Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

# Gaps in the achievement of effectiveness of HCV treatment in national VA practice

Jennifer R. Kramer[1,2,*], Fasiha Kanwal[4], Peter Richardson[1,2], Minghua Mei[1,2], Hashem B. El-Serag[1,2,3]

[1]*Houston VA Health Services Research and Development Center of Excellence, Michael E. DeBakey VA Medical Center, Houston, TX, United States;* [2]*Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, TX, United States;* [3]*Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, TX, United States;* [4]*John Cochran VA Medical Center, Department of Gastroenterology and Hepatology, St. Louis University School of Medicine, St. Louis, MO, United States*

**Background & Aims**: Antiviral treatment for hepatitis C virus (HCV) has high efficacy rates for achieving sustained viral response (SVR) in randomized controlled trials (RCTs) (40–80%); however, it can be lower in community-based practice settings. We wanted to determine the effectiveness of HCV treatment in Veterans Administration (VA) hospitals nationwide.

**Methods**: Using the nationwide VA HCV Clinical Case Registry (CCR), we examined a cohort of veterans who had HCV viremia between 2000 and 2005 and identified patients who received pegylated-interferon (PEG-INF) and ribavirin. The duration of treatment and proportion of patients completing treatment was calculated. The effectiveness of treatment was measured as the proportion of patients who achieved SVR (negative viremia at least 12 weeks after the end of treatment) in the entire cohort, and among patients who initiated and completed treatment.

**Results**: We identified 99,166 patients with HCV viremia. Of those, 11.6% received PEG-INF with ribavirin and 6.4% completed treatment. Contraindications were present in 57.2% of the patients that did not receive treatment. SVR was documented in 39.9% and 58.3% of patients who completed treatment; 23.6% and 50.6% of patients who initiated treatment; and 3.9% and 11.2% of the entire HCV cohort for genotype 1 or 4 and 2 or 3, respectively. Overall, only 3.5% of the entire HCV viremic cohort had a documented SVR.

**Conclusions**: Treatment effectiveness for HCV is low. In addition to fixed factors, such as race and virus genotype, the drop in effectiveness is due to low rates of antiviral treatment initiation and treatment completion.



Keywords: Hepatitis C virus; Antiviral therapy; Pegylated-interferon.
*Received 18 January 2011; received in revised form 2 May 2011; accepted 20 May 2011; available online 12 July 2011*

* Corresponding author. Address: 2002 Holcombe Blvd, (152) Houston, TX 77030, United States. Tel.: +1 713 794 8530; fax: +1 713 748 7359.
*E-mail addresses:* jkramer@bcm.edu, jennifer.r.kramer@va.gov (J.R. Kramer).

*Abbreviations:* HCV, hepatitis C virus; SVR, sustained viral response; RCTs, randomized controlled trials; VA, Veterans Administration; CCR, Clinical Case Registry; PEG-INF, pegylated-interferon; COPD, chronic obstructive pulmonary disease.

## Introduction

The major goal of treating patients with hepatitis C virus (HCV) is to achieve a sustained viral response (SVR). This has been associated with improvement in health-related quality of life; hepatic histological features; and even a reduction in long-term outcomes such as cirrhosis, hepatocellular carcinoma, and mortality [1–4]. Currently, the recommended antiviral treatment for HCV is a combination of pegylated-interferon (PEG-INF) and ribavirin. This combination has relatively high efficacy in achieving SVR, with rates in patients with genotype 1 from randomized controlled trials (RCTs) ranging from 41% to 52% [5–7].

