Hepatitis C: Diagnosis and Natural History

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Risk Factors

Prevalence

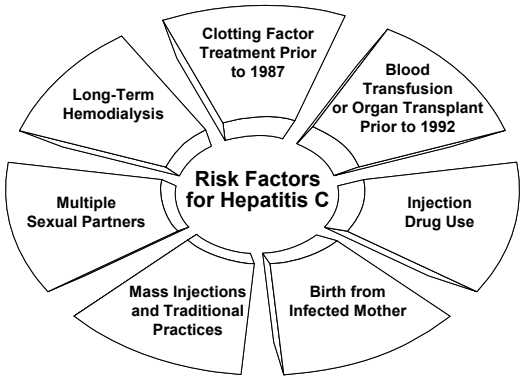
Worldwide 170 million (3%)

United States

Anti-HCV positive 3.9 million(1.8%)

HCV RNA positive 2.7 million(1.4%)

Alter MJ et al., New Engl J Med 1999; 341:556
Lavanchy D & McMahon B, In: Liang TJ & Hoofnagle JH (eds.) Hepatitis C. New York: Academic Press, 2000:185



Current Likelihood of Transmission

- Transfusion ~ 1 in 1,000,000
- Heterosexual partner ~1 in 1,000 per yr
- Needlestick injury
  - HCV-positive source ~ 5%
  - HCV status unknown ~ 1%
- Maternal-Infant
  - Mother HIV-negative ~ 5%
  - Mother HIV-positive 15 - 20%

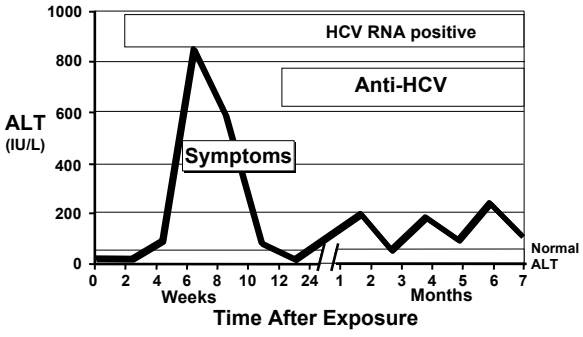
Terrault NA, Hepatology 2002 ;36(Suppl 1):S99
Roberts EA, Yeung L. Hepatology 2002 ;36(Suppl 1):S106

Diagnostic Tests

- Hepatitis C antibody tests
- Qualitative HCV RNA tests
- Quantitative HCV RNA tests
- Genotyping
- Liver biopsy

Diagnosis and Evaluation

Acute Hepatitis C Infection



Hoofnagle JH, Hepatology 1997; 26:15S

Antibody tests for hepatitis C

- Indicates past or present infection
- Inexpensive, sensitive and specific
- Poor positive predictive value in low prevalence populations
- Low sensitivity in immunosuppressed patients

HCV Genotypes

- Six major genotypes found throughout the world
- Major determinant of response to antiviral therapy
- In Europe and U.S., 60-70% of patients have genotype 1 infection

Qualitative tests for HCV RNA

- Confirms diagnosis of HCV infection
- Useful in the early diagnosis of acute hepatitis C
- Demonstrates the presence of active infection
- "Gold standard" for documenting response to treatment

Virological Tests Do Not Predict Natural History of Disease

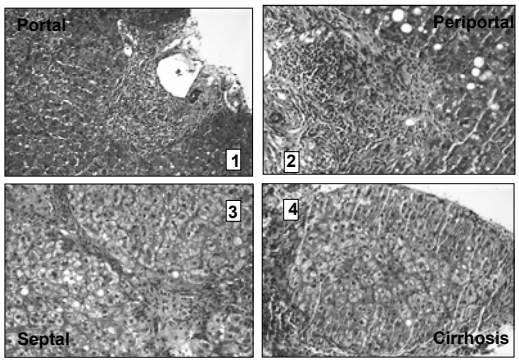
- No correlation between genotype and progression of disease
- No correlation between HCV RNA level and progression of disease

Liver Biopsy

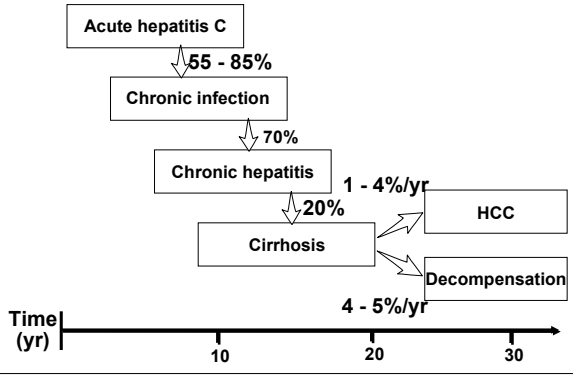
- Degree of fibrosis is most important predictor of prognosis
- Useful in determining need for anti-viral therapy
- Advanced cirrhosis associated with reduced response to treatment

