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Virologic Response Rates of Telaprevir-based Hepatitis C Triple Therapy in Patients with and without HIV Co-infection

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Abstract

Objectives—Pegylated-interferon/ribavirin dual therapy for hepatitis C virus (HCV) has a lower sustained virologic response (SVR) rate in HIV/HCV-co-infected patients than in HCV mono-infected patients, but little is known about the relative effectiveness of teleprevir-based triple therapy in the two groups.

Methods—Data on 33 co-infected and 116 mono-infected patients were analyzed on an intention-to-treat basis. SVR12 was defined as undetectable HCV RNA at week-12 post-end-of-treatment, severe anemia as hemoglobin ≤89 g/L or a drop ≥45 g/L, and advanced fibrosis/cirrhosis as Fib-4 ≥3.25. All co-infected patients had well-controlled HIV.

Results—The groups were similar in age, gender, percentage with Fib-4 ≥3.25, and HCV viral load, but differed in previous treatment response, with more co-infected patients non responders/treatment intolerant (75.8% vs. 50.0%, <0.01). During treatment, the percentages of patients with undetectable HCV RNA were similar, but, surprisingly, tended to be higher in co-infected patients. SVR12 rates were 60.6% (co-infected) vs. 42.2% (mono-infected), p=0.06. In multivariable analysis, SVR12 was associated with HIV infection (OR: 3.55, p<0.01), African American race (OR: 0.37, p=0.03) and previous treatment response (OR: 0.46, p=0.03). Rates of severe anemia (45.5% vs. 58.6%, p=0.18) were similar in the two groups, but rash (15.2% vs. 34.5%, p=0.03) and rectal symptoms (12.1% vs. 43.1%, p<0.01) were less common in co-infected patients.

Conclusions—Virologic responses of co- and mono-infected patients did not differ significantly, but tended to be higher in co-infected patients, who had a 60.6% SVR12 rate.

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Telaprevir-based triple therapy is a promising option for co-infected patients with well-controlled HIV.

Keywords

hepatitis C virus; HIV; co-infection; telaprevir; side effects

Introduction

Due to shared routes of transmission, 30% of European and American HIV-infected patients are co-infected with the hepatitis C virus (HCV) and 8% of HCV-positive patients are co-infected with HIV (1, 2). Compared to HCV mono-infection, HIV/HCV co-infection results in accelerated liver fibrosis progression in patients with a detectable HIV viral load, although it is not accelerated in patients with undetectable HIV viral load (3). Mortality is higher in co-infected patients, underscoring the urgent need for more effective treatments (4). Numerous studies have demonstrated lower sustained virologic response (SVR) rates in co-infected patients receiving dual therapy with pegylated-interferon (pegIFN) and ribavirin (RBV). Among co-infected patients receiving dual therapy, SVR rates vary from 14% to 38% in patients with genotype 1 HCV and from 44% to 72% in patients with genotype 2–3 HCV (5–9). These SVR rates are about 10–20% lower than among genotype-matched mono-infected patients (10).

In May 2011, the approval of the first two direct-acting antiviral drugs, telaprevir (TVR) and boceprevir, significantly changed the treatment of patients infected with HCV genotype 1. For HCV mono-infected patients previously naïve to treatment, the SVR rate in clinical trials of TVR-based triple therapy increased to 72–75% (11, 12). For patients who had previously relapsed after achieving an end of treatment (EOT) response during dual therapy, the SVR rate increased to 83% (13). Difficult to treat populations also had improved outcomes, with SVR rates reaching 59% for previous partial responders and 29% for previous null responders (13).

TVR-based triple therapy has not yet received Food and Drug Administration approval for HIV/HCV co-infected patients, but a phase III trial is underway. A phase II study of 60 co-infected patients who were naive to HCV treatment at the start of the trial has been completed. The SVR rate was 74% among the 38 people in the TVR arm, which is similar to the rate in treatment naïve mono-infected patients (14). Among the patients in the TVR arm of this phase II trial, discontinuations for adverse events were rare. Two patients discontinued all medications, and one discontinued TVR. Eighteen percent developed an hemoglobin level < 100 g/L. One patient developed severe anemia, defined as an hemoglobin between 70 and 89 g/L or a decrease in hemoglobin from baseline by > 45 g/L. Thirty-four percent developed mild to moderate rash, compared to 23% of patients on dual therapy (without TVR).

