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Sustained virologic response rates with telaprevir by response after 4 weeks of lead-in therapy in patients with prior treatment failure☆

Graham R. Foster[1,*], Stefan Zeuzem[2], Pietro Andreone[3], Stanislas Pol[4], Eric J. Lawitz[5], Moises Diago[6], Stuart Roberts[7], Paul J. Pockros[8], Zobair Younossi[9], Isabelle Lonjon-Domanec[10], Sandra De Meyer[11], Don Luo[12], Shelley George[13], Maria Beumont[11], Gaston Picchio[12]

[1]*Queen Marys University of London, Institute of Cell and Molecular Science, London, UK;* [2]*Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany;* [3]*Università di Bologna, Bologna, Italy;* [4]*Université Paris Descartes, INSERM Unité 1016, and Assistance Publique–Hôpitaux de Paris, Cochin Hospital, Paris, France;* [5]*Alamo Medical Research, San Antonio, TX, USA;* [6]*Hospital General de Valencia, Valencia, Spain;* [7]*Department of Gastroenterology, Alfred Hospital, Melbourne, VIC, Australia;* [8]*Scripps Clinic and The Scripps Research Institute, La Jolla, CA, USA;* [9]*Center for Liver Diseases and Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, USA;* [10]*Janssen Pharmaceuticals, Paris, France;* [11]*Janssen Infectious Diseases BVBA, Beerse, Belgium;* [12]*Janssen Therapeutics Inc., Titusville, NJ, USA;* [13]*Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA*

Background & Aims: For hepatitis C virus (HCV)-infected patients who have not responded to previous PegIFN/ribavirin treatment, it is unclear whether subsequent direct-acting antiviral therapy outcomes are better predicted by prior treatment response or by on-treatment response to a PegIFN/ribavirin lead-in.

Methods: In REALIZE, treatment-experienced patients randomized to the lead-in telaprevir arm received 4 weeks of PegIFN-α-2a (180 μg/week) and ribavirin (1000–1200 mg/day), then 12 weeks of telaprevir (750 mg every 8 h) plus PegIFN-α-2a/ribavirin, followed by 32 weeks of PegIFN-α-2a/ribavirin. This subanalysis only included patients in the lead-in telaprevir arm with available week 4 on-treatment response data ($n = 240$).

Results: After 4 weeks of PegIFN/ribavirin, 90% of relapsers, 60% of partial responders, and 41% of null responders in the lead-in telaprevir arm had $\geqslant 1$ $\log_{10}$ HCV RNA reduction. Sustained virologic response (SVR) rates for telaprevir-treated patients with $\geqslant 1$ versus <1 $\log_{10}$ HCV RNA reduction after the PegIFN/ribavirin lead-in were 94% versus 62% in relapsers, 59% versus 56% in partial responders and 54% versus 15% in null responders.

Conclusions: In prior relapsers and partial responders there is no apparent benefit of assessing response after a PegIFN/ribavirin lead-in with the aim of guiding telaprevir-based treatment. For patients known to be prior null responders, on-treatment response after a 4-week PegIFN/ribavirin lead-in may provide clinically useful prognostic information. However, withholding telaprevir-containing therapy in uncategorised treatment-experienced patient populations (i.e., that could include prior relapsers or partial responders), using response after a PegIFN/ribavirin lead-in could potentially exclude some patients with a high chance of SVR.

Keywords: Direct-acting antiviral; Hepatitis C virus; Response prediction; Null responder; Telaprevir; REALIZE.

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* Corresponding author. Address: Queen Marys University of London, Blizard Institute of Cellular and Molecular Science, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London E1 2AT, UK. Tel.: +44 (0) 207 882 7242; fax: +44 (0) 207 882 2187.

E-mail address: g.r.foster@qmul.ac.uk (G.R. Foster).

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response; DAA, direct-acting antiviral; FDA, Food and Drug Administration; EMA, European Medicines Agency; SD, standard deviation; BMI, body mass index.

Introduction

The importance of early on-treatment viral response in predicting treatment outcome in patients receiving peginterferon (PegIFN)-α plus ribavirin for hepatitis C virus (HCV) infection is well established. Notably, a decline in HCV RNA of <2 $\log_{10}$ at week 12 has the highest negative predictive value (98.4%) for sustained virologic response (SVR) [1]. A <1 $\log_{10}$ decrease in HCV RNA at week 4 is also a predictor of non-response to PegIFN-α/ribavirin therapy, as <5% of those patients achieved an SVR in the IDEAL study [2].

