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Renal Transplantation in Uppsala

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ABSTRACT

The history and progress of organ transplantation in Uppsala are reviewed. Renal transplantation was begun in 1969, and the programme now comprises 50 to 60 transplants per year. Since 1976 the operation is performed at the department of urology. Close collaboration has been established with other departments in the hospital, especially with the medical nephrology unit. The indications for active management of uraemic patients have broadened, and maintaining resources on a par with the demands has constantly been a problem. This report concerns immunosuppressive therapy, transplantation results and research connected with the transplantation programme and deals briefly with the prospects for Uppsala as a transplantation centre in the future.

INTRODUCTION

Clinical renal transplantation was begun in the early 1960s. In Uppsala the first renal transplant was performed in June 1969. The first patient was a 30-year-old man with polycystic kidney disease. Already in this case special Uppsala treatment was used, as frozen autoblood, which at that time was thought to suppress immunologic reactions between the patient and the donor organ, was infused preoperatively and postoperatively. This patient still has a functioning transplant and is in full-time work.

The first renal transplantation was performed by Professor Lars Thorén, head of the surgical department who, together with Karl-Erik Fjellström, in charge of the nephrologic unit in the medical department and Claes Högman, head of the blood bank, introduced the procedure in Uppsala. Initially the patients remained for a few days in the intensive care unit and then returned to the nephrology unit. During the first postoperative weeks joint daily visits were made. Throughout the evolution of this work, very close collaboration between the involved departments has been typical for our transplantation centre.

This collaboration includes surgeons, urologists, nephrologists, clinical immunologists, radiologists, anaesthesiologists and many scientists involved in basic research within the field.

EVOLUTION AND CAPACITY

As more and more patients have been accepted for dialysis, the numbers of renal transplants have increased over the years. In addition to the centre in Uppsala, dialysis units have been established elsewhere within the health service region (Bollnäs, Östersund, Sundsvall, Gävle and Västerås). The total beds for dialysis were 14 in 1969, and the figure for 1984 is 46. Diabetics have been accepted for active therapy since 1975, and older patients have increasingly entered the programme.

The need for more transplantations has of course required extension of resources - surgical, medical and in the auxiliary services. Initially the operations were done in the department of surgery as part of the routines there. The first surgical post specifically for transplantation was established in 1971. In 1974 a new department of urology was opened at the hospital and, as most of the surgeons interested in urology moved to this service, a logical consequence was that the renal transplant programme was taken over by the urology department. In 1976, therefore, this department become wholly responsible for transplantations, and one of the associate professors at the department was delegated to lead the work. As yet, however, no surgeon was working full time with these patients. Not until 1983 was the decision made to permit two surgeons to work full time on the transplantation programme.

The waiting list nevertheless has continued to grow, and the number of transplantations has not kept pace. The progress that has been made despite this inadequacy would not have been possible without the extraordinary work done by the nephrologists. Table I surveys the growth of the transplant and dialysis programmes at Uppsala. The number of transplantations planned for 1985 is 55 - 60, and extension of the facilities at the departments of urology and nephrology is expected. The numbers of dialyses reflect the growing need for active management of renal failure in Uppsala region's total population of 1.2 million.

DONOR ORGANS

The Uppsala transplantation centre has used a low percentage (c. 5 %) of kidneys from living related donors. Initially this was because of the assumed risk of removing an organ from a healthy individual. Although gradually we

Table 1. Growth of the renal transplantation and dialysis services in Uppsala*

Year	No of transplants	No of dialyses	Approximate no on waiting list
1969	6	-	-
1970	11	900	-
1971	20	-	-
1972	17	1 900	-
1973	21	-	-
1974	30	1 500	-
1975	31	2 400	-
1976	34	2 500	16
1977	26	3 000	20
1978	31	4 100	24
1979	30	3 800	15
1980	32	3 100	30
1981	40	3 900	37
1982	42	4 000	37
1983	42	5 500	62
1984	61	6 000	60
Total	474	42 600	301

* - = no figures available

are increasing use of such sources, the percentage of living donors still is relatively low at our centre. A contributory factor is that harvesting has always been well organized in the Uppsala region, as a result of close collaboration with the other departments of surgery and anaesthetics within the region. The doctors at the university hospital and elsewhere in the region have shown a highly positive attitude concerning management of uraemic patients. At many regional meetings arranged by different disciplines, harvesting of kidneys has been a topic of discussion.

