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Low-density lipoprotein and other predictors of response with telaprevir-based therapy in treatment-experienced HCV genotype 1 patients: REALIZE study

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Keywords
HCV – LDL – predictors – REALIZE – response – telaprevir

Abbreviations
ALT, alanine amino transferase; AST, aspartate amino transferase; AUC, area under the curve; BMI, body mass index; CI, confidence interval; eRVR, extended RVR; GGT, gamma-glutamyltranspeptidase; HCV, hepatitis C virus; HDL, high-density lipoprotein; IFN, interferons; LDL, low-density lipoprotein; OR, odds ratio; ROC, receiver–operator characteristic; RVR, rapid virologic response; SVR, sustained viral response.

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Abstract

Background & Aims: Predictors of response to treatment with peginterferon plus ribavirin are well established. In these post-hoc analyses of the REALIZE study, we sought to identify predictors of response for telaprevir-based triple therapy. *Methods:* Patients from the REALIZE study with baseline data for all predictors evaluated (including baseline disease characteristics and demographics, prior treatment response and baseline laboratory assessments) were included in the post-hoc analyses (n = 465). Univariate and multivariate analyses were used to evaluate factors predicting treatment outcomes. *Results:* Sustained viral response (SVR) rates were 86% in prior relapsers, 63% in prior partial responders and 32% in prior null-responders. In the final multivariate analysis, baseline factors predicting SVR were prior response to treatment [Odds ratio (OR) = 2.80; 95% confidence interval (CI), 2.13–3.69], low-density lipoprotein (LDL) (≥2.6 mmol/L) (OR = 2.11; 95% CI, 1.52–2.93), HCV genotype (OR = 0.58; 95% CI, 0.36–0.93), and maximum alanine amino transferase and aspartate amino transferase (OR = 0.62; 95% CI, 0.40–0.97). *Conclusions:* Prior response to peginterferon plus ribavirin treatment and LDL levels are the main independent predictive markers of response with telaprevir-based triple therapy.

- Reliable predictors of response can allow physicians to refine hepatitis C treatment schedules for individual patients. However, minimal data exist, showing predictors of response to telaprevir-based treatment.
- Predictors of sustained virologic response (SVR) with telaprevir-based triple therapy were therefore examined in 465 treatment-experienced genotype 1 chronic hepatitis C-infected patients.
- Prior response to treatment [odds ratio (OR) = 2.80] and low-density lipoprotein levels (≥2.6 mmol/L) (OR = 2.11) were the main independent predictive markers with telaprevir-based triple therapy.
- Identifying predictors of response to new hepatitis C combinations may be important in individualising hepatitis C treatment.

Predicting response to treatment with antiviral therapy is an important consideration in patients infected with hepatitis C virus (HCV). A number of pretreatment host and viral factors have previously been associated with peginterferon plus ribavirin treatment outcome, these factors include baseline viral load, HCV genotype, age, gender, body mass index (BMI), insulin resistance, cholesterol, gamma-glutamyltranspeptidase (GGT), serum ferritin, hepatic steatosis and hepatic fibrosis (1–11). More recently, nucleotide polymorphisms upstream of the interleukin 28B (*IL28B)* gene have been reported to be strongly associated with spontaneous (12, 13) and peginterferon plus ribavirin treatment-induced clearance of HCV (14–18). Finally, baseline levels of CXCL10 (also known as interferon induced protein-10 or IP-10), an inducible chemokine stimulated at the transcription level by interferons (IFN types I, II and III) (19), are predictive of the failure to respond to HCV treatment (20, 21).

Identifying reliable predictors of response could enable physicians to refine treatment schedules for individual patients and lead to improved treatment outcomes.

Telaprevir is a potent and selective inhibitor of the HCV NS3•4A protease (22). The REALIZE study showed higher sustained virologic response (SVR) rates for the telaprevir with peginterferon plus ribavirin triple therapy regimen vs. treatment with peginterferon plus ribavirin alone in treatment-experienced patients across all *IL28B* genotypes (23). Although, many factors are known to affect successful treatment outcome with peginterferon plus ribavirin, there are currently few data describing the predictors of response to telaprevir-based triple therapy. Therefore, it is important to determine whether baseline predictors of response following inclusion of telaprevir in the treatment regimen are different than those with peginterferon plus ribavirin alone.

The objectives of the present retrospective analysis of the REALIZE study were to identify predictors of SVR for telaprevir-based triple therapy in treatment-experienced genotype 1 chronic HCV-infected patients.

Methods

The methodology for the international, randomised, double-blind, multicentre, placebo-controlled, Phase III REALIZE study, has been previously described (24). This study was approved by each centre's institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients. The clinicaltrials.gov identifier for this study was NCT00703118.

