

Risk Factors for Relapse in Genotype 3 High Viral Load Patients With Hepatitis C in the WIN-R Trial

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Background

- More than 50% of patients with hepatitis C virus (HCV) infection achieve sustained virologic response (SVR)—undetectable HCV RNA at 24 weeks after treatment cessation—with pegylated interferon (PEG-IFN) and ribavirin therapy.^{1,2}
- Genotype 2 (G2) and G3 patients are generally more amenable to therapy, with SVR rates of up to 82% among patients receiving PEG-IFN alfa-2b (PegIntron®) plus ribavirin.³
 - Furthermore, SVR rates are higher among patients receiving >10.6 mg/kg ribavirin than among patients receiving ≤10.6 mg/kg ribavirin (88% vs 79%).
- Many clinical trials have assessed the treatment response among G2 and G3 patients as a single group and, thus, are unable to detect subtle differences in treatment response between the 2 genotypes. However, other studies suggest that G2 patients typically achieve higher SVR rates than G3 patients (93% vs 79%) and G3 patients with high baseline viral load may represent a particularly difficult population to treat because of higher relapse rates (~20%).⁴
- To test the hypothesis that weight-based-dose (WBD) ribavirin is more effective than flat dose (FD), the Weight-Based Dosing of Peginterferon alfa-2b and Ribavirin (WIN-R) trial was conducted.
- In this analysis we present the efficacy of 24 weeks versus 48 weeks of therapy among patients infected with HCV G2 versus those infected with G3.

Aim

- To determine the predictors of relapse among patients with G3 receiving WBD or FD ribavirin plus PEG-IFN alfa-2b.

Methods

- This was a prospective, multicenter, community- and academic-based, open-label, investigator-initiated study conducted at 225 sites in the United States.

Patient Selection

- Treatment-naïve patients with chronic hepatitis C, 18 to 70 years of age, weighing <125 kg. Additional inclusion criteria:
 - Elevated alanine aminotransferase level within 6 months prior to entry.
 - Liver biopsy result consistent with chronic hepatitis C within 36 months prior to entry.
 - Compensated liver disease.
 - An α-fetoprotein level ≤100 ng/mL in the year preceding entry.
- Patients with a positive test result for hepatitis B surface antigen or HIV were excluded.

Treatment

- Patients were randomized (1:1) to PEG-IFN alfa-2b 1.5 µg/kg/wk administered subcutaneously and oral, daily ribavirin as either
 - FD: 800 mg/d or
 - WBD (Figure 1)
- G2/3 patients were initially randomized to treatment groups for 48 weeks of treatment. However, shortly after the study began, the protocol was amended to offer randomization to treatment groups for 24 or 48 weeks of therapy.
- All patients were followed up for 24 weeks posttreatment.

