

Wait For Transplantation: The Correct Choice in Compensated HCV Cirrhotic Treatment Nonresponders

Ramsey K. Umar, MD
Aaron I. Benson, MD
Richard M. Green, MD

Position Statement

- Better therapeutic options are needed for hepatitis C/cirrhotic patients who are non-responders to conventional therapy.
- Therapeutic options available *right now* are either ineffective or unproven in terms of efficacy and sustained virologic response (SVR).
- The decision to wait, rather than to subject patients to treatments with questionable benefit, is ultimately the correct decision to make.

Clarification

- “Wait for transplantation” is not “wait for decompensation”.
- The current standard of care is to provide:
 - Hepatoma screening
 - Variceal diagnosis and management
 - Supportive care
- As physicians, we have a role to do no harm.

You Are Not Forced to Act

- The natural history of chronic hepatitis C cirrhosis is not as bad as one may believe.
- The overall 10 year survival rate is 82%. Even with decompensation, the survival rate at 5 years is 51%.
Tong et al. Hepatology. 1999 Apr;29(4):1311-6.
- In a European cohort, 5 and 10 year overall survival rates were 91% and 79%.
Fattovich et al. – Gastroenterology. 1997 Feb; 112(2):651-5.

Medical Options

- Maintenance Pegylated Interferon therapy.
- Consensus Interferon therapy.
- Wait / Consider enrollment in Clinical Trials.

Maintenance Pegylated Interferon

- Present data is scant.
- Data examining non-pegylated interferon monotherapy is unimpressive, showing no favorable change in the natural history of the disease, if any benefit at all.

Spadaro et al. Hepatogastro 1999. Nov-Dec;46(30):3229-33
Pol et al. J Hepatol. 1999 Jul;31(1):1-7.

- There may be histologic benefits with pegylated interferon monotherapy.

Pockros et al. Am J Gastro 2004 Jul;99(7):1298-305.

- 3 Clinical trials are ongoing to help address this question:

– HALT-C

– EPIC

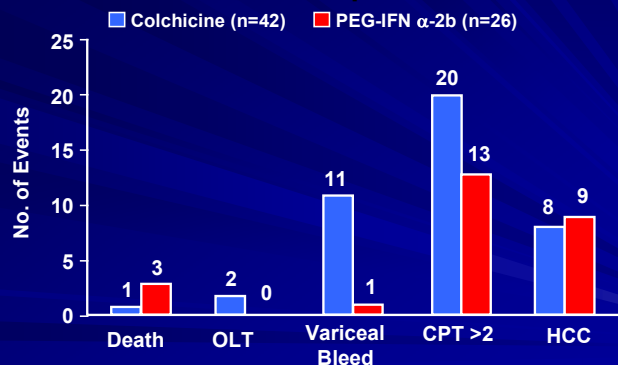
– COPILOT

Maintenance Therapy Trials

	HALT-C	COPILOT	EPIC
Fibrosis stage	Ishak 4–6	Ishak 3–6	METAVIR 2–4
No. patients	1000	600	2200 (3 studies)
End point	Fibrosis/clinical	Fibrosis/clinical	Fibrosis/clinical
Initial Tx	PEG-IFN α -2a + RBV 800 mg	None	PEG-IFN α -2b + RBV WBD*
Maintenance Tx	PEG-IFN α -2a 90 μ g	PEG-IFN α -2b 0.5 μ g/kg	PEG-IFN α -2b 0.5 μ g/kg
Control Tx	Placebo	Colchicine	Observation
Duration (years)	3.5	4	4
Recruitment status	Complete	Midpoint analysis	Enrolling

* WBD – weight based dosing

COPILOT: Primary End Points in ITT Population



CPT, Child-Pugh-Turcotte; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation

Afdhal N et al. *Hepatology*. 2004; 40(suppl 1):239A. Abstract 171.

