



# **Anemia Associated With the Treatment of Hepatitis C Virus (HCV) Infection**

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# National Anemia Action Council

[www.anemia.org](http://www.anemia.org)

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# NAAC Mission



The National Anemia Action Council, Inc. (NAAC) is dedicated to raising the awareness of health care professionals and the public regarding the prevalence, symptoms, consequences, and treatment options of anemia.

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# NAAC's Online Resources for Medical Professionals



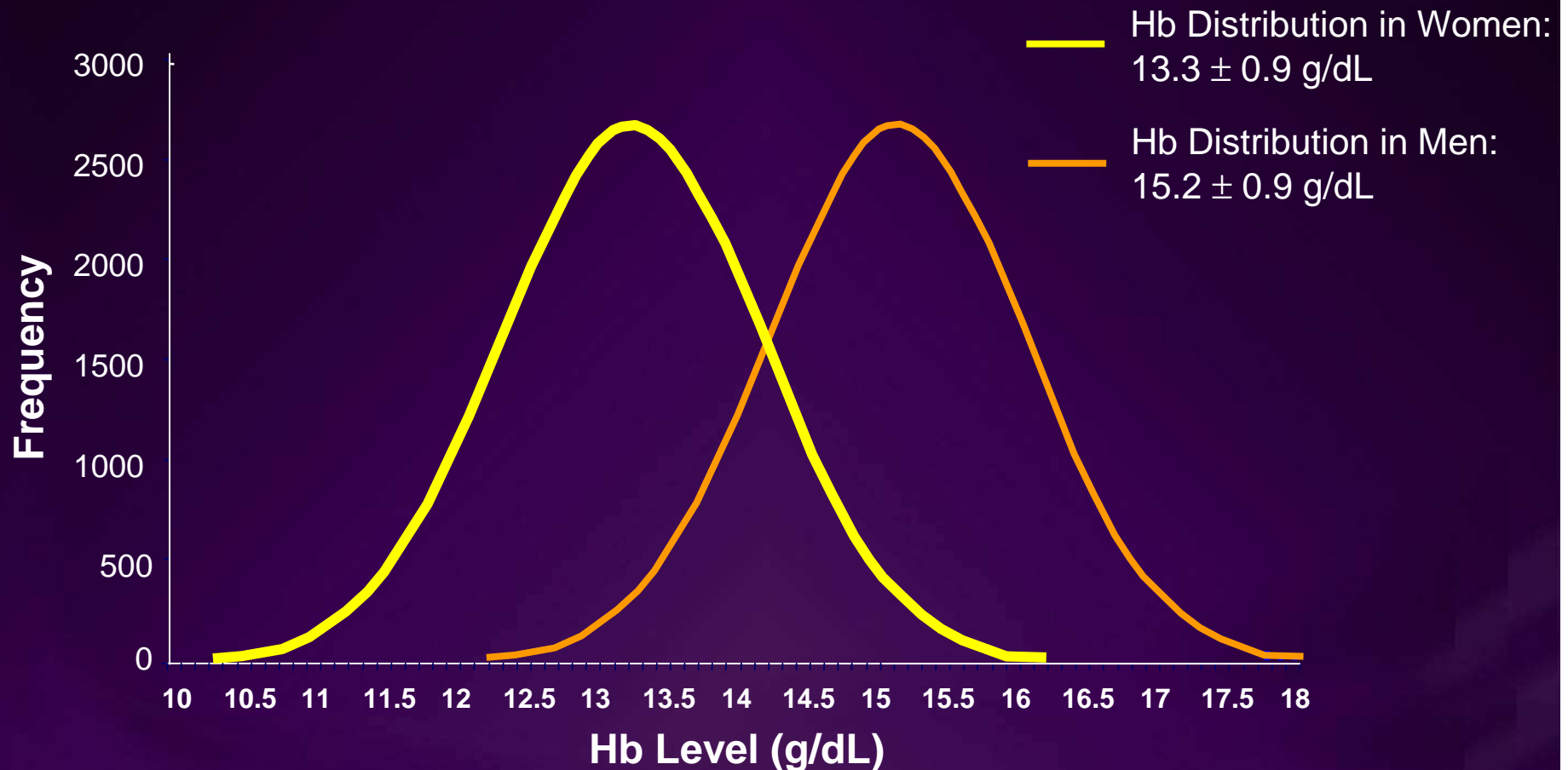
- Research Reviews - Recent clinical trials reviewed
- Ask the Expert - Your anemia questions answered
- Monograph - In-office handbook on anemia
- Feature Articles - Anemia related news and research
- Anemia Alert - Free monthly e-newsletter
- Slide Sets - Educational presentations about anemia
- We have materials for your patients too!

