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Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program

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ABSTRACT

With the advent of the direct acting antivirals (DAA), or all oral HCV treatment regimens, there exists a great opportunity to provide HCV treatment to people who inject drugs (PWID) enrolled in an opioid treatment program (OTP). This retrospective study conducted in the context of routine clinical care explores the outcomes of HCV treatment with DAAs in PWID enrolled in an OTP. Our study showed treatment outcomes among our first 75 patients treated with DAAs were nearly equivalent to patients in the general population. Ninety-eight percent of patients completing treatment obtained a sustained virologic response, with 10 patients lost to follow-up. Ninety-nine percent of patients adhered to HCV treatment. Ongoing drug use occurred in 23% of patients, however this did not alter HCV treatment outcomes. Treating HCV infection with DAAs in PWID onsite in an OTP is feasible.

1. Introduction

Injection drug use is the main risk factor for Hepatitis C virus (HCV) transmission in industrialized countries.(Thursz & Fontanet, 2014) Studies of the prevalence of HCV in people who inject drugs (PWID) in 77 countries show that 60–80% of new cases of HCV infection occur among PWID.(Nelson et al., 2011) Most (60%) of existing infections are among former and current PWID.(Hajarizadeh, Grebely, & Dore, 2013) Of note, non-injection drug use is increasingly recognized as a risk factor for HCV, as is sharing of non-injection drug implements.(Martinez & Talal, 2008) In addition, intranasal use of illicit substances via drug-sniffing implements is a potential source of viral infection.(Aaron et al., 2008)

HCV is the most common cause of chronic liver disease and cirrhosis in the world with 20% of all patients with chronic HCV infection developing cirrhosis. Cirrhosis accounts for major morbidity and healthcare spending with about $2.5 billion of direct costs and $10.5 billion of indirect costs in the US·(Neff, D., & Schiff, 2011)

Though the burden of HCV disease is great among PWID, <10% of HCV-infected PWID have been treated for HCV.(Mehta et al., 2008) Some of the barriers to treating HCV-infected PWID include limited access to treatment, concerns for ongoing substance use, and uninsurance or underinsurance.(Grebely, Oser, Taylor, & Dore, 2013; Oramasionwu, Moore, & Toliver, 2014) Lack of treatment access for PWID include stigma in health settings, drug use status as a criterion for treatment exclusion requirements prior to treatment initiation, and incarceration in prisons and rehabilitation center where treatment is limited (Wolfe et al., 2015). Lastly, education around HCV disease among PWID is lacking, and certain educational programs may promote treatment access, particularly in a methadone treatment program (Marinho et al., 2016; Walley, White, Kushel, Song, & Tulsky, 2005).

Early guidelines from the National Institute of Health (NIH), American Association for the Study of Liver Disease (AASLD), and Infectious Disease Society of America (IDSA) excluded PWID from being considered for HCV therapy, citing concerns about adherence, side effects from the standard therapy (which at the time consisted of interferon-based treatment regimens) such as depression, and potential for HCV re-infection ("National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C,", 1997). However, these guidelines have been subsequently revised, and current international guidelines from AASLD and IDSA, among other organizations, recommend HCV treatment for all persons including PWID (AASLD, 2016; Grebely et al., 2015). According to the most recent AASLD/IDSA/IAS guidelines released in July 2016, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by liver transplantation, or by other directed therapy. Scale-up of treatment for PWID could improve individual health and achieve the goal of eliminating HCV transmission among this high-risk and vulnerable group (Doyle et al., 2015).

Studies have shown that current or former PWID with HCV infection can be successfully treated for HCV on-site in an opioid treatment

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program (OTP) rather than being referred off-site to a liver or infectious diseases clinic. OTPs combine behavioral therapy and medications (i.e., methadone, buprenorphine) to treat substance use disorders in a biopsychosocial framework. Most OTPs are staffed by an inter-professional team and some OTPs provide onsite medical and psychiatric care. This model of care delivery improves access to HCV treatment and minimizes drop off along the HCV treatment cascade (Lalezari et al., 2015; Woodrell et al., 2015). In one study, pegylated interferon in combination with ribavirin delivered in a methadone maintenance program produced treatment rates nearly equivalent to published HCV historical controls despite having a high prevalence of ongoing drug use and psychiatric comorbidity (Litwin et al., 2009).

