History of pediatric liver transplantation

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The article below gives an historical perspective to the state of the art in pediatric liver transplantation.

The historical background

Pioneering years, in USA. The experimental design of orthotopic liver replacement in dogs paved the road to the first attempts in human beings. This history cannot be dissociated from one man, Thomas E. Starzl whose pioneer efforts contributed more than anyone else to what has become a routinely successful clinical procedure. Thomas E. Starzl’s first clinical attempt was made in 1963, in Denver, USA, on a 3-year old child who had developed end-stage liver disease from biliary atresia. It was followed by a self-imposed moratorium of more than 3 years devoted to the experimental refinement of the preservation techniques and of the immunosuppressive therapy based on steroids and azathioprine. The trials were resumed in 1967 on eight infants and children. All survived surgery and four patients had a remarkable long survival time, one of them transplanted in 1970 being still alive, more than 37 years after transplantation, and off medication for about 13 years. Her original disease was biliary atresia with an incidental hepatocellular carcinoma which never recurred.

Progress in immunosuppression By March 1980, cyclosporine A became available. Of 12 patients who entered a study on this new immunosuppressant, 11 patients lived for 1 year or longer. Quoting Thomas E. Starzl: “For the first time, it looked as liver replacement might become more than a curiosity and a subject of ethical debate. The stampede began for the development of other liver transplant centers.” Thomas E. Starzl transferred his liver program to Pittsburgh in 1981 where it reached an unparalleled expansion including 808 children (<18 year of age) receiving a liver transplant between 1981 and 1998. For the last 10 years, substitution of tacrolimus to cyclosporine further improved the results.

In United Kingdom, the first attempt at liver transplantation in a child (10 months old) was performed in 1968 in Cambridge by Sir Roy Calne; the child who had biliary atresia died during surgery. Continental Europe In continental Europe, the first successful liver transplantation was performed by our team at the Université catholique de Louvain in 1971 in a 17-month-old child with biliary atresia. The child recovered uneventfully until he developed acute rejection which was reversed by steroids; sadly he died 7 weeks after transplantation from massive intrathoracic bleeding caused by a liver biopsy. After the transfer of our Medical School and University Hospital from the city of Louvain to the outskirts of Brussels (at Saint-Luc university Clinics), we resumed our program of liver transplantation in 1984. The four children transplanted in 1984 all become long-term survivors and are still alive, more than 20 years later with the exception of the youngest child who died in 2007 from hepatitis C-related cirrhosis probably acquired at the time of transplantation either by the organ or blood donor (in Belgium, detection of hepatitis C in both blood and organ donors started in 2000).

On 11-12 October 1986, our team organized in Brussels an International Symposium on Liver Transplantation in Children. The results obtained in the eight centers of Europe and USA who had experience with at least 20 pediatric liver transplants were presented by the following centers: Boston, Brussels, Cambridge, Dallas, Hanover, Minneapolis, Pittsburgh and Los Angeles. With the exception of Pittsburgh, most of these pediatric programs were started in the early 1980s. Long-term (>1 year) patient survival reached 57-83% (83% at 2-year post-transplant in Brussels). All centers used cyclosporine-based immunosuppression. The major indications were biliary atresia being the most frequent one; were already delineated.

Since its inception, our pediatric liver program was established on a multidisciplinary basis, which attracted the trust of Daniel Alagille (Hôpital Bicêtre, Paris) who was the leading pediatric hepatologist in Europe. The confidence given to our team by this enthusiastic advocate of liver disabled children gave the impulse to an accelerating phenomenon that would attract to our Institution waves of pediatric liver transplant candidates from many European and non-European countries waiting for the development of local programs.

Between 1 March 1984 and 30 June 2007, 670 consecutive children received a liver transplant in our Institution; several programs of similar magnitude have been developed in several European and North American Institutions and in Kyoto, Japan.

Progresses made during the last decades

Technical developments The shortage of size-matched post-mortem donor liver stimulated the development of technical innovations, based on the segmental anatomy of the liver, which facilitated transplanting parts of a large post-mortem adult donor liver into smaller recipients.

The technique of ex-situ reduction was described and validated in the 1980s. It contributed significantly to the expansion of liver transplantation in children since the majority of candidates are young and small in size. In order to avoid to discard the right part of the liver graft, the concept of splitting the liver into two grafts was subsequently developed. It consists of dividing all vascular and biliary structures and parenchyma for the benefit of two recipients (usually the right lobe is transplanted into an adult and the left lobe or the left lateral segment into a child). In several centers around the world, the split technique is the main source of grafts to be transplanted in children.

