



ABSTRACT

BACKGROUND: Failure to achieve an early virologic response (EVR), defined in clinical trials as a 100-fold decrease in HCV RNA by 12 weeks, predicts eventual non-response to HCV therapy. Most evidence on predictors of EVR in HIV/HCV-coinfected patients come from randomized clinical trials and may not reflect the experience in routine medical practice. We evaluated the EVR rate of Veterans Affairs (VA) HIV/HCV-coinfected patients receiving pegylated interferon (pegIFN) and ribavirin (RBV) in routine medical care.

METHODS: Patients were identified from the VA HIV Clinical Case Registry with a first VA prescription for pegIFN by 31 March 2005, a RBV prescription within 7 days of first pegIFN, a detectable quantitative HCV RNA VA result prior to HCV therapy and at least 9 weeks of pegIFN within 16 weeks of initiation. Patients had to have a follow-up HCV RNA test between 8 and 16 weeks of starting treatment. EVR was defined as an undetectable HCV RNA or a 100-fold decrease in HCV RNA by 16 weeks. We conducted univariate analyses to compare patient demographics, baseline lab results and other clinical characteristics. We then performed multiple logistic regression analyses that included those variables differing at P<0.1 between groups in univariate analyses.

RESULTS: Of 421 HIV/HCV-coinfected patients who began therapy with pegIFN and RBV, 303 patients (72%) received at least 9 weeks. Of these, 208 had at least one follow-up HCV RNA test between 8 and 16 weeks of starting therapy. 116 had an EVR ("responders") while 92 did not ("non-responders") for an EVR rate of 56% calculated from those on treatment and tested and 40% on an intention-to-treat basis. Of multiple factors examined, only race/ethnicity, baseline CD4 count, HCV RNA, HCV genotype, being on ARVs, starting on a recommended RBV dose and form of pegIFN (2A vs 2B) differed in univariate analyses. In multivariate analysis, higher baseline CD4 count, lower baseline HCV RNA HCV genotype and form of pegIFN, were significant independent predictors of an EVR.

CONCLUSION: Our results confirm that patients with lower baseline HCV RNA and with HCV genotype 2 or 3 are more likely to respond to HCV treatment. Initiating treatment when patients have higher CD4 counts may also increase response rates. Among patients with HCV genotype 1, treatment with pegIFN 2A compared with pegIFN 2B in conjunction with ribavirin may also increase the likelihood of a response. Our experience also serves as a reminder that response rates in routine medical practice may be substantially lower than that reported in clinical trials from both higher early discontinuation rates and lower efficacy rates.

Early Virologic Response to Pegylated Interferon and Ribavirin in a Large Cohort of HIV/HCV-Coinfected Veterans

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BACKGROUND

In the US, up to 300,000 persons are coinfecting with HIV and HCV. With survival of HIV-infected patients much improved through the use of ARVs for HIV, coinfection with HCV has emerged as a significant threat to the health and survival of persons with HIV. Several randomized clinical trials have shown that the combination of peginterferon (pegIFN) and ribavirin (RBV) can achieve a sustained HCV viral response in some HIV/HCV-coinfected patients.¹⁻³ These clinical trials have also demonstrated the potential clinical utility, particularly the negative predictive value, of early virologic response (EVR). The RIBAVIC¹ and APRICOT² trials had EVR rates of 67% and 71% respectively on an intention-to-treat basis for the pegIFN/RBV arms. Conversely, 99% and 98% of patients in the pegIFN/RBV arms who did *not* have an EVR did not achieve a sustained virologic response.

The large VA patient population provides the opportunity to determine the EVR rate of HIV/HCV-coinfected patients receiving pegIFN/RBV in routine medical care and to identify laboratory and clinical factors that predict an EVR.

METHODS

*Data from the VA Clinical Case Registry-HIV (CCR-HIV)

*To be in the study cohort, patients had to
1) Receive their first VA-prescribed pegIFN by 31 March 2005 - the first fill served as the patient's start date
2) Not receive pegIFN/RBV in a clinical trial
3) Have a VA prescription for RBV within +/- 7 days of their first VA-prescribed pegIFN
4) Have a detectable VA quantitative HCV RNA result closest to and within 1 year prior to the start date
5) Receive at least 9 weeks supply of pegIFN within 16 weeks after the start date
6) Have a follow-up qualitative or quantitative HCV RNA test between 8 and 16 weeks of the start date

On follow-up testing, "responders" had an EVR, defined as a 100 fold decrease in HCV RNA from baseline, a quantitative result below the limit of detection for the test (e.g. <50) or a negative result on a qualitative test. The remaining patients in the cohort comprise the "non-responder" control group.

