Spring 2016

Effect of Early Intervention with Combination Ledipasvir/ Sofosbuvir (Harvoni®) in Patients with Chronic Hepatitis C Virus Infection

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ABSTRACT

Introduction: In the United States, hepatitis C virus (HCV) is the most common bloodborne infection with an estimated prevalence of 3.2 million people. Although new cases of HCV have been declining since the 1980s there are still approximately 17,000 new cases diagnosed each year. HCV infection has become the most frequent reason for hepatologic consultation and the single leading indication for hepatic transplantation, accounting for 30% of such procedures in the United States. Until late 2013, the treatment of choice for chronic HCV was pegylated interferon-α plus ribavirin, which achieved a cure rate of 54%-63%. Recently, novel antiviral drugs that specifically target HCV have provided better options in HCV treatment. Use of ledipasvir, an HCV NS5A replication complex inhibitor in combination with sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor, in patients with chronic HCV, achieves high rates of sustained viral response (SVR) with just 12-weeks of treatment.

Methods: This prospective cohort study represents a collaboration between James Madison University and the Harrisonburg-Rockingham Free Clinic. This is a pilot study including only 10 patients. Patients received a five fixed-dose combination of ledipasvir-sofosbuvir (90mg/400mg), or Harvoni®, for a total of 12-weeks. During this time various physiologic parameters were measured to monitor ledipasvir-sofosbuvir efficacy including liver function tests, complete blood counts, and HCV-RNA levels.

Results: Patients experienced statistically significant decreases in ALT/AST values just 30 days after initiating treatment with ledipasvir-sofosbuvir and maintained this response throughout duration of therapy. Additionally, HCV RNA levels declined to undetectable levels in 60% of patients within 8 weeks of therapy.

Discussion: This study is a work in progress, and patients will continue to be monitored for response to ledipasvir-sofosbuvir for at least 6 months after completions of HCV treatment. Improvements to consider would be improving study power by increasing the number of study participants and expand scope of research to include quality of life assessments. The results of this study are congruent with other published research on the efficacy of 12-weeks of ledipasvir-sofosbuvir However, this study has not yet reached an endpoint to evaluate the rate of HCV relapse associated with ledipasvir-sofosbuvir treatment.

INTRODUCTION:

Epidemiology of Viral Hepatitis C Infection

Chronic Hepatitis C virus (HCV) infection is one of the most common chronic liver diseases and results in thousands of deaths each year.[1] There are six major genotypes (1-6) of HCV; with genotype 1 being the most common and accounting for 70 to 80% of the hepatitis C cases in the United States.[2] Globally, areas with the highest prevalence of HCV include Central and East Asia, North Africa, and The Middle East. The Asia Pacific, Latin America, and North America are among the places that were noted to have the least prevalence of HCV.[1]

Hepatitis C can be separated into acute and chronic; however, 75% of patients with acute hepatitis C develop the chronic infection.[2] The Centers of Disease Control and Prevention (CDC) estimate 2.7 million people in the United States living with chronic hepatitis C virus.[3] The CDC also states the infection is most prevalent among those born in 1945 to 1965, with the majority of this population being infected during the 1970s and 1980s which were when rates of HCV were the highest.[3]

Table 1[3] is derived from statistics updated in the current year by the CDC showing the risk of developing chronic HCV, chronic liver disease, cirrhosis, and chronic infection resulting in death due to hepatitis C virus.

Table 1: Of every 100 persons infected with HCV, approximately	
75–85	Will go on to develop chronic infection
60–70	Will go on to develop chronic liver disease
5–20	Will go on to develop cirrhosis over a period of 20–30 years
1–5	Will die from the consequences of chronic infection (liver cancer or cirrhosis)
75–85	Will go on to develop chronic infection
Centers of Disease Control and Prevention: *Updated October 2015*	

