plasma drug concentrations were similar across populations, but only ineligible/intolerant patients experienced failure. Analysis of baseline parameters failed to identify other factors that may have influenced outcomes. However, these analyses were limited by the relatively small study population and may have been confounded by unreported non-adherence or baseline parameters not quantified absolutely, such as the stage of liver fibrosis. This issue requires further study in larger populations to confirm the apparent difference in outcomes and to identify factors predictive of virologic failure.

The adverse event profile of the study regimen was generally more favorable than that typically observed with alfa/RBV-containing regimens.[26] There were no significant hematologic or psychiatric abnormalities; the most common adverse events were non-specific in nature and generally mild to moderate in intensity. Mild diarrhea was experienced by 26% of study patients, consistent with previous studies of asunaprevir and other drugs of this class.[4, 6, 14] The four observed grade 3/4 ALT elevations resolved with continued therapy or after discontinuation and were not associated with significant clinical events. A role for study drugs in the reported serious adverse events cannot be ruled out except for the gastroenteritis; however, four of the six events resolved spontaneously with continued treatment. The case of hyperbilirubinemia with gastroenteritis was complicated by multiple confounding factors, and the contribution of study drugs is uncertain.[7]

In conclusion, dual oral therapy with daclatasvir and asunaprevir elicited rapid clearance of detectable HCV RNA and achieved high rates of SVR in two difficult-to-treat patient populations. These results confirm initial findings that HCV genotype 1b infections can be cured with daclatasvir combined with asunaprevir, without alfa/RBV.[7, 8] Thus, this regimen has potential to offer

effective treatment to null responders who have previously shown little or no response to alfa/RBV, and to alfa/RBV ineligible/intolerant patients who have no current treatment options. Further research will assess the benefits of this and other DAA combinations in larger and more diverse patient populations, but the promise of all oral and well-tolerated HCV therapy is on the horizon.

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FIGURE LEGENDS

Fig. 1. Patient disposition.

Patient flow through treatment and follow-up is shown. d/c, discontinuation of study medication; SVR_4, SVR_{12} and SVR_{24}, sustained virologic response 4, 12 or 24 weeks posttreatment. [a]On-study follow-up continued to posttreatment week 4; HCV RNA remained undetectable at posttreatment week 24 after study discontinuation, reported as failure for SVR_{24} per statistical protocol requirements; [b]HCV RNA was undetectable at posttreatment week 24 after study discontinuation due to addition of alfa/RBV, reported as failure for SVR per statistical protocol requirements; [c]On-study follow-up to assess SVR continued after discontinuation of study drugs.

Fig. 2. Outcomes by IL28B genotype.

Virologic outcomes at milestone time points are shown for the overall population by IL28B (rs12979860) genotype. End of treatment is week 24 or the last on-treatment visit for patients who discontinued early. RVR, rapid virologic response; cEVR, complete early virologic response; SVR_{12} and SVR_{24}, sustained virologic response 12 or 24 weeks posttreatment.

Fig. 3. HCV RNA levels, individual patients.

Serum HCV RNA levels over time are shown for each patient. Panel A, null responders; panel B, ineligible/intolerant patients. EOT, end of treatment; SVR_{24}, sustained virologic response 24 weeks posttreatment; LLOQ, lower limit of quantitation=15 IU/mL.

Fig. 4. Daclatasvir and asunaprevir trough plasma concentrations.

Available trough plasma concentrations of asunaprevir and daclatasvir for individual patients are plotted and color-coded according to each patient's virologic outcome. Multiple determinations are shown for some patients. *Indicates values from a single patient with documented noncompliance.

