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Optimized threshold for serum HCV RNA to predict treatment outcomes in hepatitis C patients receiving peginterferon alfa-2a/ribavirin

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SUMMARY. It is unclear whether the current threshold for 'high' hepatitis C virus (HCV) RNA level (800 000 IU/mL) is optimal for predicting sustained virological response (SVR). We retrospectively analysed pretreatment HCV RNA levels and SVR rates in 1529 mono-infected and 176 HIV–HCV co-infected patients treated with peginterferon alfa-2a (40 kD) plus ribavirin. We improved the threshold for differentiating low and high viral load by fitting semiparametric generalized additive logistic regression models to the data and constructing receiver operating characteristics curves. Among HCV genotype 1 mono-infected patients, the difference in SVR rates between those with low and high baseline HCV RNA levels was 27% (70% *vs* 43%) when 400 000 IU/mL was used and 16% (59% *vs* 43%) when 800 000 IU/mL was used. In HIV–HCV genotype 1 co-infected patients, the difference was 51% (71% *vs* 20%) when 400 000 IU/mL was used and 43% (61% *vs* 18%) when 800 000 IU/mL was used. A lower threshold (200 000 IU/mL) was identified for genotype 1 mono-infected patients with 'normal' alanine aminotransferase (ALT) levels. No threshold could be identified in HCV genotype 2 or 3 patients. A threshold HCV RNA level of 400 000 IU/mL is optimal for differentiating high and low probability of SVR in genotype 1-infected individuals with elevated ALT.

Keywords: alanine aminotransferase, baseline predictor, HCV genotype 1, HCV viral load, sustained virological response.

Hepatitis C virus (HCV) genotype and pretreatment HCV RNA level are important determinants of the outcome of treatment with pegylated interferon plus ribavirin [1,2]. Infection with HCV genotype 1 and the presence of a 'high' baseline HCV RNA level portends a lower probability of sustained virological response (SVR) [1–3]. A 'high' HCV RNA level was originally defined as $>2 \times 10^6$ copies/mL [4] on the basis of the results of phase 3 studies of conventional interferon alfa-2b plus ribavirin [5,6]. This definition was utilized in phase 3 registration trials of peginterferon alfa-2a in monotherapy [7–9] and in combination with ribavirin [10–12]. Serum HCV RNA levels have since been standardized and reported in International Units (IU) [13]. Despite this, the cut-off between high and low viral load has not been modified, and the current licences for these products continue to reflect the older data.

The time required to become HCV RNA undetectable after initiating treatment impacts the rate of SVR, and this information can be utilized to adjust treatment duration. Patients with HCV genotype 1, a rapid virological response (RVR) and low viral load have similar rates of SVR whether treated for 24 or 48 weeks [2]. Consequently in the EU, 24 or 48 weeks of treatment with peginterferon alfa-2a plus ribavirin is recommended for HCV genotype 1 and 4 patients

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; FPF, false-positive fraction; GAM, generalized additive logistic regression model; HCV, hepatitis C virus; IU, international units; MLR, multiple logistic regression; OR, odds ratio; PCR, polymerase chain reaction; ROC, receiver operating characteristics curve; RVR, rapid virological response; SVR, sustained virological response; TPF, true-positive fraction.

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with a 'low' baseline viral load and RVR [14]. In this recommendation, the definition utilized for low viral load was <600 000 or <800 000 IU/mL. Furthermore, an abbreviated 16-week regimen of peginterferon alfa-2a plus ribavirin has been licensed in the EU for patients infected with HCV genotypes 2 or 3 with a low HCV RNA level [14]. Similar recommendations have been suggested for patients with HIV and HCV co-infection and genotypes 2 and 3 [15].

Patients achieving an RVR with a high pretreatment serum HCV RNA level have a lower probability of achieving an SVR than those with a low level when treated with abbreviated regimens [16–19]. Thus, in the era of response-guided therapy, a precise definition of what constitutes a low and high HCV RNA level is needed.

We analysed pretreatment HCV RNA levels and SVR rates in patients treated with the combination of peginterferon alfa-2a (40 kD) plus ribavirin in several randomized international phase 3 trials.

METHODS

This retrospective analysis included data from randomized, phase 3 trials of peginterferon alfa-2a (40 kD) plus ribavirin [10,11,19–21]. Four trials recruited HCV mono-infected patients; in three of these studies, patients had elevated serum alanine aminotransferase (ALT) levels at baseline [10,11,19], one of which was restricted to patients with HCV genotype 2 or 3 infection [19]. Only noncirrhotic patients with persistently normal ALT levels were eligible for the fourth study [20]. We also analysed data from the APRICOT trial, which enrolled patients with HIV–HCV co-infection [21].

