Estradiol and/or Ibandronate Therapy Ameliorates A Case Series Describing the Outcomes of Treatment in Co-infected Patients with HIV and Hepatitis C on the United States-Mexico Border

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Authors' contributions

This work was done as a collaborative effort by SJA and GH. Both authors contributed equally to the design, analysis of the data and writing of the manuscript.

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ABSTRACT

According to the National Health and Nutrition Examination Survey 2007-2010 (NHANES) and the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the prevalence of Hepatitis C in people of Hispanic descent is 1.5-2%. However, this percentage is estimated to increase as the Hispanic population continues to grow in the United States. Currently there is minimal information on Hepatitis C treatment outcomes in the Hispanic population and even less data in the HIV co-infected, Hispanic population. This study was done to see if there was any differences in the clinical features and treatment outcomes in a population where the predominant race was that of Hispanics. In this small study, we enrolled 36 patients to evaluate the demographics, efficacy of various direct acting anti-Hepatitis C medications in HIV co-infected patients. All the patients were male with over 94% being of Hispanic origin. The average CD4 count at enrollment was 234 cell/cu

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mm and at the end of treatment was 256 cells/cu mm. A sustained viral response (SVR) or the definition of cure, was noted in all but one of the patients regardless of the medication used, underlying liver stage, or stage of HIV infection.

Keywords: HIV; hepatitis C; treatment; outcomes.

1. INTRODUCTION

In the United States, there are about 1.2 million people living with HIV and about 25% are also infected with Hepatitis C [1-3]. Co-infection of hepatitis C and HIV is a well-studied relationship and studies have shown that HIV accelerates liver disease progression [4]. There are also racial differences in liver disease progression and Hispanics have a higher incidence of cirrhosis and hepatocellular carcinoma when compared to non-Hispanic Whites and African Americans [5]. However there is currently minimal data on the rate of co-infection with Hepatitis C and HIV in this population and treatment outcomes with direct acting antivirals as seen in the Photon 1 trial. HIV and HCV have common transmission routes and therefore co-infection is a common occurrence [6]. This is of particular concern because liver-related complications occur faster and are more severe in co-infected patients [4]. In fact, a third of HIV patients in the United States are co-infected with HCV and 90% of deaths related to liver disease in HIV positive patients are attributed to HCV [7]. Because HIV co-infected patients have lower T-cells, higher level of T-cell activation, enhanced HIV and HCV replication, the patients are much less likely to clear the Hepatitis C virus on their own [7]. Overall, all-cause mortality is much higher in the HIV/HCV co-infected population [7]. The objective of this small study in two U.S.-Mexico border Infectious disease clinics was to explore treatment outcomes of HIV co-infected patients treated with direct acting anti-hepatitis C regimens.

2. PATIENTS AND METHODS

Data was collected on co-infected patients from medical electronic records of patients at two infectious disease clinics in El Paso, Texas between July 2014-September 2015. El Paso, Texas is a U.S. Mexico border city with a predominantly Hispanic population [8]. Inclusion criteria for analysis included (1) patients with documented active Hepatitis C infection as defined as a positive Hepatitis C antibody and HCV RNA, (2) patients getting treatment for Hepatitis C at the clinic. (3) Patients with underlying HIV regardless of viral load and stage of disease. Institutional review Board approval was obtained at the start of the study and informed consent was obtained from all the patients enrolled in the study.

Patients were assigned to specific Hepatitis C regimen based on current HIV regimen, specific genotype, AASLD/IDSA Hepatitis C guideline recommendations, and available HCV agents at the time of treatment. The type of medication was also directed by what antiretroviral regimen the patients were on. Patients were then followed throughout the treatment and monitored every 4 weeks until treatment completion and 12 weeks after finishing therapy. Cure was defined as a negative HCV RNA at 12 weeks post-treatment or what is commonly referred as a sustained virologic response (SVR). Failure was defined as a recurrence of hepatitis C RNA 12 weeks post-treatment. Data collected included age, ethnicity, gender, CD4 count, ARV regimen, serum creatinine, liver fibrosis score per Fibrosure®, HCV RNA, and genotype.