Natural History

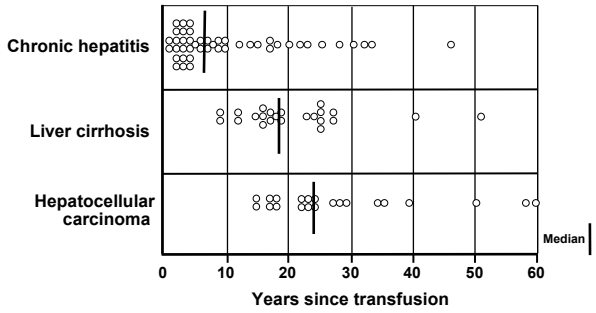
Stages of Fibrosis In Chronic Hepatitis



Outcome Following Hepatitis C Infection

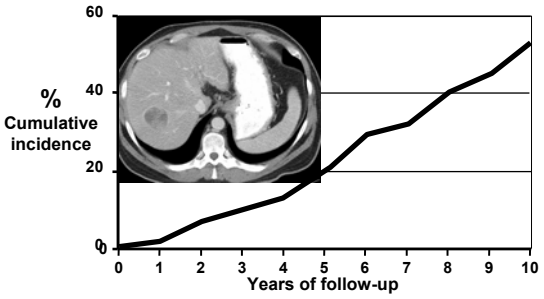


Stage of Disease Correlates With Duration of Infection



Kiyosawa K, et al., Hepatology 1990; 12:671

Hepatocellular Carcinoma
Incidence in HCV-Positive Cirrhosis



Adapted from Ikeda K et al, Hepatology 1993;18:47

Outlook for Those With Compensated Cirrhosis

	Study A	Study B	Study C
Number	**384**	**112**	**103**
Follow-up (yr)	**5.0**	**4.5**	**3.3**
Decompensation (%/yr)	**3.9**	**4.4**	**5.0**
HCC (%/yr)	**1.4**	**2.3**	**3.3**
5-Year Survival (%)	**91**	**83**	**84**
Post decompensation (%)	**50**	**51**	**--**

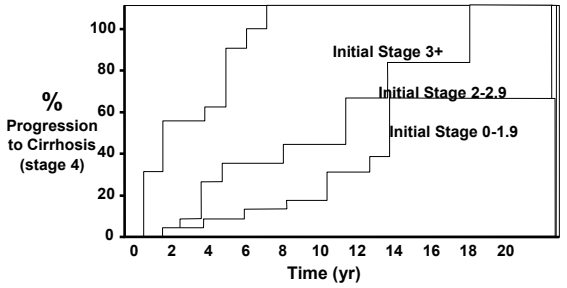
A: Fattovich G et al. Gastroenterology 1997;112:463
B: Hu K & Tong MJ. Hepatology 1999;29:1311
C: Serfaty L et al. Hepatology 1998;27:1435

Factors Associated With Fibrosis

- **Duration of infection**
- **Alcohol > 50 gm per day**
- **Age > 40 years at infection**
- **Male gender**

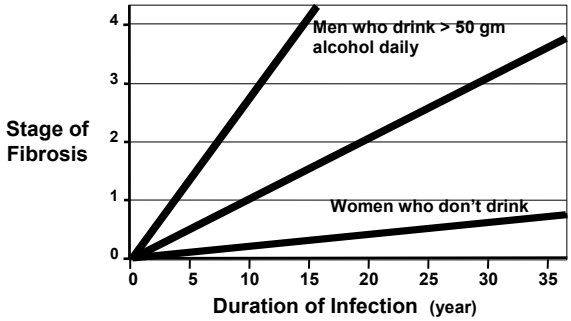
Poynard T, et al., Lancet 1997; 349:825

Progression to Cirrhosis Can Be Estimated From Initial Stage of Liver Biopsy Fibrosis



Yano M, et. al., Hepatology 1996; 23:1334

Fibrosis Rate Varies Among HCV-Infected Individuals

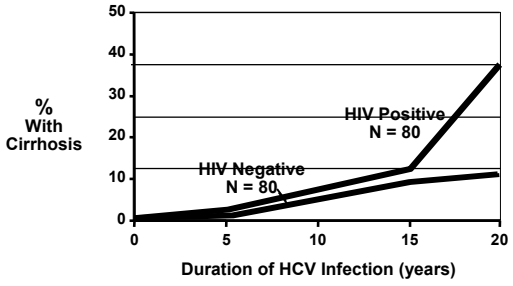


Fibrosis Risk Varies Among Individuals

	Patient A	Patient B
Age at infection	25	42
Alcohol use	Seldom	3-4 drinks/day
Sex	Female	Male
Fibrosis stage/yr	0.10	0.25
Years to cirrhosis	40	16

Poynard T, et al., Lancet 1997; 349:825

HIV Co-Infection May Accelerate Progression to Cirrhosis

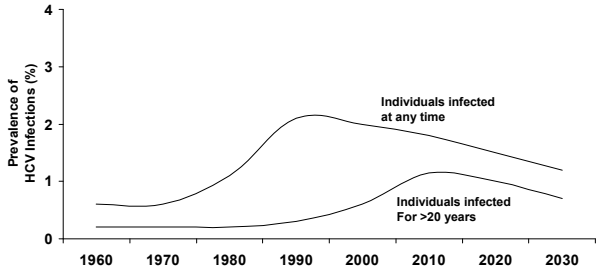


Adapted from Di Martino V et al. Hepatology 2001;34:1193

Should we treat Hepatitis C?

