Advantages of Mizoribine Over Azathioprine in Combination Therapy With Cyclosporine for Renal Transplantation

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REMARKABLE improvements in clinical renal allotransplantation have been achieved since the introduction of cyclosporine (CyA), as evidenced by a significantly higher graft survival than in the pre-CyA era. Powerful as an immunosuppressant, CyA has never been used without fear of its nephrotoxicity.[1,2] In an attempt to minimize the nephrotoxicity of CyA and optimize its immunological potential, the protocol of triple therapy that combines reduced dose of CyA with azathioprine (Aza) and steroids (St) has been widely accepted, becoming the mainstay of current immunosuppressive regimen in organ transplantation.[3,4] However, the administration of Aza tends to be limited because of its untoward bone marrow suppression and hepatotoxicity as well, both being major adverse side effects of the agent. Mizoribine (Mz), a product of Toyo-Jozo Co, Japan,[5] which was shown to be less toxic than Aza in these regards,[6] came into clinical use in 1980 in our country.[7,8] Soon we started to use Mz in place of Aza in that combination therapy.

This study compared renal recipients given Mz with those given Aza to examine if Mz had any advantage over Aza in clinical results, when used as part of combination therapy with CyA and St.

MATERIALS AND METHODS

Sixty-one consecutive renal transplantations were performed from one-haplotype-identical, living, related donor between October 1984 and March 1989. Group I comprised 48 recipients and was treated with Mz, in combination with CyA and St. The starting and maintenance doses of Mz were 2 mg/kg/d, with a trough level of 1.04 ± 0.65 μg/mL. The dose of CyA was 6 to 10 mg/kg/d initially and 2 to 4 mg/kg/d during maintenance. This was tapered down by 0.2 mg/kg/d every week to a maintenance dose of 0.2 mg/kg/d 2 to 3 months later. Group II comprised 13 recipients and was treated with Aza in place of Mz. The initial and maintenance doses of Aza were 1 mg/kg/d. The initial and maintenance doses of CyA and St were the same as those in group I. Potential recipients in group II who showed hepatic functional abnormalities indicated by high serum glutamic-oxaloacetic transaminase (SGOT) and/or serum glutamic-pyruvic transaminase (SGPT) (>50 IU/L) levels or demonstrated low peripheral white blood cell count (WBC) (<4000/mm^3) at transplant surgery were allocated to group I.

In both groups of recipients the original immunosuppressive dose schedules were occasionally changed because of various complications. After the complications had been treated, care was taken to return to the original dose schedule.

A rejection crisis was treated by two to four boluses of methylprednisolone (10 mg/kg), supplemented at times by local irradiation.

There were no statistically significant differences in the recipient age and sex, donor age and sex, or donor–recipient relationships between the groups (Table 1). There were also no statistically significant differences in the number of human leukocyte antigen (HLA)-A, -B, and -DR antigen matches and missmatches (Table 2).

Patients and graft survival rates were calculated by actuarial techniques. Graft loss was defined as either return to dialysis or death with a functioning graft. All causes of graft loss were included, as well as all deaths.

The incidence of rejection episodes that occurred during the initial 3 months was calculated and comparisons were made between the two groups. Miscellaneous complications arising within 3 months after transplantation were also collected and compared.

Hepatic dysfunction was defined as the development of high SGPT or SGOT levels (>100 IU/L) in at least one set of repeated blood collections. Bone marrow suppression was defined as a decrease in the number of peripheral WBC to less than 3000/mm.^{3} Patients with immunosuppression-induced diabetes were defined as those who needed insulin therapy during the postoperative course. Patients who needed insulin therapy before transplantation were not included in this study.

RESULTS

Actuarial Patient and Graft Survival Rates

Actuarial patient and graft survival rates are summarized in Figs 1 and 2. In both groups we experienced no patient

Table 1. Recipient and Donor Profile in Two Treatment Groups

		Group I*	Group II†
Recipient	Male/female	40/8	10/3
	Age (y)	31.4 ± 8.4	31.5 ± 5.3
Donor	Male/female	19/29	3/10
	Age (y)	54.6 ± 11.0	55.3 ± 11.0
Kidney source	Parent	38	11
	Sibling	10	2

*Group I, mizoribine + cyclosporine + steriods.
†Group II, azathioprine + cyclosporine + steriods.