Figure 1

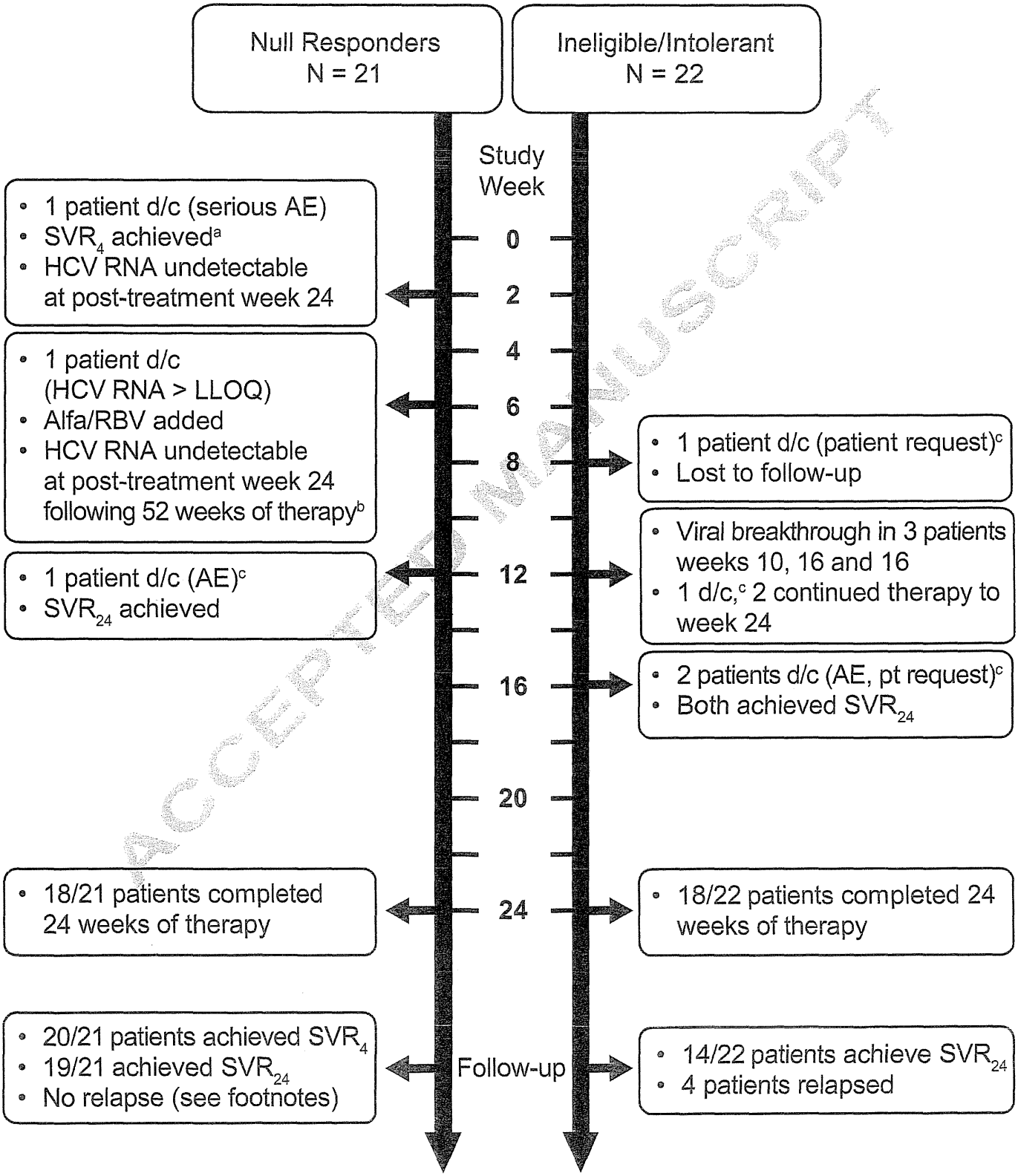


Figure 2