Study design

Patients were stratified according to viral load and previous response to peginterferon plus ribavirin. Null-response was defined as a reduction of less than 2 $\log_{10}$ in HCV RNA after 12 weeks of therapy. Partial response was defined as a reduction of 2 $\log_{10}$ or more in HCV RNA after 12 weeks of therapy but with detectable HCV RNA while on treatment. Relapse was defined as undetectable HCV RNA at the end of therapy with subsequent reappearance. Non-responders included both partial and null-responders.

A total of 663 patients were randomly assigned to receive either 12 weeks of telaprevir in combination with 48 weeks of peginterferon plus ribavirin (with or without a 4 week lead-in period of placebo plus peginterferon plus ribavirin; LI T12/PR48 or T12/PR48, respectively) or 16 weeks of placebo in combination with 48 weeks of peginterferon plus ribavirin (PR48) in a 2:2:1 ratio.

SVR rates according to rapid virologic response (RVR) and extended RVR (eRVR) were evaluated. SVR was defined as plasma HCV RNA <25 IU/ml at the last observation within the Week 72 visit window. Viral breakthrough was defined as an increase in greater than 1 $\log_{10}$ HCV RNA compared with the lowest recorded on-treatment value, or if the HCV RNA had become <25 IU/ml, an increase in HCV RNA greater than 100 IU/ml. RVR was defined as HCV RNA <25 IU/ml, target not detected 4 weeks after the start of telaprevir and eRVR was defined as HCV RNA <25 IU/ml, target not detected 4 and 12 weeks after the start of telaprevir.

Examination of baseline pre-treatment factors for prediction of response to treatment

Regression analyses

In this post-hoc analysis, multiple logistic regression analyses were used to explore the prognostic value of

a number of baseline host and viral factors on SVR. Telaprevir-treated patients with all evaluable baseline data available (n = 465) were included in the models and patients in both telaprevir arms (LI T12/PR48 and T12/PR48) were pooled since there were no differences in efficacy between the two groups. Patients were excluded if they had a missing value for one or more of the predictor variables used in the analysis. On-treatment response, as defined by eRVR, was evaluated as an on-treatment prognostic factor, after controlling for other pre-treatment factors. In addition, patient baseline disease characteristics and demographics including age, gender, race, BMI, HCV genotype, screening HCV RNA levels, baseline $\log_{10}$ HCV RNA, prior response, baseline fibrosis stage and history of hypertension were evaluated as prognostic factors. Laboratory assessments were also evaluated as prognostic prediction factors, including baseline values of homeostasis model of assessment-insulin resistance (HOMA-IR), GGT, aspartate amino transferase (AST), alanine amino transferase (ALT), high-density lipoprotein (HDL), triglycerides, total cholesterol, low-density lipoprotein [LDL; cut-off of ≥2.6 mmol/L (median value)], maximum ALT and AST, total cholesterol/HDL ratio. Odds ratios, 95% confidence intervals (CI), receiver-operator characteristic (ROC) analyses and ROC area under the curve (AUC) values were obtained from the logistic regression model.

Results

Patient disposition and baseline characteristics

Patient baseline characteristics are shown in Table 1. In total, 530 patients were treated with telaprevir and 465 of these patients (88%) had evaluable baseline data available and were included in the multiple logistic regression analysis. The remaining 12% of telaprevir-treated patients were excluded from the analysis because they had at least one missing baseline value for a predictor used in the analysis. Patient characteristics were similar between the total telaprevir-treated population and the patients in the telaprevir-treated arms who were included in the multiple logistic regression analysis. Of the patients included in the analysis, 251 (54%) were prior relapsers, 84 (18%) were prior partial responders and 130 (28%) were prior null-responders. Only patients who had received telaprevir were included in the analyses.

Efficacy

For the multiple logistic regression analysis subset, the SVR rates in telaprevir-treated patients were 86% (215/251) in the prior relapsers, 63% (53/84) in the prior partial responders and 32% (42/130) in the prior null-responders.