The HCV mono-infected patients with elevated ALT levels included in this analysis were treated with peginterferon alfa-2a (40 kD) 180 μg per week plus ribavirin 1000/1200 mg per day for 48 weeks (HCV genotype 1 infection) or peginterferon alfa-2a (40 kD) 180 μg per week plus ribavirin 800 mg per day for 24 weeks (HCV genotype 2 or 3 infection). The genotype 1-infected patients with persistently normal ALT levels and the genotype 1-infected patients with HIV–HCV co-infection included in this analysis were treated with peginterferon alfa-2a (40 kD) 180 μg per week plus ribavirin 800 mg per day for 48 weeks.

Measurement of serum HCV RNA levels

Serum HCV RNA levels were quantified with the COBAS AMPLICOR HCV MONITOR Test, v2.0 (limit of quantitation 600 IU/mL; Roche, Rotkreuz, Switzerland). Samples were analysed using the COBAS AMPLICOR HCV Test, v2.0, limit of detection 50 IU/mL (Roche, Pleasanton, CA, USA).

Primary efficacy outcome

The primary efficacy endpoint in each trial was SVR, defined as undetectable HCV RNA by the qualitative PCR assay (<50 IU/mL) at the end of a 24-week untreated follow-up period.

Data analysis

The association between pretreatment serum HCV RNA level and SVR was examined by multiple logistic regression (MLR) analysis. Factors considered for inclusion in the MLR models were pretreatment serum HCV RNA level ($\log_{10}$ IU/mL), age, body weight and ALT quotient, gender (male *vs* female), histological diagnosis (cirrhosis/transition to cirrhosis *vs* no cirrhosis/transition to fibrosis) and race.

To evaluate the possibility of nonlinear associations between continuous explanatory factors and SVR, a semiparametric generalized additive logistic regression model (GAM) was fitted to the data [22]. For ease of interpretation, and to visualize the relationship between SVR and viral load, the probability of SVR was plotted as a function of $\log_{10}$ pretreatment HCV RNA values using univariate GAM curves. Receiver operating characteristics (ROC) curves of pretreatment serum HCV RNA level were plotted for the prediction of SVR. These show the true-positive fraction (TPF = sensitivity) and corresponding false-positive fraction (FPF = 1−specificity) for each of the observed HCV RNA values used as a cut-off to predict SVR.

SAS version 8.2 software and S-PLUS were used in all statistical analyses.

RESULTS

Data from 1529 patients with HCV mono-infection, including 140 with persistently normal serum ALT, and 176 patients with HIV–HCV co-infection, were included in the analysis. The baseline characteristics of these individuals are presented in Table 1.

Patients with HCV mono-infection

HCV genotype 1, elevated serum ALT levels

Baseline factors predictive of SVR in the MLR analysis of data from HCV mono-infected genotype 1 patients with elevated serum ALT levels included lower pretreatment HCV RNA level ($P < 0.0001$), higher ALT quotient ($P < 0.0001$), lower body weight ($P = 0.0003$), younger age ($P = 0.0012$) and absence of advanced liver fibrosis ($P = 0.0356$) (Table 2). Analysis of the linearity of the logit for SVR indicated a nonlinear effect of pretreatment HCV RNA level and age.

The semiparametric GAM analysis showed a decrease in SVR with increasing HCV RNA values in the range from ~4 $\log_{10}$ to 6 $\log_{10}$ IU/mL. For example, in a patient with a pretreatment HCV RNA level of ~5.6 $\log_{10}$ IU/mL (~400 000 IU/mL) (and any set of disease characteristics), the probability of an SVR was identical to that for a patient

