Innovations in Kidney Transplantation

PhD Thesis

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1. INTRODUCTION

Transplantation is a revolutionary opportunity for end stage renal disease suffering patients for receiving back their normal daily life. The number of end stage renal diseased people and wait-listed patients continues to grow, and aggressive attempts to increase the number of transplants have failed to keep pace with demand. To enhance the successfully treated end stage renal disease we need to find safe sources to expand the donor pool and to try to reserve the already transplanted organs as far as possible; to improve the rejection rate with the lowest side effects even for patients with higher genetical risk for rejection and to look for new therapeutic possibilities to save already rejecting kidneys if they do not respond to the usual therapy.

Among older donors the use of both kidneys for one recipient was introduced. It was supposed that a single kidney would not be enough for long term function so the recipients require both kidneys of the same donor as dual kidney transplantation ("two to one"). Another group of extreme aged donors are the very young ones. Nonetheless, there is some reluctance to accept kidneys from deceased donors below the age of 5 years. Recently in the transplantation pediatric grafts into adult recipients became an accepted practice.

Over the past 30 years, progress in basic science, immunopharmacology, and clinical practice has engendered exciting improvements in the field of transplantation that have resulted in longer patient and graft survivals and a better quality of life. After decades of wide use of cyclosporine, side effects and leak in efficacy

in regular dose in premature higher risk races became clear. In the absence of selective and specific drugs the decreased incidence and severity of side effects can be achieved by the combination of synergistic drugs only. Sirolimus and reduced dose cyclosporine combination reduced the rejection rate under 10% while infectious complication rate was not significantly increased. However there is no evidence on the effect of this combination of patients with various genetic constitutions.

The time to failure of a renal allograft is determined by the initial function achieved after transplantation, the number and severity of rejections to the graft. Prevention and treatment of acute rejection in kidney transplant patients play a key role in their daily care due to the permanently worsening organ function and to reduce the progression of chronic allograft nephropathy. It is necessary to look for newer drugs for the treatment of acute rejection in kidney transplantation.

According to clinical studies the use of sirolimus causes wound healing impairment. Our group's previous studies proved the usefulness of dietary nucleotides in certain medical contexts. To reduce the side-effects of sirolimus suggests a faster healing and possible less complication after surgery.

2. AIMS

The main aim of our investigation was to evaluate and to look for alternative ways extending the life expectancy of end stage renal disease suffering patients.

We looked for possibilities to explore sources for expanding the donor pool

a. Using extended criteria donors for dual kidney transplant
b. Using pediatric kidneys for single transplant
c. To study the risk for both donors and recipients with special disease-fibromuscular dysplasia

We have tried to find a more effective protection of grafts with immunosuppressant drug combinations to decrease the number of patients getting back to the waiting list.

d. To study newer drug combinations to achieve a better graft and patient survival among various risk races
e. To study an induction treatment drug (Campath-1H) for handling of non-refracter acute rejection to usual therapies

We intended to diminish the sirolimus disadvantageous effects on wound healing in experimental circumstances on an mouse model.

f. To document the sirolimus negative effect on wound healing
g. To look for a possible usfulness of a topical containing nucleotide derivates in eliminating the wound healing disturbances caused by sirolimus.

3. METHODS

Investigations on donor side

Double kidney transplantation

For the retrospective analysis we have used the data of the Division of Immunology and Organ Transplantation at the University of Texas – Houston USA, in the period of 1998 January and 2004 July. Having the results we transplanted 5 extended criteria donor kidneys, regretted by all local transplant services, as dual kidney transplantation according to our strict protocol. The kidneys were implanted to the same side into the iliac fossa. We compared the patients and grafts survival rates, kidney function after the transplant and in a two years follow-up period.