Recently, two direct-acting antivirals (DAAs), telaprevir and boceprevir, both HCV protease inhibitors, were approved (in combination with PegIFN-α/ribavirin) for the treatment of chronic HCV genotype 1 infection [3–6]. Significantly improved SVR rates have been reported with DAA-based therapy versus PegIFN-α/ribavirin alone in both treatment-naïve and treatment-experienced patients [7–11]. However, viral resistance has been reported in a proportion of patients failing to respond to DAA-based regimens [12–17]. This may be particularly

significant in prior null responders (defined as having <2 $\log_{10}$ decline in HCV RNA at week 12 of prior treatment) who are the most difficult-to-cure patient population with the lowest reported SVR rates [7]. Although the long-term impact of resistance remains unclear, minimizing ineffective therapy through early identification of patients unlikely to respond to treatment (and therefore at risk of developing drug-resistance mutations) may be important in preserving future treatment options and reducing the costs and inconvenience of therapy that is likely to be futile.

Given the importance of predicting response to DAA-based therapy, baseline and on-treatment response data from phase 3 clinical trials of protease inhibitors have been examined in an effort to find determinants of treatment outcome. For patients with prior PegIFN-α/ribavirin experience, two strategies have been used: one based on response to a previous course of PegIFN-α/ribavirin therapy (i.e., relying on prior response classification of patients into prior relapsers, prior partial responders, or prior null responders) [7], and another based on the response to a 4-week PegIFN-α/ribavirin lead-in phase before adding a protease inhibitor to therapy. However, it is unclear whether these two approaches yield similar information or whether combining them would provide additional benefit.

The boceprevir phase 3 trial (RESPOND-2) used a 4-week PegIFN-α/ribavirin lead-in phase before introducing the protease inhibitor. It enrolled prior relapsers and prior partial responders (the latter defined as patients with ⩾2 $\log_{10}$ HCV RNA reduction at week 12 of prior therapy but never achieving undetectable HCV RNA), and excluded prior null responders. Patients with <1 $\log_{10}$ HCV RNA reduction during the lead-in achieved SVR rates of 33–34% with boceprevir-based therapy, whereas patients with ⩾1 $\log_{10}$ HCV RNA reduction achieved SVR rates of 73–79% [8].

The telaprevir phase 3 REALIZE trial enrolled prior relapsers and partial responders as well as prior null responders, and it also included a telaprevir treatment arm with a 4-week PegIFN-α/ribavirin lead-in phase. The trial showed no significant difference in SVR rates between the telaprevir arms with or without a PegIFN-α/ribavirin lead-in; SVR rates were 88% and 84%, 56% and 61%, and 33% and 31% in prior relapsers, partial responders and null responders, respectively [4]. The design of the REALIZE trial allowed a direct comparison of two different approaches to response prediction: categorization of patients based on response during a prior course of PegIFN-α/ribavirin treatment or based on an on-treatment PegIFN-α/ribavirin lead-in phase. Here we examined treatment outcomes for these two different approaches, both individually and in combination.

Patients and methods

Patients and study design

REALIZE was a phase 3 randomized, double-blind, placebo-controlled, multicenter trial conducted in Australia, Europe, Israel, North America and South America. The study design and inclusion criteria were reported in full previously [7]. Briefly, patients were aged 18–70 years, had a confirmed diagnosis of chronic HCV genotype 1 infection with a liver biopsy within 18 months of screening, and had failed at least one prior course of PegIFN-α/ribavirin treatment. The main exclusion criteria were a history of decompensated liver disease, significant liver disease due to other (non-HCV) causes, active malignancy, and co-infection with human immunodeficiency virus or hepatitis B.

The protocol was approved a priori by the relevant independent ethics committees for all participating study centers and the trial was performed in accordance with the 1975 Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. REALIZE is registered with ClinicalTrials.gov (NCT00703118).

Patients were randomized 2:2:1 to receive telaprevir/PegIFN-α-2a/ribavirin (T12PR48) with or without a PegIFN-α-2a/ribavirin lead-in phase, or PegIFN-α-2a/ribavirin only (PR48 control), as previously described [7]. Patients in the lead-in T12PR48 arm received 4 weeks of placebo plus PegIFN-α-2a (Pegasys, 180 μg/week subcutaneously; Roche, Basel, Switzerland) and ribavirin (Copegus, 1000–1200 mg/day orally; Roche, Basel, Switzerland and Pantheon Inc., Toronto, Canada), followed by 12 weeks of telaprevir (750 mg orally every 8 h; Tibotec, Beerse, Belgium) plus PegIFN-α-2a/ribavirin, then 32 weeks of PegIFN-α-2a/ribavirin alone. The T12PR48 arm without a PegIFN-α-2a/ribavirin lead-in and the PR48 (control) arm were not included in this subanalysis.

