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RESEARCH ARTICLE

Outcomes of Low Barrier Hepatitis C Treatment in High Risk Populations From Primary Care

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Abstract

Hepatitis C (HCV) can be treated in the primary care setting; however, most patients are referred to subspecialists. Marginalized populations may be refused treatment due to stigma or substance use. We aimed to treat HCV in these high-risk patients, and prevent a delay in time from diagnosis to the time of treatment and sustained virologic response (SVR), by utilizing a multidisciplinary treatment team in a primary care clinic. Outcomes assessed included achieving SVR at 3 months, time from diagnosis to treatment initiation, and liver fibrosis stage compared between cohorts with previous subspecialty referral and those treated initially from primary care. Among the 32 patients who initiated treatment, 29 (90.6%) completed the regimen and 27 (84.3%) had documented SVR. Patients treated in a primary care setting without prior referral had a significantly shorter median time from viral load testing to treatment initiation (161 days), compared to those who were previously referred (median time of 954 days). Aggregated fibrosis scores suggest those referred to subspecialists had significantly higher scores. We demonstrate successful HCV treatment in primary care achieving SVR, and a decrease in the median days between viral load and treatment initiation, with lower fibrosis scores.

Keywords: Hepatitis C, Primary care, Sustained virologic response

1. Introduction

Infection with Hepatitis C Virus (HCV) is among the primary causes of liver-related morbidity and mortality in the US,[1] and a leading reason for liver transplantation.[30] Transmission of HCV primarily occurs through exposure to bodily fluids, with injection drug use as the primary mode of transmission.[3] The development of direct-acting antiviral (DAA) medications has allowed for increased rates of sustained virologic response (SVR), with limited side effects, and shorter treatment courses,[2,4] and have shown to improve liver-related and all-cause mortality.[5] The advent of DAAs should contribute to achieving the Center for Disease Control's (CDC) goal of at least 85% HCV clearance in those infected by 2030.[6]

Globally there are an estimated 71 million people with chronic HCV infection[7] with an estimated 2.4 million people living with chronic HCV in the United States.[8] Rates of infection have increased in younger populations as a result of the opioid epidemic.[9,10] In 2018 there were over 50,000 estimated acute cases.[10] The HCV epidemic in the United States is primarily driven by marginalized populations including people who inject drugs (PWID),[11,12] those with alcohol use disorder,[2] those with over 20 lifetime sexual partners,[12] and those with no insurance or without private health insurance.[13] Previous qualitative studies have examined how social factors have influenced HCV prevention and treatment among people who inject drugs, and found that risk perception, uncertain knowledge, perceived lack of care continuity, dissatisfaction with provider interactions, and stigma are important determinants.[14-16] Access to treatment has been a recognized barrier in underserved populations including black[17] and Hispanic patients,[18]

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Medicaid beneficiaries,[17] and those with lower annual incomes.[17]

Substance use is not a contraindication to initiation of treatment with DAAs. Per the American Association for the Study of Liver Diseases (AASLD) guidelines, all patients with chronic HCV infection, except those with a short life expectancy, should be treated.[19] Traditionally, once a patient with chronic HCV has been identified in the primary care setting they are referred to a subspecialist for further care and treatment.[20] Despite the aforementioned recommendations, there is resistance to treating marginalized populations with chronic HCV, which may, in part, be derived from prior National Institutes of Health (NIH) guidelines which did not recommend treatment for PWID; however, these guidelines were later revised.[12,22] Providers may have concerns regarding follow-up or inability to achieve sustained virologic response (SVR) which may increase the risk of medication resistance.[23] This notion is not borne out in the literature and should not be a barrier to treatment.[5] HCV treatment among PWIDs has shown a treatment completion rate of nearly 97% and SVR of over 87%, success that is in line with the general population.[24] In fact, the concept of 'treatment as prevention' in high risk PWIDs has shown decreased HCV infections and re-infections.[25] Creating barriers to treatment access in vulnerable populations limits the ability to achieve the HCV elimination targets. Primary care clinicians have been shown to treat HCV as effectively as subspecialists,[26] but over 70% of primary care clinicians refer patients to subspecialists for treatment.[20,21] However, it has been shown subspecialists have limited success in achieving SVR particularly in marginalized populations due to both patient and provider factors, including perceived lack of continuity, perceptions of stigma, and even denial of treatment.[14-16]

