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Renal cadaveric transplantation in diabetics using total lymphoid irradiation or cyclosporin A

A controlled randomized study

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Abstract. A total of 20 renal transplant patients with end-stage diabetic nephropathy entered a randomized controlled trial comparing preoperative, fractionated total lymphoid irradiation (TLI) (radiation dose, 20-30 Gy) with postoperative cyclosporin A (CsA). Both groups received postoperative low-dose methylprednisolone maintenance therapy. The 3-year patient and graft survival was similar for both groups (100% and 71% in the TLI and 75% and 75% in the CsA group, respectively). Rejection crises occurred significantly more frequently ($P<$ 0.01) in the TLI-treated recipients. The incidence of infectious or diabetic complications was not significantly different in both groups. It is concluded that TLI and CsA are both effective treatment modalities for cadaveric renal transplantation in diabetics; CsA, however, is superior in preventing rejection crises.

Key words: Renal transplantation - Diabetes - Cyclosporin A - Total lymphoid irradiation.

Before 1980, patient and graft survival in diabetic recipients of cadaveric grafts was significantly worse than in nondiabetics. This was mainly due to a high incidence of complications related to the high doses of steroids needed to prevent or treat allograft rejections [2]. In 1981 we started a feasibility trial using preoperative, fractionated total lymphoid irradiation (TLI) in diabetics, with the major aim of reducing the need for steroids [14].

TLI was chosen because investigators at Stanford University have found that it resulted in a long-term suppression of several cellular immune functions in patients with Hodgkin's disease [10]. This was not associated with the significantly increased risk for infections or secondary tumors usually observed with other forms of immunosuppression [10]. An experimental technique similar to that used in lymphoma patients was developed, and it has been shown by several groups [8, 10], including ours [12, 13], that TLI allowed the induction of long-term, stable, allogeneic bone marrow chimerism and solid organ graft survival in the rodent model. In several other transplantation models in larger animals, it has also been shown that TLI significantly enhanced the immunosuppressive action of various other drugs [4, 9]. TLI has subsequently been used for clinical kidney transplantation in several pilot studies (reviewed in [9]).

Low-dose steroids were added to TLI in the present study because, on the one hand, TLI alone has not been efficient in most large animal models [9], and on the other, it was hoped that low-dose steroids might enhance the immunosuppressive action of TLI as they do that of other, mainly lymphotropic, agents such as azathioprine or cyclosporin A (CsA).

The results of our TLI feasibility study have been published [14]. In the present study we report the results of a randomized controlled trial comparing preoperative TLI with postoperative CsA, both combined with low-dose postoperative corticosteroids.

Patients and methods

Patient characteristics are given in Table 1. All patients had insulin-dependent diabetes, presented with end-stage diabetic ne-

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Table 1. Patient characteristics

	TLI (range)	CsA (range)
Number	10	10
Mean age	40 (32-53)	42 (26-57)
Female/male	1/9	4/6
Mean duration of diabetes (years)	22 (15-29)	23 (13-27)
Mean duration of hemodialysis (months)	10 (0-24)	4 (0-9)
Mean number of pretransplant transfusions per patient	8 (0-14)	7 (2-14)
Mean HLA, B-DR match with donor	1,7 (0-4)	1,8 (0-4)
Follow-up post-transplantation (months)	27 (8-43)	26 (10-43)

phropathy, and were randomly allocated to either TLI or CsA treatment. Potential advantages and disadvantages were discussed with all patients and informed consent was obtained. The only exclusion criterion was the presence of circulating antihuman leukocyte antigen (HLA) antibodies, reactive against more than 30% of a panel, because this seriously limited the possibility of finding a suitable crossmatch-negative kidney soon after TLI. An early transplantation has indeed been shown to be necessary for TLI to exert its optimum effect [10]. Because of uncontrolled hypertension, a bilateral nephrectomy was carried out in three TLI and five CsA patients. In four TLI patients a pre-TLI splenectomy was done in order to limit the radiation field and reduce the radiotherapy-induced side effects.

Radiotherapy

Fractionated TLI was carried out with 18 MeV X-rays produced by a linear accelerator at a focus skin distance of 100 cm. The mantle and inverted-Y fields were always irradiated concomitantly. Five fractions of 1 Gy each were given each week. The anterior and posterior fields were treated on alternate days. The ports were individually adapted and included the lymphoid tissues. A minimal dose of 20 Gy was given to all patients. Three, six, and ten supplementary fractions, respectively, of 1 Gy were given to three patients as weekly booster fractions when a crossmatch-negative donor was not found within 1 week after the end of the main course of 20 Gy. Before each fraction, the total white blood cell and platelet counts were determined. Irradiation was interrupted when these values were below 2,000 or 75,000/mm^3. The radiotherapy-related side effects of our TLI-treated patients have been previously described in detail [14].

