Long-term complications of immunosuppression in pediatric liver recipients

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Abstract

Liver transplantation (LT) today constitutes a well-standardized and efficient therapy for children with acute and chronic hepatic failure. Appropriate pre-transplant management, organ preservation, adequate surgical techniques, and the progressive introduction of new immunosuppressive regimens have contributed to significantly improve, over the years, the general outcome after LT. Consequently, these good overall results has allowed the constitution of a growing cohort of children, adolescents and young adults submitted to chronic immunosuppression. The long-term complications of immunosuppression administered to transplant recipients include the adverse effects secondary to the depression of the immune system, the toxicities specifically related to the individual immunosuppressive drugs, and the sense of lack of rehabilitation for the transplant patient, with, secondarily, the question of non-adherence to the medications. This review will essentially focus on these three issues in the particular context of paediatric liver transplantation.

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Abbreviations

EBV : Epstein-Barr virus
IS : Immunosuppression
LT : Liver Transplantation
PTLD : Post-Transplant Lymphoproliferative Disorde.

Liver transplantation (LT) today constitutes a well-standardized and efficient therapy for children with acute and chronic hepatic failure. Appropriate pre-transplant management, organ preservation, adequate surgical techniques, and the progressive introduction of new immunosuppressive regimens have contributed to significantly improve, over the years, the general outcome after LT. Except for children with hepatic malignancy or fulminant hepatitis, the current figures for one year patient survival now reach 90% in many experienced centres (1,2,3,4), whereas late graft or patient loss is encountered only in a small minority of these one-year survivors (when compared to kidney, heart and lung transplants) (1,2). Consequently, these good overall results has allowed the constitution of a growing cohort of children, adolescents and young adults submitted to chronic immunosuppression (IS) in the long-term. In most instances, unfamiliarity of the primary physician with the management of IS medications lead many long-term transplant patients to regularly attend the outpatient clinics of the transplant centre for overseeing IS (5,6). Local doctors, particularly paediatricians, should however be aware of the major side-effects inherent to the calcineurin inhibitors cyclosporine A (Neoral®) and tacrolimus (Prograft®), the two immunosuppressors almost universally prescribed in paediatric solid-organ transplant recipients (Table).

Table. — **Comparative, specific side-effects of cyclosporine A and tacrolimus, to be monitored in long-term liver transplant children (adverse events in brackets are uncommon in patients with low or infratherapeutic through blood levels of the calcineurin inhibitor)**

Cyclosporine A	Tacrolimus
Arterial hypertension	Arterial hypertension
Nephrotoxicity	Nephrotoxicity
Hirsutism	(Hyperkalemia)
Gingival hypertrophy	(Diabetes)
(Neurotoxicity)	(Pruritus)
(Diabetes)	(Insomnia)
(Hypercholesterolemia)	(Neurotoxicity)

Adverse events related to IS in transplant recipients may be categorized as follows : (i) the generic effects related to the depression of the immune system, whatever the type and dosage of the IS molecules administered ; (ii) the toxicities specifically related to the individual IS drugs ; (iii) the sense of lack of rehabilitation for the transplant patient, with, secondarily, the more and more important issue of non-adherence to the medications (7) as well as the question whether IS might be totally withdrawn at some stage (8). This brief review will essentially focus on these three issues in the specific context of paediatric LT.

Common complications of pharmacological immunosuppression

Opportunistic infections and post-transplant *de novo* malignancies represent the two main complications non-specifically related to the level of immune depression induced by pharmacological IS (6). In paediatric LT, the incidence of late opportunistic infections has been considerably reduced since the progressive introduction of

