Research Article

EASL JOURNAL OF HEPATOLOGY

Viral Hepatitis

Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence – The ANRS CUPILT study

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Background & Aims: HCV recurrence remains a major issue in the liver transplant field, as it has a negative impact on both graft and patient survival. The purpose of this study was to investigate the efficacy and safety of treating HCV recurrence with sofosbuvir (SOF) and daclatasvir (DCV) combination therapy.

Methods: From October 2013 to March 2015, 559 liver recipients were enrolled in the prospective multicentre France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) Compassionate use of Protease Inhibitors in viral C Liver Transplantation cohort. We selected 137 patients with an HCV recurrence receiving SOF and DCV, whatever the genotype or fibrosis stage. The use of ribavirin and the duration of therapy were at the investigator's discretion. The primary efficacy end point was a sustained virological response (SVR) 12 weeks after the end of treatment.

Results: The SVR rate 12 weeks after completing treatment was 96% under the intention-to treat analysis and 99% when excluding non-virological failures. Only two patients experienced a virological failure. The serious adverse event (SAE) rate reached 17.5%. Four patients (3%) stopped their treatment prematurely because of SAEs. Anaemia was the most common AE, with

Keywords: Daclatasvir; Direct-acting antiviral agents; Hepatitis C; Liver transplantation; Recurrence; Sofosbuvir.

Received 27 November 2015; received in revised form 19 May 2016; accepted 23 May 2016; available online 1 June 2016

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Abbreviations: AE, adverse events; DAAs, direct-acting antiviral agents; DCV, daclatasvir; EOT, end of treatment; GFR, glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMS, immunosuppressive; LLOQ, lower limit of quantification; LT, liver transplantation; MDRD, modified diet in renal disease; MELD, model for end-stage liver disease; PegIFN, pegylated interferon; RBV, ribavirin; SAE, serious adverse events; SOF, sofosbuvir; SVR, sustained virological response; TBC, trough blood concentration; W, week.

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significantly more cases in the ribavirin group (56% *vs.* 18%; p <0.0001). A slight but significant reduction in creatinine clearance was reported. No clinically relevant drug-drug interactions were noted, but 52% of patients required a change to the dosage of immunosuppressive drugs.

Conclusions: Treatment with SOF plus DCV was associated with a high SVR12 and low rates of serious adverse events among liver recipients with HCV recurrence.

Lay summary: The recurrence of hepatitis C used to be the first cause of graft failure in infected liver transplanted recipients. Our study demonstrates the great efficacy of one combination of new all-oral direct-acting antiviral, sofosbuvir and daclatasvir, to treat the recurrence of hepatitis C on the graft. Ninety-six per cent of recipients were cured. The safety profile of this combination seemed to be good, especially no relevant drug-drug interaction with immunosuppressive drugs.

Introduction

Hepatitis C virus (HCV) represents a major healthcare issue, in that some 170 million people are chronically infected worldwide [1]. When patients develop end-stage liver disease or hepatocellular carcinoma, liver transplantation (LT) remains the only curative option. In France, more than 20% of candidates for LT are infected with HCV [2]. Among patients with a positive viral load, a recurrence of HCV infection on the graft is constant and constituted a challenge in the past because fibrosis progression may be accelerated when compared to the situation in non-transplant patients. Twenty to 30% of HCV-infected recipients develop graft cirrhosis within 5 years of LT [3]. This results in poorer graft and patient survival rates compared to those of recipients transplanted for another indication [4].

The clearance of HCV is the only way to improve the outcome of these patients. The standard of care for treating HCV recurrence used to be 48 weeks of peg-interferon (PegIFN) with ribavirin (RBV), although this was only effective in 30% of patients, mainly because of poor tolerance which led to premature treatment discontinuation in 30% of cases. The combination of a first-generation protease inhibitor (telaprevir or boceprevir) with PegIFN and RBV subsequently improved sustained virological response (SVR) rates to 50%–65% in genotype 1 HCV-infected recipients, but at the cost of an even poorer safety profile and potent drug-drug interactions [5,6]. Although feasible, these regimens required close monitoring and considerable clinical expertise.