Pediatric kidneys

We studied our single center review of 38 recipients of single pediatric donor grafts less than 5 years of age. All pediatric donors were above 24 and below 60 months of age. The outcomes of pediatric grafts were compared with 121 non-obese (BMI < 25 kg/m^2) recipients of kidneys from "ideal donors", defined as deceased individuals between the ages of 18 and 45 years, who were transplanted during the same time. All groups were limited to recipients of first transplants. To estimate the creatinine clearance the Cockroft-Gault equation and for the glomerular filtration rate the Modification of Diet in Renal Disease Study Group (MDRD) estimation was used.

Seven cases of kidneys with the disease fibromuscular dysplasia was analyzed in connection of the transplantation of a case.

Investigations on recipient side

Sirolimus-cyclosporine-steroid combination

To asses the 6-year impact of a sirolimus-based regimen with modest exposures to cyclosporine among three ethnic groups with different rejection risk, we performed a retrospective analysis of 470 renal transplant recipients who were treated contemporaneously: Group 1, high risk African Americans (n=122), Group 2, moderate risk Hispanics (n=132) and Group 3, mild risk Caucasians (n=216). Maintenance therapy consisted of sirolimus, reduced doses of cyclosporine and steroids. Sirolimus was initiated on the first postoperative day using an oral loading dose, followed by 5-10 mg/day doses to maintain a trough level between 10 and 15 ng/ml for weeks 1 through 12 and thereafter at 10±2 ng/ml. Treatment with oral cyclosporine was initiated when the serum creatinine fell below 2.5 mg/dl.. The doses were adjusted to achieve an average target concentration (C_{av}), which was calculated as the quotient of the area under the concentration curve and the dosing interval, of 100-200 ng/ml for weeks 1 through 12, generally correlating with a trough level of 75-125 ng/ml. Thereafter the target value was reduced to 100-150 ng/ml (trough level between 50-75 ng/ml). At 6 months the exposure was further lowered to 75-100 ng/ml (trough level <50 ng/ml). The average follow up period was 78.7, 84.6, and 81.6 months, respectively. Multivariate models were used to compare the outcomes in Group 1 with those of the other groups.

Campath-1H in acute rejection

Campath-1H is not widely accepted as a drug used by transplantation, however selected transplant groups use it for induction therapy. Between January and August 2004, five patients presented with acute cellular rejection with or without combined humoral rejection. These subjects either had a medical history of previous acute rejection episodes treated with rabbit anti-thymocyte globulin (rATG) or muromonab-CD3 (OKT3) or displayed allergic reactions to these antibodies on the initial exposure. After a transplant biopsy-proven rejection (classified by the Banff score), the patients received peripheral intravenous infusions of Campath-1H, starting with an initial dose of 3 mg, increasing to a total dose of 55 to 93 mg divided over 4 to 5 days. The baseline immunosuppressive regimen of cyclosporine (C_2 = 200 ± 50 ng/mL), sirolimus (C_0 = 10 ng/mL), and occasionally prednisone (5 to 15 mg/d) was not changed during the period of Campath-1H treatment. We assessed the recovery of renal function by the serum creatinine and blood urea nitrogen (BUN) levels, as well as by estimated creatinine clearance using the Cockcroft-Gault equation, and the glomerular filtration rate (GFR), using the equation described in the Modification of Diet in Renal Disease Study (MDRD). Patient responses were assessed at inception as well as after 2 weeks and 2 months of Campath-1H therapy. The mean follow-up was 107.4 days**.**

Experimental studies on wound healing

For both experimental studies we used forty, eight week old, female Balb/c mice (weight: 19-20 grams) each, kept in individual cages with free access to water and devided into four equal

groups. All wounds were created in the same way on the shaved back of intra-peritoneally narcotised (ketamine/xylazine at 100-200mg body weight) animals with an 8 mm in diameter full thickness skin punch.

In the study for determining the effect of sirolimus on wound healing sirolimus was administered (gavaged) daily for three weeks in three groups 4mg/kg, 8mg/kg and 12mg/kg and saline (control) prior to the wound creation. No wound coverage was used.