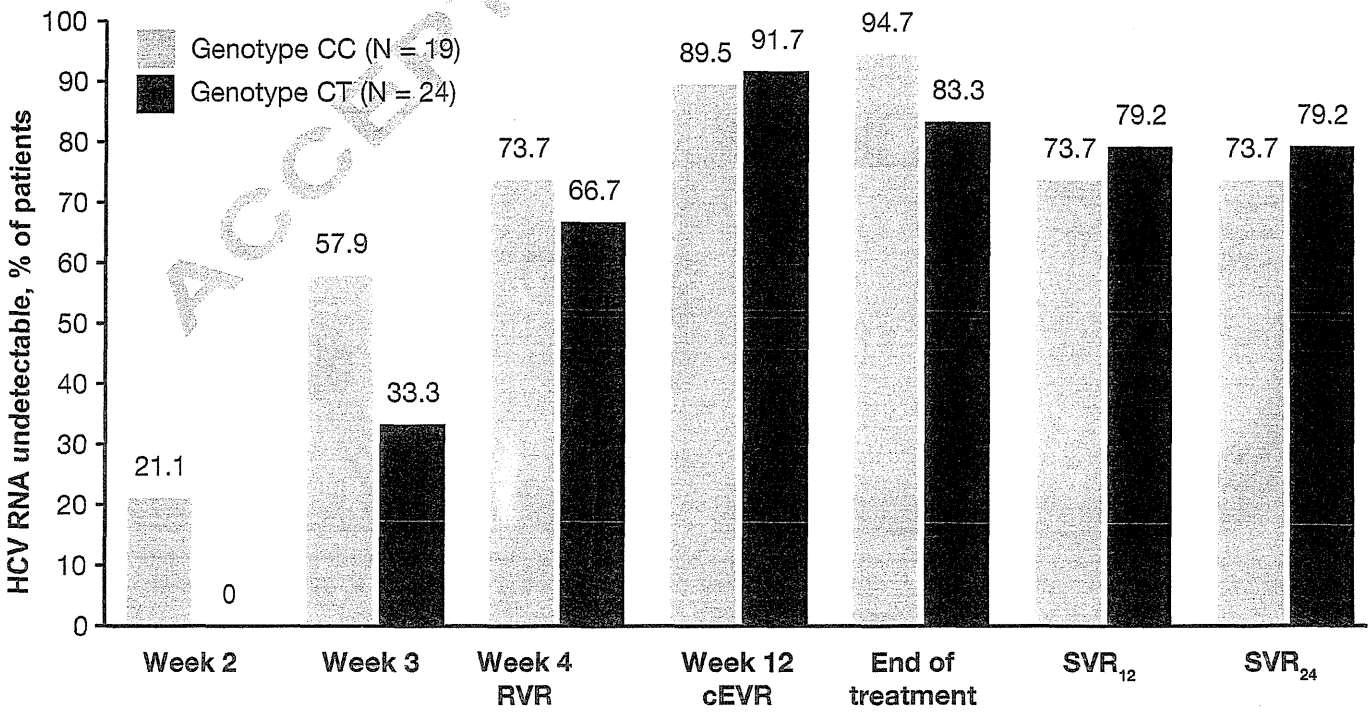
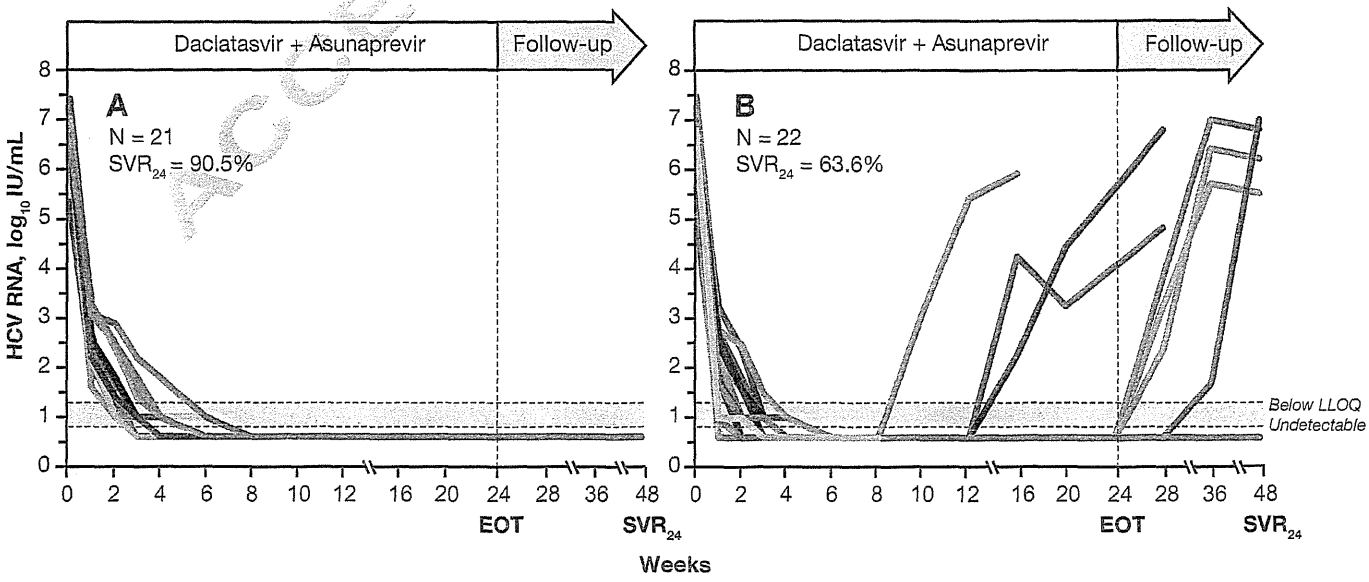