The linking of the transplantation programme to urology also has had positive effects. Many young urologists thus have worked with problems of uraemic patients during training in Uppsala, and have learned techniques of harvesting and transplanting kidneys. Vascular access surgery has also been included in their training. Many of these doctors subsequently work in hospitals within the Uppsala region and contribute considerably to the harvesting programme.

Uppsala is one of the centres in "Scandia Transplant", an organization within which kidneys are exchanged. Table 2 shows that Uppsala has had the most positive exchange balance of all the Scandinavian centres. This implies possibilities for increasing the numbers of cadaver kidney transplantations. Use of more living, related donors is another possibility.

Table 2. Utilization of kidneys in "Scandia Transplant" from 1/6 1969 to 31/12 1982

Donor centre	Kidneys transferred	Kidneys used locally	Kidneys imported	Total transplanted	Exchange balance
Århus	274	175	388	563	- 114
Copenhagen	388	431	490	921	- 102
Odense	131	41	233	274	- 102
Gothenburg	401	547	463	1 010	- 62
Malmö/Lund	204	175	206	381	- 2
Stockholm	279	281	203	484	76
Uppsala	364	200	150	350	214
Oslo	482	459	287	746	195
Helsinki	204	631	489	1 120	- 285

IMMUNOSUPPRESSIVE THERAPY AND RESULTS

Immunosuppressive therapy has undergone several modifications since we began to transplant kidneys in 1969. Initially fairly high doses of steroids were given, in accordance with policy in most countries (5). The dosage usually was 200-300 mg on the first postoperative day, tapered to a maintenance dose of 5 to 10 mg/day.

Azathioprine was always given together with steroids, beginning with an intravenous dose before transplantation. The initial dose usually was 2-3 mg/kg/day, with tapering thereafter according to evidence of bone-marrow depression or severe infection.

Because of severe side effects, the immunosuppressive therapy was changed in 1980 to the low-dosage schedule introduced by McGeown in Belfast (3). The steroid dose thus was reduced to 20 mg/day, which was maintained for one month and then very slowly reduced to 5 mg/day. With this therapy there was a high

incidence of acute rejections. The survival rates of transplants and of patients, however, were higher than in the earlier period (Table 3).

Table 3. Immunosuppressive therapy in different periods compared with one-year patient and graft survival (approximate figures)

One-year survival	1969 - 1980 Prednisolone high dose + azathioprine 2-3 mg/kg/day	1980 - 1983 Prednisolone low dose + azathioprine 2-3 mg/kg/day	1983 - 1984 Prednisolone low dose + cyclosporin A
Patients	75 %	82 %	93 %
Grafts	37 %	55 %	72 %

After one year with this regimen, we introduced a modified steroid schedule, starting with 0.6 mg/day. The aim was to diminish the high incidence of rejections while maintaining good patient survival.

In 1983 we were given the opportunity to participate in a multicentre study using cyclosporin A as immunosuppressive agent instead of azathioprine. With this agent a low steroid regimen could be used. During the first 10 days the prednisolone dose is tapered from 100 mg/day to 20 mg/day and then slowly reduced to 10 mg/day within 3 months. The dosage of cyclosporin A starts with 15 mg/kg/day and is then reduced by 2 mg every 14th day in accordance with the clinical picture and the level of cyclosporin A in plasma.

With this regimen the graft survival was considerably prolonged (Table 3). There were also less problems with infections and the incidence of graft rejection was reduced from about 70 % to 30 %. The postoperative period thus being relatively uneventful, the hospital stay was shortened to 3-4 weeks, as compared with 6-8 weeks earlier. A major problem with cyclosporin, however, is its nephrotoxic effect, and so far the long-term results are unknown. Hopefully, some new analogue of cyclosporin will be found to combine the same good immunosuppressive action with absence of nephrotoxic effect.

