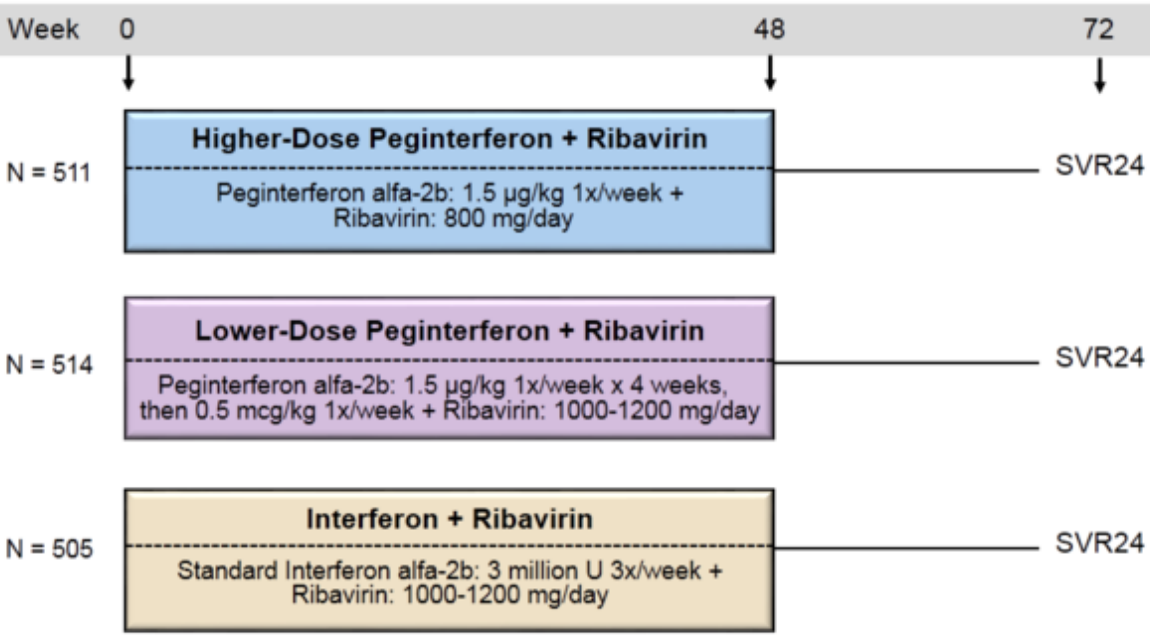
HEPATITIS WEB STUDY HEPATITIS C ONLINE

Peginterferon alfa-2b (*PegIntron*)

Prepared by: David Spach, MD & H. Nina Kim, MD
Last Updated: February 3, 2014

Hepatitis web study

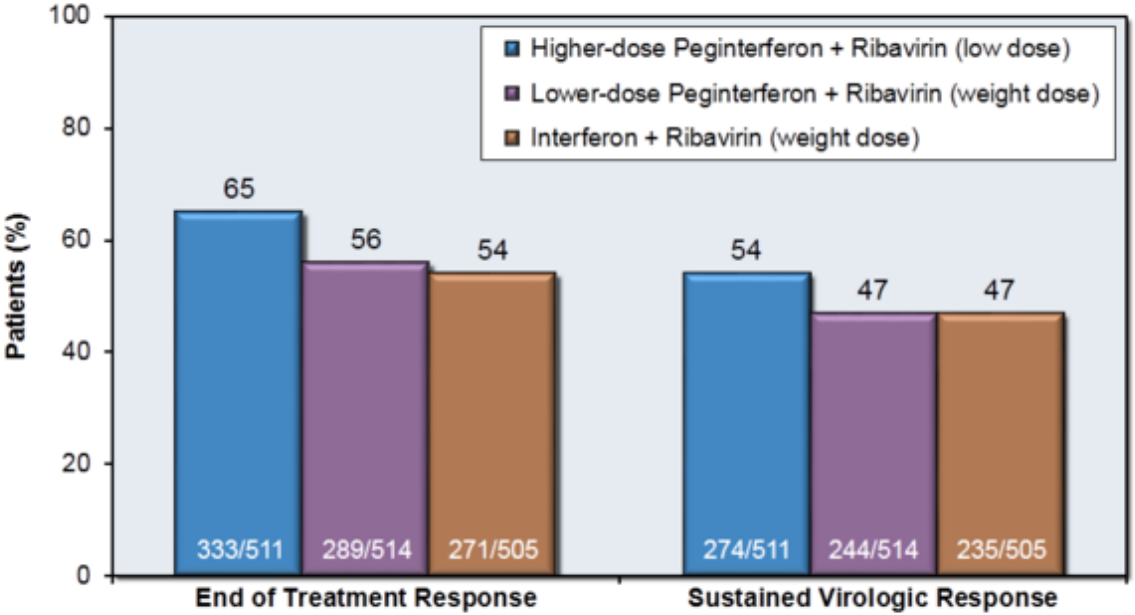
Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
Study Design



From: Manns MP, et. al. Lancet. 2001;358:958-65.

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
Results

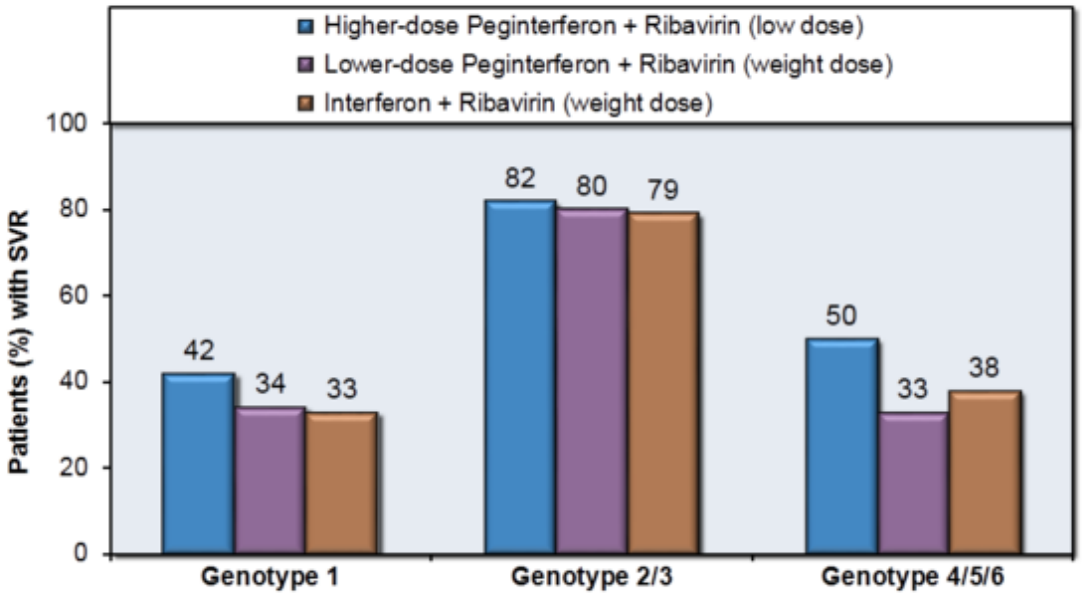
Response after 48 Weeks of Treatment



Source: Manns MP, et. al. Lancet. 2001;358:958-65.

