

Current Therapy for Chronic HCV in General Population

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The ultimate goal of antiviral therapies for chronic HCV is to prevent progression of liver fibrosis progression, cirrhosis, complications of endstage liver disease (decompensation; HCC), need for liver transplantation, and deaths due to HCV. However, the best indicator of treatment efficacy is the sustained virological response (SVR), defined as an undetectable serum HCV RNA at the end of treatment that persists long-term after treatment is discontinued (for ~ 6 months). Patients who achieve a SVR have a > 95% probability of maintaining undetectable serum HCV, improvement in liver biopsy hepatitis activity features, and decreased rates of hepatic fibrosis compared to non-SVR.

Several major advances in antiviral therapy for chronic HCV have occurred since 1990 when interferon alfa (IFNa)-2b (3 million units 3 times per week for 6 months) became the first FDA-licensed treatment for chronic HCV in the USA. However, less than 10% of treated subjects experienced a SVR. The efficacy of IFNa monotherapy was increased considerably by increasing the duration of therapy to 12 months. Still, the SVR was then 20 % overall. In 1998, combination therapy with IFN alpha-2b 3 times weekly with oral ribavirin for 48 weeks was licensed by the FDA based on superior efficacy compared to IFN alfa monotherapy (1). The SVR in patients treated with combination therapy was 38% compared to 13% in patients receiving IFNa monotherapy. Treatment for 48 weeks was superior to 24 weeks in patients infected with HCV genotype 1 (29% vs. 17%). The SVR in HCV genotype 2 and 3 patients was the same regardless of the 24-week or 48 week treatment duration (65-66%). Subsequent studies found conjugating IFNa-2a to either a 40-Kd polyethylene glycol (PEG) moiety (Roche) or IFNa-2b (Schering Plough) to a 12 Kd-PEG moiety improved the pharmacodynamic properties of IFNa, increasing the serum half life by 8-10 times, and allowing IFNa to be administered once per week(2). This improved pharmacokinetics of PEG-IFNa resulting in a greater efficacy compared to IFNa monotherapy with an SVR ranging between 23-39%.(3,4) PEG-IFNa-2b (Schering Plough) was approved for initial therapy of chronic HCV in the USA in early 2000.

In August 2001, combination therapy with a 12 Kd-peginterferon alfa-2b I (1.5 mcg/kg /wk S.C.) plus oral ribavirin 800 mg per day (Schering Plough) for 48 weeks was approved by the FDA for initial therapy of chronic HCV in the USA (5). A 40 Kd-peginterferon alfa-2a and ribavirin combination (Roche) has been licensed in the European Union and is being considered for licensure in the USA (6). The efficacy and safety of both peginterferon/ribavirin combination regimens were compared to standard IFNa-2b/ribavirin combinations in large international clinical trials of patients with compensated liver disease. The inclusion criteria and patient pre-treatment characteristics were similar and the primary endpoint in both trials was the SVR. Table 1 compares the results of most effective PEGIFNa/ribavirin combinations to standard IFNa plus ribavirin.

The 12 Kd PEGIFNa-2b (1.5 mcg/kg/wk SC) plus ribavirin (800 mg per day) for 48 weeks was compared to a lower dose PEGIFNa-2b (1.5 mcg/kg for 4 wk; 0.5 mcg/wk for 44 weeks) and ribavirin 1000 - 1200 mg combination and standard IFNa-2b/ribavirin in a RCT enrolling 1530 previously untreated chronic HCV patients (5) (See Table 1; Schering). The higher dose PEGIFNa-2b combination regimen showed superior efficacy relative to the other treatment arms (54% vs. 47% vs. 47%). The higher dose PEGIFNa-2b combination also showed greater efficacy in patients with genotype 1 in lower pre-treatment serum HCV RNA levels (< 2,000,000 copies/ml) but not in patients with a higher HCV loads and HCV genotypes 2/3. The pretreatment independent predictors of a SVR were HCV genotype other than 1, HCV load, age < 40 years, baseline weight, absence of cirrhosis, and PEGIFNa-2b and ribavirin doses. The SVR was also lower in patient with body weight above 85 kg. A post hoc analysis indicated the optimum dose of ribavirin to be above 10.6 mg/kg/d. A comparison of pretreatment and the week 24 post-treatment liver biopsies revealed a 90% decrease in inflammation and a 21-26% experienced a decrease improvement in fibrosis in sustained responders regardless of the treatment arm. The non-SVR had mean improvements of 40-50% and 14-19% respectively (NS).

