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Cyclosporine—Nursing and Paraprofessional Aspects

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SUPPLEMENT 2
CYCLOSPORINE: NURSING AND PARAPROFESSIONAL ASPECTS

SPECIAL EDITORIAL ANNOUNCEMENT

Cadaveric Renal Transplantation with Cyclosporine: Experiences in 148 Patients at a Single Institution

W. Land, L. A. Castro, K. Günther, C. Hammer, C. Hillebrand, W.-D. Illner, N. Schmeller, B. Schneider, W. Siebert, R. A. Zink, and H. Zöttlein

SINCE NOVEMBER 1980, 195 renal transplantations have been performed at our center using cyclosporine as a new immunosuppressive agent. Twenty-five patients were treated with cyclosporine as the sole immunosuppressive agent in the European Multicentre Trial.[1] Outside a control study, cyclosporine, in combination with small doses of methylprednisolone, was used in 157 cadaveric renal transplantations as well as in 5 living related donor transplantations. Cyclosporine, in combination with steroids, was used in 8 combined renal and pancreatic transplantations. This article reports our experiences with 148 cadaveric renal transplantations performed by March 1983, using cyclosporine in combination with steroids as basic immunosuppressive therapy.

MATERIALS AND METHODS

Patient Population

This study includes 140 consecutive transplants of cadaveric renal allografts performed between March 1982 and March 1983 on recipients aged 9–61 years. No patients were excluded from cyclosporine treatment, neither patients with known liver disease nor patients with primarily nonfunctioning kidneys without immediate diuresis. Of the 140 patients, 115 got a primary renal allograft and 25 received a secondary or tertiary allograft. All recipients had received at least 3 random type-specific blood transfusions prior to transplant. Eight patients (aged 25–49 years) suffering from Type I diabetes mellitus and end-stage renal disease received combined renal and pancreatic allografts.

Immunosuppressive Protocol

Basic immunosuppression. Cyclosporine was administered intravenously before the operation and on day 1 postoperatively in a dose of 4 mg/kg of body weight and continued by oral administration in a dose of 15 mg/kg for 1 month after transplantation, when it was decreased by 2 mg/kg monthly to a maintenance level of 6–7 mg/kg. Methylprednisolone was begun at 8 mg daily immediately after the operation and maintained at that level.

Antirejection treatments. Antirejection treatment consisted of 3 i.v. bolus injections of 500 mg methylprednisolone during the first rejection episode. The second and third rejection episodes were treated by administration of ALG/ATG over a period of 7 days, in combination with methylprednisolone in a dose of 125 mg i.v. daily until reversal.

"Triple" immunosuppressive therapy. In recipients of a secondary or tertiary renal allograft and in patients with preformed antibodies higher than 50%, cyclosporine, azathioprine, and methylprednisolone were administered during the first week posttransplant as follows: cyclosporine was given as described above; azathioprine in a dose of 2 mg/kg initially, then decreased to 1 mg/kg; methylprednisolone (i.v.) in a dose of 500 mg daily, tapering to 30 mg daily.

From the second week after transplantation, the original basic immunosuppressive treatment was continued. Antirejection treatment was applied as described above.

Combined Renal and Pancreatic Transplantation

Pancreas transplantation was performed using the technique of segmental pancreatic allografting by occluding the duct system with Ethibloc. Postoperative management consisted of cyclosporine administration in combination with steroids; in addition, administration of heparine, antibiotics, and Somatostatine.

Incidence of Infections Under Cyclosporine Therapy

The incidence of infections described in this report concerns only the manifestation of severe infections requiring hospitalization of the transplant patient. In addition to careful clinical assessment and appropriate

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microbiologic tests for evidence of infectious diseases, detailed laboratory investigations were carried out whenever an overt virus disease was suspected.

Fine-Needle Aspiration Cytology

The methodology used has been described elsewhere.[2] In brief, fine-needle aspiration has to be done under sterile conditions by placing a spinal needle into the cortex of the graft. The aspirated material was dispersed into a centrifuge vial by means of 5 ml RPMI medium held in the suction syringe.

The mouse monoclonal antibodies used were directed against pan-T lymphocytes (OKT3), helper-inducer T lymphocytes (OKT4), and cytotoxic/suppressor T lymphocytes (OKT8).

RESULTS

Cadaveric Renal Transplantation

The overall graft survival rate (graft survival probability as calculated by the Cutler-Ederer test) after primary cadaveric renal transplantations in 115 consecutively treated patients under cyclosporine-methylprednisolone therapy is depicted in Fig. 1; the result in the historical control group (steroids + azathioprine; $N = 150$) is shown for comparison. At 1 year, the graft survival probability is 70% in the cyclosporine group compared to 50% in the control group. The difference of 20% is statistically significant. The overall graft survival rate after secondary or tertiary cadaveric renal transplantation in 25 patients under cyclosporine-methylprednisolone therapy is depicted in Fig. 2. The 1-year graft survival probability of 70% is identical to that obtained in the primary renal allograft group, although during the first 6 months after transplantation there was a slightly higher incidence of graft losses. Of these 25 patients, 18 were treated during the first week following transplantation by using the "triple" immunosuppressive protocol (see below).

