"RE-RELAPSE" IN A PATIENT TREATED WITH DIRECT ACTING ANTIVIRAL THERAPY FOR HEPATITIS C INFECTION: DOUBLE THE TROUBLE

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ABSTRACT

Introduction: Direct Acting Antivirals (DAA's) has become the gold standard for the treatment of Hepatitis C Virus (HCV) infection due to its efficacy and low relapse rates. Only 6% of patients treated with DAA's relapse, and only 8 cases have been reported worldwide to have relapsed on 2 different DAA regimen, making "re-relapse" cases a rare occurrence.

Case: This is a case of a 62-year old Filipino female nurse, diagnosed with Genotype 1a HCV infection last 2014, probably acquired from a blood transfusion in the 1970's or an accidental needlestick injury, and with Child Pugh A liver cirrhosis. The patient had incomplete treatment with pegInterferon + Ribavirin. In 2016, the patient was retreated with Ledipasvir + Sofosbuvir for 12 weeks. Baseline HCV RNA level was 39,834,498 IU/ml. At 4 weeks post-treatment, repeat HCV RNA was undetectable, however, at 12 weeks post-treatment, relapse was noted with an HCV RNA of 41,930,515 IU/ml. In 2017, a repeat ultrasound showed worsening cirrhosis and the patient was retreated with 24 weeks of Sofosbuvir + Daclatasvir + Ribavirin and initially responded with an undetectable HCV RNA 4 weeks post-treatment. However, relapse was again noted 12 weeks post-treatment with an HCV RNA of 32,461,845 IU/ml with signs of cirrhotic decompensation and patient eventually succumbed.

Conclusion: Factors that may increase the risk of relapse in DAA therapy are decompensated liver cirrhosis, a history of prior HCV treatment, and a high titer HCV RNA. Further investigations as to identifying the cause and treatment for relapse cases is recommended.

Keywords: case report; Hepatitis C; direct acting antivirals; relapse; re-retreatment

Introduction

The treatment and management of Hepatitis C Virus infection has come a long way since the advent of Interferon. What started as Interferon monotherapy, became pegylated Interferon plus Ribavirin. However, high rates of treatment failure, adverse effects, and relapse cases, led to the discovery of Direct Acting Antivirals (DAA's)[1] [3]. DAA's work by inhibiting specific stages of the HCV replication cycle and result in a 95-100% success rate in achieving sustained virologic response at 12 weeks post treatment (SVR12)[1] [2] [3]. But despite the efficacy of these newer agents, reports of HCV infected individuals treated with DAA's who relapsed not just once, but twice, on 2 different DAA combinations. Only 8 cases of these so-called "re-relapsers" have been reported worldwide, and the characteristics of these patients are still being investigated[1].

Case

This is a case of a 62-year old Filipino female nurse, who was diagnosed with HCV infection last 2014. Risk factors for the possible infection was a history of blood transfusion in the 1970's or from an unrecalled needlestick injury. Initial tests showed that the patient had Child Pugh A liver cirrhosis and an unrecalled HCV RNA level. She claimed to have received an unrecalled number of doses of pegInterferon + Ribavirin and was lost to follow-up.

In 2016, the patient noted to have easy fatigability and was admitted in a tertiary hospital. Work-up showed that the patient was genotype 1a, had Child Pugh A cirrhosis, had a baseline ultrasound showing hepatic parenchymal disease, and had a baseline HCV RNA level of 39,834,498 IU/ml. The patient was treated with Ledipasvir + Sofosbuvir 90mg/400mg/tab 1 tablet once daily for 12 weeks. A repeat HCV RNA at 4 weeks post treatment showed undetectable levels. However, the patient had her first relapse when an HCV RNA level at 12 weeks post treatment showed an increased value of 41,930,515 IU/ml. in the interim, the patient remained asymptomatic.