Hepatitis C viral infection is primarily transmitted through large or repeated percutaneous exposures to infected blood such as injection drug use, receiving donated blood, blood products or organs, needlestick injuries in healthcare settings and birth to an HCV-infected mother.[1,3] HCV can also be spread through sexual intercourse with an HCV-infected person, sharing razors or toothbrushes, or other health care procedures that involve invasive techniques. Currently the most common means of transmission in the US is injection drug use with the sharing of needles.[3,4] This accounts for approximately one third of young aged injection drug users (IDUs) that are HCV-infected and approximately 70-90% of older and former IDUs who also have hepatitis C virus.[1,3]

Etiology

Risk factors for infection with Hepatitis C Virus (HCV) in the United States include intravenous drug use, blood transfusion sex with an intravenous drug user, incarceration for more than three days, religious scarification, blood-carrying fomite exposure, piercings, and immunoglobulin injection.[4] Overall, intravenous drug use is the most significant risk factor for HCV infection and also the most efficient means of transmission;[3,4] According to a global systematic review of 77 countries intravenous drug use accounts for 60-80% of HCV transmission, with China, USA, and Russia having the largest populations at 1.6 million, 1.5 million, and 1.3 million respectively.[5]

Approximately 80% of patients in the United States with chronic HCV were born between 1945 and 1965[3,6], however age of infection appears to be decreasing, with the largest increases occurring east of the Mississippi River.[7] Data from the National Notifiable Disease Surveillance System for Kentucky, Tennessee, Virginia, and West Virginia for the period between 2006 and 2012 confirms a total of 1,377 cases of acute HCV infection reported with 44.8% of these cases among persons aged ≤ 30 years old.[7] Approximately 70% of these individuals reported intravenous drug use as the principal risk factor,[7] suggesting a correlation between increased intravenous drug use and decreasing age of HCV infection.

Pathophysiology

Hepatitis C virus (HCV) was first cloned in 1989 and identified as the main causative agent of a disease previously known as post transfusion non-A, non-B hepatitis virus infection.[8] HCV is an enveloped RNA virus belonging to the Hepacivirus of the family Flaviviridae.[9] HCV has a sense-strand RNA genome that is composed of a highly conserved 5'-untranslated region (UTR), which includes an internal ribosome entry site, and open reading frame that encodes both structural and non-structural proteins, and a 3'-UTR.[10] One non-structural protein of importance is the NS5B RNA dependent RNA polymerase (RdRp), an effective target for anti-HCV agents.[11] Viral RdRp lack proof-reading function, which accounts for the high genetic variability of HCV.[10] Of the nine genetically distinct HCV genotypes, genotype 1 is the predominant type in the United States, affecting 72% of patients with HCV infection.[12]

HCV only infects humans and chimpanzees. Hepatocytes are the main target of HCV but infection of B cells, dendritic cells, and other cell types has also been reported.[10] Circulating HCV particles can be associated with low and very-low density lipoproteins, and viral entry to hepatocytes may involve the low-density lipoprotein receptor, glycosaminoglycans scavenger receptor class B type-I and the tetraspanin protein CD81 and claudin-1 (CLDN1).[13-15] CLDN1 functions to mediate incorporation into the hepatocyte, a process involving clathrin-mediated endocytosis.[16] Infection with HCV triggers the non-specific immune response involving type I interferon (IFN) secretion and natural killer cell activation.[17] Recent studies of liver samples from chimpanzees infected with HCV show that IFN-alpha inducible genes are broadly and rapidly induced, but that this response fails to control viral replication.[18] The adaptive immune response occurs approximately 7-31 weeks after infection when anti-HCV antibodies are detectable. It is not known whether these antibodies play a role in viral clearance, but they may be capable of preventing HCV reinfection.[19] Spontaneous HCV clearance is related to a sustained virus-specific CD4+ T-cell response. This response is weak in individuals who develop chronic infection, and that this may be due to direct HCV infection of immune cells or modulation of function.[20-22]

