Pegylated interferon fractal pharmacokinetics: individualized dosing for hepatitis C virus infection

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Abstract (n=250)
ABSTRACT:

Background: Despite recent advances in hepatitis C virus (HCV) therapeutics, the combination of pegylated interferon (PEGIFN) and ribavirin (RBV) remains the cornerstone of treatment. Optimization and individualization of PEGIFN dosing could improve outcomes.

Methods: Week one PEGIFN serum concentrations in 42 HCV genotype 1 infected patients treated with conventional PEGIFN/RBV were analyzed using multi-compartmental pharmacokinetic models. For each patient, pharmacokinetic parameter estimates, weight, age, IL-28B single nucleotide polymorphism, CD4 count, baseline HCV RNA, gender, race, and HIV status were examined using classification and regression tree analysis to identify factors predictive of sustained viral response (SVR). Survival analysis was performed to compare the time to undetectable viral load in patients with and without the highest scoring predictor.

Results: PEGIFN concentrations varied at least 87-fold. Pharmacokinetics were best described by a two-compartment model with an 8.4hr absorption lag. Patient weight correlated with PEGIFN systemic clearance based on fractal geometry relationships. SVR was achieved in 36% of patients; PEGIFN cumulative one week area-under the curve (AUC) ≤ 0.79 mg*h/L scored highest in predicting poor response, followed by weight ≥ 93.7 kg. Patients with a PEGIFN AUC > 0.79 mg*h/L achieved undetectable viral load more rapidly than those with a lower AUC (Hazard ratio=1.63; 95% confidence interval 1.21-2.04).

Conclusions: PEGIFN exhibits wide pharmacokinetic variability, mainly driven by patient weight, so that the standard dose may not reach levels needed to achieve SVR. Optimizing dose to patient weight and PEGIFN AUC in the first week offers a solution to improve SVR, and to potentially shorten duration of therapy.
Treatments for hepatitis C virus (HCV) are rapidly changing. The combination of pegylated interferon (PEGIFN), ribavirin (PEGIFN/RBV) and a directly acting antiviral (DAA) is becoming the standard of care for HCV genotype 1 infected patients. PEGIFN/RBV combined with the recently licensed NS3/4A protease inhibitors (PIs) such as telaprevir and boceprevir, achieves an overall response rates of ~70% in treatment naïve patients (1-3). When these PIs are administered as monotherapy or as dual therapy with an NS5A replication complex inhibitor, there is rapid emergence of drug resistance (4-6). Therefore, combination therapies will continue to include PEGIFN for the near future although “interferon–free” regimens are currently being studied. Finally, in resource poor countries, the PEGIFN/RBV regimen is likely to continue as the main regimen for all HCV infection for the foreseeable future.

Recently, single nucleotide polymorphisms (SNPs) of the IL-28B gene have been shown to predict response to PEGIFN (7). Patients with the IL-28B rs12979860 CC genotype demonstrated a 2-fold higher likelihood of sustained virologic response (SVR) than those with CT/TT SNPs (8). Although HCV RNA and IL-28B SNPs can predict likelihood of response, they are not modifiable. We sought to determine if PEGIFN pharmacokinetics could have similar predictive power; if so these are modifiable to improve SVR. To test this, we performed a prospective pharmacokinetic-pharmacodynamic (PK/PD) study in patients, given the success of this approach in optimizing other anti-infective agents (9). Uniquely, we examined compartmental pharmacokinetics of PEGIFN and examined the effect of patient weight (body mass) based on fractal geometry methods. Fractal mathematics describes the non-linear relationship between processes such as metabolic rates and weight over several scales of magnitude as well as to non-regular, rough, and continuously branching surfaces and edges such as
as human organs’ often based on the “3/4 power law” (10-13). It is an analytic tool that is better at identifying the effect of weight compared to standard methods. Here, we apply this to the relationship between PEGIFN pharmacokinetics and body weight, and to SVR.

MATERIALS AND METHODS

Regulatory compliance. The study was approved by the Institutional Review Board (IRB) of the University of Texas (UT) Southwestern Medical Center (IRB#102005-009). The study was registered at www.clinicaltrials.gov (NCT00703560).