Despite its high efficacy in clinical trials, the effectiveness of antiviral therapy in community-based practices is unclear. Clinical trials typically evaluate carefully selected participants with few or no contraindications; closely monitor patients; and have less ethnic and racial diversity than would be seen in most clinical practice settings [8]. A few studies in Europe, Canada, and Australia reported SVR rates among community-based patients that were comparable to those reported in clinical trials. However, these studies did not incorporate the uptake of treatment among all patients presenting to these setting. In addition, the treated patients had favorable features for achieving SVR (e.g., predominantly Caucasian with a high prevalence of HCV genotypes 2 or 3) [9–13]. On the other hand, studies of drug users and racial and ethnic minorities have shown substantially lower SVR rates in clinical practice settings [14,15]. No study has examined the overall effectiveness of care among all patients presenting with chronic HCV in a national healthcare system, while examining various steps in clinical care such as HCV genotype testing; contraindications to treatment; initiation of treatment; completion rates; and SVR.

It is important to understand the current state of treatment effectiveness so we can identify the gaps along the spectrum of care and the magnitude with which each of these gaps contributes to the drop in effectiveness. Such knowledge is essential for a rational and efficient approach to ensuring that more patients get access to treatment and ultimately, achieve SVR. In addition, with the anticipated release of newer, more efficacious therapies, addressing the gaps of effectiveness in clinical practice is very timely [16].

The Veterans Administration (VA) has the largest integrated healthcare system in the United States. It provides care for more

than 190,000 chronically infected HCV patients [17], which is approximately 6% of the estimated 3.2 million HCV-infected individuals in the United States [18]. In this study, we sought to determine the overall effectiveness of HCV treatment in the VA, focusing on receipt of treatment and SVR rate in all patients with chronic HCV diagnosed from 2000 to 2005. We determined contraindications in patients with chronic HCV infection who did not receive treatment. We also examined SVR stratified by HCV genotype and race, among patients who received treatment.

## Materials and methods

### *Data sources*

This study was approved by Baylor College of Medicine's Institutional Review Board and all procedures conform to the ethical guidelines of the 1975 Declaration of Helsinki. We used data from the VA HCV Clinical Case Registry (CCR), which contains health information for all known HCV-infected patients from 128 VA facilities nationwide. The CCR automatically identifies patients with positive HCV antibody tests as well as HCV-related ICD-9 codes. Data elements in the CCR include demographics; laboratory test results; outpatient and inpatient VA pharmacy data; and inpatient and outpatient diagnoses codes. These data are extracted all the way back to the mid 1990s through December 31, 2006. Additional details of the CCR data are published elsewhere [17]. We examined datasets obtained from the VA HCV CCR database for patients diagnosed in the VA between January 1, 2000 and January 1, 2005. For patients with missing race/ethnicity, we linked the CCR to the VA Patient Treatment File and the Outpatient Care File to identify additional race/ethnicity information.

### *Study population*

Patients had to have at least one positive HCV RNA test or HCV genotype test result; at least one visit at a VA facility; and an HCV index date between 2000 and 2005 to be included in the study cohort. The index date for HCV diagnosis reflected the date of the earliest positive HCV test or the first appearance of an ICD-9 code for HCV (070.51, 070.54, 070.41, 070.44, or V02.62). To be included in the treatment cohort, patients had to have at least two prescriptions for PEG-INF plus ribavirin with the first one occurring before September 30, 2005. This date was chosen based on the fact our CCR database ended on December 31, 2006 which ensured at least four months of follow-up time to determine SVR after a 48-week treatment course.

### *Definitions of study variables*

We identified sociodemographic characteristics such age at HCV index; gender; and race/ethnicity (African American, white, Hispanic, other, or unknown) for all patients in the study cohort. We also defined variables based on ICD-9 codes (see Supplementary material for definitions) indicative of conditions that constitute absolute, or relative contraindications to treatment, based on the American Association for the Study of Liver Disease guidelines [19]. We used diagnoses in the two years before or after the HCV index date to define these conditions. Absolute contraindications included major depressive illness; renal, heart, or lung transplant; autoimmune hepatitis; severe hypertension; severe heart failure; significant coronary artery disease; poorly controlled diabetes; and severe chronic obstructive pulmonary disease (COPD). Relative contraindications included drug or alcohol use; HIV co-infection; chronic renal disease; decompensated cirrhosis; liver transplant; and uncontrolled psychiatric disease.