On-site HCV treatment with interferon-based regimens has been demonstrated to be feasible within an OTP·(Harris, Arnsten, & Litwin, 2010; Litwin et al., 2009; Stein et al., 2012). The Direct Acting Antivirals (DAAs), however, present a unique opportunity for on-site treatment due to decreased treatment duration, more favorable side effect profile, and marked increase in efficacy for the outcome of sustained virologic response (SVR) (Ara & Paul, 2015; Zuccaro et al., 2016). These unique features of DAAs, compared with interferon-based treatment regimens, are attractive when considering treatment of patients with opioid use disorder who might not have previously been considered treatment candidates and in whom viral clearance may make a real impact on the spread of disease.

Recent literature recommends the use of DAAs in HCV-infected patients on opioid agonist therapy (OAT) (Dore et al., 2016; Harris et al., 2010). One study examined two different regimens, ombitasvir/paritaprevir/ritonavir and dasabuvir, plus ribavirin in treating HCV genotype-1 infected patients on methadone or buprenorphine as an interferon-free regimen (Lalezari et al., 2015). The study suggested that an all-oral regimen may provide an effective alternative to interferon-based therapies for HCV infected patients with concurrent intravenous drug use. The study also emphasized that injection drug use should not be treated as a barrier to HCV treatment, though the study was limited by small sample size, and selected patient population with only patients on stable opioid replacement therapy enrolled, excluding those with active drug use. The recent C-Edge Co-Star Study, which was the first ever study with DAAs including PWID on OAT, determined the efficacy of elbasvir/grazoprevir fixed dose combination for 12 weeks in HCV infected PWID, supporting treatment for HCV among subjects receiving OAT (Doyle et al., 2015).

Since the shift to all oral DAAs for the treatment of chronic HCV, there is scant literature, to our knowledge, with regard to on-site DAA treatment for HCV-infected patients within an OTP. As such, the purpose of this quality improvement study is to examine the feasibility of implementing onsite DAA treatment for HCV infected patients into routine clinical care at an OTP.

2. Materials and methods

The APT Foundation is a not-for-profit addiction treatment program which focuses on access to care and management of co-morbid psychiatric and medical conditions among patients with substance use disorders. The vast majority of patients enrolled in services at the APT Foundation have a primary opioid use disorder. One of the services the APT Foundation provides is a comprehensive OTP which offers opioid agonist treatment (methadone or buprenorphine), intensive outpatient services, residential treatment, onsite psychiatric care and onsite primary medical care within the Central Medical Unit (CMU). All patients presenting to the APT Foundation OTP undergo medical and psychiatric evaluation by physicians boarded in Internal Medicine, Family Medicine, Psychiatry, Addiction Medicine or Addiction Psychiatry. HCV and HIV antibody screening are offered to all patients who present for treatment in an opt-out fashion. Those who screen positive for HCV antibody are offered testing with confirmatory HCV RNA and genotype testing, further biochemical work-up, and exploration of treatment options. Patients who are aware of HCV status opt-out of initial testing at intake.

Patients diagnosed with chronic HCV infection (evidenced by the presence of HCV RNA) are offered further workup and treatment for HCV. At the initial visit we provide HCV education, review risk factors and modes of transmission, discuss the natural history of HCV infection, and if desired by the patient, we involve the patient's family in the treatment evaluation process, and offer screening to contacts who might be at-risk. For the patients undergoing treatment with DAAs, we arrange frequent weekly or bi-weekly visits and coordinate care with APT Foundation's social workers and psychiatrists, if applicable. Our on-site treatment program consists of an integrated primary care team who perform HCV screening, education, and treatment. Two of the primary physicians at the practice have interest and experience treating HCV (JLB and JMT) and provide patient management and oversight to the program. Patients attend clinic every other week for follow-up, and have blood drawn if necessary. Utilizing a specialty pharmacy, DAAs are dispensed to the patient in office in blister-packed 2 week aliquots. Alongside this model, patients are concurrently receiving substance use treatment at the OTP daily, weekly, or monthly, depending on the patient's individualized treatment plan.