Of the original 115 patients treated with cyclosporine after primary renal transplantation, 111 are currently alive. Of the 4 patients who died, 2 did so with functioning grafts, 1 from spontaneous intracerebral hemorrhage at 1 month and the other from acute cardiac failure at 6 months. One patient with a primary nonfunctioning kidney (ATN) died

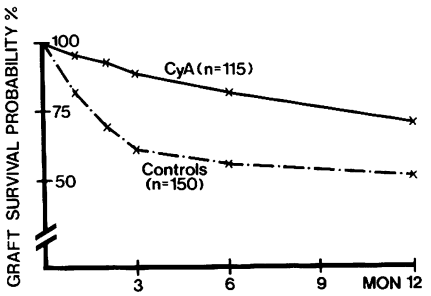

Fig. 1. Graft survival rates in primary renal transplantation, comparing cyclosporine-methylprednisolone treatment (CsA) vs. historical controls (azathioprine-steroids treatment).

from acute cardiac failure at 1 week, another patient from sepsis at 6 months. There was an immunologic cause of graft loss only in 14 patients, and a nonimmunologic cause of graft loss in 3. All the original 25 patients treated with cyclosporine after retransplantation are alive. There was an immunologic cause of graft loss in 6 patients and a nonimmunologic cause of graft loss in 1.

"Triple" Immunosuppression in Immunologically High-Risk Patients

As described in Materials and Methods, 26 immunologically high-risk patients (18 retransplantations and 8 recipients with preformed antibodies > 50%) were treated with cyclosporine, azathioprine, and steroids during the first week after transplantation. The result of this pilot study is depicted in Fig. 3. We observed a 1-year graft survival probability of 70%. Remarkably, all irreversible graft rejections occurred during the first 3 months after transplantation. In none of these 26 patients treated initially with the "triple" immunosuppressive regimen has either severe infection or malignancy been seen so far.

Combined Renal and Segmental Pancreatic Transplantation

The results obtained with this kind of surgical treatment in Type I diabetics with end-stage renal disease are listed in Table 1. Although our experience with cyclosporine therapy in combined renal and pancreatic transplantation is limited to 8 cases, the

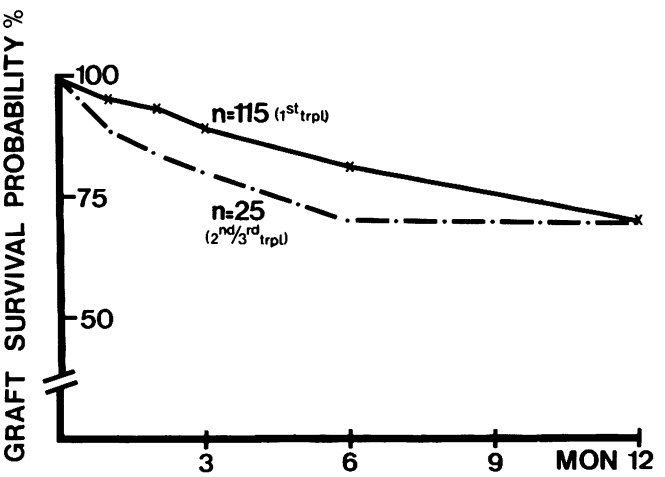

Fig. 2. Graft survival rates in primary renal transplantation (*N* = 115) compared to retransplantation (*N* = 25).

results obtained with this new immunosuppressive agent are encouraging and promising.

Incidence of Infectious Diseases Under Cyclosporine Treatment

The incidence of clinically manifested severe infections that required hospitalization is listed in Table 2. Of the original 140 patients treated with cyclosporine after cadaveric renal transplantation, only 13 (9%) were hospitalized with a bacterial infection (1 death due to sepsis), 9 (6%) with a viral infection, and 2 (1.3%) with a fungal infection.

Immunologic Monitoring: Fine-Needle Aspiration Cytology

Due to the difficulty in detecting acute rejections in patients treated with cyclosporine, recourse was made to fine-needle aspiration cytology. The method allows not only estimation of onset, severity, and course of rejection but also measurement of the impact of treatment and differentiation between cyclosporine side effects, acute tubular necrosis, and acute cellular rejection. Differentiation of the inflammatory cell populations by monoclonal antibodies has proved that with increasing severity of rejection, high numbers of lymphocytes of the cytotoxic/suppressor cell compartment invade the graft. Helper cells therefore decrease relatively in terms of percent (Fig. 4).