A discernible care gap exists for patients who are not offered HCV treatment from their primary care provider, are subsequently referred to a subspecialty provider for treatment, and have been denied HCV treatment by the subspecialist. Here we describe successful treatment of HCV, including in patients who were denied treatment by subspecialists, by a multidisciplinary team at a primary care clinic, which primarily cares for marginalized inner-city populations. This paper aims to describe our experience in achieving SVR utilizing our multidisciplinary team in the aforementioned population, along with important clinical implications.

2. Methods

This project was carried out in an urban internal medicine clinic which is part of a large ten-hospital healthcare network. The Institutional Review Board reviewed the project protocol and determined it to be a non-research activity (i.e., Quality Improvement). Patients who attended the clinic and had positive HCV antibodies were reviewed from October 2018 to February 2021. To implement this project a HCV treatment protocol was established and the multidisciplinary team included prescribing resident and attending physician providers, a clinical pharmacist, social worker, and a medical assistant. All patients were seen by a resident. Patients with untreated active HCV infections were identified through screening. Their interest in treatment was assessed along with history of infection, ability to adhere to medication, vaccination history, and family history by the physicians. Education regarding harm reduction and treatment options was provided by the physicians, pharmacist and social worker. All care and follow-up was provided directly from the patient's primary care clinic. The lead physician provided a 1 h didactic training to the physicians prior to the study implementation. The outcome of SVR and cure rate, as well as time to treatment and liver fibrosis scores, were monitored.

At the patients' initial appointment, a comprehensive assessment and discussion was conducted. This included: (1) history of HCV infection, (2) history of related symptoms, (3) prior treatment, (4) substance use history, (5) hepatitis A and B vaccination history, (6) family history, (7) physical exam, (8) assessment of capability of medication adherence, (9) counseling and education regarding substance use, transmission, and harm reduction (10) a discussion regarding treatment options, and (11) a discussion of birth control if the patient was a female of childbearing age.

Initial labs were obtained within 90 days of treatment initiation including a HCV PCR, a complete blood count with differential, and a complete metabolic panel (CMP). Additional initial labs included PT/INR, FibroTest for fibrosis evaluation, hepatitis A total antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, HIV p24 antigen/antibody, HCV genotype. If there was suspicion for an acute HCV infection (defined as the first 6 months of an infection), a repeat HCV PCR was obtained after 2–3 months. If appropriate, a pregnancy test was performed.

Our clinical pharmacist completed a medication adherence assessment via the Modified Morisky Adherence Scale (Supplement 1 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1404&window=additional_files&context=jchimp)). Scores were not collated. A decision regarding treatment was made by the multidisciplinary team in consultation with the patient. If treatment was to be initiated, a treatment agreement was signed by the provider and patient (Supplement 2 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1404&window=additional_files&context=jchimp)). Counseling was provided regarding ongoing drug and alcohol use. If a patient had decompensated cirrhosis, concern for hepatocellular carcinoma or other liver diseases, hepatitis B or HIV co-infection, or prior history of HCV treatment, further treatment was deferred to a subspecialist and a referral was provided. One patient was excluded for decompensated cirrhosis and referred to hepatology for discussion of treatment. No other patients were excluded. Prior authorization was obtained with the assistance of the multidisciplinary team.

A checklist was created and used for data tracking (Supplement 3 (https://scholarlycommons.gbmc.org/cgi/editor.cgi?article=1404&window=additional_files&context=jchimp)). The multidisciplinary team performed treatment monitoring. Anti-viral medication was procured for insured patients through a specialty pharmacy via the insurance. Patients without insurance were still able to receive anti-viral medication by utilizing grant programs through pharmaceutical companies. The importance of adherence and harm reduction was reviewed at each checkpoint. At 4 weeks, patients had a follow-up phone or in-person visit to discuss adherence, side effects and new medications. Labs were performed at four weeks and at the end of therapy. At 3 months after treatment completion, patients had a phone call to check in and a HCV PCR was obtained. If the HCV PCR was not detectable it was indicative of SVR, and the patient was deemed cured.