Patients were stratified for baseline HCV RNA < or ⩾800,000 IU/ml and prior response to PegIFN-α/ribavirin therapy. Patients were classified as prior relapsers (having undetectable HCV RNA after ⩾42 weeks of PegIFN-α/ribavirin therapy, but having detectable HCV RNA thereafter), prior partial responders (having ⩾2 $\log_{10}$ HCV RNA reduction at week 12 of prior PegIFN-α/ribavirin therapy but never achieving undetectable HCV RNA), or prior null responders (having <2 $\log_{10}$ HCV RNA reduction at week 12 of prior PegIFN-α/ribavirin therapy).

Assessments

Plasma HCV RNA levels were measured at screening, baseline, regularly during treatment, at early discontinuation, follow-up visits 4, 12 and 24 weeks after the end of treatment, and at week 72 (including in patients who discontinued early) [7]. Allowed time windows were: ±1 day for visits before week 6; ±2 days from weeks 6–20; ±4 days from week 24 onward; ±1 week after the follow-up visit 4 weeks after last intake of study drug. Plasma HCV RNA was quantified using the COBAS TaqMan® assay (Roche, Basel, Switzerland), version 2.0 (lower limit of quantification 25 IU/ml; lower limit of detection 10 IU/ml). SVR was defined as undetectable (<10 IU/ml) HCV RNA 24 weeks after the last dose of study medication.

Virologic stopping rules for discontinuation of treatment have been described elsewhere [7]. Briefly, telaprevir was discontinued if patients had HCV RNA >100 IU/ml at 4, 6 or 8 weeks after starting telaprevir treatment, and all treatment was discontinued if patients had <2 $\log_{10}$ decline in HCV RNA 12 weeks after starting telaprevir or detectable (⩾10 IU/ml) HCV RNA at weeks 24 or 36. Patients who discontinued telaprevir due to stopping rules were considered virologic failures.

Endpoints and statistical analysis

The primary endpoint of the trial was the proportion of patients in the prior relapser and non-responder (partial and null responders) groups achieving an SVR. Statistical analysis was performed by SGS-LSS (Mechelen, Belgium) using SAS® version 9.1 as reported previously [7].

This subanalysis included patients in the lead-in T12PR48 arm with available week 4 on-treatment response data. SVR rates were calculated according to week 4 on-treatment response (either < or ⩾1 $\log_{10}$ HCV RNA decrease from baseline) and for each prior response category (prior relapse, partial response or null response). A *post-hoc* exploratory logistic regression analysis including type of prior response (relapse, partial response or null response), week 4 on-treatment response (< or ⩾1 $\log_{10}$ HCV RNA reduction) and their interaction as factors, and baseline HCV RNA as a covariate was conducted.

Results

This subanalysis included 240 patients from the lead-in T12PR48 arm with available HCV RNA data at week 4, representing 91% of patients enrolled into that treatment arm [7]. In the lead-in T12PR48 arm, 126 patients (53%) were prior relapsers, 45 (19%) were prior partial responders, and 69 (29%) were prior null responders.

Baseline demographics and disease characteristics were generally similar to the overall trial population [7] with no noteworthy trends across prior response categories (Table 1; baseline

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Table 1. Baseline characteristics. Baseline characteristics in the lead-in T12PR48 arm according to prior PegIFN-α/ribavirin response category.

Baseline characteristic	Prior relapsers (n = 126)	Prior partial responders (n = 45)	Prior null responders (n = 69)
Mean age, yr (SD)	51 (7.8)	51 (8.7)	51 (8.5)
Mean BMI, kg/m^2 (SD)	26.7 (4.53)	28.3 (5.11)	27.0 (4.60)
Male, n (%)	88 (70)	34 (76)	49 (71)
Race*, n (%)			
Caucasian/white	123 (98)	43 (96)	65 (94)
Black	2 (2)	2 (4)	2 (3)
Asian	1 (1)	0	1 (1)
Other	0	0	1 (1)
Ethnicity*, n (%)			
Hispanic or Latino	11 (9)	7 (16)	4 (6)
Not Hispanic or Latino	115 (91)	38 (84)	65 (94)
Mean time since HCV diagnosis, yr (SD)	9.0 (5.50)	9.6 (7.00)	9.4 (6.06)
Mean HCV RNA, $\log_{10}$ IU/ml†, (SD)	6.5 (0.63)	6.7 (0.41)	6.7 (0.44)
Baseline HCV RNA ≥800,000 IU/ml†, n (%)	106 (84)	44 (98)	66 (96)
HCV genotype‡, n (%)			
1a	68 (54)	26 (59)	41 (59)
1b	57 (46)	18 (41)	28 (41)
Assessment of fibrosis§, n (%)			
No or minimal fibrosis	44 (35)	11 (24)	9 (13)
Portal fibrosis	32 (25)	12 (27)	19 (28)
Bridging fibrosis	22 (18)	9 (20)	18 (26)
Cirrhosis	28 (22)	13 (29)	23 (33)

SD, standard deviation; BMI, body mass index; HCV, hepatitis C virus.
*Race and ethnicity were self-reported.
†HCV RNA levels measured by COBAS® TaqMan® HCV assay (v2.0; lower limit of quantification = 25 IU/ml).
‡HCV genotype determined by NS3 assay.
§Minimal or no fibrosis: Metavir F0–F1 and Ishak 0–2; portal fibrosis: Metavir F2 and Ishak 3; bridging fibrosis: Metavir F3 and Ishak 4–5; cirrhosis: Metavir F4 and Ishak >5.

data according to week 4 on-treatment response available as Supplementary material). Mean baseline viral loads were 6.5–6.7 $\log_{10}$ IU/ml, with 84–98% of patients having baseline HCV RNA ⩾800,000 IU/ml.

