Research Article

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Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study

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Background & Aims: All oral direct acting antivirals (DAA) have been shown to improve the liver function of patients with decompensated cirrhosis but it is presently unknown whether this clinical improvement may lead to the delisting of some patients. The aim of this study was to assess if and which patients can be first inactivated due to clinically improvement and subsequently delisted in a real life setting.

Methods: 103 consecutive listed patients without hepatocellular carcinoma were treated with different DAA combinations in 11 European centres between February 2014 and February 2015.

Results: The cumulative incidence of inactivated and delisted patients by competing risk analysis was 15.5% and 0% at 24 weeks, 27.6% and 10.3% at 48 weeks, 33.3% and 19.2% at 60 weeks. The 34 patients who were inactivated showed a median improvement of 3.4 points for MELD (delta MELD, p <0.0001) and 2 points for Child-Pugh (CP) (delta-CP, p <0.0001). Three variables emerged from the most parsimonious multivariate competing risk model as predictors of inactivation for clinical improvement, namely, baseline MELD classes (MELD 16–20: HR = 0.120; p = 0.0005, MELD >20:HR = 0.042; p <0.0001), delta MELD (HR = 1.349; p <0.0001) and delta albumin (HR = 0.307; p = 0.0069) both assessed after 12 weeks of DAA therapy.

Conclusions: This study showed that all oral DAAs were able to reverse liver dysfunction and favoured the inactivation and delisting of about one patient out-of-three and one patient out-of-five in 60 weeks, respectively. Patients with lower MELD scores had higher chances to be delisted. The longer term benefits of therapy need to be ascertained.

Lay summary: The excellent efficacy and safety profile of the new drugs against Hepatitis C virus, "direct acting antivirals" or DAAs, have made antiviral therapy possible also for patients with advanced liver disease and for those on the waiting list for liver transplantation (LT). This study shows for the first time that the DAAs may lead to a remarkable clinical improvement allowing the delisting of one patient out of 5.

Keywords: Direct acting antivirals; Liver transplantation; Delisting; HCV; Cirrhosis.

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Abbreviations: DAAs, direct acting antivirals; HCV, hepatitis C virus; LT, liver transplantation; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; ELITA, European Liver and Intestine Transplant Association; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HE, hepatic encephalopathy; HPS, hepato-pulmonary syndrome; HCV-RNA, hepatitis C virus-ribonucleic acid; SOF, sofosbuvir; RBV, ribavirin; DCV, daclatasvir; LDV, ledipasvir; SMV, simeprevir; INR, international normalized ratio; SD, standard deviation; IQR, interquartile range; CP, Child-Pugh; WL, waiting list; RVR, rapid virological response; EVR, early virological response; SVR, sustained virological response; EOT, end of treatment; EMA, European Medicines Agency; FDA, Food and Drug Administration.

Introduction

The availability of new direct acting antivirals (DAAs) has radically changed the approach to the treatment of hepatitis C virus (HCV) infection and also the prognosis of patients with HCV-related liver disease. The excellent efficacy and safety profile of these drugs and the potential to use all interferon-free regimes, have made antiviral therapy possible also for patients with advanced liver disease and for those on the waiting list for liver transplantation (LT).

Interim and preliminary data from on-going clinical trials indicate that new DAAs given to patients with decompensated cirrhosis are highly effective in eradicating HCV infection and may lead, in some cases, to a significant clinical improvement [1–6] with reversal of de-compensation. These data are prompting the liver transplant community to explore whether the same favourable results can be obtained in liver transplant candidates but, more importantly, whether they may eventually allow the inactivation/delisting of some patients due to clinical improvement [7]. Several transplant centres across Europe have started using these drugs, but clinical trials or reports of field experience are lacking.

To verify the validity of this new scenario, we initially conducted a survey focused on HCV positive liver transplant candidates with decompensated cirrhosis without hepatocellular carcinoma (HCC) and who had been treated with the new DAAs at different European liver transplant centres. The preliminary results of this survey were discussed at an "ad hoc" European Liver and Intestine Transplant Association (ELITA) monothematic conference in Milan and were the basis for the development of an extended database recording patients with HCV-related decompensated cirrhosis and no HCC, listed for transplantation and treated with second generation DAAs while on the waiting list. The objective of this multicentre European study was to understand the impact of DAAs on inactivation/delisting due to clinical improvement in a real life setting.

Patients and methods

A monothematic conference organized by ELITA regarding the use of second generation DAAs both before and after LT was held in Milan on 6 March 2015. This event allowed experts from several liver transplant centres across Europe to share their experience on the day to day use of these novel treatments which became available about 1 year earlier.