Donor selection

Immediately after finishing the last TLI fraction or after being allocated to the CsA arm of the study, patients were put on the high-urgency waiting list of the Eurotransplant Organization in order to find a crossmatch-negative graft as soon as possible. Donor-recipient selection was only based on ABO blood group compatibility and the presence of a negative, standard T-cell crossmatch. Since rapid transplantation was the aim, HLA matching was not taken into account.

Pharmacological immunosuppression after transplantation

On the day of transplantation all patients were given 0.5 g methylprednisolone IV. From the second day on, oral methylprednisolone was given daily at a dose of 16 mg/day, tapered down to 8 mg/day within 2 months. A maintenance dose of 8 mg/day was subsequently given to all patients. CsA patients received the drug in a dose of 15 mg/kg daily, tapered down in order to keep the serum trough levels of CsA around 100 ng/ml. Rejection crises were diagnosed and treated as previously described elsewhere [14]. In TLI patients, when rejection crises responded insufficiently to corticosteroids or when repeated rejection crises occurred, CsA was added to the treatment.

Statistics

The Student's t-test and chi-square test were used where appropriate. Values of $P<0.05$ were considered significant.

Results

Patient characteristics

The groups were not significantly different with regard to age at the time of transplantation, the male/female ratio, duration of pretransplantation diabetic nephropathy, duration of dialysis, or the number of pretransplantation blood transfusions. The mean follow-up after transplantation in both groups was more than 2 years. The level of B-DR HLA compatibility was not significantly different and was poor in both groups, since only a negative crossmatch and not the HLA compatibility was taken into account for donor selection in the present trial (see Materials and methods).

Patient and graft survival

Patient survival (Fig. 1 A) was excellent for both groups: 100% and 75%, respectively, at 3 years for the TLI and CsA groups. The CsA patient who died committed suicide after the amputation of a leg. Similar results were found for the graft survival rate (Fig. 1 B). Graft survival at 3 years was 71% for the TLI patients. The two graft losses were due to chronic rejection at 22 and 28 months, respectively, after transplantation. The graft loss in the CsA group was due to the death of the patient.

Occurrence of rejection crises (Table 2)

Patients treated with TLI underwent significantly more rejection crises than CsA-treated recipients ($P<0.01$). Three TLI patients had one and seven had more than one rejection crisis, compared with

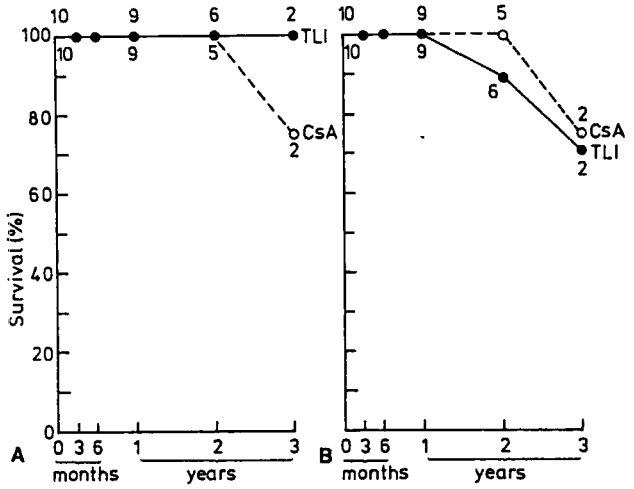

Fig. 1 A, B. Actuarial patient (A) and graft (B) survival of diabetic cadaveric allograft recipients treated with TLI or CsA

Table 2. Occurrence of rejection crises after transplantation

Number of rejections	TLI ($N=10$)	CsA ($N=10$)
0	0*	6
1	3	3
>2	7*	1

* $P<0.01$

three and one, respectively, of the patients treated with CsA. Because of rejection crises that responded insufficiently to high doses of steroids or because of recurrent rejection crisis, 5/10 TLI patients were given CsA as a part of their maintenance immunosuppression. This was done within the first months after transplantation in three patients and at 3 and 4 months, respectively, in two others.

Complications

Before transplantation (Table 3 A), all patients in both groups had severe diabetic retinopathy, leading to blindness in one TLI and two CsA patients, respectively. Most patients (9/10) in each group had severe vascular calcification on X-ray examination, and one patient in each group underwent amputation before transplantation. Hypertension was common, and in each group one patient had a myocardial infarction and another a cerebrovascular accident.