Clinical Diagnosis of Chronic Hepatitis C Infection

Patients with chronic hepatitis C need to have a thorough history and physical exam that focuses on factors associated with accelerated disease progression. The history should include questions regarding alcohol use, complications associated with fatty liver or underlying cirrhosis, and menopausal status (in women). Also included would be factors that may affect their ability to qualify for antiviral therapy (cardiopulmonary disease, past or present psychiatric problems, autoimmune disease, and other comorbid conditions).[23] The physical exam for these patients needs to evaluate for signs of advanced liver disease such as spider angiomata, palmar erythema, splenomegaly, jaundice or caput medusa.[24]

People who develop HCV are usually asymptomatic, however, they may present with mild symptoms that are shown in Table 2. Patients who develop symptoms will usually develop them within 4-12 weeks after exposure to the virus. It is noted that approximately 20 to 30% of newly infected individuals present with abdominal pain, jaundice, poor appetite and fatigue.[3] The vast majority of patients with chronic HCV are also minimally symptomatic, however, in these patients the most common complaint is fatigue.[25] Chronic hepatitis C may also be associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda and possible non-Hodgkin B-cell lymphoma.[2]

There are also several extrahepatic manifestations associated with chronic HCV that are listed in Table 2.[3,24-26]

Table 2

Clinical Manifestations associated with Chronic HCV Infection	Extrahepatic Manifestations associated with Chronic HCV Infection
• Fatigue • Abdominal pain • Loss of appetite • Weight loss • Jaundice • Weakness • Fever • Nausea and Vomiting • Dark urine • Clay-colored stool • Myalgias and Arthralgias	• Hematologic diseases, such as essential mixed cryoglobulinemia and lymphoma • Renal disease, particularly membranoproliferative glomerulonephritis • Autoimmune disorders, such as thyroiditis and the presence of autoantibodies • Dermatologic conditions, such as porphyria cutanea tarda and lichen planus • Diabetes mellitus

A thorough diagnostic lab work up is required for individuals with hepatitis C viral infection. These tests can be divided into two main categories:[23] (1) Serologic assays that detect antibodies to hepatitis C and (2) Molecular assays that detect or quantify HCV RNA.

Antibody testing can be done through a number of assays including the standard immunoassays. Several options are available for patients with chronic HCV including laboratory testing, rapid point of care testing, and home tests on specimens collected by the patient. To detect anti-HCV antibodies in serum and plasma the enzyme-linked immunosorbent assay (EIA or ELISA) is most commonly used in clinical laboratories.[23,27] There has also been use of chemiluminescence immunoassays, which have shown to have performance that is comparable to the third generation EIAs.[28]

Two essential tools in the diagnosis and management of individuals with chronic HCV are detection and quantification of HCV-RNA. These assays are used to confirm the presence or absence of infection and to quantify the amount of HCV-RNA. Quantitative assays, such as the real time PCR (polymerase chain reaction) assay, are used before treatment to measure baseline HCV viral load and during treatment to assess therapy response.[23,29] Likewise, qualitative tests are capable of detecting low levels of HCV-RNA to confirm the diagnosis of HCV infection and are also used to assess sustained virologic responses (SVR) to antiviral therapy.[23,29] Both qualitative and quantitative tests will help pinpoint the amount of HCV-RNA at specific times during treatment, which helps guide clinical decision making throughout treatment of chronic HCV infection.

Additional evaluation laboratory tests are needed to monitor the disease progression in these patients. These tests include:[2,23,27,30]

- Genotype testing
- Serum fibrosis panels
- Liver biopsy
- Basic laboratory tests including:
    - Serum aminotransferase activity

- Measures of synthetic function: Bilirubin, prothrombin time, and albumin
- Complete blood count
- Renal function, glucose, lipid panel, thyroid function tests
- Urinalysis
- 25-hydroxy vitamin D
- Pregnancy test for women of childbearing potential

