Excellent Results With High-Dose Mizoribine Combined With Cyclosporine, Corticosteroid, and Basiliximab in Renal Transplant Recipients: Multicenter Study in Japan

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ABSTRACT

We performed a multicenter study in Japan to assess the efficacy and safety of immunosuppressive therapy with high-dose mizoribine (MZR; 6 mg/kg) combined with basiliximab (Bas), cyclosporine (CyA), and a corticosteroid in 90 patients. MZR was adjusted to maintain a target trough level of 1 to 2 μg/mL. CyA was started at 7 mg/kg to maintain blood levels in the target therapeutic range of 200 ng/mL (trough [C0]), 1200 ng/mL (2-hour post-dose [C2]), and 6000 ng · h/mL (area under the curve$_{0-9}$). Bas (20 mg/body weight) was administered on the day of transplantation and on postoperative day 4. Rejection was diagnosed by episode and protocol biopsies. Cytomegalovirus (CMV) antigenemia (direct immunological staining of leukocytes using peroxidase-labeled monoclonal antibody [C7-HRP]) levels were measured every 2 weeks for 6 months. At 12 months, all patients and grafts were surviving except for one death from infection: the 1-year patient and graft survival rate was 98.9%. The acute rejection rate was 21.1%. The mean serum creatinine level at 1 year was 1.51 ± 0.61 mg/dL. The incidence of CMV disease was 0% with 28.9%, CMV antigenemia and 5.6%, ganoyclovir treatment. The incidence of BK virus disease was 2.2%. The mean serum uric acid level was 7.15 ± 1.79 mg/dL at 1 month and 7.06 ± 1.78 mg/dL at 3 months. We observed that a high-dose MZR regimen in combination with CyA, Bas, and corticosteroid was safe and effective to reduce the frequency of CMV and BK virus-related events in renal transplant recipients.

WIDESPREAD USE of a four-drug immunosuppressive therapy (basiliximab [Bas], calcineurin inhibitor, corticosteroid, mycophenolate mofetil [MMF]) has markedly lowered the rate of acute rejection episodes in renal transplantation recipients in Japan. However, the use of MMF leads to complications such as infections, particularly those involving cytomegalovirus (CMV) and BK virus (BKV).[1,2] Mizoribine (MZR) blocks inosine 5′-monophosphate dehydrogenase in the same manner as MMF. It has been shown to exhibit a low incidence of severe adverse effects, such as hepatotoxicity and bone marrow suppression. In addition, it has been reported that MZR inhibits CMV proliferation in vitro.[3]

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However, the immunosuppressive activity of MZR at a clinically approved dosage (2–3 mg/kg) has been reported to be weak compared with MMF.[4] In this multicenter study, we assessed the efficacy and safety of immunosuppressive therapy with high-dose MZR combined with Bas, cyclosporine (CyA), and a corticosteroid.

MATERIALS AND METHODS

The 90 patients were treated with high-dose MZR (6 mg/kg), CyA, Bas, and a corticosteroid. The MZR was adjusted to maintain a target trough level of 1 to 2 μg/mL. CyA was started at 7 mg/kg to maintain blood levels in the target therapeutic range: 200 ng/mL (trough [C0]), 1200 ng/mL (2-hour post-dose [C2]), and 6000 ng · h/mL (area under the curve$_{0-9}$). Bas (20 mg/body weight) was administered on the day of transplantation and on postoperative day 4. Rejection was diagnosed by episode and protocol biopsies. CMV antigenemia (C7-HRP) was measured every 2 weeks for 6 months. To screen for polyomavirus replication, urinary cytology, or quantification of BKV deoxyribonucleic acid (DNA) in serum was performed at 10 days and 3 months after the operation. All patients were followed for 12 months. The study was approved by the ethics committees of the participating institutions.

RESULTS

Patient characteristics are shown in Table 1 After 12 months, all patients and grafts survived, except for one death due to infection; the 1-year patient and graft survival rate was 98.9%. The mean doses of MZR at 1, 3, 6, and 12 months were 312 ± 65, 299 ± 63, 287 ± 71, and 290 ± 85 mg, while the mean serum creatinine levels were 1.38 ± 0.67, 1.46 ± 0.51, 1.52 ± 0.53, and 1.51 ± 0.61 mg/dL, respectively. According to the Banff 2007 classification, an acute rejection episode occurred in 19 cases (21.1%): border line (n = 3); I A (n = 11); I B (n = 2), II A (n = 1), and II B (n = 1) while two subjects did not undergo a biopsy. Table 2 summarizes the adverse events. The incidence of CMV disease was 0%, with 28.9% CMV antigenemia and 5.6% gancyclovir treatment. The incidence of BKV disease was 2.2%. The mean serum uric acid levels at 1 and 3 months were 7.15 ± 1.79 and 7.06 ± 1.78 mg/dL, respectively. Forty-two cases (46.7%) were diagnosed with hyperuricemia and 25 (27.8%) were treated with antihyperglycemic drugs.