In the study for the observation of RNA derivates enhanced topical effect on wound healing the animals received 8mg/kg oral sirolimus gavaged daily for three weeks prior wounding and during the experiment. The wound surfaces were treated with variuos concentrations of RNA in KY jelly as topical. Three groups were treated with daily application of nucleotide supplemented KY jelly as 0.025% (0.4mg RNA/100gm gel) (Group B), 0.25% (4mg RNA/100gm gel) (Group C) and 2.5% (40mg RNA/100gm gel) (Group D) nucleotide concentration.

All animals were weighted every 4 days, digital pictures of the wounds were taken every other day (Nikon Coolpix 4500), using the same 1cm x 1cm template around the wound, starting on the day of wounding. Picture analyzing software (Optimas 6, Optimas Inc) was used to measure the wound surface area as percentage of the standard template area we used. During the analysis of the photos we compared the healing wound area as the percentage of the initial one of the same animal. We followed the healing process for 14 days.

4. RESULTS

Results of the investigations on the donor side

Double kidneys transplantation

5 recipients received double kidneys from deceased adult donors rejected all local transplant services for transplant as single organs. All of them were males, mean age of 44.4 years (±10.67). This was the first transplant for all cases. The cause of the recipients renal failure was hypertension in 4 patients (80%) and IgA nephropathy in 1 patient (20%). The mean Body Mass Index (BMI) was 28.0±6.4 kg/m^2.

The immediate renal scan score was 8/10 (maximal: 10/10). The mean hospital length of stay (LOS) was 6.25 days. All five recipients were alive and avoided hemodialysis 1 year after their transplant. There was no severe surgical complication, no ureteral or kidney necrosis and no disturbances in the graft blood supply. Immediate kidney function was observed in all cases after the transplantation. Serum creatinine levels rapidly decreased from the pre-transplant mean 12.5mg/dl (1100µmol/l) level to the 3.8 mg/dl (334.4 µmol/l) level on the 5th post-operative day. 1 year after the transplant the creatinine concentration in the serum was 2.8mg/dl (246.4 µmol/l), 2 years after the transplant 1.9 mg/dl (167.4 µmol/l). The mean GFR increased from 7 ml/min to 41.8 ml/min within a week and 1 year after the transplant it was 39.07 ml/min and 2 years after transplant 47.5ml/min. Two patients suffered acute rejection with significantly worsened kidney function during this periods.

Pediatric kidney transplantation

Using very young pediatric kidneys with the mean age of 2.8±1.0 we compared to ideal adult ones with the mean age 31.3±9.2. The mean ages of the recipients of pediatric donors were 42.0±12.4 versus 45.7±14.8 years for recipients of adult grafts (p=ns). The mean recipient BMI values of pediatric donors were 21.8±2.9 versus 22.4±2.0 kg/m^2 for recipients of adult donors (p=ns). Sixty-six percent (n=25) of pediatric donor recipients were women versus 44% (n=53) of adult donor recipients (p=0.03). Thirteen pediatric donor recipients (34%) suffered an acute rejection episode compared to 16 (13%) adult graft recipients (p<0.01). Death-censored actuarial graft survival rates at one and 5 years for recipients of pediatric donor grafts were 93% and 84% compared with 93% and 85% for recipients of adult donor grafts (p=ns). There were no graft losses due to technical complications among the pediatric donor cohort. At one and 5 years post-transplantation, the mean estimated creatinine clearances of pediatric donor graft recipients were 52.9±19.6 and 54.0±17.8 ml/min, respectively, compared with 56.4±19.8 and 49.1±21.7 ml/min for recipients of adult donor grafts at the same times (p=ns).

Fibromuscular dysplasia

In our material a few patients with this extremly rare disease served as donors. According to our results fibromuscular dysplasia disease had no maior effect neither on donor not on recipient expected life expectancy.

Results of the investigations on the recipient side

Sirolimus-cyclosporine-steroid combination

There was no significant difference in age, gender, body weight, BMI, antibody titer, number of transplantations, and number of diabetic patients between the race groups. The primary cause of kidney failure was more frequently hypertension among African Americans and Hispanics than among Caucasians.