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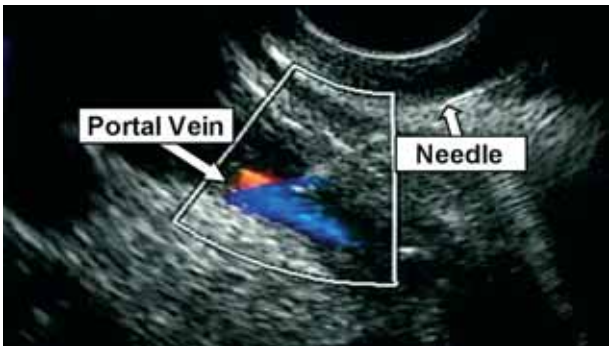
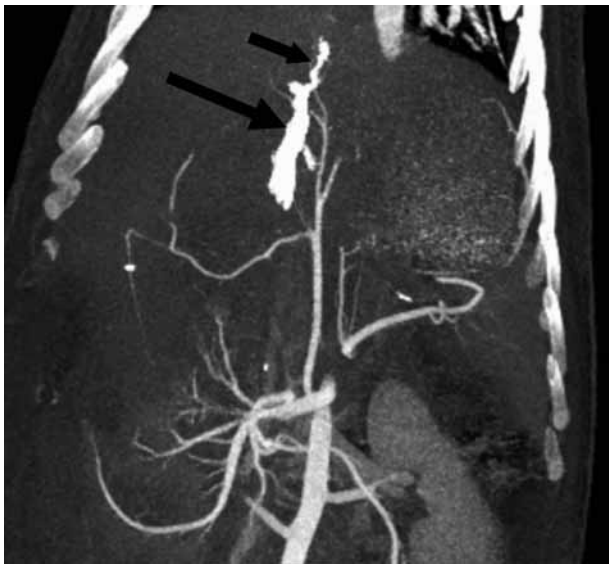


Fig. 1.



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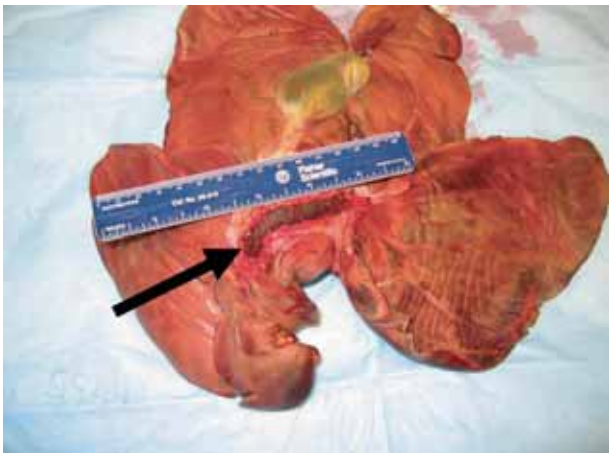

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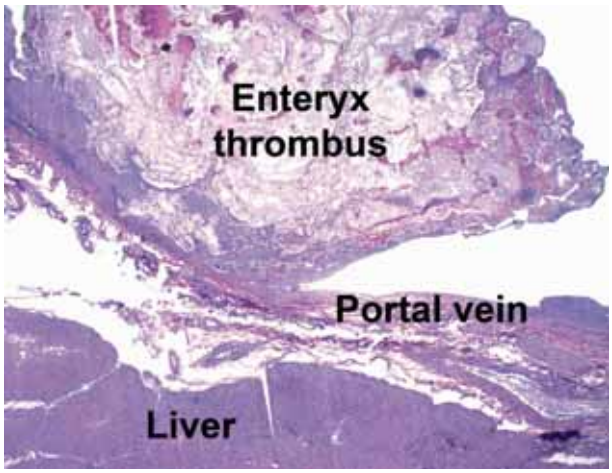

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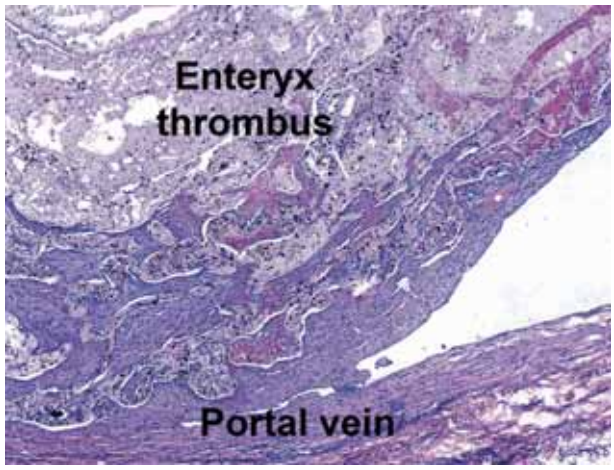

Fig. 4.

minimized IS schemes, and nowadays the risk for transplant patients to develop severe community acquired bacterial or viral infections, particularly cytomegalovirus, herpes and varicella-zoster, is not any more clinically significant (9,10). Similarly, the occurrence of *Pneumocystis carinii* pneumonia has become a very rare event with the wide use of appropriate oral trimethoprim or aerosol pentamidine prophylaxis, as administered during the first year post-transplant in many centres including ours. From a clinical perspective, a LT patient presenting with fever in the long-term should also be investigated with respect to the possibility of unresolved technical problems with secondary sepsis, particularly bile duct complications and cholangitis.

