The paediatric liver transplantation program at the Université catholique de Louvain (1)

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Abstract

The Paediatric Liver Transplant Program at Saint-Luc University Clinics constitutes a substantial single centre experience, including 667 transplantations performed between March 1984 and April 2003, and the history of this program reflects the tremendous progress in this field since twenty years. Liver transplantation in children constitutes a considerable undertaking and its results depend on multiple, intermingled risk factors. An analysis of the respective impact of several surgical and immunological parameters on patient/graft outcome and allograft rejection after paediatric liver transplantation showed a significant learning curve effect as well as the respective impact of pre-transplant diagnosis on survival and of primary immunosuppression on the rejection incidence. The introduction of living related liver transplantation in 1993 not only permitted to provide access to liver replacement in as many as 74% more candidate recipients, but also resulted in better graft survival and reduced retransplantation rate. The results of a recent pilot study suggest that steroid avoidance is not harmful, and could even be beneficial for paediatric liver recipients, particularly regarding growth, and that combining tacrolimus with basiliximab (anti-CD25 chimeric monoclonal antibody) for steroid substitution appears to constitute a safe alternative in this context. The long-term issues represent the main future challenges in the field, including the possibility of a full rehabilitation through immunosuppression withdrawal and tolerance induction, the development of adolescence transplant medicine, and the risk of early atherogenesis in the adulthood. (Acta gastroenterol. belg., **2004**, 67, **176-178**).

Key words : liver transplantation, children, surgical technique, immunosuppression.

A total of 667 paediatric liver transplantations have been performed at Saint-Luc University Clinics between March 1984 and April 2003, and the history of this substantial single centre experience, initiated and developed by professor Jean-Bernard Otte, reflects the tremendous progress in this field since twenty years. The main originality of this program was probably to be integrated from its start within a specifically paediatric surgical environment, whereas in many other centres, paediatric cases were done on the side of adult liver transplant programs and essentially performed by adult surgeons. Since the majority of the paediatric candidates to receive a liver graft has a biliary atresia and should be transplanted before the age of four, the first crucial step was to be able to alleviate the shortage of size-matched postmortem donors by using left liver lobes as reduced or split grafts (1). This latter technical alternative paved the way towards the concept of living-related liver donation (2,3). Concomitantly, the other limiting factor related to the risk of allograft rejection could be progressively overcome, with the introduction of two generations of calcineurin inhibitors (cyclosporine A, its micro-emulsion formulation, and tacrolimus), as well as of other immunosuppressive molecules including anti-lymphocyte monoclonal antibodies (anti-CD3 and anti-CD25) and anti-metabolites (Table 1) (4). This paper addresses several issues relevant to the field of paediatric liver transplantation, including the multifactorial nature of its results, living-related donation, new immunosuppressive strategies, as well as its future challenges.

Impact of surgical and immunological factors

Liver transplantation in children constitutes a considerable undertaking and its results depend on multiple, intermingled risk factors. An analysis of the respective impact of several surgical and immunological parameters on patient/graft outcome and allograft rejection after paediatric liver transplantation was conducted among the first 500 recipients (median age : 2.1 years ; range : 0.2-14.5) of a primary hepatic graft transplanted at Saint-Luc University Clinics from the program start up to July 2000 (5). Pre-transplant diagnosis was a biliary atresia in 328 children (66%), a metabolic disease in 47 (9%), a progressive familial intrahepatic cholestasis in 36 (7%), a fulminant hepatitis in 29 (6%), an Alagille's syndrome in 22 (4%), and an hepatic malignancy in 13 (3%). Actuarial survival rates at 1, 5, and 10 years were 85%, 81%, and 79% for patients, and 76%, 71%, and 70% for grafts, respectively. The retransplantation rate was 16%, and the acute and chronic rejection rates were 62% and 3%, respectively. The results of the multivariate analysis studying the impact of risk factors on patient survival and acute rejection rates are given in Table 2 :

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Table 1. — **Significant milestones in the development of the Paediatric Liver Transplantation Program at the Université catholique de Louvain**

1971	First paediatric liver transplantation in continental Europe at the University Hospital of Louvain
1984	Initiation of the Paediatric Liver Transplant Program at the Université catholique de Louvain ; first reduced-size graft
1988	First spit liver transplantation
1989	Introduction of anti-IL2-R monoclonal antibody LO-Tact-1
1990	Introduction of tacrolimus therapy
1991	Paediatric liver unit
1993	First living related donor transplantation
2000	Medico-surgical unit of paediatric gastroenterology
2001	Steroid-free immunosuppression in paediatric liver transplantation

Table 2. — **Summary of the multivariate analyses of surgical and immunological factors impacting on patient survival and acute rejection rate in 500 primary paediatric liver transplant recipients at the Université catholique de Louvain (March 1984 - July 2000) (5)**

Variables	Patient survival	Acute rejection
Recipient age	NS	NS
Diagnosis*	P = 0.001	NS
Donor age	NS	P < 0.001
Type of graft	NS	NS
Year of transplant	P = 0.001	NS
ABO-incompatibility**	P < 0.001	NS
HLA mismatch	NS	NS
T-cell crossmatch***	NS	P = 0.016
Immunosuppression****	NS	P < 0.001

* worst results with hepatic malignancy.
** worst results with ABO-incompatible grafts.
*** worst results with a positive T-cell crossmatch at the time of transplant.
**** best results with tacrolimus as primary immunosuppressant.

