TIMELINE

Liver transplantation: past, present and future

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Abstract | The first human liver transplant operation was performed by Thomas Starzl in 1963. The next two decades were marked by difficulties with donor organ quality, recipient selection, operative and perioperative management, immunosuppression and infectious complications. Advances in each of these areas transformed liver transplantation from an experimental procedure to a standard treatment for end-stage liver disease and certain cancers. From the handful of pioneering programmes, liver transplantation has expanded to hundreds of programmes in >80 countries. 1-year patient survival rates have exceeded 80% and outcomes continue to improve. This success has created obstacles. Ongoing challenges of liver transplantation include those concerning donor organ shortages, recipients with more advanced disease at transplant, growing need for retransplantation, toxicities and adverse effects associated with long-term immunosuppression, obesity and NASH epidemics, HCV recurrence and the still inscrutable biology of hepatocellular carcinoma. This Perspectives summarizes this transformation over time and details some of the challenges ahead.

Zarrinpar, A. & Busuttil, R. W. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 434–440 (2013); published online 11 June 2013; doi:10.1038/nrgastro.2013.88

Introduction

Liver transplantation has evolved dramatically over the past 50 years and has gone from a mostly futile endeavour to the definitive treatment of most types of liver failure, as well as hepatocellular carcinoma (HCC), in both children and adults (Timeline 1). In this Perspectives, we will describe the maturation of liver transplantation from its experimental beginnings, to the present challenges and how it needs to advance in the future; challenges in the future will be juxtaposed with current status to maintain perspective.

Past

Experimental models

The liver was considered a privileged organ, with its safe anatomical location behind the rib cage, its dual blood supply and its ability to perform multiple complex metabolic and synthetic functions. Although other organs were first experimentally transplanted close to 100 years ago,[1] liver transplantation was not reported until 1952 by Vittorio Staudacher from Milan, Italy, though this was not recognized until the past few years.[2] Prior to this discovery, C. Stuart Welch was credited with the first heterotopic liver transplant operation in a canine model[3] and Jack Cannon of University of California, Los Angeles (UCLA), USA, with the first orthotopic liver transplantation (OLT), also in a canine model.[4]

Despite these pioneering attempts, it is universally recognized that liver transplantation, as we know it today, would not exist without the pioneering work of Thomas Starzl who in 1958 successfully transplanted a liver in a canine model.[5] By 1960, Starzl had accumulated an experience of 80 canine liver replacements, which was augmented by the experience of Francis Moore from the Peter Bent Brigham Hospital, USA, (now known as Brigham and Women's Hospital) who had performed over 30 canine transplants.[6] From these experiments, the foundation was set for the development of the many advances that we use in liver transplantation today, including venovenous bypass, methods of organ preservation, tissue matching, immunology and immunosuppression.

Competing interests
The authors declare no competing interests.

