Small Bowel Transplantation: How Successful Can It Be?

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Abstract

Intestinal transplantation is the only curative treatment for intestinal failure. Before the introduction of intestinal transplantation, parenteral nutrition and intestinal lengthening procedures, like the Bianchi operation in selected patients, were the only treatment options for intestinal failure. After the first intestinal transplant in 1987, the results were disappointing. In the following years, since the introduction of tacrolimus and further developments in immunosuppressive protocols, patient and graft survival have significantly improved with one-year survival rates exceeding 80% nowadays. Better treatment of acute cellular rejection, which occurs in up to 65% of patients after intestinal transplantation, has contributed towards this improvement. Today, about 130-150 intestinal transplants per year are performed worldwide. Compared with parenteral nutrition, intestinal transplantation seems to improve quality of life significantly after intestinal failure. In terms of costs, intestinal transplantation is cost effective after two years. Thus, intestinal transplantation has become a realistic alternative to parenteral nutrition. **(Trends in Transplant. 2008;2:24-31)**

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Key words

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Introduction

Intestinal transplantation (ITx) is the only curative treatment for intestinal failure. Intestinal failure can either be caused by short-bowel syndrome or by functional insufficiency of the intestine. Several diagnoses can lead to the final diagnosis of irreversible intestinal failure. Referring to the data from the Intestinal Transplant Registry, gastroschisis (21%), volvulus (18%), and necrotizing enterocolitis (12%) account for more than half of the indications in infants. In adults, ischemia is the most common reason for intestinal failure (22%), followed by Crohn's disease (13%) and trauma (12%)[1].

If the length of the small bowel is shorter than 80-100 cm in adults and 40 cm in children, intestinal failure is most likely due to missing capacity of the bowel remnant for intestinal adaptation. Apart from total parenteral nutrition (PN), various surgical procedures have been proposed and investigated to lengthen the residual intestine or prolong passage time. Intestinal lengthening operations like the Bianchi procedure and serial transverse enteroplasty, which basically optimize the relationship between bowel content and mucosal surface rather than just lengthening the small bowel, have been shown to improve enteral nutrition. The average enteral intake in pediatric patients was increased from 15 kcal/kg before lengthening to 85 kcal/kg one year after. With these procedures more than half of the patients could be weaned from PN[2]. Noteworthy, the different lengthening techniques may be performed sequentially.

However, loss of quality of life caused by intestinal failure is not completely restored by PN[3] because it is not a curative but a supportive treatment of intestinal failure. Nevertheless, it has been the treatment of choice in the last decades in lack of other satisfactory treatment options. Parenteral nutrition can also cause multiple complications, such as catheter-related complications (loss of access, infections) and hepatotoxicity (steatohepatitis, fibrosis and cirrhosis), which lead to an estimated 60% five-year survival rate on PN[4]. The outcome is further dependent on a variety of individual factors such as total remaining bowel length, absence of the ileocecal valve, resection of specialized portions of the intestine, age, etiology of short-bowel syndrome, and missing enteral continuity[5]. These data indicate that PN is not a satisfactory option for long-term treatment of intestinal failure. Today's philosophy is changing towards an earlier indication for ITx for patients in whom an unfavorable outcome may be expected, on the grounds of published data, e.g. in ultra-short-bowel syndrome[6]. Accordingly, there is a poorer outcome in patients who are hospitalized at the time of transplantation compared to those under stable home PN[7]. This knowledge and the continuous increase in patient and graft survival after ITx have inspired a new approach towards an earlier indication in order to avoid long-term sequelae of PN and to transplant short-bowel syndrome patients prior to the onset of irreversible liver damage.

Success rates/outcome

The first ITx was performed as part of a multi-visceral transplantation at the University of Pittsburgh, USA, in 1987[8]. The first successful isolated ITx was performed as a living donor transplantation in 1988 by Deltz, et al.[9] at the University of Kiel, Schleswig Holstein, Germany. Since the introduction of tacrolimus in the early 1990s, the numbers of ITx and multi-visceral transplantation has increased steadily worldwide to approximately 130-150 per year since 2005. In total, over 1300 ITx and multi-visceral transplantations have been performed worldwide so far, the majority of them in children[1,10].