Table 1. Baseline characteristics of telaprevir-treated patients from the REALIZE study included in the multiple logistic regression analysis

Characteristic	Total telaprevir-treated population (N = 530)	Patients in telaprevir arms eligible for multiple logistic regression analysis (N = 465)
Male, *n* (%)	372 (70)	324 (70)
Caucasian race, *n* (%)	498 (94)	434 (93)
Black race, *n* (%)	19 (4)	18 (4)
Years of age, median (range)	51 (23–70)	51 (23–70)
HCV RNA ≥800 000 IU/ml, n (%)*	462 (87)	408 (88)
BMI, mean (SD)	27 (4.9)	27 (5.0)
HCV genotype, *n* (%)†		
1a	285/524 (54)	259/465 (56)
1b	239/524 (46)	206/465 (44)
Type of prior response, *n* (%)		
Null-response	147 (28)	130 (28)
Partial response	97 (18)	84 (18)
Relapse	286 (54)	251 (54)
Bridging fibrosis, *n* (%)‡	118 (22)	102 (22)
Cirrhosis, *n* (%)‡	139 (26)	117 (25)

*Patients with all evaluable baseline data were included in the model. HCV RNA level was determined using the Roche COBAS TaqMan (Pleasanton, CA, USA)® HCV assay version 2.0 which has a limit of quantification of 25 IU/ml and a limit of detection of 15 IU/ml.

†HCV genotype and subtype were determined with the use of the Trugene HCV genotyping assay (Siemens, Malvern, PA, USA) except for one patient in the lead-in T12PR48 group, in whom the subtype was determined with the use of an NS3 sequencing assay.

‡Patients were grouped into four categories of fibrosis as assessed by liver biopsy according to the following Metavir and Ishak fibrosis scores: minimal or no fibrosis (Metavir, F0–F1; Ishak, 0–2), portal fibrosis (Metavir, F2; Ishak, 3), bridging fibrosis (Metavir, F3; Ishak, 4), cirrhosis (Metavir, F4; Ishak, 5–6).

Pre-treatment factors for prediction of response to treatment

The results of the multiple logistic regression analysis in the pooled telaprevir arms demonstrated that baseline factors independently associated with SVR were different for univariate and multivariate analyses. Type of prior response to treatment with peginterferon plus ribavirin, LDL levels, baseline fibrosis stage, baseline $\log_{10}$ HCV RNA, HCV genotype, GGT and maximum ALT/AST were all significant predictors of SVR in the univariate analysis (Fig. 1A). However, only type of prior response to treatment with peginterferon plus ribavirin, LDL levels, HCV genotype and maximum ALT/AST were significant predictors of SVR in the final multivariate analysis (Fig. 1A).

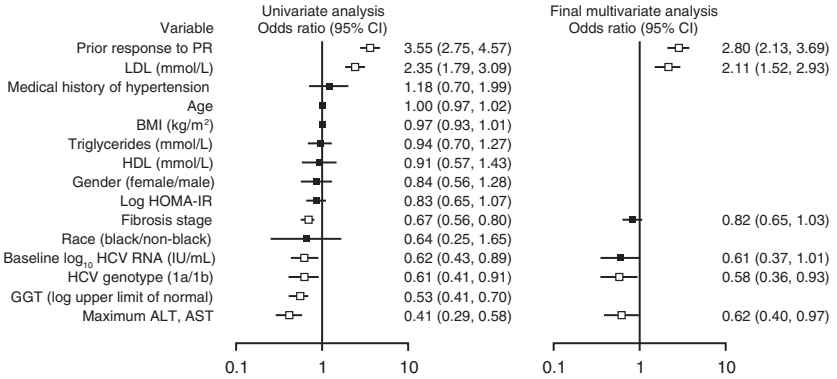

Fig. 1. Baseline predictors in telaprevir-treated patients. CI, confidence interval; PR, peginterferon plus ribavirin,eRVR, extended RVR; LDL, low-density lipoprotein; BMI, body mass index; HDL, high-density lipoprotein; HCV, Hepatitis C virus; GGT, gamma-glutamyltranspeptidase; ALT, alanine amino transferase; AST, aspartate amino transferase. Closed boxes indicate where the 95% CI spans an odds ratio of 1.

Further analysis of telaprevir-treated patients subdivided by type of prior response to treatment showed that for prior relapsers and null-responders, higher baseline LDL levels were prognostic for SVR. For prior partial responders, lower fibrosis stage and HCV genotype 1b were positive prognostic factors for SVR.

ROC analyses of the baseline predictors of SVR in the pooled telaprevir arms indicted that type of prior response to peginterferon plus ribavirin was the most accurate predictor of SVR (ROC AUC: 0.7661), followed by LDL levels (ROC AUC: 0.6773) and maximum ALT/AST (ROC AUC: 0.6572), with an overall ROC AUC for the model of 0.8224 (Fig. 2). Further, higher baseline LDL levels were associated with an increased probability of predicting SVR and an increased probability of achieving SVR than lower baseline LDL levels. The probability of achieving SVR according to baseline LDL and type of prior response to peginterferon plus ribavirin was higher in prior relapsers than in prior non-responders. Higher baseline LDL levels were associated with an increased probability of predicting SVR in prior relapsers, and prior non-responders compared with lower baseline LDL levels (Fig. 3).