Three main categories of post-transplant malignancies can be distinguished in paediatric LT recipients : (i) the recurrence of a pre-LT malignancy, as observed in children transplanted for an hepatoblastoma or an hepatocarcinoma ; (ii) Epstein-Barr virus (EBV)-related post-transplant lymphoproliferative disorders (PTLD), with a classically increased incidence in small children and infants who are more likely to be EBV-negative at the time of the LT from an EBV-positive donor ; (iii) the non-PTLD *de novo* malignancies, mostly skin cancers of all types, particularly in areas in which sun exposure is intense. Initially considered as a regularly lethal complication, the clinical presentation of PTLD in middle- and long-term paediatric LT recipients has been significantly attenuated in most instances ; this currently milder pattern of PTLD is most probably a result of early monitoring of circulating EBV load by means of PCR technology, as well as of better knowledge of the therapeutic

measures to apply to these children without delay (prompt IS reduction or withdrawal, surgical resection and anti-CD20 monoclonal antibody therapy) (11).

Specific toxicities of immunosuppressors

In the long term, calcineurin inhibitors, steroids, antimetabolites and rapamycine represent today's the four types of IS administered chronically in transplant patients.

Calcineurin inhibitors. A recently published multicentre European study in 181 paediatric LT recipients demonstrated the significantly better efficacy of tacrolimus primary therapy in the prevention of acute rejection as well as of steroid-resistant acute rejection, when compared to cyclosporine A microemulsion therapy (12). Accordingly, the majority of the long-term LT children are treated today with tacrolimus (Prograf®), either following primary immunoprophylaxis, or after a secondary switch from cyclosporine A (Neoral®) mainly in the context of insufficient IS or cosmetic side-effects specific to this latter molecule (hirsutism, gingival hypertrophy) (Table). Beyond one year post-transplant, a significant proportion of these recipients is maintained under tacrolimus therapy with low target trough blood levels (3-5 ng/ml) ; tacrolimus is commonly administered in combination with low dose steroids, either in accordance to centre experience, or when insufficient IS or post-transplant immune hepatitis is suspected at liver graft histology (13). Classically, long-term toxicity under tacrolimus includes chronic nephrotoxicity (both glomerular and tubular), arterial hypertension and, occasionally, hyperkalemia. The issue of chronic nephrotoxicity under calcineurin inhibition deserves much attention by the transplant clinicians, in order to prevent the development of late end-stage kidney insufficiency : regular monitoring of drug trough levels, tapering of dosages, tight control of blood pressure, and the preferential use of renal-sparing IS drugs constitute important general measures in all long-standing organ recipients. At our centre in Brussels, a majority of children now receives tacrolimus monotherapy *bid*, with maintenance of normal liver graft function and histology despite infratherapeutic blood levels (< 3 ng/ml) (14). The safety profile of such low IS load includes very little clinically-significant side-effects, and this condition delineates the state of *prope* (Latin word for almost) tolerance, as defined by Calne (15). The very long-term evolution of renal function in *prope* tolerant patients will require further longitudinal studies.

Steroids. Historically, high doses of corticosteroids have been part of the IS prophylaxis of solid-organ recipients, with their well-known, severe side-effects including cushingoid facies, arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, osteopenic bone disease, and growth failure in children (16). To alleviate this toxicity profile, the successive trends have been to opt to low-dose steroids schemes, early transition to alternate day steroid therapy, and secondary steroid withdrawal (8,17). More recently, a fully steroid-free, tacrolimus and basiliximab (Simulect®) IS regimen has been proposed in a pilot series of paediatric LT recipients, with significant advantages observed in terms of early post-transplant growth and lower rate of arterial hypertension ; interestingly, these beneficial effects were not associated with increased rates of acute rejection within the first year post-LT (9). Despite such encouraging perspective, it should be emphasized that a significant proportion of children will still require chronic steroid administration to reinforce IS or to treat post-transplant immune hepatitis, with the aim to keep steroid dosages as low as possible, under an alternate day regimen if possible (8,13).

