

High Dose Induction Therapy with PEG-IFN- α 2b plus Ribavirin Seems Not More Effective than Standard Dose PEG-IFN- α 2b plus Ribavirin for Treatment of cHCV in HCV/HIV co-infected Patients.

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Background

Sustained virological response rates to current treatments with PEG-IFN plus ribavirin are unsatisfying in patients co-infected with HIV-1.

Methods

This study was an open-label pilot study in which patients were randomized 1:1 to 48 weeks of therapy with PEG-IFN- α 2b (Pegintron) plus ribavirine.

standard arm: PEG-IFN- α 2b 1.5 μ g/kg/wk plus ribavirin (1000-1200mg/day)

induction arm: PEG-IFN- α 2b 3.0 μ g/kg/wk during the first 4 weeks,

2.0 μ g/kg/wk during the next 4 weeks, and 1.5 μ g/kg/wk during the

remaining 40 weeks, plus ribavirin in the same dose as the standard arm.

Minimization factors at randomisation included the HCV genotype (genotype 1 and 4 versus 2 and 3), CD4 cell count (< or > 400/mm³) and plasma HCV-RNA

(< or > 5.0 x 10e6 IU/mL).

The primary efficacy endpoint was a Sustained Viral Response (negative HCV-RNA with TMA assay) 24 week after end of therapy. Safety was assessed. The analysis was conducted according to the intention-to-treat principle.

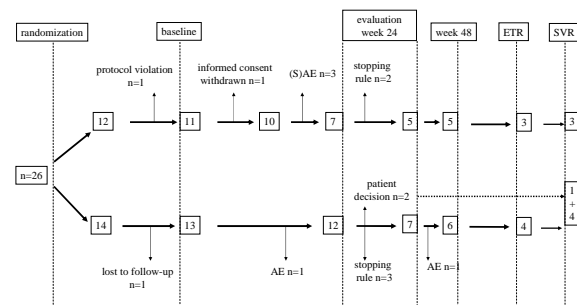
Results

The patient disposition and baseline characteristics are shown in figure 1 and table 1, respectively. The patient who withdrew informed consent was considered as a failure. A SVR was achieved in 8 of 23 pts (35%); 3 pts (30%) in the standard arm and 5 pts (38%) in the induction arm ($p=0.98$).

Only the decrease in serum HCV RNA during the first 4 wks (OR 2.62 per log₁₀ IU decrease: [95% CI: 1.04 to 6.61]) and genotype (OR for genotype 1 or 4: 0.12 [95% CI: 0.02 to 0.87]) were significant predictors of SVR.

Adverse events were typical of those previously reported for combination therapy (not shown). Clinically relevant events and hematological toxicity are shown in table 2 and 3, respectively. Noteworthy, one patient died of a pneumonia (possible TB), no other HIV-related complications occurred. No decompensation of the liver or clinical manifestation of mitochondrial toxicity (pancreatitis, lactic acidosis) was observed. However, during the first month of therapy dose reduction or treatment discontinuation of PEG-IFN because of neuropsychiatric toxicity was necessary in almost a quarter of the patients in the induction arm versus none in the standard arm.

Figure 1. Patient disposition



Stopping rule: Patients who had still detectable HCV RNA after 24 weeks, measured with a sensitive qualitative HCV RNA assay had to stop with the study treatment.

Table 1. Baseline characteristics

	Standard arm	Induction arm
Age (years)	43 (40-48)	38 (34-43)
Sex (male/female)	9/1	12/1
Weight (kg)	75 (67-87)	77 (71-84)
Ethnic group Caucasian	10	11
Hispanic	0	1
Black	0	1
HCV-genotype 1	5	5
3	5	5
4	0	3
Log ₁₀ HCV-RNA (IU/ml)	5.9 (3-6.5)	6.2 (4.2-6.9)
ALT (IU)	101 (24-209)	104 (34-290)
Cirrhosis/grade 4 fibrosis	1	1
CD4 <=400	5	6
CD4 >400	5	7
CD4+T-cells	395 (240-970)	410 (150-1454)
Patients with HAART	7	9
Patients with HIV-1 RNA<50 cp/mL	6	9

Presented are medians (range) for continuous variables and number of individuals for categorical data

Figure 2. The mean log₁₀ HCV-RNA by visit.

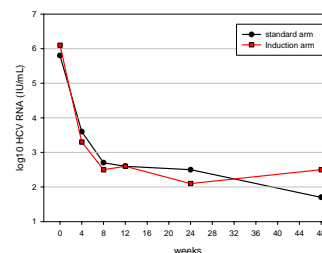


Table 2. Clinically relevant adverse events

Clinical events	Standard arm	Induction arm
Severe adverse events	3	2
Adverse event grade 3 and 4	4	5
Death	1	0
Nephrolithiasis	0	1
Appendicitis	0	1
Blood transfusion (3 packet cells)	1	1
Neuro-psychiatric toxicity (any grade)	7	7
Depression as reason for Peg-IFN dose reduction or stop	1	4
Toxicity as reason for Peg-IFN or RBV dose reduction or stop	3	5

Table 3. Hematological adverse events

Test	Toxicity grade	Standard arm	Induction arm
Hemoglobin	0 (>10.5 g/dL)	7 (70.0%)	9 (69.2%)
	1 (9.6-10.5 g/dL)	0	2 (15.4%)
	2 (8.0-9.5 g/dL)	2 (20.0%)	1 (7.7%)
	3 (6.5-7.9 g/dL)	1 (10.0%)	1 (7.7%)
Neutrophils (abs)	4 (<6.5 g/dL)	0	0
	0 (> 1500/mm ³)	4 (40.0%)	3 (23.1%)
	1 (1000-1500/mm ³)	3 (30.0%)	5 (38.5%)
	2 (750-999/mm ³)	1 (10.0%)	3 (23.1%)
Thrombocytes	3 (500-749/mm ³)	2 (20.0%)	1 (7.7%)
	4 (<500/mm ³)	0	1 (7.7%)
	0 (>99.000/mm ³)	7 (70.0%)	10 (76.9%)
	1 (75.000-99.000)	1 (10.0%)	3 (23.1%)
	2 (50.000-74.999)	1 (10.0%)	0
	3 (20.000-49.999)	1 (10.0%)	0
	4 (< 20.000)	0	0

Conclusions

Treatment with high dose PEG-IFN plus ribavirin did not improve SVR compared with standard combination therapy. High dose PEG-IFN caused more neuropsychiatric toxicity, making it an unattractive treatment option.

Acknowledgements

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