Review

EASL JOURNAL OF HEPATOLOGY

ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients

Coordinators: Luca S. Belli[1,2,*,†], Christophe Duvoux[3,†]
Panel of experts (in alphabetical order): Marina Berenguer[12,‡], Thomas Berg[4,‡], Audrey Coilly[11,‡], Isabelle Colle[9,‡], Stefano Fagiuoli[6,‡], Saye Khoo[7,‡], Georges Philippe Pageaux[8,‡], Massimo Puoti[10,‡], Didier Samuel[11,‡], Mario Strazzabosco[2,5,‡]

Summary

The advent of safe and highly effective direct-acting antiviral agents (DAAs) has had huge implications for the hepatitis C virus (HCV) transplant field, and changed our management of both patients on the waiting list and those with HCV graft re-infection after liver transplantation (LT). When treating HCV infection before LT, HCV re-infection of the graft can be prevented in nearly all patients. In addition, some candidates show a remarkable clinical improvement and may be delisted.
Alternatively, HCV infection can be treated post-LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence, as was carried out in the past. In either case, some DAAs have a limited use because of their drug to drug interactions with various immunosuppressants as well as the many other drugs liver transplant recipients are often prescribed. In addition, some DAAs should be avoided in case of severe renal failure, which is not an unusual complication after LT.
The present document provides a series of consensus statements on the LT issues that have not been extensively addressed previously. These statements have been developed to support physicians and other stakeholders in charge of LT candidates and recipients when deciding to treat HCV, especially in difficult situations.

Keywords: Antiviral agents; Liver transplantation; Liver transplant candidate; Liver transplant recipient; Recurrent hepatitis C; Hepatitis C, chronic; Interferons; Guidelines; Waiting lists; Liver failure.

Received 11 December 2016; received in revised form 1 March 2017; accepted 9 March 2017

Introduction

Chronic hepatitis C virus (HCV) infection related advanced liver disease is the most common indication for liver transplantation (LT), which accounts for about 10% to 50% of LTs performed in Northern and Southern Europe, respectively (www.ELTR.org). Until very recently, all HCV recipients who underwent LT had detectable viremia. Virtually all of them had HCV re-infection shortly after transplant. Between 10% to 30% developed cirrhosis within 5 years from LT and 40% presented signs of liver decompensation within 1 year from the diagnosis of recurrent cirrhosis.[1–3] The combination of pegylated interferon (PegIFN) and ribavirin (RBV) has been the only therapeutic option available for the last 20 years but it was rarely effective, particularly in patients with more advanced graft hepatitis. Due to the high risk of severe disease recurrence, re-transplantation was controversial because of the risk of HCV-induced graft failure. These factors clarify why HCV infected recipients had a reduced survival rate by at least 10% after 5 years of follow-up, compared to non-HCV infected individuals.[4]

The advent of safe and highly effective direct-acting antiviral agents (DAA) has had huge implications for the HCV transplant field, and changed the management of both patients on the waiting list and those with HCV graft re-infection after LT. When treating HCV infection before LT, some candidates show a remarkable clinical improvement and may be delisted. If not, HCV re-infection of the graft may be prevented in nearly all patients when a HCV RNA negative status is achieved by DAAs at least 4 weeks before transplantation (>95%).

Alternatively, HCV infection can be treated post-LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence, carried out in the past. In

[1]*Department of Hepatology and Gastroenterology, Niguarda Hospital, Italy*;
[2]*International Centre for Digestive Health, School of Medicine and Surgery, University of Milano Bicocca, Italy*;
[3]*Department of Hepatology and Liver Transplant Unit, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris, Paris-Est University, Creteil, France*;
[4]*Section of Hepatology, Clinic for Gastroenterology and Rheumatology, University Clinic Leipzig, Germany*;
[5]*Yale University Liver Center, Department of Medicine New Haven, USA*;
[6]*Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, Bergamo, Italy*;
[7]*Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool*;

either case, some DAAs have a limited use due to their drug to drug interactions (DDI) with various immunosuppressants (IS), as well as the many other drugs often prescribed to liver transplant recipients. In addition, some DAAs should be avoided in cases of severe renal failure, which is not an unusual complication after LT.