Anti-metabolites. This category of molecules, which are inhibitors of DNA synthesis, essentially includes azathioprine (Imuran®) and mycophenolate mofetil (CellCept®), the latter drug inhibiting more specifically proliferating lymphocytes. Suspected insufficient IS or post-transplant immune hepatitis represents the more common indication of antimetabolite administration in long-term LT children (13). Another promising indication could also be the reduction of cyclosporine or tacrolimus impregnation in order to spare the kidney function. Chronic toxicity of these molecules includes leucopoenia, thrombocytopenia, and anorexia with diarrhoea, particularly in children with mycophenolate mofetil daily dosage above 20 mg/kg.

Rapamycine (sirolimus). This molecule (Rapamune®) is a macrolide antibiotic which blocks the signal pathway between the IL-2 receptor and the nucleus, with secondary inhibition of lymphocyte proliferation. The data available are limited in paediatric LT (5,17) ; however, according to our unpublished experience, rapamycine seems to constitute an efficient therapeutic alternative in case of early chronic liver rejection, even after the establishment of clinical jaundice. Particular *in vitro* properties of rapamycine include the inhibition of smooth muscle proliferation, anti-tumour and anti-EBV effects, and permissiveness for activation-induced T cell death (17). Among the side-effects of the molecule, impairment of wound healing, thrombocytopenia, oral and oesophageal ulceration, as well as elevated cholesterol and triglyceride levels should be emphasized.

Rehabilitation and non-adherence

The daily, life-long intake of IS drug(s) constitutes for the transplant patient a continuous reminder of his/her lack of full rehabilitation, even if he/she is apparently enjoying a fully normal life. This sense is even reinforced in *adolescent* patients transplanted in early childhood or even during their infancy : from a psychological point of view, it should be kept in mind that their past medical history and daily drug(s) do not really "belong" to them, but rather to their parents, with consequently a tendency towards untold refusal of the ther-

apy which leads to non-adherence (18,19). Assessment of risk factors for such non-compliance in transplanted adolescents represents a crucial, sometimes underscored issue in the long-term management of this patient population (5) : more emphasis will be required in the future with respect to the psychosocial development of patients transplanted during their childhood, and followed up through adolescence and early adulthood.

Immunosuppression withdrawal and tolerance assays

The ultimate aim in transplant patients is to reach full rehabilitation through complete and definitive IS withdrawal. Unfortunately, although a small number of grafts are not rejected after removal of all medications used for the maintenance IS, trials involving the deliberate withdrawal of IS drugs according to a protocol do not suggest that it is safe to do so for most patients : such trials are associated with the inherent risk to induce acute or even chronic rejection with the need for higher levels of IS, when compared to the stable situation before attempting at drug withdrawal (8,20-22). In this context, the development of tolerance assays and the implementation of clinical tolerance trials are intimately dependent upon each other : the introduction of tolerance induction protocols in solid-organ transplantation will require the identification of simple, robust, ideally non-invasive surrogate biomarkers reflecting the immune alloreactivity of the recipient towards his/her donor. Promising candidate assays include the detection of post-transplant Th1/Th2 immune deviation, of circulating precursors of dendritic cells subtypes, and of regulatory T cells.

Conclusion

Currently, the evaluation of the level of IS required for a given patient (choice of molecule or drug combination, dosage adjustment, and target therapeutic window according to blood monitoring) is still determined only on an empiric basis, according to the experience of the transplant clinician balancing the quality of graft acceptance and the individual toxicity profile encountered. A major progress in the management of long-term IS will reside in the determination of rationale-based strategies leading to the administration of the lowest possible IS load, for a minimal duration, an evaluation to be based on laboratory tests assessing the recipient allogenic responsiveness. In the meantime, a regular follow-up program is required for children and adolescents under long-term IS therapy, for assessment of graft status and possible complications of the IS therapy, within multidisciplinary transplant teams.

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