HEPATITIS WEB STUDY HEPATITIS C ONLINE

Peginterferon alfa-2a (*Pegasys*)

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Last Updated: February 14, 2014

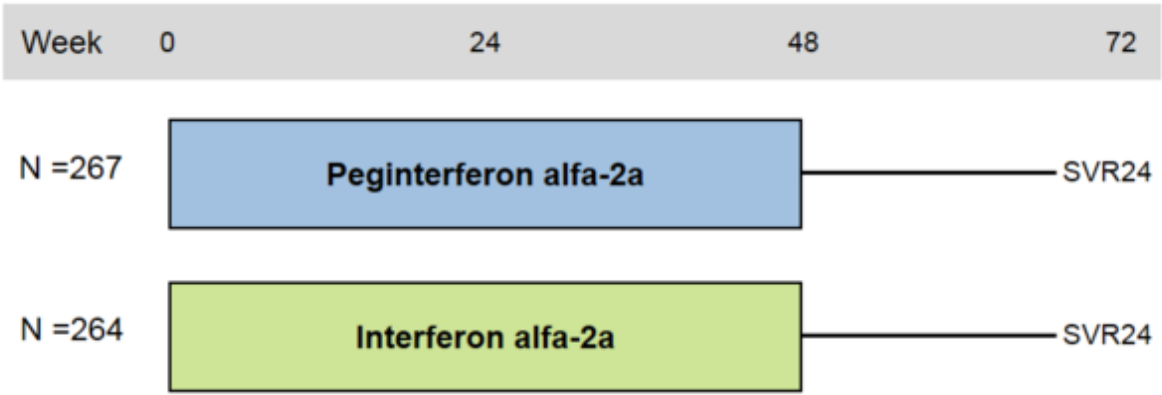
Hepatitis web study

Peginterferon alfa-2a versus Interferon alfa-2a
Study Features

- **Study**
  - Randomized, open label, parallel dose, phase 3 trial
  - 36 international centers
- **Subjects**
  - N = 531 with chronic hepatitis C
  - Treatment naïve
  - Any genotype (62% with genotype 1)
  - 18 years of age or older
- **Regimens**
  - Peginterferon alfa-2a: 180 µg 1x/week x 48 weeks
  - Interferon alfa-2a: 6 million units 3x/week x 12 weeks, then 6 million units 3x/week x 36 weeks
- **Primary Endpoint: Sustained Virologic Response (SVR24)**
  - SVR = undetectable serum HCV RNA 24 weeks after 48-week treatment
  - Undetectable serum HCV RNA = less than 100 copies/ml

Source: Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.

Peginterferon alfa-2a versus Interferon alfa-2a Study Design

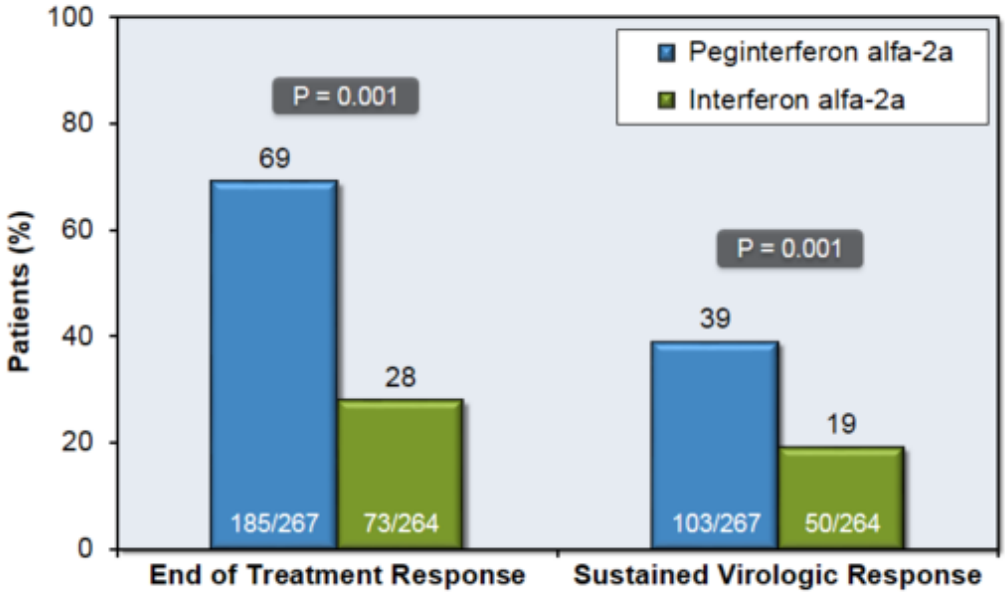


Drug Dosing
Peginterferon alfa-2a: 180 µg once weekly
Interferon alfa-2a: 6 million units 3x/week x 12 weeks, then 6 million units 3x/week x 36 weeks

Source: Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.

Peginterferon alfa-2a versus Interferon alfa-2a Study Results

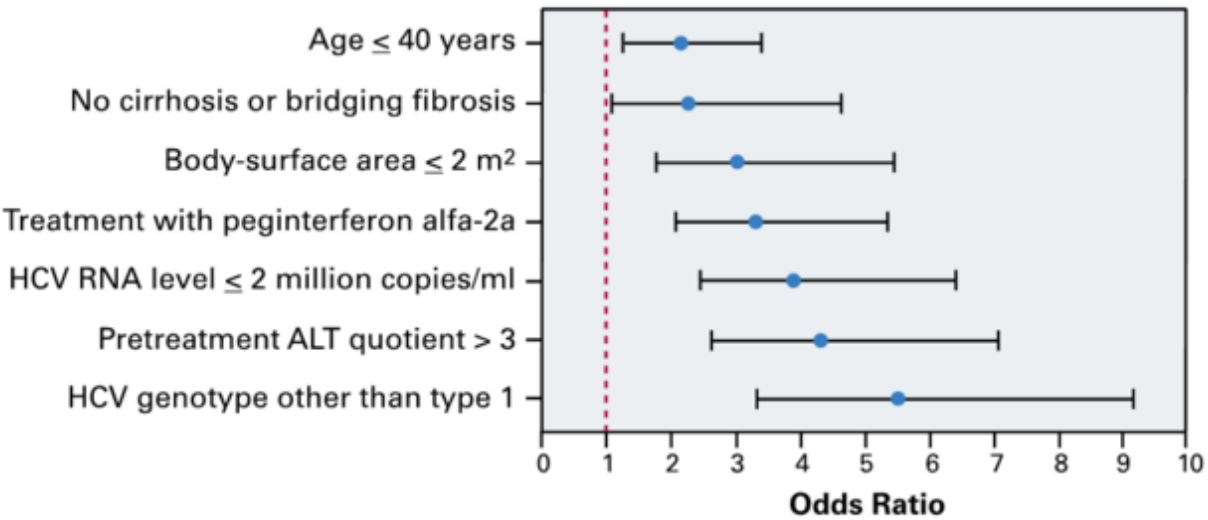
Virologic Responses by Treatment Regimen (ITT Analysis)



Source: Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.

Peginterferon alfa-2a versus Interferon alfa-2a Study Results

Independent Factors Associated with SVR, Multiple Regression Analysis



Source: Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.