We collect information on patients undergoing treatment as part of routine clinical care. Here we report on the first 75 consecutive patients enrolled in CMU's HCV treatment program with DAAs. Patient information was de-identified and included, age, race, gender, HCV RNA viral load measured by COBAS® AmpliPrep/COBAS® Taqman® HCV Test v2.0., HCV genotype measured by line probe assay (LiPA), type and dose of opioid agonist therapy (methadone or buprenorphine), fibrosis score, and/or calculated AST to platelet ratio index (APRI), presence of cirrhosis, HCV DAA regimen and duration, psychiatric and medical comorbidities, relapse to or ongoing drug use during HCV treatment measured via self-report and/or urine toxicology testing, incarceration during HCV treatment, OTP treatment adherence (measured via self-report, clinic dosing documentation, clinical observation and/or collateral information from OTP team members), self-reported HCV treatment adherence (measured using a composite variable of clinic attendance, on time medication pick-up, and self-report of compliance with the treatment plan), rapid virologic response (RVR), which is an undetectable HCV-RNA 4 weeks after starting treatment, end of treatment virologic response (EOTR), or an undetectable HCV-RNA at the end of treatment, and sustained virologic response (SVR), which is defined as an undetectable HCV-RNA, 12 weeks after completion of treatment. We evaluated urine drug analyses (UDA) periodically assessing for the presence of unexpected substances using a 15-drug panel screening.

DAA treatment regimen and duration was guided based on genotype, presence of cirrhosis, and viral load. Patients with genotype 1a or 1b HCV infection were treated with fixed-dose ledipasvir/sofosbuvir for a total of 8, 12, or 24 weeks. Those who were treatment naïve, without evidence of cirrhosis, and had a viral load <6 million IU/mL were treated for 8 weeks; those where were treatment naïve or treatment experienced and without evidence of cirrhosis, with a viral load of >6million IU/mL were treated for 12 weeks; while those treated for 24 weeks were treatment experienced and had evidence of cirrhosis. Patients with genotype 2 infection were treated with a regimen of sofosbuvir plus weight-based ribavirin given for 12 or 24 weeks, for those without cirrhosis and with cirrhosis, respectively. Patients with genotype 3 infection were treated with sofosbuvir plus weight-based ribavirin for 12 or 24 weeks, for those without cirrhosis and with cirrhosis, respectively.

3. Results

In 2015, our OTP reported treating 4326 unique patients with methadone and 720 patients with buprenorphine. There were on-site 7312 medical visits to our primary care unit, with 585 of those visits documented as a visit for HCV evaluation. Clinical data at our OTP suggests

that we have a roughly 60% sero-prevalence rate for HCV antibody positivity. Not all patients enrolled in our OTP receive onsite primary care and others who receive primary care at our site may seek offsite referral for specialty care. Additionally, although we screen for HCV at treatment enrollment, some patients are lost to follow up, choose not to undergo further work up or treatment, or are counseled to concentrate on recovery prior to undergoing further workup and treatment of HCV. We evaluated treatment data for the first 75 consecutive patients with chronic HCV infection who opted to undergo further evaluation and enroll in on-site treatment with DAAs between mid-2013 until mid-2015.

The distribution of ages was the following: <4% <25 years, 18% between 25 and 35 years, 35% between 36 and 45 years, and 43% above age 45. Seventy-six percent of our patients were white, 16% were Hispanic, and 8% were Black. Twenty-seven percent of patients treated were female, while the majority treated were males (73%). The majority of treated patients had genotype 1 infection (80%), followed by genotype 2 and 3 (9.3%, 9.3% respectively), and 1.3% with genotype 4. The majority of patients on treatment had psychiatric comorbidities (76%) which included major depression, anxiety disorder, and bipolar disorder; 53% had a documented medical comorbidity, such as COPD or diabetes. Seventeen percent of the patients had cirrhosis, in contrast to 83% of patients without clinical signs of cirrhosis. Twenty-five percent of patients had HCV RNA quantitative load <1 million IU/mL, 64% had between 1 and 6 million IU/mL, and 11% had a viral load >6 million IU/mL. Sixty-eight percent of patients who were enrolled in our OTP were prescribed methadone at a median dose of 73.8 mg, 19% percent were prescribed buprenorphine at a median dose of 19.27 mg, and 13% of patients were not receiving a pharmacological opioid agonist treatment. Of these 13% not receiving opioid agonist treatment, all were receiving counseling (Table 2). Most patients received the regimen ledipasvir/sofosbuvir for either 8 or 12 weeks, 36% and 36% respectively. Sofosbuvir with weight-based ribavirin was given for 12 or 24 weeks, with 8% of patients receiving each regimen. Of note, none of the patients were treated with the new pangenotypic regimen, sofosbuvir/velpatasvir, as this data was collected prior to FDA approval of this medication. None of the patients treated were co-infected with HIV.