Table 1 Baseline characteristics of patients included in the analysis

Characteristic	HCV mono-infection (n = 1529)				HIV–HCV genotype 1 co-infection (n = 176)
	Elevated ALT levels (n = 1389)			Persistently 'normal' ALT levels	
	Genotype 1 (n = 568)	Genotype 2 (n = 395)	Genotype 3 (n = 426)	Genotype 1 (n = 140)	
Male, n (%)	388 (68.3)	238 (60.3)	283 (66.4)	54 (38.6)	146 (83)
Age*, years	43.8 ± 10.4	48.7 ± 9.5	41.5 ± 9.4	44.1 ± 9.6	39.8 ± 7.9
Weight*, kg	79.6 ± 16.9	83.6 ± 19.1	79.0 ± 17.1	75.1 ± 17.6	73.0 ± 14.1
BMI*, kg/m^2	26.9 ± 4.9	28.4 ± 5.8	26.5 ± 5.0	26.6 ± 5.3	24.5 ± 4.4
Race, n (%)					
Caucasian	485 (85.4)	336 (85.1)	386 (90.6)	120 (85.7)	137 (77.8)
Non-Caucasian	83 (14.6)	59 (14.9)	40 (9.4)	20 (14.3)	39 (22)
Histological diagnosis, n (%)					
No cirrhosis	452 (79.6)	298 (75.4)	338 (79.3)	139 (99.3)	152 (86.4)
Bridging fibrosis/cirrhosis	116 (20.4)	97 (24.6)	88 (20.7)	0	24 (13.6)
Unknown	0	0	0	1 (0.7)	0

ALT, alanine aminotransferase. *Values are mean ± standard deviation.

Table 2 Multiple logistic regression analysis of explanatory factors for SVR in HCV genotype 1 patients

Factor	HCV mono-infection		HIV–HCV co-infection
	Elevated ALT levels (n = 568)	'Normal' ALT levels (n = 138)	Elevated ALT levels (n = 176)
	Odds ratio (95% CI); P-value	Odds ratio (95% CI); P-value	Odds ratio (95% CI); P-value
HCV RNA per 1-log$_{10}$ IU/mL increment	0.524 (0.388–0.708); $P < 0.0001$	0.362 (0.160–0.822); $P = 0.0152$	0.312 (0.186–0.523); $P < 0.0001$
ALT ratio per 1-unit decrement	0.821 (0.744–0.906); $P < 0.0001$	0.505 (0.045–5.619); $P = 0.5780$	0.741 (0.566–0.969); $P = 0.0284$
Body weight per 10-kg increment	0.802 (0.712–0.904); $P = 0.0003$	0.808 (0.637–1.024); $P = 0.0778$	0.830 (0.589–1.168); $P = 0.2851$
Age per 10-year increment	0.737 (0.613 to −0.887); $P = 0.0012$	0.806 (0.542–1.196); $P = 0.2841$	0.710 (0.415–1.215); $P = 0.2116$
Bridging fibrosis/ cirrhosis (yes *vs* no)	0.604 (0.378–0.967); $P = 0.0356$	NA	0.370 (0.103–1.327); $P = 0.1271$
Race (non-Caucasian *vs* Caucasian)	0.697 (0.418–1.162); $P = 0.1665$	0.350 (0.102–1.196); $P = 0.0939$	0.963 (0.344–2.696); $P = 0.9431$
Gender (male *vs* female)	0.887 (0.585–1.347); $P = 0.5746$	0.756 (0.320–1.785); $P = 0.5236$	0.608 (0.214–1.731); $P = 0.3516$

ALT, alanine aminotransferase; SVR, sustained virological response.

with the same set of disease characteristics when HCV RNA levels in the model were ignored. Similarly, a univariate GAM analysis with pretreatment HCV RNA level as the exploratory variable showed that the probability of an SVR at an HCV RNA level of 400 000 IU/mL was 0.5, which is close to the crude SVR rate (Fig. 1a). For HCV RNA values above 400 000 IU/mL, the curve of predicted SVR probabilities is flat, and the decrease in SVR rate is moderate.

These findings are consistent with the observed SVR rates shown in Fig. 2a. Among patients with a pretreatment HCV RNA level ≤400 000 IU/mL, the SVR rate was 70% (91/