Peginterferon alfa-2a versus Interferon alfa-2a Study Conclusions

Conclusions: "In patients with chronic hepatitis C, a regimen of peginterferon alfa-2a given once weekly is more effective than a regimen of interferon alfa-2a given three times weekly."

Source: Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.

Treatment Naïve, Chronic HCV

Peginterferon alfa -2a+/- Ribavirin
versus
Interferon alfa-2b + Ribavirin

Fried MW, et al. N Engl J Med. 2002;347:975-82.

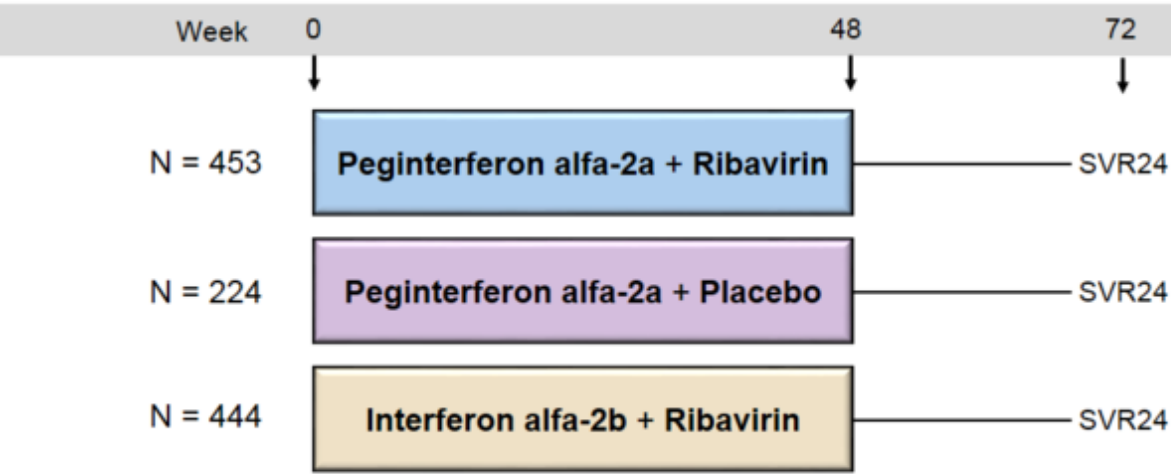
Peginterferon +/- Ribavirin versus Interferon + Ribavirin Study Features

- **Study**
  - Open-label randomized controlled trial
- **Subjects**
  - N = 1149 with chronic hepatitis C randomized
  - Treatment naïve; 62% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months
- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 µg 1x/week + Ribavirin 1000-1200 mg/day
  - Peginterferon alfa-2a 180 µg 1x/week + Placebo
  - Interferon alfa-2b 3 million U 3x/week + Ribavirin 1000-1200 mg/day
- **Primary Endpoint**
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

*Ribavirin dosing: <75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day

Source: Fried MW, et. al. N Engl J Med. 2002;347:975-82.

Peginterferon +/- Ribavirin versus Interferon + Ribavirin Study Design



Drug Dosing

Peginterferon alfa-2a 180 µg 1x/week

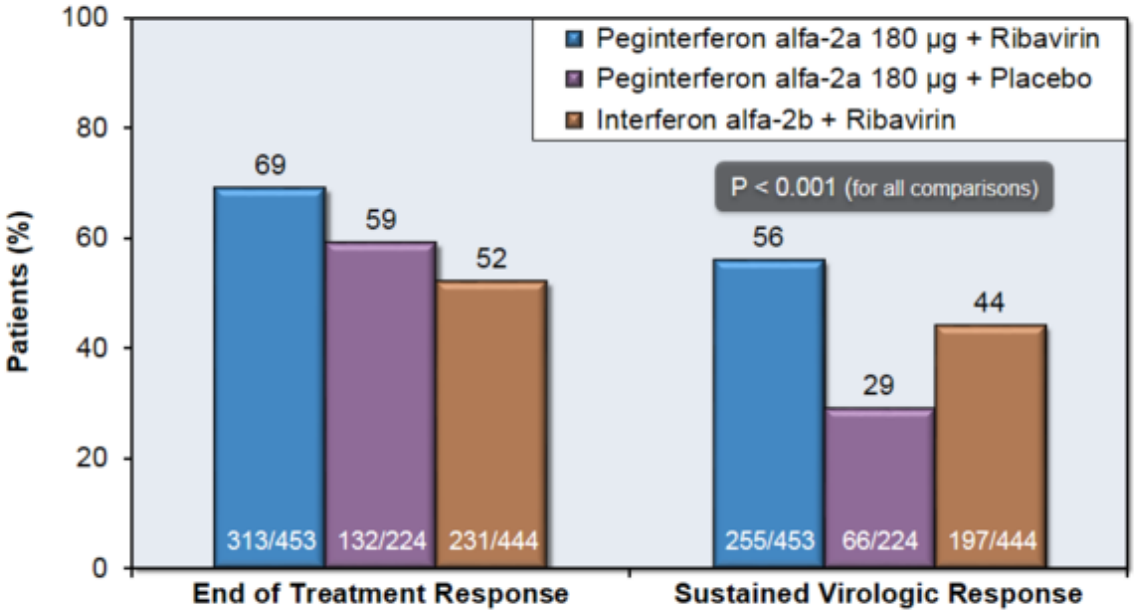
Weight-based Ribavirin (divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

Interferon alfa-2b 3 million U 3x/week

Source: Fried MW, et. al. N Engl J Med. 2002;347:975-82.

Peginterferon +/- Ribavirin versus Interferon + Ribavirin Results

Virologic Responses, by Treatment Regimen



Source: Fried MW, et. al. N Engl J Med. 2002;347:975-82.

Peginterferon +/- Ribavirin versus Interferon + Ribavirin
Conclusions

Conclusions: "In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone."

Source: Fried MW, et. al. N Engl J Med. 2002;347:975-82.

PEGINTERFERON ALFA-2A (*PEGASYS*)

Background and Dosing

Phase 3

Treatment Naïve, Chronic HCV

Duration and Dose Finding Peginterferon alfa-2a + Ribavirin

Randomized study of low-dose versus weight based ribavirin and 24 versus 48 weeks of therapy

Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

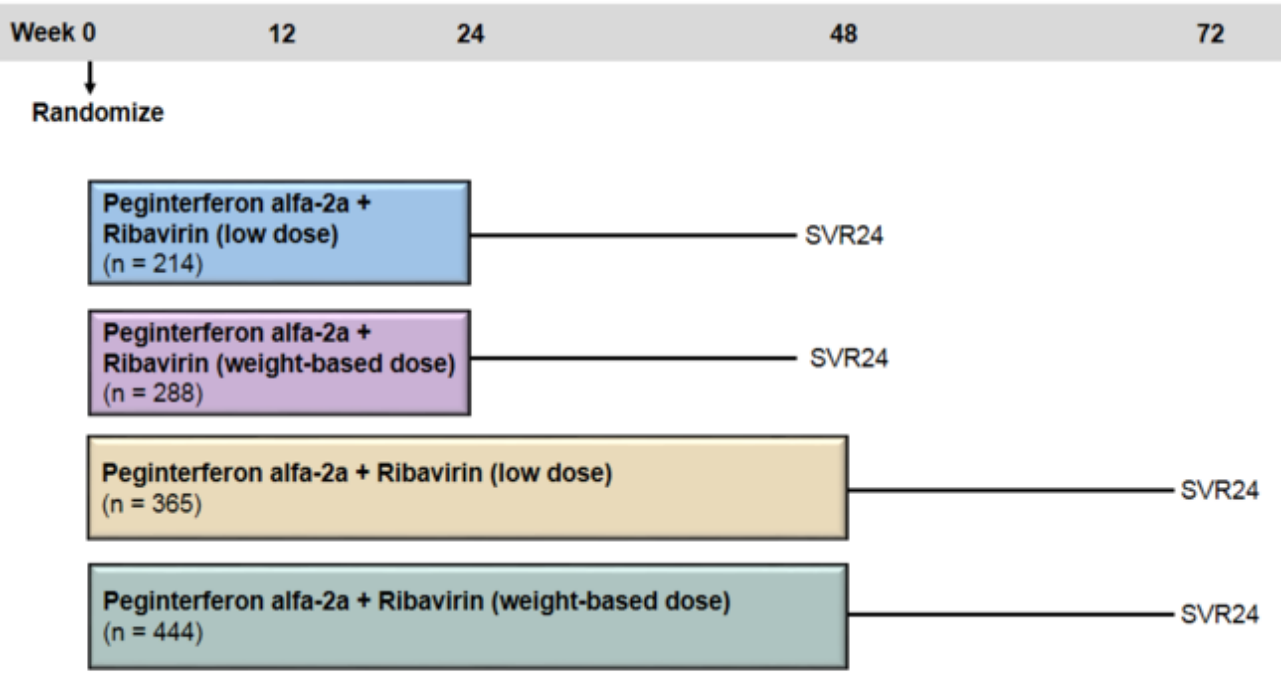
Peginterferon alfa-2a + Ribavirin for Chronic HCV
Treatment Duration and Ribavirin Dose

- **Study**
  - Randomized, double-blind trial, with 2 x 2 factorial design
- **Subjects**
  - N = 1311 with chronic hepatitis C (1284 treated)
  - Treatment naïve adult patients; 58% genotype 1
  - Serum ALT above upper limit of normal x prior 6 months
- **Regimens**
  - Peginterferon alfa-2a: 180 µg/wk + Ribavirin: 800 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 µg/wk + *Ribavirin: 1000-1200 mg/day x 24 wks
  - Peginterferon alfa-2a: 180 µg/wk + Ribavirin: 800 mg/d x 48 weeks
  - Peginterferon alfa-2a: 180 µg/wk + *Ribavirin: 1000-1200 mg/day x 48 wks
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

*Ribavirin dose: Ribavirin 1000 mg/day for Wt <75 kg, 1200 mg/day for Wt ≥75 kg

Source: Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

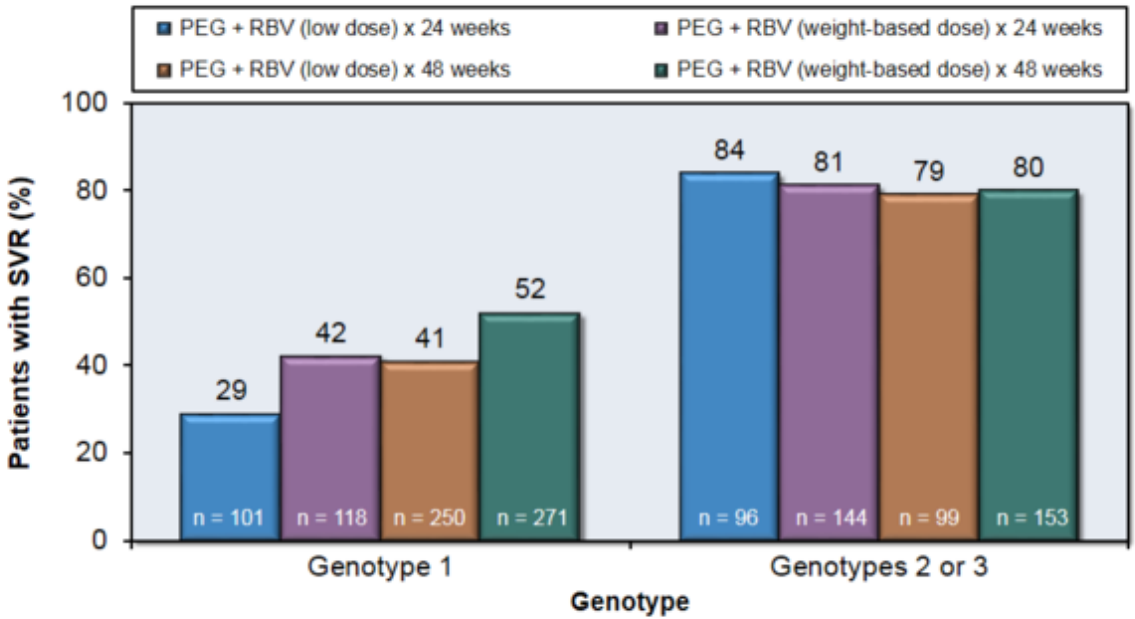
Peginterferon alfa-2a + Ribavirin for Chronic HCV
Treatment Duration and Ribavirin Dose



Source: Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Peginterferon alfa-2a + Ribavirin for Chronic HCV
Treatment Duration and Ribavirin Dose

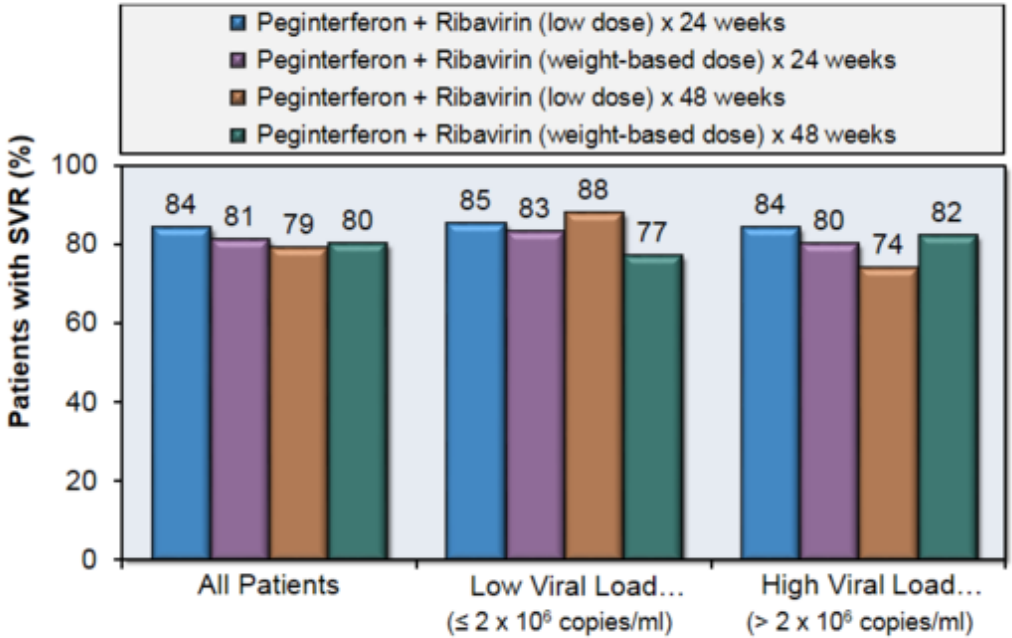
SVR24 Rates, by Regimen



Source: Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

Rates of SVR with Different Peginterferon + Ribavivirn Regimens



Source: Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Peginterferon alfa-2a + Ribavirin for Chronic HCV
Treatment Duration and Ribavirin Dose

Conclusion: "Treatment with peginterferon-alpha2a and ribavirin may be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin; those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks."

