Tacrolimus Rescue Therapy for Corticosteroid-Resistant and Polyclonal Antibody-Resistant Kidney Allograft Rejections

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Introduction: The conventional treatment of acute kidney allograft rejection consists of high-dose corticosteroids and polyclonal antibodies. We report our experience of tacrolimus rescue therapy in patients with acute rejections refractory to corticosteroids and polyclonal antibodies.

Materials and Methods: A total of 34 patients with a mean age of 42.3 years and clinical diagnosis of acute kidney allograft rejection underwent tacrolimus rescue therapy when treatment with corticosteroids and polyclonal antibodies failed. Kidney allograft biopsy results were available in 21 patients. All of the patients received tacrolimus, 0.1 mg twice daily, and in those who responded to the therapy after 4 to 6 months, tacrolimus was replaced with cyclosporine.

Results: Pathologic examination of 21 biopsy specimens of the kidney allografts showed acute vascular rejection in 7 patients (33.3%), acute humoral rejection in 6 (28.6%), acute cellular rejection in 3 (14.3%), and accelerated acute rejection in 3 (14.3%). Twenty-six patients (76.5%) responded to rescue therapy with tacrolimus and discharged with a mean serum creatinine level of 1.4 mg/dL (range, 1.1 mg/dL to 1.7 mg/dL). Allograft nephrectomy was done in 8 patients (23.5%) because of no response to treatment of rejection, the pathology reports of which consisted of acute vascular rejection in 5 patients and extensive necrosis in 3.

Conclusion: Tacrolimus therapy is able to salvage kidney allografts with acute refractory rejection. We recommend that tacrolimus be used as an alternative to the conventional drugs used for antirejection therapy. However, severe infectious complications as a result of overt immunosuppression must be considered.

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INTRODUCTION

Refractory kidney allograft rejection is still a major cause of graft loss and poor graft survival despite the use of newer immunosuppressive drugs. Until now, there are no effective and reliable therapeutic approaches for accelerated acute rejection (AAR) or acute vascular rejection (AVR).[1] In addition, the gold standard treatment of acute humoral rejection has remained undefined.[2] Therefore, the graft loss rates are still high.

Tacrolimus is a new immunosuppressive agent that has undergone clinical trials for efficacy as a primary treatment in kidney transplantation

and as an agent for salvage in kidney allograft rejection.[1] Several studies have suggested tacrolimus as an effective rescue therapy to reverse ongoing acute rejection or AAR refractory to conventional immunosuppressive agents.[3-7] However, some recent studies have disputed its efficacy.[8] The aim of this study was to report the experience of tacrolimus rescue therapy in patients with acute allograft rejection refractory to conventional immunosuppressive agents. Most of the kidney recipients had received their kidneys from living donors and were not anuric after transplantation.

MATERIALS AND METHODS

During a 5-year period between March 2001 and November 2006, we had 34 patients with a clinical diagnosis of acute allograft rejection who had undergone tacrolimus rescue therapy at Shariati Hospital in Tehran, Iran. In all of them, treatment with corticosteroids and polyclonal antibodies, consisting of antithymocyte or antilymphocyte globulin, had failed. The cross-match and panel reactive antigens tests had been negative between each donor and his/her recipient. Diagnosis of rejection had been made by clinical and laboratory findings, Doppler ultrasonography, renal scintigraphy, and kidney allograft biopsy (in 21 patients). Rejections had occurred in the third posttransplant day or thereafter.

They had received an induction therapy including prednisolone, 1.5 mg/kg, and mycophenolate mofetil, 1 g twice daily. The maintenance therapy regimen included prednisolone, 1.5 mg/kg, plus mycophenolate mofetil, 1 g twice daily, and cyclosporine, 8 mg/kg. The antirejection therapy consisted of methylprednisolone, 1 g daily for 3 days and then 500 mg daily for 2 further days, and antithymocyte globulin, 1.5 mg/kg for 10 to 14 days, or antilymphocyte globulin, 15 mg/kg for 10 to 14 days. Plasmapheresis was used in 1 patient. Allograft rejections did not respond to methylprednisolone in all of the patients. Therefore, other treatment options were discussed with the patients and they consented to start tacrolimus rescue therapy. All of the patients received tacrolimus, 0.1 mg twice daily, after prior unsuccessful conventional therapies. The expenses of tacrolimus rescue therapy were high and serum level of tacrolimus was not measured. Thus, tacrolimus was changed to cyclosporine in patients who responded to the therapy after 4 to 6 months.

RESULTS

The mean age of the patients was 42.3 years (range, 22 to 62 years), and they were 18 men (52.9%) and 16 women (47.1%). A living donor was the source of kidney allograft in 27 patients (79.4%) and a deceased donor in 7 (20.6%). Three patients (8.8%) had their second transplantation. The mean follow-up period was 31.7 months (range, 6 to 67 months). Pathologic examination of 21 biopsy specimens of the kidney allografts showed AVR in 7 patients (33.3%), acute humoral rejection in 6 (28.6%), acute cellular rejection in 3 (14.3%), and AAR in 3 (14.3%). Pathologic examination of 2 biopsy specimens was not possible.

