Intestinal transplantation

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Two main advances have allowed small bowel transplantation (SBTx) to become a promising option for the treatment of end-stage intestinal failure. The introduction in the early 1990s of a new macrolide immunosuppressive agent, tacrolimus (FK506), has allowed long-term survival of several adult or pediatric recipients of small bowel graft (1). Such a long-term survival has never been achieved with cyclosporine except in one child who received at 5 months of age an isolated small intestinal allograft from an anencephalic neonate (2). This child is now 10 years old, growing normally and living at home. The second refinement has been the successful outcome after combined small bowel/liver transplantation in an adult patient treated with CsA (3). This result has opened the field of this life saving procedure for patients who have developed intestinal failure-related liver disease and has raised the question of liver induced small bowel graft tolerance.

Current results

Data on long term patient and graft survival after small intestinal transplantation are now available from the international registry and several reports from specific programs (4-8). Patient and graft survival depends on the type of transplantation, ie. isolated small bowel (SB), combined liver SB, (LSB) or multivisceral (MV) allografts, and immunosuppressive treatment. The first results from the International Intestinal Transplant Registry were published in 1996 (4). Graft/patient survival (%) at 1 and 3 years treated with tacrolimus were : 65%/83% and 29%/47% ; 64%/66% and 38%/40% ; and 51%/59% and 37%/43%. Death was due mainly to infections (42%), multiorgan failure (30%) or lymphoma (11%) ; 80% of survivors had a functional intestinal graft and had been weaned from parenteral nutrition (PN).

In 1994 actuarial patient survival rate at 18 months was reported as being 62% for liver-bowel transplants, 64% for isolated bowel transplants and 86% for multiorgan transplants (1). In a serie of 71 consecutive intestinal transplantation (with the colon in 29 patients) performed in Pittsburgh, the one-year, 2-year and 4-year actuarial patient survival is 72%, 57%, and 45% respectively (5). More recent results concern 55 children having received 58 intestinal transplantation under tacrolimus/steroids immunosuppression (6). They included the isolated SB (n = 16), liver/small bowel (LSBTx) (n = 32) and multivisceral (MV) (n = 7) allografts. The respective 5-year survival rates for the primary graft after SBTx and LSBTx transplantation were 61% and 45%. Twenty-six pediatric transplants, 17 of the liver and bowel and 9 of the isolated bowel alone, were reported by the University of Nebraska, who observed patient survival rates of 73% and 100%, respectively, at one year (7). Among 9 isolated small bowel and 10 combined small-bowel liver transplantations performed in Paris from November 1994, 40% of SB recipients and 80% of SB-liver graft recipients are alive with functioning graft 6 months to 4 years after transplantation, all but one have been weaned from PN (8).

Thus, intestinal transplantation has become a therapeutic option for patients with permanent intestinal failure, definitively dependent on parenteral nutrition, some having life threatening liver disorders requiring combined liver transplantation. The hypothetic liver-induced immune tolerance has given conflicting results in experimental models (9, 10) or in clinical experience (4, 6, 8). The large pediatric serie reported by Pittsburgh's team does not show any advantage on long-term graft survival when combined liver transplantation is performed (6). Nevertheless, intestinal graft rejection episodes are less frequent and severe in recipients of combined small bowel-liver allograft. From our experience involving 19 patients, graft and patient survival rate after combined liver-small bowel grafting is higher than after isolated small bowel transplantation (8).

Complications after intestinal transplantation

Given the large number of immunocompetent cells in the graft, most experimental work has focused on the prevention of graft *versus* host disease (GvHD). It has been shown that GvHD could be prevented by immunosuppressive treatment, removal of mesenteric lymph nodes and irradiation of the graft (11). Studies in humans have demonstrated the presence of circulating donor-derived lymphocytes during the first few weeks after transplantation, without clinical GvHD (12). Clinical signs of GvHD have rarely been reported, mostly after combined liver-small bowel transplanta-

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tion, and have always resolved favorably. GvHD therefore is not a major complication after intestinal transplantation contrary to graft rejection.