Maintenance Pegylated Interferon

- Data provided was not convincing enough to stop the trial at a midpoint analysis.
- More data is required before judging the efficacy of this regimen.
- Use of pegylated interferon for maintenance therapy is **not standard of care**.

Consensus Interferon

- A Italian pilot study has suggested that consensus interferon may be efficacious in the HCV treatment nonresponder group.
Barbaro et al. *Eur J Gastroenterol Hepatol*. 2002 May;14(5):477-83.
- A clinical trial is ongoing to determine the efficacy of this therapy.
- Initial data has been presented in abstract form only.
- An SVR of 37% 24 weeks post-therapy was observed.
Leevy et al. AASLD 2005.

Not Enough Data

- A single center experience is not enough.
- As experienced clinicians, we have been overly optimistic before based on single center treatment experiences.
Brillanti et al. *Ital J Gastroenterol Hepatol*. 1999 Mar;31(2):130-4.
Younoussi et al. *J Hepatol*. 2001 Jan;34(1):128-33.
Hasan et al. *Antivir Ther*. 2004 Aug;9(4):499-503.
- Toxicity rates of consensus interferon are at least comparable to currently available treatment regimens.

Summary

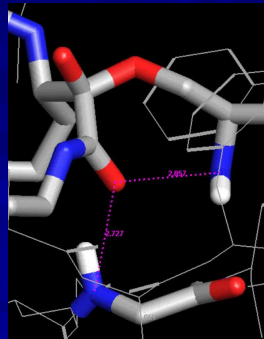
- Maintenance interferon regimens have never been shown to favorably influence the clinical course of patients in the HCV nonresponder group.
- Pegylated interferon data is pending, but preliminarily is unconfirmed.
- Consensus interferon may be a recognized option, but current data is limited to a single center experience.

HCV Replication Enzyme Inhibitors

- Protease inhibitors
 - BILN 2061
 - VX 950
 - SCH 503034
- Polymerase inhibitors
 - Nucleoside (NM 283)
 - Non-nucleoside (JTK-003)
- Helicase inhibitors
 - In development

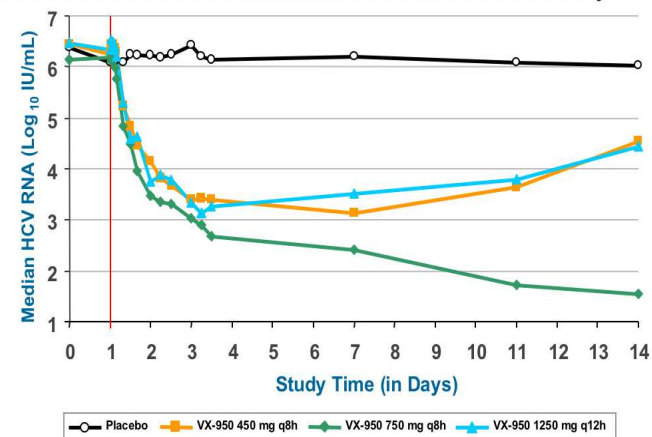
VX - 950: HCV Protease Inhibitor

- Phase 1a/b trial completed
- No dose-limiting toxicities
- Adequate serum and liver concentrations
- 3-4 log reductions in 14 days with TID dosing



Reesink et al. DDW 2005.

Substantial Decrease in HCV RNA with VX-950



Conclusions

- You are not forced to act in compensated hepatitis C cirrhotic patient nonresponders.
- You are not forced to use expensive and either unproven or unimpressive therapies.
- In the vast majority of patients, you have the time to follow the standard of care and do what it is right for the patient.
- Enrollment in clinical trials is always an option.

Conclusions

- Both maintenance pegylated interferon and consensus interferon therapy are unproven.
- Toxicities of these therapies may make transplantation difficult or enrollment in promising trials impossible.
- Avoiding these available options is the correct choice, while supporting your patient as per current standard of care.