

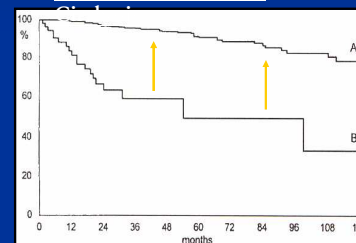
## Management of Cirrhotic Nonresponders: Building a Consensus

Kevin G. Schaefer, M.D.  
RUSH University Medical Center  
Division of Digestive Diseases  
November 29<sup>th</sup>, 2005

## What is this debate REALLY about?

Fattovich et al. *Gastroenterology*. 1997; 112(2).

Survival Rates in HCV



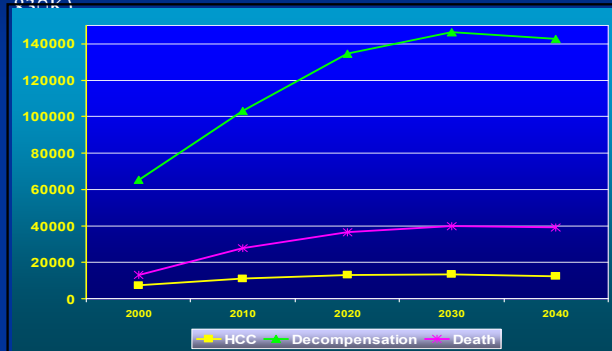
Compensated: 5-yr survival = 91%

Decompensated: 5-yr survival = 50%

Subject of Debate: Modifying the Natural History of HCV Cirrhosis

## The Scope of the Problem

- Over the next several decades, the number of patients with HCV cirrhosis is projected to increase dramatically (475K - 830K)



Davis et al. *Liver Transplantation*. 2003. 9(4): 331-38.

## The Options

- Wait for Liver Transplant

vs.

- Maintenance Therapy with PEG-IFN

vs.

- Treatment with *Consensus* Interferon

## OLT: Shifting the Problem, Not Solving It

- Liver transplantation & Hepatitis C.
  - Demand will outpace supply at even faster rate.
- HCV recurrence is nearly universal post-OLT and is difficult to treat.
  - 45% of patients will require dose reduction. (Transplantation 2004).
  - 30% of patients will discontinue therapy.
- Recurrent HCV is aggressive and can rapidly progress to cirrhosis.
  - Mean interval from OLT to cirrhosis = 10 years. (J Hepatol 2000).
  - ~20% with HCV recurrence will be cirrhotic by 5 yrs post-OLT.
- HCV(+) recipients vs. HCV(-) recipients.
  - Increased rates of graft loss and death and 1, 3 & 5 years post-OLT.

## Putting a Square PEG in a Round Hole

- Does Maintenance PEG Improve Liver Histology?<sup>1</sup>
  - Meta-Analysis of 3 RCTs assessing treatment effects of PEG-IFN.
  - Comparison of pre- and post-tx biopsies.
  - Overall, significant improvement in liver histology.
  - Amongst nonresponders, NO significant improvement noted with respect to inflammation or fibrosis.
- Treatment of patients with advanced liver disease (LADR).<sup>2</sup>
  - Previous nonresponders to IFN + RBV were EXCLUDED.
  - Overwhelming majority (96%) received traditional IFN, not PEG.
  - Genotype 1 was independent predictor of poor response.

<sup>1</sup>Camma et al. *Hepatology*, 2004; 39: 333-42.  
<sup>2</sup>Everson et al. *Hepatology*, 2003; 42: 255-62.

## Consensus Interferon (CIFN)

- Recombinant type I IFN  $\alpha$  created by combining amino acid sequences from multiple IFN  $\alpha$  subtypes.
- *In vitro* & *In vivo* studies have shown CIFN to be more 10-100x potent than traditional IFNs.<sup>1</sup>
  - Stronger anti-viral activity via IFN stimulated gene (ISG) production.
  - Enhanced antiproliferative effects.
  - Superior anti-tumor activity.
- Currently approved for treatment of chronic HCV.
  - 9 mcg SQ TIW in treatment-naive HCV.
  - 15mcg SQ TIW in HCV relapsers and/or nonresponders.

