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The Effect of Interferon-Free Regimens on Disparities in Hepatitis C Treatment of US Veterans

Paul G. Barnett, PhD[1,2,], Vilija R. Joyce, MS[1], Jeanie Lo, MPH[1], Risha Gidwani, DrPH[1,2,3], Jeremy D. Goldhaber-Fiebert, PhD[4], Manisha Desai, PhD[5], Steven M. Asch, MD, MPH[2,3], Mark Holodniy, MD[6,7], Douglas K. Owens, MD[2,4]*

[1]*Health Economics Resource Center, VA Palo Alto Health Care System, Menlo Park, CA, USA;* [2]*VA Center for Innovation to Implementation, Menlo Park, CA, USA;* [3]*Division of Primary Care and Population Health, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA;* [4]*Stanford Health Policy, Centers for Health Policy and Primary Care and Outcomes Research, Stanford University, Stanford, CA, USA;* [5]*Quantitative Sciences Unit, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA;* [6]*Public Health Research Center, VA Palo Alto Health Care System, Palo Alto, CA, USA;* [7]*Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA*

ABSTRACT

Objectives: To determine whether implementation of interferon-free treatment for hepatitis C virus (HCV) reached groups less likely to benefit from earlier therapies, including patients with genotype 1 virus or contraindications to interferon treatment, and groups that faced treatment disparities: African Americans, patients with HIV co-infection, and those with drug use disorder. **Methods:** Electronic medical records of the US Veterans Health Administration (VHA) were used to characterize patients with chronic HCV infection and the treatments they received. Initiation of treatment in 206,544 patients with chronic HCV characterized by viral genotype, demographic characteristics, and comorbid medical and mental illness was studied using a competing events Cox regression over 6 years. **Results:** With the advent of interferon-free regimens, the proportion treated increased from 2.4% in 2010 to 18.1% in 2015, an absolute increase of 15.7%. Patients with genotype 1 virus, poor response to previous treatment, and liver disease had the greatest increase. Large absolute increases in the proportion treated were observed in patients with HIV co-infection (18.6%), alcohol use disorder (11.9%), and drug use disorder (12.6%) and in African American (13.7%) and Hispanic (13.5%) patients, groups that were less likely to receive interferon-containing treatment. The VHA spent $962 million on interferon-free treatments in 2015, 1.5% of its operating budget. **Conclusions:** The proportion of patients with HCV treated in VHA increased sevenfold. The VHA was successful in implementing interferon treatment in previously undertreated populations, and this may become the community standard of care.

Keywords: access to care, hepatitis C treatment, hepatitis C virus infection, veterans.

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Introduction

Interferon-free direct-acting antiviral regimens have become the primary treatment for chronic hepatitis C virus (HCV) infection [1–3]. Sustained virologic response (SVR) is achieved by 90% or more of those treated [4–6]. The regimens have replaced the combination of pegylated interferon α and ribavirin, which is only 70% effective for viral genotypes 2 and 3 and less than 50% effective for genotype 1 [7]. The direct-acting antiviral medications boceprevir and telaprevir improved the effectiveness of interferon therapy, but exacerbated side effects [8]. The new regimens are easier to administer, have a shorter treatment duration, and have fewer side effects than interferon-containing treatments [9].

The high cost of interferon-free treatment has limited its use throughout the world [9–11]. In the United States, private insurance [12,13], Medicaid programs [14–16], and the US Indian Health Service [13] restricted interferon-free treatment to reduce its budgetary impact. Treatment was also limited by the lack of insurance coverage associated with the most important risk factors for HCV infection, including mental illness, substance use disorders, and homelessness [12,17].

The total budgetary impact is large because of the high price of medication (>$80,000/patient) and the high prevalence of chronic HCV infection. Treatment of 2.3 million treatment-eligible patients in the United States over 5 years represents an annual cost of $136 billion (in 2014 US dollars) [18]. Total cost may approach $250 billion (also in 2014 US dollars), which is the annual US expenditure on all medications [12]. Although competition from newer treatments, negotiated discounts, and manufacturer rebates to health plans have lowered cost [3,12], concerns about affordability still limit treatment.

Conflicts of interest: No financial disclosures were reported by the authors of this article.

* *Address correspondence to:* Paul G. Barnett, Health Economics Resource Center, VA Palo Alto Health Care System, 795 Willow Road (152 MPD), Menlo Park, CA 94025.

E-mail: paul.barnett@va.gov

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These new treatments are reaching patients with genotype 1 infection [19] and those with HCV-HIV co-infection [20,21], but they have not eliminated the historical treatment disparity for African Americans [19,22–24] and patients with substance use disorder [24]. Initial reports were about orders and approvals for interferon-free therapies [24,25] or did not separate them from direct-acting antiviral regimens that included interferon [23]. More information is needed about medications dispensed to patients, especially to those in disadvantaged groups.

We examined the adoption of interferon-free treatment for HCV in the US Veterans Health Administration (VHA) to learn who received this therapy and whether the limitations of interferon-containing treatments have been overcome, including their lack of efficacy against genotype 1 virus, and their low rates of use in VHA patients who were African American [26–29] or Hispanic [26,30] and in patients with HCV-HIV co-infection [31], mental illness [26,28], or substance use disorder [26,28].