Patients and setting. The study was performed at UT Southwestern Medical Center teaching hospitals in Dallas, Texas. The first patient was enrolled March 1, 2004 and the last patient enrolled January 25, 2010. All subjects gave written informed consent after the study was explained to the participant in detail.

Inclusion criteria was HCV infection by serum anti-HCV enzyme immunoassay, an HCV viral load of >1000 IU/mL, documented HCV genotype by a CLIA certified lab, age>18 to 65 years, and willingness to use two or more methods of birth control in women of childbearing age. Subjects were excluded if they had uncontrolled diabetes mellitus, psychiatric illness, autoimmune disease, decompensated liver disease, or prior interferon therapy. Patients with other liver diseases such as alcohol, hepatitis B virus infection, Wilson’s disease, hemochromatosis, or alpha-1 antitrypsin, were excluded. Patients were excluded from the study if they were unwilling to be admitted for a 48-hour period for serial blood draws. Patients who did not have serum samples at needed time points were excluded. HIV-infected patients had either to be anti-retroviral therapy (ART) naïve, or if on ART they had to be on a stable ART regimen for at least 12 weeks. The ART regimen could not include didanosine due the risk of fatal hyperlactatemia.
Patients had to have a CD4 T-cell count >200 cells/mm³ within the 12 weeks prior to enrollment. Subjects were excluded if they had symptomatic HIV disease including an AIDS-defining illness.

**Study procedures.** This was an open label observational study of HCV infected patients who were otherwise candidates for treatment with PEGIFN/RBV. Patients that met inclusion criteria and consented to participate were admitted for 48 hours to initiate treatment. All patients received subcutaneous pegylated interferon –α-2a 180 µg/week plus ribavirin (PEGIFN/RBV), which was dosed based on weight: if ≤75 kg 1000 mg daily or if > 75 kg 1200 mg daily for 48 weeks. Ribavirin doses were administered as a twice-daily regimen. Blood was drawn at 0, 4, 24, 96, and 168hrs after the initial subcutaneous injection, and then spun at room temperature at 1500 rpm for 10 minutes within 4 hours of collection. The plasma was decanted into freezer tubes and stored in a -80°C freezer for subsequent HCV RNA quantification and for drug assays. Blood was also collected on day 3, 5, 9, 11, 14, 21, 28, 42, and 56 days for additional HCV RNA quantification, which was performed using the VERSANT® 3.0 branched DNA technology (Siemens Medical Solutions Diagnostics, Tarrytown, N.Y.), with a dynamic range of 615-7,692,310 IU/mL.

Standard safety assessments, and urine pregnancy tests in women, were conducted at each study visit. As PEGIFN/RBV was the standard of care, adverse events that were known side effects of the medications were monitored and managed by study investigators as dictated by best practice.

**Genotype studies.** Human genomic DNA was extracted from whole blood or serum samples with QIAamp DNA Blood Mini Kit (Qiagen). The targeted region, including SNP rs12979860, was amplified by PCR and PCR products were purified and sequenced (14).
Interferon assay. Serum samples were kept frozen at -80°C after processing, and then sent to Hoffman-La Roche, Inc., laboratories in Nutley, NJ, on dry ice. PEGIFN concentrations were determined using a sandwich ELISA, in which capture antibody (affinity purified rabbit polyclonal anti-PEG-IFN) was coated onto micro-titer plates. Serum samples were added to the plate and incubated. The plate was washed and detection antibody (mouse monoclonal anti-PEG) was added and then further incubated. The plate was washed again and peroxidase conjugated goat anti-mouse IgM) was added and incubated. After a final wash, a substrate solution was added. Color developed in proportion to the amount of PEGIFN present in the sample. This assay has a range of 250-5,000 pg/mL. The intra-batch precision was 2.5-8.4%, and the accuracy was -5.5-13.2%. The inter-batch precision was 11.7-16.6% and the accuracy 0.4-9.0%.

