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Triple Immunosuppression With Tacrolimus in Pediatric Renal Transplantation: Single-Center Experience

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ABSTRACT

Aim. In this single-center cohort, we retrospectively analyzed the efficacy and safety of tacrolimus in pediatric renal transplantation.

Methods. We examined the medical records of 22 consecutive renal transplantation recipients (12 boys, 10 girls) receiving tacrolimus, to evaluate occurrence of acute rejection (AR) episodes, glomerular filtration rates (GFR), and side effects.

Results. The mean recipient age was 15.07 ± 3.96 years. Seven grafts came from cadaveric, and 15 from living related donors. The patients were placed on immunosuppression with prednisolone and tacrolimus plus azathioprine ($n = 8$) or mycophenolate mofetil (MMF) ($n = 12$) or enteric-coated mycophenolate sodium ($n = 2$). Eighteen patients received basiliximab on days 0 and 4. There were three AR episodes at 5, 9, and 12 months. Mean GFR at the end of 1 and 2 years were 97.1 ± 24.0 mL/min/1.73 m^2 and 116.9 ± 42.2 mL/min/1.73 m^2, respectively. There was no graft loss. Hypertension, hyperlipidemia, and hyperglycemia were present in 14 (63.6%), 3 (13.6%), and 3 (13.6%) patients, respectively, without gingival hyperplasia, tremor, or hypertrichosis. Supraventricular tachycardia was noticed in five patients (22.7%), three of whom needed antiarrhythmic drugs (13.6%).

Conclusion. Our single-center experience with tacrolimus, steroid plus azathioprine or MMF or enteric-coated mycophenolate sodium regimen in pediatric kidney recipients showed a low rate of AR with excellent graft survival and function at 1 and 2 year posttransplantation. The increased rate of supraventricular tachycardia in this regimen had not been previously reported; this association merits further studies.

CALCINEURIN INHIBITORS (cyclosporine and tacrolimus) are the principal immunosuppressive drugs used in kidney transplantation. In adults a lower risk of acute rejection has been reported from multicenter trials comparing tacrolimus with the old formulation of cyclosporine.[1] Tacrolimus was more effective in preventing acute rejection when used in combination with azathioprine in pediatric renal transplantation, as well.[2] This difference disappeared when cyclosporine or tacrolimus was used in combination with mycophenolate mofetil (MMF).[3] However, tacrolimus was associated with improved graft function at 1 and 2 year posttransplantation.[3,4] Hypomagnesemia (34.0% vs 12.9%) and diarrhea (13.6% vs 3.2%) were significantly more frequent among the tacrolimus compared with the cyclosporine group.[2]

In this single-center cohort, we retrospectively analyzed the efficacy and safety in pediatric renal transplantation of tacrolimus in combination with azathioprine or MMF or mycophenolic acid. Our results were comparable to previ-

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ous reports of multicenter studies; interestingly we noticed an increased rate of supraventricular tachycardia, which had not been reported previously.

PATIENTS AND METHODS

We retrospectively examined 22 consecutive pediatric renal transplantation recipients from May 2000 to May 2006, all of whom were Caucasian with 12 boys and 10 girls. The mean recipient age was 15.07 ± 3.96 years.

All patients received prednisolone and tacrolimus. Prednisolone, started at 60 mg/m^2/d (maximum daily dose 60 mg), was tapered to 5 to 10 mg/d at 6 months. Tacrolimus was administered orally as capsules every 12 hours. The initial oral daily tacrolimus dose was 0.2 to 0.3 mg/kg. The target blood tacrolimus levels were 15 to 20 ng/mL in the first month, 10 to 15 ng/mL for the second and third months, and 5 to 10 ng/mL after 3 months. Eighteen patients received basiliximab (12 mg/m^2 on days 0 and 4). Eight patients received azathioprine (2 mg/kg); 12, MMF (800 to 1000 mg/m^2/d; maximum 1500 mg/d) and two, enteric-coated mycophenolate sodium. Acute rejection (AR) was defined as a requirement for antirejection therapy. Renal function was assessed using the Schwartz formula.[5]

