Peginterferon alfa-2a (40KD) plus 800 or 1000/1200 mg/day ribavirin in genotype 1 HIV–HCV co-infected patients: early responses to treatment and predictability for SVR in the PARADIGM study

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INTRODUCTION

Among patients with HCV mono-infection, clearance of HCV RNA from serum at week 4 and 12 of treatment with pegylated interferon plus ribavirin is highly predictive of achieving a sustained virological response (SVR).[1, 2] Similar findings have been reported for HIV-HCV co-infected patients[3-5] but there are no data available on the influence of ribavirin dose on the positive predictive value of a negative serum HCV RNA at week 4 or 12.

The objective of the randomised, multinational PARADIGM study was to compare the efficacy and safety of two ribavirin dosage regimens (800 mg/day and 1000/1200 mg/day) administered in combination with peginterferon alfa-2a (40KD) in HIV-HCV co-infected patients. HCV RNA levels were monitored throughout the study, which provides the opportunity to examine the predictive value of early clearance of HCV RNA for SVR.

OBJECTIVE

The objective of this analysis is to explore the impact of ribavirin dosing regimen on the time to undetectable HCV RNA and the predictive value of a rapid virological response (RVR) or early virological response (EVR) for SVR.

METHODS

Patients

Patients eligible for PARADIGM were co-infected with HIV-HCV (genotype 1) infection with a serum HCV RNA titre >600 IU/mL who had not received previous interferon-based therapy for chronic hepatitis C.

Patients were required to have stable HIV disease with a CD4+ cell count ≥100 cells/mm^3. Individuals on stable anti-retroviral therapy (ART) and those not requiring ART were both eligible.

Treatment

Patients were randomised (1:2) to receive 48 weeks of treatment with oral ribavirin at either a fixed standard dose of 800 mg/day or a higher dose (1000 mg/day for patients with a body weight <75 kg, or 1200 mg/day for those with a body weight ≥75 kg) in combination with subcutaneous peginterferon alfa-2a (40KD) 180 µg/week (**Figure 1**).

Figure 1. Study design

Outcomes

HCV RNA levels were assessed by COBAS® Ampliprep/COBAS® TaqMan® HCV test; detection limit 20 IU/mL, Roche Diagnostics) at baseline, at week 4, 12, 24, and 48 during treatment and after 24 weeks of untreated follow-up (study week 72).

RVR was defined as undetectable HCV RNA in serum at week 4. Complete EVR was defined as undetectable HCV RNA in serum at week 12. Partial EVR was defined as greater than 2-log_{10} drop in HCV RNA at week 12. SVR was defined as undetectable HCV RNA at the end of untreated follow-up (study week 72).

RESULTS

Among the overall population of 410 patients with HIV-HCV co-infection, 80% were male, 64% were Caucasian, 11% had bridging fibrosis or cirrhosis, 80% had an HCV-RNA level >800,000 IU/mL and 89% were receiving ART at baseline (Table 1).

Table 1. Baseline characteristics of patients in PARADIGM

	Peginterferon alfa 2a (40KD) plus:	
	ribavirin 800 mg/day (n=135)	ribavirin 1000/1200 mg/day (n=275)
Male gender, n (%)	106 (79)	224 (81)
Mean age ± SD, years	45.2 ± 8.4	45.5 ± 8.2
Mean weight ± SD, kg	77.2 ±14.1	78.0 ± 17.5
Race/ethnicity, n (%)		
Non-Hispanic Caucasian	60 (44)	116 (42)

Hispanic	33 (24)	76 (28)
Hispanic Caucasian	26 (19)	60 (22)
Hispanic non-Caucasian	7 (5)	16 (6)
Non-Hispanic African American	40 (30)	77 (28)
Other	2 (1)	6 (2)
Alanine aminotransferase quotient ≤1.5, n (%)	76 (56)	144 (52)
Bridging fibrosis/cirrhosis, n (%)	16 (12)	30 (11)
Child Pugh score >5, n (%)	2 (1)	6 (2)
Mean HCV RNA ± SD, $\log_{10}$ IU/mL	6.4 ± 0.82	6.5 ± 0.90
HCV RNA >800,000 IU/mL, n (%)	106 (79)	223 (81)
Mean CD4+ cell count ± SD, cells/mm^3	489 ± 243	519 ± 273
CD4+ cell count <200/µl, n (%)	7 (5)	18 (7)
On ART, n (%)	120 (89)	241 (88)

SD = standard deviation; ART = anti-retroviral therapy

A total of 120/135 (89%) and 243/275 (88%) patients randomised to 800 mg/day and 1000/1200 mg/day of ribavirin completed the first 12 weeks of treatment.

There was no statistically significant difference in the overall SVR rates between patients randomized to ribavirin 800 mg/day or 1000/1200 mg/day (19% versus 22%, respectively, **Figure 2**).

Figure 2. Overall SVR rates

Rates of relapse (detectable HCV RNA during 24 weeks untreated follow-up among patients with an undetectable HCV RNA at the end of scheduled treatment) were similar between patients randomized to ribavirin 800 mg/day (32%) and 1000/1200 mg/day (36%).

Among patients randomised to ribavirin 800 mg/day or 1000/1200 mg/day the rates of RVR (8% versus 7%, respectively) and complete EVR (26% in both groups) were similar. In contrast the partial EVR rate was somewhat lower among patients receiving the lower dose of ribavirin (25% versus 35% in patients randomised to 1000/1200 mg/day, **Figure 3**).

Figure 3. Rates of RVR, complete EVR (cEVR) and partial EVR (pEVR)

In both ribavirin dosage groups, achievement of an RVR or complete EVR was associated with a high probability (positive predictive value; PPV) of achieving an SVR. Conversely, patients with a slow response to treatment (partial EVR) had a low probability of achieving an SVR after 48 weeks of treatment regardless of the dose of ribavirin (**Figure 4 and Table 2**).

Figure 4. Rates of SVR in patients with an RVR, complete EVR (cEVR) and partial EVR (pEVR)

Failure to achieve an on-treatment response defined as an RVR, cEVR or pEVR was also associated with a high probability of not achieving an SVR defined as the negative predictive value (NPV) (**Table 2**).

Table 2. Positive and negative predictive values for on-treatment virological responses for SVR

On-treatment response category	Predictor	Ribavirin 800 mg/day	Ribavirin 1000/1200 mg/day
RVR	PPV	64%	75%
	NPV	85%	82%
cEVR	PPV	63%	66%
	NPV	96%	94%
pEVR	PPV	9%	13%
	NPV	77%	74%

PPV = Positive predictive value defined as the probability a patients with an on-treatment response achieving an SVR

NPV = Negative predictive value defined as the probability that a patients without an on-treatment response not achieving an SVR

CONCLUSIONS

The use of a higher dose of ribavirin (1000/1200 mg/day) in combination with peginterferon alfa-2a (40KD) did not significantly increase on-treatment virological response rates or SVR rates in HIV-HCV co-infected patients with difficult-to-treat HCV genotype 1 infection in the PARADIGM study.

Consistent with previous reports, achievement of rapid clearance of HCV RNA from serum at week 4 (RVR) and at week 12 (complete EVR) was highly predictive of SVR, regardless of the ribavirin dosing regimen, whereas failure to achieve a cEVR was highly predictive of not achieving an SVR.

Some treatment guidelines recommend a longer 72-week course of treatment among patients with a partial EVR who go on to achieve an undetectable HCV RNA at week 24.[6]

References

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