Liver transplantation in humans

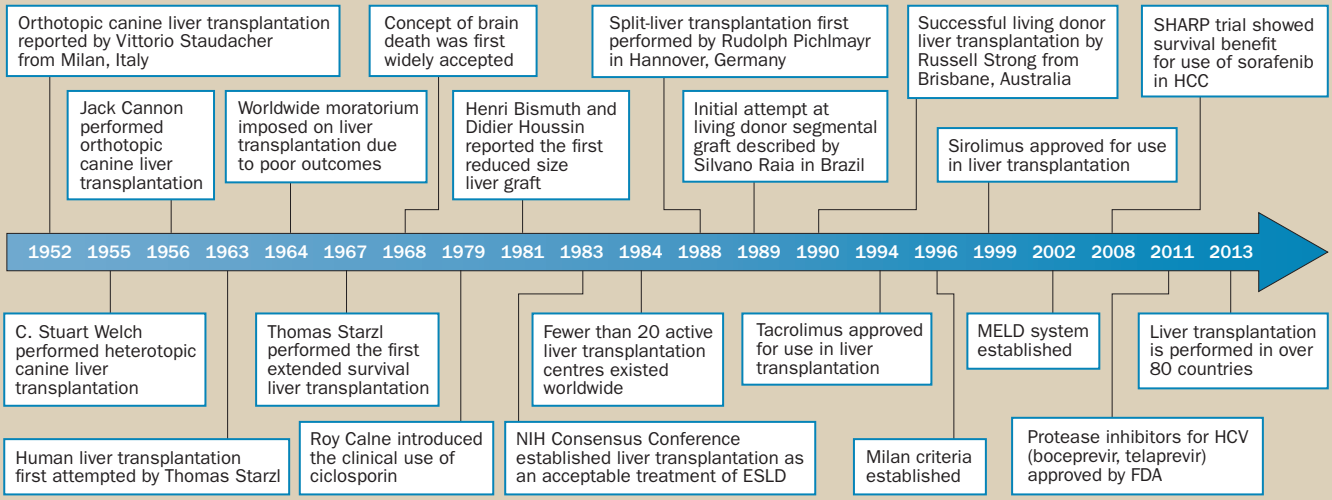
The first attempt at human liver transplantation was a paediatric operation performed in Denver, CO, USA, by Starzl on 1 March 1963.[7] The recipient was a 3-year-old child with biliary atresia, who died intraoperatively as a result of uncontrollable bleeding. Several other attempts at liver replacement were made up to January 1964; four by Starzl, one by Francis Moore in Boston, USA, and one by Demirleau in Paris, France, which was the first recorded attempt outside of the USA. Owing to the fact that no recipient had survived for more than a month a worldwide moratorium on further attempts at clinical liver transplantation was self-imposed by the community in 1964. However, with the development of advances in several areas, including improved organ preservation with the use of *ex vivo* perfusion systems, advances in immunosuppression with the development of antilymphocyte globulin and an understanding that tissue matching was less important in liver grafting than in kidney transplantation, a new enthusiasm for clinical liver transplantation was generated.

On 27 July 1967, Starzl performed the first successful liver transplantation on a 19-month-old girl with HCC who survived 13 months before dying of metastatic disease.[8] Another pioneer in liver transplantation was Roy Calne of Addenbrookes Hospital in Cambridge, UK, who performed a liver transplantation on 2 May 1968, on a woman with a primary hepatic malignancy; she died 2.5 months later from sepsis.[9] Calne then teamed up with Roger Williams of Kings College Hospital London, UK, and reported their initial experience of five cases of liver transplantation in the UK,[9] establishing the first true liver transplant unit outside of the USA. Not only was the Cambridge–Kings College consortium the first to perform successful liver transplantation abroad, they were also innovators of surgical techniques, performing the first human heterotopic graft and first human caval preserving (piggyback) procedure (Figure 1).[9]

Immunosuppression

From 1968 until the late 1970s, fleeting successes occurred with clinical liver transplantation from numerous centres

Timeline 1 | Selected important milestones in liver transplantation



Abbreviations: ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

worldwide, but the overall 1-year survival rate was <30%.[10] Several advances eventually improved overall results. In 1968, the concept of brain death was accepted,[11] which enabled a more controlled procurement procedure with improved graft quality. Additionally, the introduction of the calcineurin inhibitor ciclosporin in 1979 by Calne helped achieve clinically superior immunosuppression by promoting the evolution of regimens from antilymphocyte globulin, azathioprine and prednisolone for Starzl's first successful transplantation to drugs that were less toxic without increasing rejection or opportunistic infections.[12] These two advances, along with improved recipient selection and surgical techniques, resulted in 1-year survival rates of ~70%.[13]

Growing experience

By 1983, four centres worldwide had accrued substantial experience in clinical liver transplantation. This development led to a collective series presented at a NIH Consensus Conference on 20–23 June 1983.[14] The experience of 540 cases of patients treated with liver transplantation at centres in Denver (USA), Pittsburg (USA), Cambridge–King's College (UK), Hannover (Germany) and Groningen (Netherlands), headed by Starzl, Calne, Pichlmayr and Krom, respectively, was compared with a similar cohort of patients who did not receive transplants. The survival advantage for liver transplantation was dramatic and ushered in the era of liver transplantation as the best therapeutic intervention for all types of end-stage liver disease (ESLD). The development of the University of Wisconsin solution by Belzer in 1988 reliably extended the length of time a liver could be preserved from <8 h to >12 h, thus leading to increased sharing of organs, effectively increasing both the quality and quantity of useable organs.[15] The worldwide acceptance and utilization of this procedure is demonstrated by the fact that in 1984 there were fewer than 20 active liver transplant centres, whereas in 2013 liver transplantation is performed in hundreds of liver transplant centres in over 80 countries.