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
Results

SVR24, Based on Genotype



Source: Manns MP, et. al. Lancet. 2001;358:958-65.

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
IDEAL Study: Conclusions

Interpretation: "In patients with chronic hepatitis C, the most effective therapy is the combination of peginterferon alfa-2b 1.5 µg/kg per week plus ribavirin. The benefit is mostly achieved in patients with HCV genotype 1 infections."

Source: Manns MP, et. al. Lancet. 2001;358:958-65.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin in GT 1-6

(Flat versus Weight-Based Ribavirin Dosing)

WINR Study

Jacobson IM, et. al. Hepatology. 2007;46:971-81.

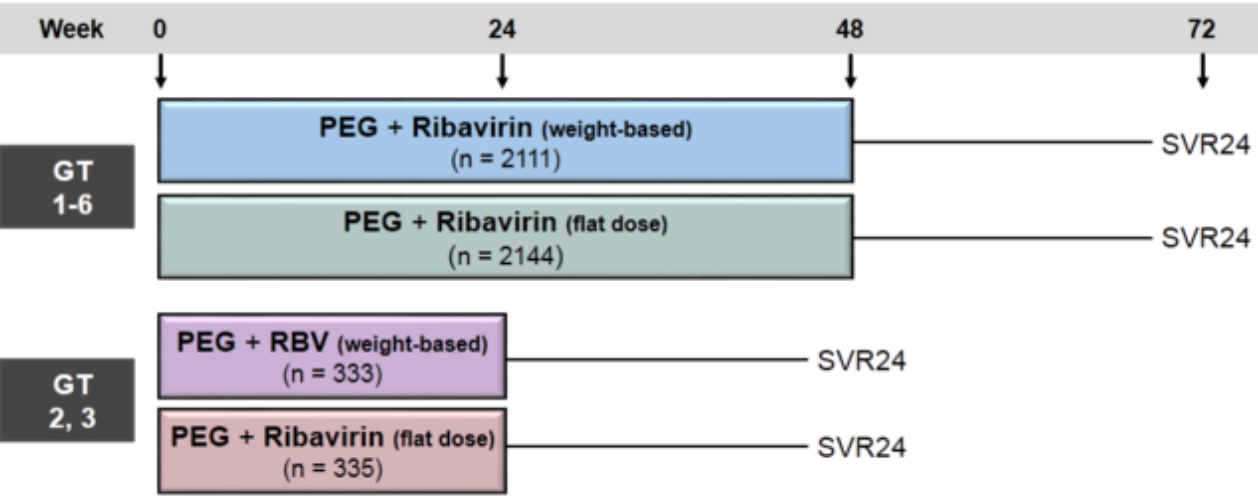
Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Design

- **Study**
  - Prospective, randomized, open-label trial
- **Subjects**
  - N = 5027 with chronic hepatitis C (4913 analyzed)
  - Treatment naïve adult patients (Age 18-70)
- **Treatment Regimens**
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Wt-based* Ribavirin: 800-1400 mg/d
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Flat-dose Ribavirin: 800 mg/d
- **Treatment Duration**
  - Genotypes 1,4,5,6: duration of 48 weeks
  - Genotypes 2,3: duration of 24 or 48 weeks
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 weeks after cessation of treatment (SVR)

*Weight-based ribavirin dosing: < 65 kg: 800 mg/d; 65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105 kg: 1400 mg/d

Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Design



Drug Dosing

Peginterferon alfa-2b: 180 µg once weekly

Weight-based Ribavirin (in 2 divided doses):

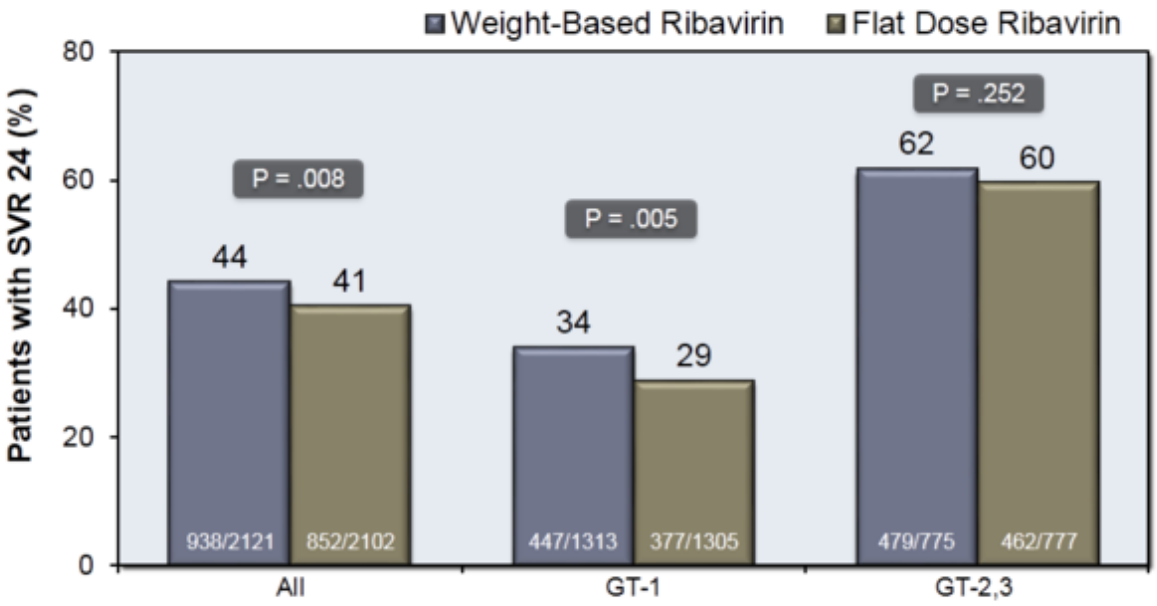
- 800 mg/d if < 65 kg; 1000 mg/d if 65-85 kg; 1200 mg/d if >85-105 kg; 1400 mg/d if >105 kg