We hypothesized that interferon-free treatment was provided to persons for whom interferon treatment was especially ineffective, those with genotype 1 virus, and to persons in which interferon-containing treatment was contraindicated, including those with alcohol use disorder and depression. We also hypothesized that the expansion of treatment helped remove past disparities in the treatment of African American and Hispanic patients and in the treatment of patients with a diagnosis of HIV or drug use disorder.

Methods

Treatment initiation in patients with chronic HCV infection was studied in VHA over 6 years from 2010 to 2015 (unless otherwise noted, year refers to the federal fiscal year, which ends on September 30).

Cohort

All VHA patients with a positive test result for HCV RNA between 2000 and 2014 were considered for inclusion. We excluded those who died before 2010, those who were successfully treated before 2010, and those who did not use VHA services between 2010 and 2014. Those with a positive test result before 2010 entered the cohort on the first day of the study. Those with tests done after 2010 entered the cohort on the date of their first positive result.

Cohort members were characterized by a series of observations that ended with a change in treatment status, the end of each fiscal year, death, or the end of the study. Patients left the cohort at treatment initiation, but rejoined if they failed to achieve SVR or there was re-infection or relapse. Mortality risk continued regardless of treatment status. Race, ethnicity, sex, and HCV genotype were assumed to be time-invariant. All other covariates were specific to the time interval and included an indicator for year. Covariates were selected a priori to address study hypotheses or because they were previously associated with treatment or death.

Data Sources, Variables, and Data Set Structure

Laboratory test results, pharmacy records, inpatient and outpatient utilization, and patient demographic characteristics were obtained from the VHA Corporate Data Warehouse, supplemented by vital status data from Medicare and information on race from the Department of Defense.

HCV viral genotype was represented as an indicator variable for genotype 1, the genotype less effectively treated with interferon-containing regimens. SVR was defined with the definition used in clinical trials and for regulatory approval: no detectable serum HCV RNA in a test that was at least 12 weeks after conclusion of HCV treatment [32,33]. Treatment without SVR was regarded as a partial response if there was a 2 log 10 IU/ml decrease in serum HCV RNA relative to pretreatment levels, or as a null response if this improvement was not achieved.

Liver disease was characterized by Fibrosis-4 (FIB-4), an index based on three laboratory test results and age. We used standard categories of low, moderate, and high risk of cirrhosis (FIB-4 $<$ 1.45, between 1.45 and 3.25, and $>$3.25, respectively) [34,35]; liver enzyme and platelet results outside the range of plausible values were excluded [36]. Patients were considered HIV-positive from the date of a positive Western blot or a viral load test with detectable virus.

HCV treatments dispensed since 2000 were extracted from VHA pharmacy data. We defined HCV treatment episodes as starting when the first prescription was dispensed and as ending when the supply of the last prescription should have been exhausted. Gaps of 100 days defined a new treatment episode. The direct cost of HCV medications was obtained from the VHA Managerial Cost Accounting system and was adjusted to 2015 US dollars using the consumer price index for all goods.

Comorbidities were defined using diagnosis codes assigned in the preceding year. We used previously developed lists of *International Classification of Diseases, Ninth Revision*, diagnosis codes to define cirrhosis [37], decompensated cirrhosis [27], medical comorbidities [38], mental illness [39,40], substance use disorder [41], and medical contraindications to treatment with the combination of interferon and ribavirin [42,43].

The distances to the nearest VHA primary care clinic and the nearest VHA tertiary care facility were actual road miles calculated by the VHA Planning Systems Support Group on the basis of the residential address at the time of risk. Study procedures, waiver of consent, and waiver of authorization specified by the Health Insurance Portability and Accountability Act were approved by the Institutional Review Board of Stanford University.

Statistical Analysis

Cox regression was used to model the time to event, the start of HCV treatment. Although the event represents a benefit, not a harm, this article uses the standard nomenclature and refers to this as the "hazard" of starting treatment. The Cox technique estimates this hazard up until the time the observation is censored by death or the end of the study. Cohort members faced the hazard of starting two different treatments and the risk of dying before treatment could be initiated. Competing risks may bias parameters if the assumption of independent censoring is violated (e.g., if the reason for censoring is related to interferon-free treatment initiation) [44].

A stratified Cox model [45] estimated baseline hazard and parameter estimates for three competing events: initiation of interferon-containing treatment, initiation of interferon-free treatment, and death. The hazard at time t, for event k, for subject i, depended on covariates (X_{ik}) and can be expressed as follows:

$$\gamma_{ik}(t)=\gamma_{0k}(t)e^{X_{ik}\beta_k}.$$

The data set had one observation per time period per strata, with covariates specific to the strata [45]. There were up to three observations for each time period, depending on the events that were at risk. Baseline hazard (γ_{0k}) and parameters (β_k) were specific to each of the three events. Robust standard errors were estimated to account for correlation of observations over time from the same individual. We estimated 98 parameters for risk of treatment initiation. Using a threshold individual parameter of P less than 0.001, the studywide probability of a type 1 error is a P value of 0.09 (i.e., $1 - [1 - 0.001]^{98}$).

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