Survival rates before 1991 were disappointing, and one- and three-year patient sur-

vival rates did not exceed 30 and 20%, respectively. With the introduction of tacrolimus, a cornerstone in the field of ITx and multi-visceral transplantation, the one- and three-year patient and graft survival rates increased to 60 and 50%, respectively, between 1995 and 1997. Currently the one-year graft survival rate is exceeding 80% according to the Intestinal Transplant Registry data presented at the X International Small Bowel Transplant Symposium in Santa Monica, USA, in September 2007[1,10-12].

Because of the high immunogenicity of the intestinal graft owing to the high number of lymphocytes in the gut-associated immune system, ITx remains one of the biggest challenges in transplant immunology. However, the inevitable potent immunosuppression has long been associated with serious sequelae and complications such as high rates of infectious complications and posttransplant lymphoproliferative disease (PTLD) as well as secondary kidney failure.

Baseline immunosuppression predominantly consists of antibody induction therapy, tacrolimus, antiproliferative drugs, i.e. mycophenolate mofetil and sirolimus, and steroids. In 1990, Murase, et al. reported on the successful use of tacrolimus in a rat ITx and multivisceral transplant model[13], which is commonly considered as a breakthrough in immunosuppression for ITx. The higher efficacy of tacrolimus compared with cyclosporin A was confirmed by others subsequently[14,15]. Since then, tacrolimus has become the baseline immunosuppressant of choice in ITx. Due to the high rate of acute rejection, in some series exceeding 80%, a high level of immunosuppression has to be achieved particularly in the early posttransplant period, thus provoking a high susceptibility for serious adverse side effects. After the advent of several potent immunosuppressive drugs during the 1990s that helped to reduce the rate of severe acute rejections and increased the short-term graft survival rates impressively, the focus of today's immunosuppressive regimens has been shifted towards a reduction of side effects and improve long-term patient and graft survival.

Immunosuppressive protocols, focusing on reduction of total immunosuppressive burden, mostly include antibody induction therapy. Since 1998, monoclonal interleukin 2 (IL-2) receptor antagonists, such as daclizumab and basiliximab, have contributed to significantly reduced rejection rates and allowed reduced initial tacrolimus levels. Thereby, calcineurin inhibitor-induced side effects were reduced and graft survival rates increased[16-19]. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, were reported to help further reduce calcineurin inhibitor toxicity, while proving to be effective in reducing the rate of rejections. However, delayed onset after ITx has been proposed due to myelotoxicity side effects, the risk of impaired wound healing, and development of hernias[20]. Alemtuzumab, a depleting monoclonal anti-CD52 antibody, revealed promising results with regards to rejection and patient as well as graft survival rates, but it has been withdrawn from pediatric immunosuppressive protocols due to unacceptably high rates of side effects[21]. Induction therapy with the depleting rabbit antithymocyte globulin was reported to result in excellent one- and two-year survival rates of 100 and 94%, respectively[22]. In this trial, nearly half of the patients were on tacrolimus or sirolimus monotherapy after a mean follow-up time of 15.8 months, accompanied by a low acute rejection rate of 44% in the first month[22].

Apart from medical aspects, such as improving long-term survival as well as avoiding side-effects of PN like liver and bone disease, quality of life aspects have gained increasing importance. It has been demonstrated that intestinal failure after acute incidents such as mesenterial infarction will not be restored by

home PN. Accordingly, quality of life may be improved in chronically ill patients suffering from malnutrition due to Crohn's disease by a certain range, but it does not restore autonomy of a patient[3].

In contrast, ITx shows encouraging results with regard to improving posttransplant quality of life, regaining personal autonomy, and social and occupational rehabilitation, although available data are limited[3]. This is achieved by the majority of patients who are completely off PN as soon as one year after transplantation[23,24]. Of the investigated patients, 85% had a Karnofsky score of 90-100% as soon as six months after ITx[3].

With regard to the economic aspects of ITX, the average costs for isolated transplants were assessed by the Pittsburgh (1994-1998) and Omaha groups (2002-2003), independently. Both groups calculated an approximate cost of US$ 132,000-135,000 for isolated ITx[3,25]. The respective costs for combined liver-ITx and multi-visceral transplantation were reported to range from US$ 207,000-214,000 and US$ 219,000, respectively[3,26]. Considering average re-hospitalization costs of about US$ 9,000-23,500 per year after ITx, and opposed to annual costs of about US$ 100,000-150,000 for PN, ITx proved to be cost effective as soon as two years after transplantation[3,27].

Factors influencing patient and graft outcome

Due to the technical complexity of the procedure, there is a variety of possible technical complications in the early postoperative period.