This observation of a high influx of cytotoxic cells into the graft during rejection was not changed after introduction of cyclosporine as the immunosuppressant. Despite its powerful effect on graft rejection, no change in lymphocyte numbers in the peripheral blood could be seen. During rejection under cyclo-

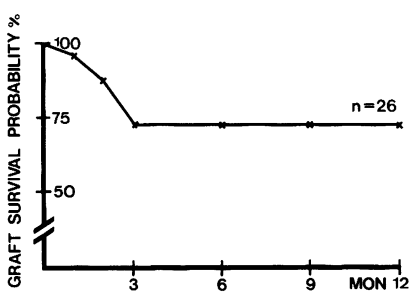

Fig. 3. Graft survival rate in immunologically high-risk patients treated with cyclosporine, azathioprine, and methylprednisolone during the first week following transplantation.

Table 1. Results of Combined Pancreatic and Renal Transplantation in 8 Patients Treated with Cyclosporine and Steroids*

Patients alive	7
Function of both grafts	5†
Function of the renal graft (2 years)	1
Rejection of both grafts (1 month)	1
Death (acute liver failure)	1

*At the Transplantation Center, Munich, 1979–1983; *N* = 12/11.

†2 years, 1 year, 5 months, 4 months, and 3 months, respectively.

Table 2. Incidence of Infectious Diseases in 140 Cyclosporine-Methylprednisolone–Treated Patients

No. of Patients (N = 13/140)	Bacterial Infections		
	Manifestation	Associated with ART*	Outcome
9	UTI, prostatitis, pyelonephritis	No	Recovery
1	Graft infection at biopsy	Yes	Transplantectomy
1	Otitis media	No	Recovery
1	Endocarditis	No	Recovery
1	Pneumonia, sepsis	No	Death

No. of Patients (N = 9/140)	Viral Infections			
	Manifestation	Pathogen	ART	Outcome
5	Interstitial pneumonia: cerebral signs, general symptoms	CMV	Yes (3) No (2)	Recovery
2	Herpes genitalis, Herpes simplex (generalized)	Herpes virus	Yes (1) No (1)	Recovery
2	Fever, pneumonia	Unknown	No	Recovery

No. of Patients (N = 2/140)	Fungal Infections			
	Manifestation	Pathogen	ART	Outcome
1	Tracheitis	*Candida albicans*	No	Recovery
1	Sepsis, UTI	*Candida albicans*	Yes	Recovery with graft loss

*ART: Antirejection therapy.

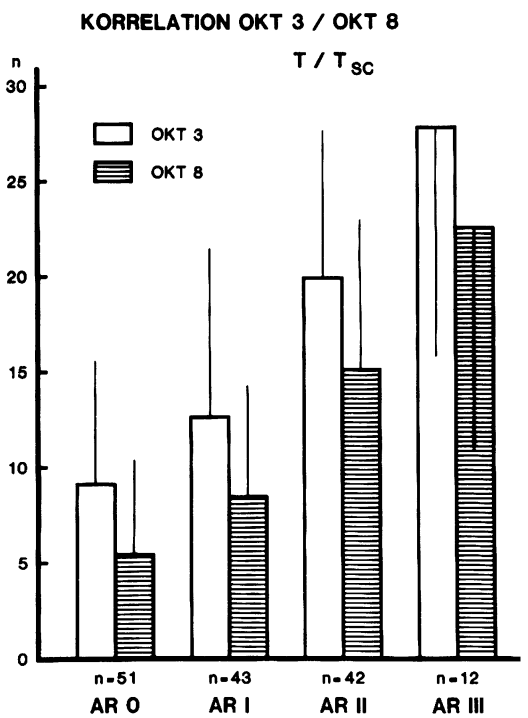

Fig. 4. OKT8$^+$ cells increase in the graft with increasing severity of the rejection reaction.

sporine therapy, lymphocyte numbers increased in the graft, but less than with conventional therapy. Surprisingly enough, no impact on helper cells was seen under cyclosporine therapy. A new aspect was analyzed (Table 3) when conversion of numbers of helper and cytotoxic suppressor cells was measured in the peripheral blood and in the graft. High numbers of lymphocytes in the periphery and the graft, preferably belonging to the

Table 3. Behavior of Peripheral Granular Lymphocytes and T4/T8† Cells in Rejection Episodes vs. Viral Infections

	Rejection Episode 0	Rejection Episode 2	Virus Infection
Lymphocytes in fine-needle biopsy	8.5	23.9	31.7
Lymphocytes in peripheral blood	7.7	6.3	18.3
OKT3	9.8	18.3	29.2
OKT4	4.8	8.2	4.5
OKT8	4.9	13.3	25.6
OKT4/OKT8 ratio	1.2	0.7	0.2
In peripheral blood	2.6	2.4	0.45

T8 compartment, heralded in virus infection. The ratio of T4 to $T8^+$ cells was below 0.5 in aspirate and peripheral blood.