In the entire cohort the target serum concentration for SRL was 10±2 ng/ml. There was no significant difference in the groups. To reach the target serum drug concentration, the African American recipients needed higher dose than the Hispanic ones. The CsA serum level and the daily dose was similar in all groups during the whole follow-up period. The patient survival rates were similar at one and six years after transplantation (95.5% vs 94.4% vs 94.9% and 87.7% vs 85.3% vs 81.9%). There was also no difference in the graft survival rates. The acute rejection rates and transplant biopsy proved chronic rejection rate were similar at 1, 3 and 6 year. The cumulative incidence of acute rejection episodes over the entire follow-up period was similar among the groups: Group 1 22%, Group 2 24.2% and Group 3 23.0%. Although there were no significant differences in overall or individual infection rates, Group 1 and 2 recipients displayed higher but not significant incidence of postoperative wound infection (14.0%, 16% and 10.6% p= ns). In Group 2 and 3 pneumonia was significantly more frequent than Group 1 (25.7%, 32.0%, 22.0% p=0.05). The Hispanic patients suffered significantly

less CMV infection then the others (3.8% vs 8.2% and 6.9% p=0.01). Thrombocytopenia, anemia and leukopenia were similar in all groups.

Campath-1H in acute rejection

Five patients included three women and two men raging from 30 to 39 years of age had experienced repeated previous acute rejection episodes. After Campath 1H administration four of the five patients showed good responses to the therapy. At the time of Campath-1H administration for cellular rejection according to the patients rejection type (cellular and humoral rejection together) supportive treatment was needed.

The overall patient survival was 100%, and renal function recovery rate was 80%. As a group, the serum creatinine levels fell to 20% of the peak value by the end of the treatment. Two weeks later, the creatinine level was 35% to 50% of the pre-treatment value. The treatment course was associated with a transitory decrease in absolute lymphocyte and monocyte count with recovery after 6 months.

Experimental wound studies

There was no animal mortality or wound infection during the study period. 4mg/kg sirolimus dose showed no effect on wound healing. 8mg/kg and 12mg/kg sirolimus dose had the same effect however; the animals tolerated the 8 mg/kg better. 8mg/kg daily oral dose of sirolimus significantly ($p<0.04$) impaired wound re-epithelization after day 3 during the whole healing period, however, after day 12 all wounds were less than 10% in size.

Wound healing was faster with 0.25% nucleotide topical compared to the control group. Between day 4-day 10 the wound shrinkening was

significantly faster. There was no significant difference between the 0.25% concentration containing topical and the 2.5% concentration containing one. At day 14 the treated animals wound was still smaller, but at this point there was no significant difference.

5. MAIN CONCLUSIONS

1. With careful selection marginal organs can be used safely for kidney transplantation. Extended criteria donor kidneys with dual kidney transplantation can give good short and long term graft and patient survival and graft functions. Regarding the surgical technique using one side of the recipient is a more challenging task but gives better re-transplant chances
2. Using single pediatric (under the age of 5) deceased donor grafts transplanted into selected adult recipient, provided long-term graft survivals that were comparable to that of putatively optimal donors.
3. The risk for later complications with proved fibromuscular dysplasia is low compared with the potential benefits of transplantation.
4. Among genetically high risk recipients (African-Americans) the concentration controlled sirolimus-cyclosporine-steroid regimen showed higher one year survival rate than Caucasians (95,5% vs 94.9%) and reduced the incidence of acute rejection episodes without an augmented toxicity profile.
5. We are the first to publish the successful use of Campath-1H in acute kidney rejection. Campath-1H is efficient even in

extremely high immunological risk situations and relatively free of adverse events.

6. In an experimental mouse model we could prove significant wound healing impairment in sirolimus treated animals.
7. Using our animal model we observed significant improvement in wound healing among sirolimus fed animals with the use of topical containing nucleotides in the early fase (2-6 days).

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