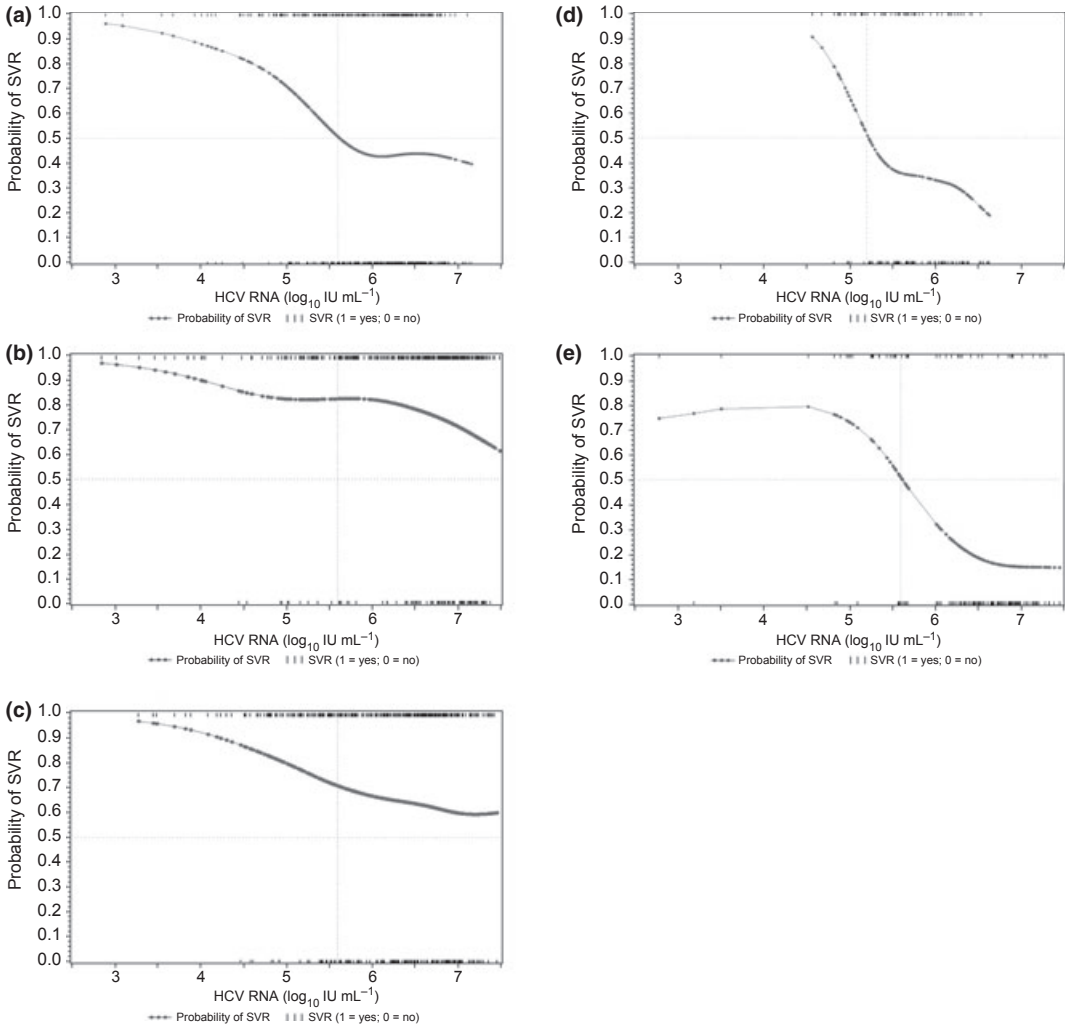

Fig. 1 Generalized additive logistic regression model plotting the effect of hepatitis C virus (HCV) RNA ($\log_{10}$ IU/mL) on the probability of achieving a sustained virological response (SVR). Higher values on the vertical scale correspond to a higher probability of predicting an SVR, while a value of 0.5 corresponds to no contribution towards predicting SVR. (A) HCV genotype 1-infected patients with elevated alanine aminotransferase (ALT) levels; (B) HCV genotype 2-infected patients with elevated ALT levels; (C) HCV genotype 3-infected patients with elevated ALT levels; (D) HCV genotype 1-infected patients with persistently 'normal' serum ALT levels; (E) HCV genotype 1-infected patients co-infected with HIV.

130). The SVR rate was considerably lower among patients with an HCV RNA level >400 000 IU/mL (43%; 188/438). Thus, when 400 000 IU/mL was selected as the cut-off, the difference in SVR rate was 27%. By contrast, when using the conventional cut-off of 800 000 IU/mL, the difference in SVR rate decreased to 16% (Fig. 2a). Interestingly, the rate of SVR in patients with a high viral load was the same (43%) irrespective of whether the cut-off was defined as 400 000 or 800 000 IU/mL.

The appropriateness of the 400 000 IU/mL cut-off was confirmed by the ROC analysis. The point on the ROC curve that maximizes the vertical distance from the 45-degree line is close to 400 000 IU/mL and represents the cut-off with the lowest total error rate (TPF + FPF) and with the maximal sum of sensitivity (TPF) and specificity (1−FPF) (Fig. 3a). The sensitivity of a cut-off of 400 000 IU/mL was 0.33, and the specificity was 0.87. The positive and negative predictive values were 0.70 and 0.57, respectively.

