



Toward Zero Hepatitis C Virus-Related Mortality as a Prerequisite for the Release of Resources in a Center for Follow-up of Liver Transplant

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ABSTRACT

Taking charge of a liver transplanted (LT) patient implies not only to follow up the transplanted organ (eg, immunosuppression and cancer risk) but also to deal with the prevailing patient's active problems.

The recurrence of hepatitis C on the graft has historically been one of the main active problems to be addressed, leading to 30% to 40% mortality per se in these patients and has involved many resources in the hepatological centers responsible for the follow-up.

We verified how much the availability of the new drugs with direct-acting antiviral agents (DAAs) against hepatitis C virus (HCV) has impacted the mortality within the assisted population, changing its characteristics and addressing new clinical issues in the LT-patients. We performed a retrospective comparison between 230 LT patients followed up during pre-DAA era (group 1, with 88 HCV RNA-positive) and 244 patients observed from 2014 onward when DAAs became available (group 2, with 79 HCV RNA-positive).

Fifty-two antiviral therapies were performed in group 1 with 18 sustained virologic response (SVR) (35%) and 53 treatments, of which 37 were retreatments, in group 2 with 51 SVR (96%), $P = .0001$. Deaths for HCV-related causes were 19 of 33 (57%) in group 1 and 7 of 24 (24%) in group 2, $P = .01$. The Kaplan-Meier showed a dramatic reduction in excess mortality in HCV-LT patients after the availability of DAAs.

These results suggest that HCV is no longer the main active problem of follow-up in liver transplants, therefore the resources can be relocated to take care of other clinical aspects.

TRANSPLANT patients require strict follow-up owing to their higher risk of developing complications also in follow-up, mainly for their immunosuppressed state [1,2].

Some models of intensive surveillance for liver transplanted patients, including hepatic and extra-hepatic, metabolic and neoplastic features have been proposed [3,4].

Taking charge of a liver transplanted patient involves the organization of work aimed not only at a continuous follow-up of the transplanted organ (eg, monitoring of immunosuppressive drugs levels, monitoring of good liver function) but also at facing the prevailing active clinical problems at that time (eg, kidney's disease, cancer recurrence on the graft, new cancer occurrence). The recurrence of hepatitis C has historically been one of the main issues to be focused on in the follow-up and has been absorbing a lot

of resources in the hepatological centers responsible for the follow-up.

AIM

In times when resources seem increasingly limited, the aim of the present study was to verify how much the availability

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Table 1. Characteristics of the Liver Transplanted Patients in Group 1 (Pre-DAA, Before 2014) and in Group 2 (Post-DAA, After 2014)

	Group 1 Pre DAA (before 2014) N = 230	Group 2 Post DAA (after 2014) N = 244	P Value
Age at LT, median (range)	54 (17-67)	54 (1-72)	.53
Age at follow-up, median (range)	62 (31-78)	66 (27-84)	< .0001
Months of follow-up after LT, median (range)	99 (2-299)	140 (2-429)	< .0001
Men:Women	177:53	184:60	.78
Liver-transplanted HCV patients	N = 108	N = 111	
Successful HCV therapy before LT (%)	2 (2)	20 (18)	.0001
Active recurrence of HCV after LT	N = 88	N = 79	
HCV therapy after LT (%)	52 (59)	53 (67)	.33
Retreatment of HCV after first therapy failure (%)	0	37 (70)	.0001
SVR (%)	18 (35)	51 (96)	.0001
HCV RNA still positive after therapy (%)	34 (65)	2 (4)	.0001
Number of deaths in the whole group (%)	33 (31)	29 (26)	.54
HCV positive dead/global deaths (%)	22 (67)	12 (41)	.07
Deaths for HCV-related causes in HCV positive	19 (57)	7 (24)	.01

DAA, direct-acting antiviral agent; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response.

of the new drugs with direct-acting antiviral agents (DAAs) against hepatitis C virus has impacted the mortality within the assisted population, thus modifying their characteristics and needs, a prerequisite for a different commitment of the limited resources available.