Table: PEGIFN α /Ribavirin Therapies compared to standard IFN α /Ribavirin Combination Therapy

	PEGIFN α -2a (IFN α -2b) Roche	PEGIFN α -2b (IFN α -2b) Schering
Overall	56% (44%)	54% (47%)
HCV genotype 1	46% (36%)	42% (33%)
≤ 2 million copies/ml	56% (43%)	NR
≥ 2 million copies/ml	41% (33%)	30% (29%)
HCV genotype 2/3	76% (61%)	82% (79%)
≤ 2 million copies/ml	81% (65%)	ND
≥ 2 million copies/ml	74% (58%)	ND
Fibrosis Stage		
Early	Not reported	57% (49%)
Advanced	43% (33%)	44% (41%)
Predictors of SVR	HCV genotype not 1	HCV genotype not 1
Age < 40 years	Age < 40 years	HCV load
(pretreatment)	Body weight < 75 kg	Age < 40 years
		Baseline weight*
		Absence of cirrhosis
		PegIFN and ribavirin doses

A detectable serum HCV RNA at week 24 weeks of therapy was predicted the lack of SVR during subsequent 24 weeks of continued therapy in > 99% of subjects. Thus an adequate trial of therapy is 24 weeks. The predictive value of earlier virological data is unclear. Previous studies had shown 24 weeks of standard interferon-ribavirin combination therapy to be as effective as 48 weeks of treatment in patients infected with HCV genotype 2&3. However, this question was not addressed in this trial. No new adverse events were discovered during PEGIFNa-2b compared to the standard IFNa-2b combination. The higher-dose PEGIFNa-2b combination was associated with a higher frequency of some adverse events, particularly fever, rigors, weight loss, arthralgias and myalgias, nausea, diarrhea, anorexia, and injection site reactions. Dose reductions due to anemia were similar, but dose reductions for neutropenia were higher in the PEGIFNa-2b combination arm. Patients treated with peginterferon alfa-2b and > 10.6 mg/kg/d of ribavirin experienced more frequent asthenia, weight loss, and alopecia, and had a more frequent dose modifications related to neutropenia than the lower ribavirin dosage. The discontinuation rate was similar in the PEGIFNa-2b and standard IFN combination arms (13%-14%) and did not vary based on ribavirin dose.

PEGIFNa-2a (180 mcg/week SC) plus oral ribavirin (1000-1200 mg/d) for 48 weeks was compared to standard IFNa-2b plus ribavirin and PEGIFNa-2a (180 mcg/week SC) plus placebo in a RCT of 1121 previously untreated chronic HCV patients (6). The SVR was significantly higher in the PEGIFNa- 2a plus oral ribavirin combination (56% vs. 44% vs. 29%). Also, the PEGIFNa-2a/ ribavirin combination showed a higher efficacy in HCV genotypes 1 and genotypes2/3, including patients with either low or high pretreatment viral loads (Table 1; Roche). This study showed that the week 12 virological response had a 97% negative predictive value. Thus, only 3% of patients who failed to achieve a 2-log decline in serum HCV RNA compared to baseline or undetectable serum HCV RNA at week 12 experienced a SVR despite continued therapy. In a subsequent study, 24 weeks of PEGIFNa-2a plus ribavirin is adequate in patients infected with HCV genotype 2, with a similar SVR (78% vs.73-77%) as 48 weeks of therapy (Hadziyannis, SJ et al. EASL, 2002). The predictors of a SVR were HCV genotype other than 1, age < 40 years, and body weight <75 kg. Twenty two percent of patients in the PEGIFNa-2a/ribavirin withdrew during the treatment compared to 32% in the standard IFNa combination.

One-third of the withdrawals in both arms were due to insufficient response. Another third withdrew due to adverse events, and the rest due to laboratory abnormalities and refusal of treatment. Dose modifications due to adverse events were similar in the three treatment arms. Yet dose modifications due to laboratory abnormalities particularly neutropenia and thrombocytopenia (but not anemia) were more common in the PEGIFNa-2a combination arm (20% vs. 5%). Interestingly, the frequency of flu-like symptoms and depression were lower in the PEGIFNa-2a combination arm compared to the standard treatment.

Several post hoc analyses of HCV clinical trials have found a significantly lower SVR in Black Americans exhibit a significantly lower rates of HCV clearance following treatment with both standard IFNa or both PEGIFNa when used alone and when combined with ribavirin relative to White Americans. The lower response is due in part to a higher prevalence of HCV genotype 1 infections in African Americans. Yet, interim results of a clinical trial of PEGIFNa-2a plus ribavirin in African American and Caucasians infected with HCV genotype 1 showed a lower end-of treatment virological response in African Americans (32% vs. 52%) Oeffers et al. *Hepatology*, October 2002, in press). The NIH VIRAHEP-C study will investigate the basis for this racial disparity in treatment outcome. However, this has important implications for renal disease patients, since the incidence of end-stage kidney disease is 4 times higher in African Americans compared to White Americans.

Chronic HCV patients who failed to achieve a SVR following standard IFNa +/- ribavirin appear to benefit from retreatment with PEGIFNa plus ribavirin, though few studies have reported SVR results. The rate of HCV clearance during 24 weeks of therapy depends in part on the pattern of nonresponse during the initial treatment. Overall, patients who had a relapse after either IFN monotherapy or combination therapy have shown higher rates of HCV clearance at 24 weeks of retreatment with PEGIFNa /ribavirin compared to the true non responders.

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