Adult small intestinal transplantation in Europe

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Abstract

The results of clinical adult intestinal transplantation in eight European centres between 1988 and 1998 are presented. Data were available on a total of 29 transplants in 28 adult patients. Nine patients received ten isolated small intestinal grafts and a further 2 patients received grafts of small intestine and colon. Seventeen patients received multivisceral grafts including small bowel.

After 1994 all cases have received FK506 as their primary immunosuppressive agent, more recently increasingly often in combination with Mycophenolate. Ten out of twenty patients surviving more than one week after transplantation had no recorded episodes of rejection, five one episode of rejection, three two episodes of rejection and two three or more episodes. Eighteen patients have died, Sepsis being the cause of death in twelve of these cases.

Actuarial survival figures for patients/grafts following isolated small intestinal transplantation are 64/53% at one year and 48/36% at three years following transplantation. Patient and graft survival are identical following multivisceral transplantation and are 44% at one year and 30% at three years in the thirteen patients managed under FK506 immunosuppression, none of the four patients transplanted under Cyclosporin therapy having survived beyond three months. (Acta gastroenterol. belg., **1999**, 62, **239-243**).

Key words : intestinal transplantation, multivisceral transplantation.

Introduction

The first intestinal graft in a human subject was a short segment of duodenum transplanted by Lillehei in association with a pancreatic graft at the University of Minnesota at the end of 1966 (1). In the same paper Lillehei reports a combined graft of stomach, intestine and pancreas in a patient with mesenteric venous thrombosis. The outcome in these cases as in many other attempted grafts over the coming years was unsuccessful in achieving full long term normal enteral nutrition (2-8). Grant and his colleagues reported the first long term success with a small intestinal graft in combination with a liver graft in a patient transplanted in 1988 using Cyclosporin based immunosuppression. The initial post operative was stormy with infection and prolonged mechanical ventilation but the eventual outcome was good with discharge from hospital 8 months after the initial operative procedure on full enteral nutrition (9). Further successes with Cyclosporin based immunosuppression were reported (5, 10) but there were also many disappointing failures due to rejection (3, 11, 12). The introduction of FK 506 contributed to a resurgence of interest in this area of transplantation and its widespread application has coincided with improved clinical outcomes (12-14). An International Intestinal Registry has been establishes in London Ontario and in the last biannual report in 1996 recorded the results of 25 intestinal transplant programmes worldwide with a total of 180 transplants in 170 patients (12). Indications for transplantation have included cases of short gut syndrome due to intestinal resection, malabsorption syndromes, motility disorders and extensive tumours requiring resection of the patients own small bowel. Grafts have ranged from small intestine transplanted alone (including living donor grafts (15-19)) to more complex grafts of liver and small bowel or multivisceral grafts including liver, intestine, pancreas, duodenum stomach and kidney (20).

In this paper I have selected out the European Centres who have reported cases of intestinal transplantation to the Registry and have updated their experience up to the end of September 1998 paying particular attention to the experience in adults.

Results

The ten European centres that have provided information for this study are given in table I.

Table I.

Abteilung fur Transplanationschirurgie, Landeskrankenhaus, Innsbruck, Austria
Transplant Unit, Queen Elizabeth Hospital, Birmingham, England.
Department of Surgery, Addenbrooke's Hospital, Cambridge, England.
Transplant Unit, St. James's University Hospital, Leeds, England.
King's College Hospital, London, England.
Hopital Necker — Enfants Malades, Paris, France.
University Hospital, Hamburg, Germany.
Friedrich-Ebert-Krankenhaus, Neumunster, Germany.
Ospedale Maggiore, Milan, Italy.
Universita' Degli Studi di Roma "La Sapienza", Rome, Italy.