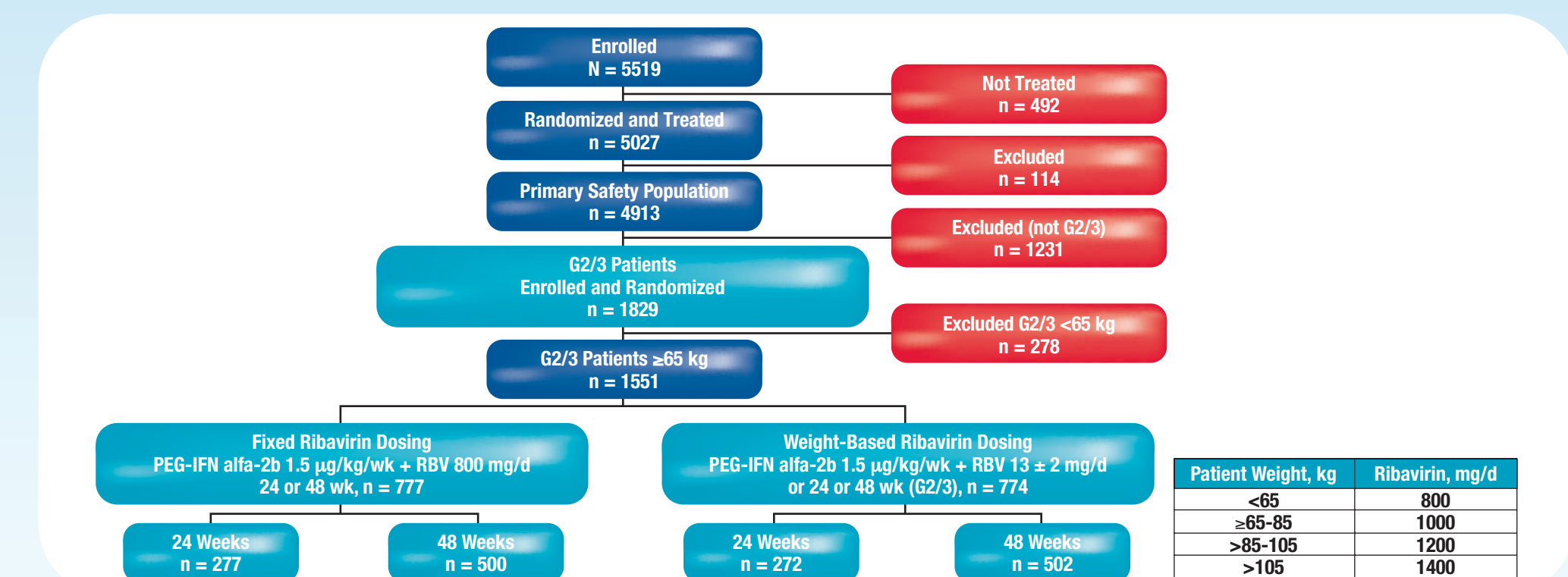


Figure 1. WIN-R study design

Assessments

- The primary efficacy end point was SVR, defined as undetectable serum HCV RNA at 24 weeks posttreatment.
 - The primary efficacy analysis was restricted to patients who weighed ≥65 kg at baseline; all patients <65 kg received ribavirin 800 mg/d.
- The secondary efficacy end point was the difference in SVR rates among G2 and G3 patients treated for 24 or 48 weeks.
- Safety was monitored by clinical and laboratory evaluations.

Results

- In total, 1829 patients with G2/3 were included in the WIN-R study and randomized to one of the following treatments:
 - 919 patients received WBD ribavirin (24 weeks n = 317; 48 weeks n = 602).
 - 910 patients received FD ribavirin (24 weeks n = 322; 48 weeks n = 588).
- 1551 patients with G2/3, who were ≥65 kg, were included in the primary efficacy analysis of the WIN-R study and randomized to one of the following treatments (Figure 1).
 - 774 patients received WBD ribavirin dosing (24 weeks n = 272; 48 weeks n = 502).
 - 777 patients received FD ribavirin dosing (24 weeks n = 277; 48 weeks n = 500).
- Baseline characteristics of the patients ≥65 kg are presented in Table 1.
- Overall, G2 patients achieved higher SVR rates and experienced lower rates of relapse than G3 patients with WBD and FD regimens (Figure 2 and Tables 2 and 3).
- SVR rates were lower in the 48-week treatment group than the 24-week treatment group among G2/3 patients receiving both WBD and FD ribavirin.
- Higher drop out rates (missing follow up assessments reported as non-responders) in the 48-week treatment group may account for lower SVR rates.

Table 1. Baseline Characteristics of G2/3 Patients ≥65 kg in WIN-R

	Weight-Based Dose (WBD)		Fixed Dose (FD)	
	24 Weeks (n = 272)	48 Weeks (n = 502)	24 Weeks (n = 277)	48 Weeks (n = 500)
Male, %	66	68	70	69
Mean age, y	45.2	45.3	45.4	46.0
Median weight, kg	88.5	88.5	87.0	87.9
Mean BMI, kg/m ²	29.8	29.8	28.9	30.0
HCV viral load >600,000 IU/mL, %	39	38	38	36
Fibrosis stage F3-F4, %	29	32	33	31
G2, %	52	55	56	59
G3, %	48	45	44	41

BMI = body mass index; G2 = genotype 2; G3 = genotype 3.

