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Photochemical Donor Pretreatment in Clinical Kidney Transplantation – Preliminary Report

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Summary. Extended experimental experience with the efficiacy of pretreating the kidney donor and the allograft by means of photochemotherapy (photosensitizer + UVA irradiation = PUVA) was adopted in clinical kidney transplantation. In a preliminary unrandomized study similar patient populations were treated by generally uniform methods. Thirty-three PUVA-pretreated kidneys (group A) were compared with the experience regarding 26 non-pretreated kidney allografts (group B). The number of rejection episodes was significantly lower in the first 3 months in group A ($p < 0.05$ vs group B) and fewer grafts failed because of irreversible rejection (2 vs 5). Furthermore, in group A the rate of infectious complications was lower (18% vs 34%). The cumulative allograft survival at 3 months was improved from 65% in group B to 81% in group A and at 12 months from 65% 76%, respectively. These differences were not significant. Therefore, our preliminary clinical experience with a photochemical donor pretreatment is encouraging and further use in a randomized study seems to be necessary.

Key words: Kidney transplantation, Donor pretreatment, PUVA, Ultraviolet irradiation.

Introduction

A recent paper [17] showed that photochemical pretreatment of the rat kidney donor with 8-methoxypsoralen (8-MOP) and ex vivo longwave ultraviolet irradiation (UVA) of the kidney graft (PUVA therapy) significantly prolonged survival in allogeneic recipients without further immunosuppression. Similar results were obtained in the rat heart allograft model [20]. The long-term survival of PUVA-treated rat renal allografts is mediated by both a strong reduction of graft immunogenicity – which probably represents the loss or depletion of highly immunogenic dendritic cells – and the development of graft protecting humoral as well as cellular effectors [22]. Furthermore, a synergistic effect of PUVA donor pretreatment and temporary immunosuppressive therapy of the recipient with azathioprin plus prednisolone (18) or cyclosporin A [21] was demonstrated suggesting a possible clinical application of this type of immunoregulation and immunosuppression.

In the present paper we report our preliminary experiences and results of introducing PUVA donor pretreatment in human kidney transplantation.

Materials and Methods

Between January 1984 and Jan 1986 84 cadaveric kidneys were harvested by the organ procurement teams of the University hospital and the Friedrichshain hospital, 69 of the harvested kidneys were transplanted. 59 transplantations (Tx) were performed in the 3 transplant centers (Berlin, Halle, Rostock) and 10 in other countries (Belgium, Hungary, Czechoslovakia, Poland). The latter transplants were excluded from this study because of lack of complete follow-up data. Thirty-three of the 59 transplanted kidneys were PUVA-pretreated (group A) and 26 were non-pretreated (group B). In both groups the blood pressure of the brain-death kidney donor was maintained by administering large quantities of intravenous (i.v.) electrolyte infusions, and dopamine at 4 μg/kg body weight (BW)/min was used if necessary. Furthermore, the α-blocking agent phenoxybenzamine (100 mg, Dibenzyline®, Smith Kline & French Labs. Ltd., Welwyn Garden City, England) and heaprin (25,000 IU, Thrombophob®, Nordmark-Werke GmbH, Uetersen, FRG) were injected i.v. 10 min before cross-clamping the suprarenal aorta and initiation of in-situ perfusion with 1,000–2,000 ml Euro-Collins® solution. After en-bloc removal each kidney was flushed with cold Euro-Collins® solution for 1 min. Fifty-three kidneys were preserved by cold storage and 6 kidneys by pulsatile machine perfusion.

PUVA Donor/Graft Pretreatment. 8-MOP, obtained from Gerot Pharmazeutika (Vienna, Austria) as a 0. 5% solution (Oxsoralen®) was given i.v. at a dosage of 1 mg/kg BW 10 min before onset of in-situ perfusion and en-bloc graft removal. As soon as possible after removal the kidneys were irradiated with a 20 W mercury arc medium pressure lamp (UVS 20-2, NARVA, Berlin, GDR) for 4 h during hypothermic preservation. The UVA intensity during this time was measured as 19,3 $J \cdot cm^{-2}$.

Pre-Tx parameters of transplants and patients are summarized in Table 1. These parameters were similar in both groups except the higher median age (39 vs 35 years) and the higher portion of "high-risk" patients (52 vs 27%) in group A. Patients in group A received

Table 1. Patient and transplant data

	Group A $n = 33$	Group B $n = 26$
First Tx	30	22
Re-Tx	3	4
Age		
Median (yr)	39	35
Range (yr)	14–55	15–49
"High-risk" patients (age ⩾ 45 yr, diabetics)	17 (52%)	7 (27%)
HLA-A, -B mismatches	2.2	2.4
HLA-DR mismatches	0.7	0.7
Cold ischemic time		
Median (h)	27.00	26.30
Range (h)	12–42.00	17–37.20
Machine perfusion (n)	4	2
Revascularization time		
Median (min)	44	52
Range (min)	20–75	30–105

Table 2. Follow-up data in the first 3 months post-Tx

	Group A $n = 33$	Group B $n = 26$
Onset of graft function		
Median (d)	11	11
Range (d)	0–65	0–15
Rejection episodes		
Median	0.7	1.1
(None)	12	8
(1)	18	8
(2)	3	9
(3)	–	1
Infectious complications (viral, bacterial, mycosis)	6 (18%)	9 (34%)
Surgical complications (rupture, urinary fistula, bleeding, thrombosis)	11 (33%)	7 (27%)
Cause of graft failure (n)		
Rejection	2	5
Arterial bleeding	2	1
Allograft rupture	1	–
Thrombosis	1	2
Serum creatinine value at hospital discharge (μmol/l)		
Median	139	153
Range	67–306	77–290

slightly better HLA-A,B-matched grafts (2.2 vs 2.4 mismatches) and had a shorter revascularization time during Tx (44 vs 52 min). All differences were not significant.

