Review Article

Living donor liver transplantation: where do we stand and where are we going?

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Abstract: Liver transplantation (LT) remains a lifesaving therapy for patients with end-stage liver disease, but the shortage of graft donor (deceased donor) limits development of LT. Living donor liver transplantation (LDLT) is the only alternative to deceased donor liver transplantation (DDLT), but LDLT requires more sophisticated surgical techniques. In addition, LDLT does not have the advantage in their survival in response to immunosuppressive therapies. In this paper, we reviewed recent development of LDLT in China mainland, especially surgical technique and immune therapy.

Keywords: Living donor liver transplantation (LDLT); small-for-size syndrome (SFSS); immune therapy; regulatory T cells (Tregs)

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Introduction

Living donor liver transplantation (LDLT) is the only alternative to deceased donor liver transplantation (DDLT) currently. Under the conditions that ensure the safety of donors, LDLT increases the global pool of transplantable organs, with decreased post-operative complications. While LDLT requires more sophisticated surgical techniques and higher qualifications of transplant surgeons, which limit its wider applications, it does dramatically promote the developments of liver surgery and transplant surgery. LDLT, even living related liver transplantation (LRLT), however, does not have the advantage in their survival in response to immunosuppressive therapies. To improve transplantation outcomes and promote transplant tolerance, we have begun to test the therapeutic efficacy of autologous regulatory T cells (Tregs), which are regarded as the most promising biological agent in inducing transplantation immune tolerance.

Transplant surgery technique advance

The advances in LDLT have witnessed the efforts to extend the donor pool under the conditions that ensure the safety of donors, so as to ultimately ease donor shortage. In 1989, the first LDLT was performed by Raia *et al.* in Brazil (1). In 1989, the Australian doctor Strong RW successfully performed one case of living-related partial liver transplantation (LT), predicting the feasibility of LDLT (2). In 1993, Tanaka *et al.* reported the first adult-to-adult right liver LDLT, making LDLT also become feasible for adult patients (3). The development of LDLT in China keeps pace with those in developed countries. In 1995, Wang *et al.* successfully performed the first case of LDLT in mainland China (4). In 1995, Fan *et al.* of Hong Kong University reported the worldwide first case of expanded right-lobe LDLT including middle hepatic vein, which further expanded the donor pool (5). In 2001, Wang *et al.* implemented the first case of expanded right-lobe LDLT including middle hepatic vein in emergency settings (6).

In 2001, considering the donor's safety, Lee *et al.* selected two donors, each of whom donated one left lateral lobe to the same recipient (7). In 2002, Sugawara *et al.* performed the transplantation of hepatic segments VI and VII (8). In 2003, Sato *et al.* reported a successful case of heterotopic auxiliary partial LT with extremely small-for-size graft (a left lobe volume of 24% in the standard liver volume of the donor) for fulminant liver failure accompanied with renal failure (9). In 2005, Wang *et al.* performed the global first "left at right" LDLT, as an auxiliary LT that reserves the left liver (10); in 2006, Chan *et al.* performed the second "left at right" LDLT, with a main purpose of avoiding vena cava oppression and the first porta hepatis distortion (11).

Therefore, along with the development of LDLT, the grafts have been expanded from right lobe grafts only to the right liver with the middle hepatic vein, and the recipients have expanded from children only to adults. Meanwhile, the development of different LDLT procedures lower the donors' risks, save the recipients' lives, and reduce the post-operative complications. The advances in LDLT mark the development of human civilization. While it dramatically promotes the progression in liver surgery and transplantation, it also faces some ethical issues. For the healthy adult donor, who must undergo a complicated major surgery without any physical or health benefit; even worse, the donor may suffer from certain complications and even lose his/her life. Currently, the incidence of the complications after LDLT ranged 8.6% to 59%, and about 0.2% to 1% of the donors died (12,13). Right lobe LDLT is related to a higher mortality (13), and the direct death causes included liver failure, pulmonary embolism, and cardiovascular events (14-16). Therefore, LDLT has higher requirements for the surgeons in terms of both surgical skills and teamwork. As a result, LDLT is mainly performed in large transplantation centers.

According to the data released by China Liver Transplantation Registry (CLTR), over 1,700 cases of LDLT had been completed in mainland China till December 2012, among which no donor death was reported. LDLT, to certain degree, effectively eases the graft shortage and allows more patients to be treated. Compared with the DDLT, LDLT has its unique post-operative complications. Biliary tract reconstruction is considered to be a challenge during LDLT. Its common complications include cholestasis, bile leakage, and bile duct stricture. During the biliary anastomosis in LDLT, a lower vena cava anastomosis or a sufficiently long level-2 bile duct dissected inside the liver may help to lower the anastomotic tension and thus reduce the incidence of anastomotic stenosis. During the donor liver harvesting, the blood supply of bile duct should be preserved as possible, so as to avoid postoperative bile leakage due to bile duct ischemic necrosis.