The largest single experience is that of Dr Olivier Goulet and the group at the Hopital Necker who have carried out 28 transplants in children — these cases are not the subject of this paper and will not be discussed further. A further 36 transplants in 35 patients have been performed by the remaining 9 centres, of these 36 cases 29 transplants (including one second

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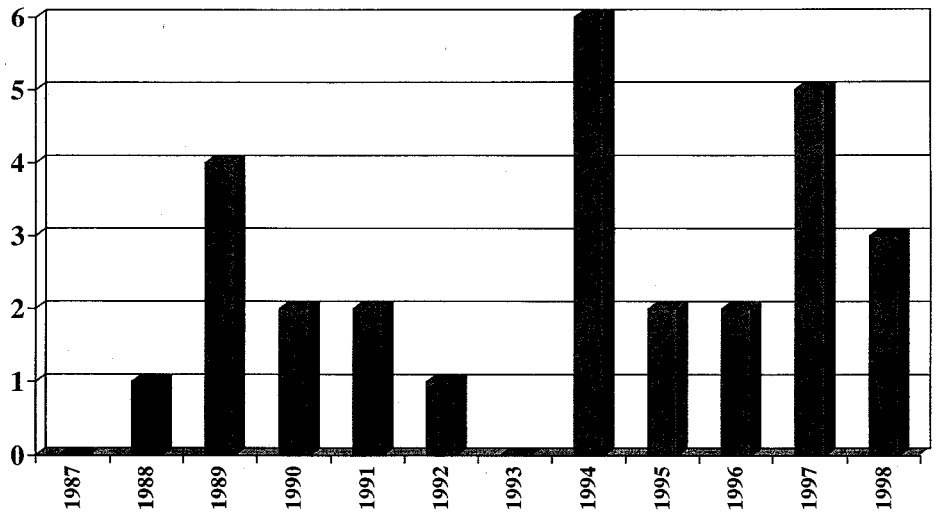

Fig. 1. — Indications for transplantation.

graft) were performed in 28 adults in 8 centres (The Birmingham perform only paediatric transplants) and will be presented in more detail. The number of cases performed per year is illustrated in Figure 1. Individual centres have undertaken from one to eight adult cases in total. The indications for intestinal transplantation in these adult cases are summarised in figure 2 and the types of graft performed in table II. Cyclosporin A was used as the principal immunosuppressive agent in the early transplants but following the introduction of FK 506 there has been a universal switch to using this agent, more recently with the addition of Mycophenolate to the immunosuppressive protocols, this

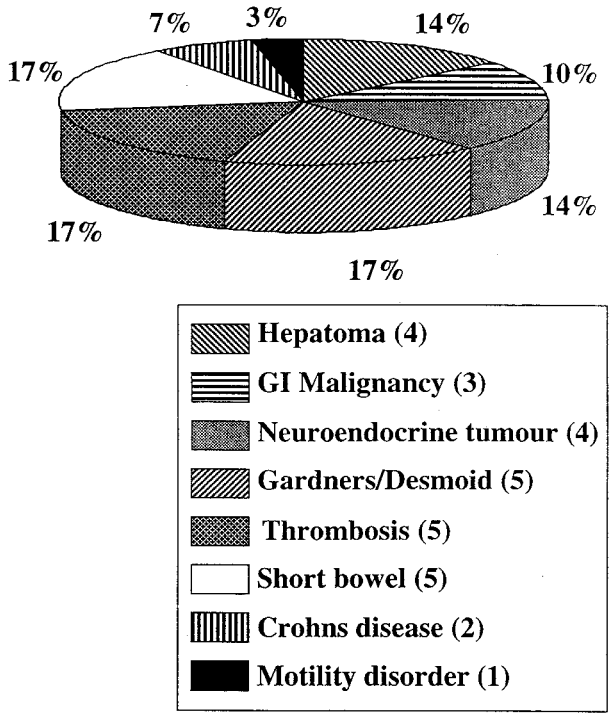

Fig. 2. — Indications for transplantation.

Table II. — **Types of intestinal graft**

Small Bowel alone*	10
Small bowel and colon	2
Liver and small bowel	1
Multivisceral	16

* Including 3 living related (one identical triplet).

