No Difference in Effectiveness of 8 vs 12 Weeks of Ledipasvir and Sofosbuvir for Treatment of Hepatitis C in Black Patients

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BACKGROUND & AIMS: **Treatment with the combination of ledipasvir and sofosbuvir for 12 weeks has been approved by the Food and Drug Administration for patients with genotype 1 hepatitis C virus (HCV) infection; some patients can be treated with an 8-week course. Guidelines recommend a 12-week treatment course for black patients, but studies have not compared the effectiveness of 8 vs 12 weeks in black patients who are otherwise eligible for an 8-week treatment regimen.**

METHODS: **We conducted an observational study of Kaiser Permanente Northern California members with HCV genotype 1 infection who were eligible for 8 weeks of treatment with ledipasvir and sofosbuvir (treatment-naïve, no cirrhosis, no HIV infection, level of HCV RNA <6 million IU/mL) and were treated for 8 or 12 weeks from October 2014 through December 2016. We used χ^2 analyses to compare sustained virologic response 12 weeks after the end of treatment (SVR12) among patients treated for 8 vs 12 weeks, and adjusted Poisson models to identify factors associated with receipt of 12 weeks of therapy among patients eligible for 8 weeks.**

RESULTS: **Of 2653 patients eligible for 8 weeks of treatment with ledipasvir and sofosbuvir, 1958 (73.8%) received 8 weeks of treatment and 695 (26.2%) received 12 weeks; the proportions of patients with SVR12 were 96.3% and 96.3%, respectively ($P = .94$). Among 435 black patients eligible for the 8-week treatment regimen, there was no difference in the proportions who achieved an SVR12 following 8 vs 12 weeks' treatment (95.6% vs 95.8%; $P = .90$). Male sex, higher transient elastography or FIB-4 scores, higher INR and level of bilirubin, lower level of albumin, obesity, diabetes, and ≥15 alcohol drinks consumed/week were independently associated with receiving 12 weeks of treatment among patients eligible for the 8-week treatment regimen, but were not associated with reduced SVR12 after 8 weeks of treatment.**

CONCLUSION: **In an observational study of patients who received ledipasvir and sofosbuvir treatment for HCV genotype 1 infection, we found that contrary to guidelines, 8-week and 12-week treatment regimens do not result in statistically significant differences in SVR12 in black patients. Patient characteristics were associated with receipt of 12-week regimens among patients eligible for 8 weeks, but were not associated with reduced SVR12 after 8 weeks. Shorter treatment courses might therefore be more widely used without compromising treatment effectiveness.**

Keywords: Direct-acting Antiviral Agents; Sustained Virologic Response; Race; Effectiveness.

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; IDSA, Infectious Diseases Society for America; KPNC, Kaiser Permanente Northern California; LDV/SOF, ledipasvir/sofosbuvir; RR, risk ratio; SVR, sustained virologic response.**

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The recent emergence of direct-acting antiviral agents for hepatitis C virus (HCV) infection, including the combination of ledipasvir and sofosbuvir (LDV/SOF), has dramatically increased the number of HCV-infected patients for whom treatment can be tolerated and successful.[1–3] Labeling for LDV/SOF by the Food and Drug Administration and clinical guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society for America (IDSA) recommend 12 weeks of treatment for genotype 1, treatment-naive patients and state that an 8-week course can be considered in those who also have no cirrhosis, are human immunodeficiency virus (HIV)–uninfected, and have HCV RNA <6 million IU/mL.[4,5] Recent revisions to the AASLD/IDSA guidelines further specify that black patients should not be treated with 8-week courses of LDV/SOF. However, the addition of race as a criterion for treatment duration is based on limited evidence and could exacerbate observed racial/ethnic disparities in HCV treatment initiation.[6]