As a consequence of increased immunosuppression, graft rejection may further precipitate opportunistic infections that become additive factors in patient and graft losses. As rejection can occur rapidly and be life-threatening, close monitoring is required. This has led to the development of numerous diagnostic methods, which are not validated in human intestinal transplantation or are not relevant (13, 14). Apart from intestinal permeability studies (15), that are not fully reliable, and, more recently, scintigraphic scanning using ^{99}technetium-labelled leukocytes (16), there are no simple tests reflecting the state and/or function of the whole graft. Hence regular biopsies of the proximal and distal ends of the graft for histologic or immunohistochemical analysis, are required (17-19). Clinical signs of rejection occurr later than histological and immunohistochemical signs and reflect to a relatively advanced rejection process with marked histological lesions. In addition clinical manifestations of intestinal disease such as abdominal distension, pain, diarrhea or fever are non specific markers of rejection. It seems that the combination of conventional histology, using hematein eosin staining, and immunohistochemistry on repeated mucosal biopsies, provides not only early and rapid diagnosis, but information on mechanisms of rejection-related mucosal injury (20). Morphological changes are graded from crypt cell necrosis to total villous atrophy. In the absence of any morphological changes, immunohistochemical patterns include (i) appearance of pericryptic $CD3^+$ cells in the deep mucosa, some of which are activated and expressing the p55 chain of the IL-2 receptor (CD25) ; (ii) appearance of HLA-DR antigens on crypt enterocytes reflecting a local increase in lymphokine release (IFN) by activated T-cells ; (iii) a decreased number of $Ki67^+$ proliferating cells within the crypts.

It is of importance to differentiate others sources of potential intestinal allograft disease that may clinically mimic rejection such as post-transplant lymphoproliferative disease (PTLD), Epstein-Barr virus (EBV), cytomegalovirus (CMV) or other bacterial/viral enteritis (21-25). From a biopsy specimen, histological analysis should not only assess for graft rejection but look for the presence of intranuclear and intracytoplasmic viral inclusions. Polymerase chain reaction (PCR) for several virus, especially CMV, EBV or enterovirus, is very helpful for the diagnosis (26, 27).

Ischemia-reperfusion injury may increase the risk of graft rejection and bacterial translocation. Rejection and sepsis can be intimately related following SBTx when rejection compromises normal intestinal barrier mechanisms, that result in bacterial translocation. Macrophages have been shown to play a role in controlling the transfert of intraluminal bacteria and are also involved in intestinal rejection (28). Bacterial recolonization of the digestive tract after antibiotic prophylaxis for endoluminal bacterial overgrowth, and/or episodes of rejection, carry a risk of infection through bacterial translocation with consequent multiorgan failure (29). Addition of some component in preservation solution might minimize ischemia-reperfusion graft injury and inhibit bacterial translocation after SBTx (30). Trophic factors such as ornithine-alpha-ketoglutarate has been shown in a rat model to improve intestinal barrier after SBTx (31).

Viral infections are frequent after intestinal transplantation. Primary cytomegalovirus (CMV) infection or reactivation is not always prevented by preemptive treatment. Diagnosis of CMV infection is routinely based on serological assessment, blood antigenemia, search for CMV inclusion on routine histology and use of immunofluorescence staining. Polymerase chain reaction (PCR) was show as a sensitive method for the early detection of CMV in solid organ (26) and intestinal graft recipients (27). Incidence of CMV infection has been reported as 29% of pediatric recipients of intestinal graft (6). Although CMV disease produces significant morbidity, it can be treated sucessfully in most patients. It is recommanded to avoid using seropositive graft in a seronegative recipient (21). Nevertheless, patients who are awaiting composite grafts are too sick to await a CMV-seronegative donor. Standard CMV prophylaxis is now well established with wide use of gancyclovir (22).