Flat-dose Ribavirin (in 2 divided doses): 800 mg/day

Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Results

SVR 24, by Genotype and Treatment Regimen

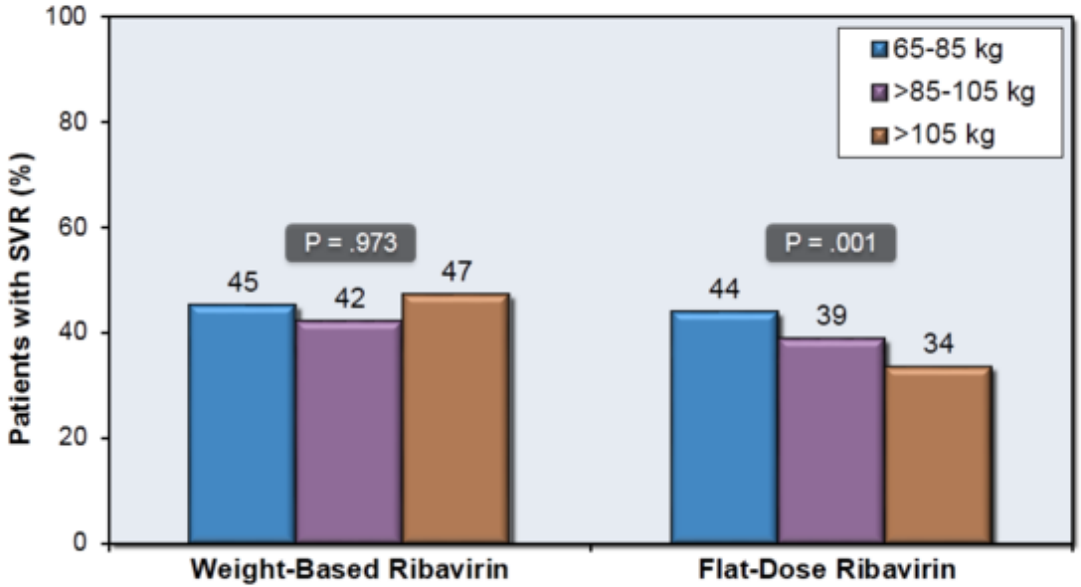


Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Hepatitis web study

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Results

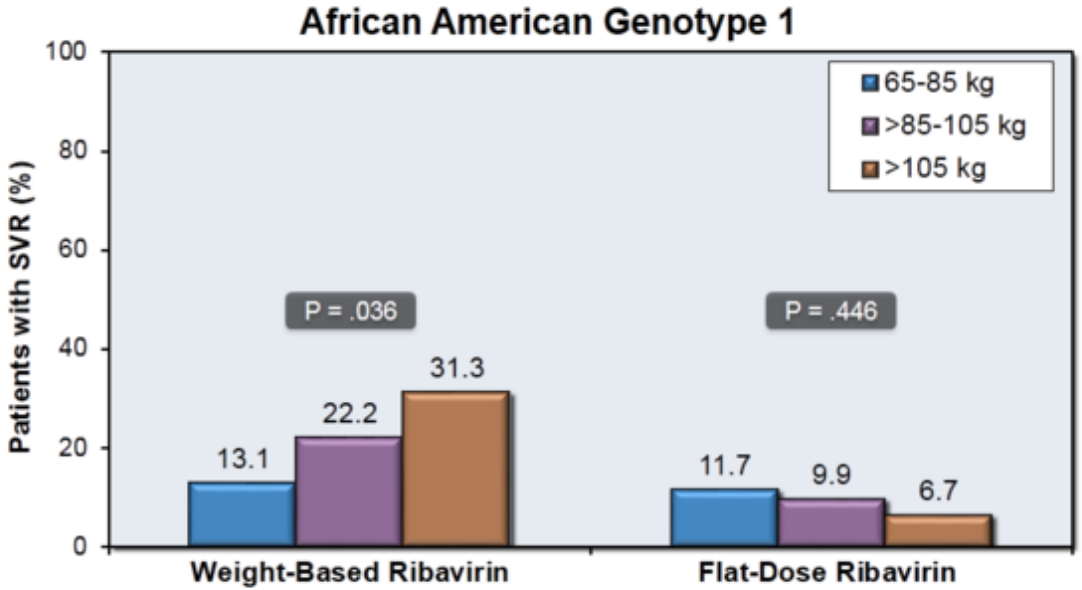
All Treated: SVR24 by Weight Distribution



Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Results

Sustained Virologic Response (SVR) by Weight Distribution



Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

PEGINTERFERON ALFA-2B (*PEGINTRON*)

Background and Dosing

Peginterferon alfa-2b and Weight-based or Flat-dose Ribavirin
WIN-R Study: Conclusions

Conclusion: "Peginterferon alfa-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in genotype 1 patients, providing equivalent efficacy across all weight groups. Ribavirin 1400 mg/day is appropriate for patients 105 to 125 kg. For genotype 2/3 patients, 24 weeks of treatment with flat-dose ribavirin is adequate; no evidence of additional benefit of extending treatment to 48 weeks was demonstrated."

Source: Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Weight-based Ribavirin in HCV GT 2,3

Zeuzem S, et al. J Hepatol. 2004;40:993-9.

Peginterferon alfa-2b + Ribavirin for GT 2 or 3
Study Design

- **Study**
  - Single arm, open-label, historical-control, phase 4 study
  - Conducted in 39 centers in Europe
- **Subjects**
  - N = 224 with chronic hepatitis C enrolled (223 treated)
  - Treatment naïve adult patients with genotype 2 or 3 HCV
- **Regimens**
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Ribavirin*: 800-1400 mg/d x 24 wks
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

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

Source: Zeuzem S, et al. J Hepatol. 2004;40:993-9.