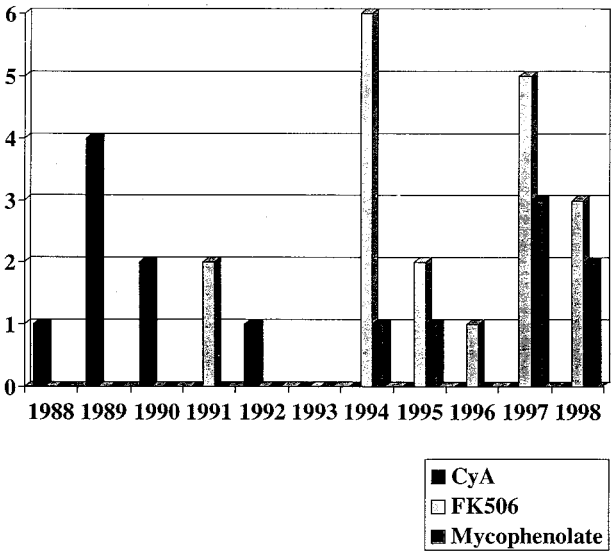

Fig. 3. — Immunosuppression.

is illustrated in figure 3. Information is available on the incidence of rejection in twenty cases who survived at least one week following transplantation and this data is summarised in figure 4. Ten out of twenty patients surviving more than one week after transplantation had no recorded episodes of rejection, five one episode of rejection, three two episodes of rejection, one three episodes and one patient four episodes of rejection. Eighteen adult recipients have died and ten are still alive, the causes of death are illustrated in figure 5.

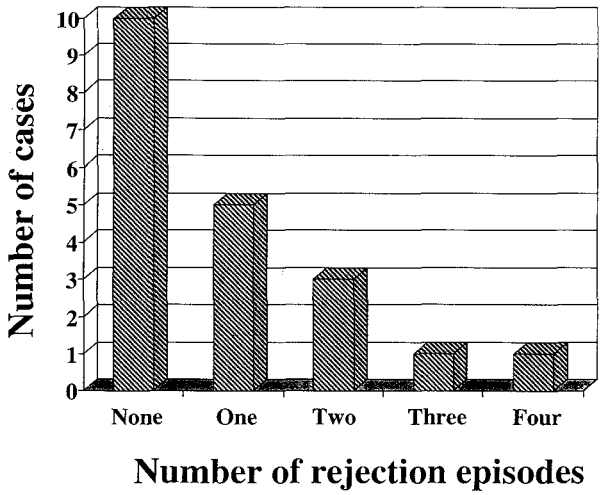

Fig. 4. — Number of rejection episodes in patients surviving at least one week.

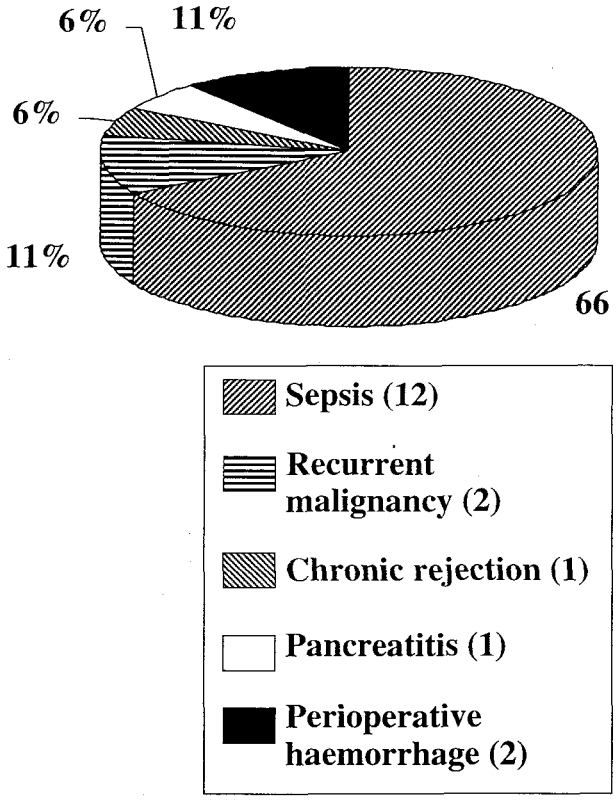

Fig. 5. — Causes of death of 18 patients dying after intestinal transplantation.

