Treatment Failure with Direct Antiviral Agents in Patients with Hepatitis C Virus Genotype 1 Infection at the Veteran Affairs Caribbean Healthcare System in San Juan, Puerto Rico

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Objective: We performed a descriptive study of patients who have failed to DDAs in our Veteran population. The primary outcome of this study is to describe the clinical profile of these patients and to evaluate their respective resistance mutation panel.

Methods: This investigation is a descriptive retrospective study of patients with chronic hepatitis C between the ages of 21 to 89 years from the Veteran Affairs Caribbean Healthcare System in P.R. Eligible cases were Veterans treated for hepatitis C with second generation of DAAs from January 1, 2015 to December 31, 2016 who failed to therapy. Patient records were reviewed and those who met inclusion criteria were included.

Results: Among Hispanic Veterans treated with DAA for genotype 1 HCV infection, 3.9% had failure to treatment with the second generation DAAs. 90% were genotype 1a; while 10% were 1b. 80% of these were identified as cirrhotic and the other 20% were non-cirrhotic. 90% had resistant variants for Ns5a. Eight patients had Ns3 RASs testing requested of which 50% had presence of resistant variants. Five patients had Ns5b RASs testing performed of which 40% had positivity for resistant variants to Ns5b.

Conclusion: Despite DAA effectiveness, phase III clinical trials with new IFN-free DAA-based therapies have a 5-7% treatment failure rates. Real-life data has showed that <15% of patients fail to achieve SVR in the most difficult to cure groups such as those with cirrhosis or subtype 1a. These findings are comparable with our current study. [*P R Health Sci J 2019;38:266-268*]

Key words: Hepatitis C, DAA, HCV antiviral, Chronic HCV

Chronic hepatitis C virus (HCV) affects an estimated 170 million people worldwide, among which 60% have the genotype 1 strain of the virus (1). In the United States alone, four million persons are infected with the virus, of which HCV subtypes 1a and 1 b are the most common genotypes encountered in the population (2). After exposure to the virus, the infection fails to resolve in the majority (80%) of the patients. Many will have progression to decompensated cirrhosis; hepatocellular carcinoma, and other liver complications, and it is the leading reason for liver transplantation in the United States.

The treatment of chronic HCV has been evolving rapidly in these past few years and cure is now possible. For the past 15 years, interferon and later peginterferon, in conjunction with ribavirin (RBV) were the mainstay therapy for HCV, however with a major side effect profile, poor tolerability and poor sustained virological response (SVR) (3). The development of direct-active antiviral agents (DAAs) revolutionized the treatment of HCV infection. In 2011, the protease inhibitors, boceprevir and telaprevir were approved by the Food and Drug Administration (FDA) in combination with peginterferon and RBV for genotype 1 infection. This regimen was more efficacious, but brought additional side effects, drug-drug interactions and antiviral resistance (3). By the end of 2013, the FDA approved two new classes of DAA: the nucleotide polymerase inhibitor sofosbuvir and the protease inhibitor simeprevir. Sofosbuvir is highly effective in suppressing replication in all HCV genotypes. Resistance is extremely rare and SVR rates of over 90% are archieved (4). By 2014, interferon-free all oral combination therapies began to emerge. Ledipasvir is a NS5A inhibitor with potent antiviral activity against genotypes 1a and 1b. The combination of ledipasvir and sofosbuvir with or without RBV resulted in high rates of SVR of over 94% (1,5,6). Another regimen includes ombitasvir, a NS5A inhibitor, paritaprevir, a NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a non-nucleoside NS5B polymerase inhibitor. By 2015, daclatasvir, a NS5A inhibitor in

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The author/s has/have no conflict/s of interest. Disclaimer: The contents of this publication do not represent the views of the Veterans Affairs Caribbean Healthcare System, the U.S. Department of Veterans Affairs, or the United States Government.

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combination with sofosbuvir was introduced. Furthermore, in 2016 the FDA approved the combination of elbasvir, a NS5A inhibitor, with grazoprevir, an NS3/4A protease inhibitor and the combination of velpatasvir, a new pangenotypic NS5A with sofosbuvir.

DAAs have demonstrated very high response rates, better tolerability, few drug-drug interactions and minimal side effects. Drug resistance against these DAAs is common and demonstrated in preclinical studies and in the early clinical trials7. The data on Hispanic population with DAAs is very limited for which the aim of this study is to identify and evaluate Hispanic patients within our Veteran population who have failed to DAAs.

The goal of this research was to perform a descriptive study of patients who have failed to DDAs in our Veteran population. The primary outcome of this study was to describe the clinical profile and resistance mutation panel.

Methodology

This investigation is a retrospective study of patients with chronic hepatitis C between the ages of 21 to 89 years from the Veteran Affairs Caribbean Healthcare System in P.R. The study was approved by the local Institutional Review Board. Eligible cases were Veterans with hepatitis C genotype-1 mono-infection treated with the second generation of DAAs from January 1, 2015 to December 31, 2016 who failed to therapy. Patient records were reviewed, and those meting inclusion criteria were included. HCV Ns3, Ns5a and Ns5b resistance genotype testing was reported by the Veteran's Health Administration Public Health Reference Laboratory and Quest Diagnostics. Non-Hispanic subjects and those without a resistance panel were excluded.