<sup>1</sup>Blatt et al. *J Interferon Cytokine Res.* 1996; 16: 489-99.

## CIFN & Cirrhotic Nonresponders

- Kaiser et al. *Gastroenterology*, 2004; 124(2): 668A.
  - Open-label study of 60 nonresponders to PEG + RBV.
  - Patient characteristics.
    - 90% Genotype 1 or 4.
    - 25% with stage 5/6 fibrosis (Ishak).
  - Regimen: CIFN "induction" x 4 wks followed by CIFN + RBV for  $\geq$  44 wks.
    - End of Treatment Response = 45%.
    - SVR = 27%.
  - Tolerability.
    - No patients experienced grade 3/4 anemia.
    - 2/60 patients experienced ANC < 500.
    - No growth factors used in study.

## CIFN & Cirrhotic Nonresponders

- Leevy et al. Gastroenterology. 2005; 128(4), 714A.
  - 137 nonresponders to PEG + RBV given CIFN 15 mcg + RBV x 48 wks.
  - Patient characteristics.
    - 94% genotypes 1 or 4.
    - 32% African-American.
    - 30% with cirrhosis.
    - Mean HCV RNA = 1.6 million copies.
  - Overall SVR rate = 37%.
    - SVR rate for AA race = 27%.
  - No patients discontinued therapy!
  - Multivariate model to determine predictors of outcome.
    - HCV genotype NOT a predictor.
    - Baseline viral load NOT a predictor.
    - Presence of fibrosis/cirrhosis on biopsy NOT a predictor.

## CIFN & Cirrhotic Nonresponders

- Chen et al. Hepatology. 2005; 42(4), 670A.
  - 79 nonresponders to PEG-IFN + RBV or IFN + RBV.
    - 80% genotype 1.
    - 47% with fibrosis stage F3/F4 (Metavir) and/or cirrhosis on biopsy.
  - CIFN 15mcg daily + weight based RBV x 48 wks.
    - End of Treatment Response = 72%.
    - SVR = 50%.
- In nonresponders, overall response rates to CIFN + RBV (~40%) appear to be superior to those attained by PEG + RBV.
  - HALT-C lead-in phase: Overall SVR = 18%.
    - SVR in genotype 1 = 14%.
    - SVR in cirrhotics = 11%.
    - SVR in AA race = 6%.

## CIFN & HCC

- In cirrhotics, annual incidence of HCC estimated to be 1-4%.<sup>1</sup>
- Incidence and mortality rates from HCC likely to double over next 10-20 years.<sup>1</sup>
- Hisaka et al. J Hepatol. 2004; 41: 782-89.
  - HCC cell lines transplanted into nude mice.
  - Mice received daily SQ injection of CIFN or control x 2 wks.
  - Compared to controls, CIFN treated mice experienced:
    - Suppressed cellular proliferation (dose-dependent) (p < .01).
    - Increase in number of apoptotic cells (p < .05).
    - Decrease in number of blood vessels (p < .05).
- CIFN may be efficacious in prevention and treatment of HCC.
  - Clinical RCTs needed to verify treatment effects.

<sup>1</sup>El-Serag, Hepatology. 2002; 36: S74-83.

## Conclusions

- The number HCV cirrhotics who do not respond to standard therapy will increase dramatically over the next several decades.
- Consensus interferon is a synthetic IFN $\alpha$  that is more potent than traditional interferons.
- Recent data suggests that CIFN is effective in treatment of cirrhotic nonresponders with SVR rate = ~40%.
- Compared to traditional agents, CIFN shows enhanced efficacy in "difficult to treat" patients (genotype 1, AA race).
- CIFN suppresses HCC tumor growth in a dose dependent fashion.

**Thank You!**