A major factor in internationalizing liver transplantation, especially to areas with cultural and religious limitations to cadaveric donation such as Asia, was further developments of the procedure using graft variants. The use of partial cadaveric and living donor grafts began in the 1980s; again, innovations started in the paediatric population. In 1981, Bismuth and Houssin reported the first reduced-size liver graft.[16] This development paved the way for split-liver transplantation first performed by Pichlmayr in Hannover, Germany, in 1988.[17] In 1989, Raia and co-workers from Brazil described the initial attempt at living donor segmental grafting for a child.[18] 1 year later, the first successful living donor segmental liver transplantation was reported by Russell Strong and colleagues from Brisbane, Australia.[19] Living donor liver transplantation was expanded to adults using left[20] or right lobe grafts.[21] These graft variants in most series have had results comparable to whole organs, particularly in recipients with low-to-moderate disease severity. Living donation has been used predominantly in countries, such as Japan and Korea, in which brain death is not culturally accepted despite laws supporting it.[22] There has, therefore, been a powerful driving force to make further refinements to the living donor operation. These include the extended right lobe graft with the middle hepatic vein,[23] the modified right lobe graft with middle hepatic vein tributary reconstruction[24] and the dual graft transplant to overcome small-for-size grafts.[25]

The 1990s witnessed a great expansion of liver transplant programmes. With that expansion, the number of patients placed on liver transplant waiting lists exceeded the available supply of cadaveric livers, requiring a 'sickest first' allocation policy for scarce donor livers. In the USA, the United Network for Organ Sharing (UNOS) utilized an allocation protocol assigning value to accumulated waiting time, in addition to medical urgency. Medical urgency (UNOS status) was determined by the level of care required. Patients in the intensive care unit were higher priority than inpatients not in the intensive care unit, who in turn were higher priority than outpatients.[26] As each local organ distribution area in the USA had many possible recipients at a given UNOS status, the accumulated waiting time became the deciding factor, which led US centres to place patients on the waiting list very early in the course of their disease. UNOS responded by adopting 'minimal listing criteria' for being placed on the waiting list and augmenting the disease severity grading. These criteria were based on Child–Turcotte–Pugh