Treatment Options for Chronic Hepatitis C Infection Genotype 1

The goal of treatment in patients with chronic HCV infection is permanent eradication of HCV-RNA which is shown by SVR, which is defined as absence of HCV-RNA by polymerase chain reaction for three to six months after stopping treatment.[31] This is coupled with the permanent normalization of aminotransferase and cessation of histologic progression.[2] Attaining an SVR has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and other liver-related complications.[30,32] All patients with virologic evidence of chronic HCV should be considered for treatment, however, the evaluation and selection of patients for antiviral therapy is determined based upon history, physical exam, laboratory values, and noninvasive assessment of liver fibrosis.[30,32] Liver biopsies are only done in select patients with HCV infection, these include: liver transplant, suspected autoimmune liver disease, drug induced liver disease, and in those with which the diagnosis is doubtful.[30,32]

Until late 2013, all genotypes were treated with pegylated INF-alpha plus ribavirin; however, now patients are being treated with antiviral drugs that specifically target HCV. Each HCV genotype can be treated differently with variable combinations of drug therapy. Common direct-acting antiviral (DAA) medications are shown in Table 3.[2]

Table 3. Direct Acting Antiviral Medications used to Treat HCV
• Telaprevir and boceprevir: 1st-generation protease inhibitors with activity against HCV genotype 1
• Simeprevir: A 2nd-generation genotype 1–specific protease inhibitor
• Sofosbuvir: A polymerase inhibitor with activity against HCV genotypes 1 to 6
• Paritaprevir: A protease inhibitor
• Ledipasvir: A protease inhibitor
• Dasabuvir: A polymerase inhibitor
• Ombitasvir: An inhibitor of the viral nonstructural protein 5A

Deciding when and whom to treat is mainly based off the presence of contraindications associated with the available treatment regimens. Those who are candidates for antiviral therapy such as, Ledipasvir/Sofosbuvir (Harvoni ®)[2,33], should be further assessed by evaluating the following labs: renal function, complete blood count with differential, concurrent alcohol or drug use, extrahepatic manifestations of HCV infection, HIV coinfection, presence of severe comorbidity, potential drug interactions.[33]

This study focuses on the treatment of chronic hepatitis C viral infection using ledipasvir/sofosbuvir (Harvoni ®). Below consists of compiled information discussing the medication's mechanism of action, indications, clinical use, contraindications, and adverse reactions.

Mechanism of Action

Ledipasvir/Sofosbuvir (Harvoni ®) is a combination antiviral drug that includes ledipasvir and sofosbuvir. Ledipasvir is an HCV NS5A protein inhibitor and Sofosbuvir is a prodrug converted to its pharmacologically active form that inhibits NS5B RNA-dependent RNA polymerase, both of which are essential for viral replication.[33]

Indications: Treatment of chronic hepatitis C genotype 1 in both treatment naïve and treatment-experienced patients. The treatment duration is dependent on prior treatment and cirrhosis.

- Genotype 1 treatment-naïve patients with or without cirrhosis: 12 weeks
- Genotype 1 treatment-experienced patients without cirrhosis: 12 weeks
- Genotype 1 treatment-experienced patients with cirrhosis: 24 weeks
    - Treatment experience is defined as patients who have failed treatment with either peginterferon plus ribavirin or peginterferon plus ribavirin plus a HCV protease inhibitor.
    - Note: Treatment duration of 8 weeks can be considered in treatment-naive patients without cirrhosis who have a baseline HCV RNA level less than 6 million IU/mL.

Clinical Use

Harvoni ® has been identified as an interferon free combination regimen for the treatment of treatment-naïve and treatment-experienced patients with genotype 1 chronic HCV infection. Phase 3 studies have consistently shown SVR rates greater than 90% with a 12-week course of Ledipasvir/Sofosbuvir (Harvoni ®).[33]

Contraindications

There are currently no contraindications listed in the manufacturer's U.S. labeling, however, Canadian labeling states a hypersensitivity to any component of the formulation. There are warnings and precautions with this medication that include drug-to-drug interactions with specifically potent P-gp inducers (eg, rifampin, St. John's wort) or amiodarone. It is also advised to avoid using this drug concurrently with other sofosbuvir containing products.[33,34]

Adverse Reactions

These reactions are also seen with the individual components of Ledipasvir/Sofosbuvir (Harvoni ®).[33,34]

- Central Nervous System: fatigue, headache, insomnia
- Gastrointestinal: nausea, diarrhea, increased serum lipase
- Hepatic: hyperbilirubinemia

METHODS

Patient Population

This is a pilot study is a collaboration between James Madison University (JMU) and the Harrisonburg-Rockingham Free Clinic (HRFC). JMU Physician Assistant students Caitlin Johnson and Jamie Taylor worked closely with Sharon Maiewski, PA-C, Susan Adamson, FNP, and Janice Gandy, RN of the HRFC to gather data, determine inclusion-exclusion criteria, and generate protocols.