MATERIALS AND METHODS

Our liver unit in Caserta, Italy is a spoke of the “Campania Liver Transplant Follow-up Network” and is located in a referral tertiary hospital that does not have a liver transplantation center. The unit is the reference for patients who live far from their transplant centers and who are enrolled at any time in their lives with liver transplants. These patients need local support because their transplant centers, located in other Italian regions and even abroad, are far from their home. We have so far followed a population of 311 liver transplanted patients, heterogeneous in their transplant centers but rather homogeneous for region of birth and stay.

Object of this retrospective study were 230 patients actively in follow up during pre-DAA era (group 1, until December 2013), and 244 patients alive in January 2014 and followed until December 2017, group 2, in which we compared several clinical characteristics and analyzed survival between patients transplanted with HCV RNA-positive and patients with HCV RNA-negative or transplanted for other etiologies.

The results are presented as median value (range) for continuous variables and as percentages for categorical variables. Chi square or Fisher's exact tests were used to compare categorical variables, and differences between unpaired quantitative variables were analyzed by Mann-Whitney test. The difference in mortality between groups are illustrated by log-rank tests applied to Kaplan-Meier estimates. Statistical significance was defined as a *P* value of less than .05. All statistical analyses were performed with SPSS version 13 (SPSS Inc, Chicago, IL) and the survival analysis was performed using MedCalc version 12.1.4.0 (MedCalc Software, Ostend, Belgium).

RESULTS

General characteristics of transplanted patients are shown in Table 1. Patients who underwent liver transplant for HCV disease were 108 with 88 HCV RNA-positive in group 1 and 111 with 79 HCV RNA-positive in group 2.

Overall, most of the patients were men; patients of group 2 had become older ($P < .0001$). The median follow-up after liver transplantation was 99 months (range, 2-299) and 140 months (range, 2-429) for patients before and after DAA introduction, respectively ($P < .0001$).

Fifty-two antiviral treatments were performed in group 1 with 18 SVR (35%) compared with 53 therapies done in group 2, of which 37 were retreatments of previously failed interferon-based therapies, with 51 SVR (96%), $P = .0001$. As a result, the patients still HCV-RNA positive after therapies were 34 in group 1 and only 2 in group 2 ($P = .0001$).

Figure 1 shows that the well-known reduced 10-year survival of patients transplanted for HCV disease, compared with those transplanted for other etiologies and nonviremic, almost disappears after the availability of DAAs.

Patients who died of virus C-related causes were 19 of 33 (57%) in group 1 and 7 of 29 (24%) in group 2 ($P = .01$), as a consequence of the much more efficacious treatment of recurrent C virus.

DISCUSSION

These results show that HCV is no longer the main active problem of follow-up in liver transplants and suggest that, as a consequence, resources have been freed for other clinical issues.

Our results reflect those obtained worldwide, which have made the “historical” problem of hepatitis C in transplantation. This outcome is now shown also in a population of transplanted patients followed and treated in a peripheral specialized center that is not within the transplantation center.

We have a high number of liver-transplanted patients, born, living, and residing in Campania but who have been transplanted far from home in almost all Italian centers and many abroad. Some peripheral specialized liver units, which are not liver transplantation centers, are currently ensuring patients of the presence of a qualified reference point that is

