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CASE REPORT
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Sofosbuvir, ribavirin and pegylated interferon for a daclatasvir-resistent genotype 3 hepatitis C virus: case report and review

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ABSTRACT

Chronic Hepatitis C relapse after liver transplantation can lead to graft failure within a short time period. The high efficacy and good safety profile of direct-acting antivirals has led to consensual recommendations for using interferon-free treatment after liver transplantation. However, pegylated interferon may still be required for genotype 3 non-responders. We treated a liver graft recipient with grade 1 fibrosis in the biopsy with daclatasvir and sofosbuvir for 12 weeks. He did not respond and progressed to grade 3 fibrosis. Lacking other options, we obtained a sustained virological response with pegylated interferon, ribavirin and sofosbuvir for 12 weeks. The combination of pegylated interferon, ribavirin and sofosbuvir is a viable option after the failure of direct acting antivirals in economically disadvantaged countries.

KEYWORDS: Hepatitis C virus. Liver transplantation. Treatment.

INTRODUCTION

Chronic Hepatitis C Virus (HCV) infection is one of the most common diagnoses in candidates for liver transplantation (LT) throughout the world. HCV relapses in more than two thirds of those recipients that still have detectable viremia when they are submitted to LT. Furthermore, they have much higher viral loads and an accelerated disease course in the setting of immunosuppression[1].

The high efficacy and good safety profile of direct-acting antivirals (DAA) has led to consensual recommendations for using interferon-free treatment after LT[2-4]. However, there are very few options for patients who fail to respond to DAA, especially in developing countries where newer drugs are not yet available. We report the case of DAA failure after LT with successful retreatment using pegylated interferon with ribavirin (PR) and sofosbuvir, and review the pertinent literature.

CASE PRESENTATION

We describe the case of a male patient submitted to LT due to hepatocellular carcinoma (HCC) and compensated cirrhosis caused by HCV when he was 67 years old. The HCC had been treated with alcohol injections and was completely necrotic on the liver explant. He had failed to respond to treatment twice before LT, once with standard interferon and ribavirin and once with PR. On

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Table 1 - Anatomopathological results of liver biopsies.

Postoperative Time	Inflammation	Fibrosis	Conclusion
6 months	Severe (grade 3)	Absent	Acute hepatitis C
9 months	Moderate (grade 2)	Mild (grade 1)	Chronic hepatitis C Metavir A2F1
48 months	Mild (grade 1)	Mild (grade 1)	Chronic hepatitis C Metavir A1F1

the 17th postoperative month, he began a 48-week course of PR. Viremia lowered from 3 million international units (IU) to 92 IU at treatment week 12. It was undetectable at week 24 and at the end of treatment, but he suffered a relapse 6 months later, with a viral load of approximately 1 million IU. PR caused mild pleural and pericardial effusion and mild ascites, leading to the interruption of these drugs at week 48 instead of 72. Liver biopsy results are shown in Table 1. Four years and 3 months after LT, he was treated with daclatasvir and sofosbuvir for 12 weeks according to the Brazilians' public health protocol at that time, which restricted treatment duration to 12 weeks for all patients. Notwithstanding, post-treatment viral load was 580.000 IU. One year after that, a fibroelastogram showed a liver stiffness of 9.6 kPa, equivalent to grade 3 fibrosis. Two different liver ultrasound examinations did not disclose any signs of chronic liver disease or portal hypertension. The patient then received PR plus sofosbuvir for 12 weeks. The viral load fell to 35 IU after 4 weeks of treatment. Within 7 weeks, ribavirin had to be reduced from 1 g to 500 mg daily, because serum hemoglobin fell from 12.8 to 7.6 mg/dL. He received two red blood cell transfusions; ribavirin was reduced to 250 mg per day, which he was able to receive until the end of treatment. Viral load was undetectable (less than 12 IU/mL) 24 weeks after treatment and remained so when tested after another year.