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Table 2. Human Leukocyte Antigen Missmatches Between the Two Groups

		Group I*	Group II†
No. of A and B missmatches‡	2	29	5
	10	19	8
No. of DR missmatches‡	1	30	8
	0	18	5

*Group I, mizoribine + cyclosporine + steriods.
†Group II, azathioprine + cyclosporine + steriods.
‡Not significant.

loss during the observation period. The actuarial graft survival rate in group I was 97.9% at 1 year, decreasing slightly thereafter. The graft survival rates in groups II were 90.9%, at 1 year and remained stable at 3 years. None of the differences in graft survival rates between groups I and II was statistically significant.

Comparison of Incidence of Rejection Episodes

Acute rejection occurred in 18 of 48 recipients (37.5%) within 3 months after transplantation in group I. Likewise in group II episodes of acute rejection were observed in 4 of 13 (30.8%) (Table 3). The incidence of acute rejection was not significantly different between groups I and II.

Comparison of Renal Function

Renal function, expressed as the level of serum creatinine, in both groups is summarized in Fig 3. A gradual increase in serum creatinine level occurred in both groups during 3 years after transplantation. Between 1 year and 3 years after transplantation, there were no statistically significant differences in serum creatinine levels between groups I and II.

Comparison of Incidence of Miscellaneous Complications Due to Immunosuppression Within 3 Months

Bone marrow suppression occurred in 3 of 48 recipients (6.3%) in groups I and 5 of 13 recipients (38.5%) in group II. There was a significant difference between groups I and II ($P < .005$).

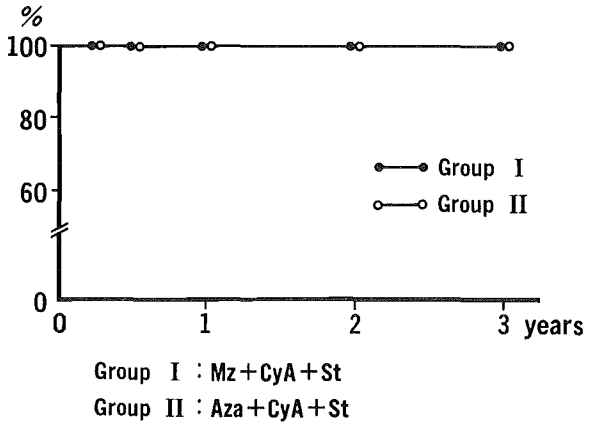

Fig 1. Actuarial life survival rate of renal allotransplant one-haplotype-indentical, living, related recipients.

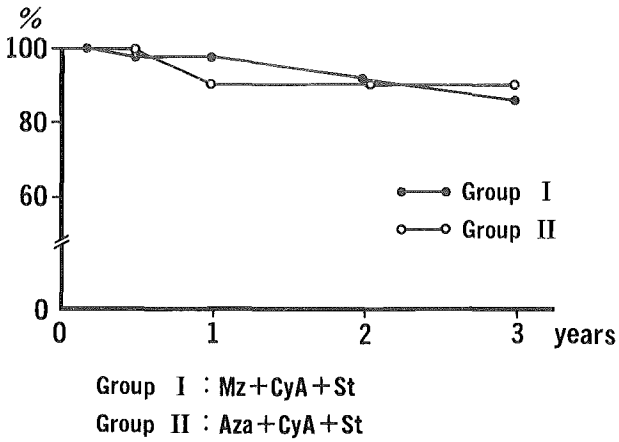

Fig 2. Actuarial graft survival rate of renal allotransplant one-haplotype-identical, living, related recipients.

Severe systemic infections such as bacterial, fungal, protozoal, and viral lung or central nervous system infections occurred in 5 of 48 recipients (10.4%) in group I and 5 of 13 recipients (38.5%) in group II. The difference was statistically significant ($P < .02$) (Table 4).