Epstein-Barr virus (EBV) infection can produce a spectrum of disease. EBV-induced post-transplant lymphoproliferative disease (PTLD) has been reported as particularly frequent (15%) in a serie of intestinal graft recipients (23). Their incidence increased with the degree of immunosuppression. In fact, in the early experience with FK506, high IV doses, with limited monitiring of plasma levels, might have contributed to the development of lymphoproliferative syndromes. Poor results have been shown with the use of traditional therapeutic interventions, which have included decrease or withdrawal of immunosuppressive treatment, antiviral therapy, immunoglobulins, or cytokine therapy. Quantitative EBV-PCR in the peripheral blood has recently allowed for early diagnosis as well as follow-up of patients with EBV infection. Nuclear staining with in situ hybridization for EBV early RNA transcript (EBER) using EBER-1 probe has confirmed the presence of EBV within the graft of children with PTLD (24). This may allow the diagnosis of EBV infection before the development of PTLD. In case of established EBV-related PTLD, therapeutic changes based on quantitative PCR is helpful in preventing the end phases of this disease (32). Donor selection and prevention of EBV infection are unsolved problems.

Graft function

Studies performed in animals have shown that intestinal transplantation disturbs the absorption of carbohydrates, lipids, glutamine, water and electrolytes

(33-35). There are several potential explanations, such as denervation, disruption of lymphatic drainage, ischemia-related injury, increased intestinal permeability and immunosuppressive treatment. Feeding must resume as early as possible, orally or enterally, as this ensures optimal mucosal trophicity and reduces gastrointestinal stasis, which is a source of intraluminal bacterial overgrowth. Radiological studies of intestinal transit show normal or sometimes hyperactive peristalsis. Myoelectrical measurements in animal model as well as manometry in humans have shown abnormal intestinal motility and disorganization of interprandial phase III migrating motor complexes (MMC) due to the loss of extrinsic innervation of the small bowel. Because of water-electrolytes malabsorption and abnormal motility, several weeks may be needed to achieve normal intestinal transit and stool volume. If the recipient has no colon, combined small-large bowel transplantation has physiological advantages on the water and electrolyte reabsorption, on the time of intestinal transit and on trophic factors, from colonic synthesis of short-chain fatty acids.

Finally, it is currently considered that intestinal transplantation restores an enteral axis capable of ensuring digestion and absorption, and that full function allow PN to be withdrawn completely. Growth in children and stool balance analysis confirm normal intestinal function.

Indications for small bowel transplantation

Short bowel syndrome due to extensive resection of the small bowel, is the first indication for intestinal transplantation. After extensive resection of the small bowel, most neonates can restore gastrointestinal autonomy with a delay depending on the length and nature (jejunum or ileum) of remnant small bowel and the presence of the ileocecal valve and/or colon (36). However, a 10 to 15%l of children do not acquire gastrointestinal autonomy after several years of parenteral nutrition. This is linked either to an inadequate remnant small bowel (less than 10 to 20 cm) or to severe motility disorders associated with bacterial overgrowth. In these situation the risk of onset of liver disease is high.

In older children or adolescents, intestinal adaptation, and intestinal absorption sufficient for meet growth, can only be obtained after extensive intestinal resection if the length of remaining small bowel is more than 40 cm beyond the angle of Treitz (36). Some children in this situation do not become autonomous even after more than 10 years of PN, and are thus candidates for intestinal transplantation. In all these short small bowel conditions, transplantation can only be proposed after the demonstration that the remnant bowel cannot adapt, and/or after surgical lengthening of the small bowel, loop interposition or assembly of a "reverse" intestinal loop (37). If the use of trophic factors such as human growth hormone is successful, it will probably contribute to decrease the need for intestinal transplantation in the future (38).

Apart from these anatomical indications, intestinal transplantation can also be indicated in children with two other types of disease : primary disorders of intestinal motility (chronic intestinal pseudo-obstruction syndrome or extensive Hirschsprung's disease involving the small bowel), and constitutional diseases of the intestinal mucosa such as microvillous inclusion disease or epithelial dysplasia (39, 40).