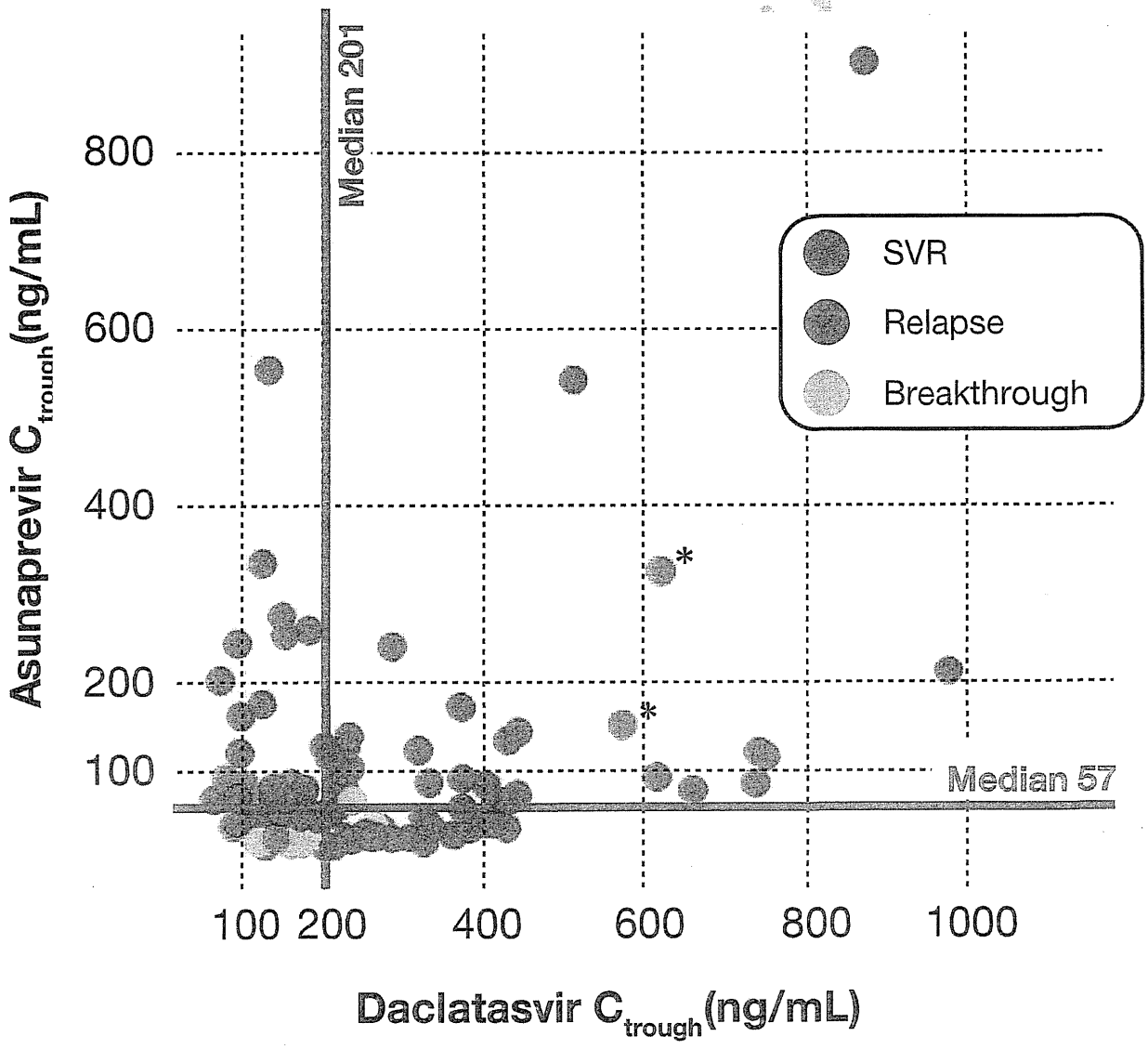