Data was abstracted via the electronic medical record through chart reviews conducted by members of the project team as well as electronic data pulls completed by the data analysts on the team. Measures of interest included: (1) patient characteristics (age, race, gender, insurance, housing status, and substance use history), (2) date of diagnosis defined as the earliest positive HCV viral load test in the electronic medical record, (3) prior referral/visit to a subspecialist for treatment of HCV, (4) treatment initiation and completion, (5) virologic response at 12 weeks post-treatment, and (6) fibrosis stage at the time of evaluation for treatment in the primary care clinic (Table 1). Time from diagnosis to treatment initiation was calculated in calendar days.

Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Continuous variables were compared using a t-test or Mann–Whitney U test, as appropriate. Categorical data were analyzed using a chi-squared test or Fisher's exact test, as appropriate. Univariate logistic regression models were created to determine the odds ratio of patients having a previous referral to a subspecialist. SAS Enterprise Guide 7.15 HF3 (SAS Institute, Inc, Cary, NC) was used to conduct the statistical analysis.

3. Results

The primary aim of this paper is to describe our experience in treating HCV to achieve SVR in a primary care clinic, utilizing a multidisciplinary team to overcome treatment barriers in marginalized populations including those for whom subspecialists previously refused treatment.

At the time of writing, the overall analytic cohort was 43 patients. From this cohort, 32 were initiated on treatment, and the other eleven were not due to a variety of extrinsic factors (Fig. 1). Of the 32 patients who were treated, their current status is as follows: (1) 29 completed treatment, (2) 3 without treatment completion due to medication self-discontinuation or lost to follow-up. Of the 29 patients who have completed treatment, 27 had an HCV PCR obtained at 3 months and 100% of those achieved SVR, with the other 2 not having completed testing for confirmation of SVR (Fig. 1). Overall, 62.7% (n = 27) of the analytic cohort achieved SVR at 3 months, and 93% (n = 27) of those who completed treatment achieved SVR. Of the 27 patients who achieved SVR and cure, 12 (44.4%) had active alcohol use during treatment. Fifteen (55.6%) had a history of remote injection drug use, with 13 (48.2%) on medication assisted therapy during HCV treatment. One patient was uninsured, and one patient was unstably housed during treatment. There were no complications related to the treatment, and 0 patients had to cease treatment earlier than anticipated.

From the overall cohort of 43 patients, 22 were referred to a subspecialist regarding their HCV. Patient characteristics are shown in Table 1 according to if they were or were not referred to subspecialty care. The group of patients who were referred to subspecialty care had a higher percentage of Blacks (72.7% vs. 9.5%, $P < 0.0001$) and current alcohol use (63.6% vs 28.6%, $P = 0.02$) compared

Table 1. Patient characteristics.