Genotype 1, persistently 'normal' serum ALT levels

Baseline serum HCV RNA level was the only factor that significantly predicted SVR (odd ratio [OR] 0.362, 95% confidence interval [CI]: 0.160, 0.822; $P = 0.0152$) in the MLR analysis of data from genotype 1-infected patients with 'normal' ALT levels (Table 2). Other exploratory factors showed the same trends as those for genotype 1-infected patients with elevated ALT levels.

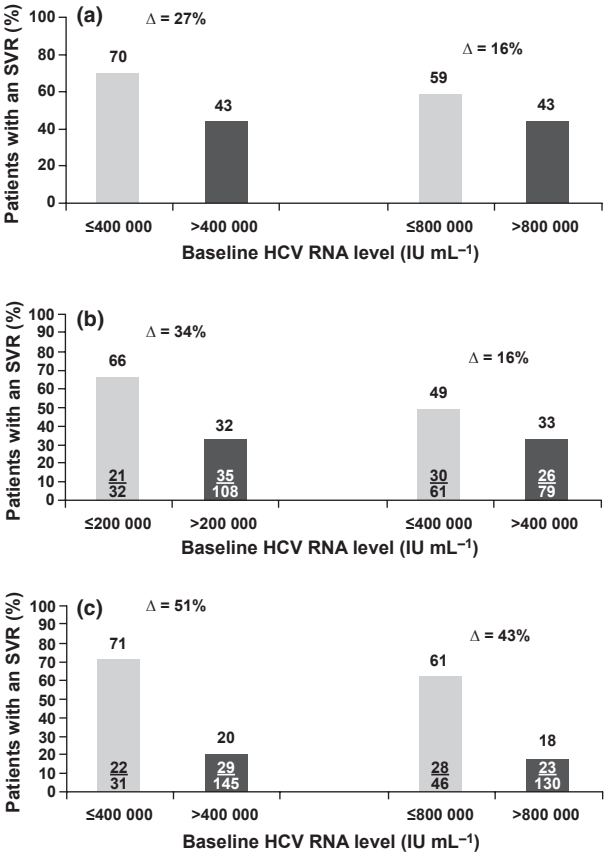

Fig. 2 Difference in sustained virological response (SVR) rates between genotype 1 patients with high and low pretreatment hepatitis C virus (HCV) RNA levels. The impact of different thresholds to define low serum HCV RNA level (≤400 000 and ≤800 000 IU/mL) on the difference (Δ) in SVR rates between patients with low and high serum HCV RNA levels. (a) HCV mono-infected patients with elevated alanine aminotransferase (ALT) levels; (b) HCV mono-infected patients with persistently 'normal' ALT levels; (c) HIV–HCV co-infected patients.

The general shape of the GAM curve for patients with 'normal' ALT levels (Fig. 1d) is similar to that for patients with elevated ALT levels (Fig. 1a). However, when compared with patients with elevated ALT levels, the decrease in the probability of SVR for each 1 $-\log_{10}$ drop in HCV RNA level is greater for patients with 'normal' ALT levels, and the probability of SVR is lower for individuals with pretreatment HCV RNA values above 100 000 IU/mL.

Among patients with 'normal' ALT levels, the probability of achieving an SVR was 50% for individuals with a pretreatment HCV RNA level of ~5.25 $\log_{10}$ IU/mL (~180 000 IU/mL) and was 40% (identical to the overall observed SVR rate) for individuals with a pretreatment HCV RNA level of 5.41 $\log_{10}$ IU/mL (~260 000 IU/mL).

The point on the ROC curve that maximized the vertical distance from the 45-degree line and therefore minimized the total error rate corresponded to a pretreatment HCV RNA level of 5.21 $\log_{10}$ IU/mL (~163 000 IU/mL) (Fig. 3d).

The sensitivity (TPF) for a cut-off of 163 000 IU/mL was 0.36, and the specificity (1−FPF) was 0.93. The positive predictive value and negative predictive value were 0.77 and 0.68, respectively.

When a pretreatment HCV RNA level of 163 000 IU/mL was selected as the cut-off to differentiate low from high pretreatment viral load, the difference in SVR rates was 45% (77% *vs* 32%). The use of higher cut-offs resulted in lower differences in SVR rates: 34% if the cut-off was set at 200 000 IU/mL (66% *vs* 32%) (Fig. 2b); 16% if the cut-off was set at 400 000 IU/mL (49% *vs* 33%) (Fig. 2b); and 20% if the cut-off was set at 800 000 IU/mL (47% *vs* 27%).