Hepatic artery thrombosis is severe complication after LDLT. The recipients are often had advanced cirrhosis, in whom the hepatic arterial wall often becomes fibrotic, and the arterial intima is easy to fall off. In addition, the unmatched vascular diameters between donors and recipients of LDLT can easily cause stenosis and then embolism, particularly in pediatric patients. During the transplantation of left lateral lobe, the accessory left hepatic artery typically arises from the left gastric artery; since the internal diameter of the donor artery is <1.5 mm, the matching between the donor's and recipient' arteries is extremely difficult. Then, a patch for arterial anastomosis can be employed (17). For grafts with two arteries, we typically perform a single anastomosis using the larger one, and then checked the backflow in the second artery after enough graft reperfusion. If there was good backflow, one anastomosis is enough. Some authors also have performed the anastomosis of both arteries or anastomosis after arterial molding (18,19). However, a sufficiently long hepatic artery branch should be preserved, and the branches around the hepatic artery should be carefully protected, so as to facilitate the reconstruction of the dual arteries.

Small-for-size syndrome (SFSS) occurs along with LDLT. It represents a series of clinical symptoms and signs caused by portal hypertension and excessive portal venous perfusion due to the relatively and absolutely small graft volume (GRWR <0.8%, or ESLM <40%). It includes severe liver cell damage, delayed liver secretion, prolonged intrahepatic cholestasis, gastrointestinal bleeding, and drop in graft survival rate. The incidence of SFSS is inversely proportional to the residual liver volume or graft volume. Thus, during the harvesting of liver graft, the liver parenchyma cells should be preserved as possible, so as to avoid the occurrence of SFSS. In addition to the use of sophisticated surgical instruments such as cut-ultrasound aspiration (CUSA) and water dissector, the application of anatomic segmental resection is particularly useful in ensuring the blood supply of grafts. Also, splenic artery ligation, spleen resection, or vena cava shunt can be performed to decrease portal vein blood flow and portal vein pressure. In our center, the construction of sufficiently large outflow tracts for the hepatic vein and vena cava anastomoses is a key technique for preventing SFSS.

Table 1 Current issue of Treg therapy for liver transplantation

Clinical trial	Group lead	Context	Participating centres (and cell product administered)
Autologous Treg	Lu Ling, Xuehao Wang	Living donor liver transplantation	Phase I and II, Nanjing, China
Donor-alloantigen-reactive regulatory T cells	Sandy Feng, Jeffrey Bluestone, *et al.*	Liver transplantation	Phase I and II, California, United States
Treg-based therapy	Okamura	Treg-based therapy in the context of liver transplantation	Phase I, Sapporo, Japan
Safety and efficacy study of regulatory T cell therapy in liver transplant patients	Alberto Sanchez-Fueyo	Treg-based cell therapy in the context of liver transplantation	Phase I, King's College, London, UK

Phleboplasty of left hepatic vein-middle hepatic vein and right hepatic vein-middle hepatic vein, followed by the expanded phleboplasty with vena cava and the improved portal vein anastomosis and hepatic artery reconstruction, can ultimately solve the poor patency of small hepatic outflow tract and avoid the injuries caused by high portal perfusion. As a result, the graft viability and functions can be rapidly restored.

Immune therapy: can we find new way to protect chronic rejection

Immunosuppressive drugs, although have not been available decades ago, are key to graft and recipient survivals. Nevertheless, transplant rejection remains a big challenge for surgeons and immunologists (20). Although the immunosuppressive drugs, to a great extent, reduce the incidence of acute rejection, they still have nothing to do with chronic rejection (21). How to consolidate the existing transplantation outcomes, explore the pathogenesis of chronic rejection, and promote the clinical and translational research has become the current research priorities in this regard (22). A small amount of evidences have shown that the graft functions can be maintained, together with immune tolerance, in some recipients after the complete withdrawal of immunosuppressive drugs. Such a phenomenon was initially seen in patients with extremely poor adherence. These patients often stopped taking drugs by themselves and survived for a long period of time without experiencing graft rejection. However, the outcomes of drug withdrawal were not satisfactory in various transplantation centers. Thus, search for strategies that can mimic the biological organism's self-tolerance is particularly important. Currently, some promising treatment that can be used for the clinical induction of immune tolerance include tolerance DC, Tregs, regulatory macrophages (Mregs), mesenchymal stromal cells (MSCs), myeloid-derived suppressor cells (MDSCs), and regulatory B cells (Bregs) (23). The induction of immunological tolerance is held by many to be the Holy Grail of transplant research.

The Tregs are the most promising induction therapy that may be applied for inducing immune tolerance after organ transplantation (24). In the face of these challenges, and in order to answer many of these questions, there are currently four noteworthy trials of Treg therapy underway in the context of LT (*Table 1*). In our center, ten LDLT patients have been enrolled in the study on Treg immune tolerance-inducing therapy, and 8 of them have received the treatment. According to the pre-set drug withdrawal protocol, the immunosuppressive drugs will be withdrawn around ten months in volunteers, with an attempt to achieve operation tolerance. Recently, Yamashita *et al.* reported the application of Treg therapy in ten patients after LDLT, among whom the immunosuppressive drugs were not completely withdrawn in three patients (25). The risk of acute rejection is relatively low after LT. In the later stages, the chronic rejection induced by autoantigens may be the key issue for Treg therapies. The role of Tregs in the introduction of transplantation tolerance requires more detailed and reliable immunological test mechanisms, and results from multi-center studies are still on the way. Nevertheless, strategies that enable immune tolerance after organ transplantation can be expected.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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