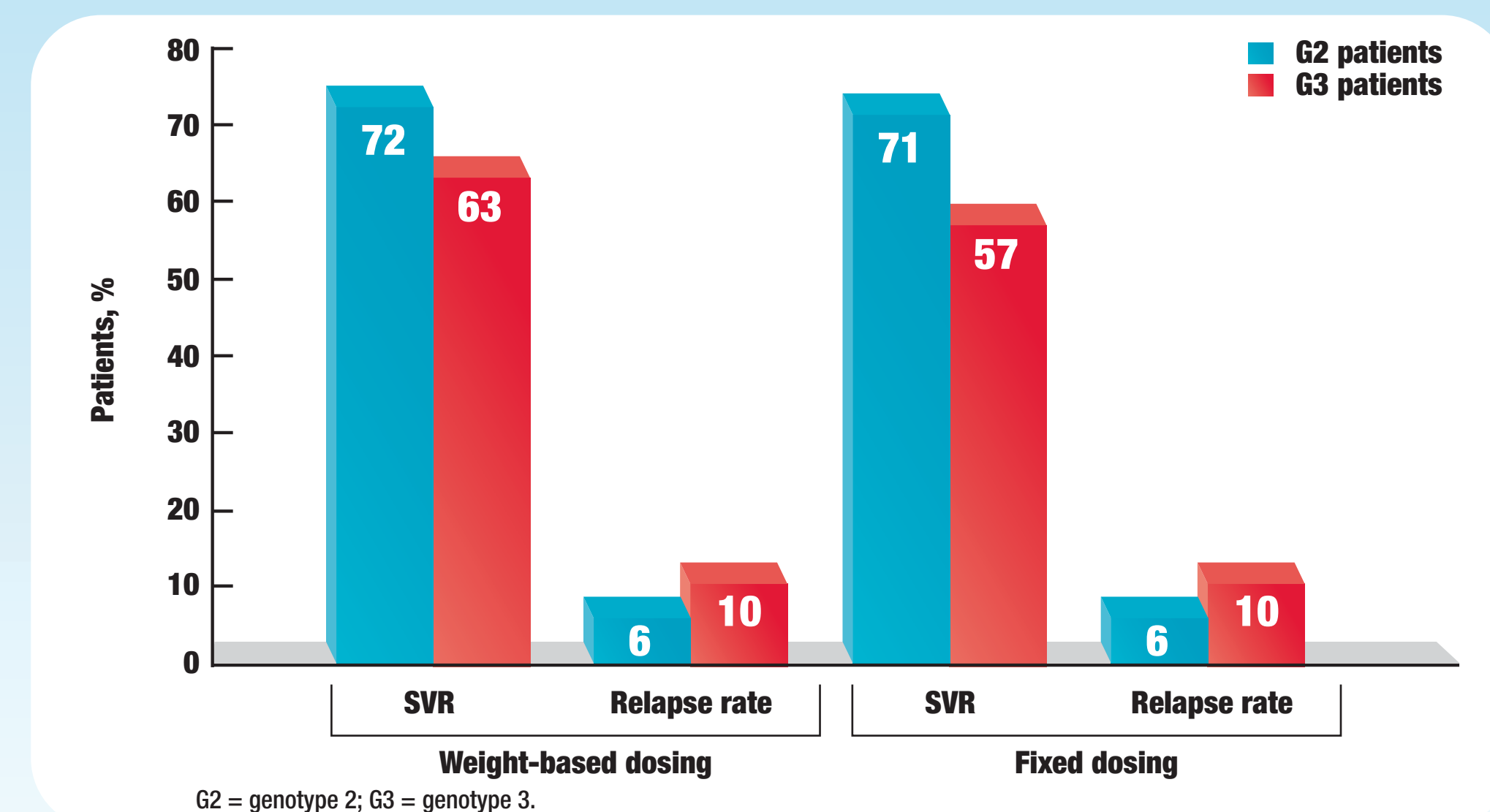


Figure 2. Sustained virologic response (SVR) and relapse rates among G2 and G3 patients