Although results of the Phase II trial are promising, it is a small study carried out in the setting of a prospective clinical trial. Effectiveness in clinical practice often falls short of the efficacy reported in clinical trials, and side effects may be worse. The primary objective of the current study is to compare virologic responses to off-label TVR-based therapy in HIV/HCV co-infected vs. HCV mono-infected patients in a real-life setting. The secondary objectives are to assess the safety and tolerability of TVR-based triple therapy in co-infected patients by analyzing rates of severe anemia, hospitalization, rash, and rectal symptoms.

Methods

Study design and patients

This study is a medical record review of patients who began TVR in combination with pegIFN and RBV before December 2011 at the Icahn School of Medicine at Mount Sinai (MSSM), New York, NY and John Hopkins University (JHU), Baltimore, MD. Seventeen co-infected patients and 116 mono-infected patients were treated at MSSM and 16 co-infected patients were treated at JHU. None of the patients had previously received a liver transplant and none was treated for more than 48 weeks. All patients were treated with weight-based ribavirin dosing. TVR was administered at a dose of 750 mg three times a day, except when co-administered with efavirenz where a dose of 1,125 mg three times a day was used. Mono-infected patients who were naïve to HCV treatment or who previously relapsed after treatment with pegIFN/RBV, who were not cirrhotic and who had undetectable levels of HCV RNA at week-4 and -12 were eligible for a shortened treatment course of 24 weeks [response guided therapy (RGT)]. For this subset of patients, week-24 data were carried forward for the week-48 analysis (EOT). Co-infected patients were not considered for RGT.

Data were collected at baseline, week-4, -12, -24, -48 and 12 weeks post-EOT. Data recorded included demographics, baseline medical conditions and medications, previous HCV treatment history, laboratory values, adverse events including rash, rectal symptoms, emergency room visits and hospitalizations. To evaluate the workload associated with treatment planning, pre-treatment medical visits were counted. The education visit for injection learning was not counted, as it is standard of care for all patients. HCV and HIV viral loads were measured by RT-PCR (Roche Cobas Ampliprep Cobas Taqman version 2.0). HCV viral load below the lower limit of detection (18 IU/mL) was recorded as “undetectable”. HCV virologic failure was defined as a viral load > 1000 IU/mL at week-4 or -12 or a detectable HCV viral load after week-24. Patients were considered to have advanced fibrosis or cirrhosis if they had a Fib-4 score ≥3.25 (15). Anemia was defined as an hemoglobin < 135 g/L in men and < 120 g/L in women. Based on theDAIDS criteria, severe anemia was defined as an hemoglobin ≤ 89 g/L and/or a decrease ≥ 45 g/L(16). IRB approval was received from each institution.

Statistical analysis

Chi-square or Fisher exact tests were used for discrete variables and students T tests or Mann-Whitney U tests were used for continuous variables. Baseline characteristics of the HIV/HCV co-infected patients from MSSM and JHU were compared to each other and were combined because no statistically significant differences were found. Treatment outcomes were evaluated on an intention-to-treat basis. Patients lost to follow up were considered to have a virologic failure.

Data of co- and mono-infected patients were included in a multivariable logistic regression analysis of factors independently associated with SVR12. Factors known to influence SVR during dual therapy were included: age, sex, race (African American or not), previous treatment response [favourable (naïve or relapser) vs. not favourable (non-responder or treatment intolerant)], body mass index (BMI), logarithm of the HCV viral load, fibrosis stage (Fib-4 score below vs. above 3.25), and HIV infection status. To confirm the comparability of the patients, the treatment site was also evaluated. The multivariable model was built using forward and backward likelihood ratios. Entry and exit p-values were both fixed at 0.10 and factors with p-values below 0.05 in the final model were retained. Data were analyzed in SPSS (Chicago, IL, version 20). A p-value below 0.05 was considered statistically significant.

Results

The baseline characteristics of the study group are presented in Table 1. Mono- and co-infected patients were similar in age, sex, BMI, HCV viral load, and the percentage with advanced fibrosis/cirrhosis. The groups were different in their racial composition, with a higher percentage of African Americans in the co-infected group (42.4 vs. 16.4%, p<0.01). The previous treatment responses were also different, with more non-responders and patients who were intolerant to dual therapy in the co-infected group (75.8% vs. 50.0%, p<0.01). Co-infected patients had significantly more pre-treatment visits than mono-infected patients (median: 2 (range: 1–4) vs. 1 (1–5); p<0.01).