Patients were enrolled in this study beginning May 15, 2015 in the United States. The duration of this study has yet to be determined, and is dependent on preliminary results and number of participating

patients. Eligible patients were 18 years or older with chronic HCV genotype 1. Full inclusion and exclusion criteria are detailed in (Table 4).

Table 4. Study inclusion and exclusion criteria for patient selection.

Inclusion Criteria	Exclusion Criteria
● Confirmed Hepatitis C Virus Infection ● Genotype 1a or 1b ● Males and females ≥ 18 years of age ● Subject able to comply with treatment requirements, monitoring requirements, and reduction of risk factors following treatment completion. ● Patient of the Harrisonburg-Rockingham Free Clinic	● Pregnant or Nursing

Study Design and Assessments

In this single center prospective cohort study patients received care from the Harrisonburg-Rockingham Free Clinic, and are administered a fixed-dose combination table containing 90mg of ledipasvir and 400mg of sofosbuvir (LDV-SOF) administered orally once a day for three months. Assessments during treatment included standard laboratory testing, vital signs, and symptom directed physical examinations. Complete blood counts, liver function tests, and HCV RNA levels were obtained before and after treatment with LDV-SOF (Table 5). An AST to Platelet Ratio Index (APRI) was calculated and included for evaluation as a viable measure of liver fibrosis or cirrhosis. In a meta-analysis of 40 studies it was concluded that an APRI score greater than 1.0 had a sensitivity of 76% and a specificity of 72% for predicting cirrhosis, and a score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting hepatic fibrosis (http://www.ncbi.nlm.nih.gov/pubmed/19034235).

Table 5. Laboratory and follow-up protocol for study participants taking LDV-SOF. CBC, complete blood count; LFT, liver function tests including AST/ALT; HCV-RNA measures viral load.

Weeks following treatment	Laboratory evaluation
2 weeks	CBC, LFT
4 weeks	CBC, LFT, HCV-RNA
5 weeks	Follow up with Free Clinic Provider
8 weeks	CBC, LFT
12 weeks	CBC, LFT, HCV-RNA
24 weeks	HCV-RNA

Study Oversight

This trial did not require oversight or approval by the institutional review board or independent ethics committees. All patient identifiers were removed by Harrisonburg-Rockingham Free Clinic providers prior to use by researchers and it was determined that this population did not qualify as vulnerable. The primary efficacy endpoint was an HCV RNA level of less than 15 IU per milliliter at 12 weeks after the end of therapy.

Statistical Analysis

To grossly evaluate statistical significance between laboratory evaluations prior to, during, and following administration of LDV-SOF a t-test was used. Data was compiled in Microsoft Excel and statistical analysis was performed using this program. Currently sample size is small at 10 patients. As sample size and statistical power increases other statistical analysis methods will be considered to better assess overall differences between groups.

RESULTS

Patient Demographics

Of the 10 patients who underwent treatment with LDV-SOF for 12-weeks 30% of the patients are female and 70% are male. 89% of patients are white, and 11% of patients are black. 100% of patients have been diagnosed with hepatitis C genotype 1a infection. Due the patient population, comorbid conditions were fairly common. It was decided that these conditions would not be considered in evaluation of the data or statistical analysis. We would consider the contraindications issued by the manufacturer which only apply to coadministration with ribavirin.[33]

Treatment Efficacy

Complete patient data is detailed in Appendix A. All patients received 12 weeks of LDV-SOF for 12-weeks and were monitored according to the protocol outlined in Table 5. Patients are in various stages of treatment, and this complicates statistical analysis. Preliminary data supports a significant decrease, p-values less than 0.05, in AST and ALT values 30 days following treatment initiation with LDV-SOF (Figure 1 and 2). Total patient number in this group is 8. When following AST, significant changes were also seen 60 days following treatment initiation where total patient number was 6 (Figure 1).