Figure 3



LLOQ, lower limit of quantitation = 15 IU/mL

Figure 4



TABLES

Table 1. Baseline demographic and disease characteristics

Parameter		Null Responders (N=21)	Ineligible/Intolerant (N=22)
Age, median years (range)		61 (31–70)	68 (47–75)
Male, n (%)		8 (38.1)	6 (27.3)
HCV genotype 1b, n (%)		21 (100)	22 (100)
IL28B genotype, n (%)			
(rs12979860)	CT	18 (85.7)	6 (27.3)
	CC	3 (14.3)	16 (72.7)
HCV RNA, mean $\log_{10}$ IU/mL (SD)		6.8 (0.47)	6.6 (0.64)
ALT, mean U/L (SD)		57.9 (24.86)	45.7 (25.79)
APRI score			
Score >2, n (%)		3 (14.3)	1 (4.5)
Median (range)		(0.24–3.41)	(0.40–2.79)
Alfa/RBV ineligible, n (%)		na	18 (81.8)
Alfa/RBV intolerant, n (%)		na	4 (18.2)

Table 2. Virologic outcomes

n (%)	Null Responders (N=21)	Ineligible/Intolerant (N=22)
HCV undetectable, week 4 (RVR)	11 (52.3)	19 (86.4)
HCV undetectable, week 12 (cEVR)	19 (90.5)	20 (90.9)
HCV undetectable, end of treatment	19 (90.5)	19 (86.4)
SVR_4	20 (95.2)[1]	15 (68.2)[2]
SVR_{12}	19 (90.5)[1]	14 (63.6)[2]
SVR_{24}	19 (90.5)[1]	14 (63.6)[2]
Viral breakthrough	0	3 (13.6)
Posttreatment relapse	0	4 (18.2)

Intention to treat (missing=failure) analysis. End of treatment is week 24 or last on-treatment visit for patients who discontinued early. RVR, rapid virologic response; cEVR, complete early virologic response; SVR_4, SVR_{12}, and SVR_{24}, sustained virologic response 4, 12 or 24 weeks posttreatment. [1]Two patients discontinued from the study before completion of follow-up. One patient received added alfa/RBV per protocol criteria and is counted as failure for SVR_4, SVR_{12}, and SVR_{24} for DAA-only therapy; one patient had missing HCV RNA data for follow-up weeks 12 and 24 and is counted as failure for SVR_{12} and SVR_{24} per statistical protocol. [2]One patient was lost to follow-up for assessment of SVR_{12} and SVR_{24}.

Table 3. Resistance-associated polymorphisms in patients with virologic failure

Patient			NS5A				NS3	
			L31	Q54	P58	Y93	Q80	D168
Viral Breakthrough	1	Baseline	L/M			Y/H		
		Post-VBT	M		A	H		A
	2	Baseline		Y		Y/H	L	
		Post-VBT	M	Y		H		V
	3	Baseline		Y		H		
		Post-VBT	M	Y		H		V
Posttreatment relapse	4	Baseline			P/S	Y/H		
		Post-relapse	M			H		A
	5	Baseline			L			
		Post-relapse	M		L	H		V/D
	6	Baseline						
		Post-relapse	V			H		V
	7	Baseline				H		
		Post-relapse	V/M			H		V