After treatment with tacrolimus, 26 patients (76.5%) responded to the therapy and discharged with a mean serum creatinine level of 1.4 mg/dL (range, 1.1 mg/dL to 1.7 mg/dL). One of the patients died due to herpetic encephalitis 6 months after discharge. Allograft nephrectomy was done in 8 patients (23.5%) because of no response to treatment of rejection, the pathology reports of which consisted of AVR in 5 patients and extensive necrosis in 3.

DISCUSSION

Accelerated acute rejection and acute vascular rejection are uncommon aggressive forms of kidney allograft rejection. To date, effective and reliable therapeutic approaches to the treatment of AAR or AVR do not exist, and graft loss rates remain high.[1] Conventional treatment of acute kidney allograft rejection is high-dose pulses of corticosteroids, and treatment of corticosteroid-resistant rejection is done with polyclonal antibody preparations such as muromonab-CD3, equine antithymocyte globulin, and rabbit antithymocyte globulin. In some cases of recalcitrant rejection, graft salvage can be achieved by conversion of one baseline immunosuppressive

regimen to another, even in the presence of corticosteroid-resistant rejection.[9]

In recent years, several studies have shown that tacrolimus can effectively reverse the ongoing accelerated or acute rejection refractory to conventional immunosuppressive agents including corticosteroids and antithymocyte globulin.[3-7] Tacrolimus, formerly known as FK506, selectively inhibits transcription of interleukin-2 and several other cytokines and is also a macrolide antibiotic.[10] Although most of its effects may be attributed to an inhibitory effect on T-cell function, tacrolimus has also a direct inhibitory effect on calcium-dependent B-cell activation. Additionally, it inhibits human B-cell proliferation in response to certain calcium-independent stimuli.[11] The introduction of tacrolimus in 1990s significantly improved the survival of transplanted organs. This immunosuppressive drug is also becoming popular in the therapy for various immune-mediated diseases.[10]

Jang and associates reported that with a mean follow-up of 8.1 months (range, 1 to 15 months), all of their 11 kidney allografts were successfully salvaged by tacrolimus therapy. Overall graft survival was 59%. They concluded that tacrolimus therapy is able to salvage kidneys with acute refractory rejection and that it is an alternative in patients with cyclosporine toxicity. Moreover, their study confirmed that tacrolimus therapy has a beneficial effect on patients with AAR or AVR who had been considered to have a poor prognosis.[1] Pascual and colleagues demonstrated that a therapeutic approach of combining plasma exchange and tacrolimus/mycophenolate mofetil rescue therapy has the potential to improve the outcome of acute humoral rejection.[2] Jordan and colleagues attempted graft salvage with tacrolimus conversion in a total of 169 patients with ongoing rejection on baseline cyclosporine immunosuppression after failure of high-dose corticosteroids and/or antilymphocyte preparations to reverse rejection. With a mean follow-up of 30 months, 74% were successfully rescued. Of the 144 patients previously treated with antilymphocyte preparations, 81% were salvaged. They recommended that tacrolimus could be used as an alternative to the conventional drugs used for antirejection therapy.[11] However, Schwarz and coworkers showed that the efficacy of tacrolimus/mycophenolate mofetil rescue therapy in established C4d-positive chronic allograft dysfunction is not satisfactory.[8]

All the patients of the current study had decreased urine volume or had become anuric in their third posttransplantation day or thereafter. In all of the patients, Doppler ultrasonography showed a resisting index of 100% and open functional arteries and veins. Renal scintigraphy showed impaired perfusion in all of the kidneys which was in contrast to acute tubular necrosis. Hence, the diagnosis of rejection was made by the clinical, laboratory, and radiological evidences in these patients who had a refractory rejection to corticosteroids and polyclonal antibodies. Biopsy was taken in some of the patients and not all of them. In this cohort of patients, 76.5% were successfully rescued by tacrolimus when used after unsuccessful conventional immunosuppressive therapy. These 26 successfully rescued kidney allografts were followed-up for a mean duration of 31.7 months (range, 6 to 67 months). Their serum creatinine levels were below 1.7 mg/dL at discharge that demonstrates the success of tacrolimus rescue therapy. Although the technique of measuring the trough level of tacrolimus was not available in our hospital during the study, it seems that the dosage of tacrolimus used in our patients (0.1 mg twice daily) was enough, especially when the serum level of tacrolimus was in normal ranges in the following studies. Death of one of the kidney allograft recipients 6 months after discharge due to herpetic encephalitis could be possibly an adverse effect of overt immunosuppression related to tacrolimus therapy. Therefore, it is important to consider the possible complications of this treatment including opportunistic infections.

CONCLUSION

Our findings are compatible with the previous reports that tacrolimus provided potent suppression of antibody-mediated rejection episodes in the liver and kidney allografts. We recommend tacrolimus be used as an alternative

to the conventional drugs used for antirejection therapy in kidney transplantation. However, determination of the optimal dosing scheme for tacrolimus rescue therapy is important, so as to avoid life-threatening risks of excessive immunosuppression.

CONFLICT OF INTEREST

None declared.

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