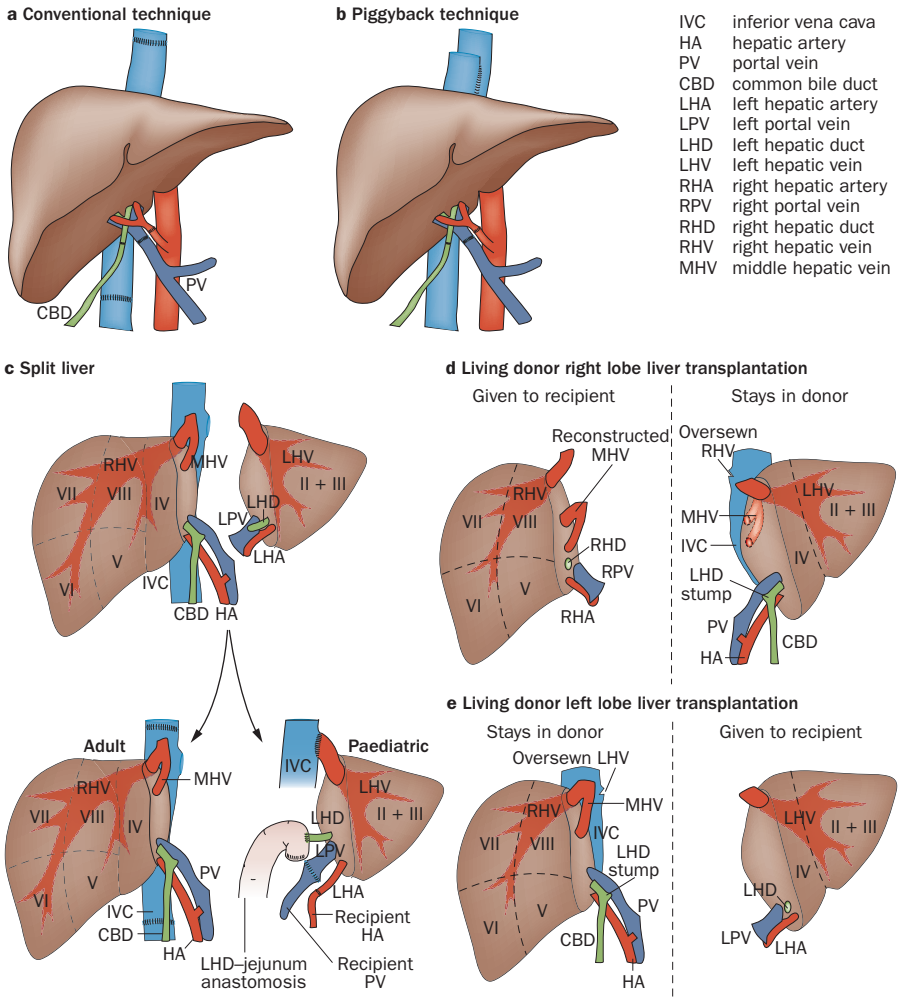


Figure 1 | Liver transplantation techniques. Many techniques have been developed for liver transplantation. From the conventional technique first developed by Starzl to partial liver transplantation techniques developed in the 1980s and 1990s, modifications in liver transplantation techniques have improved outcomes and allowed the expansion of the donor pool. **a** | Conventional, **b** | piggyback, **c** | cadaveric split, **d** | living donor right lobe, and **e** | living donor left lobe liver transplantation.

scores, composed of five factors (bilirubin levels, international normalized ratio [INR], albumin level, encephalopathy and ascites). As the amount of ascites and the level of encephalopathy are subjective clinical assessments, there was great controversy over making prioritization more objective and fair. In 1999, the US Department of Health and Human Services, in consultation with the Institute of Medicine, mandated a change in the allocation policy to one incorporating uniform medical criteria.[26] In response, UNOS replaced the Child–Turcotte–Pugh classification with the Model for End-Stage Liver Disease (MELD) score developed at the Mayo Clinic, USA.[27] This continuous score, which is based only on serum bilirubin level, INR and serum creatinine level, went into effect in the USA in February 2002. Countries within Eurotransplant (Austria, Belgium, Croatia, Germany, Luxembourg, Netherlands and Slovenia) adopted the MELD score for prioritization in 2006, though not without some controversy.[28]

Present and future

Today, with the standardization of donor organ procurement and recipient implantation operations (Figure 1), recognition and application of a multidisciplinary team approach, improved immunosuppression and enhanced perioperative care, liver transplantation is the definitive treatment of virtually all types of ESLD. A remarkable accomplishment in a procedure that was first experimentally performed just over 50 years ago.

Availability of quality donor grafts

The success of liver transplantation has brought about its primary obstacle. As liver transplantation has matured, indications for liver transplantation have grown to include more causes of acute and chronic liver failure, cirrhosis, metabolic disorders and selected cancers.[29] As the world's experience has grown over the years, the understanding of the prognosis and survival rates of liver transplantation in different populations has improved. For example, whereas previously HIV infection was an absolute contraindication, experience with HIV-infected patients who meet specific criteria has been positive.[30]

However, not only is the pool of donor livers failing to keep pace with the growing number of potential recipients added to the transplant waiting list, but in some areas it is diminishing. The annual number of recovered deceased donor livers has decreased in the USA from 7,017 in 2006 to 6,683 in 2011, according to data collected by the Organ Procurement and Transplantation Network.[31] Living donation numbers have also stagnated in the USA, peaking in 2001 at 524 donors, this number fell to 247 in 2011.[31] This trend necessarily reflects the annual liver transplantation numbers and further highlights the fact that liver transplantation in the USA is limited by the supply of usable donor organs. The European Liver Transplant Registry similarly reports a plateau in the number of liver transplantation operations decreasing from a peak of 6,278 in 2007 to 5,964 in 2010.[32] In Asia, where the deceased organ donation rate remains below 5 per million per year, and in Europe, this low level of deceased donors has been made up for by expanding living donation.[32,33] In China, where regulations are being implemented, especially with regard to obtaining consent prior to obtaining organs from executed prisoners, in an attempt to conform to international standards for organ donation, the number of liver transplantation procedures has decreased.[34]