# Key Points



- Anemia is a major side effect of therapy in patients with hepatitis C virus (HCV) infection
- Anemia causes decreased quality of life and may lead to dose reduction or discontinuation of HCV therapy
- Treatment with rHuEPO improves anemia in HCV patients and may help maintain therapeutically optimal HCV treatment dose levels

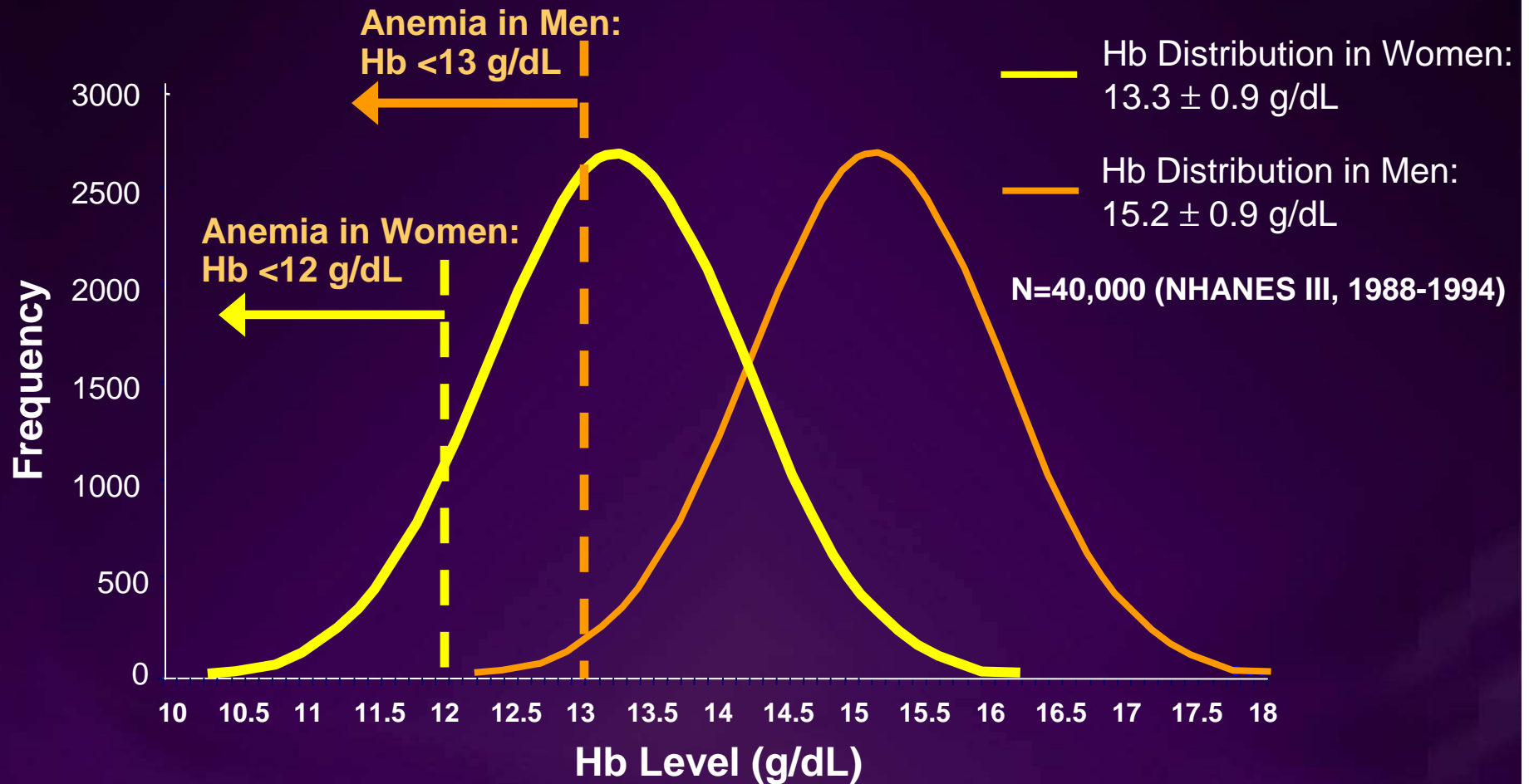
# Hemoglobin (Hb) Distribution in the General Population