Table 4. Most frequent adverse events and laboratory abnormalities

Event, n (%)		Null Responders (N=21)	Ineligible/Intolerant (N=22)
Adverse Events Occurring in ≥ 3 Patients in Either Group	Headache	8 (38)	6 (27)
	Nasopharyngitis	6 (29)	8 (36)
	ALT increase	6 (29)	6 (27)
	Diarrhea	9 (43)	2 (9)
	AST increase	6 (29)	4 (18)
	Pyrexia	3 (14)	5 (23)
	Eosinophilia	1 (5)	4 (18)
	Abdominal discomfort	3 (14)	2 (9)
	Malaise	2 (10)	3 (14)
	Constipation	2 (10)	3 (14)
	Back pain	3 (14)	1 (5)
	Decreased appetite	0	3 (14)
Grade 3 or 4 Lab Abnormalities	ALT	2 (10)	2 (9)
	AST	1 (5)	2 (9)
	Lymphocytes	2 (10)	1 (5)
	Phosphorus	1 (5)	1 (5)
	Bilirubin, total	1 (5)	0

	Leukocytes	1 (5)	0

Title:

Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection

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Keywords:

HBV DNA, HBeAg, nucleos(t)ide analogues, prevention, propensity score, risk score

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Original Article

Exploratory study on telaprevir given every 8 h at 500 mg or 750 mg with peginterferon-alpha-2b and ribavirin in hepatitis C patients

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Aim: The aims of this study are to assess the antiviral effects, safety and telaprevir (TVR) pharmacokinetics in two cohorts given TVR every 8 h (q8h) at doses of 500 mg and 750 mg with peginterferon-α-2b and ribavirin in chronic hepatitis C patients.

Methods: Twenty chronic hepatitis C (HCV) patients with genotype 1b in high viral loads were randomly assigned to two TVR-based regimens of 750 mg q8h (group A) and 500 mg q8h (group B) in combination with peginterferon-α-2b and ribavirin for 12 weeks.

Results: Although the difference was not statistically significant other than trough concentration (C_{trough}) at week 4, the parameters of maximum concentration (C_{max}), the area under the concentration time curve ($AUC_{0-\infty}$) and C_{trough} tended to be higher in group A than those in group B. The antiviral effects were similar in the two groups (sustained virological response rates [SVR], 40% in group A, 50% in group B). The discontinuation rates by anemia were 30% in group A and 20% in group B. Serum creatinine concentrations were lower in group B than those in group A.

Conclusion: Although the exposure to TVR tended to be lower in 500 mg q8h than that in 750 mg q8h, the SVR rates in both groups were similar. The result suggests that the 500 mg q8h dose may be one option for treatment. In addition, the present findings indicate that the development of adverse events which increase with a TVR-based regimen, specifically anemia and creatinine, could be avoided by dose adjustment of TVR.

Key words: anemia, chronic hepatitis C, creatinine increase, pharmacokinetics, telaprevir

INTRODUCTION

THE WORLD HEALTH organization (WHO) estimates that approximately 170 million people are infected with hepatitis C virus (HCV).[1] Decompensated cirrhosis and hepatocellular carcinoma (HCC) develop in approximately 30% of individuals infected with HCV and result in a fatal outcome.[2,3] In Japan, it is estimated that more than 1.5 million people are chronically infected with hepatitis C. Telaprevir (TVR), a potent HCV protease inhibitor, has recently been approved for the treatment of people suffering from chronic genotype 1 HCV infection in the USA, European Union (EU) and Japan. The overseas phase 3 studies demonstrate that patients who received TVR in combination with peginterferon (PEG IFN)-α-2b and ribavirin (RBV) achieved significantly higher rates of sustained virological response (SVR) than those who received only PEG IFN and RBV, regardless of their prior treatment experience with the anti-HCV agents.[4–6] The high SVR rates were also observed in the Japanese phase 3 studies of the TVR-based triple regimen.[7,8] In Japanese patients, anemia was the most common side-effect in the TVR-based triple regimen. The epidemiology of chronic hepatitis C (CHC) in Japan takes on a different aspect

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