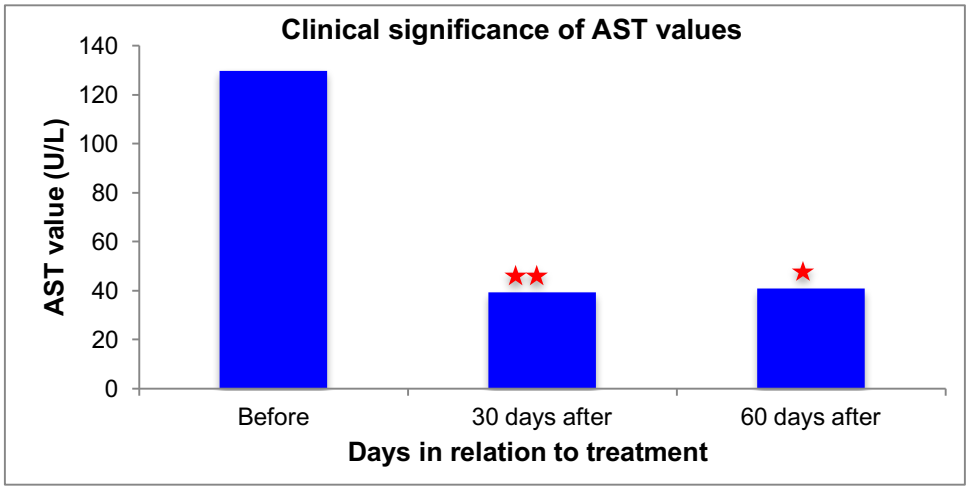

Figure 1. Average AST values before (n = 8), 30 days after (n=8), and 60 days after ledipasvir-sofosbuvir (90mg/400mg) treatment initiation (n=5). Double stars represent a p-value less than 0.01, single star represents p-values less than 0.05.

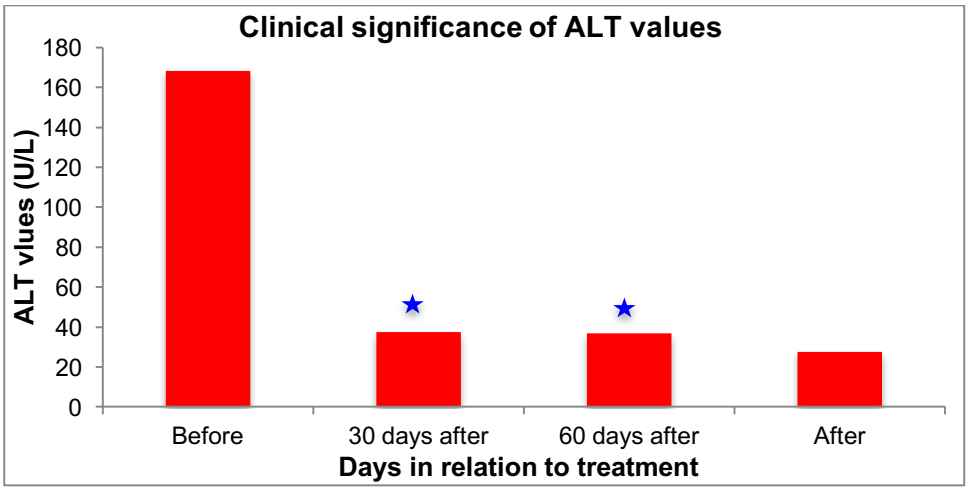

Figure 2. Average ALT values before (n = 8), 30 days after (n=8), 60 days after (n=5), and after completion of ledipasvir-sofosbuvir (90mg/400mg) treatment initiation (n=2). Single star represents p-values less than 0.05.