Table 1. Demography and Basement Characteristics

Cause of uremia (%)	
Chronic glomerulonephritis	41 (45.5%)
Diabetic nephropathy	14 (15.6%)
Focal gromerulosclerosis	5 (5.6%)
Others	17 (18.9%)
Unknown	13 (14.4%)
Recipient sex (men/women)	56/34
Recipient age (y)	42.5 ± 13.5
Recipient weight (kg)	56.0 ± 11.1
Duration of hemodialysis (mo)	54 (0–30 y, 4 mo)
Donation source	
Living donors	86 (95.6%)
Cardiac death donors	3 (3.3%)
Brain death donor	1 (1.1%)
Donor type	
Father	18 (20.0%)
Mother	26 (29.0%)
Brother or sister	19 (21.1%)
Son or daughter	3 (3.3%)
Spouse	20 (22.2%)
Others (death donor)	4 (4.4%)
HLA-AB mismatches	1.85 ± 0.98
HLA-DR mismatches	0.94 ± 0.63
ABO blood type	
Identical	63 (70.0%)
Compatible	27 (30.0%)

HLA, human leukocyte antigen.

DISCUSSION

MZR has been approved in Japan for induction and maintenance of immunosuppressive therapy after renal transplantation at standard doses of 1 to 3 mg/kg per day.[5] Although it has also been released in South Korea and China, it has not seen wide acceptance throughout the world, although it has fewer adverse events, it is less potent for immunosuppression.[6] Therefore, MZR is often used as an alternative immunosuppressant after various complications in the stable phase; there are few cases of de novo until recently. Akiyama et al noted that patients treated with ≥5 mg/kg per day of MZR showed fewer acute rejection episodes than those treated with <5 mg/kg per day.[7] In the present study, high-dose induction (6 mg/kg) MZR treatment was effective; we observed high 1-year graft and patient survival rates, as well as low incidence of acute rejection episodes and adverse events. Based on these findings, high-dose (6 mg/kg) MZR may be useful de novo after transplantation.

The incidence rates of CMV infection and disease in renal transplant recipients are about 60% and 25%, respectively,[8] while the prevalence of BK viruria and viraemia is about 40%.[9] Although MMF is most frequently used in Japan, because of its stronger immunosuppressive effects compared with MZR, its administration is well known to be associated with CMV infection and BK nephropathy.[10] However, in a previous study, MZR showed anti-CMV activity, potentiating anti-CMV activity of gancyclovir in an apparently synergistic manner.[3] Another report described conversion from MMF to MZR in patients with positive urinary BKV to decrease the level of BKV DNA in the urine, without acute rejection episodes or deterioration of graft function.[2] In our patients, we noted no incidence of CMV disease (0%), and encouraging rates of CMV antigenemia (28.9%), ganciclovir treatment (5.6%), and BKV disease (2.2%). Although 42 cases (46.7%) developed hyperuricemia, the most well-known adverse event related to MZR, it was easily controlled by administration of allopurinol in most cases. Therefore, we consider that high-dose MZR (6 mg/kg) is safe.

Table 2. Main Adverse Events and Infections

Infection	26 (28.9%)
CMV antigenemia	
CMV disease	0
Ganciclovir treatment	5 (5.6%)
Peak CMV antigen (cells/50,000)	5.7 ± 24.6
Mean occurrence time after transplantation (days)	37 ± 14
BKV	2 (2.2%)
Herpes simplex virus	2 (2.2%)
Herpes zoster virus	2 (2.2%)
Sepsis (MRSA)	1 (1.1%)
Viral nephritis/viral nephritis susp.	2 (2.2%)
Pneumocystis carinii pneumonia	0
Diffuse peritonitis	0
Hyperuricemia	42 (46.7%)
Treatment	25 (27.8%)
Non-treatment	17 (18.9%)
Gastrointestinal disorder (Inappetence, diarrhea, nausea, vomiting)	3 (3.3%)
Leukocytopenia, anemia	0
Inpaired glucose tolerance	2 (2.2%)
Boredom, fever, trembling	4 (4.4%)

CMV, cytomegalovirus; BKV, BK virus; MRSA, methicillin-resistant *Staphylococcus aureus.*

The therapeutic serum trough concentration range of MZR has been reported to be 0.1 to 3 μg/mL.[11] MZR is directly excreted through the kidney, thus its dose must be adjusted based upon the improved renal function.[12] Sugitani et al reported the appropriate dose of MZR to maintain a trough level of 1.0 μg/mL to be about 4 mg/kg/d in the presence of good renal function; with the excellent renal function, at least 5 to 6 mg/kg/d was needed to achieve the target trough level.[6] In our study, we began MZR administration at an initial dose of 6 mg/kg despite poor renal function after the operation, changing the dosage according to the individual's renal function to maintain a trough level of 1 to 2 μg/mL. This strategy resulted in adequate immunosuppressive effects and fewer adverse events. Therefore, the initial dose and trough level of MZR may be appreciated during the acute phase following kidney transplantation.

In conclusion, the regimen of high-dose MZR (6 mg/kg/d) in combination with CyA, Bas, and a corticosteroid, was safe and effective to reduce the frequency of CMV and BKV-related events in renal transplant recipients.

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