Furthermore, as a result of improved perioperative and postoperative management of liver transplant recipients, those who are being considered for liver transplantation have more comorbidities. Data from the Scientific Registry of Transplant Recipients show that the recipient population in the USA is growing older, more likely to have diabetes, more likely to be obese and with increasing incidence of portal vein thrombosis.[31] More detailed analysis of data from

UCLA, which now includes >5,400 patients, also corroborates this fact. The mean MELD of patients transplanted at UCLA has increased from 22 in 2002 to 33 in 2011, with almost 30% of all transplanted patients after 2007 having a MELD >40.[35] Attempts to expand the pool of potential donors through changes in national policies are fraught with many contentious elements and their implementation has been delayed.[36,37] Expanding the types of donor grafts by using extended criteria donors, donation after cardiac death, and *in situ* splitting of livers, among others, has increased the number of useable donor organs, but this effect seems to have plateaued.[31,38] In the absence of increasing deceased donation to meet the need, living donor liver transplantation has become what many have latched onto as the answer. Questions of safety for living donors have arisen repeatedly as morbidities and mortalities have affected a number of living donors worldwide.[39] As the quality of donated organs has deteriorated over the years,[40] attempts to improve the quality of marginal donor grafts after procurement by pharmacological therapy or by machine perfusion have shown some promise.[41–45]

Another way to mitigate the organ supply and demand imbalance is transplantation across blood groups. Increasingly transplant centres are developing protocols for performing blood-type-incompatible liver transplantation in an attempt to improve outcomes and decrease related complications, including plasmapheresis, splenectomy, preoperative mycophenolate mofetil administration, infusion of prostaglandin E1, methylprednisolone and gabexate mesilate into the portal vein, and intravenous immunoglobulin or rituximab.[46,47]

Organ allocation

With prognoses for prospective transplant recipients deteriorating, some difficult questions need to be addressed. One result of the improved ability to get a patient through the liver transplant operation safely is a more generous set of criteria for acceptable liver transplant candidates. Especially in areas where several centres compete for the same pool of cadaveric donor organs, the MELD score at transplantation increases and outcomes are negatively affected,[48] leading the field to transplant patients who might survive the operation, but not ever leave the hospital. The question of who should and should not get a liver transplant is beginning to be examined by looking at risk factors for the futility of the operation.[49] Although these analyses have not yet made their way into recipient selection and organ allocation protocols, they signal a need to re-evaluate the current system.

The question of what principles should drive prioritization—such as medical urgency, utility, overall benefit, or other factors—has yet to be resolved. Many in the transplant community have also voiced ethical concerns over who 'deserves' a life-saving organ, especially whether patients with alcoholic cirrhosis or those who have already received a liver transplant should be eligible.[50–52] Either way, a clear need exists for a different prioritization paradigm for more judicious organ allocation. One well-studied concept is the transplant benefit model.[53,54] In this model, patients are ranked according to the net survival benefit they would receive from transplantation. To calculate the gain in life expectancy, one subtracts the area under the survival curve without transplantation from the area under the survival curve after transplantation. Although the MELD score is an excellent predictor of wait-list and post-transplant mortality, further refinements are necessary to identify factors that increase mortality without increasing MELD, which is especially apparent in patients with HCC.[55]

HCV treatment and recurrence

HCV accounts for ~30–45% of all liver transplantations in the USA and Europe; in areas with high rates of hepatitis B, such as Asia, that fraction is lower.[22,31,56] HCV portends the lowest patient and graft survival of all indications for transplantation.[31,57] Reinfection of the transplanted liver with HCV is universal and greatly compromises both patient and graft survival.[58] Recurrent infection can lead to damage within 3 months of transplantation with ~20–30% of patients after transplantation progressing to cirrhosis within 5 years. The association of the immune response and the pathogenesis of the hepatic damage caused by HCV is probably exacerbated by current immunosuppressive regimens, leading to rapid disease progression post-transplantation. Some limited inroads have been made into achieving a sustained virologic response (SVR) to the current standard of care regimen (PEG-IFN plus ribavirin).[59] However, two protease inhibitors approved by the FDA in 2011, boceprevir and telaprevir, have already shown higher rates of SVR in the pretransplant setting than PEG-IFN.[60] However, these new protease inhibitors are substantially limited by their drug–drug interactions with calcineurin inhibitors and high rates of bone marrow suppression, and are not yet approved for use in a post-transplant setting. However, trials examining their use after transplantation are ongoing as they are promising avenues towards a 'cure' for HCV.