Persisting organ shortage in Europe and North America despite the innovative techniques previously described for post-mortem donor liver transplantation was the reason and justification to develop living related liver transplantation (LRLT).
It was the only option in Japan and other Asian countries where organ procurement from brain-dead donors was very seldom performed for legal and/or cultural reasons. LRLT poses a unique ethical issue because the donor, who is put at risk, will not derive any benefit from donation other than psychological. Therefore, a prerequisite is to strictly adhere to a protocol approved by the Ethics Committee or the Institution Review Board, with informed consent and guaranteeing the donor’s autonomy and safety (exclusion of any extra-risk factor, expertise in major liver resection, limitation of the extent of resection). When the recipient is a child, the procurement can usually be restricted to the left lateral segment of the donor’s liver, which minimizes the operative risk and almost universally excludes long-term sequellae. These conditions being fulfilled, the experience has shown that LRLT delivers the best results. Significant progress has also been achieved in the operative procedure of the recipient, in order to reduce the incidence of vascular and biliary complications.

Progress in pre-operative management  It is in the field of preparation before transplantation that the multidisciplinary approach was the most helpful, particularly regarding nutrition with new milk formulas developed for cholestatic children, enteral or parenteral nutrition when needed, control of bleeding esophageal varices and correction of salt and water retention (ascites). The impressive improvement in the results of liver transplantation, including infants, has induced an earlier referral of patients, allowing the elective transplantation of more children than in the past.

Progress in peri- and postoperative management  Liver transplantation has derived benefit from the expertise of anesthesiologists managing babies with serious conditions, of surgeons trained in pediatric surgery, concerned about limiting blood loss and ischemia time and of pediatric intensivists having large experience in managing high-risk patients, sometimes with multiorgan failure.

Progress in immunosuppression  Transplanting an allogenic liver requires depressing the immune system of the recipient for preventing rejection. It is recognized that children require more immunosuppression than adults, at least at an early post-transplant stage. As alluded to earlier, the first breakthrough in prevention of rejection came with the introduction of cyclosporine A in combination with steroids, which more than doubled the 1-year patient survival rate. The next advance was afforded by FK 506-tacrolimus with low-dose prednisone allowing steroid withdrawal within the first year post-transplant in most patients. Beside its efficacy, the steroid-sparing effect of tacrolimus is of utmost importance to preserve the growth potential of children. Moreover, the cosmetic side effects of cyclosporine A (hypertrichosis, gingival gum hyperplasia) are not seen with tacrolimus, which helps the patient and familial and social entourage accept the procedure. More recently, the introduction of anti-IL2-receptor monoclonal antibodies in combination with tacrolimus allowed complete avoidance of steroids and a low incidence of early acute rejection.

Long-term maintenance immunosuppression increases the risk of infectious and malignant complications. There are also concerns about other side-effects like nephrotoxicity, disturbances of the lipid profile, arterial hypertension and cardiovascular disease. A first objective is to minimize immunosuppression during the first months after transplantation and in the long run, regarding steroids avoidance and lowering the target blood levels of calcineurin inhibitors. This is currently the preferred policy of our group, in order to avoid the risks linked to full discontinuation of immunosuppression, as pioneered by the Pittsburgh group (with however some 25% of acute rejection following immunosuppression withdrawal). The uncertainty of the latter approach results from the absence of markers able to identify the patients who have developed operational tolerance.

Due to its immunologic privilege, the liver is likely to be the top candidate for research protocols of tolerance induction aiming at an indefinite allograft survival in the absence of continuous immunosuppression. This approach is still limited to experimental protocols in animals but, when becoming available for clinical application, would be of particular interest in children with a life expectancy post-transplant which is currently counted in decades.

Results currently obtained at Saint-Luc university Clinics  The overall results of pediatric liver transplantation at Saint-Luc university Clinics were regularly analysed and published in several scientific articles which appeared in major journals of the scientific literature. Overall, this clinical experience may be summarized as follows: (1) since the first cases performed in 1984, a continuing improvement of outcome was observed, from 75% patient survival in the initial cohort of children transplanted before 1990 to a current 95% survival among the children transplanted since 2000 (no patient was lost after liver transplantation at our center in 2007); (2) the introduction of living donor liver transplantation since 1993 allowed a significant expansion of the program, allowing timely access to transplantation for children in worsening clinical condition; moreover, it was recently shown at our center that overall outcome is significantly better with a living donor when compared to pediatric liver transplantation after cadaveric donation; (3) since 2001, children at our center are transplanted under tacrolimus and anti-IL2R monoclonal antibody; this strategy is particularly efficient at preventing acute rejection in the post-transplant period, avoiding the need to administer steroids to most of these children.