DISCUSSION

The benefits of treating HCV relapse after LT have been more thoroughly evaluated with interferon. There is progression to cirrhosis in more than 20% of patients in 5 years without treatment , with a minimum decompensation rate of 30% in the first year. Sustained virological response (SVR) leads to favorable outcome with improvement of fibrosis, graft and patient survival and reduced rates of decompensated cirrhosis[5-8].

DAA have revolutionized HCV treatment by means of high efficacy and a favorable safety profile. In Brazil, DAA has been provided by the public health system since 2015. We have only two options available for the treatment of genotype 3 HCV: PR plus sofosbuvir or sofosbuvir plus daclatasvir, with the possibility of adding ribavirin, for 12 or 24 weeks. At the time the reported patient was treated, there was no recommendation from the Brazilian public health system to use ribavirin in all LT patients.

Genotype 3 HCV is associated with fewer treatment options, faster rates of progression to fibrosis and lower SVR rates, especially in the presence of advanced fibrosis or decompensated cirrhosis[9]. Due to its lower prevalence, it was underrepresented in clinical trials, especially those that included LT patients[10-14].

We have previously published our real-life data on HCV treatment after LT with a 12-week course of sofosbuvir and daclatasvir, with or without ribavirin. There were 4 treatment failures in 39 patients (89.7% SVR) and one of them is the case reported here. It is worth noticing that all failures occurred in the subgroup of 26 patients with genotype 3 HCV[15]. The CUPILT study included 137 mono-infected HCV LT patients treated with sofosbuvir and daclatasvir, with or without ribavirin, but only 15 patients were genotype 3[16]. Ally-1 Phase 3 trial is currently underway and its preliminary results have shown up to 91% of SVR rates, but genotype 3 was represented by only 11 of 53 LT recipients treated with a 12-week course of sofosbuvir, daclatasvir and ribavirin[17].

Considering the accelerated rate of progression to fibrosis in these immunocompromised patients, they should be treated without delay, using other classes of drugs. Current options for retreating DAA-experienced genotype 3 patients include combinations such as sofosbuvir, velpatasvir and voxilaprevir[18], glecaprevir and pibrentasvir or triple combinations including these drugs[19]. However, these recently released DAA are still unavailable in many countries.

Resistance-associated variants (RAVs) are selected when treatment with daclatasvir or other nonstructural protein 5A (NS5A) inhibitors fails, and they might persist for a long time after treatment discontinuation[1]. RAVs can compromise DAA retreatment results with regimens that include NS5A inhibitors. On the other hand, the Y93H RAV has been shown to increase susceptibility to interferon-based therapy in comparison with the Y93 wild type, favoring interferon-containing regimens in these cases[20].

Unlike NS5A inhibitors such as daclatasvir, sofosbuvir is a NS5B polymerase inhibitor with a high genetic barrier to resistance. A sofosbuvir and PR combination was recommended in EASL and AASLD editions in 2015 for genotype 3 HCV infection, excluding patients with decompensated cirrhosis and LT recipients[3,4]. The TARGET real-life study included a subgroup of 19 patients that received PR plus sofosbuvir with 84% SVR, although most of them were genotype 1 with no history of LT[21]. Although it is not a currently recommended option after LT, there is a large experience with PR treatment in these patients before DAAs were available.

The therapeutic success that we obtained in this case is relevant, because it shows there is an economically viable option for LT patients, in whom the disease can progress too rapidly to wait for new drugs to become available in countries that cannot afford to distribute the top line DAA treatment.

CONFLICT OF INTERESTS

We certify that we have no commercial associations that might pose a conflict of interest in connection with the submitted article.

AUTHORS' CONTRIBUTIONS

Marcos Mucenic: data collection, text writing, review of the literature Ajacio B. M. Brandao, Claudio A. Marroni, Alfeu M. Fleck-Junior, Ane M. Costabeber, Fernanda K. F. Sacco, Giovana Rossato: text editing and review of the literature. Maria L. Zanotelli, Ian Leipnitz, Mário H. Meine, Guillermo Kiss, Juliano Martini, Eduardo S. Schlindwein, Guido P.C. Cantisani: text editing

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