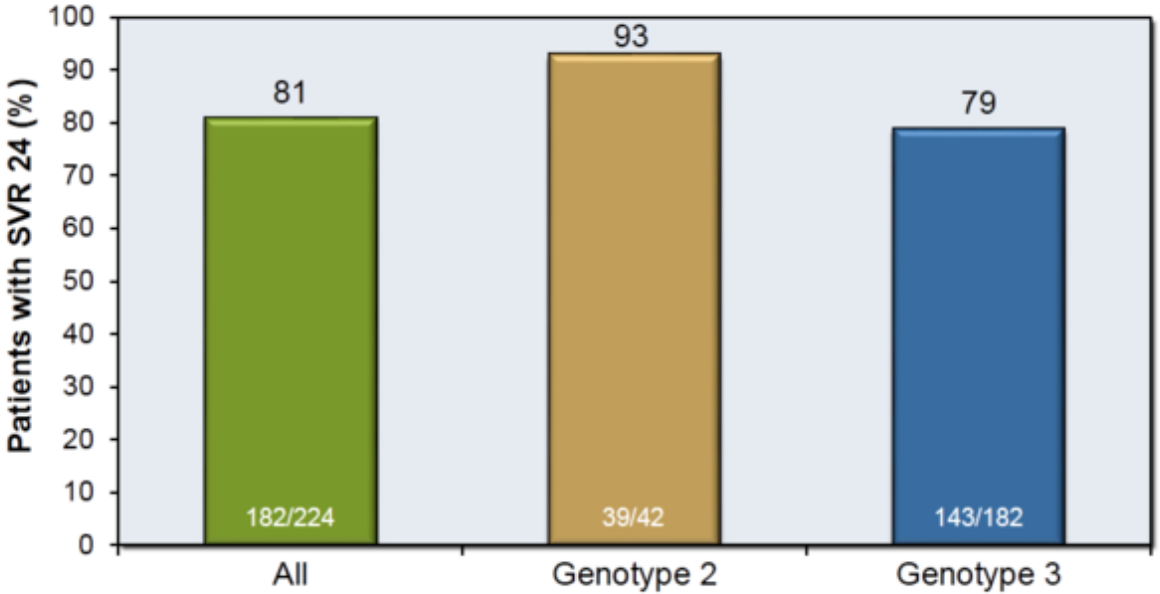
Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Treatment Duration and Ribavirin Dose

Drug Dosing
Peginterferon alfa-2b: 1.5 µg/kg 1x/week
Ribavirin (divided bid): 800-1400 mg/day
Ribavirin dosing: <65 kg = 800 mg/d; 65-85 kg = 1000 mg/d; >85-105 kg = 1200 mg/d; >105 kg = 1400 mg/d

Source: Zeuzem S, et al. J Hepatol. 2004;40:993-9.

Peginterferon alfa-2b + Ribavirin for GT 2 or 3
Results

SVR24 Rates, by Genotype



Source: Zeuzem S, et al. J Hepatol. 2004;40:993-9.

Peginterferon alfa-2b + Ribavirin for GT 2 or 3
Conclusions

Conclusions: "Treatment for 24 weeks with peginterferon alfa-2b and ribavirin is sufficient in HCV 2 or 3 infected patients. The lower SVR in patients infected with HCV-3 compared with HCV-2 infected patients may be related to higher levels of steatosis in this population."

Source: Zeuzem S, et al. J Hepatol. 2004;40:993-9.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin for 12 or 24 Weeks in GT 2,3

Mangia A, et al. N Engl J Med. 2005;352:1609-17.

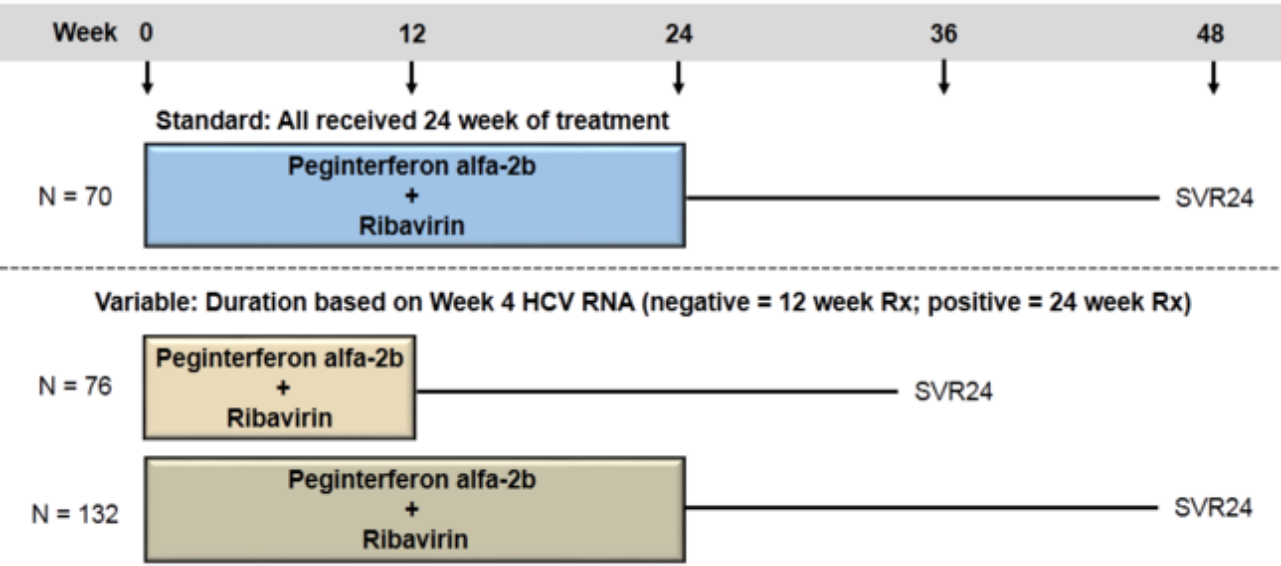
Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Study Design

- **Study**
  - Randomized, open-label trial
  - Conducted in 12 centers in Italy
- **Subjects**
  - N = 283 with chronic hepatitis C
  - Treatment naïve adult patients
  - Genotype 2 or 3
- **Regimens**
  - Peginterferon alfa-2b: 1.0 µg/kg/wk + Ribavirin: 1000-1200 mg/d x 24 wks
  - Peginterferon alfa-2b: 1.0 µg/kg/wk + Ribavirin: 1000-1200 mg/d x 12 or 24 wks*
- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

*Duration based on whether week 4 HCV RNA negative (12 weeks) or positive (24 weeks)

Source: Mangia A, et al. N Engl J Med. 2005;352:1609-17.