Source: Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + RBV vs. Peginterferon alfa-2a + RBV
IDEAL STUDY

McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Design

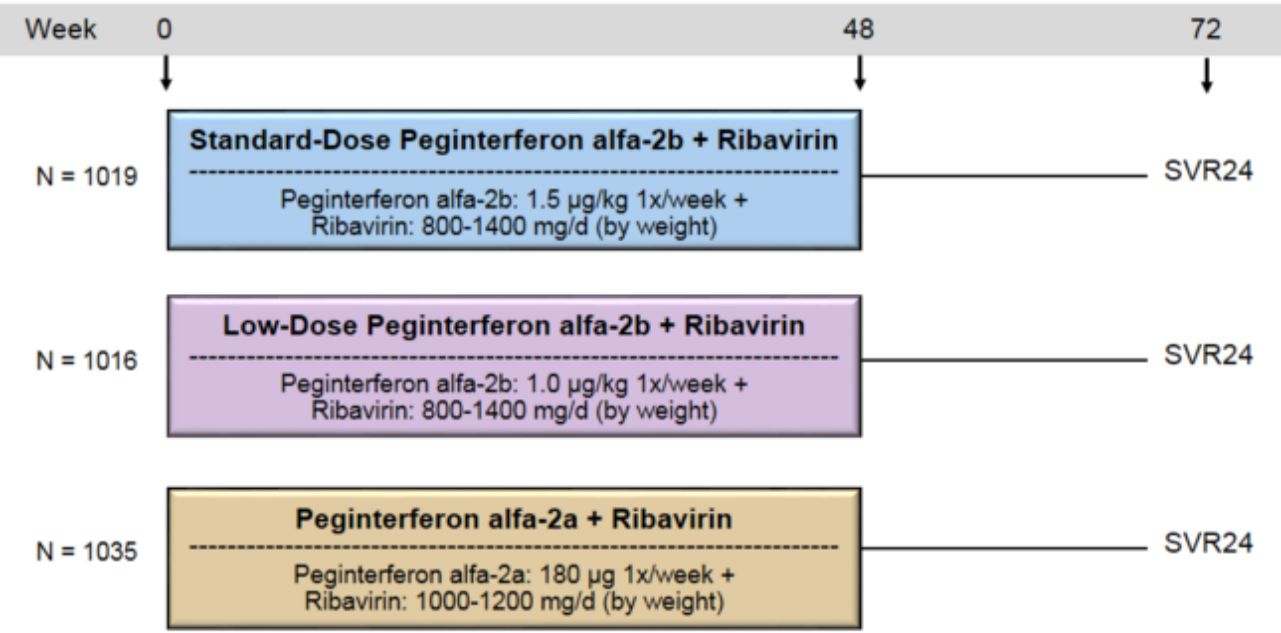
- **Study**
  - Randomized comparative trial
  - 118 centers in United States
- **Subjects**
  - N = 3070 with chronic hepatitis C
  - All genotype 1 (other genotypes excluded)
  - Treatment naïve
  - Subjects were 18 years of age or older
- **Regimens (Ribavirin Dosed by Weight)**
  - Peginterferon alfa-2b: 1.5 µg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2b: 1.0 µg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2a: 180 µg 1x/week + Ribavirin 1000-1200 mg/day^
- **Primary Endpoint (Sustained Virologic Response [SVR])**
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

*Ribavirin dosing: 40-65 kg: 800 mg/d; >65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105-120 kg: 1400 mg/d

^Ribavirin dosing: < 75 kg: 1000 mg/d; ≥75 kg: 1200 mg/d

Source: McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

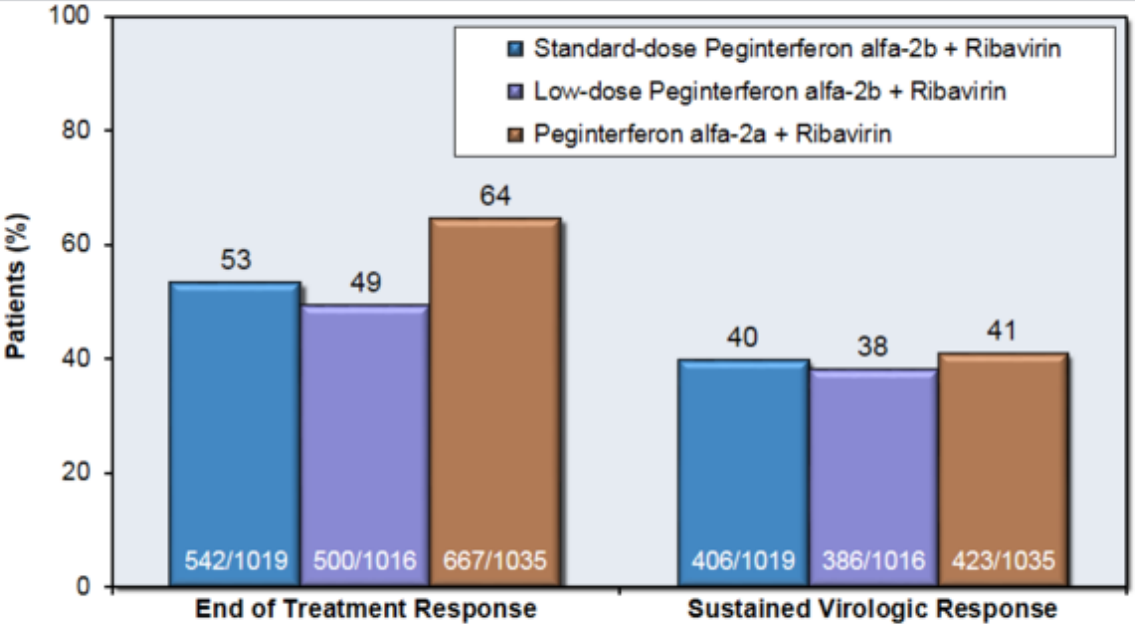
Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Design