**N=40,000 (NHANES III, 1988-1994)**

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

# WHO Definition of Anemia vs Hb Distribution in General Population



1. World Health Organization. Geneva, Switzerland; 2001.

2. Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

# Laboratory Reference Ranges

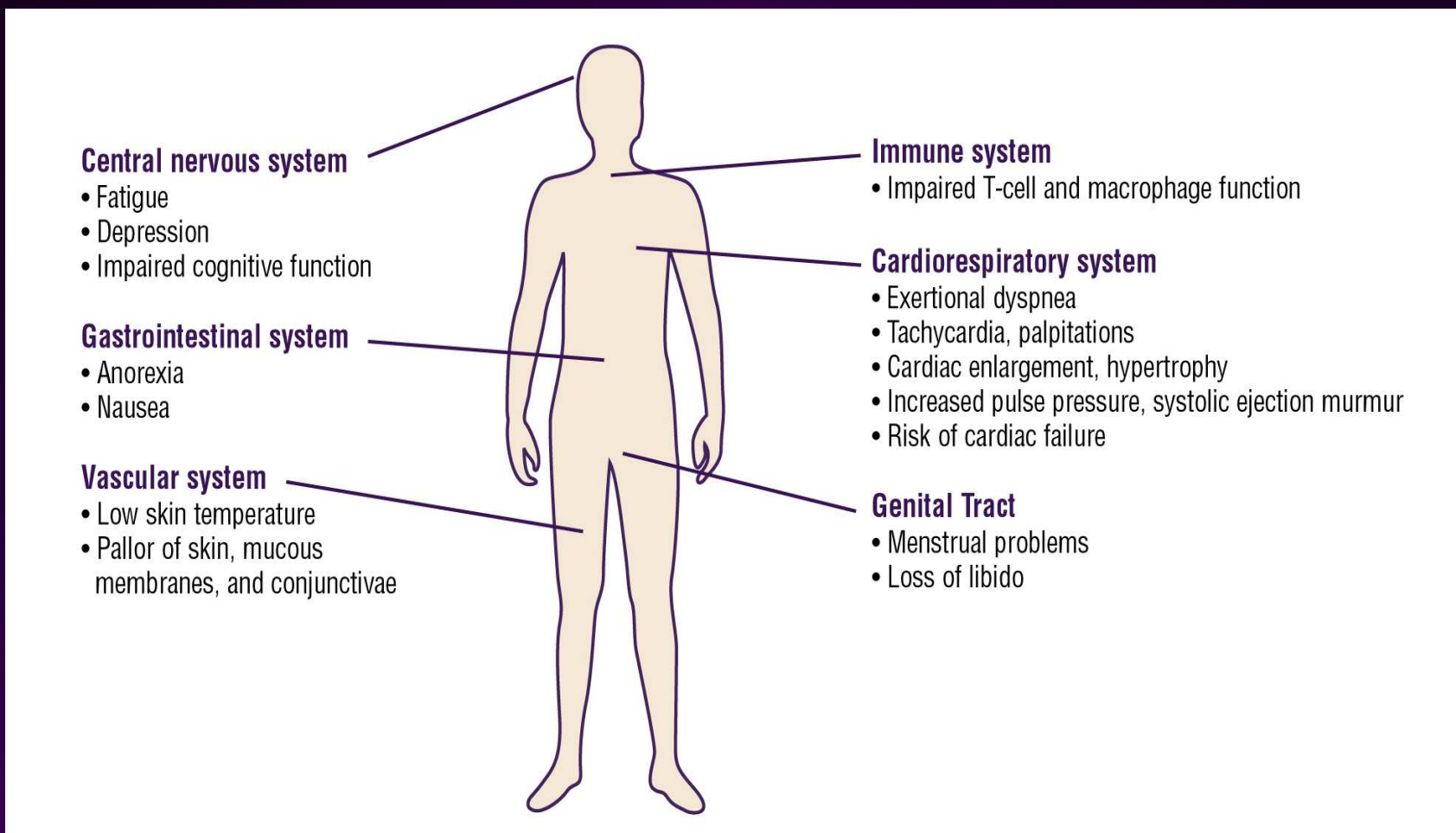


Parameter	Male	Female
Hb (g/dL)	14.0 – 17.4	12.3 – 15.3
Hct (%)	41.5 – 50.4	36.0 – 45.0
RBC count ( $10^6/\mu\text{L}$ )	4.5 – 5.9	4.5 – 5.1
Reticulocyte count (% of RBC count)	0.5 – 2.5	
Mean corpuscular volume (fL)	80 – 96	
Mean corpuscular Hb (MCH) (pg)	27.5 – 33.2	
MCH concentration (g/dL)	33.4 – 35.5	

Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell

Perkins S. In: Lee G et al, eds. *Wintrobe's Clinical Hematology (Vol. 2)*. 10th ed. Baltimore, Md: Lippincott, Williams & Wilkins; 1998:2738.

# Anemia Signs and Symptoms



Ludwig H, et al. *Semin Oncol* 1998;25(suppl 7):2-6.

# Hepatitis C Virus (HCV) Infection Is Common



- Affects 3% of world population<sup>1</sup>
- Affects 1.8% of general US population, and in this group 74% are chronically infected<sup>2</sup>