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Treatment Duration and Ribavirin Dose



Drug Dosing

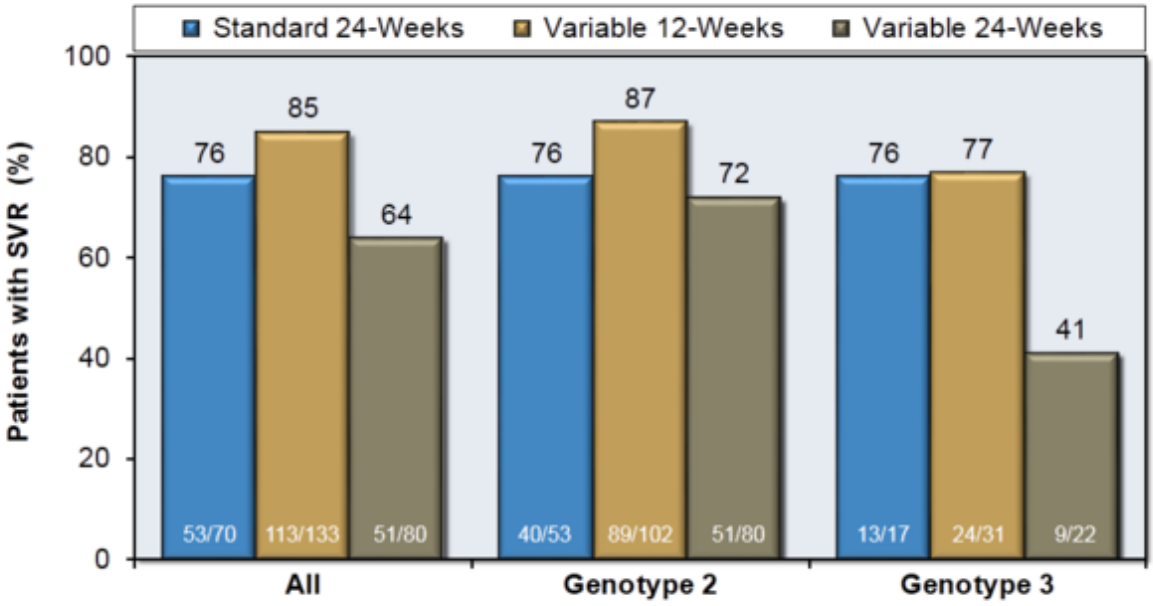
Peginterferon alfa-2b: 1.5 µg/kg 1x/week

Ribavirin (divided bid): <75 kg (1000 mg/day); ≥75 kg (1200 mg/day)

Source: Mangia A, et al. N Engl J Med. 2005;352:1609-17.

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Treatment Duration and Ribavirin Dose

SVR24 Rates, by Regimen



Source: Mangia A, et al. N Engl J Med. 2005;352:1609-17.

Peginterferon alfa-2b (*PegIntron*) Summary

- **Approval Status**: FDA approved in 2001
- **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:**
  - 1.5 mcg/kg 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-2b (*PegIntron*) Prescribing Information. Merck & Co.

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Conclusions

Conclusions: "A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at 4 weeks."

Source: Mangia A, et al. N Engl J Med. 2005;352:1609-17.

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.

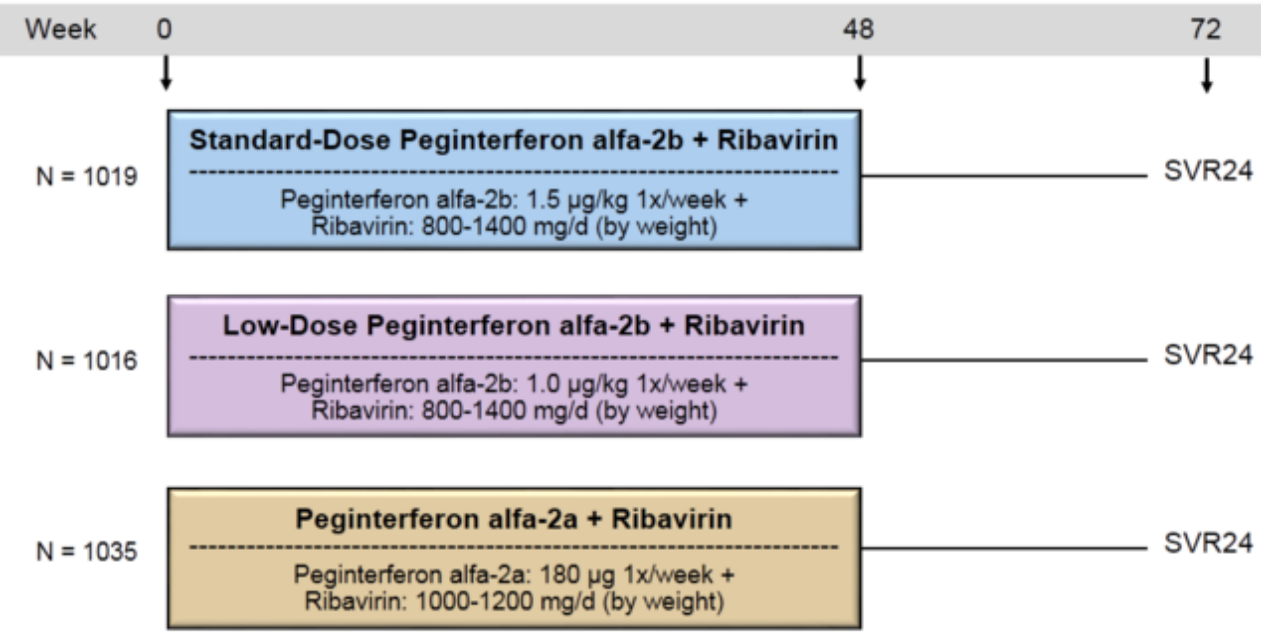
Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Design

- **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.