On-treatment response (<1 or ⩾1 $\log_{10}$ HCV RNA reduction) following a 4-week PegIFN-α/ribavirin lead-in phase

After 4 weeks of PegIFN-α/ribavirin, ⩾1 $\log_{10}$ HCV RNA reduction was observed in 70% of patients in the lead-in T12PR48 arm, including 90% of prior relapsers, 60% of prior partial responders, and 41% of prior null responders (Fig. 1). A <1 $\log_{10}$ reduction in HCV RNA was observed in 30% of patients, including 10% of prior relapsers, 40% of prior partial responders, and 59% of prior null responders.

Treatment outcomes based on prior response category compared with those based on response following a 4-week PegIFN-α/ribavirin lead-in phase

Overall, 67% of patients in the lead-in T12PR48 treatment arm with available HCV RNA data at week 4 achieved a SVR (Fig. 2). Overall SVR rates in the lead-in T12PR48 arm based on prior response category were 90% for prior relapsers, 58% for prior partial responders, and 30% for prior null responders (Fig. 2). Since patients may present without any prior response history, SVR rates were also determined for patients with <1 or ⩾1 $\log_{10}$ HCV RNA reduction at week 4 of the lead-in phase, regardless of prior response category. In the lead-in T12PR48 arm, SVR rates were 33% and 82% for patients with <1 or ⩾1 $\log_{10}$ HCV RNA reduction at week 4, respectively (Fig. 2). Further subdividing week 4 response categories beyond the <1 or ⩾1 $\log_{10}$ HCV RNA reduction groups showed a trend for incrementally greater reductions in $\log_{10}$ HCV RNA to correlate with increases in SVR rates (Table 2). Logistic regression analyses showed that prior response category (relapse versus null response: OR 4.4, 95% CI 1.6–12.0; partial versus null response: OR 2.9, 95% CI 1.0–8.2) and week 4 on-treatment response (⩾1 versus <1 $\log_{10}$ HCV RNA: OR 5.1, 95% CI 2.6–10.1) were both significant factors for SVR (primary end point).

SVR rates according to a combination of prior response category and week 4 on-treatment response following the lead-in phase

For patients with <1 or ⩾1 $\log_{10}$ reduction in HCV RNA at week 4, respectively, SVR rates were 62% and 94% for prior relapsers, 56% and 59% for prior partial responders, and 15% and 54% for prior null responders (Fig. 3). Logistic regression analyses showed that

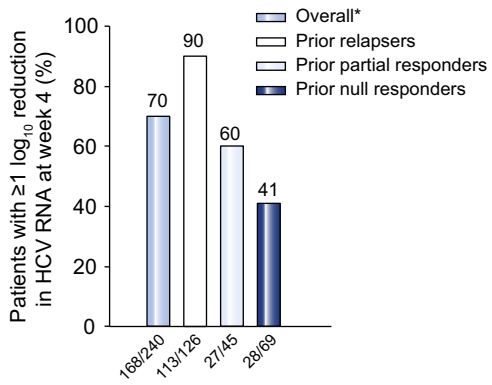

Fig. 1. Week 4 response. Proportion of patients in the lead-in T12PR48 arm with $\geqslant 1$ $\log_{10}$ HCV RNA reduction after a 4-week PegIFN-α/ribavirin lead-in, overall and according to prior PegIFN-α/ribavirin response category. *Excluding patients without available data at week 4 of the lead-in phase. HCV, hepatitis C virus.