- **HCV is the only chronic virus infection that can be eradicated (cured) by antiviral therapy.**
- **Cure of infection (SVR) essentially eliminates risk of decompensation in patients with cirrhosis and dramatically reduces risk of HCC.**

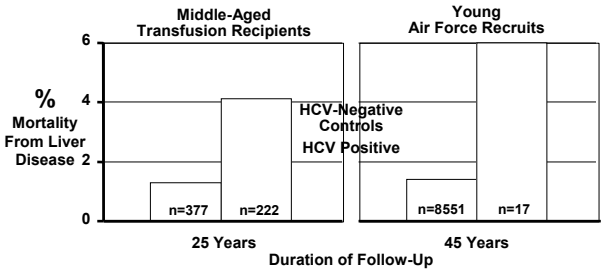
Future Prevalence of HCV



Davis, et al. Liver Transplantation 2003.

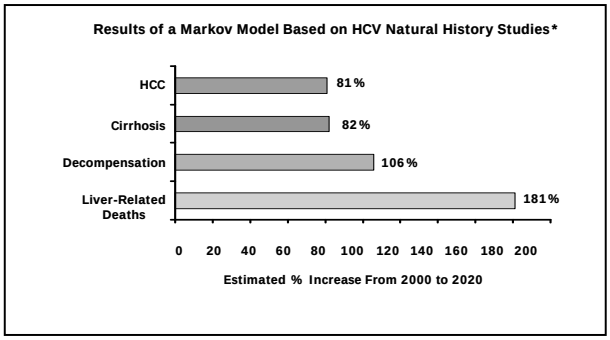
Armstrong GL et al. Hepatology 2000; 31:777-782

Liver-Related Mortality in Chronic Infection



Seeff LB et al, Ann Intern Med 2000; 132:105
Seeff LB et al, Hepatology 2001;33:455

HCV Related Complications Expected to Increase Greatly in the Coming Years



*Assumes no HCV treatment.
Davis GL, et al. *Liver Transpl.* 2003;9:331-338.

Pre-treatment evaluation

Mental Health Evaluation

- **Psychopathology (e.g., substance abuse, depression, anxiety) is prominent in individuals with chronic HCV**
- **Pegylated IFN, with or without ribavirin, is associated with depression rates of 20%-34%**
- **IFN-α and ribavirin can worsen and/or induce depression and other underlying psychiatric conditions**

→ Patients should be screened and have any pre-existing psychiatric conditions treated before initiating HCV treatment

1. Asnis GM, De La Garza R II. *J Clin Gastroenterol.* 2006;40:322-335. 2. Rifai MA, et al. *Curr Treat Options Gastroenterol.* 2006;9:508-519.

Current Practice

HCV viral load
Anti-HAV
HBsAg
TSH
ALT
CBC

Hepatitis A/ B immunizations
AFP
+/- US, EGD

Liver Biopsy

Patient referral
Counseling and review
- **Natural history of HCV**
- **Treatment options**
- **Adverse effects of Rx**
- **Expected benefits of Rx**
- **Duration of treatment**

Mental Health Evaluation
Consent to treat
Specialist review as appropriate
(ID, optho, card etc)

Treatment with regular follow-up visits

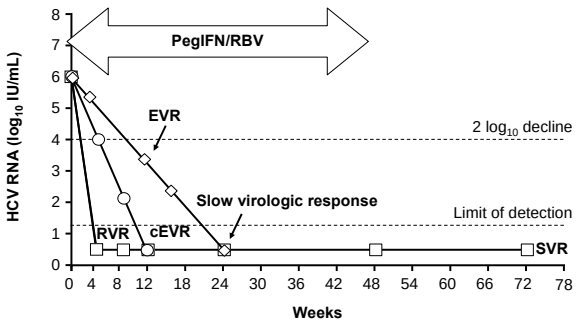
Predictors of Response to Antiviral Therapy in Chronic Hepatitis C

- **Genotype 1 and 4 are less responsive than other genotypes**
- **High viral load is less responsive**
- **Advanced fibrosis is less responsive**

Hepatitis C Current and Future Treatment

Maher Azzouz,MD
Associate Professor of Medicine
Director of Endoscopy
Division of Gastroenterolgy Hepatolgy and Nutrition
The Comprehensive Transplant Center
The Ohio State University

Virologic Responses

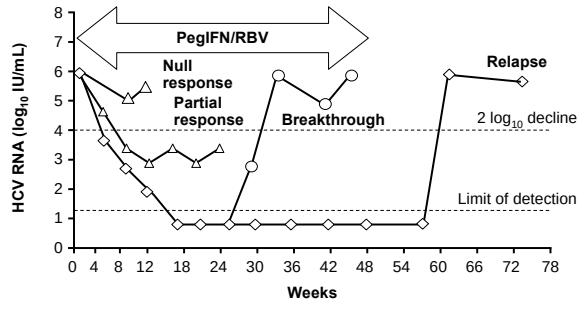


Goals of HCV Therapy

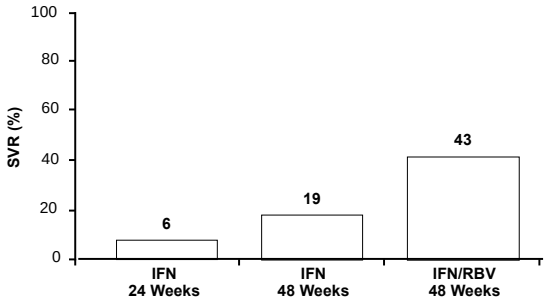
- **Primary goal: eradicate the virus**
- **Secondary goals**
  - ✓ **Slow disease progression**
  - ✓ **Minimize risk of HCC**
  - ✓ **Improve liver histology**
  - ✓ **Enhance quality of life**
  - ✓ **Prevent transmission of virus**
  - ✓ **Reduce extrahepatic manifestations**

Lindsay KL. Hepatology. 2002;36(suppl 1):S114-S120.