At baseline, the median $CD4^+$ T cell count of the co-infected patients was 478 cells/μL [inter quartile range (IQR), 362–763; min, 194; max, 1346]. Eighty percent had an undetectable HIV viral load and the remainder a viral load < 1000 copies/mL. All were on HIV antiretroviral therapy. Tenofovir and emtricitabine were the most common reverse transcriptase inhibitors. They were generally combined with ritonavir-boosted atazanavir, efavirenz, and/or raltegravir. Before initiating TVR-based therapy, 51.5% of the patients had to switch their HIV regimen out of concern about potential drug-drug interactions with TVR.

Virologic responses are presented in Fig. 1. A similar percentage of co- and mono-infected patients had undetectable HCV RNA at week-4 (42.4% vs. 43.1%, p=0.94), week-12 (69.7% vs. 65.5%, p=0.65), week-24 (75.8% vs. 57.8 %, p=0.06) and at the EOT (69.7% vs. 54.3%, p=0.11). There was a trend toward a better SVR12 rate in co-infected patients (60.6% vs. 42.2%, p=0.06). Among co-infected patients, $CD4^+$ T cell counts were similar in patients with and without SVR12: median, 466 cells/μL (with) vs. 614 cells/μL (without), p=0.83.

In univariable logistic regression analysis, there was a trend for an association between the SVR rate and race, previous HCV antiviral treatment response, and HIV status. In the multivariable model, HIV infection was positively associated with SVR [odds ratio (OR)= 3.55; 95% CI: 1.44–8.75] and African American race and an unfavourable response to previous dual therapy (non-response or treatment intolerance) were inversely related to SVR (OR= 0.37,95% CI: 0.15–0.92 and OR=0.46, 95% CI: 0.23–0.93, respectively) (Table 2).

Side effects and major adverse events were common in both co-infected and mono-infected patients (Table 3). There was no statistically significant difference in the proportions with a hospitalization (27.2% vs. 18.1%, p=0.25), emergency department visit (18.2% vs. 13.8%, p=0.53), anemia (87.8% vs. 91.4%, p=0.54), or severe anemia (45.5% vs. 58.6%, p=0.18). Rash and rectal symptoms were less common among co-infected patients (p= 0.03 and p<0.01, respectively). Treatment had to be discontinued because of side effects in a similar percentage of patients in the two groups. Early discontinuation of TVR (with continuation of pegIFN/RBV) occurred in 6.0% of co-infected patients vs. 0.9% of mono-infected patients, p=0.12; early discontinuation of all three drugs occurred in 21.1% vs. 12.9%, p=0.27; and early discontinuation of any drug occurred in 24.2% vs. 13.8%, p=0.18.

Based on the SVR12 rates in clinical trials, we expected an SVR12 rate of 60.7% in our population of mono-infected patients (11–13), which is significantly higher than the 42.2% we observed, p<0.01 (Table 4). The lower overall rate in our study was largely due to the unexpectedly poor outcomes in two subgroups: patients who were previously naïve to treatment and patients who relapsed after an EOT response (p= 0.02 and p=0.01, respectively, compared to comparable groups in published trials). Among treatment naive patients, 10/35 (28.5%) discontinued triple-therapy early due to side effects. These patients accounted for 62.5% of all mono-infected patients who discontinued for side effects. Among former relapsers, 4/23 (17.4%) relapsed again after EOT. The previous non-responders had a

response rate similar to comparable patients in clinical trials (p=0.30). Nineteen mono-infected patients were eligible for RGT. Thirteen (68.4%) achieved SVR12, whereas three relapsed and three were lost to follow up.

Discussion

To our knowledge, our study provides the first information about the effectiveness of TVR-based triple therapy in HIV/HCV co-infected patients receiving care outside of a clinical trial. Consistent with the outcome achieved in a phase II trial in 38 treatment-naïve patients (SVR24 rate of 74%)(14), the SVR12 rate of our co-infected patients was 60.6%, a promising result. Our findings are particularly encouraging because 42.4 % of the co-infected patients were African American, and 48.5% had advanced fibrosis/cirrhosis, factors associated with lower SVR rates among co-infected patients receiving dual therapy (17, 18). Even though the patients in our study received triple therapy without the structure and resources of a clinical trial, the SVR12 rate was higher than reported in major clinical trials of dual therapy for co-infected patients with genotype 1 HCV, which had SVR rates of 14–38% (5–9). Our data are consistent with those of an ongoing study of treatment-experienced co-infected patients (19). This study has an unusual design that includes a 4 week lead-in phase of pegIFN/RBV followed by 12 weeks of TVR-based triple therapy and a final 32 or 56 weeks of dual therapy. At week 12 of triple therapy, 88% of the patients were HCV viral load undetectable (19). In the co-infected phase II trial, 79% of patients were undetectable after 12 weeks of treatment and this translated in an SVR rate of 74% (14). These findings and our results suggest that triple-therapy is likely to be more effective in patients than dual-therapy in co-infected patients with well-controlled HIV. In contrast to the promising (60.6%) SVR12 rate observed in our co-infected patients, the lower (42.2%) rate we observed in our mono-infected patients was disappointing, although the difference between the two groups was not statistically significant (p=0.06).