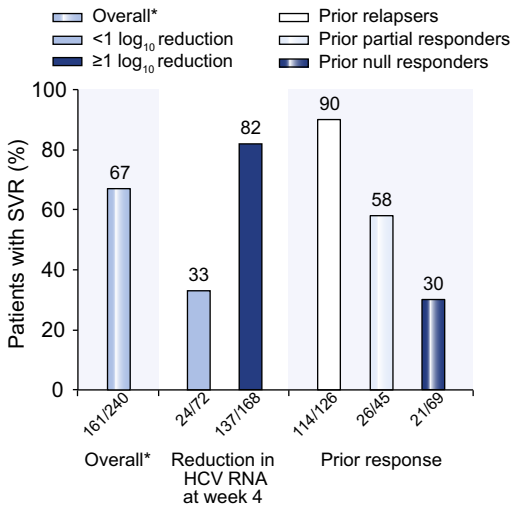

Fig. 2. SVR rate according to either week 4 response or prior response category. SVR rates in the lead-in T12PR48 arm, overall and according to either on-treatment response after a 4-week PegIFN-α/ribavirin lead-in or prior PegIFN-α/ribavirin response category. *Excluding patients without available data at week 4 of lead-in phase. Overall SVR rates for the lead-in T12PR48 arm (all patients) were 88%, 54% and 33% for prior relapsers, partial responders and null responders, respectively [7]. SVR, sustained virologic response; HCV, hepatitis C virus.

the differences in SVR rates between <1 and $\geqslant 1$ $\log_{10}$ HCV RNA reduction categories at week 4 of the lead-in were significant for prior null responders and relapsers (both p <0.01), but not for prior partial responders ($p = 0.27$).

Since distinguishing between prior relapsers, partial responders and null responders may not always be possible, we determined SVR rates for combined subgroups (Fig. 3). The overall SVR rate for the combined subgroup of prior relapsers and partial responders in the lead-in T12PR48 arm was 82%; among the patients with <1 or $\geqslant 1$ $\log_{10}$ response at week 4, 58% and 87% achieved an SVR, respectively (Fig. 3). The overall SVR rate for the combined subgroup of prior partial and null responders was 41%; among the patients with <1 or $\geqslant 1$ $\log_{10}$ response at week 4, 27% and 56% achieved an SVR, respectively (Fig. 3).

For prior relapsers and partial responders, further subdividing week 4 response categories (Table 2) produced generally similar SVR rates to those using the <1 or $\geqslant 1$ $\log_{10}$ HCV RNA categorization, although the number of patients in some subgroups was small. Among prior null responders, a trend for increasing SVR rates was seen with incrementally greater reductions in $\log_{10}$ HCV RNA after the 4-week PegIFN/ribavirin lead-in. Similarly, incrementally lower reductions in $\log_{10}$ HCV RNA levels at week 4 (than <1) appeared to correlate with a worsening in SVR rates.

Discussion

This REALIZE study subanalysis provides an insight into the value of prior response characterization, on-treatment response at week 4 of a PegIFN-α/ribavirin lead-in phase, and a combination of both in predicting SVR with a telaprevir-containing regimen in treatment-experienced patients. These findings provide clinically useful prognostic information that may help guide patient selection in terms of the initiation of telaprevir-based therapy.

As expected, in the lead-in T12PR48 arm most patients with a prior relapse showed a good response to the 4-week PegIFN-α/ribavirin lead-in treatment phase; 90% had $\geqslant 1$ $\log_{10}$ reduction in HCV RNA. SVR rates were high among prior relapsers with $\geqslant 1$ $\log_{10}$ reduction in HCV RNA after 4 weeks of PegIFN-α/ribavirin; 94% following telaprevir-based therapy. The remaining 10% of prior relapsers had <1 $\log_{10}$ HCV RNA at week 4; however, the SVR rate in these patients was also high (62%). The majority of prior partial responders (60%) had $\geqslant 1$ $\log_{10}$ HCV RNA reduction at week 4, although these patients achieved similar SVR rates with telaprevir-based therapy regardless of response during the 4-week lead-in phase (56% and 59% for those with <1 or $\geqslant 1$ $\log_{10}$ HCV RNA reduction, respectively). Furthermore, subdividing week 4 response categories beyond the <1 or $\geqslant 1$ $\log_{10}$ HCV RNA reduction groups did not appear to provide additional clinical guidance in prior relapsers or partial responders. Therefore, for prior relapsers and partial responders, response after a PegIFN-α/ribavirin lead-in does not provide substantial useful prognostic information for subsequent telaprevir-based therapy.

For prior null responders, response rates differed according to treatment outcome after the 4-week lead-in phase: a low SVR rate (15%) was observed for the prior null responders with <1 $\log_{10}$ HCV RNA at week 4, whereas those with $\geqslant 1$ $\log_{10}$ HCV RNA reduction had an SVR rate of 54%. This suggests that prior null responders (i.e., <2 $\log_{10}$ HCV RNA reduction at week 12 of prior therapy) with a poor (<1 $\log_{10}$) week 4 lead-in phase response probably represent the most difficult-to-cure patients. Unlike prior relapsers and partial responders, further subdividing week 4 response categories beyond the <1 or $\geqslant 1$ $\log_{10}$ HCV RNA reduction groups showed some utility in predicting response in prior null responders. Taken together, this information suggests that using a combination of both prior and on-treatment response data may identify prior null responders for whom telaprevir plus PegIFN-α/ribavirin therapy could be suboptimal, and for whom the benefits versus risks of initiating telaprevir-based therapy should be carefully considered. This subgroup of patients may benefit from alternative, investigative therapeutic approaches such as DAA-based combination regimens [18,19], or longer exposure to treatment; further studies are required to evaluate this possibility. If triple therapy is initiated in this subgroup, then as with all patients receiving telaprevir-based therapy, it is important that stopping rules are closely followed

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Table 2. SVR rate according to incremental week 4 response, overall and prior response category. Patients with SVR in the lead-in T12PR48 arm according to prior PegIFN-α/ribavirin response category and incremental on-treatment response after a 4-week PegIFN-α/ribavirin lead-in phase.