Characteristic	Referred to Gastroenterology (n = 22)	Not referred to Gastroenterology (n = 22)	P-value
Mean age (SD), years	57.59 (10.41)	40.33 (10.1)	<0.0001
Race (%)			
White	6 (27.3)	18 (85.7)	<0.0001
Black	16 (72.7)	2 (9.5)	
Other	0	1 (4.8)	
Insurance			
Medicare	7 (31.8)	5 (23.8)	0.796
Medicaid	14 (63.6)	14 (66.7)	
Other	1 (4.6)	2 (9.5)	
Housing			
Stably Housed	19 (95)	16 (84.2)	0.6053
Unstably Housed	0	1 (5.3)	
Homeless Shelter	1 (5)	1 (5.3)	
Homeless Street	0	1 (5.3)	
Men (%)	13 (59.1)	10 (47.6)	0.451
Substance Use (%)			
Prior alcohol use	13 (65)	5 (33.3)	0.064
Current alcohol use	14 (63.6)	6 (28.6)	0.021
IVDU History (%)			
No Prior IVDU	7 (31.8)	4 (19.1)	0.466
Prior IVDU	10 (45.5)	9 (42.9)	
Current IVDU	5 (22.7)	8 (38.1)	
Other Drug (%)			
Current tobacco use	19 (86.4)	17 (81)	0.698
Maintained on medication assisted therapy (MAT)	5 (22.7)	13 (61.9)	0.009
Fibrosis stage, (%)			
0	9 (42.9)	12 (66.7)	0.009
1	0	4 (22.2)	
2	7 (33.3)	2 (11.1)	
3	1 (4.8)	0	
4	4 (19.1)	0	
Fibrosis stage, aggregated (%)			
0-1	9 (42.9)	16 (88.9)	0.006
2-4	12 (57.1)	2 (11.1)	
Treatment			
Time from HCV viral load test positive to treatment initiation in days (Interquartile range),	954 (252–1645)	161 (102–347)	0.017
Treatment initiated by primary care clinic (%)	18 (81.8)	14 (66.7)	0.310
Treatment completed	16 (88.9)	13 (92.9)	1.000
Sustained virologic response at 12 weeks (%)	15 (83.3)	12 (85.7)	1.000

to those who were not referred. There were no differences between the groups in health insurance, housing status, and intravenous drug use (current or prior). A higher percentage of patients who had not been previously referred were maintained on medication assisted treatment (61.9% vs. 22.7%, P = 0.009).

Among those referred, subspecialists offered treatment to 2 (9%), and initiated 0 patients on treatment. However, within this group, 18 (81.8%) were subsequently initiated on treatment by our primary care clinic with 16 patients completing treatment. SVR at three months was documented in 83.3% (n = 15) among this group who received treatment. Of the patients who were not offered treatment by the subspecialist (Fig. 2), reasons included: (1) active or recent alcohol use in 10 patients, (2) active or recent illicit drug use in 5 patients, and (3) both active or recent alcohol and illicit drug use in 4 patients. Additionally, one patient was not offered treatment due to lack of insurance. Two patients were not offered treatment due to the need for a biopsy, and further staging of cirrhosis.

Table 1 shows that the rate of treatment initiation by our primary care team, completion among those who were started on treatment, and SVR in those who completed treatment was similar between those who were referred to subspecialty and those who were not. However, significant differences in time to treatment and stage of fibrosis exist between the groups. The median time from HCV viral load positivity to treatment initiation is significantly longer (P = 0.017) in those referred to a subspecialist

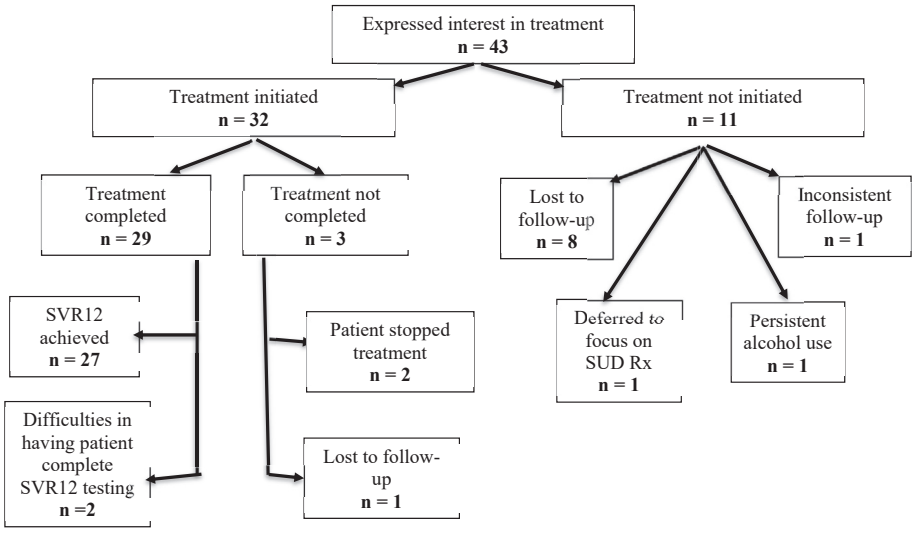

Fig. 1. Patient's interested in HCV treatment.