3. RESULTS AND DISCUSSION

A total of 126 patients were identified to have co-infection with HIV and hepatitis C over this period of time. Of those patients, 36 patients met the criteria for treatment and were followed throughout treatment for Hepatitis C at the two Infectious disease clinics. The group included all male and a large majority of Hispanic patients. The average age of the group was 48 years (28-67 years). The average baseline CD4 count was 248-cells/cu mm (range 67-918) and the average CD4 after finishing treatment was 256-cell/cu mm (116-1166) (Table 1). The most common genotype was genotype 1a and a majority of the patients were treatment naïve. (31/33) Most patients were on antiretroviral treatment (94%) 34/36 and the most common backbone for HAART was abacavir/lamivudine. All patients had a HCV RNA drawn 12 weeks after completion of treatment (SVR12) and 35/36 were found to be undetectable (Table 2). The liver fibrosis score per Fibrosure® stage ranged from F0 (4), F1 (6), F2 (7), F3 (8), F4 (11).
There was no obvious difference in the underlying demographics of these patients. No adverse effects were reported that merited discontinuation of the medications. We did not observe any significant difference in the outcomes in patients receiving different anti-HCV treatments. There was no difference in the outcomes or side effects when compared to the current literature in the Hispanic population.

Table 1. Baseline characteristics

| Characteristic          | Mean, n          |
|-------------------------|------------------|
| Average Age, years.     | 48 years         |
| Male %                  | 100% (36/36)     |
| Hispanic %              | 94% (34/36)      |
| Genotype 1a, %          | 90% (27/36)      |
| Average HCV RNA         | 2,340,000 copies |
| Fibrosis Stage 4, %     | 30.5% (11/36)    |
| Treatment naïve, %      | 52% (19/36)      |
| Average CD4+ Count      | 248 (67-918)     |
| Serum Creatinine        | 0.9 mg/dL        |
| ALT                     | 84 International Units/L |
| AST                     | 74 International Units/L |
| Tbil                    | 0.5 mg/dL        |
| Hgb                     | 9.8 g/dL         |
| Platelets               | 154 x10^3/uL     |
| ARV-Treated             | 34/36 patients   |

Abbreviations: HCV: Hepatitis C; ARV: Anti-retroviral

3.1 Discussion

The Hepatitis C virus is a single stranded RNA virus from the family flaviviridae and there are six different types of genotypes that occur worldwide [9]. By far, the most common genotype in the United States is genotype 1 as it occurs in about 70% of patients infected with Hepatitis C [10]. In the past couple of years, many new drugs to treat Hepatitis C have been developed, and genotype 3 has emerged as very difficult to treat genotype although 2 regimens have been shown to produce SVR rates in excess of 95% as already displayed in Table 3 [11]. Before the direct acting anti-virals were introduced into the market, cure rates with peg interferon alfa and ribavirin, were as low as 40% in genotype 1 and side effects were extremely problematic [12]. Treatment lasted from 24 to 48 weeks depending on genotype, co-morbidities, and other factors [13]. In HIV co-infected patients, treatment had to be extended to 48 weeks and treatment discontinuation was extremely common [13]. In fact, HIV co-infection was considered a special population and had different recommendations when compared to mono-infected patients [13-17].

Table 2. Study treatment outcomes by genotype

| Genotype 1a-Treatment outcomes (Undetectable HCV RNA) |
|-------------------------------------------------------|
| Treatment week | Simeprevir + Sofosbuvir (12 weeks) | Ledipasvir + Sofosbuvir (12 weeks) | Sofosbuvir + Ribavirin (12 weeks) | Ombitasvir/ Paritaprevir/ ritonavir/ Dasabuvir + Ribavirin (12 weeks) |
|-----------------|------------------------------------|------------------------------------|----------------------------------|---------------------------------------------------------------|
| Wk 4            | 100% (5/5)                         | 90% (19/21)                        | 100% (3/3)                       | 100% (1/1)                                                   |
| Wk 12           | 100% (5/5)                         | 100% (21/21)                       | 100% (3/3)                       | 100% (1/1)                                                   |
| EOT             | 100% (5/5)                         | 100% (21/21)                       | 100% (3/3)                       | 100% (1/1)                                                   |
| SVR12           | 80% (4/5)                          | 100% (21/21)                       | 100% (3/3)                       | 100% (1/1)                                                   |

| Genotype 2-Treatment outcomes (Undetectable HCV RNA) |
|-------------------------------------------------------|
| Treatment week | Sofosbuvir+ Ribavirin (12 weeks) |
|-----------------|---------------------------------|
| Wk 4            | 100% (2/2)                      |
| Wk 12           | 100% (2/2)                      |
| EOT             | 100% (2/2)                      |
| SVR12           | 100% (2/2)                      |

| Genotype 3-Treatment outcomes (Undetectable HCV RNA) |
|-------------------------------------------------------|
| Treatment week | Ledipasvir + Sofosbuvir + Ribavirin (12 weeks) |
|-----------------|-----------------------------------------------|
| Wk 4            | 100% (1/1)                                    |
| Wk 12           | 100% (1/1)                                    |
| EOT             | 100% (1/1)                                    |
| SVR12           | 100% (1/1)                                    |