The higher SVR12 rate among the co-infected patients may reflect a selection bias. Adherence was not measured in this study, and may have been lower in the mono-infected patients. All of the co-infected patients were receiving combination anti-retroviral therapy and maintained HIV viral loads below 1000 copies/mL. This prior experience with managing treatment side effects and ability to maintain adherence may have contributed to the high SVR12 rate of the co-infected patients. As formal possibilities to explain the higher SVR rate in the co-infected patients, one can also speculate that the HIV medications boosted levels of the HCV medications, giving an advantage to the co-infected patients, and/or that the altered immunological status of the co-infected patients somehow promoted HCV suppression in the unusual setting of TVR-based therapy. Further studies are needed to explore these possibilities. The mechanism of action of TVR almost certainly enhanced the SVR rate compared to dual therapy in the co-infected patients. TVR is a direct-acting antiviral agent that targets the HCV NS3/NS4A protease. It does not rely on host antiviral defences for efficacy. The direct antiviral effect of TVR may be especially important for HIV/HCV co-infected patients because these individuals have a residual immunological impairment, even when HIV is well controlled. In our study, $CD4^+$ T counts were not associated with SVR.

Compared to results in Phase III trials, our results in HCV mono-infected patients were significantly lower than expected among previous relapsers and naïve patients. Several factors likely contributed to these differences. Our study analyzed outcome of clinical care provided in a real-life setting. Clinical practice is less controlled than clinical trials, and may include a broader range of patients. The discontinuation rates of all three drugs for side effects were higher in our patients than in the phase III trials (12.9–21.2% vs. 6–10%) (11–13). The high rate of treatment discontinuation was especially pronounced for the previously

treatment-naive mono-infected patients. One explanation for the higher discontinuation rates in treatment-naïve patients compared to patients who previously failed therapy is the possibility that patients who experienced severe side effects on dual therapy declined triple therapy. In addition, those who experienced mild side effects during dual therapy may have used this experience to cope with the side effects of triple therapy. Among patients receiving RGT, the SVR rate was 68.4%, significantly better than in the other mono-infected patients (37.1%, p=0.01), but lower than in Phase III trials (92%; p=0.08)(12).

In terms of safety, major events such as hospitalizations, emergency room visits, severe anemia and transfusion occurred at similar rates in co- and mono-infected patients. One death occurred in the mono-infected group. The patient had liver cirrhosis and died of cerebral hemorrhage after falling while riding in a bus that was involved in an accident eight weeks after the end of his treatment. Co-infected patients had lower rates of rectal symptoms and rash. The rate of rash observed in the mono-infected group is similar to the ones seen in the registration trials (34.5 vs. 34–37%) (11, 13, 14). The immunological impairment of the co-infected patients may have contributed to their lower incidence of rash. In a separate study, a reduced incidence of rash was observed in patients with advanced fibrosis/cirrhosis, a condition associated with reduced immune function (20). Both immunological impairment and experience with drug side effects may have contributed to the lower incidence of rectal complaints expressed by the co-infected patients.