Population pharmacokinetic analyses. PEGIFN concentrations were modeled using the ADAPT 5 program (15). One compartment model, one compartment model with lag, two-compartment model, two-compartment model with lag, and a three compartment model, were examined. First, initial guesses of the population pharmacokinetic parameter estimates for each model were identified using the standard two-stage approach. The estimates were then used in further pharmacokinetic analysis using the maximum likelihood solution via the expectation-maximization (MLEM) algorithm. Four criteria were used to choose the best compartment model: Akaike’s Information criteria, Bayesian Information Criteria, negative log likelihoods, and the law of parsimony (16-18). Next, the relationship between pharmacokinetic parameter and the following covariates were examined in log-log scatter plots for the selected model: self-identified race (African-American versus other) given the known poor treatment response in this group, IL-28B SNPs, HIV status, weight, CD4 count, gender and age. Fractal relationships are easiest to spot with log-transformed data, i.e., in log-log plots [11]. When a relationship was
identified, the slope of the relationship between covariate and pharmacokinetic parameter was calculated. Those covariates and initial estimates of slope were then added in the subroutine COVMOD of ADAPT. The relationship between covariate and pharmacokinetic parameter was then determined using MLEM to yield the final model estimates.

**Classification and regression tree (CART) and survival analysis**

CART analysis was used to identify the best predictors of virologic outcome, and to identify the threshold cut-off values for such predictors. CART analysis models are very accurate at identifying and estimating complex high-order nonlinear interactions. The outcomes of this non-parametric and recursive partitioning analysis is **predictive accuracy**, as opposed to statistical association with the standard statistical approaches. The outcomes examined were SVR, defined as HCV RNA <615 IU/ml at least 24 weeks after termination of antiviral therapy, as well as rapid virologic response (RVR), defined as (HCV RNA <615 IU/mL) at week 4. Variables examined for prediction of RVR and SVR included PEGIFN peak concentration, trough concentration, 168h (1 week) area under the concentration-time curve (AUC), patient weight, age, IL-28B SNPs, CD4 count, initial HCV viral load, gender, race, and HIV status. All outcomes were examined so that they could be ranked by the most important determinant of outcome. First, CART analysis was used for rank variables. Significant variables were chosen if the CART score was \( \geq 20\% \). The analysis also identified clinically meaningful cut-offs points for the selected continuous variables. The splitting criterion was based on the Gini index (19). Several trees were constructed, pruned and went through 10-fold cross-validation (20). The optimum tree was selected based on relative misclassification costs, PK/PD considerations and biological plausibility. CART was performed using the Salford Predictive Miner System software, San Diego, CA (20).
Next, we validated the CART analysis findings using standard statistical approaches familiar to most clinicians. First, the main predictor of SVR (highest decision node) in CART was examined in a survivor analysis to determine time to undetectable viral load in patients above the cut-off value versus those below. Since patients who failed therapy were taken off PEGIFN/RBV after week 12 and had no viral loads done after that, data for these patients was censored at the 12-week time point. In addition, since the ratio of hazard functions was not the same at all time points, the Gehan-Breslow-Wilcoxon method was used to compare the survival curves. Next, the CART outputs, including data obtained by examination of surrogate and competitor variables, were used as inputs for parametric univariate analysis and multivariate logistic stepwise analyses. Modifiable and clinically important variables were initially added in the several models examined and then sequentially (stepwise) removed using backward regression if \( p \) was <0.1 based on the Wald statistic. The survival analysis and the multivariate analyses were performed in SPSS version 12.

RESULTS

Clinical Features

Of 58 HCV genotype 1 patients eligible for the study, 42 (72%) met inclusion criteria and are included in the present analyses. The patients’ demographic, clinical and laboratory characteristics are shown in Table 1. The IL-28B SNP could not be determined in 4 (9.5%) patients. Table 1 shows that self-identified “race”/ethnicity was associated with IL-28 genotype allele distribution. Liver disease severity prior to start of therapy did not significantly differ between the race/ethnic groups (Table 1). The three most common adverse events among the 42 patients were neutropenia (83%), depression (79%) and anemia (62%); one patient was admitted
to the hospital for pulmonary related issues not thought to be due to HCV treatment. These adverse events, including hospitalization for anemia, were at expected rates.