- Much more prevalent in disadvantaged groups in US, such as the homeless, prisoners (39% to 54%)<sup>3</sup>
- In US, most prevalent among people 40 to 59 years old, especially African Americans<sup>4</sup>

1. World Health Organization. *Wkly Epidemiol Rec.* 1997;72:341-344.

2. Alter MJ, et al. *N Engl J Med.* 1999;341:556-562.

3. Kim WR. *Hepatology.* 2002;36(5 suppl 1):S30-S34.

4. NIH Consensus Development Conference. *Hepatology.* 2002;36(suppl 1):S3-S30.

# Certain Groups Are at High Risk of HCV Infection



## Highest risk

- Current injection drug users 72% - 86%
- Hemophiliacs treated before 1987 74% - 90%
- People on chronic hemodialysis 0% - 64%

## Intermediate risk

- Infants born to infected mothers 0% - 25%
- People with abnormal ALT levels 10% - 18%
- Men who have sex with men 2% - 18%
- People with >50 lifetime sex partners 6% - 16%
- People transfused before 1992 5% - 9%

Centers for Disease Control and Prevention. Hepatitis C: epidemiology.  
[http://www.cdc.gov/ncidod/diseases/hepatitis/c\\_training/edu/1/epidem-demo.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/c_training/edu/1/epidem-demo.htm).