Nonalcoholic steatohepatitis

NASH is the fastest growing aetiology for ESLD in the world and will likely become the most common indication for liver transplantation by 2020.[61] NASH can lead to both ESLD and HCC. The effect of the NASH epidemic on transplantation is amplified by the fact that it also decreases the number of possible donors with acceptable grafts. NASH, as the hepatic manifestation of obesity and metabolic syndrome (both of which are increasing at an unprecedented pace), is not likely to abate, and no treatment is in sight. The one positive aspect of this disease is that patients with NASH undergoing liver transplantation, despite being older, and more likely to have diabetes, obesity and hypertension, still have excellent 5-year outcomes, similar to patients transplanted for primary biliary cirrhosis or primary sclerosing cholangitis.[57]

Hepatocellular carcinoma

Liver transplantation for HCC has dramatically increased in the past 10 years.[61] HCC develops almost exclusively in a context of cirrhosis, most commonly from chronic infection with HBV or HCV, and continues to be the third most common cause of cancer deaths worldwide with a mean survival of 6–20 months from diagnosis. Currently, ~50% of transplant recipients in China, 25% in the USA, 15% in Europe, and <10% in Australia and New Zealand had HCC.[31,62–64]

Prior to the landmark study by Mazzaferro and colleagues who in 1996 proposed the Milan criteria, liver transplantation achieved poor results with 5-year survival rates of <40%.[65] Adoption of the MELD system with points granted for tumours that meet and continue to remain within the Milan criteria (one tumour ≥2 cm and ≤5 cm in diameter, or up to three tumours ≤3 cm in diameter) has led to 5-year survival rates upwards of 80% and correspondingly a fivefold increase in the proportion of patients with HCC who receive liver transplantation worldwide.[31,66]

Ideally, tumours would be detected early with high sensitivity and specificity

and treated when they are most likely to respond to local ablative therapy. Advances in ablative modalities have made them more widely applicable to patients with HCC, with new treatments such as irreversible electroporation that are more localized and thus 'forgiving' in livers with more advanced cirrhosis.[67] Many centres allow tumours that have been shrunken to within Milan criteria by these means to qualify for transplantation. Current surveillance programmes are comprised of ultrasonography and measurements of α-fetoprotein levels. However, the sensitivity of these modalities is 60–65%.[68] Other diagnostic serological markers including des-γ-carboxyprothrombin (DCP, also known as protein induced by vitamin K absence) and the ratio of the glycosylated α-fetoprotein L3 fraction correlate with prognosis and tumour recurrence, but lack the sensitivity and specificity required for common use in screening.[69,70] Work is underway to discover and confirm other biomarkers for the earlier detection of HCC.

Since the adoption of the Milan criteria, its limits have been challenged many times, with other centres suggesting that these criteria are overly restrictive and that expansion or modification of these criteria could achieve comparable survival rates. Indeed, multiple studies have shown that the criteria can be expanded. These prognostic models for HCC rely on radiographic appearance (tumour number and size), histology (vascular invasion and differentiation) and overall liver function (MELD).[66] Some centres are beginning to incorporate aspects of the biology of the tumour into their selection criteria, for example by excluding patients with high preoperative DCP or α-fetoprotein levels.[71,72] This development is especially true in centres with large living donor programmes (such as most Asian countries) because there is no need for a prioritization scheme in this setting. The next step, linking personalized genomic profiling of the tumour to prognosis and treatment, is already underway.[73] By classifying tumours according to gene expression patterns, several groups have found prognostic factors for recurrence,[74] vascular invasion[75] and drug sensitivity.[76]

With the emphasis on deciphering the signalling pathways in HCC comes hope of identifying methods to halt disease progression and even curing HCC. Currently, the only pharmacological agent shown to be effective in prolonging survival is sorafenib, a multikinase inhibitor.[77] Other molecules such as sunitinib and dasatinib have shown some efficacy, but clinical data are lacking.[76,78] Genomic profiling of individual patient tumours on the basis of molecular parameters, as opposed to the identification of more generalizable oncogene addiction loops, is driving the direction of research.