### *Treatment outcomes*

All prescriptions for any interferon and/or ribavirin, including prescriptions dispensed as part of a clinical trial, were identified. Antiviral treatment initiation was defined by the date of the earliest prescription for PEG-INF released from any VA pharmacy. Duration of treatment was calculated from the earliest prescription date to the most recent prescription date plus days of supply. Prescriptions separated by time gaps of more than 45 days were not included as part of the treatment course. This definition has been used in previous studies [20]. Overlapping prescriptions were not considered. Treatment completion was defined as at least 48 weeks for genotypes 1 or 4 and at least 24 weeks for genotypes 2 or 3. Since patients in the clinical setting may have a shorter treatment course, we also considered patients who completed at least 80% of expected treatment duration to have completed therapy as done in a previous study (i.e. 38.4 weeks for genotypes 1 or 4 and 19.2 weeks for genotypes 2 or 3) [21]. The proportion of patients who discontinued treatment before 12 weeks was also examined. SVR was defined as all RNA tests being negative after treatment completion with one being recorded at least 12 weeks after treatment completion. Non-response to antiviral treatment was defined by all RNA tests during treatment being positive. Relapse was defined as any negative RNA test after treatment initiation, followed by a positive test at anytime. Undetermined response status was defined by the absence of an RNA test required to define SVR, non-response, or relapse.

### *Data analysis*

We calculated the proportion of patients with SVR out of those who initiated treatment, those who completed treatment, and the entire cohort (all veterans with chronic HCV diagnosed in FY2000–2005). Among patients who did not receive treatment, we calculated the proportion with the contraindications defined above. Among treated patients, we calculated the treatment response outcomes (SVR, non-response, relapse, and undetermined) stratified by viral genotype (1 or 4 *vs.* 2 or 3) and further stratified by patient race (African American, white, and Hispanic). For all proportions of treatment response outcomes, we calculated 95% confidence intervals and used Chi-square tests and *t*-tests to determine statistical significance when appropriate.

## Results

### *Study cohort*

There were 99,166 patients in the study cohort. Most were men (97%) with a mean age of 51.2 years (SD = 7.9). The racial/ethnicity composition of the cohort was 55.2% white, 29.9% African American, 3.5% Hispanic, 1.1% other, and 10.2% unknown. Almost half had HCV genotypes 1 or 4 (48.0%; of which approximately 1% were genotype 4), 12.2% had genotypes 2 or 3, and 39.8% were not tested for genotype. Only 11.6% of patients had a liver biopsy in the VA during the two years before and two years after their HCV index date. Approximately 16.5% (n = 16,381) had *any* prescription for interferon *or* ribavirin before September 30, 2005, while 83.5% (n = 82,785) had no prescription for any antiviral treatment. Patients who were not tested for genotype were significantly less likely to receive any antiviral treatment (3.3% *vs.* 25.2%, $p$ <0.0001). Untreated patients were significantly older (51.6 *vs.* 49.5 years old, $p$ <0.001 and more likely to be African American (26.0% *vs.* 16.7%, $p$ <0.001) than patients who received treatment. Approximately 43% of patients who did not receive antiviral treatment had none of the contraindications to treatment listed in Materials and methods and in Table 1. The remaining 57% had at least one contraindication, with 37.2% having at least one absolute contraindication and 38.3% having at least one relative contraindication. The most common contraindication was current use of drugs or alcohol (29.7%), followed by depressive illness (16.3%), COPD (11.5%), poorly controlled diabetes (8.1%), and significant coronary artery disease (7.5%) (Table 1). All contraindications were significantly different across racial/ethnic groups ($p$ <0.05). African Americans were less likely to have a diagnosis of depression, severe coronary artery disease, severe COPD, and decompensated cirrhosis than whites. However, African Americans were more likely to be diagnosed with severe hypertension, severe heart failure, poorly controlled diabetes, HIV, chronic renal disease, and uncontrolled psychiatric disease than whites. African Americans and Hispanics had