Management of Cirrhotic Nonresponders: Building a Consensus

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What is this debate REALLY about?

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

Subject of Debate: Modifying the Natural History of HCV Cirrhosis

Survival Rates in HCV

Compensated: 5-yr survival = 91%
Decompensated: 5-yr survival = 50%

The Scope of the Problem

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

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 = 15 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?\(^1\)
  - 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).\(^2\)
  - Previous nonresponders to IFN + RBV were EXCLUDED.
  - Overwhelming majority (96%) received traditional IFN, not PEG.
  - Genotype 1 was independent predictor of poor response.

Consensus Interferon (CIFN)

- Recombinant type I IFN α created by combining amino acid sequences from multiple IFN α subtypes.

- In vitro & In vivo studies have shown CIFN to be more 10-100x potent than traditional IFNs.\(^1\)
  - 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 relapers and/or nonresponders.

CIFN & Cirrhotic Nonresponders

  - 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 ≥ 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

- 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.
  - 82% 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%.
- Incidence and mortality rates from HCC likely to double over next 10-20 years.
  - 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.

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 IFNα 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!