects with genotype 1 chronic HCV
Duration	44 weeks
Assignment	Four week lead-in with PegIFN + ribavirin Arm 1: PegIFN + ribavirin + placebo Arm 2: PegIFN + ribavirin + boceprevir for 44 weeks Arm 3: PegIFN + ribavirin + boceprevir for 24 weeks (plus 20 additional weeks if partial response)
Primary Endpoint	Sustained virologic response

SPRINT-2 – Overall Efficacy



SPRINT-2 – Adverse Events

- ▶ **Grade 3 neutropenia (500 to <750 per mm³)**
 - ▶ 25% boceprevir vs 14% placebo (p<0.001)
 - ▶ G-CSF use significantly higher in boceprevir groups
- ▶ **Any grade anemia (Hgb <11 mg/dL)**
 - ▶ 49% boceprevir vs 29% placebo (p<0.001)
 - ▶ Erythropoietin use significantly higher in boceprevir groups (p<0.001)
- ▶ **Symptomatic**
 - ▶ Dysgeusia, headache

SPRINT-2 - Conclusions

- ▶ Boceprevir added to standard regimen significantly improved SVR among HCV treatment-naïve patients
 - ▶ **Genotype 1**
 - ▶ Overall absolute SVR = 63-66% for boceprevir groups
 - ▶ ~70% improvement in SVR rates versus standard therapy
- ▶ Further study is warranted to define optimal therapy
 - ▶ No clear advantage of fixed versus response-guided duration
- ▶ Boceprevir associated with increased rates of anemia and neutropenia
 - ▶ Subjects treated with boceprevir utilized G-CSF and erythropoietin more frequently

RESPOND-2

ORIGINAL ARTICLE
N ENGL J MED 364:175-182, 2011

Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection

Bruce R. Bacon, M.D., Stuart C. Gordon, M.D., Eric Lawitz, M.D., Patrick Marcellin, M.D., John M. Vesting, M.D., Stefan Zeuzem, M.D., Fred Poordad, M.D., Zachary D. Goodman, M.D., Ph.D., Heather L. Singer, Ph.D., Hridayesh Bhatnagar, M.S., Margaret Burroughs, M.D., Clifford A. Brass, M.D., Ph.D., Janice K. Albrecht, Ph.D., and Rafael Esteban, M.D.

Study design	Randomized, double-blind, placebo-controlled trial
Subjects	403 previously-treated subjects with genotype 1 chronic HCV
Duration	44 weeks
Assignment	Four week lead-in with PegIFN + ribavirin Arm 1: PegIFN + ribavirin + placebo for 44 weeks Arm 2: PegIFN + ribavirin + boceprevir for 36 weeks (plus 12 additional weeks if partial response at week 8-12) Arm 3: PegIFN + ribavirin + boceprevir for 44 weeks
Primary Endpoint	Sustained virologic response

RESPOND-2 Efficacy

Subgroup	Group 1 no. with sustained virologic response/total no. (%)	Group 2	Group 3	Odds Ratio (95% CI)
All patients	17/80 (21)	95/162 (59)	107/161 (66)	10.7 (6.3-18.1)

- SVR
 - Arm 1 (placebo) – 21%
 - Arm 2 (response-guided) – 59%
 - Arm 3 (fixed duration) – 66%
- Statistical analysis
 - Placebo versus fixed dose OR=10.7 (p < 0.001)
 - Placebo versus response-guided therapy, OR=7.3

Bacon, 2011

AASLD Dosing Recommendations

- Genotypes 2-6 (Dual-therapy)
 - Use previous dosing recommendations
- Genotype 1 (Triple-therapy)
 - Boceprevir
 - Boceprevir 800 mg TID
 - PegIFN alfa + weight-based ribavirin
 - Duration: 24-44 weeks
 - 4 weeks of lead-in treatment PegIFN alfa + ribavirin alone
 - Telaprevir
 - Telaprevir 750 mg TID
 - PegIFN alfa + weight-based ribavirin
 - Duration: 12 weeks
 - Followed by an additional 12-36 weeks of PegIFN alfa + ribavirin

Ghany, 2011

Case Study – Part 3

- At recent primary care visit (December 2011):
 - HCV RNA = 1,698,185
 - Liver fibrosis = moderate
- Interested in restarting therapy for Hepatitis C
- Recently heard about new medications on evening news
 - Asks about new “pills” to treat HCV
 - Heard from a friend that these can be taken without IFN and ribavirin

Case Study – Part 3

- Is HC an appropriate candidate for protease inhibitors?
- What information do you provide HC about HCV PI?