Results

A total of 358 Hispanic Veterans were treated during the study period. Among these, only 14 (3.9%) had treatment failure. Only 10 (2.8%) met the study inclusion criteria. (See Table 1) All treatment failures were post-treatment relapses. All patients were men, with a median age of 67.1 years. Most (90%) patients that had a treatment failure were genotype 1a; while 10% were 1b. Eighty percent (80%) were treated with Sofosbuvir/Ledipasvir, 10% with Elbasvir/Grazoprevir and 10% with the combination of Dasabuvir/Ombitasvir/Paritaprevir and Ritonavir. Half (50%) of this cohort were treatment experienced. Most patients (80%) were identified as cirrhotic (either by radiologic imaging and/or transient elastography). Resistance-associated substitutions (RASs) testing for Ns5a was requested for all patients of which 90% had resistance to Ns5a agents. Eight patients had Ns3 RASs testing of which 50% had resistant variants. Five patients had Ns5b RASs testing of which 40% had resistant variants to Ns5b.

Case	Genotype	Treatment naïve	Cirrhotic	DAA	Ns5a RAS	Ns3 RAS	Ns5b RAS
1	1a	no	yes	Ledipasvir/Sofosbuvir	Yes to all Ns5A	yes	N/A
2	1a	naïve	no	Ledipasvir/Sofosbuvir	negative	negative	yes
3	1a	no	yes	Ledipasvir/Sofosbuvir	Yes to all Ns5a	yes	negative
4	1a	naïve	yes	Ledipasvir/Sofosbuvir	Yes to all Ns5A	negative	negative
5	1a	no	yes	ombitasvir/paritaprevir/ritonavir & dasabuvir	Yes to all Ns5A	yes	yes
6	1b	no	no	Ledipasvir/Sofosbuvir	all Ns5a except elbasvir and velpatasvir	negative	N/A
7	1a	naïve	yes	Ledipasvir/Sofosbuvir	Probable to all Ns5a	N/A	N/A
8	1a	naïve	yes	Ledipasvir/Sofosbuvir	Probable to all Ns5a	negative	N/A
9	1a	naïve	yes	Ledipasvir/Sofosbuvir	Probable to all Ns5a	N/A	N/A
10	1a	no	yes	Elbasvir/Grazoprevir	Yes to all Ns5a	yes	negative

Discussion

Treatment of HCV infection has advanced substantially with the approval of direct-acting antiviral agents. DAAs have achieved high rates of virological cure with few drug-drug interactions and side effects enhancing great patient outcomes and tolerability. Despite DAA effectiveness, there is still 5-7% treatment failure rates. Real-life data has showed that <15% of patients fail to achieve SVR in the most difficult to cure groups such as those with cirrhosis or subtype 1a and 3 infection (8).

Resistant variants are seen in most patients who do not achieve SVR. Nevertheless, the presence of resistance-associated substitutions does not preclude successful treatment (9). Variants resistant to NS3-4A protease inhibitors have shown to disappear over time after drug discontinuation. NS5a inhibitor-resistant viruses on the other hand persist for years. Ns5b inhibitors are classified as nucleotide (e.g., sofosbuvir) and nonnucleoside analogs. There is a very high genetic barrier to resistance development for the nucleoside analog sofosbuvir (Ns5b inhibitor), making this agent a first-line choice DAA (10). DAA combinations geared to multiple targets and including sofosbuvir had been a strategy to treat patients with NS5A resistant associated variants. Although viral resistance testing has emerged as an exceptional tool for alternative individualized and personalized treatment care, new studies have shown a comparable SVR between those with baseline viral substitutions versus those without resistant-associated substitutions (11).

Current guidelines have conferred regimen-specific recommendations for use of RAS testing in clinical practice, specifically for genotype 1a and genotype 3-infected patients (12). In our study, only 3.9% of

the patients failed to respond, mostly those with cirrhosis and genotype 1a. Resistance patterns observed in our population were similar to those observed in other populations.

Resumen

Objetivo: Realizamos un estudio descriptivo de los pacientes con hepatitis C crónica que fracasaron a los nuevos antivirales de acción directa (AAD). El objetivo principal es describir el perfil clínico y el panel de mutación de estos pacientes. Metodología: Esta investigación es un estudio observacional retrospectivo de pacientes entre las edades de 21 a 89 años. Los casos elegibles fueron Veteranos infectados con el genotipo 1, tratados por con AAD de segunda generación desde el 1 de enero de 2015 hasta diciembre 31, 2016 y que fallaron a terapia. Se revisaron los registros de pacientes y se incluyeron aquellos que cumplieron con los criterios de inclusión. Resultados: Durante el periodo estudiado, solo el 3.9% de los sujetos fracasaron a tratamiento. 90% fueron genotipo 1a; mientras que 10% fueron 1b. El 80% de estos se identificaron como cirróticos y el otro 20% no cirróticos. 90% tenían variantes resistentes para Ns5a. A ocho pacientes se le solicitaron la prueba Ns3 RAS, de los cuales el 50% tenían presencia de variantes resistentes. Cinco pacientes tenían pruebas Ns5b RAS realizadas, de las cuales el 40% tenían positividad para variantes resistentes a Ns5b. Conclusión: A pesar de la efectividad de AAD, las nuevas terapias basadas en AAD tienen tasas de fracaso a tratamiento de 5-7%. Los datos de la vida real han demostrado que <15% de los pacientes no logran la RVS en los grupos más difíciles de curar, como aquellos con cirrosis o subtipo 1a. Nuestros hallazgos son comparables o mejores que los reportados.

Acknowledgment

This material is the result of work supported with resources and the use of facilities at the Veterans Affairs, Caribbean Healthcare System San Juan, P.R.

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