Patients with SVR*, % (n/N)	Reduction in $\log_{10}$ HCV RNA from baseline to week 4				
	≤0.5	>0.5 to ≤1.0	>1.0 to ≤1.5	>1.5 to ≤2.0	>2.0
Relapsers (n = 126)	67 (2/3)	60 (6/10)	92 (11/12)	89 (16/18)	95 (79/83)
Partial responders (n = 45)	60 (3/5)	54 (7/13)	30 (3/10)	80 (8/10)	86 (6/7)
Null responders (n = 69)	6 (1/16)	20 (5/25)	44 (8/18)	60 (3/5)	80 (4/5)
Overall (n = 240)	25 (6/24)	38 (18/48)	55 (22/40)	82 (27/33)	94 (89/95)

HCV, hepatitis C virus; SVR, sustained virologic response.
*Excluding patients without available data at week 4 of the lead-in phase.

to prevent unnecessary exposure to treatment in those unlikely to achieve an SVR. Data from an analysis by Jacobson *et al.* [20] found that 17% (12/70) of prior null responders would have met the telaprevir stopping rule of >1000 IU/ml HCV RNA after 4 or 12 weeks of triple therapy in the REALIZE study. No patients meeting this stopping rule achieved SVR with continued treatment.

Interestingly, those patients who were poor responders after a 4-week lead-in phase may be quite different from patients who were null responders at week 12 of a prior course of PegIFN-α/ribavirin therapy. A proportion of prior relapsers and partial responders (i.e., patients not classified as null responders to prior treatment) showed <1 $\log_{10}$ HCV RNA reduction after the 4-week PegIFN-α/ribavirin lead-in phase, which has been suggested as equivalent to a null response. Using different datasets of patients treated with PegIFN-α/ribavirin, we and others [21,22] have also previously reported that a proportion (38–41%) of those with <1 $\log_{10}$ reduction in HCV RNA at week 4 of treatment did not then become null responders according to the classical definition (<2 $\log_{10}$ reduction in HCV RNA at week 12) used by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in their draft guidelines [23,24]. Consistent with this, prior relapsers and partial responders with <1 $\log_{10}$ HCV RNA reduction after the 4-week lead-in phase achieved a higher SVR rate (58% overall) than prior null responders (30% overall) in the lead-in T12PR48 arm.

Overall, prior response categorization provided a more granular prediction of SVR (90%, 58%, and 30% in prior relapsers, partial responders and null responders, respectively) with telaprevir-based therapy than the exclusive use of week 4 on-treatment response (82% and 33% in patients with ⩾1 or <1 $\log_{10}$ HCV RNA reduction, respectively). However in clinical practice, detailed information on viral levels during a prior course of PegIFN-α/ribavirin may not be available for some patients. For these patients, on-treatment response after a 4-week PegIFN/ribavirin lead-in phase might provide limited prognostic information. However, it may also introduce additional treatment complexity and does not in itself confer an efficacy benefit (similar SVR rates were achieved in the T12PR48 versus lead-in T12PR48 arms in REALIZE [7]). Furthermore, if patients not achieving a ⩾1 $\log_{10}$ HCV RNA reduction after a 4-week PegIFN-α/ribavirin lead-in phase were excluded from initiating telaprevir-based therapy, the opportunity to cure 62% of prior relapsers and 56% of prior partial responders with a poor on-treatment interferon response would effectively be missed, representing respectively 6% (8/126) and 22% (10/45) of all relapsers and partial responders in this analysis.

Data on concordance between definitions of response and the impact on SVR rates with other DAAs are currently limited, and cross-trial analysis of trends in outcome with protease inhibitors in the overall treatment-experienced population as a whole (and in null responders in particular) is not straightforward. The phase 3 REALIZE trial evaluated outcome with telaprevir-based therapy in classically defined prior null responders, representing 28% of the patients enrolled [7]. In the phase III RESPOND-2 trial of boceprevir-based therapy, patients with <2 $\log_{10}$ HCV RNA reduction at week 12 of prior therapy (i.e., prior null responders) were excluded and patients with <1 $\log_{10}$ HCV RNA reduction following the 4-week PegIFN-α/ribavirin lead-in were classified as poorly responsive to interferon [8]. However, since these definitions of non-response are not concordant [21,22], the absence of head-to-head studies should lead to caution when comparing SVR rates in patients treated with different protease inhibitor-containing regimens, particularly where there are differences in enrolment criteria by prior response.