(954 days) compared to those not referred (161 days). Furthermore, the aggregate fibrosis stage is significantly worse (P = 0.006) in those who had a subspecialty referral compared to those who were not. Univariate logistic regression models found that patients who were referred to a subspecialist were less likely to present to with earlier stage (F0-1) of fibrosis (OR 0.09. P = 0.007), likely due to time delay.

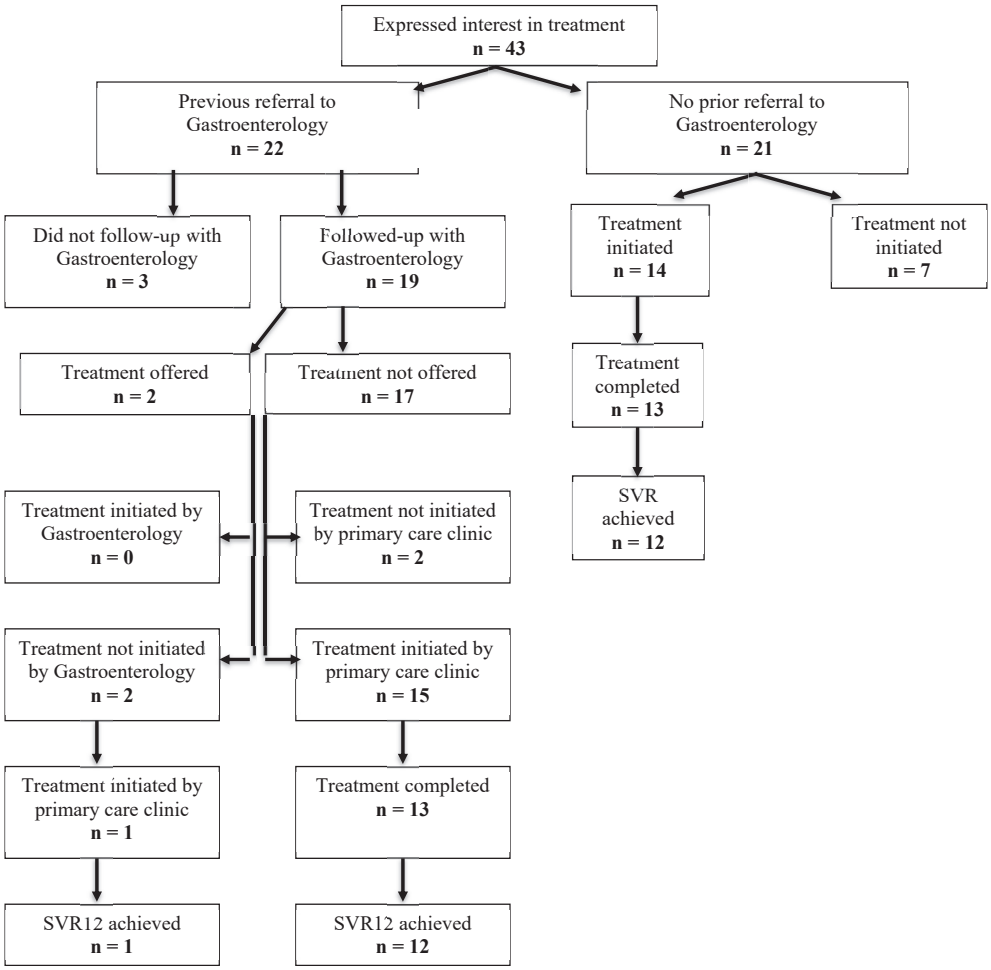

Fig. 2. SVR in patients who followed with Gastroenterology, no follow up with Gastroenterology, and those with no referral.

4. Limitations

The primary limitation of our study is a limited sample size, which can be attributed to application of the protocol in a single primary care office. We also do not have access to potential previous data outside of our health system, including possible earlier initial diagnosis of HCV.