Source: McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Results

IDEAL Study: Virologic Responses by Treatment Regimen



Source: McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

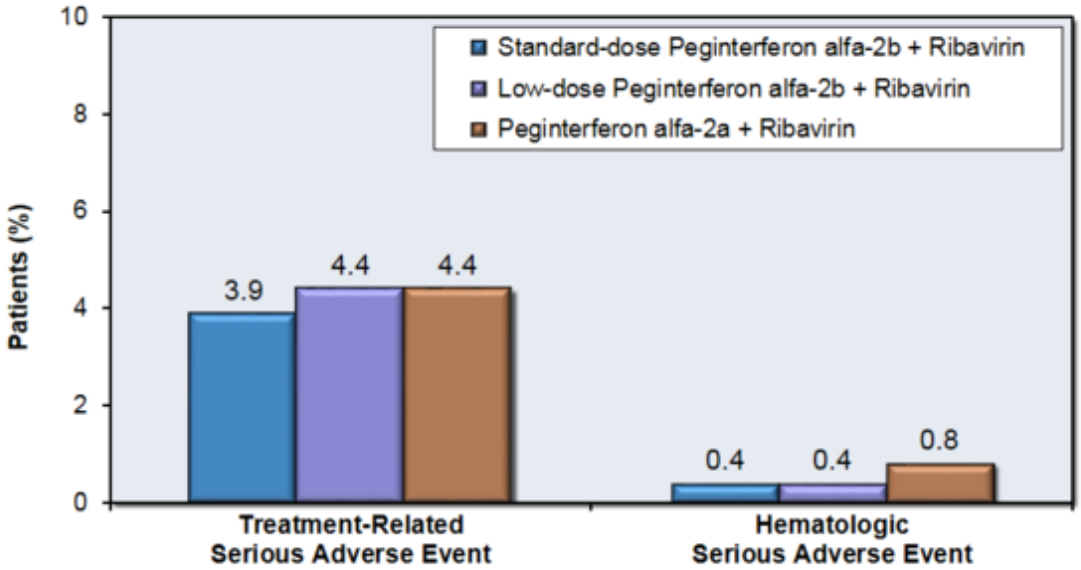
Peginterferon alfa-2a (*Pegasys*) Summary

- **Approval Status**: FDA approved in 2002
- **Indications:**
  - In combination with ribavirin for all genotypes
  - In combination with ribavirin plus protease inhibitor for GT1
- **Class & Mechanism**
  - Complex mechanism based on altering immune response to HCV infection
- **Dosing:**
  - 180 mcg subcutaneously once per week
  - Duration dependent on genotype and remaining components of regimen
- **Adverse Effects (AE)**
  - Extensive adverse effects
  - Influenza-like symptoms
  - Depression
  - Hematologic (leukopenia and thrombocytopenia)
  - Thyroid dysfunction

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech USA.

Peginterferon alfa-2b + Ribavirin vs Interferon alfa-2a + Ribavirin
IDEAL Study: Results

IDEAL Study: Serious Adverse Event Rates



Source: McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Conclusions

Conclusions: "In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or between the two doses of peginterferon alfa-2b."

Source: McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

Treatment Naïve, Chronic HCV and HIV

PEG alfa-2a + RBV *versus* PEG alfa-2a *versus* INF + RBV
APRICOT STUDY

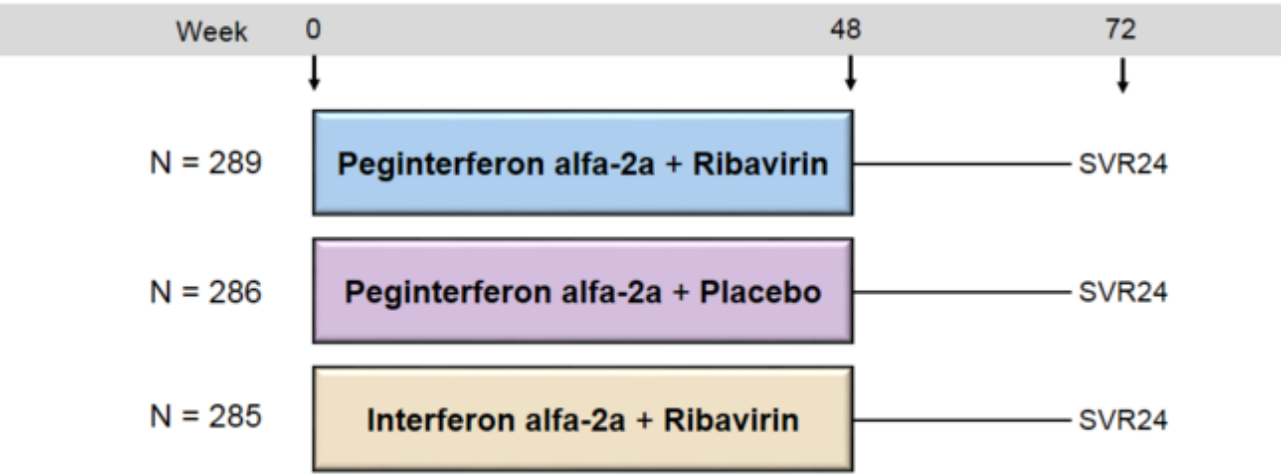
Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT Study: Features

- **Study**
  - Randomized, placebo-controlled trial
  - Conducted at 95 centers in 19 countries in U.S., Canada, & Europe
- **Subjects**
  - N = 868 chronically infected with both HCV and HIV
  - Treatment naïve; 61% genotype 1
  - CD4 >200 cells/mm^3 or
    CD4 = 100-200 cells/mm^3 + HIV RNA level <5,000 copies/ml
- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 µg 1x/week + Ribavirin 800 mg/day
  - Peginterferon alfa-2a 180 µg 1x/week + Placebo
  - Interferon alfa-2a: 3 million IU 3x/week + Ribavirin 800 mg/day
- **Primary Endpoint**
  - Undetectable HCV RNA (< 50 IU/ml) 24 weeks after stopping Rx

Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT Study: Design

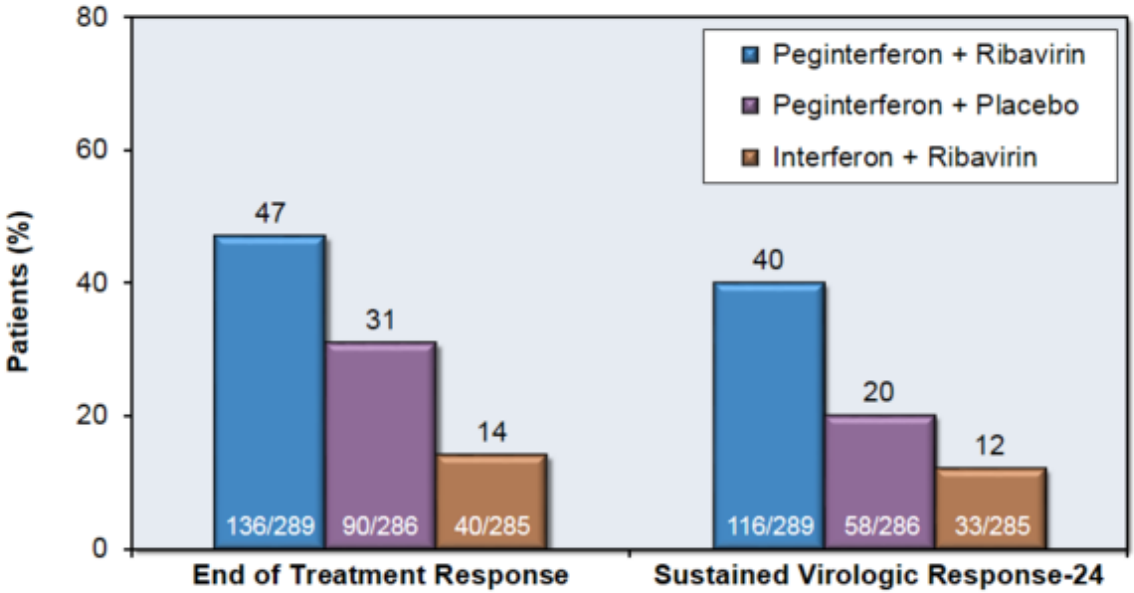


Drug Dosing
Peginterferon alfa-2a 180 µg 1x/week
Ribavirin (divided bid): 800 mg/day
Interferon alfa-2a 3 million IU 3x/week

Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT Study: Results

APRICOT Study: Virologic Responses by Treatment Regimen

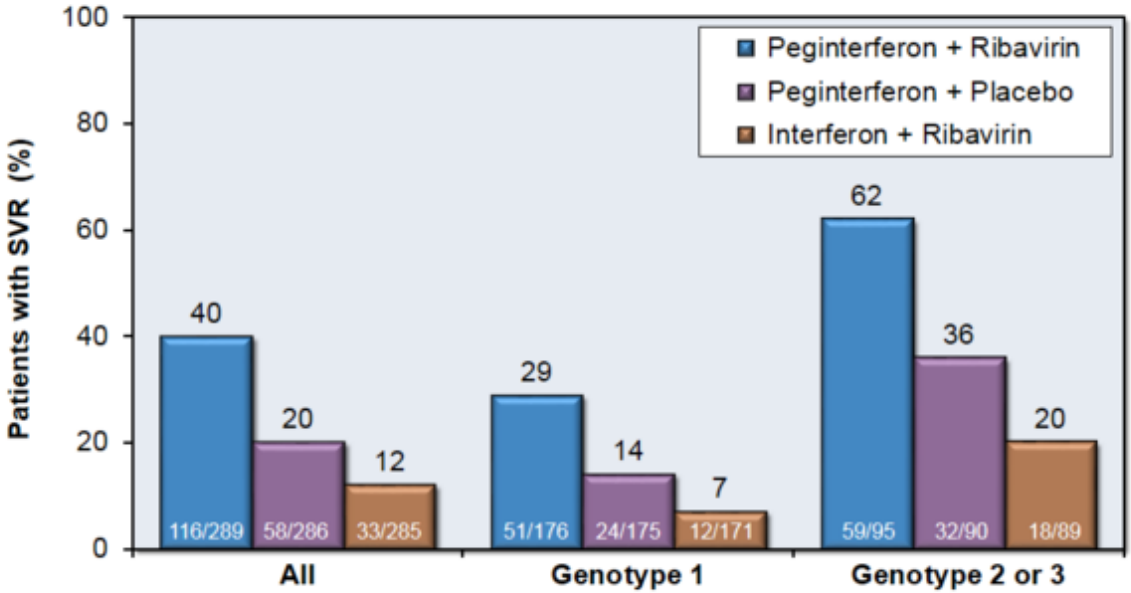


Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

Hepatitis web study

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT Study: Results

APRICOT Study: SVR24 by Treatment Regimen and Genotype

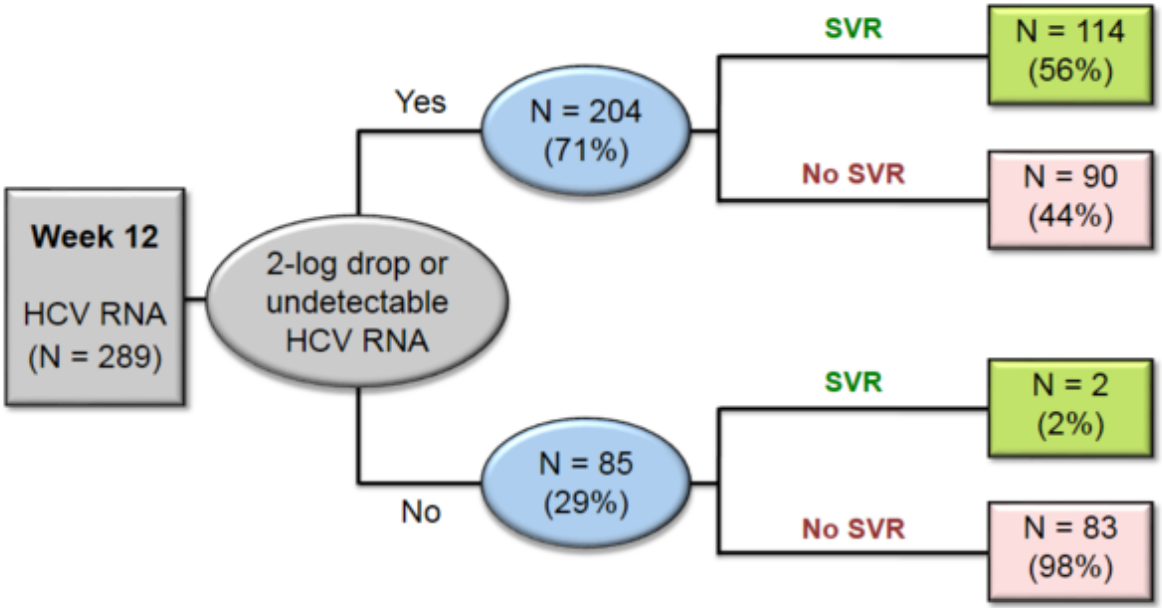


Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

Hepatitis web study

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT: Predictive Value of Early Virologic Response

Peginterferon alfa-2a + Ribavirin



Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

PEG + RBV *versus* PEG *versus* INF + RBV in HCV & HIV
APRICOT Study: Conclusions

Conclusions: "Among patients infected with both HIV and HCV, the combination of peginterferon alfa-2a plus ribavirin was significantly more effective than either interferon alfa-2a plus ribavirin or peginterferon alfa-2a monotherapy."

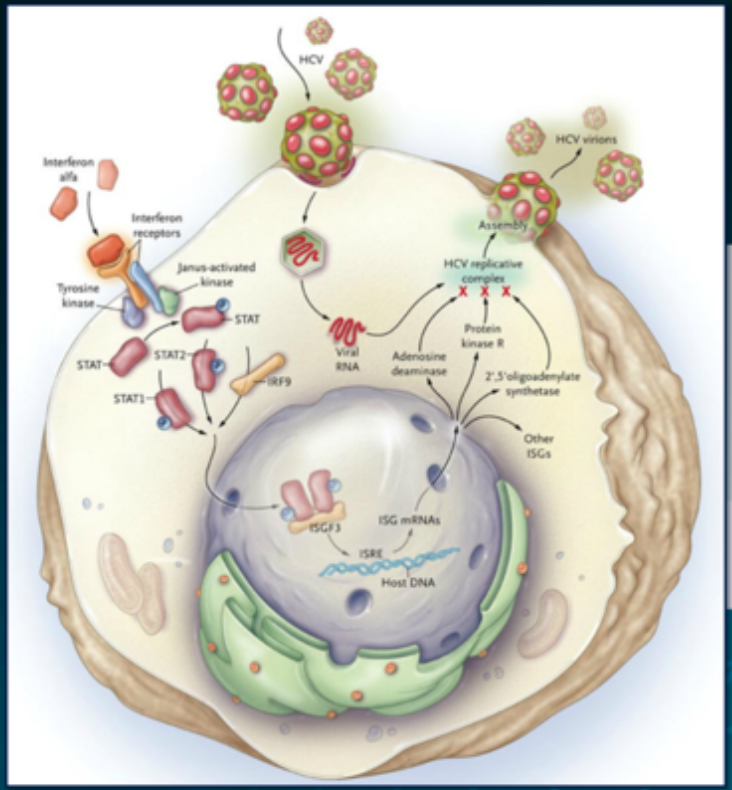
Source: Torriani FJ, et. al. N Engl J Med. 2004;351:438-50.