The treatment of patients with functional or anatomical intestinal failure has benefited from progress in PN, especially home-based PN, over the last 20 years. Intestinal transplantation is theoretically indicated for all patients permanently dependent on PN. However, as PN is generally well tolerated, even for long periods, indication for transplantation must be carefully weighed up according to iatrogenic risk and quality of life. PN is effective and well-tolerated, and can be used pending further progress in intestinal transplantation. In contrast, when PN has reached its limits, especially those associated with vascular, infectious, hepatic or metabolic complications, intestinal transplantation should be performed. Transplantation of the small bowel alone remains the first option, as combined liver-small bowel grafting is only indicated in case of life-threatening liver disease.

The timing of referral and criteria for either small bowel or combined liver-small bowel transplantation continue to be debated. In a study of Beath *et al.* at the 6th meeting of the European Intestinal Transplantation Study Group, (Milano october 4-5, 1996), the survival for 37 subjects potentially candidates was 40% at six months, and 30% at one year with the worst prognosis for subjects with esogastric varices, plasma bilirubin $>$ 100 mmol/L and severe liver fibrosis. In addition, results from Langnas *et al.* (7) show that patients referred for combined small bowel liver transplantation are more debilitated, had multiple complications, and had prolonged stays in intensive care unit. Filston and Colombani suggest that early isolated SB transplantation with such a short period of postoperative hospitalization could well prove to be cost-effective compared with the intensive use of resources that characterizes the short bowel patient with liver failure (41).

Finally, because pediatric patients represent almost two-third of indications, appropriate therapeutic strategies should be developped. It is first required to recognize as early as possible the patient with definitive intestinal failure such as extreme short bowel syndrome, or congenital disease of intestinal mucosa. These patients should be referred early to small bowel transplantation team in optimal nutritional status and before the onset of PN related complications. For the other patients dependent on long term PN and who fail to adapt after extensive small bowel resection or because

intestinal pseudo-obstruction syndrome, prevention of PN related complication and careful monitoring should allow to perform isolated small bowel transplantation instead of a life saving procedure such as combined SB liver transplantation. Thus patient's selection requires precise criteria for diagnosing irreversible intestinal failure and early referral for assessment and transplantation.

New immunosuppressive treatments

The immunosuppressive regimen required to prevent rejection causes a high rate of infection and PTLD. Thus it is crucial to develop immunomodulatory strategies to facilitate intestinal engraftment. New immunosuppressive drugs such as rapamycin (15-deoxyspergualine) and/or Mycophenolate mofetil (CellCept®) are currently under evaluation in clinical setling (42). However, since drugs such as Rapamycin or deoxyspergualine cause changes in the active transport characteristics of the intestine, their use for SBTx should be evaluated carefully (43). Combination of monoclonal antibodies such as anti CD4 and CTLA4Ig seems to induce tolerance in animal models (44). Anti-LFA-1 monoclonal antibodies (mAb) induce long-term fetal small bowel graft survival in mice (Auber *et al.*, 5th International Symposium on Intestinal Transplantation, 30 July-2 August, Cambridge, UK). The use of this mAb in clinical bone marrow and renal transplantation is currently under development suggesting they promisefull use in clinical intestinal transplantation.

One current approach based on microchimerism induced by donor-specific unmodified bone marrow transfusion, is a matter of debate as shown by negative results in a porcine model (45, 46). Simultaneous donor bone marrow cell infusion (DMBC) is currently being developed in clinical setting for liver and/or intestinal transplantation. Currently there is no difference in long-term graft survival (6). Some results, in liver transplantation suggest that dose and timing of DMBC infusions may be important factors affecting graft survival (47). More data and/or a randomized trial as well as a longer follow-up is required in small bowel recipients to evaluate its efficiency and the risk of GvHD. In addition DMBC infusion in SBTx might be affected by immunosuppression protocols.

Finally graft rejection as well as infection related to heavy immunosuppression remain the limits for long-term successfull SBTx. Current research aims to find powerfull and selective immunosuppressive treatment in order to induce graft tolerance. In addition, many experimental studies have shown that ischemia/reperfusion injury is crucial in increasing the risk of acute rejection and bacterial translocation. Current research is also focused on the improvement of the safety and efficiency of preservation solution with addition of new substrates or antoxidant agents.

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