Abbreviations: EOT: End of therapy; SVR: Sustained virologic response
Table 3. Treatment outcomes landmark trials

| Clinical trial | Genotype | Population | Regimen | SVR12 (%) |
|----------------|----------|------------|---------|-----------|
| PHOTON-1       | 1, 2, or 3 HIV co-infected | Treatment-naive | Sofosbuvir + ribavirin (RBV) x 12 or 24 weeks | Genotype 1: 76%  
Genotype 2: 88%  
Genotype 3: 67% |
| PHOTON-2       | 1, 2, 3, or 4 HIV co-infected | | Sofosbuvir + ribavirin (RBV) x 12 or 24 weeks | Genotype 1: 85%  
Genotype 2: 88%  
Genotype 3: 89%  
Genotype 4: 84% |
| TURQUOISE-1    | 1 HIV co-infected | | Paritaprevir/ritonavir/ombitasvir/dasabuvir + ribavirin (RBV) x 12 or 24 weeks | 93.5% -12 weeks  
95% - 24 weeks |
| ERADICATE      | 1 HIV co-infected | Treatment-naive | Ledipasvir/sofosbuvir x 12 weeks | 100% |
| ION-4          | 1 or 4 HIV co-infected | | Ledipasvir/sofosbuvir x 12 weeks | 96% |

In the co-infected population, patients often had to stop taking their HIV anti-retroviral because of drug interactions [18,19]. In the last year, more direct acting anti-virals have been developed and the success rates with these agents have increased to more than 90% [20-23]. The COSMOS trials showed an SVR rate of more than 90% with sofosbuvir and simeprevir for 12 weeks [23]. However, this trial was not done in co-infected patients and only a small percentage were of Hispanic descent [23]. The ERADICATE and ION-4 clinical trials demonstrated SVR rates close to 100% in the HIV co-infected patients with sofosbuvir and ledipasvir [24,25]. The TURQUOISE trial showed SVR rates of 94% with paritaprevir/ritonavir/ombitasvir and dasabuvir with ribavirin for 12 weeks [26]. (Table 3—Comparison of different trials). Because of the high SVR rates in the HIV co-infected population, the most recent update in the Hepatitis C guidelines does not consider co-infection as a special population, and it recommends to treat these patients exactly the same as mono-infected patients with careful consideration to drug-drug interactions [27]. Perhaps, the next question is if there is any benefit in treating differently based on ethnicity. Many studies have shown that Hispanics have lower adherence to HIV medications as compared to Whites [28]. Further, some studies have shown that Hispanic patients usually experience more side effects and worse outcomes when receiving treatment for Hepatitis C when compared to other ethnicities [29]. In this study, adherence or side effects did not seem to have a significant impact.

Over the past years, there has been a lot of press concerning individualizing pharmacotherapy in different disease states [30,31]. However, many insurance companies have preferred hepatitis C regimens based on [30-36] cost and very strict approval guidelines. Unfortunately, the pill burden or potential drug interactions are often not considerations for their approval of a Hepatitis C regimen. All the clinical trials currently have a relatively small Hispanic representation and there is a need for data on this specific patient population. In this study, the aim was to collect more information on Hispanic, HIV co-infected patients. Of the 36 patients who were treated, all of them had a sustained virologic response 12 weeks post-treatment. None of the patients discontinued their treatment and very few experienced side effects. This was particularly true in the ledipasvir and sofosbuvir cohort.
4. CONCLUSION

This small study highlights a few interesting facts: 1. HIV-HCV co-infected patients seem to have good treatment outcomes regardless of the baseline CD4 count and HIV viral burden as long as the selected hepatitis C treatment regimen is tolerable. 2. Newer regimens allow for better compliance and minimal drug interactions. 3. Underlying liver damage as defined by the Fibrosure score seems to have minimal impact on outcomes. 4. Hispanic ethnicity does not seem to make a difference in the outcomes in these patients. Limitations to this study included small sample size, lack of strict comparative data and not being blinded.

ETHICAL APPROVAL

Institution review Board approval was obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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