In 2013, two second-generation direct-acting antiviral agents (DAAs), the nucleotide analogue NS5B polymerase inhibitor sofosbuvir (SOF), and the nucleotide analogue NS5A polymerase inhibitor daclatasvir (DCV), became available through an early access programme and were then approved by the French Agency for the Safety of Medicines and Healthcare Products (ANSM). Although limited, the preliminary data on the combined use of SOF and DCV with or without RBV have shown high SVR rates of >90%, with minimal side effects in non-transplant patients [7]. Consequently, access to this combination was available from the outset for the sickest patients, including those undergoing a liver transplant.

Initial experience using SOF plus DCV in the transplant setting took the form of a case report [8]. Our group then reported on the efficacy and safety of this type of combination in the most urgent and difficult to treat patients. Among 15 patients suffering from fibrosing cholestatic hepatitis, a significant clinical improvement was achieved, with an SVR12 of 96% [9]. Recently, the open-label ALLY-1 study assessed the safety and efficacy of the SOF and DCV combination plus RBV to treat HCV infection in the context of advanced cirrhosis or post-LT recurrence in 53 patients [10]. SVR was achieved by 95% and 91% of patients with genotype 1 and 3 infections, respectively. We report here on our multicentre experience including a large number of patients who received SOF and DCV, with or without RBV, to treat an HCV recurrence of varying degrees of severity following LT.

Patients and methods

Study design and patients

The France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) C023 "Compassionate use of Protease Inhibitors in viral C Liver Transplantation" (CUPILT) study is a multicentre prospective cohort being implemented in 24 French and one Belgian LT centre (ClinicalTrials.gov number NCT01944527). It is being funded and sponsored by ANRS. To be enrolled in this cohort, patients must have (1) received a liver transplant for an HCV infection, (2) experienced an HCV recurrence whatever the stage of fibrosis, (3) been treated with second-generation DAAs, and (4) given their written informed consent. At enrolment, fibrosis stage was established based on a histological assessment (according to the METAVIR scoring system [11]) and/or elastometry (such as F3 $\geqslant$9.5 kPa and F4 $\geqslant$14.5 kPa). The protocol has been carried out in accordance with the Declaration of Helsinki and French laws on biomedical research, and was approved by the "South Mediterranean Ethics Committee" (France). Exclusion criteria were an age under 18 and pregnancy.

Between October 2013 and March 2015, 559 liver recipients were enrolled. For the present study, we selected patients receiving both SOF and DCV who were followed for at least 12 weeks after treatment discontinuation. Patients were excluded if they were co-infected with the human immunodeficiency virus (HIV) or diagnosed with fibrosing cholestatic hepatitis (as previously defined [9]).

This study is observational so that the type of treatment, dosing of drugs and duration of treatment are at the discretion of each investigator. However, the CUPILT Scientific Committee (Supplementary Appendix 1) issues treatment recommendations every 6 months. Patients receive SOF and DCV at a once-daily dose of 400 mg and 60 mg, respectively. When used, the RBV dose is adjusted by considering body weight, potential ribavirin-related haematological toxicity and renal function in the LT recipients. Treatment duration was initially planned for 12 or 24 weeks, but the investigators are allowed to extend this period if they deem this clinically necessary.

Efficacy assessments

For this study, plasma HCV RNA levels were quantified using the Abbott Real Time HCV PCR assay (lower limit of quantification (LLOQ) of 12 IU/ml, Abbott Diagnostics®, USA) or COBAS AmpliPrep® or COBAS TaqMan® (LLOQ of 15 IU/ml, Roche Molecular Systems, Pleasanton, California). HCV RNA was monitored at baseline, during scheduled visits throughout treatment (1, 2, 3, 4, 6, 8, 12, and if applicable 16, 20 and 24 weeks) and then at 4, 12, 24, 48 weeks after the completion of treatment. The primary endpoint was the proportion of patients who achieved undetected HCV RNA levels or an SVR at week 12 after treatment discontinuation (SVR12). Secondary endpoints included viral kinetics, and on-treatment (week 4) and end of treatment (EOT) response rates. Virological failures were also reported. Viral breakthrough and relapse were defined as plasma HCV RNA levels higher than the LLOQ after achieving a level lower than the LLOQ, during treatment and after the EOT, respectively. When a virological failure occurred, baseline and relapse resistance-associated viral (RAV) mutations in the NS3/A4, NS5A and NS5B regions were obtained by population sequencing using in-house methods. RAVs were defined according to the Geno2Pheno algorithm (http://hcv.geno2pheno.org/), developed by the Max-Planck-Institut für Informatik, Saarbrücken, Germany.