Suboptimal Virologic Responses



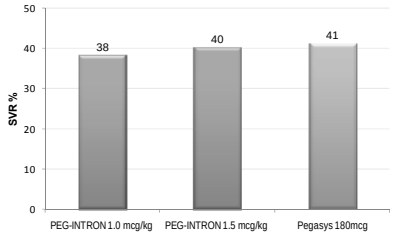
HCV Therapy
SVR/Standard Interferon (IFN)



McHutchison J, et al. N Engl J Med. 1998;339:1485-1492. Poynard T, et al. Lancet. 1998;352: 1426-1432.

IDEAL Trial
Which PegIFN is better

Genotype 1 US Patients

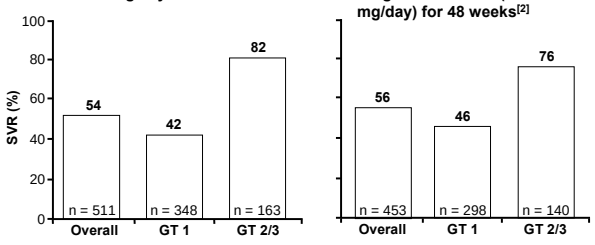


There were no statistical differences between groups

Sulkowski, M., et al. Presented at EASL 2008, Milan, Italy

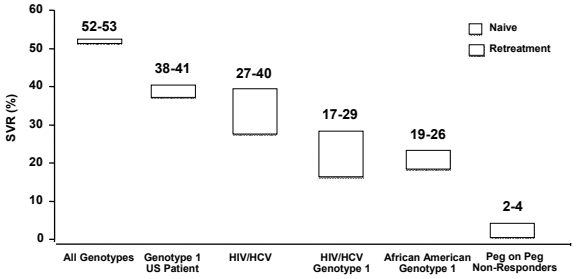
HCV Therapy
SVR With PegIFN/Ribavirin

- **> 50% of GT 1 Patients Do Not Respond**
  - **PegIFN alfa-2b 1.5 µg/kg/week + RBV 800 mg/day for 48 weeks[1]**
  - **PegIFN alfa-2a 180 µg/week + weight-based RBV (1000 or 1200 mg/day) for 48 weeks[2]**



1. Manns M, et al. Lancet. 2001;358:958-965.
2. Fried MW, et al. N Engl J Med. 2002;347:975-982.

Peg-IFN + RBV
Response Rates



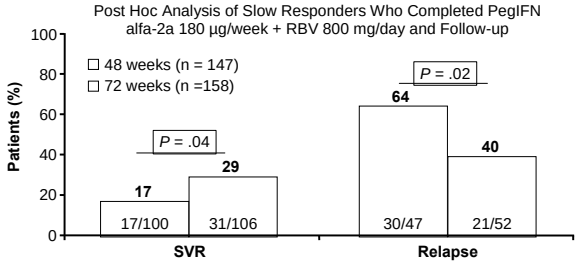
Torriani FJ, et al. *N Engl J Med.* 2004;351:438-450.
Jeffers LJ, et al. *Hepatology.* 2004;39:1702-1708.
Carrat F, et al. *JAMA.* 2004;292:2839-2848.
Muir AJ, et al. *N Engl J Med.* 2004;350:2265-2271.
Fried MW, et al. *N Engl J Med.* 2002;347:975-982.
Manns MP, et al. *Lancet.* 2001;358:958-965.
Poynard T et al. *J Hepatol.* 2005:42(Suppl 2):40-41.:Shiffman M.L., et al. *Gastroenterology* 2004; 126:1015-1023.:Boceprevir Update Press Release; Schering Plough Pharmaceuticals; Kenilworth, NJ: Oct 18, 2007.
Aldhal N, et al. EASL, 2007; NM283 Control Arm Phase 2 Trial Abstract; Barcelona, Spain. McHutchison, J., et al AASLD, 2008; Telaprevir Control Arm Phase 2 Trial, Absract; San Francisco:Schiff,.E., et al. EASL 2008; Boceprevir Control Arm – Phase 2 trial, Milan Italy

HCV Treatment Challenges

- **Difficult-to-Treat HCV Patient**
- **Preventing Relapse**
- **Retreatment Options for Treatment Failure**
- **Maintenance Therapy**
- **Future Options for Treatment**

Longer Duration of Therapy

Longer Therapy in GT 1 Pts Without cEVR but Week 24 Negative HCV RNA

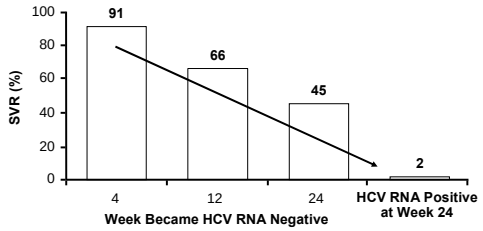


Berg T, et al. Gastroenterology. 2006;130:1086-1097.