(1) this series showed a tremendous learning curve effect over the years, which may not only be due to improvements of surgical skills but also to the overall management, including the pre-transplant nutritional support, the refinements of immunosuppressive therapies as well as better prophylaxis and management of medical complications (Table 1) ; (2) the negative impact of several pre-transplant diagnoses (fulminant hepatic failure and hepatic malignancy) and of ABO-incompatibility could be confirmed ; (3) the lack of significant impact of HLA matching on the rejection rate further illustrated the particular nature of liver allografting when compared to kidney transplants ; (4) the absence of a positive T-cell crossmatch and a primary immunoprophylaxis with tacrolimus could be associated with significantly lower rejection rates. Accordingly, the power of such a large single center, although retrospective, study contributed to delineate the relevance of several factors with a significant impact in pediatric liver transplantation.

Living-related liver transplantation in children

The introduction of living related liver transplantation in 1993 not only permitted to provide access to liver replacement in as many as 74% more candidate recipients, with accordingly a reduction of mortality on the waiting list, but it also resulted in better graft survival and reduced retransplantation rate. Between July 1993 and April 2002, a total of 236 children concomitantly received a primary liver graft at our institution, from a living related (n = 100) or a post-mortem (n = 136) donor. The main demographic data and results of both series are summarized in Table 3. Whereas patient survival rate was slightly although not significantly better in the living related donor group, its advantage in terms of graft survival and retransplantation rate reached the statistical significance. Moreover, the rate of vascular complications (hepatic artery or portal vein thrombosis) leading to graft or patient loss was 2% in the living donor group, versus 7% in the post-mortem donor group. This finding tends to confirm that, despite a somewhat higher technical difficulty for implantation, living related donor grafts constitute better quality grafts, as suggested by a previous work from our centre (6). Nevertheless, it should be mentioned that the implementation of a living donor program opens important ethical questions, to be discussed and detailed in a specific protocol, including the issue of information and consent of the donor candidate(s) (7).

Steroid-free immunosuppression in pediatric liver allografting

Corticosteroids have invariably been part of induction and maintenance immunosuppression since the early days of clinical liver transplantation (8). Despite the potential benefits to be expected from early withdrawal or even avoidance of steroid administration, steroid therapy is still combined worldwide with cyclosporine A or tacrolimus in the vast majority of liver transplant recipients (9). Accordingly, since March 2001, a pilot study was conducted at our centre to evaluate the safety of a tacrolimus-based immunosuppressive scheme, in which induction therapy using basiliximab (anti-CD25 monoclonal antibody) completely replaced the use of steroids (manuscript in preparation). Twenty paediatric liver recipients (median age : 2.5 years) were included in this protocol, and compared to a similar control group of 20 children (median age : 1.5 years) transplanted during the immediately previous interval under a conventional tacrolimus-steroids regimen. At a minimal follow-up period of one year post-transplant, all patients were alive with their first graft, except for one child in the control steroid-treated group lost on day 159 from tumor recurrence. Rejection-free graft survival at one year was 75% in the steroid-free group, versus 50% in the control group (P = 0.05). Biochemical follow-up showed similar tacrolimus blood levels in both groups, and significantly lower ALT levels during the early post-transplant period in the steroid-free group. Most importantly, at 3, 6, and 12 months post-transplant, growth was significantly better in the tacrolimus-basiliximab group. These results

Table 3. — **Comparison of demographics and results after paediatric liver transplantation using living related (n = 100) or post-mortem (n = 136) donors, transplanted at Saint-Luc University Clinics between 1993 and 2002**

	Living related donor liver transplants (n = 100)	Post-mortem donor liver transplants (n = 136)	Statistical significance
Recipient age (years) :			
median, range	1.0 (0.4-13.1)	2.4 (0.2-14.9)	P < 0.0001
Donor age (years) :			
median, range	33.3 (19.1-54.6)	14.9 (0.4-67.2)	P < 0.0001
Graft type (%)			
Left lobe	100 (100%)	(-)	
Whole liver	(-)	62 (46%)	
Reduced-size	(-)	55 (40%)	
Split	(-)	19 (14%)	ND
Patient survival *			
1 year	94%	89%	
5 years	92%	85%	NS
Graft survival *			
1 year	92%	80%	
5 years	89%	77%	P = 0.027
Retransplantation rate	3%	11%	P = 0.022
Vascular complications **	2%	7%	P = 0.078

* : Kaplan-Meier actuarial survival estimates.
** : Hepatic artery or portal thrombosis leading to retransplantation or patient death.
ND : not done.

suggest that steroid avoidance was not harmful, and could even be beneficial for paediatric liver recipients, particularly regarding growth, and that combining tacrolimus with basiliximab for steroid substitution appeared to constitute a safe alternative in this context. The series of children under steroid-free regimen has now reached 50 cases, and the early results seem to be confirmed, although longer follow-up periods and controlled trials will be required in order to fully validate this innovative approach.

Future challenges

As shown above, the surgical and immunological progresses in paediatric liver transplantation have gradually improved the overall results of the procedure over the years, to reach nowadays one and five year patient survival rates beyond 90% and 80%, respectively. Accordingly, this success opens further avenues of investigation, mainly related to the long term follow-up, which is now expected to be reached by the vast majority of paediatric liver recipients. Several issues will have to be addressed in the next decade, including the questions of growth, bone mass and increased risk of early atherogenesis in the adulthood. Moreover, a full rehabilitation could only be obtained after immunosuppression withdrawal, which opens the promising field of induction of immunological tolerance, a concept particularly attractive in living donor liver transplantation. The development of adolescence transplant medicine also constitutes a priority in a near future, in order to be able to adequately manage the specific problems encountered in this very particular population.

The paediatric liver transplant community has to pay a particular tribute to professor Jean-Bernard Otte, and beyond his achievements, to those of the many people who made this formidable undertaking a feasible and a beneficial option for children in need for a liver replacement.

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