A further sign distinguishing virus infection from acute rejection seems to be the number of large granular lymphocytes—supposedly responsible for the natural killer activity. During acute rejection, peripheral blood lacks large granular lymphocytes. In the graft, large granular lymphocytes reach up to 12% of the inflammatory cell compartment. During virus infection, however, large granular lymphocytes increase in the peripheral blood and the graft to values up to 25%, with the mean of 14, i.e., 10%.

DISCUSSION

The results reported confirm the potential usefulness of cyclosporine in combination with low doses of steroids to improve the graft survival in cadaveric renal transplantation with an extremely low incidence of morbidity and mortality. Compared with the historical controls treated with conventional therapy at our center, a 20% difference in the results obtained with the use of cyclosporine was observed. Interestingly enough, the 70% 1-year graft survival probability under cyclosporine-methylprednisolone therapy was observed in primary renal transplantation as well as in retransplantation. By using a short-term "triple" immunosuppressive regimen (cyclosporine, azathioprine, methylprednisolone) immediately after surgery, a 70% 1-year graft survival rate of cadaveric renal allografts could also be achieved in immunologically high-risk patients. Although these results are similar to those reported by others,[3-6] one has to be careful in interpreting the current improved graft survival rates as definite long-term results. Thus, within ½ year the 6-month graft survival rate of 90% came down to the 12-month graft survival rate of 70% at our own institution. Nevertheless, when evaluating the results at our institution, one has to take into account that no exclusion criteria for the use of cyclosporine were applied, as had been done in the European Multicentre Trial. This circumstance represents one of several difficulties in comparing the efficacy of the combined cyclosporine treatment with that of cyclosporine monotherapy.

As far as the results in immunologically high-risk patients are concerned, a valid conclusion cannot be drawn from the data obtained at the present time. Nevertheless, two aspects seem worthwhile to discuss: (1) Our first clinical impression of a strong immunosuppressive potency of the "triple" regimen used is confirmed by experimental studies showing a synergistic immunosuppressive effect of cyclosporine and azathioprine in three different animal allograft models.[7] (2) According to our observations (no incidence of severe infection or malignancy), such a combined immunosuppressive therapy seems to be safe for the patient, provided all three drugs are administered only for a short period of time.

Apart from the improved results in graft survival rates, the decreased morbidity, particularly in terms of decreased infectious diseases, is one of the remarkable advantages of cyclosporine treatment. Infections remain an important and typical complication of renal transplantation, which often has led to graft loss or patient death. Therefore, the decreased incidence of severe infectious diseases (of bacterial, viral, or fungal origin) as observed by us and others[3,8] is tremendously encouraging. In this context, it remains to be studied in the future why particularly the incidence of viral infections is lower than expected in light of the mode of action of cyclosporine. Despite all the advantages, there is, however, one serious disadvantage in the use of cyclosporine: It makes the early detection of rejection episodes a difficult procedure, especially in patients with primarily nonfunctioning kidneys. A lot of "classical" rejection symptoms have completely (or partially) disappeared and are no longer seen by clinicians. This obvious difficulty with cyclosporine use has given rise to a search for new and better methods for immunologic monitoring. One of us (C. H.) tried to use P. Häyry's fine-needle aspiration cytology

as a method helpful for the accurate detection of rejection episodes. Although this method is not fully convincing from the practical point of view at the present time, some conclusions can be drawn: Fine-needle biopsy, in combination with highly specific monoclonal antibodies, provides some important new information about the background of high-lymphocytic inflammation. Clinical statements like onset, severity, and progress of an acute rejection given by the aspiration cytology can be confirmed and precised with this method in certain circumstances. A possible new prominent example is to differentiate between acute rejection and virus infection with the help of monoclonal antibodies and by differentiating large granular lymphocytes from other cell populations. With this information, unnecessary and dangerous immunosuppressive therapy in cases of nondiagnosed viral infections might be avoided.

Parallel to the improvement of the results in cadaveric renal transplantation under cyclosporine therapy, the results of combined renal and pancreatic transplantation have improved, although the number of patients treated with this surgical method at our institution is too small to draw any valid conclusion. Nevertheless, in view of the current uncertain state of the art relating to the technique of pancreatic grafting, the introduction of cyclosporine in the clinical pancreatic allografting program seems to improve the results in this field of organ transplantation slightly but steadily.

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