Duration of Undetectability

- **Longer Duration of Undetectability on Treatment Increases Chance for SVR**

Retrospective analysis of GT 1 patients receiving 48 weeks of pegIFN alfa-2a + RBV (N = 453)

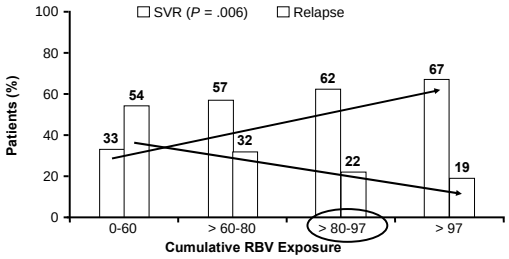


Ferenci P, et al. J Hepatol. 2005;43:425-433.

Ribavirin Dosage/Adherence

- **Higher Ribavirin dose and cumulative dose are associated with increased SVR**

Retrospective analysis of pegIFN alfa-2a/RBV phase III trials

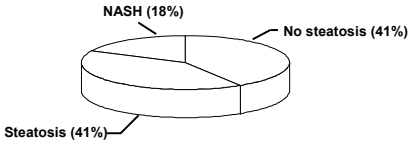


Reddy KR, et al. Clin Gastroenterol Hepatol. 2007;5:124-129.

Steatosis in HCV

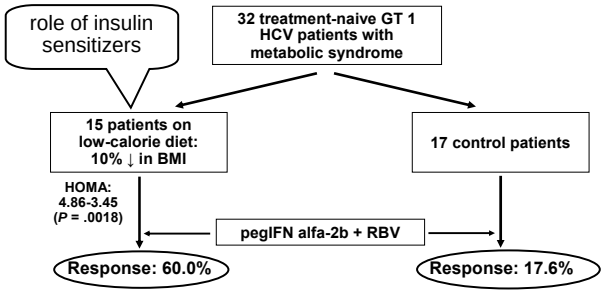
- **Steatosis is a common comorbidity of HCV**
- **Found in 50% to 60% of HCV-infected patients[1,2] vs 14% to 30% in general population[3,4]**

Proportion of Patients With Fatty Liver Disease Among 121 HCV-Infected Individuals With Available Liver Biopsies[1]



1. Younossi ZM, et al. J Clin Gastroenterol. 2004;38:705-709. 2. Asselah T, et al. Gut. 2006;55:123-130. 3. Browning JD, et al. Hepatology. 2004;40:1387-95. 4. Nomura H, et al. Jpn J Med. 1988;27:142-149.

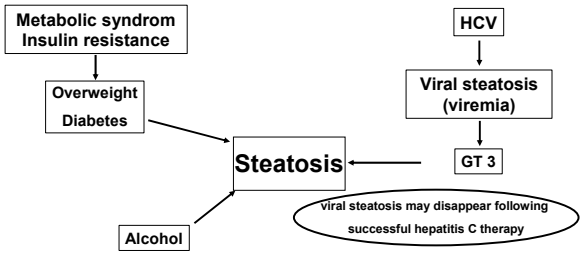
Effect of Weight Loss on Antiviral Response



Tarantino G, et al. Gut. 2006;55:585.

Steatosis in HCV

2 Types of Steatosis in Hepatitis C



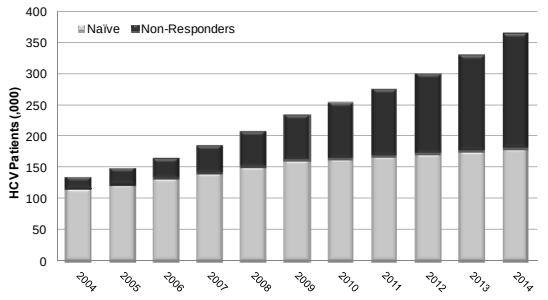
Rubbia-Brandt L, et al. J Hepatol. 2000;33:106-115. Adinolfi LE, et al. Hepatology. 2001;33:1358-1364. Serfaty L, et al. Am J Gastroenterol. 2002;97:1807-1812. Monto A, et al. Hepatology. 2002;36:729-736. Poynard T, et al. Hepatology. 2003;38:75-85.

HCV Treatment: Key Predictors of Response

1995-2000	Current
• GT 2 or 3 • Absence of fibrosis • Low HCV RNA • Younger age • Female sex • Weight	• Lack of steatosis • Adherence • Early response • RBV dosage • Race •Co-infection

Manns MP, et al. Lancet. 2001;358:958-965.
Fried MW, et al. N Engl J Med. 2002;347:975-982.
Muir AJ, et al. N Engl J Med. 2004;350:2265-2271.
Conjeevaram HS, et al. Gastroenterology. 2006;131:470-477.

HCV Patient Projections



Decision Resources Hepatitis C Report & Interactive Forecast Tool 2005.