HCV-RNA levels responded quickly to treatment with LDV-SOF, with 40% of patients demonstrating undetectable viral loads 30 days after treatment initiation. After 30-60 days of treatment 60% of patients demonstrated an undetectable viral load. This decrease in HCV-RNA levels is highly statistically significant, with a p-value less that 0.01 (Figure 3). Total patient number in the group was 6.

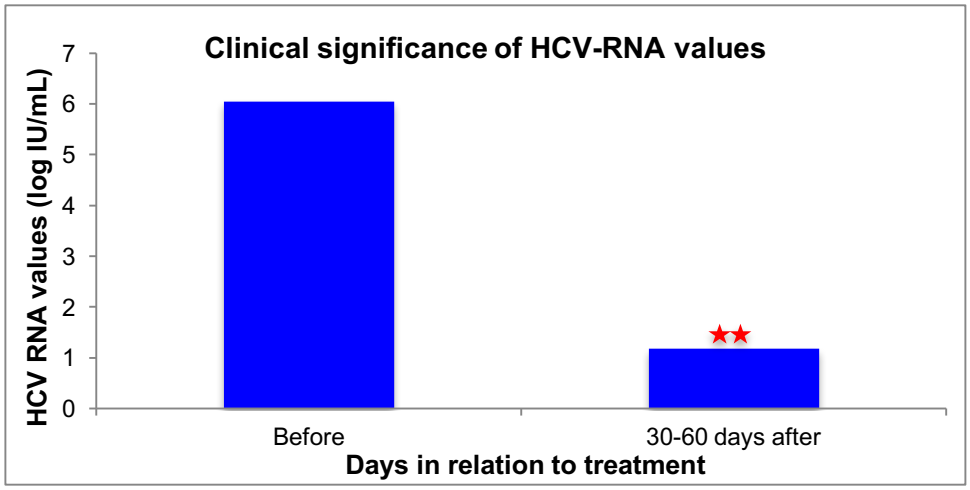

Figure 3. Average HCV RNA values before (n = 5), and 30-60 days after ledipasvir-sofosbuvir (90mg/400mg) treatment initiation (n=5). Double stars represent a p-value less than 0.01.

Although liver biopsy is recognized as the gold standard for liver fibrosis staging, the AST to platelet ratio index (APRI) has been proposed and validated as a noninvasive and moderately accurate indicator of fibrosis of cirrhosis in patients with chronic liver disease.[35] APRI ratios were calculated for study participants receiving 12-weeks of LDV-SOF (Figure 4). However, not enough data is available to perform statistical analysis and determine whether these patients had significant decreases in APRI ratios following treatment. Data will continue to be gathered to assess the appropriateness of the APRI for noninvasive evaluation of liver fibrosis in chronic HCV patients treated with LDV-SOF.

