



Opinion

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The Impact of DAA in Changing the Face of Liver Transplantation



John Fung^{1*} and Antonio Pinna²

¹Professor of Surgery, University of Chicago, Chicago, IL, USA

²Professor of surgery, Liver and Multiorgan Transplantation Unit, University of Bologna, Italy

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*Corresponding author: John Fung, MD, PhD University of Chicago Chicago IL, USA, Email: jfung@surgery.bsd.uchicago.edu

Opinion

The introduction of direct acting antiviral drugs (DAA) directed to hepatitis C virus (HCV) is certainly one of the most clinically significant breakthroughs in recent medical histories, with the promise of affecting hundreds of millions of lives worldwide. In the arena of liver transplantation (LT), the impact of the use of DAA can be felt in 3 scenarios:

- Progressive reduction of the number of patients needing LT due to decompensated HCV-related cirrhosis;
- Eliminating the consequences of post-transplant HCV recurrence by way of clearing HCV viremia pre-transplant; and
- Safely and successfully treating LT patients developing post-transplant HCV recurrence.

Hopefully, decompensated HCV-related liver cirrhosis as the primary indication for LT will disappear within the next two decades. Considering the present distribution of liver diseases that are indications for LT, the impact of DAA in the liver transplant arena has the potential to eliminate 20% to 40% of the indications for LT.

In this setting, the liver transplant community should consider how the reduced need for LT may impact the practice of LT. Specifically, how will this void be filled in the future, supposing that the proportion of donors that would otherwise be used for HCV indications could be shifted to alternative indications? Secondly, could strategies of donor pool expansion and of organ preservation change in front of a modification of this scenario?

Patients with hepatocellular carcinoma

Hepatocellular carcinoma arising in the cirrhotic liver already represents a significant indication for LT and expected to grow over the decade. Given the high association of HCC

inpatients that are HCV-positive in Western countries and the progressive aging of the general population, patients with HCC that will be referred for LT are likely to be at an increasingly advanced age. Therefore, a feature of a candidate for LT for HCC in the next few years is likely to be that of a patient older than 60-65 years, without active hepatitis virus replication, and with possible age-related co-morbidities. Thus, long-term post-transplant survival may be compromised by the risk of such co-morbidities (cardiovascular, metabolic, and oncological), posing a challenge to our current complex and multidisciplinary care. In addition, presentation of HCC at a very advanced age may preclude some patients from being considered for LT due to a high risk of postoperative morbidity and mortality. On the other hand, experiences gained in the last ten years with neo adjuvant multi-modal treatment of HCC, expansion of HCC beyond Milan criteria for LT, and strategies of salvage transplantation after liver resection for HCC could reposition the position of LT amongst therapies of HCC.

In fact, the shift away from donor utilization from end-stage liver disease due to HCV may increase availability of liver donors for HCC and lead to a further expansion of the still-restrictive criteria for LT in HCC, possibly accepting a mild-to-moderate increase of post-transplant tumor recurrence. In other words, more donors that are available may re-affirm the role of LT as a definitive and more widely available curative treatment for HCC.

Live donors already represent a significant proportion of grafts for patients with HCC worldwide, and they will presumably be still necessary in the next years. The changing feature of a typical candidate for liver transplant from a patient with decompensated cirrhosis (frequently associated with HCV infection) to a patient with better-preserved liver function and hepatic tumors, carries the possibility of maximizing living donor liver transplant by taking advantage of less severe portal hypertension and less severe liver disease. This in turn could reduce the risk to the living donor and increase the likelihood of an obtaining a living donor. From the organizational and

governmental points of view, all the above assertions will reinforce the principle that HCC should be treated in surgical units with proficiency in both liver transplant and liver surgery, as part of the multidisciplinary treatment of liver cancer and warranting a correct approach to living donor procedures based on a solid experience of hepatic resections.