RESULTS

Twelve patients (55%) had glomerular disease: Alport syndrome (n = 3), focal segmental glomerulosclerosis (n = 3), juvenile nephronophthisis (n = 2), membrane proliferative glomerulonephritis (n = 2), Bardet-Biedl syndrome (n = 1), and polyarteritis nodosa (n = 1); Structural disorders were present in nine patients (41%): vesicoureteral reflux (n = 4), posterior urethral valves (n = 2), neurogenic bladder (n = 2), and hypoplasic kidney (n = 1). The etiology of end-stage renal disease was unknown in one case (4%). Seven patients (32%) were on hemodialysis, 10 (45%) on peritoneal dialysis, and 5 (23%) were preemptive transplantations. Seven grafts came from cadaveric (32%), and 15 from living related donors (68%).

Mean glomerular filtration rate at the end of 1 and 2 years were 97.1 ± 24.0 mL/min/1.73 m^2 and 116.9 ± 42.2 mL/min/1.73 m^2, respectively. There was no patient and graft loss. There were three AR episodes in three patients (13.6%) at 5, 9, and 12 months, respectively. All patients were on a tacrolimus and MMF combination; AR episodes responded to corticosteroid.

Hypertension, hyperlipidemia, and hyperglycemia were present in 14 (63.6%), 3 (13.6%), and 3 (13.6%) patients, respectively but no gingival hyperplasia, hypertrichosis, tremor, or PTLD. Hyperglycemia resolved following tapering of prednisolone in two patients and resulted in diabetes in the third one (4.5%). Diarrhea, which developed in one patient, resolved after conversion from MMF to azathioprine.

Five patients (22.7%) developed supraventricular tachycardia; four patients within one month (early-onset) and one patient at 3 years after transplantation (late-onset). It resolved spontaneously in two patients; whereas, antiarrhythmic drug therapy was needed in three patients: two patients in the early-onset group and one patient in the late-onset group.

DISCUSSION

This retrospective study showed a 13.6% incidence of acute rejection at 12 months among pediatric renal allograft recipients treated with tacrolimus in combination with either azathioprine or MMF or enteric-coated mycophenolate sodium. The AR rate in our series was lower than the NAPRTCS series (AR rate was 29.1% in the group treated with tacrolimus, MMF, and steroid) or the 18-center study (nine European), which was reported by Filler et al (AR rate was 36.9% in the group treated with tacrolimus, azathioprine, and steroid).[3,4] This difference may be attributed to basiliximab.[6,7] However, a recent prospective, randomized, multicenter study adding basiliximab to a regimen of tacrolimus combined with azathioprine and steroid did not improve the AR rate (19.2% vs 20.4%).[8]

Glomerular filtration rates at 1 and 2 year posttransplant in our series (97.1 mL/min/1.73 m^2 and 116.9 mL/min/1.73 m^2, respectively) were comparable to those in the NAPRTCS study, namely 98.6 mL/min/1.73 m^2 and 96.7 mL/min/1.73 m^2, respectively, in the group treated with tacrolimus, MMF, and steroid. They were higher than these reported by Filler et al: 64.9 mL/min/1.73 m^2 and 64.9 mL/min/1.73 m^2, respectively, in the group treated with tacrolimus, azathioprine, and steroid.[3,4] The lower AR rate in our series probably resulted in better graft survival and function.

Hypertension and hyperglycemia were the most frequent adverse events, similar to previous reports.[1,3,4] Of particular importance was the increased rate of supraventricular tachycardia with three patients (13.6%) on an antiarrhythmic drug. This adverse event has not been reported in previous series. Among 237 adult allograft kidney recipients treated with tacrolimus, azathioprine, and steroid. Kramer et al noted six cardiovascular events: myocardial infarction, heart failure, atrial fibrillation. In contrast, no cardiovascular events were observed among recipients treated with cyclosporine, azathioprine, and steroid.[9]

Our single-center experience with a tacrolimus, steroid plus azathioprine or MMF or enteric-coated mycophenolate sodium regimen in pediatric kidney recipients showed a low rate of AR episodes and excellent graft survival and function at 1 and 2 year posttransplantation. The increased rate of supraventricular tachycardia in this regimen has not been previously reported; this association merits further study.

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