HCV Retreatment

Outcome in Nonresponders to IFN-Based Therapy

Study	Treatment	GT	N (Previous Treatment)	SVR Rate (Previous Treatment)
Jacobson[1]	**PegIFN alfa-2b + RBV x 48 weeks**	**1 (89%) 2/3 (9%)**	**47 (IFN) 219 (IFN/RBV)**	21% (IFN) 8% (IFN/RBV)
Sherman[2]	**PegIFN alfa-2a + RBV x 48 weeks**	**1**	**36 (IFN) 148 (IFN/RBV)**	22% (IFN) 20% (IFN/RBV)
		2/3	**9 (IFN) 19 (IFN/RBV)**	44% (IFN) 37% (IFN/RBV)
RENEW[3]	**PegIFN alfa-2b 1.5 or 3.0 µg/kg/week + RBV**	**1 (91%)**	**704 (IFN/RBV)**	12% 17%
HALT-C[4]	**PegIFN alfa-2a + RBV x 48 weeks**	**All**	**604**	18%
EPIC3[5]	**PegIFN alfa-2b + RBV x 48 weeks**	**1 (81%) 2/3 (15%)**	**903**	18%

1. Jacobson IM, et al. Am J Gastroenterol. 2005;100:2453-2462.
2. Sherman M, et al. Gut. 2006;55:1631-1638.
3. Gross J, et al. AASLD 2005. Abstract 60.
4. Shiffman ML, et al. Gastroenterology. 2004;126:1015-1023.
5. Poynard T, et al. EASL 2008. Abstract 988.

HCV Retreatment

HCV Retreatment

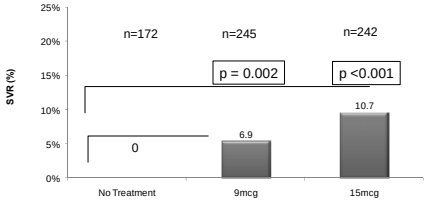
Outcomes in Nonresponders to PegIFN/RBV

Study	Treatment	GT	N (Previous Treatment)	SVR Rate (Previous Treatment)
REPEAT[1]	**PegIFN alfa-2a + RBV x 48 weeks**	**1 (> 90%)**	**473**	8%
	PegIFN alfa-2a + RBV x 72 weeks	**1 (> 90%)**	**469**	16%
EPIC3[2]	**PegIFN alfa-2b + RBV x 48 weeks**	**1 (81%) 2/3 (15%)**	**196 (PegIFN alfa-2a) 280 (PegIFN alfa-2b)**	6% (PegIFN alfa-2a) 7% (PegIFN alfa-2b)

1. Jensen DM, et al. AASLD 2007. Abstract LB4. 2. Poynard T, et al. EASL 2008. Abstract 988.

HCV Retreatment: DIRECT

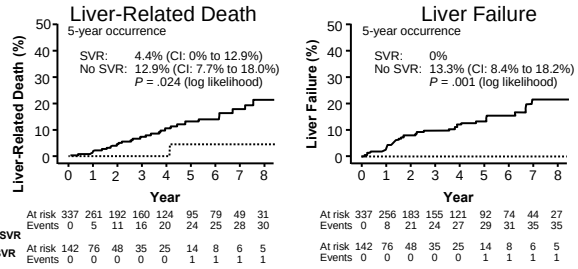
Sustained Virologic Response in Nonresponders to PegIFN/Rib



Study	Treatment	GT	N	SVR Rate
DIRECT	**CIFN 9 µg/day + RBV**	**1 (95%)**	**245**	**6.9%**
	CIFN 15 µg/day + RBV	**1 (96%)**	**242**	**10.7%**

Bacon B, et al. *Hepatology* 2009

8-Year Posttreatment Outcomes: Patients With or Without SVR



ANNALS OF INTERNAL MEDICINE. ONLINE by Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL.

HCV Retreatment: Relapsers

Outcomes in Relapsers to PegIFN-Based Therapy

Study	Treatment	GT	N	SVR Rate
Kaiser	**CIFN 9 µg/day + RBV x 72 weeks**	**1**	**120**	69%
	PegIFN alfa-2a + RBV x 72 weeks			42%

Kaiser S, et al. AASLD 2007. Abstract 1310.

Antiviral Therapy for HCV-Related Cirrhosis: Prevention of HCC

- **Does it prevent HCC?**
  - ✓ **Early studies suggested reduced risk of HCC following IFN treatment, even if treatment was unsuccessful**
  - ✓ **Later studies indicate some benefit but only in noncirrhotic patients achieving SVR**
  - ✓ **Studies in HCV patients with cirrhosis do not show significant reduction in HCC after antiviral treatment**
- **Conclusion: If advanced fibrosis or cirrhosis is present, patients remain at risk for HCC, even after achieving SVR**

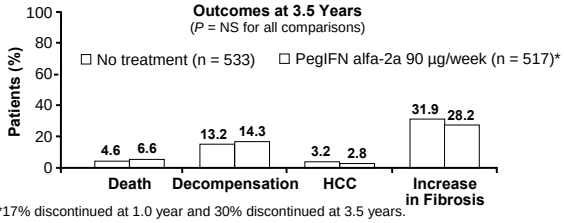
Yu ML, et al. Oncology. 2007;72(suppl 1):16-23.

Maintenance Therapy

Maintenance Therapy: HALT-C

Long-term PegIFN alfa-2a 90 µg/week in Nonresponders

- **No reduction in fibrosis and no difference between arms**
- **No significant difference between arms in any primary outcome**
  - ✓ **34.1% vs 33.8% (HR: 1.01; 95% CI: 0.81-1.26)**



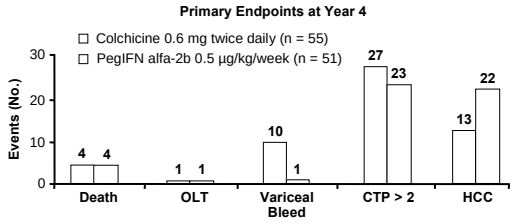
*17% discontinued at 1.0 year and 30% discontinued at 3.5 years.