In 2017, the patient was noted to have episodes of confusion, drowsiness, and anorexia. She was re-admitted in a tertiary hospital and was diagnosed to have hepatic encephalopathy and Child Pugh B cirrhosis. The patient was given Lactulose 30cc every 8 hours, Rifaximin 200mg/tab 2 tablets TID, UDCA 500mg/tab 1 tab TID, and phospholipids 1 cap TID, and was started on a 24-week regimen of Sofosbuvir 400mg/day + Daclatasvir 60mg/day + Ribavirin 1200mg/day as recommended for treatment experienced HCV infected patients with Child Pugh B cirrhosis. At 4 weeks post treatment, HCV RNA was undetectable. But at 12 weeks post treatment, HCV RNA levels again increased to 32,461,845 IU/ml, confirming the patient's second relapse (Figure 1). The patient developed recurrent episodes of hepatic encephalopathy and worsening hepatic decompensation and eventually succumbed.

Discussion

DAA's have been effective in treating HCV infected individuals. It has become the standard of care, replacing pegInterferon + Ribavirin and its high relapse rates and non-responders. Only 6% of patients treated with all oral DAA's relapse and factors associated with relapse include presence of cirrhosis prior to treatment, a history of hepatocellular carcinoma, and a prior treatment history for HCV.[2] More importantly, patients who were documented to relapse received 1st generation DAA's, namely boceprevir (BOC) and telaprevir (TVR), which inhibit the HCV serine protease, NS3/4A. These 1st generation DAA's were combined with pegInterferon and Ribavirin, and had a low barrier to resistance, accomplishing an SVR12 of only 75%.[1] Newly developed DAA's, sofosbuvir (SOF), a NS5B polymerase inhibitor, simeprevir (SMV), a second phase NS3/4A protease inhibitor, and Ledipasvir, an NS5A inhibitor, have since replaced the older DAA's owing to its Interferon-free administration, higher barrier to resistance, and their all oral route administration.[1] [3]

This patient, who was diagnosed with HCV infection in 2014, had similar characteristics to previously reported relapse cases. She had genotype 1a HCV, had liver cirrhosis documented prior to treatment, had a baseline HCV RNA more than 1 million IU/ml, and had previously been treated with pegInterferon and Ribavirin. However, this patient was treated thereafter with 2 different newer generation DAA combinations, and relapsed in both treatment periods. In contrast to 8 reported cases of "re-relapsers", this patient was not given any of the 1st generation DAA's. The patient was also able to complete both treatment regimens without any missed doses.

Another point to consider is that the patient had compensated liver cirrhosis in contrast to decompensated liver cirrhosis found in the 8 reported cases from around the world. The treatment regimen provided for the patient was based on current guidelines and currently available DAA's in the local setting. Taking all these considerations into account, the risk of relapse in this patient should have been low.

There are no easily modifiable factors to explain why treatment did not lead to SVR in this patient. Other notable points include treatment adherence, correct treatment regimen and duration, and re-infection with another strain of HCV.[4] The patient completed treatment without missed doses. She was initially given Ledipasvir + Sofosbuvir which was appropriate as she was treatment naïve. And re-treatment with Sofosbuvir + Daclatasvir + Ribavirin for 24 weeks was also appropriate treatment for a patient with noted liver cirrhosis and treatment experience. Newer salvage treatment options include combination Sofosbuvir/velpatasvir/voxilaprevir or glecaprevir/pibrentasvir but are currently not yet available in the local setting.[5]

One probable reason for multiple relapse episodes in this patient is polymorphisms and mutations that develop during exposure to antiviral drugs that may contribute to the failure of DAA-based treatments. Q80K is one of the most common resistance mutations in the HCV NS3/4A protease. Numerous low-frequency substitutions in the target of SOF, the NS5B (nonstructural protein 5B) polymerase, have also been reported but need further testing.[1] This patient did not undergo any genetic mutation testing due to unavailability and lack of finances.

Conclusion

Factors that may increase the risk of relapse in DAA therapy are decompensated liver cirrhosis, a history of prior HCV treatment, and a high titer HCV RNA. Determining the underlying cause of relapse to newer generation DAA's are still under investigation. Further investigation as to the treatment for multiple relapse episodes is needed.

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