RVR was achieved in 11 (26%) patients and SVR in 15 (36%) out of 42 patients. There were 4 patients who stopped therapy due to adverse events and 11 (26%) other patients who relapsed after a documented viral response. Twelve (29%) patients were non-responders, failing to achieve a 2-log drop at 12 weeks and for HCV to remain suppressed until 48 weeks.

Interferon Levels and CART analysis

Altogether, 198 PEGIFN concentrations collected during the first week of therapy were analyzed. The concentration-versus-time profiles for each of the 42 patients are shown in Figure 1. The figure demonstrates wide variability in concentrations at any of the time points. As an example, the ratio of the highest to the lowest drug concentration 24hrs after PEGIFN injection was 87, while the 168hr trough concentrations varied 50 fold. Population pharmacokinetic analysis revealed that a two-compartment model with absorption lag best described PEGIFN pharmacokinetics (supplementary Table 1). Scatter plots revealed that only patient weight significantly correlated with pharmacokinetic parameters (Figure 2). The slopes of the log-log plots of clearance and volume encompassed ¾, consistent with the ¾ power law of fractal geometry (11, 12, 21, 22). Therefore, weight was examined as a covariate in ADAPT. The pharmacokinetic parameter estimates for this final model are shown in Table 2.

CART analysis revealed that the highest ranked predictor of RVR was a PEGIFN trough ≤ 0.01 mg/L, which outranked the second placed IL-28B SNP (figure 3A). In this analysis, the 168hr AUC was ranked third in importance. However, RVR itself is a surrogate for SVR. On the other hand, PEGIFN AUC had the highest score for predicting SVR, making it the first “decision” node (Figure 3B) for long term outcome; the cut-off point was a 168hr AUC of 0.79.
mg*h/L. To put this into context, if one used standard statistical approaches, the odds ratio for failure below the AUC cut-off point was 7.0 (p=0.02). The next node for SVR was the patient’s weight, with higher failures above 93.70 kg. Finally, the trough concentration had the third highest score for SVR (Figure 3B). Importantly, the IL-28B genotype scored below 20%. The minimum and maximum predictive accuracy was 68% and 95%, respectively, for all trees that were examined. The overall prediction success for the CART models was 76%. We then compared time to viral load suppression in patients who achieved AUC above the cut-off of 0.79 mg*h/L versus those below, with results shown in Figure 4. The median time to viral load suppression with the higher AUC was 56 days compared to 91 days (HR=1.625; 95% CI: 1.207–2.043). This means that achievement of AUC above the threshold is associated with faster time to viral load suppression.

To confirm the CART findings, univariate and multivariate logistic were performed, with the univariate analysis results shown in supplementary Table 1. Weight and IL-28B CC allele remained significantly associated with RVR in several stepwise multivariate logistic models. The adjusted odds ratio for weight was 0.90 (95% CI 0.83–0.98) and that for IL-28B CC allele was 7.91 (95% CI 1.35–46.38). For SVR, IL-28B CC allele was not associated with outcome in multivariate analysis. Weight and the PEGIFN AUC were associated with SVR. The adjusted odds ratio of success with an AUC>0.79 mg*h/L was 9.09 (95% CI 1.23–100). Thus, the multivariate logistic analysis confirmed CART analysis.

Discussion

Our study revealed two important findings with direct clinical implications. First, the relationship between AUC and SVR superseded that of IL28B SNPs, and should therefore be more useful if dosage corrections can be made based on these parameters. Since the
pharmacokinetics were calculated after the first PEGIFN dose, early intervention based on these findings could be undertaken as early as 2 weeks of therapy, once the interferon levels were available. The determination of AUC requires multiple sampling times during the first week, however, given the slow clearance of PEGIFN, three time points during the first 1 week would be adequate, especially if optimal sampling theory is applied. With these, a full AUC for the first week can easily be determined by physicians and higher doses administered during subsequent weeks in order to achieve AUCs above 0.79 mg*h/L. The precise dose will depend on the AUCs achieved during the first week, after which each patient can begin receiving an individualized dose. With faster times to undetectable viral load encountered with the higher AUCs, and in combination with DAAs, treatment duration might be further shortened based on the concept of response-guided therapy (3).