Eighty-three percent of patients achieved a RVR. Notably thirteen patients did have an HCV viral load <15 IU/mL, but were still detectable via the COBAS® AmpliPrep/COBAS® Taqman® HCV Test v2.0. One hundred percent of eligible patients achieved an EOTR, however EOTR data was not collected on 4 patients. Among those patients who completed treatment and follow up, 98% achieved SVR. When considering all patients who entered treatment, 85% achieved an SVR (64/75). Ten patients were lost to follow up. Of the 10 patients who were lost to follow-up, 5 out of the 10 had ongoing drug use per their last clinic visit note and UDA. We had one patient who developed virologic relapse of HCV, which was in the context of ongoing drug use, however we were unable to differentiate if this was due to re-infection or virologic relapse, as his repeated genotype (1a) was the same as his baseline.

Approximately 23% of patients had ongoing illicit drug use, defined by self-report or as >1 UDA positive for an illicit substance, during or after completion of HCV treatment. Of note, the most common illicit substance used was heroin, followed by cocaine use, and we did not differentiate which route of administration of illicit drugs the patients engaged in (i.e. intranasal, intravenous, etc.). HCV treatment adherence was measured at 99%. OTP treatment adherence was 99%. Thirteen percent of patients were incarcerated during HCV treatment, with all being able to successfully complete treatment in collaboration with the Department of Correction's medical staff.

4. Discussion

This study describes the use of DAA treatment for HCV in PWID delivered on-site in an OTP. Our study, which strictly focused on patients enrolled in an OTP, showed treatment outcomes that were nearly equivalent to patients in the general population. In our study, 98% of patients who completed treatment obtained SVR, while 10 patients were lost to follow-up and 1 patient discontinued treatment due to side effects. In the intention-to-treat category, 85% of patients achieved SVR. Adherence to HCV treatment measured by clinical parameters in the setting of an OTP was 99%. Ongoing drug use during and after treatment occurred in 23% of patients, however this did not prove to alter HCV treatment outcomes.

In comparison to other studies with the use of DAAs, our study demonstrates comparable SVR outcomes. In the ALLY-3 Phase III study evaluating the 12-week regimen of daclatasvir plus sofosbuvir in genotype 3, 99% had SVR at post-treatment week 12 (D. R. Nelson et al., 2015). It is noteworthy that many studies did not include PWID, as this was exclusionary criteria. The C-EDGE CO-STAR study was pivotal in that it was the first to demonstrate that treatment of patients on OAT with DAAs for 12 weeks shows high medication adherence and efficacy, supporting treating HCV in those on OAT (Dore et al., 2015). In a randomized trial evaluating DAA therapy in those on OAT, patients treated with elbasvir-grazoprevir had high rates of SVR12, regardless of ongoing drug use thus, supporting the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving OAT (Dore et al., 2016). Our results demonstrate that PWID, including those who have history of or active substance use disorders, can be treated for HCV with outcomes equal to that of the general population.

Our study shows that treating patients with SUDs and concurrent HCV infection within an OTP has significant benefits, especially from a public health point of view. Ninety-six percent of patients were adherent to therapy despite 23% of our sample continuing to use illicit drugs. This suggests that the consistent engagement of patients in our OTP can facilitate effective adherence concurrently to HCV treatment.