Genotype 2 or 3, elevated serum ALT levels

An MLR analysis of data from all patients infected with genotype 2 or 3 (n = 818) demonstrated that HCV genotype (OR 0.373 for genotype 3 *vs* genotype 2, 95% CI: 0.258, 0.541; $P \leq 0.0001$) was a significant predictor of SVR. Therefore, separate models were constructed for each genotype. The factors predictive of SVR were similar in both analyses, although baseline serum HCV RNA level was a more important predictor of SVR for genotype 3-infected patients and a diagnosis of bridging fibrosis/cirrhosis was a more important predictor of SVR for genotype 2-infected patients.

Significant predictors of lower SVR among genotype 2-infected patients included histological diagnosis (OR 0.359 for bridging fibrosis/cirrhosis *vs* minimal fibrosis, 95% CI: 0.202, 0.635; P = 0.0004), lower ALT quotient (OR 0.810, 95% CI: 0.691, 0.949; P = 0.0094), higher body weight (OR 0.824 per 10 kg, 95% CI: 0.714, 0.950; P = 0.0078) and higher pretreatment HCV RNA level (OR 0.688, 95% CI: 0.483, 0.980; P = 0.038).

Among genotype 3-infected patients, lower SVR was predicted by histological diagnosis (OR 0.539 for bridging fibrosis/cirrhosis, 95% CI: 0.313, 0.927; P = 0.0256), lower ALT quotient (OR 0.814, 95% CI: 0.698, 0.948; P = 0.0083), higher bodyweight (OR 0.774 per 10 kg, 95% CI: 0.670, 0.893; P = 0.0005) and higher pretreatment HCV RNA level (OR 0.590, 95% CI: 0.435, 0.801; P = 0.0007).

The GAM analysis for genotype 2-infected patients showed that SVR decreased with increasing HCV RNA level up to ~100 000 IU/mL, remained fairly constant (~80%) between 100 000 IU/mL and 1 000 000 IU/mL and decreased thereafter (Fig. 1b). Among patients with HCV genotype 3 infection, SVR declined at a fairly constant rate over the range of values encountered (Fig. 1c) and remained >60% for all patients, including those with very high HCV RNA levels.

In contrast to patients infected with HCV genotype 1, ROC curves for patients infected with HCV genotypes 2 or 3