The standard post-Tx immunosuppressive protocol mainly utilizes azathioprin and prednisolone in both groups; it has been described previously [15]. The median azathioprin dosage was equal in both groups at discharge from the hospital (1.5 mg/kg BW). In 5 of the 26 patients (19%) in group B and in 8 of 33 patients (24%) in group A, the primary immunosuppression consisted of cyclosporin A and low-dose prednisolone [13]. Rejection was diagnosed by clinical signs, ultrasound and renographic evaluation, and in the Berlin transplant center by fine-needle aspiration biopsy [9]. Rejection episodes were treated with methylprednisolone, 5 mg/kg BW i.v. for 5 days. Rejection treatment was considered successful if a clear clinical and cytological response was observed. In the case of negative response an allograft biopsy was performed and according to the histological findings an additional antirejection therapy with anti-thymocyte-globulin (Fresenius, Homburg, FRG) at 3 mg/kg BW for 10–14 days was given.

All patients were followed at least 6 months and all causes of death or graft loss were included in calculating cumulative survival [23]. Differences between the groups were analyzed using the non-parametric Mann-Whitney rank sum test and the chi square test. A p value < 0.05 was considered to reflect a significant difference.

Results

The follow-up data analyzed in the first 3 months after Tx are summarized in Table 2. The median onset of graft function was similar in both groups. The number of rejection episodes was significantly lower in PUVA-treated Tx ($p < 0.05$ vs group B) and fewer grafts failed because of irreversible rejection (2 vs 5). Furthermore, in group A fewer infective complications (18% vs 34%), but slightly more surgical complications (33% vs 27%) occurred. The serum creatinine value at hospital discharge was slightly better in group A. All differences were not significant. One patient in each group died of infective complications.

The graft survival rates at 3 months were 81% in group A and 65% in group B and 76% vs 65% at 12 months, respectively. These differences were not significant.

Discussion

Although this was not a randomized study, all donor kidneys were procured exclusively by two well-trained urological teams and comparable patient populations were treated by uniform methods. With the introduction of photochemical pretreatment the graft survival rates at 3 and 12 months were improved by 16% and 11%, respectively, probably as a result of the diminished frequency of rejection episodes, but the differences as compared with group B are not significant. Furthermore, fewer infective complications were observed in the pretreated group. This could be attributed to the decreased need of anti-rejection therapy (methylprednisolone-pulse) in group A. Photochemical pretreatment has been shown to be an effective adjunct in reducing allograft immunogenicity in experimental animals, and we believe that it has assisted our program and improved our clinical results [19]. The immunological alteration of donor tissue by PUVA or ultraviolet irradiation to decrease or modify the rejection response in the host has attracted considerable interest in the use of this approach in the animal model [3, 6, 12, 14]. PUVA treatment or irradiation with ultraviolet light of the UVB region (290–320 nm) affects the function of antigen-presenting cells (APCs), like Langerhans or interstitial dendritic cells (DC; [2, 10]). Recent evidence has ascribed a key role to the MHG-class-II-anti-

gen-carrying DCs in the stimulation of the primary alloimmune response [11, 24]. The modulation of these cells should prevent the helper T cell activation and therefore reduce the strength of the host-versus-graft reaction [8]. In pretreated [16] and enhanced rat kidney allografts [7] the number of donor-type DCs was greatly reduced. Gruner et al. [4] have shown a specific inhibition of the MHC class II antigen expression in vitro by different photochemical treatment protocols. In the same way the influence of PUVA pretreatment on MHC-class-II-antigen-carrying intragraft APCs, e.g. DCs, may be improtant in the reduction of graft immunogenicity [22].

Early attempts of donor pretreatment in clinical kidney transplantation using cytotoxic drugs such as cyclophosphamide combined with prednisolone has given conflicting results. Guttmann et al. [5], Dienst [1] and Zincke et al. [26] obtained improved pretreated graft survival rates, whereas Souilillou et al. [25] observed a nullifying effect on graft survival. Different donor pretreatment approaches are desirable and should be applied if they proved to be of value in the animal model. However, a proposed treatment plan should not endanger the recipient [26]. This could be demonstrated by improved graft survival rate and fewer infective complications in our recipients of PUVA-pretreated kidneys. In spite of this, the evidence is not based on a controlled study with a longer observation in a larger series of patients. However, our preliminary clinical results with a photochemical donor pretreatment are encouraging, but a randomized clinical study and further experimental experience are necessary to maximize the effectiveness of the pretreatment protocol.

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