# Most HCV Patients Develop Chronic Liver Disease



## Acute infection

- Can be severe but is rarely fulminant<sup>1</sup>
- Symptoms are uncommon<sup>1</sup>
- 75% to 85% of infected people have chronic viremia<sup>2</sup>

## Chronic infection

- 70% of people with chronic HCV develop chronic liver disease<sup>2</sup>
- 10% to 20% develop cirrhosis<sup>2,3</sup>
- HCV is the leading single indication for liver transplantation<sup>1,2</sup>
- HCV accounts for ~33% of hepatocellular carcinoma cases<sup>1</sup>

1. NIH Consensus Development Conference. *Hepatology*. 2002;36(suppl 1):S3-S30.

2. Centers for Disease Control and Prevention. Hepatitis C fact sheet.  
<http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm>. April 1, 2003.

3. Tran TT, et al. *Curr Treat Options Gastroenterol*. 2001;4:503-510.

# Treatment for Chronic HCV



- Two components of combination therapy:
  - Interferon- $\alpha$  (IFN- $\alpha$ )
  - Ribavirin (RBV)
- Both may be associated with anemia

National Institute of Diabetes and Digestive and Kidney Diseases. Chronic hepatitis C: current disease management. NIH Publication 03-4230. Bethesda, Md; March 2003.

# IFN- $\alpha$ Therapy Can Cause Anemia



- IFN- $\alpha$  is myelosuppressive in HCV patients<sup>1</sup>
- IFN- $\alpha$  has been associated with autoimmune hemolytic anemia<sup>2</sup>
- HCV patients never treated with IFN- $\alpha$  have also been known to develop hemolytic anemia<sup>3-5</sup>
- Careful monitoring of Hb is warranted for all HCV patients<sup>6</sup>

1. Homoncik M, et al. AASLD meeting, 2001 [abstract].

2. Takase K, et al. *J Gastroenterol.* 1995;30:795-797.

3. Chao T-C, et al. *J Clin Gastro-enterol.* 2001;33:232-233.

4. Moccia F, et al. *Ann Ital Med Int.* 2001;16:256-259.

5. Srinivasan R. *J Clin Gastroenterol.* 2001;32:245-247.

6. National Anemia Action Council. *Anemia: A Hidden Epidemic.* Los Angeles; 2002, p. 55.

# HCV Combination Therapy Is Associated With Hemolytic Anemia



- The anemia is attributed mainly to ribavirin (RBV)
- Hb decline is “universal,” although its severity varies<sup>1</sup>
- Hb <10 g/dL occurred in 10% to 13% of patients in the pivotal clinical trials of peg-IFN- $\alpha$  + RBV<sup>2-4</sup>
- Symptoms of RBV anemia can include fatigue, dyspnea on exertion, reduced exercise capacity<sup>5</sup>

1. Fried MW. *Hepatology*. 2002;36(suppl 1):S237-244.

2. Fried MW, et al. *N Engl J Med*. 2002;347:975-982.

3. Manns MP, et al. *Lancet*. 2001;358:958-965.

4. *Physicians' Desk Reference*. PDR 57 Edition 2003. Thomson PDR, Montvale, NJ, 3076-3081.

5. Mangoni ED, et al. *Antivir Ther*. 2003;8:57-63.

# Hb Decline Follows a Pattern During HCV Combination Therapy



Typically, the decline in Hb:

- Is at least 2 g/dL to 3 g/dL from baseline<sup>1,2</sup>
- Starts during week 1 or week 2 of therapy<sup>1,2</sup>
- Reaches nadir by week 4 to 8 of therapy<sup>2,3</sup>
- Returns to baseline 4 to 8 weeks status post therapy<sup>3,4</sup>

1. National Institute of Diabetes and Digestive and Kidney Diseases. 2003.

2. Scott LJ, et al. *Drugs*. 2002;62:507-556.

3. *Physicians' Desk Reference*. PDR 57 Edition 2003. Thomson PDR, Montvale, NJ, 3076-3081.

4. Fried MW, et al. *N Engl J Med*. 2002;347:975-982.

# Proposed Mechanism of RBV Anemia



- RBV enters red blood cells and is converted to phosphates
- RBV is trapped in the red blood cells because the phosphates cannot cross the cell membrane
- Because of the increase in RBV triphosphate, the cells become deficient in adenosine triphosphate, which impairs their antioxidant defense mechanisms
- The cell membranes sustain oxidative damage, and the cells are removed from the circulation

De Franceschi L, et al. *Hepatology*. 2000;31:997-1004.