Multiple logistic regression analyses indicated that age, gender, race, BMI, baseline HCV RNA levels, fibrosis stage and history of hypertension were not prognostic factors for achieving SVR in patients treated with telaprevir-based triple therapy. In addition, laboratory assessments including baseline values of HOMA-IR, AST, ALT, GGT, HDL and triglycerides were not found to be predictive of SVR.

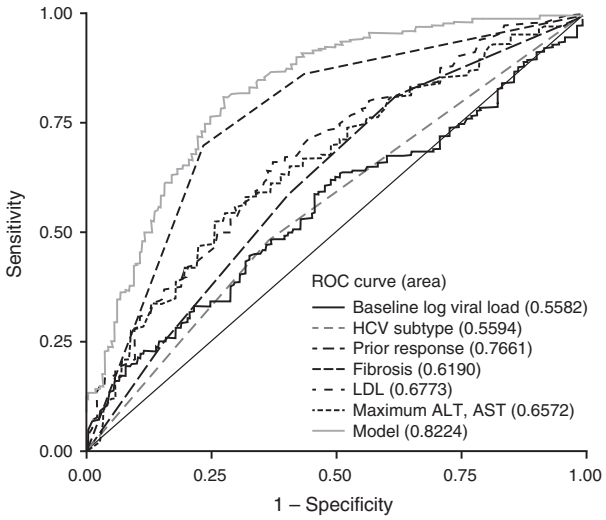

Fig. 2. Multivariate analysis of the baseline predictors of SVR in pooled telaprevir arms in the multiple logistic regression analysis subset ROC, receiver–operator characteristic, HCV, Hepatitis C virus; LDL, low-density lipoprotein; ALT, alanine amino transferase; AST, aspartate amino transferase.

Effect of viral response and LDL levels on efficacy

Multivariate analysis of patient baseline factors with or without eRVR response resulted in different baseline factors being predictors of SVR (Fig. 1B). Type of prior response to treatment and LDL levels were significant predictors of response irrespective of whether eRVR status was included in the analysis. However, fibrosis stage was only a significant predictor of SVR when eRVR status was included in the analysis, while HCV genotype and maximum ALT/AST were only significant predictors of response when eRVR status was excluded from the analysis. In addition, SVR rates were similar in the pooled telaprevir arms in patients who achieved RVR and patients who achieved eRVR (prior relapsers 91% vs. 95%; prior partial responders 68% vs. 69% and prior non-responders 67% vs. 71% respectively).

To further elucidate the LDL-related responses, analyses using a cut-off value of ≥2.6 mmol/L were conducted. In prior non-responders (null and partial responders) who achieved eRVR, those with LDL levels

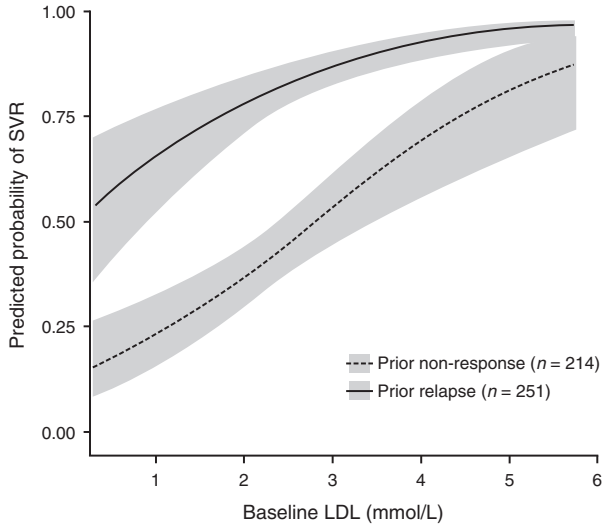

Fig. 3. Probability of achieving SVR in the multiple logistic regression analysis subset according to baseline LDL levels and prior response SVR; sustained viral response; LDL, low-density lipoprotein.

≥2.6 mmol/L had higher SVR rates than those with LDL levels <2.6 mmol/L (82% vs. 61% respectively), while no differences were observed in prior relapsers (95% vs. 94% respectively). Furthermore, in all patients who did not have an eRVR, those who had LDL levels ≥2.6 mmol/L had higher SVR rates than those who had LDL levels <2.6 mmol/L in both groups (prior non-responders 41% vs. 17%; prior relapsers 65% vs. 44% respectively).