5. Discussion

Treatment and cure of HCV can be successfully achieved in a primary care clinic, even in high-risk patients for whom treatment was not previously offered by subspecialists. Barriers to treatment in marginalized populations, including those with previous or ongoing substance use disorders, unstable housing, or lack of insurance should not prevent treatment from being offered. Our findings showing the overall SVR of 100% among patients who completed lab work 3 months after treatment completion is consistent with this assertion.

A clinical pharmacist mainly contributed to medication education, assessment of adherence, discussion of drug interactions; a social worker focused on addressing social determinants of health, harm reduction counseling, and discussion of substance use (if applicable). While immensely important to have a multidisciplinary team to allow for more comprehensive wrap around services and multiple touchpoints with patients, these services provided are not exclusive to these professional roles and could be replicated by less resources clinical teams.

Nearly half of the patients enrolled in our treatment protocol had previously sought treatment from a subspecialist. Despite AASLD recommendations that all patients with chronic HCV, other than those with a shortened life expectancy, should be treated,[19,27,28] only 2 patients (9.1%) were offered treatment and none were initiated. The majority of patients were refused due to current or recent substance use; however, this is not consistent with treatment guidelines. Patients within our primary care clinic with recent or active alcohol and illicit drug use were offered treatment, harm reduction, and referral to substance use treatment and support as appropriate with the majority of those started on treatment for HCV achieving SVR.

Patients who have unstable housing, or lack insurance, should not be precluded from treatment. Though providers may perceive these as concerns that could translate into difficulty with compliance or risk for reinfection, this apprehension is unfounded. We have successfully enrolled uninsured and unstably housed patients.

Literature demonstrates that in comparing HCV treatment between specialists, primary care physicians, and advanced practice providers, there was no significant difference in SVR among patients.[26] By treating established patients within a primary care setting, providers have direct knowledge of patients' medical and mental health history, medications, and social determinants of health. As a result of the established patient–provider relationship, improved patient-centered coordination of care, and less redundancy in lab work and provider visits can be achieved.

Furthermore, providers should aim to eliminate delays in care to avoid progression of HCV to cirrhosis. It is estimated to take 20 years from initial infection to cirrhosis.[29] However, the timing of the inciting event leading to infection is often unknown, with factors such as comorbidities, substance use, and co-infections affecting the timeline.[29] Given this, primary care providers should make an effort to treat patients with chronic HCV without delay. Our study exemplifies the setback subspecialty referral for HCV treatment may cause, which can lead to worsening of fibrosis stage during this lag time. Our results show a median time of 161 days from HCV viral load test to treatment initiation for patients without a referral, compared to a median time of 954 days to treatment for those who were referred. This is new to the literature to our knowledge, and the substantial time difference indicates a delay on the order of years when comparing groups. Additionally, in comparing aggregated fibrosis scores between groups, those with a subspecialist referral had a significantly higher score, which is also new to the literature. We cannot say with certainty the contribution to progressive liver disease that the time-lag to treatment may have had on fibrosis stage; however, we can speculate that a delay in time to treatment on the order of years may have contributed to disease progression and ultimately a higher score. While patients may suffer from disease progression during lag time, infected patients also have the potential to spread the virus to others while left untreated.

6. Conclusions

Our project demonstrates successful treatment of HCV in a primary care clinic. Patients who were denied treatment by subspecialists were successfully treated within our protocol, including those with active or prior substance use disorders. Denial of treatment based on biases, rather than guidelines, leads to a lag in treatment time, and may result in patient harm. Treatment in primary care can lead to

shorter time to SVR and decreased progression of liver fibrosis.

7. Implications

Treatment of HCV should occur within the primary care setting to prevent delays in treatment and cure. Significant delays in treatment initiation should be avoided to prevent complications of HCV, such as worsening of fibrosis or development of cirrhosis, and further spread. It is critical that both primary care practices and subspecialty practices offer HCV treatment to all patients without a shortened life expectancy, in an efficient manner, regardless of substance use, insurance status, housing stability, or other social determinants of health. These findings should lead to increased education and training for primary care clinicians on the treatment of HCV.

Conflicts of interest

None declared.

Sources of funding

None declared.

Uncited reference

21.

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