Nine patients have received ten isolated small bowel grafts ; the actuarial patient and graft survival rates are illustrated in figure 6. There are three living related grafts included in this group, one graft in the Cyclosporin era was lost to rejection at 12 days, a second was lost at 17 months when the patient died of chest sepsis. The third was from an identical triplet and has full function on no immunosuppression at 2 years. Two patients received small bowel and colon grafts, one lost the graft at 2 months due to severe rejection and subsequently died of sepsis at 5 months. The second had no rejection and at the time of the last report was alive with full function at 7 months. Out of the 11 patients in total who received 12 small intestinal grafts with or without inclusion of colon systemic venous drainage was used in 8 cases, portal venous drainage in one and the technique was not specified in two.

Seventeen patients received multivisceral grafts, four being performed in the Cyclosporin era, patient and graft survival are obviously identical in this group in the absence of any retransplants. Separate curves are shown in figure 7 for the whole series of 17 cases and the 13 later cases performed after the introduction of FK 506, none of the four patients transplanted under Cyclosporin therapy having survived beyond three months.

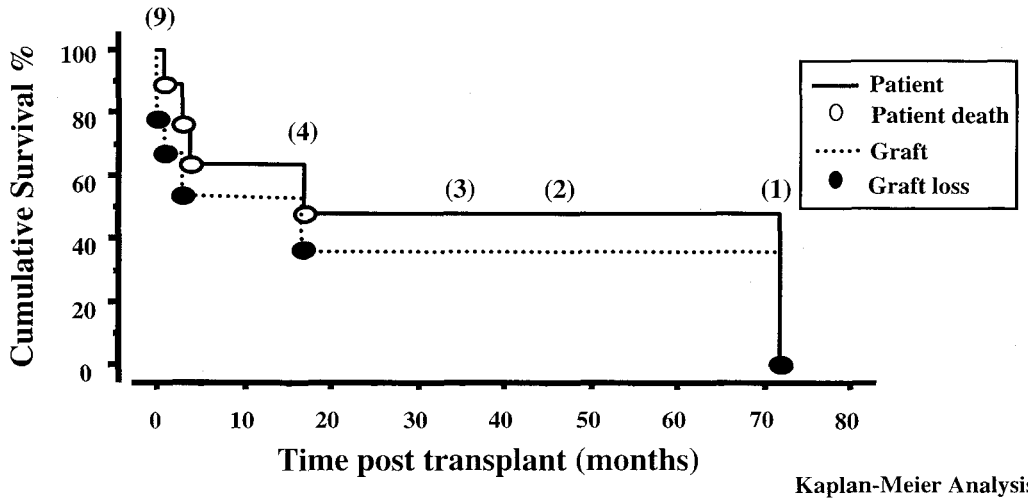

Fig. 6. — Isolated small bowel transplants — patient and graft survival, 10 grafts in 9 patients (3 living related including one identical triplet). Numbers of patients at risk shown in parentheses ( ).