The second important finding is the relationship between weight and both PEGIFN pharmacokinetics and virologic response. We identified the compartmental pharmacokinetics of PEGIFN, which allowed us to accurately estimate pharmacokinetic parameters and then examine them with relationship to such factors as weight. Clearance and volume of distribution were partly determined by weight, based on fractal geometry dependent ¾ power law (10, 13). While we and others have demonstrated that clearance of xenobiotics such as ethambutol and echinocandins obeys these fractal geometry-determined relationships (20-22), the current study demonstrates this relationship for a type 1 interferon (IFN-α). Type 1 interferons, such as IFN-α, are endogenously produced as part of the body’s response to infection: PEGIFN merely provides higher concentrations that are much more slowly cleared. Our observations suggest that metabolism of this vital component of the innate immune system is affected by body mass. The implication is that even the initial PEGIFN dose should be adjusted according to weight
especially in overweight patients, not in a linear fashion, but proportional to \((\text{weight}/\text{typical weight})^{3/4}\). Many previous studies have shown that higher body mass index (BMI) and weight are associated with reduced response (23-25). However, early viral kinetics and SVR were not associated with BMI when weight-adjusted dosing of RBV was used (26, 27). Our study suggests that the relationship of weight to response is not a linear relationship, and that the adjustment should be by the factor of \((\text{weight}/\text{typical weight})^{3/4}\).

There are several limitations to our study. Previous attempts to determine the role of drug concentrations for interferon based compounds in the treatment of HCV have generally met with limited success (28-30). Reasons for previous lack of predictive insights from others’ data might be due to limited precision of pharmacokinetic parameter estimates, use of a single time point drug “concentration”, the type of viral kinetic measurements utilized, or the statistical methods to determine the relationship (26, 27). Second, our sample size was only 42, which could throw the generalizability of our study into question. As an example, studies that established the role of IL-28B SNPs examined hundreds of patients. However, the multiple approaches we took increased the ability of our study to detect differences. Our study design allowed for intensive pharmacokinetic sampling, and compartmental pharmacokinetic analyses, which allowed for accurate discrimination of pharmacokinetic parameters for each patient. Finally, we utilized CART models, which have the advantage of accuracy for higher order non-linear relationships.

In conclusion, this study examined population pharmacokinetics of PEGIFN in HCV infected patients. Wide pharmacokinetic variability was encountered. PEGIFN AUC was determined to be the most predictive factor for SVR, its effect superseding that of IL28B polymorphism. Weight was also associated with both PEGIFN clearance (and hence AUC) and SVR, but the relationship was not linear; rather it followed fractal geometry relationships. The
major implications are that PEGIFN dosing can be improved by individualizing dosing based on weight and measured drug concentrations, leading to improved SVR and more rapid virologic response.