Other forms of therapy have also been tried together with the above - stated basic regimens. Thus in 1975 we started to give blood transfusions to previously nontransfused patients, following positive results with this regimen reported from other centres (4). We have also used donor-specific blood transfusions (DST) to one haplotype mismatched living related recipients. Three units (200 ml) of blood from the donor were given to the graft recipient at

intervals of 2 weeks. Up to now 12 patients have been treated in this way, and only one has been sensitized. This regimen is still in use in combination with conventional immunosuppressive therapy, with azathiprine and cortisone instead of cyclosporin A, in transplantation from living related donor.

Rejection therapy

Treatment of acute rejection has been, and still is, increased dose of steroids. The dose usually has been fairly high - about 1 g on 3 successive days. In patients treated with cyclosporin A, rejection therapy consists of a reduced steroid regimen (1.25 g methylprednisolone in 4 divided doses given during 4 days). In the early years we also used local irradiation to treat rejection. As the effect was questionable, however, irradiation was abandoned.

In 1982 rabbit antithymocyte globulin (RATG) was introduced for treatment of steroid-resistant allograft rejection (2). The effect was dramatic, and almost all of the patients responded with reduction of serum creatinine. This effective antirejection treatment, however, increases the incidence of infections and involves risk of malignancy, especially when given in combination with cyclosporin A.

As techniques of immunosuppression have changed, the overall results as measured by patient and graft survival have improved (Table 3). Many factors other than immunosuppressive therapy have contributed, however. Surgical procedures have been refined, in particular the management of complications. Diagnostic techniques have progressed. Gammacamera scintigraphy, ultrasonography and biopsy with advanced histologic methods have become available, and the entire clinical care has become more proficient. A retrospective survey therefore readily provides an optimistic basis for future prospects. The improvements have taken place parallel with acceptance of diabetics and elderly patients for renal transplantation.

RESEARCH

Since 1968 research on preservation and ischaemia of kidneys has continuously been conducted in Uppsala. Five postgraduates working at the department of urology have produced doctoral theses in this field. Close and fruitful collaboration has been established with the renal research group at the Institute of Physiology and at the university`s Biomedical Centre in Uppsala. The research work begun in 1968 was first conducted at the laboratories of the Pharmacia company, which has continued to provide sponsorship.

Immunologic research at Uppsala University has long traditions. Collaboration with immunologists has intensified in recent years, especially since the appointment of young surgeons with basic training in immunology to our urologic department with its transplantation service. Close contacts have thus been established between basic research and clinical work. Together with the clinicians, the departments of clinical immunology, microbiology and immunology are working on problems relating to the diagnosis, mechanism and therapy of graft rejection.

Clinical research has focused on follow-up studies of patients with different immunosuppressive regimens, and on evaluation of new diagnostic procedures. This research is done together with nephrologists, radiologists and oncologists. Uppsala is one of the five centres collaborating in a study on cyclosporin A. Parallel with this clinical study, Uppsala is conducting a special programme, together with Sandoz Ltd, on the pharmacokinetics of cyclosporin A. Most of the aforementioned departments are also in some way engaged in this project.

The field of transplantation brings together workers in basic research and clinical departments in a natural way. We are happy that so many scientists at our university show interest in this work. It is only through such collaboration that clinical progress can be made in organ transplantation.

THE FUTURE

Conclusions concerning the immediate future are readily deducible from Table 1. The Uppsala region needs expansion of the transplantation service. The current programme envisages 55-60 renal transplants per year, and resources for this volume are being provided. The future, however, is largely dependent on political decisions. A question now being discussed is if Uppsala should accept responsibility for transplantations within a larger region. This would result in about 85 renal transplants each year.

Another question is whether transplantation of pancreas, liver and heart should take place in Uppsala. There is need for 15-20 transplants of liver, 20 of pancreas and at least 20 of heart in our present region. While awaiting the political decisions, the doctors are preparing the field by extending research, acquiring skills in harvesting multiple organs and stimulating interest among all categories of hospital workers for organ transplantation.

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