After transplantation (Table 3 B), the most common complications were infections. Bacterial sepsis occurred in two TLI and four CsA patients. Cytomegalovirus infection was diagnosed in one patient in each group. As has been reported in patients with Hodgkin's disease [10], herpes zoster occurred

Table 3. Incidence of complications

	TLI ($N=10$)	CsA ($N=10$)
A Before transplantation		
Severe retinopathy	10	10
Blindness	1	2
Amputation	1	1
Signs of severe calcification on X-ray	9	9
Hypertension	10	8
Cerebrovascular accident	1	1
Myocardial infarction	1	1
B After transplantation		
Infections:		
Bacterial sepsis	2	4
CMV	1	1
Herpes zoster	3	1
Diabetes-related complications:		
Worsening of retinopathy	2	2
Gangrene necessitating vascular surgery	3	0
Amputation	0	3
Cardiovascular complications:		
Myocardial infarction	0	1
Cerebrovascular accident	2	0

Table 4. Last value of serum creatinine and incidence of hypertension and proteinuria in patients with functioning grafts

	TLI (range)	CsA (range)
Serum creatinine (mg/dl)	1.8 (1.4-3.0)	1.6 (1.2-2.2)
Number of patients with proteinuria (>0.5 g/24 h)	0/7	1/9
Number of patients with hypertension	6/7	3/9

in about one-third of the TLI-treated patients as well as in one CsA-treated patient. None of these infections, however, was life-threatening. Diabetic retinopathy could be stabilized in most patients, but in two TLI- and two CsA-treated patients, retinopathy became worse. One CsA patient had a myocardial infarction and two TLI patients a cerebrovascular accident, after transplantation. Three TLI patients developed gangrene after transplantation, necessitating surgery. Three CsA patients underwent amputation of a leg. The incidence of vascular complications in the TLI patients was not increased by the addition of CsA.

Graft function

Table 4 shows data on renal function, proteinuria, and hypertension in the patients with functioning grafts as of December 1, 1987. The mean serum creatinine was not significantly different between both groups. Significant proteinuria (>0.5 g/24 h)

was only seen in one patient in the CsA group. More TLI than CsA patients had hypertension ($P<0.05$). This was not related to whether or not bilateral nephrectomy of the native kidneys was carried out before transplantation (data not shown), but most of them (4/6) were also given CsA.

Discussion

The major aim of the present study was to see whether TLI would offer significant advantages as an immunosuppressant in renal transplantation compared with CsA. Many experimental transplantation models have shown that TLI could either induce long-term graft survival without the need for concomitant immunosuppressive drugs or synergistically act with various other immunosuppressants [4, 6, 8, 10, 12, 13]. It was therefore hoped that TLI would allow for a drastic reduction of the need for corticosteroids and hence significantly improve the results in clinical transplantation. The reduction of immunosuppression would be especially advantageous in diabetics, who until recently had generally been considered to be high-risk patients for renal transplantation, mainly because of steroid-associated side effects [2].

The excellent patient survival (100% at 3 years) obtained with TLI indicates that it can be regarded as a safe immunosuppressive regimen. As far as the capacity of TLI to prevent rejection crises is concerned, the present TLI schedule does not yet seem to be optimal. Indeed, the number of rejection crises was higher, and in five patients CsA was added in order to treat a steroid-resistant rejection crisis or to prevent the recurrence of rejections. From the results of the present trial, it seems that CsA is as safe as TLI but more effective in preventing rejection crises. It has been suggested that CsA may have a thrombogenic effect [11] and that it could also, partially through its hypertensive action, cause or worsen various forms of vasculopathy [7]. It could therefore be anticipated that CsA-treated patients might develop significantly more diabetes-related vascular side effects after transplantation. This did not seem to be the case in the present study. Because most patients had various signs of severe diabetic micro- and macroangiopathy before entering the trial, it is possible that the vascular status of these patients was too poor to indicate an advantage, if any, for TLI over CsA on the incidence of vascular complications.

As the results with CsA are at least as good as those with TLI and rejections are significantly less common with the former, it must be concluded that, in combination with low-dose postoperative steroids as used in the present study, TLI is not the method of choice. It must, however, be admitted that some of the TLI patients had an excellent course; the fact that they do not require maintenance CsA may be a major advantage in the long term. If we combine the results of the TLI patients of the present controlled trial with those of the 20 patients who entered our previous feasibility study [14], excellent results without CsA can be seen in about one-third of the cases. However, the major problem is that as yet no characteristics could be found that allow the prediction of a favorable outcome after TLI (unpublished observations). It is thus impossible to propose TLI to a subgroup of recipients who are more likely to benefit from it.

A major future advantage of TLI could be that, when combined with CsA or antithymocyte globulin from the time of transplantation on, it may enable a progressive withdrawal of all maintenance immunosuppressive drugs after 1 or 2 years in a significant number of patients. Preliminary results of TLI trials carried out at other centers [1, 3, 5] indicate that this may indeed be the case. If the latter results could be confirmed in larger groups of patients, the place of TLI in renal transplantation should be reconsidered. In the meantime, TLI combined with low-dose steroids cannot be considered as the treatment of choice for renal transplantation.

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