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Acknowledgements

Roche Pharmaceuticals measured interferon levels for this study.
References


### Table 1. Clinical and laboratory characteristics of 42 HCV patients.

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<th>ALL patients (n=42)</th>
<th>African American (n=14)</th>
<th>White/other (n=28)</th>
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<td>28 (67)</td>
<td>8 (57)</td>
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<tr>
<td></td>
<td>Female</td>
<td>14 (33)</td>
<td>6 (43)</td>
<td>8 (29)</td>
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<tr>
<td>Age (years)</td>
<td>Median (range)</td>
<td>43 (31)</td>
<td>48 (29)</td>
<td>42 (26)</td>
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<td>Body mass (kg)</td>
<td>Median (range)</td>
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<td>87.6 (27)</td>
<td>80.1 (60.8)</td>
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<td>IL-28B SNP</td>
<td>CC</td>
<td>15 (36)</td>
<td>1 (7)</td>
<td>15 (50)</td>
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<td></td>
<td>CT</td>
<td>13 (31)</td>
<td>6 (43)</td>
<td>7 (25)</td>
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<tr>
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<td>6 (43)</td>
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<td>12 (29)</td>
<td>5 (36)</td>
<td>7 (25)</td>
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<td>Median (range)</td>
<td>579 (977)</td>
<td>592 (746)</td>
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<td>Log HCV RNA (IU/mL)</td>
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<td>7 (19)</td>
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<td>6 (25)</td>
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<td>PEGIFN 168h (mg*h/L)</td>
<td>Mean(SD)</td>
<td>1.073 (0.575)</td>
<td>1.187 (0.633)</td>
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<td>Mean(SD)</td>
<td>0.011 (0.007)</td>
<td>0.013 (0.008)</td>
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<td>PEGIFN trough concentration (mg/L)</td>
<td>Median (range)</td>
<td>0.005 (0.029)</td>
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<tr>
<td>Clinical outcome</td>
<td>Non-responder:</td>
<td>12 (29)</td>
<td>8 (57)</td>
<td>4 (14)</td>
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<td></td>
<td>SVR</td>
<td>15 (36)</td>
<td>2 (14)</td>
<td>13 (46)</td>
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<td></td>
<td>Relapsed</td>
<td>11 (26)</td>
<td>3 (21)</td>
<td>8 (29)</td>
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*missing data: IQR=Interquartile range
Figure 1. Wide variability is encountered in pegylated interferon (PEGIFN) concentrations of 42 patients. We chose to highlight 5 randomly chosen patients’ PEGIFN concentrations over 168 hours, depicted by line graphs, demonstrating the highly variable concentrations achieved and patterns of decline of the concentrations. The graph for the mean naïve pooled concentration (solid black line) demonstrates how poorly the pooled data (i.e., averages) summarizes the true variability of concentration-time profiles between patients.
The figures show the relationship between weight and the pharmacokinetic parameters of (a) systemic clearance, (b) volume of central compartment, (c) volume of peripheral compartment, and (d) the transfer constant of drug from central compartment to peripheral compartment. The systemic clearance, volume of central compartment, and volume of peripheral compartment had slopes encompassing $\frac{3}{4}$, an important fractal geometry based index for body size and metabolism.
Figure 3. Panel A: RVR

Study sample = 42 patients

Rapid Virologic Response (RVR):
- Failed 31 (74%)
- Responded 11 (26%)

Trough < 0.01: 8 patients
- RVR:
  - Failed 8 (100%)
  - Responded 0 (0%)

Trough > 0.01: 34 patients
- RVR:
  - Failed 23 (68%)
  - Responded 11 (32%)

IL-28B = CT/TT: 22 patients
- RVR:
  - Failed 18 (82%)
  - Responded 4 (18%)

AUC < 0.88: 6 patients
- RVR:
  - Failed 6 (100%)
  - Responded 0 (0%)

AUC > 0.88: 16 patients
- RVR:
  - Failed 12 (75%)
  - Responded 4 (25%)
Panel B. SVR

Study sample: 42 patients

Sustained Virologic Response (SVR):
- Failed: 27 (64%)
- Responded: 15 (36%)

<table>
<thead>
<tr>
<th>AUC &lt;=0.79: 15 patients</th>
<th>AUC &gt;0.79: 27 patients</th>
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<tbody>
<tr>
<td>SVR:</td>
<td>SVR:</td>
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<tr>
<td>Failed</td>
<td>Failed</td>
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<tr>
<td>13 (87%)</td>
<td>14 (52%)</td>
</tr>
<tr>
<td>Responded</td>
<td>Responded</td>
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<td>2 (13%)</td>
<td>13 (48%)</td>
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<table>
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<td>SVR:</td>
<td>SVR:</td>
</tr>
<tr>
<td>Failed</td>
<td>Failed</td>
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<tr>
<td>5 (83%)</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>Responded</td>
<td>Responded</td>
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<td>1 (17%)</td>
<td>12 (57%)</td>
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<td>9 (50%)</td>
<td>3 (100%)</td>
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<td>Responded</td>
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<td>9 (50%)</td>
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Figure 3. Classification and regression tree analysis of factors predictive of virologic response.

Panel A shows factors that predicted rapid virologic response (RVR) and panel B shows those that predicted sustained virologic response (SVR). Baseline hepatitis C viral load was excluded from the modeling since a relationship between HCV and viral response is clearly demonstrated in the literature and in also shown for these data in Table 3.
Figure 4. Time to viral load suppression in patients with high and low interferon–α AUC.

The time to viral load suppression was calculated in days. Patients who were discontinued therapy due to therapy were censored at the time when therapy was discontinued.