When considering TVR-based therapy for HIV/HCV co-infected patients, possible drug-drug interactions need to be included in the treatment plan. TVR is a potent inhibitor of the cytochrome P450 3A4, which leads to many problematic drug-drug interactions (21). A limited number of HIV medications have been studied and proven to be safe with TVR. Tenofovir, emtricitabine, raltegravir, rilpivirine, etravirine and ritonavir-boosted atazanavir do not significantly alter TVR pharmacokinetics (22–24), while efavirenz decreases the TVR C_{min} and the area under the curve. An increased dose of TVR (1,125 mg three times daily) is recommended for combination with efavirenz (25). The HIV regimen of 51.5% of our co-infected patients was switched prior to starting TVR to avoid drug-drug interactions. The need for a medication adjustment may explain the higher number of pre-treatment visits among the co-infected patients compared to the mono-infected patients. Changing HIV regimens can be emotionally difficult for patients, especially when the established regimen is working well. For patients with multiple HIV resistance mutations, it may be difficult to find an alternative combination that is compatible with TVR. Treatment guidelines can be used to identify possible options, but input from a co-infection specialist may be required (26, 27). Boceprevir has more drug-drug interactions than TVR and is only considered suitable for use in combination with raltegravir and NRTIs, thereby significantly limiting its use in co-infected patients (28).

The main limitations of this study are the small number of co-infected patients and the dependence on medical records. Data about HIV parameters were not always available, *IL28b* polymorphisms were unknown for most patients, and because HCV genotyping was not repeated to confirm historical data, information about HCV subtype (1a vs. 1b) was lacking for some patients. The strengths of the study include the information it provides about the effectiveness of TVR-based triple therapy outside clinical trials, the likely generalizability of the results to other real-world settings, the analysis of contemporaneously-treated co- and mono-infected patients, and the inclusion of co-infected patients who had failed prior HCV treatment.

Conclusion

In conclusion, co-infected patients had similar rates of on-treatment response and SV12 than mono-infected patients when treated with TVR-based triple therapy. TVR was associated with numerous adverse events, but there were not significantly more events in the co- than in the mono-infected population. A phase III study of TVR in co-infected is currently on-going and will hopefully lead to the official approval of TVR in co-infected patients.

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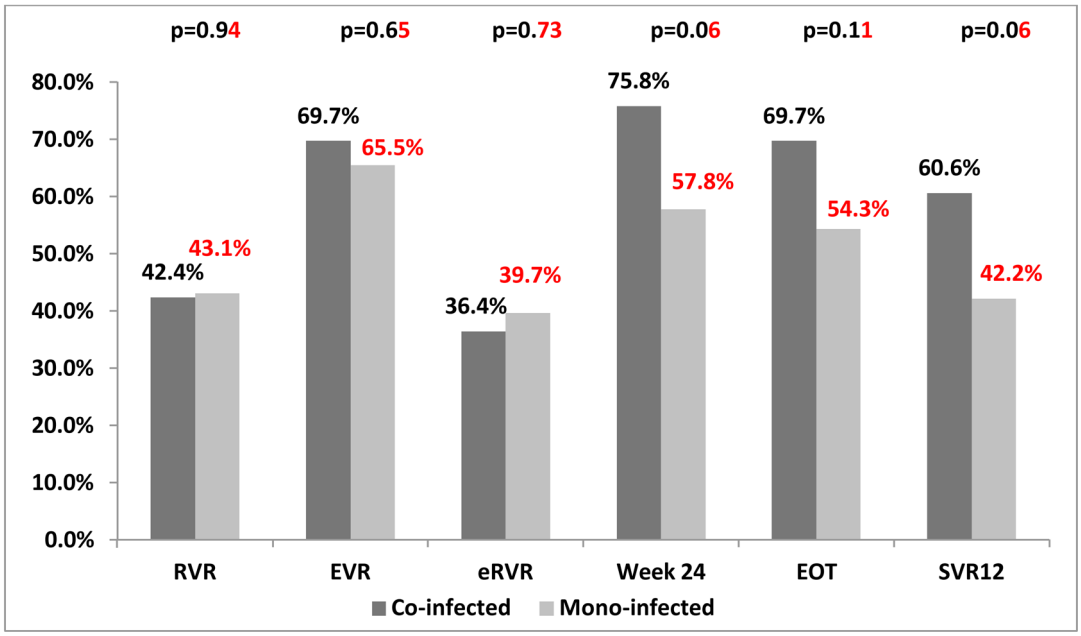

Figure 1.

Virologic treatment responses

Co-infected patients had similar rates of on-treatment response and a significantly better SVR12 rate than in mono-infected patients.