Although it provides clinically useful information, the present subanalysis is limited by the trial not being powered to show efficacy differences according to week 4 on-treatment responses, and by small patient numbers in some subgroups. Interleukin-28B (*IL28B*) genotype correlates with PegIFN-α/ribavirin response [25,26] and might have provided further information on differences between definitions of prior and on-treatment response, although a recent subanalysis of the REALIZE trial suggested that *IL28B* genotype had a limited impact on SVR rates following telaprevir-based combination therapy [27]. Since consent for genetic testing requires the de-identification of samples and analysis by an independent group, results for *IL28B* testing are not part of our study. Patients were also not randomly assigned according to this marker, since it had not been discovered at the time of enrollment. If such investigations had been possible, then subdividing patients across additional retrospective subgroups would limit any conclusions due to the small patient numbers in each group.

Analysis of additional baseline factors, such as fibrosis level and viral subtype, may also be informative. For example, progression of liver fibrosis between the initial treatment and start of triple therapy may have impacted on the prognosis of treatment response. However, in line with the *IL28B* analyses mentioned above, the conclusions of such investigations would be limited. In addition, applying multiple prognostic factors in clinical practice may have practical limitations for healthcare professionals. A final potential limitation is that our analyses were restricted to the week 4 time point, at the end of the PegIFN-α/ribavirin lead-in phase. However, week 4 is a well-established time point for assessing the probability of SVR with PegIFN-α/ribavirin

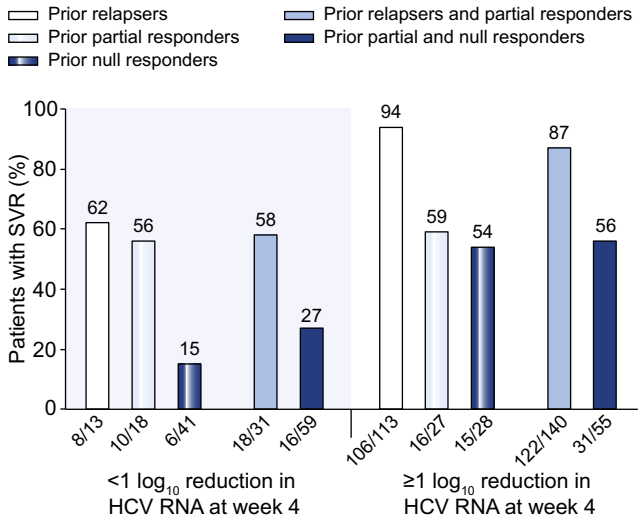

Fig. 3. SVR rate according to both week 4 response and prior response category. SVR rates in the lead-in T12PR48 arm according to both on-treatment response after a 4-week PegIFN-α/ribavirin lead-in and prior PegIFN-α/ribavirin response category. SVR, sustained virologic response; HCV, hepatitis C virus.

treatment [2] and has previously been used to assess sensitivity to PegIFN-α/ribavirin and SVR rates following the addition of boceprevir [8].

In conclusion, based on this subanalysis, the exclusive use of response at week 4 of a PegIFN-α/ribavirin lead-in phase to guide therapy may result in missed opportunities to cure prior relapsers and prior partial responders with telaprevir-based therapy. Furthermore, prior response to PegIFN-α/ribavirin, as defined in the REALIZE trial, provided a more granular prediction of SVR with telaprevir-based therapy than the exclusive use of week 4 on-treatment response to a PegIFN-α/ribavirin lead-in. Among null responders to prior treatment, response after a 4-week PegIFN-α/ribavirin lead-in phase may identify patients for whom telaprevir plus PegIFN-α/ribavirin therapy could be suboptimal.