Di Bisceglie A, et al. AASLD 2007. Abstract LB1.

Maintenance Therapy: COPILOT

Event-Free Survival With and Primary Endpoints (ITT)

49% of patients did not achieve 4-year event-free survival

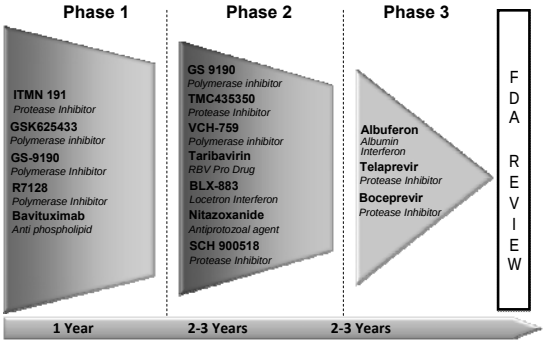


- Primary endpoints more common in both colchicine and pegIFN arms in patients with portal HTN (32% and 23%, respectively) vs without portal HTN (9% and 13%, respectively)

Afdhal N, et al. EASL 2008. Abstract 3.

Future Options for Treatment

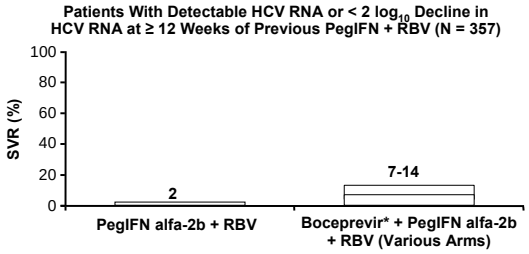
Timeline for New Therapies



http://www.hcvadvocate.org/hepatitis/hepC/hcvdrugs.html. Accessed January 2008
Franciscus A. Hepatitis C Support Project. Dec. 28, 2006.

Boceprevir + PegIFN/RBV: Phase II Nonresponder Study, GT 1

- **Response dependent on IFN responsiveness**



*100, 200, 400, and 800 mg TID.

Schiff E, et al. EASL 2008. Abstract 104.

AlbIFN Retreatment of IFN/RBV and PegIFN/RBV Nonresponders

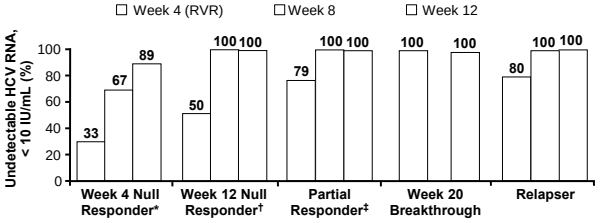
SVR, % (n/N)	AlbIFN alfa-2b + RBV*				
	Every 4 Weeks	Every 2 Weeks			
	1200 µg	900 µg	1200 µg	1500 µg	1800 µg
All patients	**25 (6/24)**	**30 (7/23)**	**13 (3/24)**	**9 (2/22)**	**9 (2/22)**
GT1, pegIFN/RBV nonresponders	**15 (2/13)**	**15 (2/13)**	**13 (2/16)**	**7 (1/15)**	**6 (1/18)**

- **Overall SVR rate: 17.4%**
- **GT1, pegIFN + RBV nonresponder SVR rate: 10.7%**

Nelson D, et al. AASLD 2007. Abstract 51.

Telaprevir + PegIFN alfa-2a + RBV in Nonresponders or Relapsers

- **Open-label treatment of patients from control arms of PROVE1-3 trials**



*< 1 log_{10} drop at Week 4. †< 2 log_{10} drop at Week 12. ‡≥ 2 log_{10} drop at Week 12; detectable HCV RNA at Week 24.

Poordad F, et al. EASL 2008. Abstract 1000.

Discontinued Clinical Programs

COMPANY	PRODUCT	PHASE	REASON FOR DISCONTINUATION	DESCRIPTION
Roche/ Ribapharm	Levovirin	Phase I	Lack of activity and formulation issues	L-isomer of RBV
Boehringer Ingelheim	BILN 2061	Phase II	Cardiac toxicity in animals	Protease inhibitor
Roche	R1626	Phase II	Safety	Polymerase inhibitor
Vertex Pharmaceutical	Merimepodib (MMPD)	Phase II	Lack of efficacy	Polymerase inhibitor
Maxim Pharmaceuticals	Maxamine®	Phase III	Lack of efficacy	Immune response modifier
Indevus	IP 501	Phase III	Unknown	Antifibrotic
Coley Pharmaceutical	ACTILON (CPG 10101)	Phase I/II	Lack of efficacy	Toll-like receptor agonist
Achillion/Gilead	ACH806	Phase II	Safety	Protease Inhibitor
Idenix/Novartis	Valopicitabine NM283	Phase II	Clinical development on hold per FDA request for safety reasons	Polymerase Inhibitor
Anadys / Novartis	ANA 975	Phase Ib	Safety	Toll-like receptor agonist

http://www.hcvadvocate.org/hepatitis/hepC/hcvdrugs.html. Accessed January 2008

HCV Therapy Conclusion

- **Relapsers are good candidates for retreatment**
- **Nonresponders to suboptimal therapy (ie, standard IFN) more likely to respond to retreatment vs those previously treated with pegIFN/RBV**
- **Nonresponders with negative predictors of response (ie, advanced fibrosis, insulin resistance) may not be good candidates for retreatment**

