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Long-Term Results in Mizoribine-Treated Renal Transplant Recipients: A Prospective, Randomized Trial of Mizoribine and Azathioprine Under Cyclosporine-Based Immunosuppression

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MIZORIBINE (MZ) is a immunosuppressive drug separated from the filtrate of culture medium of *Eupenicillium brefeldianum* M-2166. MZ is believed to show immunosuppressive effects by inhibiting DNA synthesis in the S phase of the cell cycle and thus division and proliferation of lymphocytes.[1] MZ is known to have a stronger immunosuppressive effect than azathioprine (AZ) and fewer myelosuppressive and hepatotoxic effects. However, no randomized trial of MZ in renal transplantation has been reported so far. Therefore, we designed this prospective, randomized study to evaluate the immunosuppressive effect of MZ in renal transplantation.

MATERIALS AND METHODS

Patients

Between January, 1988 and April, 1989, 116 patients were entered into a randomized trial comparing MZ and AZ under cyclosporine (CyA)-based immunosuppression. Both groups (MZ group and AZ group) consisted of 58 patients. There is no significant difference between two groups in terms of recipient sex, donor sex, donor source (such as living and cadaveric donors) donor age, HLA-AB, DR mismatches, and ABO-compatibility (Table 1).

Immunosuppression

In the induction phase, methylprednisolone (MP), CyA, and AZ or MZ were used. MP administration was started on the day of transplantation at a dose of 125 to 500 mg/day and reduced to a maintenance dose of 8 mg/day by the 4th month. Oral administration of CyA, 8 to 10 mg/kg per day, was started 2 days before transplantation. AZ administration, 2 mg/kg per day, was started 2 days before transplantation and continued for 1 week, after which it was reduced to 1 mg/kg per day and adjusted according to the peripheral white blood cell count. MZ administration, 4 to 5 mg/kg per day, was started 2 days before transplantation and continued at the same dosage unless an adverse effect, such as myelosuppression occurred, when it was discontinued.

RESULTS

Patient and Graft Survival

Overall 1-, 5-, and 9-year patient survival was 98%, 94%, and 85%, respectively; in the MZ group it was 98%, 93%, and 88%, respectively, and in the AZ group, 97%, 95%, and 83%, respectively. Overall 1-, 5-, and 9-year graft survival was 92%, 75%, and 55%, respectively; in the MZ group it was 90%, 73%, and 58%, respectively, and in the AZ group, 93%, 73%, and 52%, respectively. There was no significant difference between the two groups in terms of the graft and patient survival (Figs 1 and 2).

Rejection Episodes

The incidence of acute rejection was 56.9% in both groups.

Crossover

Sixteen AZ group patients (27.6%) were forced to discontinue AZ administration or change from AZ to MZ due to adverse effects, which were myelosuppression in 11 patients, and liver dysfunction in 5 patients. Since no MZ-related adverse effect occurred, no patient discontinued MZ in the MZ group (Fig 3).

DISCUSSION

This is a first randomized prospective long-term trial of MZ-treated renal transplantation. Our results showed the graft survival was almost the same between the AZ- and MZ-treated groups and frequency of rejection episode was also not different. Since MZ has fewer adverse effects than AZ and has synergic action with CyA, it has been used in immunosuppressive therapy after renal transplantation.[2–4] According to those results, MZ has almost the same immunosuppressive effect compared to AZ. However, since MZ showed much fewer adverse effects, no patients treated

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Table 1. Patient Characteristics