Finally, anti-HCV positive donors with favourable histological features are likely to become an important additional resource for the donor pool, particularly in areas where anti-HCV positive donors are more prevalent. The potential recipients of these grafts should be selected beforehand and treated after LT.

In the middle of this therapeutic revolution, two monothematic European Liver and Intestine Transplant Association (ELITA) conferences were held in Milan in March 2015 and April 2016, where a selected number of European experts discussed the many unsolved issues regarding the use of DAAs before and after LT. The present document provides the conclusions of these conferences, which are presented as the ELITA statements.

Methods

These "Consensus statements" were elaborated following a slightly modified Appraisal of Guidelines for Research & Evaluation methodology.[5] In brief, the promoter of this initiative was ELITA, whose governing body selected a scientific board of experts in charge of organizing the two conferences held in Milan and of writing this document. The two conferences were endorsed by the Italian Association for the study of the Liver (AISF) and by the European Association for the Study of the Liver (EASL). The scientific board defined the methodology used as well as the goals, and acted as developer and reviewer. The methodology chosen involved the following steps:

(a) The scientific board selected 13 topics of interest and relevant questions regarding both clinical practice and controversial areas.
(b) The scientific board also identified two working groups. The first addressed the issues related to "the management of the patient on the waiting list", the second "the treatment of post-transplant HCV disease recurrence". The two working groups were composed of five experts guided by a group leader. The members of the two working groups were selected based on competence, role, expertise and publications/research in the field of HCV and LT.
(c) The two group leaders together with the scientific board elaborated the provisional statements. All questions and provisional statements were circulated among the experts of each working group before the conferences were held in Milan. This policy allowed each expert to independently carry out a systematic literature search, using Medline/PubMed to support definitions and statements.
(d) The statements were discussed among the experts of the two working groups during two conferences held in Milan on 6th March 2015 and April 1st 2016, to improve the quality of the statements. The two conferences were videoed and all relevant comments were considered when preparing the final document.
(e) The scientific board prepared a draft of the "Consensus statements", which incorporated the conclusions of the two Milan conferences, as well as the relevant data from existing publications and presentations at international meetings up to April 2016. For each of the 13 issues, a short background and a summary of the evidence was presented. The evidence and recommendations were graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system[5] (Table 1).
(f) The first draft of the Consensus statements was eventually submitted to the experts of the working groups for corrections, comments and approval of the recommendations. Following a Delphi process, the experts were asked to specify whether they approved each recommendation and, if not, to justify their disagreement. Corrections and comments were considered in the final version of the Consensus statements. Agreement among experts was very high (96%).
(g) The promoter, and all members of the scientific board and working groups were asked to declare any potential conflict of interests.

Table 1. GRADE system used in the EASL Clinical Practice Guidelines.

Grade evidence	
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, uncontrolled experiments
III	Opinions of respected authorities

The questions selected by the scientific board are listed below:

Pre-transplant phase

- **Which DAAs should be used in patients with cirrhosis listed for LT?**
- **Which treatment schedules should be used in listed patients, and what are the expected sustained virological responses (SVR)?**
- **What is the impact of pre-LT DAAs on liver function and delisting?**

[8]*Department of Hepatology, Gastroenterology, and Liver Transplantation, Centre Hospitalier Universitaire, Saint Eloi, Montpellier, France*;
[9]*Hepatology and Gastroenterology, Unversity of Gent, Belgium*;
[10]*Department of Infective Diseases. Niguarda Hospital, Milan, Italy*;
[11]*Centre Hepato-Biliaire,Paul Brousse Hospital, Assistance Publique-Hôpitaux de Paris, Paris-Sud University, Villejuif, France*;
[12]*Hepatology& Liver Transplantation Unit, Hospital Universitari I Politècnic La Fe, University of Valencia & Ciberhed, Valencia, Spain*

† These authors contributed equally as co-ordinators and joint first authors.

‡ These authors acted as expert contributors to the manuscript.

* Corresponding author. Address: Ospedale Niguarda, Epatologia e Gastroenterologia, Piazza Ospedale Maggiore 3, Milano 20162, Italy. Tel.: +39 3283627044.
E-mail address: luca.belli@ospedaleniguarda.it (L.S. Belli)