# Other Risk Factors for Hb Decline During HCV Therapy



- Higher pretreatment Hb<sup>1,2</sup> ( $P < .001$ )
- Lower pretreatment platelet count due to more advanced liver disease<sup>2</sup> ( $P = .04$ )
- Higher dose of IFN- $\alpha$ <sup>2</sup> ( $P = .005$ )

1. Sulkowski MS, et al. *Hepatology*. 2000;32:368A [abstract].

2. Van Vlierberghe H, et al. *J Hepatol*. 2001;34:911-916.

# Guidelines for Monitoring HCV Combination Therapy



- Assess patients for cardiac disease before initiating treatment
- Order pretreatment ECG for patients with preexisting cardiac disease
- Monitor cardiovascular status during treatment
- Measure Hb before treatment and at weeks 2 and 4, or more frequently if clinically indicated

1. *Physicians' Desk Reference. PDR 57 Edition 2003.* Thomson PDR, Montvale, NJ, 3076-3081.

2. Fried MW, et al. *N Engl J Med.* 2002;347:975-982.

# Anemia Management Options During Combination Therapy



- RBV dose reduction
- RBV discontinuation
- Allogeneic red blood cell transfusion
- Recombinant human erythropoietin (rHuEPO)

# RBV Reduction/Withdrawal During HCV Therapy



Group	N-Combination Therapy Arm(s)	Had RBV Dose Reduced	Had RBV Withdrawn
McHutchison, 1998	228 – 24 wks	7% – 24 wks	<1%
	228 – 48 wks	9% – 48 wks	
Poynard, 1998	281 – 24 wks	6% – 24 wks	<1%
	278 – 48 wks	7% – 48 wks	
Reichard, 1998	50 – 24 wks	2%	2%
Davis, 1998	173 – 24 wks	--- 7% ---	
Andreone, 1999	26 – 24 wks	4%	0

1. McHutchison JG, et al. *N Engl J Med.* 1998; 339:1485-1492.

2. Poynard T, et al. *Lancet.* 1998;352:1426-1432.

3. Reichard O, et al. *Lancet.* 1998;351:83-87.

4. Davis GL, et al. *N Engl J Med.* 1998;339:1493-1499.

5. Andreone P, et al. *J Hepatol.* 1999;30:788-793.

# RBV Reduction/Withdrawal May Impair Response to HCV Therapy



## Study design

Retrospective analysis of data on 316 patients who received combination therapy in one of two RCTs

## Response rates

In the original intent-to-treat analysis:

41% overall, 29% genotype 1, 67% genotype 2 or 3

In the 63% of patients who received  $\geq 80\%$  of the intended doses for the full treatment period:

48% overall, 37% genotype 1, 72% genotype 2 or 3

## Conclusion

Make every effort to continue the maximum tolerable dose for the duration of treatment

McHutchison JG, et al. *Gastroenterology*. 2002;123:1061-1069.

# Principal Risks of Allogeneic Blood Transfusion



Blood transfusion risk	Estimated frequency per actual unit
Hepatitis C	1/30,000–1/150,000
Hepatitis B	1/30,000–1/250,000
Hepatitis A	1/1,000,000
HIV type 1	1/200,000–1/2,000,000
HTLV (I, II)	1/250,000–1/2,000,000
Hemolytic reaction, acute	1/250,000–1/1,000,000
Hemolytic reaction, delayed	1/1,000
Bacterial infection, platelets	1/12,000
Bacterial infection, red cells	1/500,000
Transfusion-related acute lung injury	1/5,000

Goodnough LT, et al. *N Engl J Med.* 1999;340:438-447.