Protease Inhibitor Administration

Telaprevir

- Two tablets (750 mg) TID
- Take with food
 - 20 grams of fat
 - Bagel with cream cheese
 - Peanut butter (3 Tbsp)
 - Ice cream (1 cup)
 - Cheese (2 oz)
 - Potato chips (2 oz)

Boceprevir

- Four capsules (800 mg) TID
- Take with food
 - Light snack

Inckev, 2011 Victrelis, 2011

Protease Inhibitor ADRs

- ▶ **Boceprevir**
 - ▶ Clinical Trials
 - ▶ Anemia and dysgeusia most common
 - ▶ Neutropenia
 - ▶ Increased use of colony stimulating factors (G-CSF, EPO)
- ▶ **Telaprevir**
 - ▶ Clinical Trials
 - ▶ Most common ADRs were symptomatic
 - ▶ Nausea, diarrhea, pruritus, rash, and anemia
 - ▶ Post-marketing and clinical experience
 - ▶ Anal and rectal burning/itching

Drug interactions

- ▶ **Boceprevir/Telaprevir**
 - ▶ Potent inhibitor of CYP3A4/5
 - ▶ Inhibitor of P-glycoprotein
 - ▶ Triazoles, sirolimus, tacrolimus
- ▶ **PegIFN alfa-2**
 - ▶ CYP2D6, CYP2C8/9 inhibitors
 - ▶ Effect uncertain – use with caution
 - ▶ Caution when used with HAART
 - ▶ Decreases clearance of HIV NRTIs and NNRTIs
 - ▶ Increases liver toxicity with HIV protease inhibitors
 - ▶ Increases methadone AUC
- ▶ **Ribavirin**
 - ▶ Increases didanosine concentration → acute liver decompensation

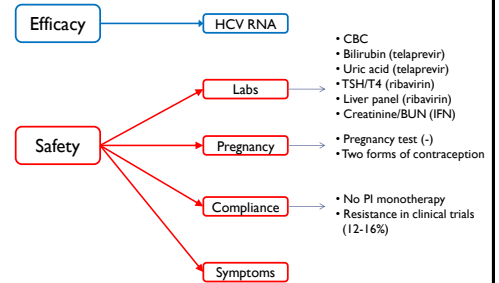
▶ Clinical Pharmacology, 2012

Pregnancy and Lactation

Drug	Effect on Fetus	Pregnancy Category	Secreted in breast milk?
Interferon alfa-2	Abortifacive	X	Unknown
Ribavirin	<ul style="list-style-type: none"> • Significant teratogenic effects in animal models** • Ribavirin Pregnancy Registry 	X	Unknown
Boceprevir Telaprevir	<ul style="list-style-type: none"> • No known fetal harm in pre-clinical trials (rat/mouse) • No controlled studies in pregnant women 	B	Unknown
Telaprevir	<ul style="list-style-type: none"> • Minor decrease in fertility associated with testicular toxicity 	B	Unknown

**Two reliable forms of contraception must be used by both male and female partners

Monitoring



Protease Inhibitor Costs

- | | |
|---|--|
| <p>Boceprevir</p> <ul style="list-style-type: none"> ▶ 84 capsules/week ▶ 24-44 week course of therapy ▶ \$14/capsule ▶ Course of therapy: \$28,600-\$52,400 | <p>Telaprevir</p> <ul style="list-style-type: none"> ▶ 42 tablets/week ▶ 12 weeks of telaprevir ▶ Course of therapy: \$49,200 ▶ Price set by manufacturer |
|---|--|

▶ <http://www.drugstore.com>

Conclusions

- ▶ PegIFN + ribavirin form the “core” of HCV treatment
 - ▶ Effective in all HCV genotypes
 - ▶ Products not bioequivalent
- ▶ Serine protease inhibitors improve SVR in HCV genotype I
 - ▶ telaprevir – treatment-naïve
 - ▶ boceprevir – treatment-naïve or previously treated
- ▶ Significant adverse reactions + extended length of therapy
 - ▶ Difficult course of therapy
 - ▶ High discontinuation of therapy

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