Table 2. Within-Group Analysis of SVR and Relapse Rates Among G2/3 Patients

	SVR		P Values	Relapse Rate		P Values
	WBD vs FD, % (n/N)	(n/N)		WBD vs FD, % (n/N)	(n/N)	
G2 patients						
Overall (24 wk)	72 (102/142)	vs 71 (111/156)	n.s.	6 (6/108)	vs 6 (7/117)	n.s.
Overall (48 wk)	63 (172/275)	vs 62 (182/295)	n.s.	3 (6/178)	vs 6 (11/187)	n.s.
LVL (24 wk)	71 (49/69)	vs 73 (65/89)	n.s.	6 (3/52)	vs 6 (4/68)	n.s.
LVL (48 wk)	66 (92/139)	vs 66 (111/167)	n.s.	5 (5/97)	vs 7 (8/116)	n.s.
HVL (24 wk)	69 (38/55)	vs 74 (34/46)	n.s.	7 (3/41)	vs 8 (3/37)	n.s.
HVL (48 wk)	59 (56/95)	vs 58 (46/79)	n.s.	2 (1/57)	vs 6 (3/48)	n.s.
G3 patients						
Overall (24 wk)	63 (82/130)	vs 57 (69/121)	n.s.	10 (9/91)	vs 10 (8/77)	n.s.
Overall (48 wk)	54 (123/227)	vs 49 (101/205)	n.s.	11 (15/136)	vs 13 (15/114)	n.s.
LVL (24 wk)	65 (50/77)	vs 61 (38/62)	n.s.	6 (3/53)	vs 7 (3/41)	n.s.
LVL (48 wk)	56 (73/130)	vs 51 (53/104)	n.s.	9 (7/79)	vs 16 (10/62)	n.s.
HVL (24 wk)	70 (28/40)	vs 53 (24/45)	n.s.	18 (6/34)	vs 14 (4/28)	n.s.
HVL (48 wk)	52 (37/71)	vs 55 (41/75)	n.s.	16 (7/43)	vs 7 (3/43)	n.s.

SVR = sustained virologic response; WBD = weight-based dose; FD = fixed dose; HVL = high viral load (HCV RNA levels >600,000 IU/mL); LVL = low viral load (HCV RNA levels ≤600,000 IU/mL); G2 = genotype 2; G3 = genotype 3.

Table 3. Between-Group Analysis of SVR and Relapse Rates Among G2/3 Patients

	SVR		P Values	Relapse Rate		P Values
	G2 vs G3, % (n/N)	(n/N)		G2 vs G3, % (n/N)	(n/N)	
Overall	66 (567/868)	vs 55 (375/683)	<.0001	5 (30/590)	vs 11 (47/418)	.0004
LVL						
WBD (24 wk)	71 (49/69)	vs 65 (50/77)	n.s.	6 (3/52)	vs 6 (3/53)	n.s.
WBD (48 wk)	66 (92/139)	vs 56 (73/130)	n.s.	5 (5/97)	vs 9 (7/79)	n.s.
FD (24 wk)	73 (65/89)	vs 61 (38/62)	n.s.	6 (4/68)	vs 7 (3/41)	n.s.
FD (48 wk)	66 (111/167)	vs 51 (53/104)	.012	7 (8/116)	vs 16 (10/62)	n.s.
HVL						
WBD (24 wk)	69 (38/55)	vs 70 (28/40)	n.s.	7 (3/41)	vs 18 (6/34)	n.s.
WBD (48 wk)	59 (56/95)	vs 52 (37/71)	n.s.	2 (1/57)	vs 16 (7/43)	.028
FD (24 wk)	74 (34/46)	vs 53 (24/45)	.043	8 (3/37)	vs 14 (4/28)	n.s.
FD (48 wk)	58 (46/79)	vs 55 (41/75)	n.s.	6 (3/48)	vs 7 (3/43)	n.s.