Sirolimus and everolimus, both inhibitors of the mammalian target of rapamycin (mTOR) pathway, are used widely for immunosuppression because of their low neurotoxicity and nephrotoxicity profiles. Moreover, observations of improved survival for patients transplanted for HCC have led to studies evaluating their efficacy in preventing HCC recurrence.[79]

Retransplantation

Accompanying the dramatic success of OLT and good long-term survival, increasing numbers of recipients will require retransplantation of the liver for various reasons. Retransplantation has been associated with ~30% lower survival rates than primary transplantation given the increased technical demands and the severity of the medical problems of retransplant candidates.[80] Financial and ethical issues are also relevant, namely the increased use of resources and denying first-time candidates access to grafts.[52] Nevertheless, the decision of whether to undertake retransplantation should involve the same questions as the first transplantation: the operative and medical risk and the likelihood of long-term survival. Improvements in tools to stratify retransplantation candidates by risk have enabled clinicians to predict with more accuracy which patients will benefit from the operation.[81] Factors associated with worse outcome include: recipient age >55 years, donor age >45 years, more than one prior OLT, serum albumin <25 g/l, intraoperative packed red blood cell transfusions >30 units, ventilator dependence, MELD score >27, and retransplantation between 15 and 180 days after the initial transplant.[81] Fortunately, technical strides continue to be made to accomplish this difficult task both medically and surgically.

Immunosuppression

Improvements in post-transplant survival can be attributed in large part to more selective and less toxic immunosuppression regimens. Liver grafts have been found to stimulate less rejection compared with other organs and might in fact provide a protective effect for other simultaneously transplanted organs, possibly by inducing peripheral microchimaerism and, with that, a level of tolerance.[82] However, immunosuppression remains an obstacle to long-term graft survival. Current regimens modulate multiple pathways, from calcineurin and mTOR inhibitors to antimetabolites and a number of antibody therapies, enabling the opportunity to tailor each recipient's regimen. Targeting different pathways in the immune system also facilitates dosage minimization and limits drug toxicities without increasing rejection or opportunistic infections and neoplasms. Monoclonal antibodies that have found use in transplantation include basiliximab and alemtuzumab; they target CD25 (IL-2 receptor) and CD52 antibodies, respectively. Although evidence exists of improved overall graft and patient survival and an improved adverse effect profile in subsets of patients, neither a clear role for these antibodies nor a means of monitoring their function or appropriate therapeutic levels has been determined. Other targets include T-cell costimulation (belatacept), B cells (rituximab), antigen presentation (efalizumab and alefacept), formation of complement complexes (eculizumab), TNF signalling (infliximab), and proteasomes (bortezomib), among many others.[83]

Immune monitoring and tolerance

Patients living long after liver transplantation are now suffering from the cumulative adverse effects of immunosuppression, including cardiovascular disease, metabolic syndrome, osteoporosis, infections, malignancies and renal failure. Some advances have been made in the development of immune monitoring assays to measure the immunosuppressive state in a transplant recipient and to correlate the results with patient mortality.[84] Ideally, this system would enable a more accurate means to minimize immunosuppression without risking more rejection. Other developments in understanding operational clinical tolerance—that is, stable normal graft function without maintenance immunosuppression—have demonstrated that with further research it remains a possibility. Published data on systematic methods to induce clinical tolerance in liver transplantation have had mixed results with success rates ranging from 0% to 38%.[85]

Conclusions

Much as the success of liver transplantation has solved many problems previously thought impassable, it now continues to present us with other challenges (as

discussed earlier). We are faced with the need to overcome the limited supply of useable donor organs; to expand living donation without compromising donor or recipient safety; to optimize selection criteria and graft–recipient matching; to treat HCV and HCC before and after liver transplantation; to detect HCC earlier and to understand which tumours would be most appropriate for liver transplantation; to individualize chemotherapeutic and immunosuppressive regimens to every recipient based on their and the graft's genetic and proteomic background; to understand and ultimately to induce tolerance in transplant recipients. Although daunting, the challenges for liver transplantation now are no more than they seemed 50 years ago. The field has overcome many such challenges and other unforeseen ones before to make liver transplantation what it is today. We are certain that it will continue to do so in the future.

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Author contributions

A. Zarrinpar and R. W. Busuttil made equal contributions to discussions of content and reviewing and editing the manuscript before submission. A. Zarrinpar researched data for and wrote the article.