Besides anastomosis leakages with subsequent intraabdominal sepsis, vascular complications constitute a major potential risk. Particularly in adult patients, hereditary coagulatory disorders as cause for mesenteric ischemia account for a large proportion of etiologies. They necessitate anticoagulation treatment posttransplantation, with the immanent risk of postoperative bleeding complications.

Apart from other technical challenges, abdominal wall management in particular frequently constitutes a serious problem in short-bowel syndrome patients and influences patient outcome. Primary closure often fails because of preexisting dehiscence secondary to multiple previous operations and a swelling of the intestinal graft post-reperfusion. The abdominal wall may be reconstructed using prosthetic mesh grafts that are serially reduced in size until complete closure of the abdomen. Alternatively, Silastic sheets, grafted fascia from the same donor, and acellular dermal matrix may be used[28]. Alternatively, transplantation of the abdominal wall has recently been proposed[29].

Acute cellular rejection (ACR) occurs more frequently after ITx as compared with other vascularized organs. Due to the high immunogenicity of the intestinal graft, approximately two-thirds of patients develop ACR after ITx[30]. The total incidence has been greatly reduced over the past years by implementing different strategies of antibody induction therapy[30]. Notably, there is a significant reduction in the incidence of severe rejection episodes when a liver and multi-visceral graft is used[30,31]. Since there is a lack of reliable serum markers of ACR in ITx, serial biopsies represent the gold standard for graft monitoring, especially in the early posttransplant period. Several noninvasive markers, e.g. serum citrulline and calprotectin, have been proposed and may play a supportive role in the future[12].

In case of steroid-resistant ACR, depleting antibodies such as OKT3, antithymocyte globulin, and alemtuzumab may be

used[32]. Our group reported on the successful use of tumor necrosis factor alpha (TNFα) inhibition in steroid- and OKT3-resistant rejection in intestinal grafts[33,34].

Although ACR is now reasonably identifiable by bowel biopsy histology, and there has been consensus on an international pathology grading system[35,36], acute rejection is less well characterized and understood than in other solid organs, and several entities of allograft alterations are still poorly understood. Since graft biopsies are taken from the intestinal mucosa, typical histologic signs of humoral and vascular types of rejection as well as chronic rejection have been difficult to establish. However, there is progress in some respects, e.g. the identification of distinct signs of acute vascular rejection and the role of subclinical rejection.

A newly proposed scoring system to evaluate subtle mucosal vascular changes identified small-vessel congestion and erythrocyte extravasation as the most prominent criteria. Patients demonstrating these early vascular lesions were shown to have significantly impaired graft survival. Acute vascular rejection lesions were not related to acute cellular rejection, human leukocyte antigen (HLA) type or HLA disparities, but correlated with significantly higher peak panel reactive antibodies and a higher incidence of positive T-cell and B-cell crossmatch[37].

A recent study analyzed the clinicopathologic characteristics associated with a subclinical rejection episode within three months after ITx. It was reported that more than 50% of patients experienced one episode of subclinical rejection. Subclinical rejection predominated in adult patients and had a significant impact on overall graft survival at five years posttransplantation. Subclinical rejection within three months posttransplantation reduced five-year graft survival from 60 to 37%, and was associated with a significantly higher rate of death due to infection[38]. Hence, it may be assumed that immediate therapy of subclinical rejection will positively influence long-term graft outcome.

Due to the high amount of transplanted lymphoid tissue, a high incidence of graft-versus-host disease has been reported after ITx. Before 1995 the incidence was as high as 47% after multi-visceral transplantation and 15% after ITx. However, the incidence has decreased markedly since then and was reported to be 7-8% after 2000[1,11]. The inclusion of the spleen in a multi-visceral graft does not seem to influence the development of graft-versus-host disease significantly[39]. On the other hand, the incidence and severity of rejections was significantly reduced by including the spleen[39].

Infections are a common problem in ITx patients. The gamut of viruses, bacteria and fungi more or less resemble the ones found in other transplanted patients. However, sepsis is still the predominant cause of death in this patient population in the short- and long-term posttransplant period[1]. The restoration of normal bowel flora may be of importance to reduce bacterial overgrowth and to reduce infection rates.