At the conference, it was decided to retrospectively collect data from patients listed for decompensated cirrhosis and consecutively treated with 2nd generation DAAs during the waiting period between February 2014 and February 2015 and were followed until 31 December 2015. Eleven European centres participated to this study: Bergamo, Bologna, Milan Niguarda, Milan Policlinico, Montpellier, Paris Mondor, Villejuif Paris Paul Brousse, Palermo, Turin, Valencia and Vienna.

Inclusion criteria

Consecutive liver transplant candidates with decompensated HCV cirrhosis without HCC treated with second generation DAAs while listed for LT.

Criteria for listing

Basically, patients were listed if they had a MELD score >15 or a MELD score <15 with MELD exceptions such as refractory ascites not treatable with transjugular intrahepatic portosystemic shunt (TIPS) (8 cases), chronic hepatic encephalopathy (13 cases), hepato-pulmonary syndrome (2 cases) and refractory bleeding (2 cases). In addition, 11 patients were judged worth listing despite a MELD score <15 and no clear MELD exception. Overall 35 patients were listed with MELD <15. The distribution of patients with MELD <15 was similar across centres.

Exclusion criteria

HIV or HBV co-infected recipients were excluded from this study as well as patients who had started DAA treatment before listing.

Definitions and patient stratifications

In case of clinical improvement due to DAAs therapy the following definitions were used:

Inactivation: patient is placed "on hold" due to clinical improvement based on clinical judgement of local investigator. For such a patient the clinician judges that, based on liver function and/or clinical improvements, LT is presently no longer indicated, but the patient is not removed from the list until a long-term clinical improvement has been verified. Defining "clinical improvement leading to inactivation" was one the aims of the study.

Delisting: patient is off the list because a durable clinical improvement has been verified based on clinical judgement of local investigator.

End points

The primary end points were the probability to be inactivated due to clinical improvement.

Secondary end points included virological efficacy, DAA-related improvement of liver function, description of the objective criteria taken into account by investigators for considering inactivation and eventually delisting.

To achieve these goals, the following parameters were retrospectively collected:

Baseline: demographics, indication for LT, genotype, previous antiviral therapy, HCV-RNA levels, DAA regimen used (sofosbuvir/ribavirin-SOF/RBV or sofosbuvir/daclatasvir-SOF/DCV or sofosbuvir/ledipasvir-SOF/LDV or sofosbuvir/simeprevir-SOF/SMV) and duration, MELD score, CP scores and individual components of MELD and CP scores (bilirubin, INR, creatinine, albumin, ascites and encephalopathy). Cofactors for liver decompensation, such as alcohol consumption, bacterial infections, haemorrhagic events and portal vein thrombosis were also registered.

During therapy and follow-up: HCV-RNA levels at 4, 8, 12, 16 and 24 weeks. MELD, CP scores and individual components of MELD and CP scores (bilirubin, INR, creatinine, albumin, ascites and encephalopathy) at 12 and 24 weeks. For those receiving ribavirin, median ribavirin dose was registered.

Outcome. Seven clinical outcomes were identified and registered: 1) liver transplantation, 2) patient still waiting for a liver transplant, 3) death while waiting for transplant, 4) patient inactive in the transplant list due to clinical improvement, 5) patient delisted due to clinical improvement, 6) patient dropout due to other causes (e.g., clinical worsening, refused liver transplant) and 7) death after inactivation or delisting.

Type and duration of antiviral treatment

Planned duration of treatment was up to 48 weeks or until transplant for patients receiving SOF/RBV and up to 24 weeks or until transplant for those receiving SOF/DCV or SOF/LDV or SOF/SMV with or without RBV. DAAs combinations were used depending on genotype and drug availability.

Ethical approval was not sought as the study utilised data provided in the course of normal patient care and no patient-identifiable data were collected.

Statistical analysis

Descriptive statistical analysis was performed where data are expressed as median (interquartile range (IQR) or range). Categorical variables were compared with the Chi-square test or 2-sided Fisher's exact test, continues variables were analysed by the student's *t* test or by Wilcoxon's rank-sum test as appropriate. McNemar's test or Bowker's test were used to compare categorical variables before and after treatment while paired student's *t* test or Mann-Whitney *U* test was used for continues variables as appropriate.

The impact of DAA on liver functions (MELD, CP score, bilirubin, creatinine, etc.) was assessed over time at 12 and 24 weeks after start of therapy. The same parameters were analysed comparing inactivated vs non-inactivated patients. For