Discussion

Predictors of response to peginterferon plus ribavirin therapy have been comprehensively studied (1–11). However, predictors of response to telaprevir-based triple therapy are currently unknown. Insulin resistance [as assessed using baseline homeostasis model assessment-estimated insulin resistance (HOMA-IR)] is not a good predictor of response to telaprevir in the REALIZE study; HOMA-IR was associated with SVR in a univariate analysis, but not once baseline prognostic factors were accounted for using a multivariate analysis (25).

In the present post-hoc analysis of the REALIZE study, prior response to treatment and LDL levels were the main predictive factors of SVR. HCV genotype, maximum ALT/AST, baseline HCV RNA levels, GGT and fibrosis stage were also independent predictors of SVR in treatment-experienced genotype 1 HCV-infected patients treated with telaprevir-based triple therapy.

Differences in the predictors of response were identified dependent on whether univariate or multivariate analyses were performed and there were also differences dependent on the patient's previous type of response to peginterferon plus ribavirin treatment. Although the other baseline parameters listed above were statistically significant as predictors of response, they do not appear to add much prognostic value for SVR. Interestingly, age, gender and BMI, which are all predictors of response for peginterferon plus ribavirin therapy, were not indicated as predictors of response in telaprevir-based triple therapy. Further studies will be required to identify whether these factors can be used as predictors in specific patient groups rather than the overall treated population. The current analysis did not evaluate predictors of response in patients treated with peginterferon plus ribavirin alone and further evaluations are required to fully elucidate if baseline predictors of response are different for treatment with peginterferon plus ribavirin vs. telaprevir-based triple therapy.

A recent real-world study has reported *IL28B* genotype, high viral load, black race, diabetes, high aspartate aminotransferase to platelet ratio index or FIB-4 scores, low platelet counts, or low levels of low-density lipoprotein cholesterol and erythropoietin use as being predictors of response for SVR in telaprevir and boceprevir (26).

Low-density lipoprotein level was found to be an independent predictor of SVR. The LDL receptor is a membrane glycoprotein and is known to be involved in the entry of HCV into hepatocytes. Further, HCV RNA levels correlate with LDL receptor expression (27, 28). Therefore, it is possible that elevated serum levels of LDL may reflect or be associated with a reduced number of LDL receptors and lead to an increased response to treatment (29). Further, LDL levels are significantly higher in HCV patients with *IL28B* CC variants vs. those with CT or TT variants (30, 31). Additionally, it has been demonstrated that *IL28B* genotype is a predictor of response for treatment with peginterferon plus ribavirin alone, with nucleotide polymorphisms on chromosome 19, upstream of the *IL28B* gene, reported to be strongly associated with spontaneous (32) and peginterferon plus ribavirin induced clearance of HCV (14–18). Therefore, it is possible that high LDL levels only reflect the *IL28B* genotype and it is the genotype that influences SVR. However, a post-hoc analysis from the REALIZE study suggests that *IL28B* genotype may have limited utility in guiding the use of telaprevir-based triple therapy in patients who have previously relapsed (23). Still, it should be noted that Pol and colleagues reported a trend for a correlation between *IL28B* genotype and response in partial and null-responders. However, in the REALIZE study all patients were treated for 48 weeks and there was no option for response guided therapy. Therefore, it is possible that *IL28B* may be of use as a marker to tailor treatment during re-treatment when response guided strategies are considered. Further investigations are required to determine if LDL is an independent predictive marker of response to telaprevir-based triple therapy or if there is a link to *IL28B* genotype. However, the effect caused by the concurrent use of lipid lowering agents such as statins requires further investigation.

High SVR rates in patients who have previously relapsed make it difficult or even impossible to determine predictors of response. However, in this study all relapsers were treated for 48 weeks. Therefore, we cannot exclude that markers may be of relevance when a response guided regimen is applied. For example, in a previous study, cirrhosis was identified as a predictor of response when patients with prior relapse were treated for only 24 weeks (33).

The ability to predict SVR may allow more informed treatment decisions to be made and identification of factors that influence early viral kinetic or likelihood of null-response could benefit patients. Therefore, the role of predictors of response should be discussed with patients both before and during treatment, as they may have a role in the choices that are made about the type and timing of therapy. Predictors of response could be influential in the individualisation of HCV treatment and the authors emphasise their use in guiding treatment decisions, together with patients. However, this analysis investigated data obtained from Phase III clinical trials following a set protocol, and therefore physicians should extrapolate to specific real-world cases with caution.

In conclusion, prior response to treatment and LDL levels are the main independent predictive markers for telaprevir-based triple therapy, but continued efforts are required to identify further biomarkers to guide the management of patients with HCV who are treated with direct-acting antivirals.

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