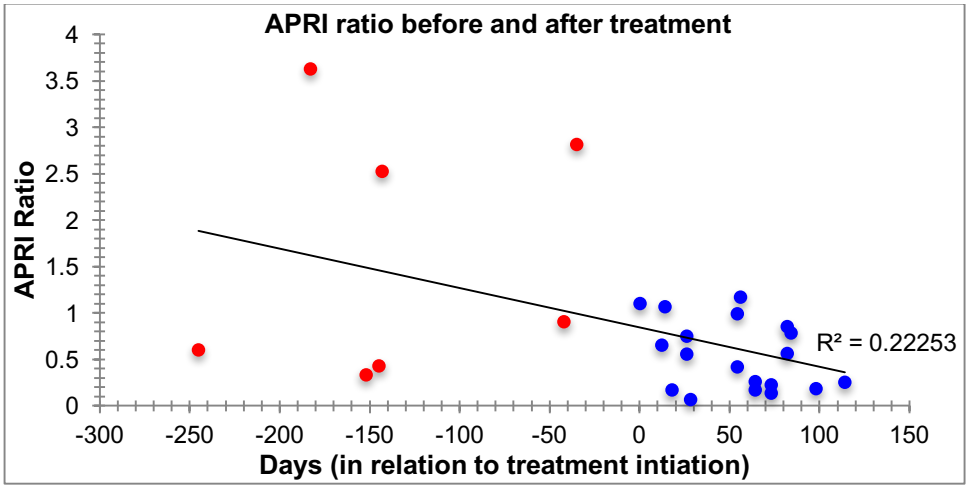

Figure 4. AST to platelet ratio index (APRI) before (red) and after (blue) treatment with 12 weeks of ledipasvir-sofosbuvir (90mg/400mg). APRI greater than 1.5 is highly suggestive of cirrhosis.

DISCUSSION

Study purpose

HCV infection is responsible for approximately 40% of all chronic liver disease in the United States and HCV-associated cirrhosis is the most common indication for liver transplantation among adults.[36] Until recently the majority of patients infected with hepatitis C virus were treated with recombinant human interferon (INF) alpha and ribavirin achieving a "cure" rate of approximately 60%.[37] These previous treatment regimens are associated with numerous side effects and often seriously impact patient's quality of life.[37] Recently, novel antiviral drugs like LDV-SOF, that specifically target HCV have provided better options in HCV treatment. Future use of these drugs has the potential to not only decrease the number of patients living with chronic HCV, but also reduce healthcare costs associated with treatment of complications of chronic HCV.

Study Analysis

In published randomized control trials LDV-SOF is able to achieve a sustained viral response (SVR) representing undetectable levels of HCV-RNA after 12-weeks of treatment.[37,38] A similar level of efficacy is seen in this study as well, with 100% of patients treated with 12-weeks of LDV-SOF achieving a SVR. However, it is important to note that our study is not yet able to evaluate whether the SVR is maintained months to years following treatment completion. Afdal et. al documents approximately 1/214 (less than 1%), and Kowdley et al records 3/216 (1.4%) patients experiencing relapse following completion of treatment with LDV-SOF.[37,38] In both studies HCV-relapse was associated with a NS5A resistant genotype as determined by deep gene sequencing.[37,38] This data suggests there may be an indication for sequencing of HCV genome prior to LDV-SOF treatment, especially if cost is a factor.

A major issue with the LDV-SOF medication and other similar treatment regimens is cost. Currently, the cost of 12-weeks of LDV-SOF costs patients without insurance $1,000-a –pill or $94,500 for 12-weeks of treatment.[39] This is further complicated by clinical observation that insurance companies require documented levels of fibrosis in patients in order to qualify LDV-SOF drug coverage. Cost and insurance requirements seriously inhibit the availability of these medications. The HRFC provides a unique population for study since all patients currently receiving treatment have qualified for the Support Path Patient Assistant Program, allowing them access to medication at no charge. These patients do not have to meet insurance requirements for treatment coverage, and therefore may represent a population receiving treatment with LDV-SOF that may have less liver damage associated with chronic HCV infection.

Future study directions

The major goal of this study is to assess long-term efficacy of LDV-SOF treatment for chronic HCV infection. This study is unique in that it is highly inclusive, assessing efficacy in newly diagnosed patients, previously treated patients, and patients with significant comorbidities affecting liver function and health. We would like to continue to gather data and increase the number of participants included in the study, with a final goal of 50 participants. These patients will be continuously followed and assessed for evidence of treatment failure and HCV relapse. Also to be included in this study are patient surveys that would assess perceived quality of life before and following treatment, and include information about adverse effects experience while on LDV-SOF treatment regimen. Currently, no study participants have disclosed adverse events associated with treatment, and have been compliant with medication administration. The health related quality of life in patients with chronic liver disease (HRQL-CLD) questionnaire has been validated as a reliable measure of liver disease severity and has been suggested for use in this study.[40] Together, this information will help the Harrisonburg-Rockingham Free Clinic gather data for continued participation in programs that reduce the cost of LDV-SOF and give patients in need the chance to live without chronic HCV infection.

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