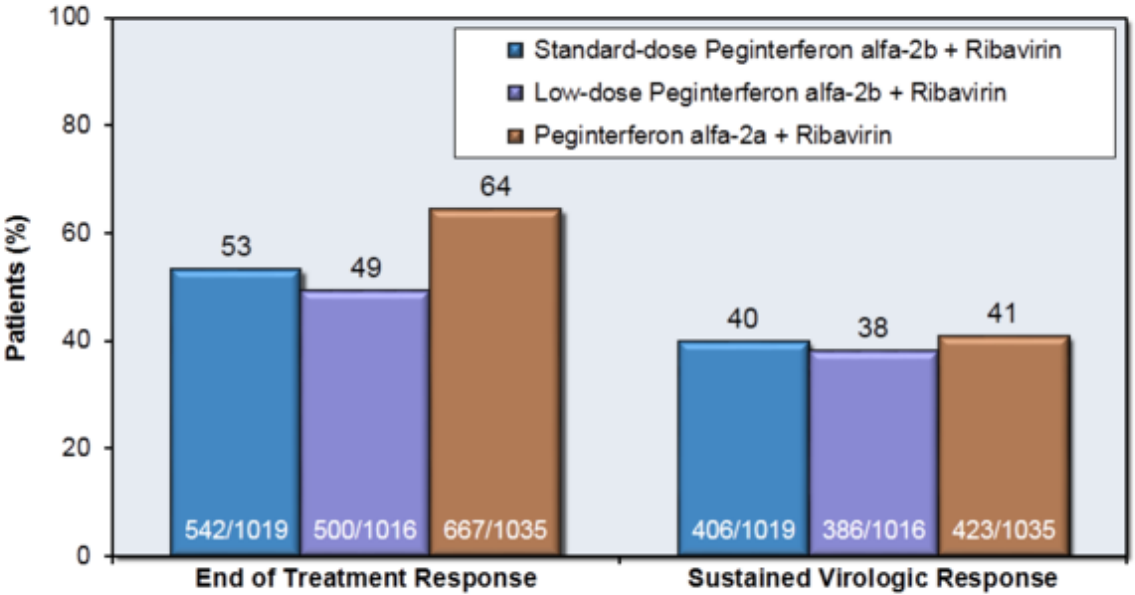
Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Design



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

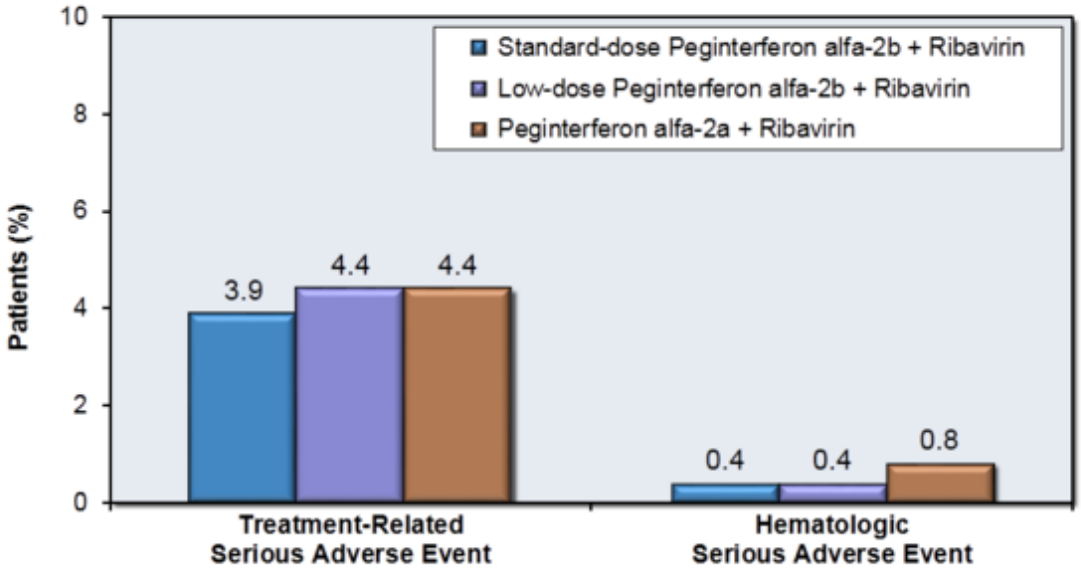
IDEAL Study: Virologic Responses by Treatment Regimen



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

Peginterferon alfa-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

Peginterferon alfa-2b + RBV *versus* Interferon alfa-2b

RIBAVIC STUDY

Carrat F, et. al. JAMA. 2004;292:2839-48.

Peginterferon + RBV *versus* Interferon + RBV in HCV & HIV
RIBAVIC Study: Design

- **Study**
  - Randomized, phase 3, open-label, parallel group trial
  - Conducted at 71 French centers
- **Subjects**
  - N = 412 chronically infected with both HCV and HIV
  - Treatment naïve; 48% genotype 1
  - CD4 >200 cells/mm^3
- **Regimens (48 Week Treatment)**
  - Peginterferon alfa-2b 1.5 µg 1x/week + Ribavirin 800 mg/day
  - Interferon alfa-2b: 3 million IU 3x/week + Ribavirin 800 mg/day
- **Primary Endpoint**
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

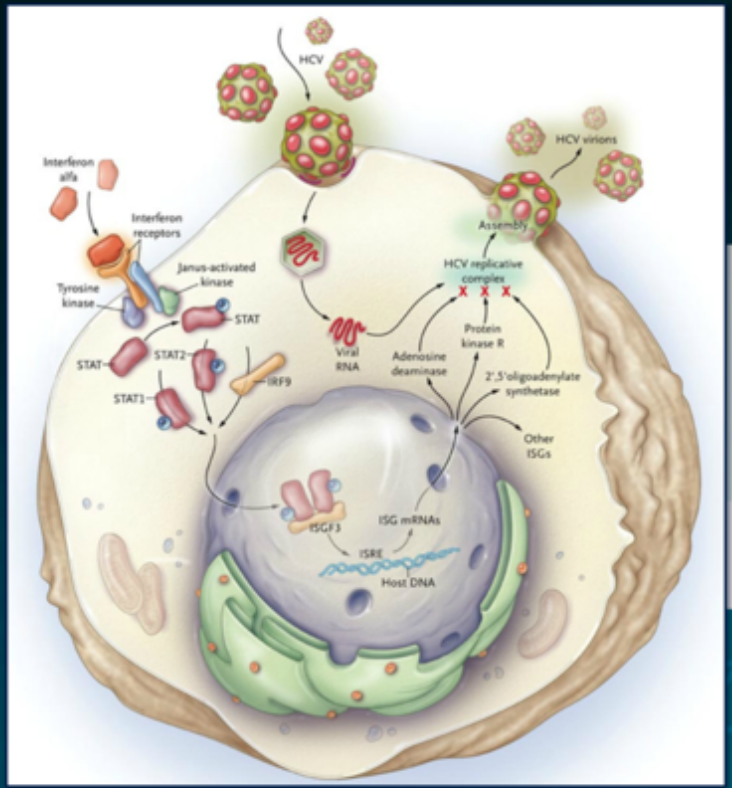
Source: Carrat F, et. al. JAMA. 2004;292:2839-48.