SVR = sustained virologic response; HVL = high viral load (HCV RNA levels >600,000 IU/mL); LVL = low viral load (HCV RNA levels ≤600,000 IU/mL); G2 = genotype 2; G3 = genotype 3.

- In G2 patients, SVR rates were similar when using WBD and FD regimens, irrespective of treatment duration or pre-treatment viral load (59%-71% and 58%-74%) (Figure 3 and Table 2).
 - Relapse rates were generally low in G2 patients irrespective of treatment duration or baseline viral load.
- In G3 patients, SVR rates were slightly better when using WBD than FD ribavirin, irrespective of pre-treatment viral load.
 - Among G3 patients treated with WBD ribavirin, relapse rates were higher among patients with high baseline viral load than among those with low baseline viral load, irrespective of treatment duration.
- Univariate analyses revealed that among G3 patients, African American patients have lower relapse rates than Caucasian patients. However, the sample size of African American patients in the study was very small (Table 4).
- Multivariate analyses controlling for genotype, viral load, treatment duration, race, and steatosis revealed G3 (versus G2) as a predictor of relapse.

Table 4. SVR and Relapse Rates Among Caucasian and African American Patients With G2/3

	SVR		P Values	Relapse Rate		P Values
	Caucasian vs African American % (n/N)	(n/N)		Caucasian vs African American % (n/N)	(n/N)	
G2 patients						
Overall	66 (500/752)	vs 49 (19/39)	.025	4 (22/515)	vs 10 (2/21)	n.s.
LVL (24 wk)	73 (98/135)	vs 62 (5/8)	n.s.	4 (4/101)	vs 17 (1/6)	n.s.
LVL (48 wk)	68 (178/261)	vs 36 (5/14)	.018	5 (10/185)	vs 0 (0/5)	n.s.
HVL (24 wk)	73 (64/88)	vs 67 (4/6)	n.s.	6 (4/68)	vs 20 (1/5)	n.s.
HVL (48 wk)	58 (91/156)	vs 50 (2/4)	n.s.	4 (4/94)	vs 0 (0/2)	n.s.
G3 patients						
Overall	55 (330/595)	vs 50 (4/8)	n.s.	11 (42/368)	vs 0 (0/4)	n.s.
LVL (24 wk)	64 (74/115)	vs 33 (1/3)	n.s.	8 (6/80)	vs 0 (0/1)	n.s.
LVL (48 wk)	53 (108/202)	vs 67 (2/3)	n.s.	12 (14/120)	vs 0 (0/2)	n.s.
HVL (24 wk)	61 (47/77)	vs 0 (0/0)	n.s.	17 (9/56)	vs 0 (0/0)	n.s.
HVL (48 wk)	57 (74/130)	vs 50 (1/2)	n.s.	11 (9/81)	vs 0 (0/1)	n.s.

SVR = sustained virologic response; HVL = high viral load (HCV RNA levels >600,000 IU/mL); LVL = low viral load (HCV RNA levels ≤600,000 IU/mL); G2 = genotype 2; G3 = genotype 3.

