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REVIEW

Treatment of hepatitis C before and after liver transplantation☆

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KEYWORDS
Liver transplantation;
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Abstract Hepatitis C recurrence after liver transplantation is universal and increases morbidity and mortality in these patients. The development of new direct antiviral agents against the hepatitis C virus is a major treatment advance. Pre-transplant treatment avoids graft infection and sometimes improves liver function, allowing the patient to be withdrawn from the transplant waiting list. Delaying treatment until the postpostransplant period may be advisable in patients with advanced cirrhosis. Generally, antiviral therapy after liver transplantation is provided in patients with histological evidence of the disease. In these patients, treatment is more effective in the initial stages of the disease. The choice of antiviral therapy in these patients is based on the degree of liver function, the presence of renal failure, and potential drug–drug interactions.

PALABRAS CLAVE
Trasplante hepático;
Hepatitis C;
Antivirales directos

Tratamiento de la hepatitis C en el pre- y postrasplante hepático

Resumen La recidiva de la hepatitis C tras el trasplante hepático es universal y condiciona un aumento en la morbimortalidad del paciente. El desarrollo de nuevos agentes antivirales directos contra el virus C es un gran avance en el tratamiento de estos pacientes. El tratamiento antes del trasplante permite evitar la infección del injerto y, en algunos casos, obtener una mejoría de la función hepática que permita la retirada del paciente de la lista de espera. En pacientes con cirrosis avanzada, podría ser preferible diferir el tratamiento hasta el periodo

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postrasplante. Generalmente, el tratamiento antiviral tras el trasplante hepático se realiza en pacientes con evidencia de lesión histológica. En estos pacientes, la eficacia del tratamiento es mayor en estadios iniciales de la enfermedad. La elección del tratamiento antiviral en estos pacientes se basa en el grado de disfunción hepática, la presencia de fallo renal y las potenciales interacciones medicamentosas.

Introduction

Recurrence of hepatitis C (HCV) after liver transplantation (LT) is widespread, and disease progression is more accelerated in comparison with immunocompetent patients. In fact, between 20% and 30% of patients develop cirrhosis within 5 years of LT.[1] The risk of decompensation in cirrhotic patients is 40% within 1 year, and as high as 70% within 3 years following diagnosis.[2] In these patients, decompensated cirrhosis is an indicator of early death, as 60% of decompensated patients die within 1 year once decompensation develops.[3] A small proportion of patients (5–10%) develop a severe form of recurrent hepatitis C known as fibrosing cholestatic hepatitis. If not treated, this infection can cause graft loss and death.[4]

The introduction of direct-acting antivirals (DAA) in recent years has marked a major breakthrough in the treatment of chronic HCV. The combination of several such interferon (IFN) free drugs has shown high rates of sustained virologic response (SVR), an excellent safety profile and good tolerability, even in patients with advanced disease.[5,6] In this paper, we review the latest developments in the treatment of HCV before and after LT.

Pre-transplant antiviral therapy

The main goal of antiviral treatment in patients awaiting LT is to prevent graft infection. Treatment can be administered in 2 regimens: (1) a short (or incomplete) course to achieve undetectable HCV-RNA levels prior to LT, or (2) a full course, to achieve SVR prior to LT.

In addition to preventing graft infection, pre-LT antiviral therapy can also improve liver function and allow some patients to be removed from the LT waiting list. However, the frequency of this improvement and the predictive factors that might identify which patients will present a significant improvement in liver function remain to be determined.[7]

Treatment of patients with compensated cirrhosis

The first study in patients on LT waiting lists evaluated administration of sofosbuvir (SOF) in combination with ribavirin (RBV) for 48 weeks in 61 patients with compensated cirrhosis of the liver (Child-Pugh A) and hepatocellular carcinoma (Milan criteria). Of the 43 patients with undetectable HCV-RNA levels at the time of transplantation, 70% achieved post-LT SVR. This study also found that the probability of achieving post-LT SVR was significantly higher in patients with undetectable HCV-RNA levels lasting more than 30 days prior to LT.[8] Despite the significance of the findings, this drug combination is still considered suboptimal in patients infected with HCV genotype (G) 1, and the combination of at least 2 DAAs is still considered necessary. Two phase 3 studies evaluated the safety and efficacy of SOF and ledipasvir (LDV, either with or without RBV) for 12 or 24 weeks in cirrhotic patients infected with G1.[9,10] The ION-1 study[9] included 865 treatment-naive patients, 136 (16%) of whom were diagnosed with cirrhosis. In this cirrhotic subgroup, the authors observed SVR rates of 100% in patients treated with RBV, and 97% in patients who did not receive RBV. The ION-2 study[10] evaluated 440 previously treated patients (including patients in whom triple therapy with first generation protease inhibitors had failed), 88 (20%) with cirrhosis. In this study, the authors observed SVR rates of 88% and 100% in patients treated for 12 and 24 weeks, respectively.

The TURQUOISE-II study evaluated the efficacy and safety of paritaprevir/ritonavir/ombitasvir (PTV/r/OBV) therapy combined with dasabuvir (DVR) and RBV in a 12- or 24-week regimen in 380 patients with compensated cirrhosis. SVR rates of 92% and 96% were observed in patients treated for 12 and 24 weeks, respectively. Virologic response was lower in patients infected with G1a, in previously treated patients, and in patients with clinical signs of portal hypertension.[11]

In the case of patients infected with HCV G2 and G3, phase 3 studies evaluating treatment with SOF and RBV for 12 or 16 weeks showed that cirrhotic patients presented lower SVR rates than their non-cirrhotic counterparts (≈80%). Despite the progress made in antiviral therapy, the treatment of cirrhotic patients infected with G3, particularly those with previous treatment failure, is still challenging. The outcome of treatment with a combination of SOF + RBV (24 weeks), or SOF + daclatasvir (DCV, 12 weeks) is suboptimal in this patient population (61% and 59%, respectively).[12,13]

Treatment of patients with decompensated cirrhosis

Recent studies have evaluated the efficacy of new antiviral drugs in patients with decompensated cirrhosis (Fig. 1). The SOLAR-1 study evaluated the efficacy and safety of SOF/LDV + RBV therapy for 12 or 24 weeks in 108 cirrhotic Child-Pugh B and C patients infected with HCV G1 and G4.