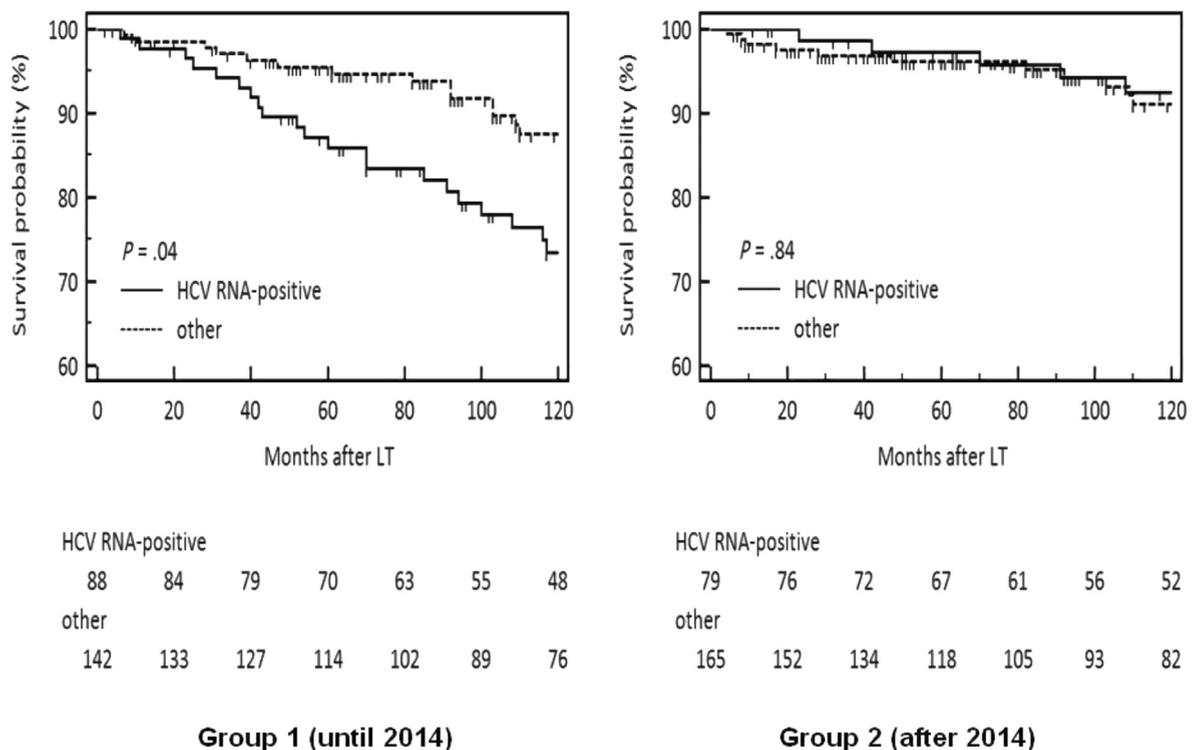


Fig 1. Overall survival in hepatitis C virus (HCV)-viremic liver transplant (LT) patients (still HCV RNA-positive) and others (LT for other causes or non-HCV-viremic), before (left) and after direct-acting antiviral agent availability (right). *P* value by log-rank test.

a short distance from their residence in coordination with the transplant centers they belong to. “Campania Liver Transplant Follow-up Network” consists of a hub center (the Regional Liver Transplant Unit in Naples) and several spoke peripheral centers in charge for the follow-up of patients, wherever they have been transplanted. The network’s component nodes also interface with transplant centers located outside the region, as required. A comparable “Hub & Spoke” model has appeared also in other different world realities, mainly because of the ease of access to the follow-up [5]. A common follow-up monitoring protocol has been adopted by all centers of the regional network [4]: its application requires considerable resources for constant surveillance.

For the last 2 decades, HCV has dominated transplantation activity worldwide. Our data are in agreement with what has emerged on a large scale in the European Liver Transplant Registry [6], with the availability of DAAs the HCV listing has been reduced from 22.8% in 2007 to 17.4% in 2017.

The prevailing consideration in the transplant community is addressed to the increased availability of organs to be transplanted in patients with different liver diseases [7].

We would like to point out that, because HCV is no longer the main active problem also in transplanted patients, care resources have been freed up and could be used for other aspects of the follow-up. HCV infection itself has a role in many comorbidities and systemic disease in all

infected patients: diabetes mellitus, renal failure, cardiovascular events, and increased risk of neoplasm. Understanding how the treatment of HCV can impact these nonhepatic diseases will be important, also because these diseases are increasingly the main causes of morbidity and mortality in transplanted patients [8].

For this reason it is necessary to devote resources to a strict surveillance of liver transplanted patients: immunosuppression and medical complications during the long-term follow-up exploit in several aspects also in a stable patient with apparently no active clinical problem, and prevention of cardiovascular disease and de novo cancers are the main issues in these chronic patients [4].

In conclusion, the results of our experience show how new resources have finally been released for a different destination in the follow-up of transplanted patients.

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