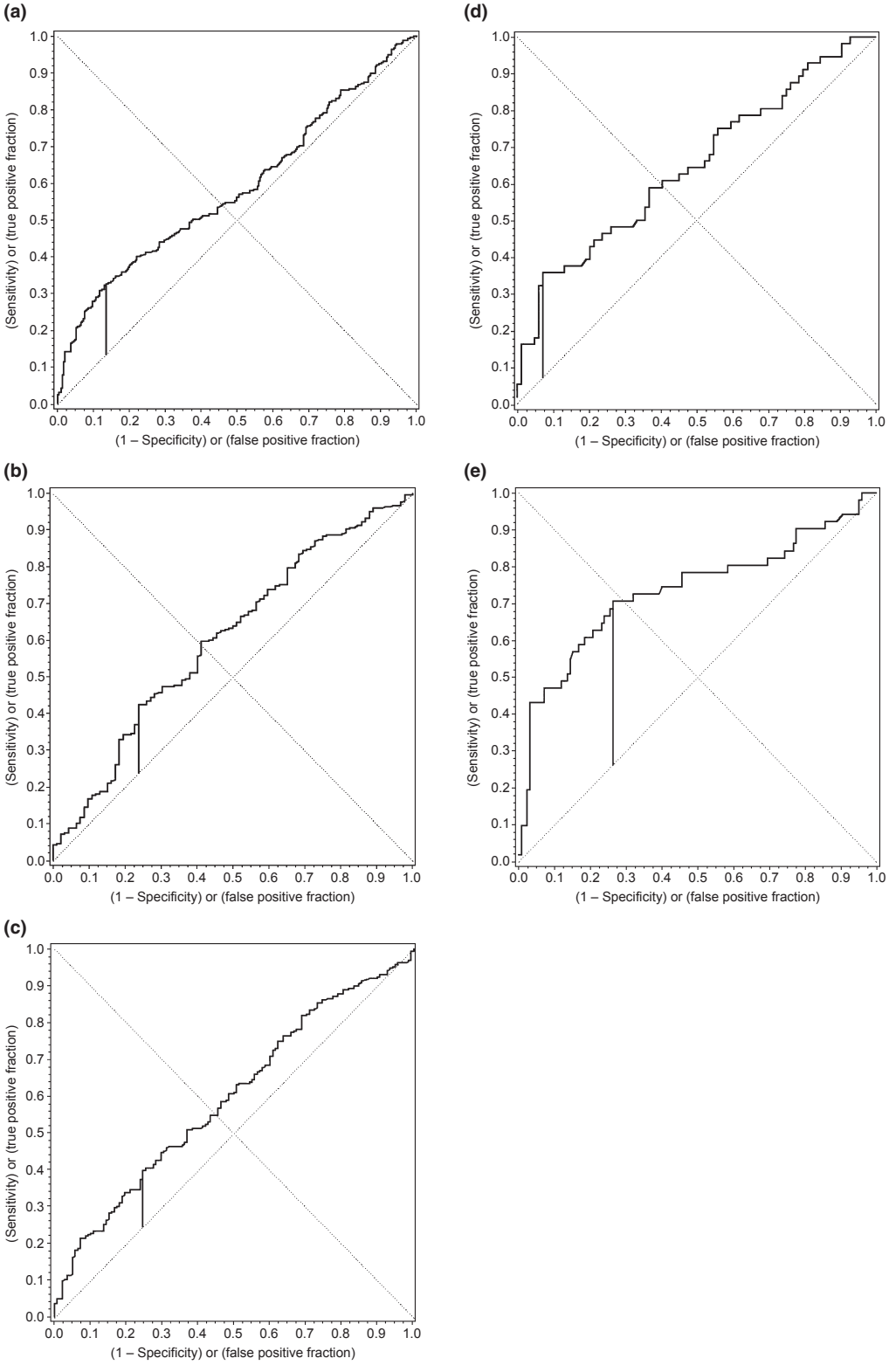

Fig. 3 Receiver operating characteristic curve of pretreatment hepatitis C virus (HCV) RNA level for the prediction of sustained virological response rate. (a) HCV genotype 1-infected patients with elevated serum alanine aminotransferase (ALT) levels; (b) HCV genotype 2-infected patients with elevated ALT levels; (c) HCV genotype 3-infected patient with elevated ALT levels; (d) HCV genotype 1-infected patients with persistently 'normal' serum ALT levels; (e) HIV–HCV genotype 1 co-infected patients with elevated ALT level.

revealed no obvious cut-off to discriminate between responders and nonresponders (Figs. 3b,c). Moreover, the differences in SVR rate between patients with low and high pretreatment HCV RNA levels when cut-offs of 400 000 and 800 000 IU/mL were selected were 9% (84% *vs* 75%) and 10% (84% *vs* 74%), respectively, for genotype 2-infected patients and 15% (79% *vs* 64%) and 13% (76% *vs* 63%), respectively, for genotype 3-infected patients.

Genotype 1-infected patients with HIV–HCV co-infection

Baseline serum HCV RNA level and ALT ratio were the only significant factors that predicted SVR in the MLR analysis of data from HIV–HCV co-infected patients (Table 2). All other exploratory factors showed the same predictive trends as observed for genotype 1-infected patients with elevated ALT levels.

The general shape of the GAM curve was similar to that from patients with HCV genotype 1 mono-infection (Fig. 1e). The steepest slope of the curve and the point at which the curve crosses the 0.5 line coincides with an HCV RNA level of ~5.6 $\log_{10}$ IU/mL (~400 000 IU/mL).

The point on the ROC curve that minimized the total error rate corresponded to a pretreatment HCV RNA level of 6.32 $\log_{10}$ IU/mL (~2 100 000 IU/mL) (Fig. 3e). The sensitivity (TPF) for a cut-off of 2 100 000 IU/mL was 0.71, while the specificity (1−FPF) was 0.74. The positive and negative predictive values were 0.52 and 0.86, respectively. When, instead of the minimal total error rate of a cut-off, the simple difference in SVR rates was used to differentiate between patients with low and high pretreatment HCV RNA; the value of 2 100 000 IU/mL was not optimal. The difference in SVR rate was 38% (52% *vs* 14%, respectively) for this cut-off, while for a cut-off of 400 000 IU/mL, the difference in SVR rate was 51% (71% *vs* 20%) and 43% (61 *vs* 18%) for the cut-off of 800 000 IU/mL (Fig. 2c).

DISCUSSION

This analysis confirms that SVR decreases with increasing viral load in patients infected with HCV genotypes 1, 2 or 3. The analysis extends our understanding for HCV genotype 1 patients by showing that the optimal cut-off that differentiates between high and low viral load is lower than the traditional threshold. The analysis also shows that for genotype 2 or 3 infection, the concept of high and low viral load is less relevant, and no defined cut-off can clearly differentiate high from low baseline viral load.