# Other Risks of Allogeneic Blood Transfusion



- Febrile nonhemolytic reaction
- Allergic reactions
- Alloimmunization
- Circulatory overload — can lead to pulmonary edema
- Metabolic complications
- Hypothermia — can lead to cardiac arrhythmia, cardiac arrest
- Anaphylactoid reactions (rare)
- Graft-versus-host disease (rare)

American Red Cross. 1999.

# Rationale for Use of rHuEPO



- HCV combination therapy with RBV causes anemia, which is associated with reduced quality of life and may lead to treatment noncompliance
- HCV treatment-related anemia may require RBV dose reduction or discontinuation, perhaps decreasing sustained response rate
- Patients who received rHuEPO had significantly higher Hb levels, fewer RBV dose reductions, and fewer therapy discontinuations than the group not receiving rHuEPO
  - rHuEPO can be used to maintain therapeutically optimal RBV dose
  - Maintenance of higher RBV dose may lead to improved sustained response rate (although this is as yet unproven)

Dieterich DT, et al. *Clin Infect Dis.* 2003;37:533-541.

# rHuEPO May Boost Hb During HCV Therapy



Study	N	Principal Finding
Wasserman et al, 2000	10 rHuEPO 9 standard care	Hb in the rHuEPO group ↑ significantly vs baseline ( $P < .01$ ) and vs standard care ( $P < .05$ )
Dumitrascu et al, 2001	6 rHuEPO	In 5 patients, Hb ↑ by at least 20%. One stopped rHuEPO due to exacerbation of hypertension.
Talal et al, 2001	18 rHuEPO 38 nonanemic	Hb in the rHuEPO group ↑ to levels similar to Hb in nonanemic patients
Gergely et al, 2002	13 rHuEPO	Median nadir Hb ↑ from 10.2 to 11.5 g/dL

1. Wasserman R, et al. *Hepatology*. 2000;32:368A. Abstract 833.

2. Dumitrascu DL, et al. *Gut*. 2001;49(suppl 3). Abstract 1544.

3. Talal AH, et al. *Am J Gastroenterol*. 2001;96:2802-2804.

4. Gergely AE, et al. *Hepatology*. 2002;35:1281-1282.

# rHuEPO May Permit More Optimal RBV Dosing



Study	N	Finding
Weisz et al, 1998	17	During rHuEPO therapy, 14 patients were able to continue HCV combination therapy  2 patients stopped combination therapy due to anemia; 1 stopped due to nonresponse
Wasserman et al, 2000	19	0 of 10 patients on rHuEPO had RBV dose reduced, vs 3 of 9 on standard care
Gergely et al, 2002	13	During rHuEPO therapy, no patient had to stop combination therapy due to anemia

1. Weisz K, et al. *Hepatology*. 1998;30:288A. Abstract 501.
2. Wasserman R, et al. *Hepatology*. 2000;32:368A. Abstract 833.
3. Gergely AE, et al. *Hepatology*. 2002;35:1281-1282.



# Special Populations

# Dialysis Patients With HCV



- The prevalence of HCV in dialysis patients is as high as 64%<sup>1</sup>
- Dialysis patients seem to experience more severe anemia during HCV therapy vs patients without kidney disease<sup>2</sup>
- Only a small fraction of RBV is eliminated during dialysis,<sup>3</sup> and the risk of RBV anemia may be elevated<sup>4</sup>
- RBV is presently contraindicated for patients with creatinine clearance <50 mL/min<sup>4</sup>

1. Centers for Disease Control and Prevention. 2003.

2. Tan AC, et al. *Nephrol Dial Transplant*. 2001; 16:193-195.

3. Bruchfeld A, et al. *J Viral Hepat*. 2001;8:287-292.

4. *Physicians' Desk Reference*. PDR 57 Edition 2003. Thomson PDR, Montvale, NJ, 3076-3081.