Peginterferon + RBV *versus* Interferon + RBV in HCV & HIV
RIBAVIC Study: Design

Drug Dosing
Peginterferon alfa-2b: 1.5 µg/kg 1x/week
Standard Interferon alfa-2b 3 million units 3x/week
Ribavirin (divided bid): 800 mg/day

Source: Carrat F, et. al. JAMA. 2004;292:2839-48.

Interferon: Proposed Mechanism of Action



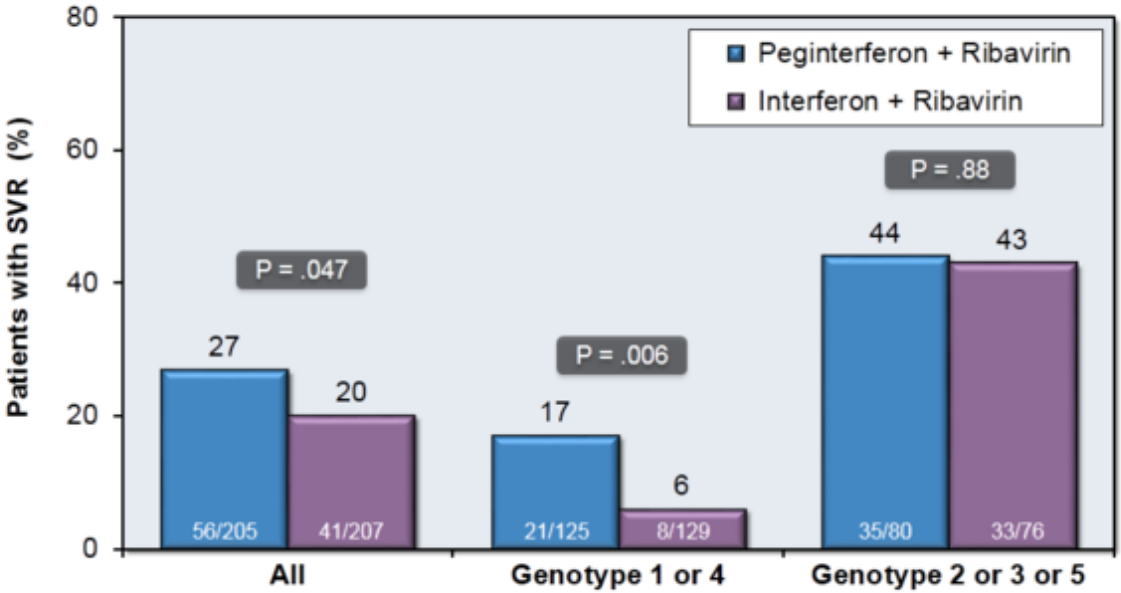
Interferon alfa engages receptors on the surface of the hepatocyte, initiating intracellular signal transduction that prompts the transcription of multiple interferon-stimulated genes (ISGs). These ISGs encode proteins that can interfere at various stages of the hepatitis C viral life cycle.

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

Peginterferon + RBV *versus* Interferon + RBV in HCV & HIV
RIBAVIC Study: Design

RIBAVIC Study: SVR24 by Treatment Regimen and Genotype



Source: Carrat F, et. al. JAMA. 2004;292:2839-48.

Peginterferon + RBV *versus* Interferon + RBV in HCV & HIV
RIBAVIC Study: Conclusions

Conclusion: "In combination with ribavirin, treatment with peginterferon alfa-2b is more effective than standard interferon alfa-2b for HCV infection in HIV-infected patients."

Source: Carrat F, et. al. JAMA. 2004;292:2839-48.

Hepatitis web study

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin in Blacks & Non-Hispanic Whites

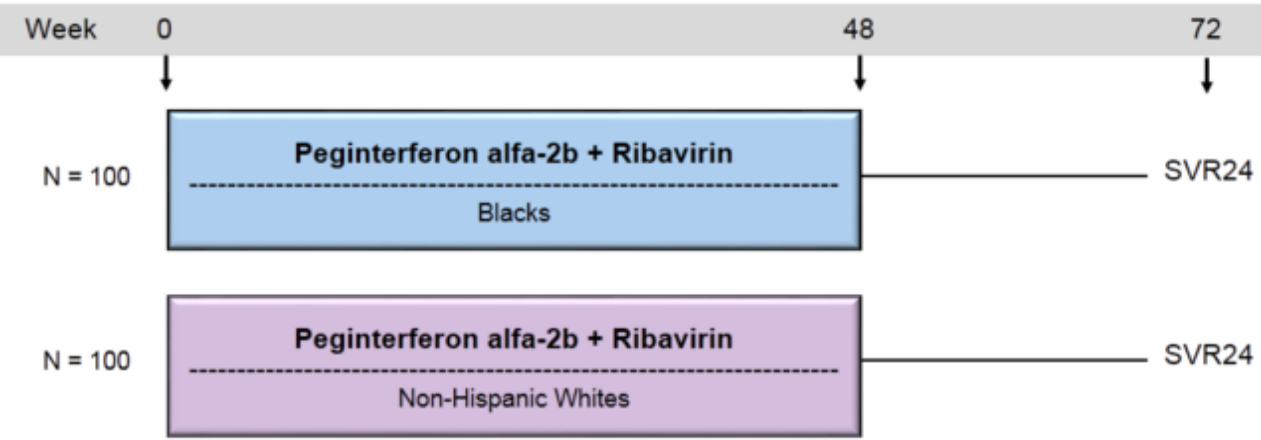
Muir AJ, et al. N Engl J Med. 2004;350:2265-71.