Conflict of interest

GR Foster has received research funding and/or been a consultant, member of an Advisory Board or Speakers' bureau for Roche, Janssen Pharmaceuticals, GlaxoSmithKline, Novartis, Gilead and Merck. S Zeuzem has received consulting and lecture fees and/or been a member of Advisory Boards for Abbott, Achillion, Anadys Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, iTherx, Merck, Novartis, Pharmasset, Santaris, Roche, Tibotec/Janssen Pharmaceuticals and Vertex Pharmaceuticals, and has been on Speakers' bureau for Bristol-Myers Squibb, Gilead, Merck, Novartis and Roche; P Andreone has been a consultant for Roche and Janssen-Cilag, received research support from Roche and Gilead, and received travel grants from Roche, Merck/Schering-Plough and Gilead; S Pol has received consulting fees and/or been a member in Advisory Boards or Speakers' bureau for Roche, Gilead, Bristol-Myers Squibb, Merck, Boehringer Ingelheim, Novartis, Sanofi, Abbott and GlaxoSmithKline, and received research/grant support from Roche, Gilead, Bristol-Myers Squibb and Merck; EJ Lawitz has received research/grant support from Abbott, Achillion, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Inhibitex Pharmaceuticals, Medarex, Medtronic, Merck, Novartis, Pharmasset, Roche, Sanofi-Aventis, Schering-Plough, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Tibotec, Vertex Pharmaceuticals, ViroChem Pharma, and ZymoGenetics, has been a speaker for Gilead, Merck and Vertex, and has been a member of Advisory Boards for Abbott, Achillion, Anadys Pharmaceuticals, Biolex Therapeutics, GlobeImmune, Inhibitex Pharmaceuticals, Merck and Pharmasset; M Diago has been an investigator in clinical trials for Roche, Tibotec, Gilead, Bristol-Myers Squibb, GlaxoSmithKline, Transgene, Schering-Plough, Novartis and Boehringer Ingelheim; S Roberts has been a member of Advisory Boards for Roche and Tibotec/Janssen Pharmaceuticals; PJ Pockros has been on Advisory Boards and/or Speakers' bureau and/or received research support/grants from Roche and Vertex, and has been on Advisory Boards and received research support from Gilead; Z Younossi has been a consultant or member of Advisory Boards for Vertex, Tibotec/Janssen Pharmaceuticals and Salix Pharmaceuticals; I Lonjon-Domanec is a full-time employee of Janssen Pharmaceuticals; S De Meyer and M Beumont are full-time employees of Janssen Infectious Diseases BVBA; D Luo and G Picchio are full-time employees of Janssen Therapeutics Inc.; S George is a full-time employee of Vertex Pharmaceuticals.

Trial investigators

The members of the REALIZE Study Group were: *Argentina* – Ruben Terg, Marcelo Oscar Silva; *Austria* – Peter Ferenci, Rudolf Stauber, Michael Gschwantler; *Australia* – Martin Weltman, Geoffrey McCaughan, Greg Dore, Hugh Harley, William Sievert, Joe Sasadeusz, Stuart Roberts, Wendy Cheng; *Belgium* – Yves Horsmans, Frederik Nevens, Hans Van Vlierberghe, Christophe Moreno; *Brazil* – Maria Patelli Lima, Raymundo Parana, Luiz Guilherme Lyra, Cassia Mendes-Correa, Roberto Focaccia, Fernando Lopes Goncales Jr; *Canada* – Curtis Cooper, Richard Lalonde, Eric Yoshida; *France* – Marc Bourlière, Jean-Pierre Bronowicki, Patrice Couzigou, Jean-Didier Grange, Patrick Marcellin, Philippe Mathurin, Christian Trepo, Jean-Pierre Zarski, Yves Benhamou, Stanislas Pol, Christophe Hézode; *Germany* – Thomas Berg, Stefan Lueth, Tobias Goeser, Heiner Wedemyer, Stefan Mauss, Jens Rasenack, Stefan Zeuzem, Hans Weidenbach; *Israel* – Yaacov Baruch, Yoav Lurie, Daniel Shouval, Assy Nimer, Ziv Benari; *Italy* – Massimo Colombo, Antonio Ascione, Pietro Andreone; *The Netherlands* – Henk Reesink, Bart van Hoek, Joost Drenth; *Poland* – Robert Flisiak, Andrzej Horban, Wieslaw Kryczka, Maciej Jablkowski, Ewa Janczewska kazek; *Spain* – Rafael Esteban, Jose Maria Sanchez-Tapias, Maria Trapero, Moises Diago, Javier Garcia-Samaniego, Manuel Romero; *Switzerland* – Beat Muellhaupt, Tilman Gerlach; *Sweden* – Ola Weiland; *United Kingdom* – Geoffrey Dusheiko, David Mutimer, Kaushik Agarwal, Graham R Foster, Ashley Brown; *United States* – Paul J Pockros, Eliot W Godofsky, Bradley L Freilich, Joseph Galati, Michael Ryan, Coleman Smith, Natalie Bzowej, Gary Davis, Gregory Everson, Norman Gitlin, Stuart C Gordon, Thomas Savides, Eric J Lawitz, David Nelson, Fred Poordad, Maribel Rodriguez-Torres, Velimir A Luketic, Eugene R Schiff, Gyongyi Szabo, Zobair Younossi, Nezam Afdhal, Sanjeev Arora, David Bernstein, Ira M Jacobson, Paul Kwo, James Strohecker, Keyur Patel, Michael Warren Fried, K Rajender Reddy, Mark Sulkowski.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.11.013.

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