RVR: rapid virologic response, EVR: early virologic response, eRVR: extended rapid virologic response, EOT: end of treatment, SVR12: sustained virologic response 12 weeks post-treatment

Table 1

Baseline characteristics

	Co-infected (N = 33)	Mono- infected (N = 116)	p-value
Age, year, median (IQR)	57 (52–59)	56 (51–61)	0.78*
Male (% of total)	26 (78.8%)	78 (67.2%)	0.20§
African American (% of total)	14 (42.4%)	19 (16.4%)	<0.01§
Previous response to dual therapy (% of total)			<0.01§,θ
Favorable group	8 (24.3%)	58 (50.0%)	
Naïve	3 (9.1%)	35 (30.2%)	
Relapser	5 (15.2%)	23 (19.8%)	
Non favorable group	25 (75.8%)	58 (50.0%)	
Non-responder	21 (63.6%)	51 (44.0%)	
Intolerant	4 (12.1%)	7 (6.0%)	
Advanced fibrosis/cirrhosis (% of total)	16 (48.5%)	40/112 (35.7%)	0.18§
Baseline HCV viral load, $\log_{10}$ IU/mL, median (IQR)	6.46 (5.92–7.00)	6.47 (5.91–6.74)	0.44†
Number of pre-treatment visits, median (range)	2 (1–4)	1 (1–5)	<0.01*
CD4+ T cell count, cells/μL, median (IQR)	478 (362–763)	-	-
HIV VL (% of total)			
Undetectable/< 20 copies/mL	24/30 (80%)	-	-
< 1000 copies/mL	30/30(100%)		
ART regimen switch required before triple therapy (% of total)	17 (51.5%)	-	-

*Mann-Whitney U Test,

§Chi-Square,

θChi-square calculated by comparing favorable and non favorable groups,

†Student T-test

‡Fisher's Exact Test

IQR: interquartile range, VL: viral load, ART: antiretroviral therapy

Table 2

Univariable and multivariable analysis with SVR12 as the outcome

	OR univariable	p-value univariable	OR multivariable	p-value multivariable
Age, year	1.00 (0.97–1.04)	0.89		
Sex, female	1.02 (0.51–2.06)	0.95		
HIV infected	2.10 (0.96–4.63)	0.07	3.55 (1.44–8.75)	< 0.01
Race, African American	0.50 (0.22–1.12)	0.09	0.37 (0.15–0.92)	0.03
Response, non- responder/intolerant	0.55 (0.29–1.06)	0.07	0.46 (0.23–0.93)	0.03
Log HCV VL	0.91 (0.60–1.37)	0.65		
BMI, kg/m^2,	0.97 (0.90–1.04)	0.34		
Advanced fibrosis/cirrhosis	0.63 (0.32–1.25)	0.19		
Diabetes	0.62 (0.24–1.58)	0.31		
Treatment site, JHU	2.09 (0.72–6.10)	0.18		

OR: Odds ratio; Log HCV VL: logarithm of hepatitis C viral load; body mass index; JHU: John Hopkins University

Table 3

Discontinuations and side effects

	Co-infected (N = 33)	Mono-infected (N = 116)	p-value
Discontinuation due to side effects (% of total)			
-Telaprevir only	2 (6.0%)	1(0.9%)	0.12‡
-All three drugs	7 (21.2%)	15 (12.9%)	0.27‡
-Any drug discontinuation	8 (24.2%)*	16 (13.8%)	0.18‡
Hospitalization (% of total)			
-Number of patients	8 (24.2%)	18 (15.5%)	0.24§
-Number of events	9 (27.2%)	21 (18.1%)	0.25§
Emergency room visits (% of total)			
-Number of patients	6 (18.2%)	12 (10.3%)	0.22§
-Number of events	6 (18.2%)	16 (13.8%)	0.53§
Anemia (% of total)	29 (87.8%)	106 (91.4%)	0.54§
Severe anemia (% of total)	15 (45.5%)	68 (58.6%)	0.18§
Rash (% of total)	5 (15.2%)	40 (34.5%)	0.03§
Rectal symptoms (% of total)	4 (12.1%)	50 (43.1%)	<0.01§

*One co-infected patient initially discontinued telaprevir only. Two weeks later, he discontinued pegylated-interferon and ribavirin.

§Chi-Square,

‡Fisher's Exact Test

Table 4

Comparison between SVR12 rates in our study compared to clinical trials

	Phase III clinical trials	Current study	p-value
Naïves (n=35)	73.5%(11, 12)	51.4%	0.02§
Relapsers (n=23)	83%(13)	47.8%	0.01§
Non-responders/intolerants (n= 58)	44%(13)	34.5%	0.30§
Total (n=116)*	60.7%	42.2%	<0.01§

§Chi-Square

*Projection of a matched population for previous treatment response