HCV Therapy Conclusion

Improving Outcome and Decreasing Relapse

- **Importance of duration of HCV RNA negativity**
- **Slow responders may require longer duration of therapy (GT 1)**
- **Weight based dose of RBV**
- **Improving Compliance**
  - ✓ **Better management of adverse effects to decrease dose reductions or interruptions**
- **Steatosis and Insulin Resistance**
- **Some patients may be inherently resistant to IFN**

HCV Therapy Conclusion

- **Maintenance therapy has not been shown to be effective for reducing fibrosis progression, other disease outcomes**
- **Promising results with new compounds, even in the setting of null response**

HCV therapy Managing side effects

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Hepatitis C Therapy

- Pegylated interferon plus ribavirin
- Consensus interferon plus ribavirin
- Both regimens associated with possibly significant side effects.
- Front-load your patient education about side effects; it saves time later. Teach them what that might experience.

Multidisciplinary team Identify / incorporate resources

- Psych: psychiatrist, psychologist, psych CNP.
- Substance abuse resources: Local / state AA information. AlAnon for friends, family. City / county resources. CD counselors.
- Opthamology: pre-treatment eye exams, especially in diabetic patients. Urgent referral is vision changes in patient on Rx.70
- Endocrinology: DM management.
- Cardiologist
- Pharmacist
- Weight management resources

Place side effects in perspective

- Patients get on the internet and read about other's bad experiences. People with bad experiences likely to be most outspoken.
- Present frequency of SEs as bell curve:
  - ✓ Outliers left: no problems
  - ✓ Outliers right: must DC treatment
  - ✓ Largest number in the middle: flu-like sx around injection time, fatigue during week, but still working, functioning.

Fatigue- most common

- Hgb / thyroid – both are monitored
  → ? EPO / ? thyroid med may be indicated
- Interventions:
  - ✓ Energy conservation measures. Be efficient.
  - ✓ Assess for sleep time / sleep hygiene
  - ✓ Plan A, B and C → patients love this.
  - ✓ Regular moderate exercise. Walking 20 minutes daily.

Injection Site Reactions

- Determine if patient is using proper technique and proper site.
- Apply cool pack / ice pack to area.
- Use small amount of hydrocortisone 1% ointment to site between cold packs.
- Reinforce site rotation.

GI issues: N/V, anorexia, diarrhea

- Encourage small, frequent meals. Some pts develop changes in smell /taste.
- Intuitive eating. Oatmeal, peanut butter.
- "Boost" or "Ensure" blended with ice.
- Diarrhea – can take OTC antidiarrheal. Avoid fatty foods. Pt to contact office if vomiting and / or diarrhea becomes severe.

Insomnia

- Assess for sleep / nap patterns.
- Sleep hygiene: dark, quiet room. Regular bedtime.
- As with fatigue – regular, moderate exercise helpful.
- Benadryl 25 or 50mg PO HS PRN.

Pruritus
Rash, Dry skin, & Alopecia Associated with both IFN and RIB

- Maintain adequate hydration, non-caffeinated beverages.
- Use warm, not hot water for bathing.
- Keep sleeping quarters cool enough to prevent perspiration.
- Lotions: Sarna or Eucerin Calming cream. Oatmeal based lotions (Aveeno).

Psychiatric Issues

- Patients should be screened for depression *prior* to initiation of therapy, and stabilized on an antidepressant if indicated. Consider psych follow-along in marginal patients.
- Journaling: encourage!
- Communication: encourage communication between patient, spouse, SO, friends and family.

Pruritus
Rash, Dry Skin, Alopecia

- Benadryl 25 mg tablets.
  - ✓ Drug is sedating. For daytime use, start at 12.5mg PO q 4-6h. Increase as tolerated.
  - ✓ 50 mg HS.
  - ✓ If rash is severe, check for autoimmune component.
  - ✓ Rash can be associated with both IFN and RIB.
  - ✓ Alopecia is reversible. Reassure patient.

Flu-like Symptoms
HA, Chills, Myalgias

- Interventions:
  - ✓ If not contraindicated, ibuprofen 400mg 30 minutes before IFN injection and continue q8h PRN the next 48 hours.
  - ✓ Tylenol, no more than 2,000mg daily. Educate re: acetaminophen in many OTCs. Read label.
  - ✓ Typically, these SEs improve over time.

Cough

- Usually associated with ribavirin.
- Interventions:
  - ✓ Maintain H2O intake. Hard candies.
  - ✓ OTC dextromethorphan.
  - ✓ Heating pad to chest (patient recommendation)
  - ✓ Rx Tessalon Perles 100mg. One or two perles TID PRN cough. (benzonatate).
  - ✓ CXR?

Red Flags

- Vision changes: Stop IFN - urgent optho referral
- Severe depression: SI, HI. Stop IFN!
- Severe rash with intractable pruritus.
- Monitor thyroid before, during, after therapy.
- Check autoimmune markers before starting.

Oral Problems

- Apthous ulcers, "sore mouth". Try Magic mouthwash. =parts: Mylanta, Benadryl, lidocaine.
- Oral / oropharyngeal candidiasis. Rare, but can be very uncomfortable: anti-fungal rinse or systemic med.