The difference in SVR rate between mono-infected patients with low and high baseline serum HCV RNA levels was considerably greater when the threshold was set at 400 000 IU/mL (27%) than when it was set at 800 000 IU/mL (16%). This is noteworthy because a definition of 800 000 IU/mL for high HCV RNA level has historically been used to define high serum HCV RNA levels in numerous guidelines for the treatment of chronic hepatitis C [4,23,24] and is reflected in the current licences for pegylated interferons.

Our findings are consistent with those of two other analyses in patients infected with HCV genotype 1, both of which identified a critical threshold of 400 000 IU/mL using the ROC curve method of analysis [25,26]. In the first of these studies, the rate of SVR was 70% among patients with pretreatment serum HCV RNA levels ≤400 000 IU/mL compared with 46% among those with pretreatment serum HCV RNA levels >400 000 IU/mL (difference 24%; $P < 0.0001$). By contrast, SVR was 58% among patients with pretreatment serum HCV RNA levels ≤800 000 IU/mL compared with 45% among those with pretreatment serum HCV RNA levels >800 000 IU/mL (difference 13%; $P = 0.007$) [25].

The results of the analysis in HCV genotype 1-infected patients with elevated serum ALT levels show that a pretreatment serum HCV RNA level of 5.6 $\log_{10}$ IU/mL (~400 000 IU/mL) is the threshold that offers an improved discrimination between a high and low probability of achieving an SVR. The definition applies to both HCV mono-infected and HIV–HCV co-infected patients. By contrast, a lower threshold (~200 000 IU/mL) appears to be more appropriate for HCV genotype 1 mono-infected patients with persistently 'normal' serum ALT levels. In contrast to the findings in patients infected with HCV genotype 1, the analyses of data from patients infected with HCV genotypes 2 or 3 did not identify a fixed threshold that can be used to differentiate patients with a high or a low probability of achieving an SVR.

Taken together, the results of our analysis and the studies of abbreviated therapy suggest that the pretreatment HCV RNA level should be an important component of response-guided therapy algorithms primarily for genotype 1-infected patients. Among patients with an RVR, those with pretreatment HCV RNA levels ≤400 000 IU/mL are the best candidates for abbreviated therapy; and those with higher HCV RNA levels retain a high likelihood of achieving an SVR, but they would be better managed with the full 48-week treatment duration.

Data from a trial conducted exclusively in patients infected with HCV genotypes 2 or 3 show that abbreviated therapy is less successful for patients with high pretreatment HCV RNA levels [19]. Among patients treated for 24 weeks with peginterferon alfa-2a (40 kD) plus ribavirin, the difference in the rate of SVR between those with a pretreatment serum HCV RNA level of ≤400 000 IU/mL and those with >400 000 IU/mL was 13% (81% *vs* 68%, respectively), and among patients treated for 16 weeks, the difference in SVR rate was 25% (82% *vs* 57%). On this basis, the authors concluded that abbreviated therapy should only be contemplated for HCV genotype 2- or 3-infected patients with a pretreatment HCV RNA level ≤400 000 IU/mL [27].

Although in the present analysis we have shown that a threshold of 400 000 IU/mL may be more discriminating

than a threshold of 800 000 IU/mL, it remains to be determined what, if any, threshold may be optimal among patients receiving peginterferon plus ribavirin in combination with new therapies, such as HCV protease inhibitors.

Recently, it has been shown that a genetic variation associated with the *IL28B* gene that confers an improved SVR to patients with genotype 1 treatment-naive HCV infection [28]. This genetic polymorphism is associated with an approximately twofold change in response to treatment and is more predictive than viral load and fibrosis stage [29]. As such, we will likely be testing for the IL28B allele prior to initiation of treatment as soon as assays are commercially available. This may diminish, but will certainly not eliminate, the importance of pretreatment viral load in genotype 1 patients.

In conclusion, among patients with HCV genotype 1 infection and elevated serum ALT levels, a pretreatment serum HCV RNA level of 400 000 IU/mL is an optimized threshold for differentiating between patients with a high and low probability of achieving an SVR when treated for 48 weeks with peginterferon alfa-2a (40 kD) plus ribavirin. The threshold can be applied in the setting of HCV mono-infection and HIV–HCV co-infection. In the era of response-guided therapy, this threshold may be useful for identifying the HCV mono-infected patients who are most likely to respond to an abbreviated treatment regimen.

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