

High-dose peginterferon α -2a sustained virologic and biochemical response in chronic hepatitis C infection with cirrhosis

Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med*. 2000 Dec 7;343:1673-80.

QUESTION

In patients with hepatitis C virus (HCV) infection and cirrhosis or bridging fibrosis, is peginterferon α -2a as efficacious and safe as unmodified interferon α -2a?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessors),* controlled trial with follow-up at 72 weeks.

SETTING

30 clinical centers in the United States, Canada, Australia, and the United Kingdom.

PATIENTS

271 patients (mean age 47 y, 72% men) with chronic HCV infection and biopsy-proven liver cirrhosis or bridging fibrosis. Inclusion criteria were an abnormal serum aminotransferase level twice in the previous 6 months and a liver biopsy in the previous year. Exclusion criteria were other liver diseases, decompensated cirrhosis, HIV infection, psychiatric conditions, seizure disorders, severe cardiac disease, retinopathy, cancer, low neutrophil or platelet counts, or an α -fetoprotein level > 100 ng/mL. The intention-to-treat analysis included all patients.

INTERVENTION

All patients received their medication subcutaneously for 48 weeks. Doses could be reduced because of adverse effects. 96 patients

were allocated to peginterferon α -2a, 90 μ g once/wk; 87 to peginterferon α -2a, 180 μ g once/wk; and 88 to unmodified interferon α -2a, 3 million units 3 times/wk.

MAIN OUTCOME MEASURES

Sustained virologic (absence of measurable HCV) and biochemical responses (normalization of aminotransferase levels at 72 weeks).

MAIN RESULTS

More patients in both peginterferon groups had sustained virologic and biochemical responses at 48 weeks ($P \leq 0.004$) than did those in the interferon group. At 72 weeks, more patients in the high-dose peginterferon group had virologic and biochemical responses than did those in the

low-dose peginterferon or interferon groups ($P < 0.001$) (Table). The groups had similar rates of adverse events.

CONCLUSION

Peginterferon α -2a, 180 μ g once/wk, was more effective than peginterferon α -2a, 90 μ g once/wk, or unmodified interferon α -2a, 3 million units 3 times/wk, at sustaining virologic and biochemical responses and was safe in patients with chronic hepatitis C infection and cirrhosis or bridging fibrosis.

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*See Glossary.

Peginterferon α -2a, 90 or 180 μ g (PI-90 and PI-180) weekly, vs interferon α -2a, 3 times/wk, for patients with chronic hepatitis C virus infection and cirrhosis or fibrosis†

Outcomes at 72 wk	Comparisons	Event rates	RBI (95% CI)	NNT (CI)
Virologic response	PI-90 vs interferon	15% vs 8%	83% (-20 to 326)	Not significant
	PI-180 vs interferon	30% vs 8%	276% (78 to 713)	5 (3 to 9)
	PI-180 vs PI-90	30% vs 15%	105% (16 to 266)	7 (4 to 30)
Biochemical response	PI-90 vs interferon	20% vs 15%	34% (-28 to 154)	Not significant
	PI-180 vs interferon	34% vs 12%	133% (33 to 317)	3 (3 to 14)
	PI-180 vs PI-90	34% vs 20%	74% (7 to 186)	7 (4 to 55)

†Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Approximately 3 million Americans have HCV infection, and 10% to 20% of infected patients will develop cirrhosis within 2 decades of infection. Combination therapy with unmodified interferon plus ribavirin eradicates HCV in about 40% of patients without cirrhosis, which may delay progression to cirrhosis. Because patients with cirrhosis and HCV infection have much lower rates of HCV eradication with antiviral therapy, they frequently do not receive therapy. Furthermore, the benefit of therapy for patients with cirrhosis is unclear. To be clinically meaningful, HCV eradication in patients with cirrhosis should delay progression to hepatocellular carcinoma or decompensated cirrhosis.

Heathcote and colleagues completed the largest trial to date of antiviral therapy in patients with cirrhosis and HCV infection. In their well-designed trial, different dosages of a new formulation of interferon (peginterferon α -2a) were compared with unmodified interferon. Patients receiving high-dose peginterferon α -2a had more histologic improvements and frequent normalization of alanine amino-

transferase levels and were much more likely to have had HCV eradicated. Adverse events did not differ between therapies. These are impressive achievements.

Thus, peginterferon appears to be as safe as, and more effective than, unmodified interferon in patients with cirrhosis and HCV infection. However, this trial, like many trials of HCV antiviral therapy, examined only intermediate end points. Future research should examine whether peginterferon slows progression to decompensated cirrhosis or hepatocellular carcinoma. Furthermore, interferon plus ribavirin is the standard treatment, not unmodified interferon alone. Fortunately, ongoing studies are comparing peginterferon plus ribavirin with unmodified interferon plus ribavirin. Given these caveats, clear recommendations about treatment of patients with cirrhosis and HCV infection cannot be made, and the decision to treat these patients must be individualized.

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