Peginterferon alfa-2b + Ribavirin in Blacks & Non-Hispanic Whites
Design

- **Study**
  - Prospective, multicenter, phase 3 trial
  - 16 centers in Southeastern United States
- **Subjects**
  - N = 200 adults with chronic HCV (100 blacks and 100 non-Hispanic whites)
  - Treatment naïve
  - HCV genotype (98% with genotype 1)
- **Regimens (Ribavirin Dosed by Weight)**
  - Peginterferon alfa-2b: 1.5 µg/kg 1x/week x 48 weeks +
    Ribavirin 1000 mg/day for weeks 1-12, then 800 mg/day for weeks 13-48
- **Primary Endpoint (Sustained Virologic Response [SVR])**
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

Source: Muir AJ, et al. N Engl J Med. 2004;350:2265-71.

Peginterferon alfa-2b + Ribavirin in Blacks and Non-Hispanic Whites
Results

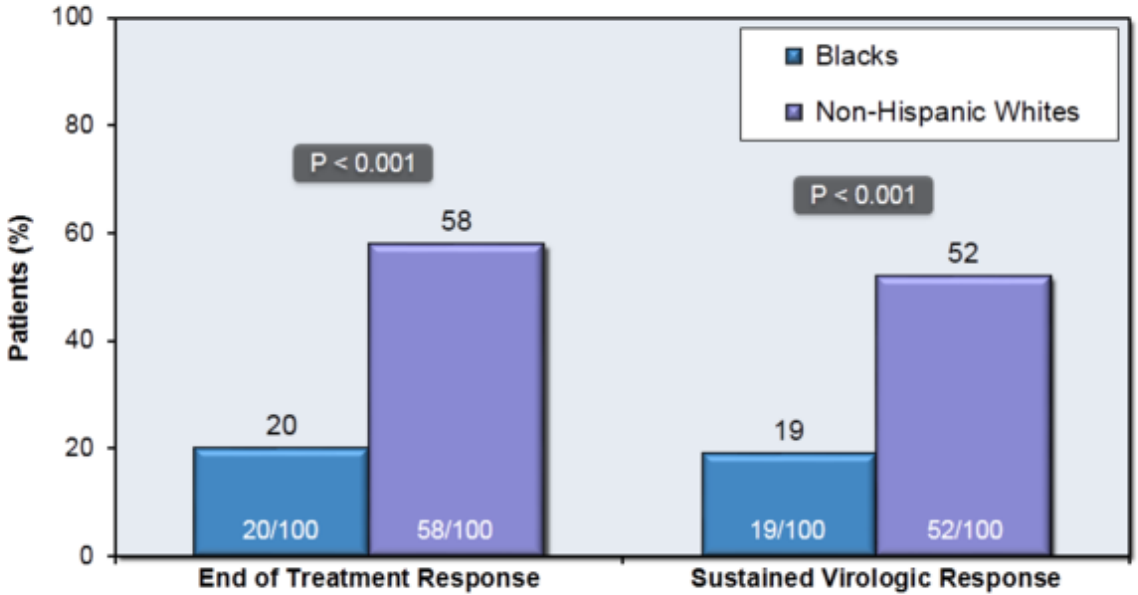


Drug Dosing
Peginterferon alfa-2b: 1.5 µg/kg 1x/week
Ribavirin (divided bid): 1000 mg/day x weeks 1-12, then 800 mg/day for weeks 13-48

Source: Muir AJ, et al. N Engl J Med. 2004;350:2265-71.

Peginterferon alfa-2b + Ribavirin in Blacks and Non-Hispanic Whites
Results

Virologic Responses by Race



Source: Muir AJ, et al. N Engl J Med. 2004;350:2265-71.

Peginterferon alfa-2b + Ribavirin in Blacks and Non-Hispanic Whites
Conclusions

Conclusions: "Black patients with chronic hepatitis C have a lower rate of response to treatment with peginterferon alfa-2b and ribavirin than non-Hispanic white patients, a difference that is not explained by differences in the viral genotype."

Source: Muir AJ, et al. N Engl J Med. 2004;350:2265-71.

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-2b (*PegIntron*) Contraindications

- Known hypersensitivity reaction
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score > 6) in cirrhotic patients
- Additional contraindications when used with ribavirin
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Coadministration with didanosine

Source: Peginterferon alfa-2b (*PegIntron*) Prescribing Information. Merck & Co.

Peginterferon alfa-2b Hematologic Dose Modification Guidelines for Adults

Dose Adjustments for Peginterferon alfa-2b In Adults		
Laboratory	**Value**	**Recommendation**
WBC	1.0 to <1.5 x 10^9/L	Reduce dose*
	<1.0 x 10^9/L	Discontinue treatment
Neutrophils	0.5 to <0.75 x 10^9/L	Reduce dose*
	<0.5 x 10^9/L	Discontinue treatment
Platelets	25 to <50 x 10^9/L	Reduce dose*
	< 25 x 10^9/L	Discontinue treatment
*Adult patients on combination therapy: 1st dose reduction is to 1 mcg/kg/week. If needed, 2nd dose reduction is to 0.5 mcg/kg/week.		

Source: Peginterferon alfa-2b (*PegIntron*) Prescribing Information. Merck & Co.

Peginterferon alfa-2b 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	Adjust dose. With combination therapy: 1st dose reduction is to 1 mcg/kg/week, 2nd dose reduction (if needed) is to 0.5 mcg/kg/week.	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-2b permanently	Obtain immediate psychiatric consultation	Psychiatric therapy as necessary		

Source: Peginterferon alfa-2b (*PegIntron*) Prescribing Information. Merck & Co.

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin

versus

Interferon alfa-2b + Ribavirin

Manns MP, et. al. Lancet. 2001;358:958-65

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
Study Design

- **Study**
  - Open-label, randomized controlled trial
  - 62 sites in Europe, North America, & Argentina
- **Subjects**
  - N = 1530 with chronic hepatitis C
  - Treatment naïve
  - Genotype 1: 68%; Genotype 2 or 3: 29%; Genotype 4,5, or 6: 3%
  - Serum ALT >34 IU/L for women, >43 IU/L for men
- **Regimens**
  - Higher Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week + ribavirin 800 mg/day
  - Lower Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week x 4 weeks then 0.5 µg/kg 1x/week + ribavirin 1000-1200 mg/day*
  - Standard interferon alfa-2b: 3 million U 3x/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: <75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day

Source: Manns MP, et. al. Lancet. 2001;358:958-65.