The ideal evidence to support the AASLD/IDSA guidelines on race and treatment duration would be from a clinical trial in which patients who were eligible to receive 8 weeks were randomized to receive either 8 or 12 weeks. The ION-3 study randomized genotype 1, treatment-naive patients without cirrhosis to receive 8 or 12 weeks, but the study included few black patients and did not use HCV RNA <6 million IU/mL as an eligibility criterion for 8 weeks.[1,7] Thus, observational data are needed to approximate a randomized comparison of treatment effectiveness between black patients receiving 8 and 12 weeks of therapy. Prior observational studies have suggested reduced response for black patients receiving 8 weeks of therapy,[8–13] whereas a more recent pooled analysis of real-world cohorts found similar response by race for patients receiving 8 weeks.[14] However, because prior studies did not limit analyses to black patients otherwise eligible for 8 weeks (ie, treatment-naive, no cirrhosis, HIV-uninfected, and HCV RNA <6 million IU/mL), black patients receiving 8 and 12 weeks may have differed with respect to these key factors that affect treatment response. Furthermore, there may be other subgroups who are at higher risk of failure after 8 compared with 12 weeks of therapy, but prior studies have not restricted analyses of risk factors for treatment failure to those eligible for 8 weeks, thus limiting their clinical relevance. Finally, studies are needed to identify factors associated with the underuse of 8-week regimens, which could guide efforts to increase access to treatment.

We investigated outcomes of LDV/SOF for 8 compared with 12 weeks among HCV-infected patients within Kaiser Permanente Northern California (KPNC). Our primary objective was to compare the effectiveness of 8 and 12 weeks of LDV/SOF among patients eligible for 8 weeks, overall and by race/ethnicity and other subgroups. To evaluate potential underuse of 8-week regimens, we also evaluated factors associated with receipt of 12 weeks of LDV/SOF among patients eligible for 8 weeks.

Methods

Study Setting, Population, and Design

2KPNC is a large integrated healthcare system that provides comprehensive medical services to 4.1 million members, corresponding to approximately one-third of insured individuals in the surrounding population.[15] We identified all adult KPNC members with confirmed HCV infection, defined as a positive HCV RNA test or a known HCV genotype, who initiated HCV treatment with direct-acting antiviral agents from October 2014 (month of approval of LDV/SOF and when direct-acting antiviral agent use became more widespread at KPNC) through December 2016. Our study population for this analysis was restricted to patients who were eligible to receive 8 weeks of LDV/SOF and received either 8 or 12 weeks without ribavirin, with eligibility for 8 weeks defined as follows: genotype 1, treatment-naive, no cirrhosis, HIV-uninfected, and HCV RNA <6 million IU/mL. Among otherwise eligible patients, we excluded 10 patients treated with durations <8 weeks, 2 patients treated with durations between 8 and 12 weeks, and 10 patients treated with durations >12 weeks. Black patients were considered eligible for 8 weeks of therapy in this analysis because the AASLD/IDSA guidelines were not updated to include the race criterion until after our study period ended, and because we aimed to assess the appropriateness of the added race criterion. KPNC follows AASLD/IDSA guidelines for HCV treatment, but final decisions about treatment duration were at the discretion of the treating clinicians.

The institutional review board at KPNC approved this study with a waiver of written informed consent.

Study Measurements

We extracted data from the clinical and administrative databases that comprise KPNC's electronic health record, including age; sex; race/ethnicity; health plan enrollment periods; height and weight; pharmacy fills for HCV medications; medical center; laboratory tests and results (ie, HCV genotype, HCV RNA, platelets, aspartate aminotransferase, alanine transaminase, creatinine, international normalized ratio, bilirubin, and albumin); number of alcoholic drinks per week, which has been systematically collected at KPNC since 2013[16]; and inpatient and outpatient diagnoses of drug abuse (International Classification of Diseases Codes, version 9 [ICD-9]: 305.2–305.5; ICD-10: F11.xx–F14.xx, F16.xx, F18.xx–F19.xx, where xx includes .10, .90, .120), smoking/tobacco use (ICD-9: 305.1, V15, V65, 649, internal social history codes; ICD-10: F17.200,