There were no significant differences in the incidence of hepatic dysfunction or immunosuppression-induced diabetes.

DISCUSSION

Clinical experiences of triple therapy with Mz, CyA, and St in renal allotransplantation have been reported from a number of transplant centers in Japan,[6,9,10] as well as those with Az, CyA, and St. To our knowledge, however, no reports have compared these two protocols on a prospective basis. Compared to Az, Mz is known to have less cytotoxicity to the bone marrow and liver. Whether such theoretical advantages can be reflected on clinical results has remained unknown in renal recipients on triple therapy.

In the present study, recipients treated with Aza, CyA, and St and having normal peripheral WBC were selected. Still, 38.4% of the recipients had developed a decrease in peripheral WBC to less than 3000/mm^3 3 months after transplantation. In contrast, only 6.3% of recipients treated with Mz, CyA, and St developed bone marrow

Table 3. Incidence of Rejection Episodes Within 3 Months

	Group I*	Group II†
No. of recipients	48	13
Rejection episodes		
Yes	18 (37.5%)‡	4 (30.8%)‡
No	30 (62.5%)	11 (69.8%)

*Group I, mizoribine + cyclosporine + steroids.
†Group II, azathioprine + cyclosporine + steroids.
‡Not significant.

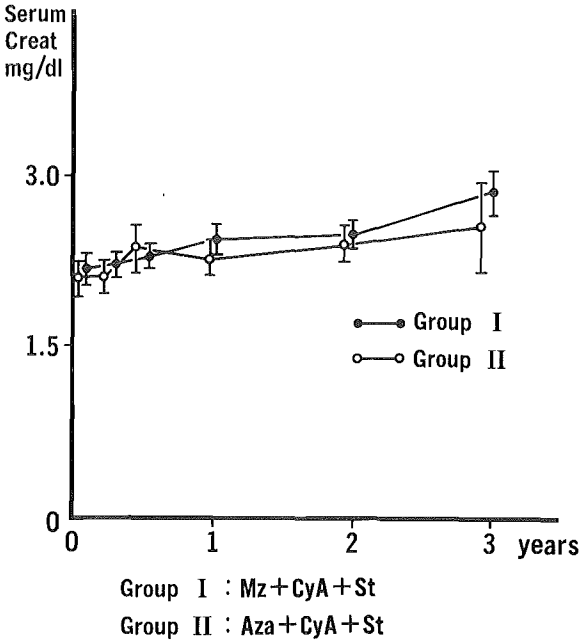

Fig 3. Levels of serum creatinine.

suppression. This difference was statistically significant. Moreover, systemic infections were more frequently encountered in recipients treated with Aza, CyA, and those treated with Mz, CyA, and St. Nephrotoxicity attributable to CyA in both triple-drug therapies was apparently less significant, as indicated by serum creatinine levels. The rationale for triple therapy consisting of Mz, CyA, and St appeared to have been confirmed in the present study, although more randomized prospective trials will be needed to confirm it.

CONCLUSION

Immunosuppression by Mz, CyA, and St in one-haplotype-identical, living, related renal allotransplant recipients demonstrated the same life and graft survival rates as that by Aza, CyA, and St. Treatment with Mz, CyA, and St resulted in significantly less bone marrow suppression and severe systemic infection comparing with Aza, CyA, and St treatment. Therefore, immunosuppressive treatment with Mz, CyA, and St appears to be superior than that with Aza, CyA, and St.

Table 4. Incidence of Miscellaneous Complications Due to Immunosuppression Within 3 Months

	Group I*	Group II†
No. of recipients	48	13
Bone marrow suppression	3 (6.3%)‡	5 (38.5%)‡
Grave systemic infections	5 (10.4%)§	5 (38.5%)§
Hepatic dysfunction	3 (6.3%)	2 (18.2%)
Immunosuppression induced diabetes	2 (4.2%)	1 (7.7%)

*Group I, mizoribine + cyclosporine + steriods.
†Group II, azathioprine + cyclosporine + steroids.
‡$P < .005$, significant.
§$P < .02$, significant.

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