There were several limitations of our study. The study is from a single institution, is retrospective, has a small sample size, and is limited to data collected within the context of routine clinical care. There is also selection bias given the small percentage of patients treated compared to the number of patients that present to our facility for treatment of SUDs. There are additional limitations in the population sample treated, excluding patients with decompensated cirrhosis. It is important to note that our treatment model may not be as easily replicated in other settings due to differences in Medicaid coverage of DAAs. In the State of Connecticut, there are no restrictions listed for DAA approval on the State Medicaid Coverage Policies for Harvoni and Viekira Pak. Our program, which was integrated into primary care practice, used billing codes commensurate for the level of activity within primary care practice for reimbursement purposes. In comparison, a majority of other states have to abide by strict limitations such as having advanced fibrosis, HIV, and complete abstinence from illicit drugs for a pre-specified duration prior to initiating treatment, even requiring submission of UDAs prior to medication approval (Center for Evidence-based Policy, 2015). Therefore, these potential barriers were not something we encountered, and as such facilitated our ability to obtain prior authorization for the DAAs in nearly all of our patients. Updated AASLD/IDSA HCV treatment guidelines in July 2016 conclude: “there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy, and these requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy” (AASLD, 2016).

5. Conclusion

The DAAs in combination with on-site HCV treatment delivery in an OTP offer an integrated approach to the care and education of all patients who have history of SUDs. With the affirmative guidance statement of the AASLD of treating all people who have an elevated risk of onward transmission of HCV, PWID should be prioritized for treatment. Lowering rates of HCV in this population would be furthered by early

detection, intervention, and maintenance in an OTP. Scaling up of HCV treatment in PWID is necessary to positively impact the HCV epidemic in the United States and globally. This may have many future implications, primarily in removing the stigma attached to treating HCV in PWID. Data on the use and feasibility of DAA-based therapies among PWID is limited and warrants further investigation. Future studies should investigate different protocols of HCV treatment for patients enrolled in an OTP, and how treatment may impact their recovery process.

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Appendix A

Table 1
Demographic and clinical characteristics of patients at baseline, $N = 75$.

Characteristic	n (%)
Age	
<25	3 (4%)
25–35	14 (18%)
36–45	26 (35%)
>45	32 (43%)
Race	
White	57 (76%)
Black	6 (8%)
Hispanic	12 (16%)
Gender	
Female	20 (27%)
Male	55 (73%)
Genotype	
1	60 (80%)
2	7 (9.3%)
3	7 (9.3%)
4	1 (1.3%)
Comorbidities	
Psychiatric	57 (76%)
Medical	40 (53%)
Cirrhosis	
Yes	13 (17%)
No	62 (83%)
Viral PCR (IU/mL)	
<1,000,000	19 (25%)
1,000,000–6,000,000	48 (64%)
>6,000,000	8 (11%)
Opioid agonist	
Methadone	51 (68%)
Buprenorphine	14 (19%)
None	10 (13%)

Table 2
HCV Treatment regimen and outcomes, $N = 75$.

Variable	n (%)
Regimen	
Ledipasvir/sofosbuvir × 8 weeks	27 (36%)
Ledipasvir/sofosbuvir × 12 weeks	27 (36%)
Ledipasvir/sofosbuvir ×24 weeks	3 (4%)
Sofosbuvir/ribavirin × 12 weeks	6 (8%
Sofosbuvir/ribavirin × 24 weeks	6 (8%)
Sofosbuvir/Daclatasvir × 12–24 weeks	3 (4%)
Ombitasvir/paritaprevir/ritonavir + ribavirin × 12 weeks	1 (1.3)
Elbasvir/grazoprevir × 12 weeks	2 (2.7)
HCV outcomes	
RVR	62 (83%)
EOTR[a]	71/71 (100%)
SVR[b]	64/65 (98%)
Virologic relapse	1 (1%)
Substance use outcomes	
Ongoing drug use	17 (23%)
HCV treatment adherence	74 (99%)
OTP treatment adherence	74 (99%)
Incarceration during treatment	10 (13%)

[a] EOTR data was collected on 71 patients.
[b] SVR data not available on 10 patients lost to follow-up.

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