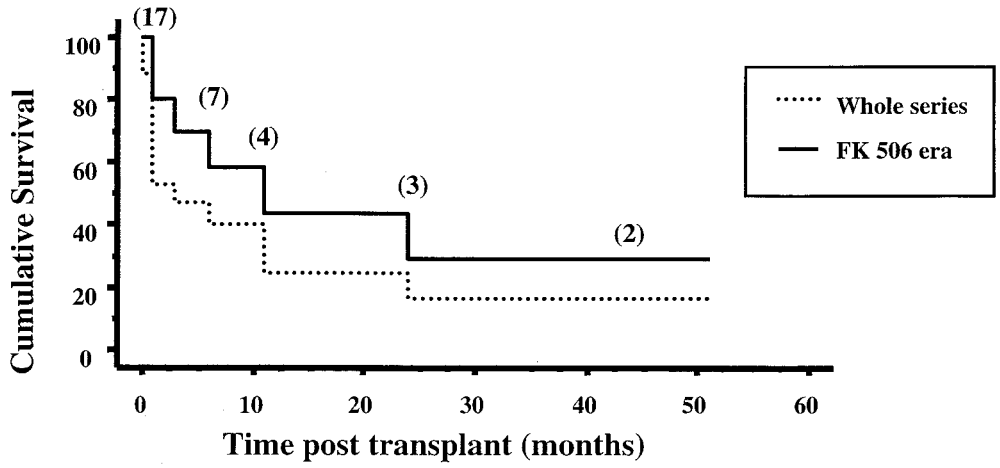

Fig. 7. — Patient survival after multivisceral transplantation. 17 grafts in 17 patients (4 using cyclosporin based immunosuppression). Numbers of patients at risk shown in parentheses ( ).

Discussion

Intestinal transplantation remains a challenging area with substantial room for improvement in patient outcome. It offers an alternative to prolonged TPN in patients where alternative management protocols for short gut syndrome have failed (13, 21). The procedure is not currently justified in patients doing well on TPN who have a relatively good outlook in the absence of complications (22). However it does have a place in patients who have developed complications of TPN or have run out of sites for venous access. Grafting of a combined liver and small bowel may be necessary in cases who have developed TPN related liver disease, a situation which appears particularly common in children (12, 23, 24).

Isolated small bowel transplantation offers a solution to the patient who has problems with venous access and no evidence of irreversible liver disease. It has the theoretical advantage that the graft can be removed if necessary and the patient returned to TPN although this frequently proves not to be the case due to sepsis and other post operative complications as illustrated by the similarity of the patient and graft survival curves in this report. The Pittsburgh group have described 12 patients undergoing graft removal with only 3 long term survivors one of whom underwent a successful retransplant (25). Combination of small bowel with colon grafts is less frequently used, only two cases being reported here. Differential rejection of the colon and small bowel has been described (26) and severe ongoing small intestinal rejection in the presence of relatively normal colonic biopsies was a major factor in the loss of the graft in one of these two cases.

Combined liver/small bowel transplantation offers a treatment option in cases where there is irreversible liver damage and appears to be more commonly applied in paediatric cases, only two such grafts being encountered in this European adult experience. Multivisceral grafting offers an option in cases with large intra-abdominal tumours whose removal may involve excision of most or even all of the intra-abdominal organs (20, 27).

The intestine presents a number of unusual challenges ; it appears to be more susceptible to rejection, carries a high load of lymphoid tissue raising the risk of Graft Versus Host Disease (GVHD) and permits the translocation of bacteria and endotoxins when rejection does occur. High levels of immunosuppression are thus inevitably used in the management of these cases to avoid rejection and this in itself leads on to a high incidence of sepsis which represented by far the commonest cause of death in these patients (12/18 deaths in this report). Lymphoproliferative disease in relation to high level immunosuppression has also been commonly reported by the Pittsburgh group from their large single centre experience (28). FK506 is now used routinely in all centres as the basis of immunosuppressive protocols and corresponds to a period during which results have improved as seen in this report and also in the international registry (12). The experimental literature is somewhat contradictory with publications showing similar outcomes with Cyclosporin/ATG protocols versus FK506 in the pig (29) but clear advantages when Cyclosporin and FK506 are compared directly (30). Recent experimental studies have suggested that the outcome can be improved further by adding Mycophenolate to FK506 (31) and this is reflected by the rapid increase in use of this agent seen in this European experience.

The experience with living related transplantation is limited but does confirm that satisfactory function can be established with acceptably short lengths of transplanted bowel (in respect to leaving the donor with normal small bowel function) and the surgical techniques are now well established (32, 33). The cases with

identical twin and triplet transplants offer an intriguing but rare option and have allowed us to confirm restoration of all aspects of intestinal function in a setting free from rejection (18, 19).

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