Characteristics	Azathioprine (n = 58)	Mizoribine (n = 58)	P
Recipient age (years)	33.5 ± 10.4 (2–56)	34.1 ± 8.6 (16–52)	NS (P = .712)
Recipient sex			
M	40 (69.0%)	37 (63.8%)	NS (P = .467)
F	18 (31.0%)	21 (36.2%)	
Donor sex			
M	24 (41.4%)	17 (29.3%)	NS (P = .220)
F	34 (58.6%)	41 (70.7%)	
Donor source			
LD	56 (96.6%)	57 (98.3%)	NS (P = .619)
CD	2 (3.4%)	1 (1.7%)	
Donor age (years)	55.7 ± 8.3 (37–70)	56.2 ± 9.6 (34–74)	NS (P = .770)
HLA-AB mismatch			
0	8 (13.8%)	10 (17.2%)	
1	18 (31.0%)	19 (32.8%)	
2	27 (46.6%)	27 (46.6%)	NS (P = .454)
3	3 (5.2%)	0 (0.0%)	
4	2 (3.4%)	2 (3.4%)	
HLA-DR mismatch			
0	16 (27.6%)	17 (28.8%)	
1	39 (67.2%)	39 (67.2%)	NS (P = .782)
2	3 (5.2%)	2 (3.4%)	
ABO compatibility			
compatible	57 (98.3%)	58 (100%)	NS (P = .496)
incompatible	1 (1.7%)	0 (0.0%)	

with MZ converted to AZ, whereas 27.6% of the patients treated with AZ were forced to change to MZ for adverse effects. These fewer adverse effects is a great advantage of MZ compared to AZ.

Sakaguchi et al suggested that the mechanism of cytotoxic effect of MZ is the inhibition of ribonucleic acid and deoxyribonucleic acid synthesis caused by alteration of the conversion of inosinic acid monophosphate to guanylic acid monophosphate in the purine biosynthetic pathway.[5] This mechanism of action is almost identical with mycophnolate mofetil (MMF), which was recently developed and proved to be much more effective than AZ.[6] However, MZ in our study did not show such potent immunosuppressive effect compared to MMF. We speculated a significant difference of administrative dose might cause this difference, namely dose of MMF is usually 2 to 3 g per day, which is almost 50 mg/kg per day, whereas the dose of MZ was much smaller, 4 mg/kg per day. MZ is not metabolized and 100% of absorbed dose exists as active form until excreted from urine, however MMF is rapidly metabolized into inactive form through liver, and active MMF is usually only 2 to 3% of absorbed MMF. We speculated MZ is not metabolized, however, it is excreted into urine rapidly, therefore a much higher dose could be administered to obtain a more potent immunosuppressive effect.

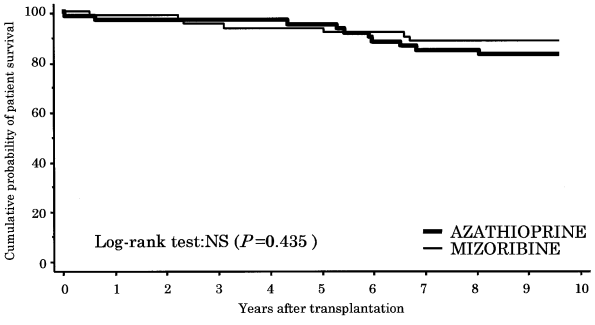

Fig 1. Patient survival.

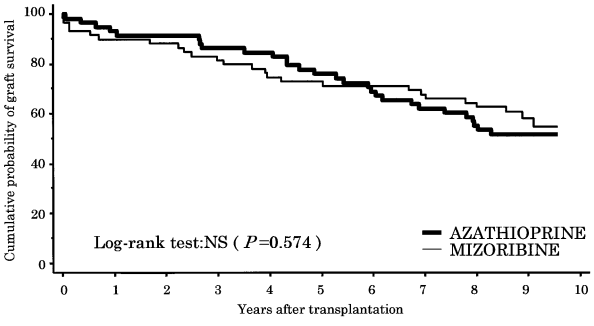

Fig 2. Graft survival.

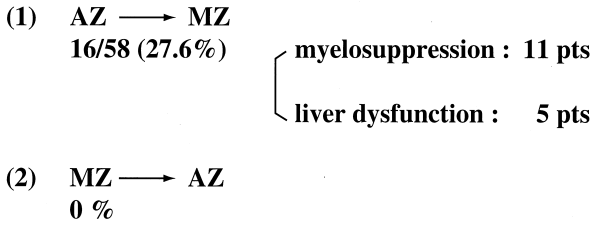

Fig 3. Crossover.

CONCLUSIONS

Although there was no significant difference in terms of patient and graft survival and the incidence of rejection episodes, MZ showed much fewer adverse effects than AZ. Therefore, MZ seems to be a much more useful immunosuppressive agent for renal transplantation than AZ.

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