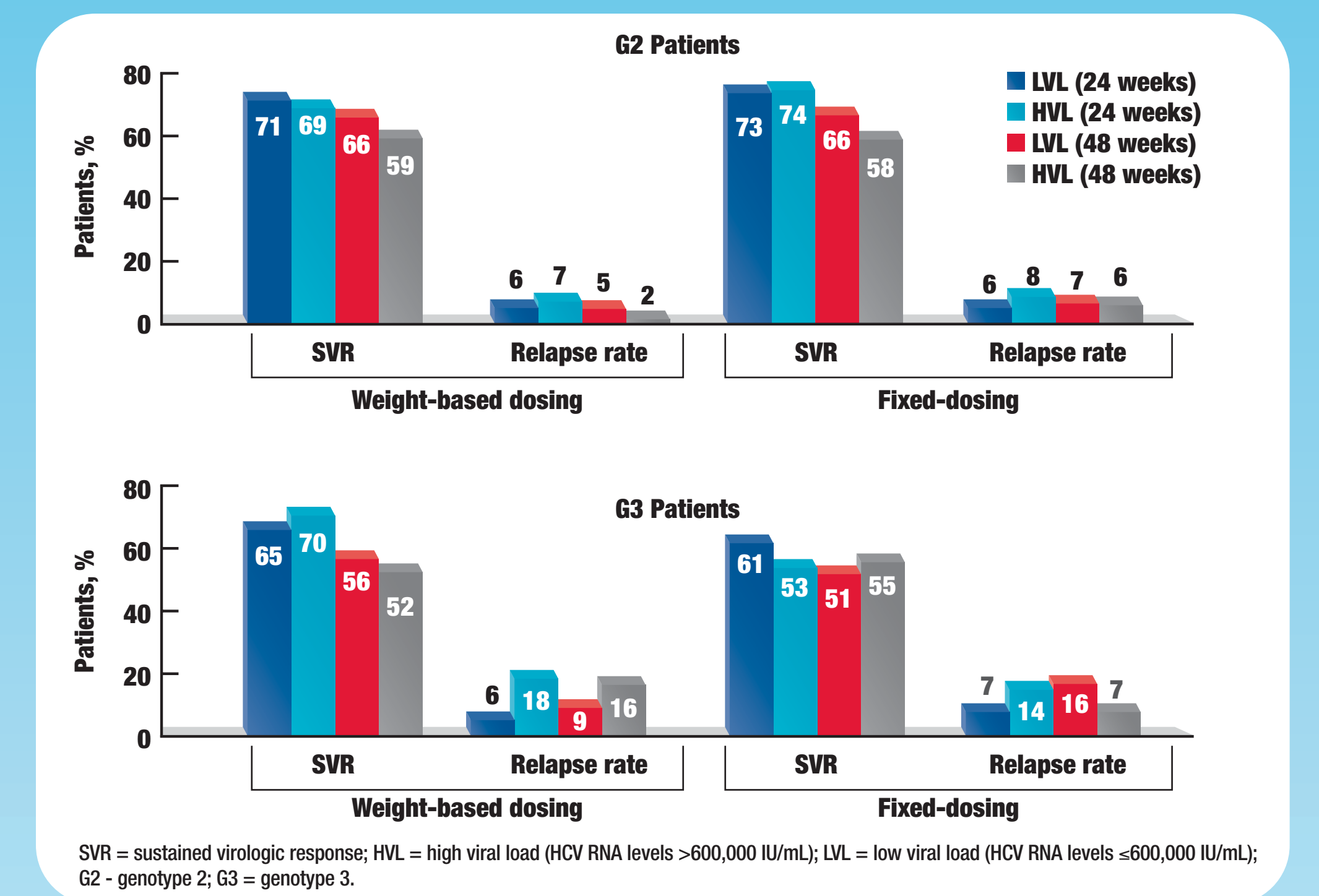


Figure 3. SVR and relapse rates among G2 and G3 patients according to baseline viral load

Summary

- Overall, G2 patients experienced higher SVR rates and lower relapse rates than G3 patients.
- Relapse rates were highest among G3 high viral load patients treated for 24 weeks.
- Multivariate analysis revealed G3 (versus G2) as the only predictor of relapse.
- Similar to G2 patients, when controlling for viral load, G3 patients do not appear to benefit from longer duration of therapy or WBD ribavirin.
- Additional research is needed to define the optimal strategy for lowering relapse rate in G3 high viral load patients.

Conclusions

- G3 high viral load is a predictor of relapse.
- G3 patients are more resistant to treatment than G2 patients.
- Higher ribavirin dose may benefit G3 patients.
- Further research is required to optimize therapy and improve response rates in G3 patients.

References

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