Treatment Naïve, Chronic HCV and HIV

Peginterferon alfa-2a + RBV *versus* Interferon alfa-2a + RBV
ACTG 5071

Chung RT, et. al. N Engl J Med. 2004;351:451-9.

Interferon: Proposed Mechanism of Action



Interferon alfa engages receptors on the surface of the hepatocyte, initiating intracellular signal transduction that prompts the transcription of multiple interferon-stimulated genes (ISGs). These ISGs encode proteins that can interfere at various stages of the hepatitis C viral life cycle.

Image reproduced from: Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. N Engl J Med. 2006;355:2444-51.

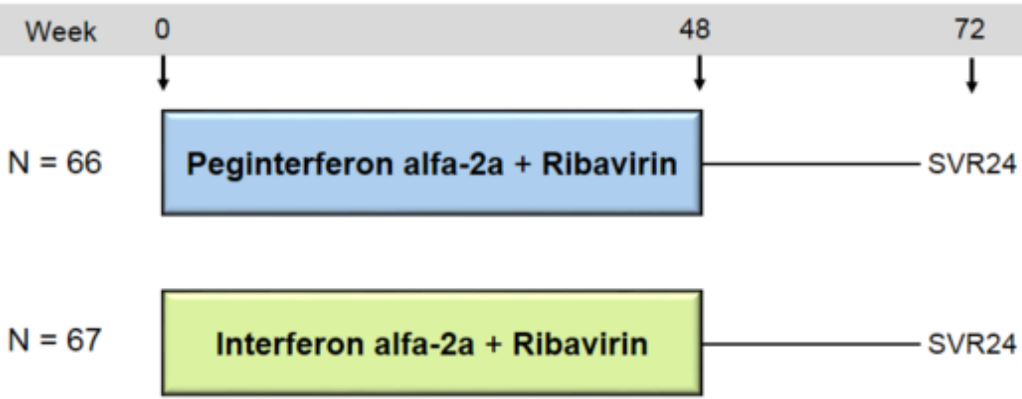
Hepatitis web study

PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Features

- **Study**
  - Randomized, placebo-controlled, phase 2 trial
  - Conducted at 21 ATG sites in United States
- **Subjects**
  - N = 133 chronically infected with both HCV and HIV
  - Treatment naïve
  - 78% genotype 1
- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2a 180 µg 1x/week + Ribavirin (dose escalation)
  - Interferon alfa-2a: 6 million IU 3x/week, then 3 million IU 3x/week + Ribavirin (dose escalation)
- **Primary Endpoint**
  - Undetectable HCV RNA (< 50 IU/ml) 24 weeks after stopping Rx

Source: Chung RT, et. al. N Engl J Med. 2004;351:451-9.

PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Design



Drug Dosing

Peginterferon alfa-2a 180 µg 1x/week x 48 weeks

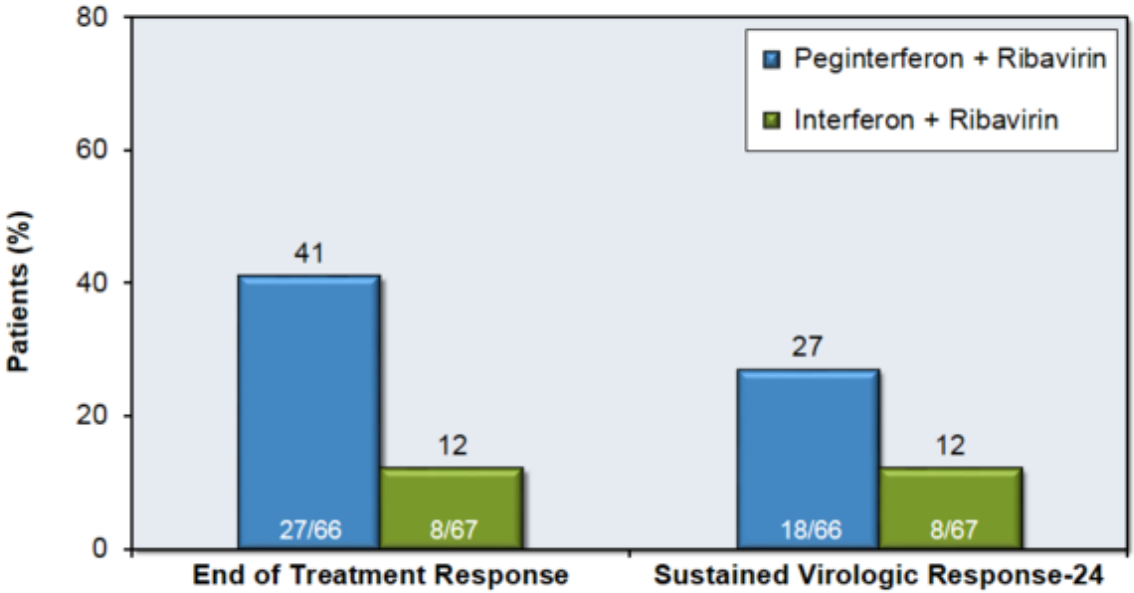
Interferon alfa-2a 6 million IU 3x/week x 12 weeks, then 6 million IU 3x/week x 36 weeks

Ribavirin (divided bid): 600 mg/day x 4 weeks, then 800 mg/day x 4 weeks, then 1000 mg/day x 40 weeks

Source: Chung RT, et. al. N Engl J Med. 2004;351:451-9.

PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Results

ACTG 5071 Study: Virologic Responses by Treatment Regimen



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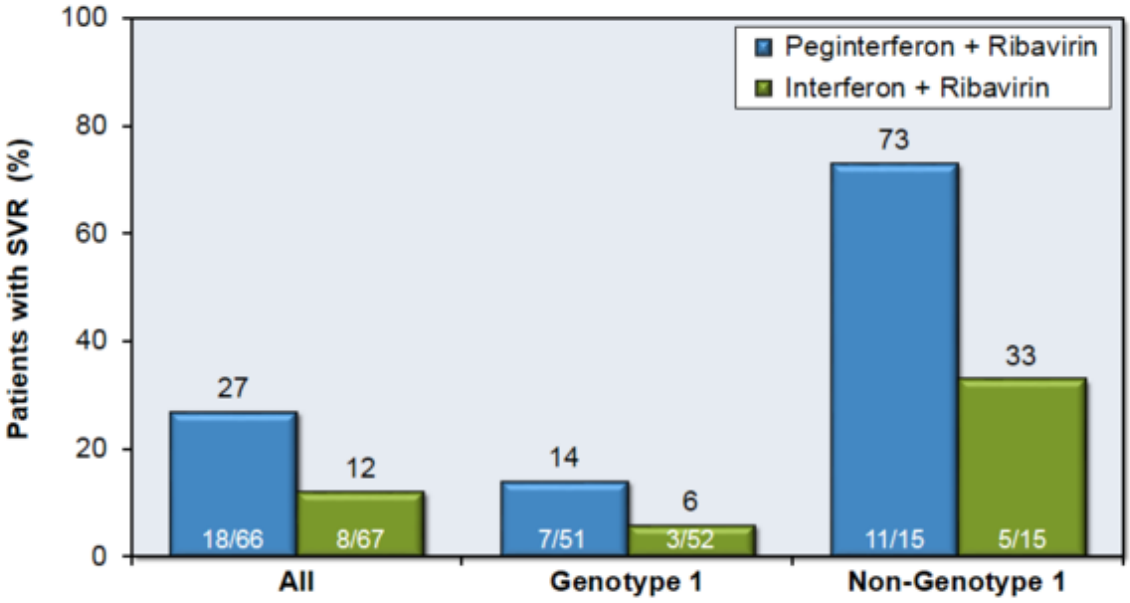
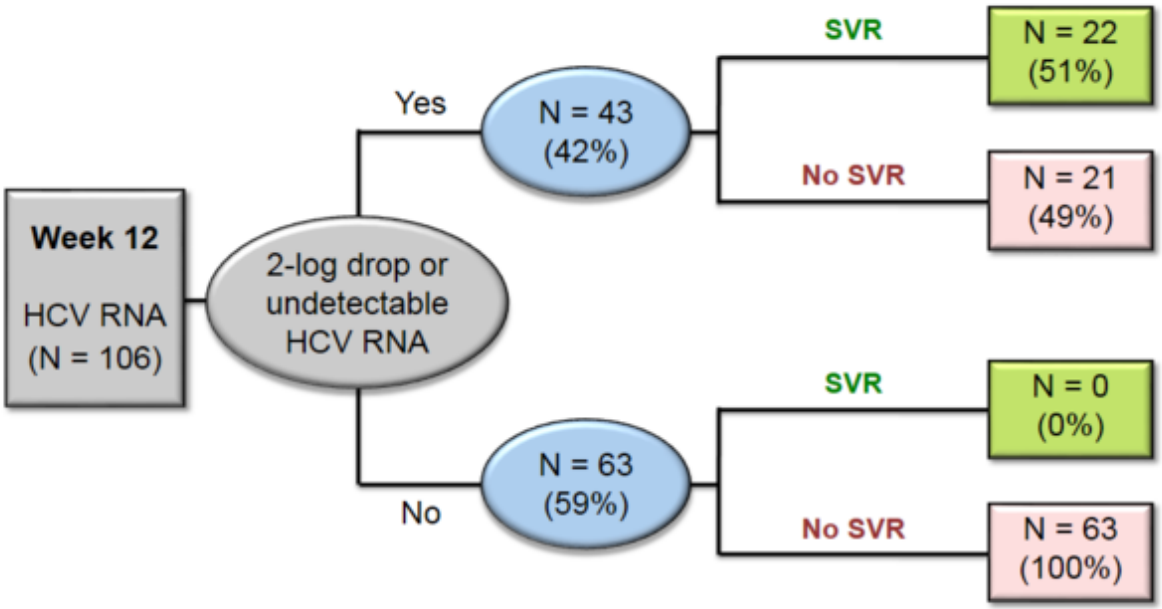
PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Results

ACTG 5071 Study: SVR24 by Treatment Regimen and Genotype



Source: Chung RT, et. al. N Engl J Med. 2004;351:451-9.

PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071: Predictive Value of Early Virologic Response



Source: Chung RT, et. al. N Engl J Med. 2004;351:451-9.

PEG alfa-2a + RBV *versus* IFN alfa-2a + RBV in HCV & HIV
ACTG 5071 Study: Conclusions

Conclusions: "In persons infected with HIV, the combination of peginterferon and ribavirin is superior to the combination of interferon and ribavirin in the treatment of chronic hepatitis C. These regimens may provide clinical benefit even in the absence of virologic clearance. The marked discrepancy in the rates of sustained virologic response between HCV genotypes indicates that strategies are needed to improve the outcome in persons infected with HCV genotype 1."

Source: Chung RT, et. al. N Engl J Med. 2004;351:451-9.

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online
www.hepatitisc.uw.edu

Hepatitis Web Study
http://depts.washington.edu/hepstudy/

Funded by a grant from the Centers for Disease Control and Prevention.

Hepatitis web study

Peginterferon alfa-2a (*Pegasys*) Contraindications

- Autoimmune hepatitis
- Hepatic decompensation in patients with cirrhosis
- Use in neonates/infants
- Known hypersensitivity reaction
- Additional contraindications when used with ribavirin
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Coadministration with didanosine

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech USA.

Peginterferon alfa-2a Hematologic Dose Modification Guidelines for Adults

Dose Adjustments for Peginterferon alfa-2a In Adults	
Laboratory Value	**Recommended Dose**
ANC <750 cells/mm^3	Reduce to 135 mcg
ANC <500 cells/mm^3	Discontinue treatment until ANC values return to more than 1000 cells/mm^3. Reinstitute at 90 mcg and monitor ANC.
Platelet <50,000 cells/mm^3	Reduce to 90 mcg
Platelet <25,000 cells/mm^3	Discontinue treatment

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech.

Peginterferon alfa-2a Dose Modification Guidelines for Adults with Depression

Depression Severity	Initial Management (4-8 weeks)		Depression Status		
	Dose Modification	Visit Schedule	Remains Stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	(See Moderate or Severe depression)
Moderate	Decrease peginterferon alfa-2a dose to 135 mcg (in some cases dose reduction to 90 mcg may be needed)	Evaluate once weekly (office visit at least every other week)	Consider psychiatric Consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	Psychiatric therapy necessary
Severe	Discontinue peginterferon alfa-2a permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech.

Peginterferon alfa-2a Hematologic Dose Modification Guidelines for Adults with Renal Impairment

Creatinine Clearance	Peginterferon alfa-2a Dose (once weekly)	Ribavirin* (*Copegus*) Dose
30-50 mL/min	180 mcg	Alternating doses, 200 mg and 400 mg every other day
< 30 mL/min	135 mcg	200 mg daily
Hemodialysis	135 mcg	200 mg daily

*Note: Other preparations of ribavirin (*Rebetol*, *Ribasphere*) are contraindicated for use with Creatinine clearance < 50 mL/min

Source: Peginterferon alfa-2a (*Pegasys*) Prescribing Information. Genentech.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2a
versus
Interferon alfa-2a

Zeuzem S, et al. N Engl J Med. 2000;343:1666-72.