METHODS (continued)

Potential predictors of EVR we analyzed from VA data

Demographics
• Age at start date, sex, race/ethnicity

Clinical characteristics at start date

• Weight
• CD4 count
• HIV viral load (HIV VL)
• ALT
• Nadir CD4 count at any time prior to start
• HCV genotype
• Hepatitis B infection - positive HBsAg or HBeAg
• Conditions from ICD9 codes (inpatient, outpatient, problem list)

-Cirrhosis
-ESLD (varices, encephalopathy or hepatorenal syndrome)
-Depression
-Diabetes
-Recent alcohol abuse (1 year prior)
-Recent hard drug use (opiates, cocaine or amphetamines)
-Recent socioeconomic instability
• On HIV ARVs at start date of pegIFN/RBV
-Types of ARVs: NRTIs, NNRTIs, PIs, AZT, ddI/d4T
• Previous HCV treatment with standard IFN
• Liver biopsy fibrosis score if biopsy within 3 years

Treatment characteristics

• Specialty of clinic initiating pegIFN/RBV (GI, ID or IM)
• Recommended or higher starting dose of pegIFN
-For 2A = 180 micrograms/week
-For 2B = at least 1.5 micrograms/kg/week or package insert
• Recommended or higher starting dose of RBV
-genotype 1/4 = 1000 mg/d if ≤ 75 kg
-genotype 1/4 = 1200 mg/d if > 75 kg
-genotype 2/3 = 800 mg/d
• Form of pegIFN (2A vs. 2B)
• Dose reduction in pegIFN or RBV
• Received opetin alfa/darboepetin alfa or G-CSF/GM-CSF
• Time to follow-up HCV RNA test
• Number of outpatient clinic visits prior to follow-up HCV test

Statistical Analysis

• Multivariate logistic regressions to predict an EVR using all candidate predictors with a P value < 0.1 in univariate analyses
• Backwards stepwise approach to find the most important predictors of starting HCV treatment

RESULTS

• 421 patients started pegIFN/RBV
• 303 patients received at least 9 weeks supply in first 16 weeks
• 208 had follow-up HCV RNA test between 8-16 weeks
• 116 responders with EVR
• 92 non-responders with no EVR

EVR rate of 56% for the 208 on treatment and tested
Extrapolating to all 303 patients on treatment (0.56 x 303 = 170) and adding in remainder of 421 patients who stopped treatment yields an EVR rate of 40% on intention to treat basis (170 / 421)

Table 1. EVR rate among the 208 study cohort for those characteristics with P<0.1 in univariate analyses

	#patients	EVR #/(%)	P value
Race/ethnicity			.004
Black, non-Hispanic	85	37 (44%)	
Other/unknown	42	31 (74%)	
White, non-Hispanic	81	48 (59%)	
CD4 count			.02
< 350 cells/mm3	45	18 (40%)	
≥ 350 cells/mm3	157	93 (59%)	
HCV RNA			.007
< 500,000 IU/ml	45	33 (73%)	
≥ 500,000 IU/ml	163	83 (51%)	
HCV genotype			<.0001
1	154	71 (46%)	
2	21	20 (95%)	
3	18	16 (89%)	
4	1	1 (100%)	
On HIV ARVs at start of pegIFN/RBV			.09
Yes	148	77 (52%)	
No	60	39 (65%)	
Started on recommended or higher RBV dose			.005
Yes	139	87 (63%)	
No	61	25 (41%)	
Form of pegIFN for course			.0006
2A	139	89 (64%)	
2B	67	26 (39%)	

No significant difference for age, sex, weight, HIV viral load, ALT, nadir CD4, Hepatitis B infection, cirrhosis, ESLD, depression, diabetes, recent alcohol abuse, recent hard drug use, recent SES instability, being on NRTIs, being on NNRTIs, being on PIs, being on AZT, being on ddI/d4T, previous IFN, liver biopsy fibrosis score, initiating clinic specialty, recommended or higher pegIFN dose, dose reduction in pegIFN, dose reduction in RBV, starting hematopoietic growth factors, time to follow-up HCV RNA test or number of clinic visits

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RESULTS

Table 2. Odds ratio for EVR from backwards stepwise multivariate regression

	OR (95% CI)	P value
CD4 count ≥ 350 cells/mm3	2.90 (1.26-6.63)	.01
HCV VL < 500,000 IU/ml	2.87 (1.23-6.66)	.01
HCV genotype		
1	1.00 (reference)	-
2/3	12.54 (3.57-43.98)	<.0001
Form of pegIFN		
2A	2.99 (1.43-6.26)	.004
2B	1.00 (reference)	-

CONCLUSIONS

• Four factors independently predict an EVR in HIV/HCV coinfecting patients treated with pegIFN/RBV:
1) having higher baseline CD4 count
2) having lower baseline HCV RNA
3) having HCV genotype 2 or 3
4) receipt of pegIFN 2A compared with pegIFN 2B

• Among patients with HCV genotype 1, we found a substantially higher EVR rate with pegIFN 2A than pegIFN 2B

• In analyses adjusted for multiple potential confounding factors, including HCV genotype, patients treated with pegIFN 2A were three times more likely to have an EVR than patients treated with pegIFN 2B

• Response rates in usual medical practice may be lower than those reported in clinical trials due to (1) higher drop-out rates and (2) lower efficacy rates - 28% of patients discontinued treatment by the end of 8 weeks while in the APRICOT trial², only 7% of patients discontinued by 12 weeks - our estimated EVR rate of 40% on an intention to treat basis is much lower than the roughly 70% reported in RIBAVIC¹ and APRICOT²

Limitations

• This is observational data and patients were not randomized between the two forms of pegIFN
• EVR rate appears to improve over time beyond that accounted for by the model, suggesting additional factors not included may influence the treatment response
• Cohort consists of US veterans in VA care, a population predominantly of men with a high level of comorbidities

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