Donor pool expansion and conditioning of the donor liver

The persistent gap between the number of donors and patients on the waiting list for LT has driven the increased utilization of all possible means to expand the number of liver grafts over the last 25 years. Donor livers with suboptimal function and/or structure, older donors, partial grafts, and non-heart-beating donors now represent, with appropriate inclusion criteria, a valid alternative to standard deceased organs. Nevertheless, the so-called "Extended Criteria Donors" (ECD), to which the above categories largely pertain, implies an increased risk of suboptimal outcome in terms of graft function recovery and post-transplant survival. In particular, the use of liver grafts from older donors is still controversial, as some report poorer outcome compared to transplants performed with younger donors.

Interestingly, a growing appreciation of the studies on this topic have clearly shown that most of the detrimental effect of grafts from old donors emerged when they were transplanted into HCV-positive recipients related to the dramatic impact of an earlier, more rapid and severe post-transplant HCV infection recurrence when using older donors. In fact, when the results obtained in non-HCV-positive patients were considered separately, they were comparable to those achieved with younger donors in most of the recent studies. Thus, the absence of active HCV replication in LT candidates may further encourage the use of older donors and/or, in a larger perspective, of ECDs in general.

In this light, the possible conditioning of marginal grafts with different techniques and may take on greater importance than in the recent past. For example, the use of machine oxygenated perfusion in a hypo- or normothermic state, has already successfully adopted in clinical setting, and could be expanded with less apprehension considering that the most dreadful recipient-related variable (disease recurrence) will not impact negatively on the functional recovery and survival outcome. Other techniques, such as ischemic preconditioning, either remote, or pharmacological, or even the use of regenerative medicine approaches may be better applied.

Immunotolerance induction

While immunosuppression protocols aimed at achieving tolerance of the transplanted live rare still in its infancy, this goal remains the holy grail of solid organ transplantation. One of the factors limiting the expansion of this approach has been the demonstration of high failure rates in attempts to wean immune suppression in HCV positive recipients, as well as concern for

accelerated HCV recurrence with induction therapy. Therefore, it is intuitive that pro-tolerant strategies with induction immune suppression regimens may be more successful with the elimination of HCV before or after LT.

Patients with metabolic disorders

Non-alcoholic steatohepatitis (NASH) as a feature of dysmetabolic syndrome represents a progressively increasing indication to LT in most Western countries, and the reduction of HCV-related decompensated cirrhosis will further increase the proportion of dysmetabolic patients listed for LT. The medical and surgical challenges faced in treating this category of patients is already significant, considering the higher prevalence of obesity, diabetes and cardiovascular diseases when compared with non-NASH patients. Nutritional awareness and surgical procedures aiming at reducing obesity and diabetes are increasingly utilized, which may curb the growth of patients with NASH. In addition, bariatric procedures during or after transplant, may reduce the long-term negative impact of obesity in these patients.

Other indications for liver transplant

One of the most intriguing consequences of the disappearance of HCV-related decompensated cirrhosis is the void, which may be filled by patients with tumors currently judged as unsuitable for LT. With strict selection criteria, patients with hepatic metastases from neuroendocrine tumors or with hilar cholangiocarcinoma (Klatskin tumor) already represent an accepted indication for LT. There is increasing interest to consider patients with non-resectable, liver-only metastases from colorectal cancer for LT, based on promising results obtained in Norway. The combination of the generally improved results of LT in the last few decades, the higher efficacy of chemotherapy for metastatic colorectal cancer, and the use of immunosuppressive drugs with anti-proliferative effects (e.g. mTOR inhibitors), may explain the 5-year post-transplant survival of 60% in selected candidates with colorectal carcinoma liver metastases. This outcome may be further improved if patients demonstrate objective response to chemotherapy prior to LT. This degree of long-term survival provides a benefit comparable to that achieved by other malignant indications. Interestingly, the ethical dilemma of providing a liver graft to such patients, while patients in other currently acceptable categories are waiting for LT could be mitigated by the use of extended criteria grafts in patients with colorectal metastasis, including small size partial and living donor grafts, based on the absence of cirrhosis and portal hypertension.

Conclusion

With the exception of mandatory hepatitis B vaccination and the development of nucleotide and nucleoside analogs for the treatment of HBV, no other clinical development except DAA for the cure of HCV has the potential of reducing the burden of end-stage liver disease on LT waiting lists throughout the world. In this setting, there is an opportunity to strategically define how the LT community will react to the changing indications and opportunities to increase the utilization of LT.



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