Special focus has to be set on viral infections in posttransplant care. Cytomegalovirus (CMV) infection and Epstein Barr virus (EBV) infection constitute the most prominent since they can induce severe allograft enteritis. Improved strategies for monitoring, prevention and therapy of CMV and EBV infections have contributed to a reduction of incidence[20]. Other causes of enteritis comprise adenovirus and enterovirus infections, which play a significant role in the pediatric recipients[20].

Prevention and advances in therapy of EBV-driven PTLD have improved patient and graft survival immensely. The incidence has

been reduced from 15-48% after ITx and multi-visceral transplantation, respectively in the early 1990s to approximately 6-8% nowadays[1].

The highest incidence of PTLD was reported to occur 25 months after transplantation[40]. Besides the improvement in prevention of EBV after transplantation, the advent of the monoclonal anti-CD20 antibody rituximab has decreased the mortality from PTLD significantly[41].

Summary/outlook

Until recently, ITx was limited in its indication to patients with severe complications of PN such as liver cirrhosis, loss of venous access, or multiple catheter sepsis. Due to significant advances with regard to patient and graft survival, the eligibility criteria for ITx have changed towards an earlier indication.

Unfortunately, most of the recent improvements of patient and graft survival in the first year posttransplantation have not affected long-term survival. Conditional patient and graft survival beyond the first year has been unchanged over the past years. The slope of patient and graft survival curves has remained almost identical, suggesting that the mortality rate and graft loss rate have not been affected beneficially by advances in immunosuppression[12].

The most important causes of long-term graft and patient loss include infections, malignancies, acute and chronic rejection, as well as less well defined chronic allograft alterations. The unchanged rate of long-term graft losses suggests that early graft injury induced by brain death, ischemia reperfusion injury and other alloantigen-independent factors contribute to chronic allograft alterations. Hence, the amelioration and reduction of such confounding influences will be one of the keys to improving long-term patient and graft survival.

Additionally, new strategies of induction therapy may guide the way towards reduced long-term immunosuppression. For example, calcineurin inhibitor minimization has been achieved by using rabbit antithymocyte globulin (thymoglobulin) just before ITx and postoperatively, with excellent one- and three-year patient and graft survival of 100 and 94%, respectively. After a mean of 15.8 months follow-up, nearly half of the patients were on tacrolimus or sirolimus monotherapy despite a low incidence of 44% ACR in the first month[42]. However, true tolerogenic protocols without any long-term immunosuppression are not within sight.

Different immunomodulatory strategies have been proposed clinically and experimentally, which may prove to be beneficial in the future. The combination of donor-specific blood transfusion, strict donor selection, short ischemic times, and low-dose tacrolimus was recently shown to promote development of regulatory cells and resulted in freedom from rejection in a small case series[43]. Apart from these promising clinical steps towards reduced long-term immunosuppression, there are experimental models evaluating potentially long-term acceptance-inducing protocols, e.g. by combining non-depleting induction with immunomodulation. Application of a non-depleting monoclonal anti-CD4 antibody together with TNFα inhibition (etanercept) as induction therapy was reported to induce long-term survival in a rat ITx model without further immunosuppression[44]. Although the transfer of such protocols into the clinic is not a realistic option in the short term, such approaches might be helpful in the clinical setting by circumventing the sequelae of depleting induction protocols and combining immunomodulatory aspects.

Apart from that, the transfer of scientific knowledge from the field of chronic inflamma-

tory bowel disease into intestinal allograft immunity may stimulate new progress in detecting individual risk constellations for graft rejection. It was shown recently that NOD2 genotypes may not only be related to the Crohn's disease, but also to clinical outcome after ITx by determining the risk of allograft rejection. The likelihood of allograft failure was significantly higher in recipients with mutant NOD2 alleles compared to recipients with wild-type NOD2 loci[45].

With the growing numbers of ITx recipients, other aspects influencing long-term graft survival will have to be focused on: further characterization and description of histopathologic entities such as chronic allograft enteropathy as well as calcineurin toxicity; investigation of the influence of HLA-matching and preexisting antibodies; definition of the importance of non-alloantigen-dependent factors, of innate immunity, of intestinal bacterial flora, and of ischemia/reperfusion injury will require further attention.

Potential future approaches may arise in the field of tissue engineering, such as the production of matrices including enterocyte stem cells on tissue scaffolds, which will eventually generate a neo-mucosa capable of nutrient absorption[46].

In summary, intestinal transplantation has developed impressively over recent years and might soon become a first-line therapeutic option in patients with irreversible intestinal failure.

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