# rHuEPO May Facilitate HCV Therapy for Dialysis Patients



Study	N	Findings
Bruchfeld et al, 2001	5 – hemodialysis 1 – peritoneal dialysis	5 patients — With rHuEPO, maintained Hb $\geq$ 9.5 g/dL throughout 28 weeks of low-dose RBV  1 patient — First patient treated; started on a higher RBV dose than the others; required transfusion despite rHuEPO
Tan et al, 2001	5 – hemodialysis	2 patients — Discontinued RBV due to severe anemia despite rHuEPO and transfusions  3 patients — With rHuEPO, stayed on low-dose RBV for $\geq$ 24 weeks, but 2 of them had transfusions for Hb $\sim$ 5 g/dL

1. Bruchfeld A, et al. *J Viral Hepat.* 2001;8:287-292.
2. Tan AC, et al. *Nephrol Dial Transplant.* 2001;16:193-195.

# HCV-HIV Coinfected Patients



- ~25% of HIV patients in the US have HCV<sup>1</sup>
- HCV-HIV coinfection has been associated with:<sup>1,2</sup>
  - Higher HCV load
  - Increased risk of cirrhosis
  - More rapid progression to fibrosis, cirrhosis
  - Increased liver-related mortality
  - Greater risk of perinatal transmission of HCV, HIV

1. Centers for Disease Control and Prevention. 2001.

2. Dieterich. *J Infect Dis.* 2002;185(suppl 2):S128-S137.

# rHuEPO May Facilitate HCV Therapy for HCV-HIV Patients



- HIV patients are already at risk of disease-related anemia and zidovudine-induced anemia
- Preliminary report on ongoing trial:
  - 14 HCV-HIV patients have received IFN- $\alpha$  + RBV
  - Anemia has occurred in 3 (21%)
  - 1 patient was withdrawn due to anemia
  - Anemia resolved with rHuEPO in remainder of population

Dieterich. *J Infect Dis.* 2002;185(suppl 2):S128-S137.

# Liver Transplant Recipients With Recurrent HCV



- Recurrent HCV status post liver transplantation is an important etiologic factor for:<sup>1,2</sup>
  - Graft loss
  - Liver failure
  - Need for retransplantation
- The association of hepatic impairment to pharmacokinetics of RBV is unknown

1. Fischer L, et al. *Transplant Proc.* 1999;31:494-495.

2. Gane EJ, et al. *N Engl J Med.* 1996;334:815-820.

# rHuEPO May Facilitate HCV Therapy for Liver Transplant Recipients



Study	N	Findings
Bizollon et al, 1997	21	<p>3 patients discontinued RBV due to anemia</p> <p>All 3 had impaired renal function</p> <p>Retreatment with RBV and rHuEPO was tolerated by all 3 patients for 12 months</p>
Fischer et al, 1999	8	<p>All patients developed anemia but were successfully treated with:</p> <ul style="list-style-type: none"><li>2 — transfusion</li><li>2 — rHuEPO</li><li>6 — reduction of RBV dose</li><li>2 — discontinuation of RBV</li></ul>

1. Bizollon T, et al. *Hepatology*. 1997;26:500-504.
2. Fischer L, et al. *Transplant Proc*. 1999;31:494-495.

# Issues Under Investigation Regarding rHuEPO for HCV Patients



- Which patient subgroups benefit?<sup>1</sup>
- Should rHuEPO be limited to symptomatic patients?<sup>1</sup>
- Does rHuEPO improve sustained virological response?<sup>1,2</sup>
- What is the proper dose?<sup>2,3</sup>
- What are the side effects?<sup>3</sup>

1. Fried MW. *Hepatology*. 2002;36(suppl 1):S237-244.

2. NIH Consensus Development Conference. *Hepatology*. 2002;36(suppl 1):S3-S30.

3. National Institute of Diabetes and Digestive and Kidney Diseases. 2003.

# Summary



- Successful management of hepatitis C requires prolonged treatment with RBV combined with IFN- $\alpha$
- Hemolytic anemia is the major adverse effect of RBV
- Optimal treatment of HCV depends on maintaining the full dose of RBV for a prolonged period
- Preliminary studies have shown rHuEPO has permitted continuation of the optimal RBV dose in certain cases

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