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Experience with the Use of Mizoribine in Human Renal Transplantation*)

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ABSTRACT

In addition to steroids and azathioprine, mizoribine was administered to 17 renal transplant recipients. In 9 of the 17, 16 acute rejections occurred. Seven of these 9 recovered without deterioration of graft function, but one lost the function. Mizoribine, which has been elucidated to produce a chronic rejection preventing effect fully when administered concurrently with steroids and azathioprine, proved to give a satisfactory immunosuppressive effect in a dose of 1 mg/kg/day when used simaltaneously with steroids and azathioprine.

INTRODUCTION

At present, azathioprine (Az) and steroids (St) are major immunosuppressive drugs in human renal transplantation. The drugs, however, have a defect of serious side effects including induction of infections, hepatopathy and bone marrow depression. For this reason, administration of these drugs, especially Az, has been frequently withdrawn. Accordingly, appearance of immunosuppresive agents having less side effects but a more potent immunosupperessive effect has been expected.

In recent years, Cyclosporin A and mizoribine (Mi) have been developed in Europe and Japan, respectively, and are giving great promise. Our recent experience with the use of Mi in addition to St and Az in human renal transplantation is reported in this paper.

MATERIALS AND METHODS

Patients: Subjects were a total of 25 patients consisting of 17 who underwent renal transplantation in the Second Department of Surgery, University of Hiroshima School of Medicine, during the period from September 1980, to May 1982, and 8 who had undergone renal transplantation.

Immunosuppressive Drugs: Anti-human lymphocyte globulin was intravenously administered in a dose of 10-20 mg/kg/day for 14 days starting one day before transplantation; methylpredonisolone (Solu-Medrol), also intravenously in a dose of 20 mg/kg/day on the day of transplantation and 1 and 2 days after transplantation; Az, in doses of 2 mg/kg/day for 2 pre-transplantation days and 5 mg/kg/day on the days of transplantation and for 2 post-transplantation days, and thereafter as indicated in Table 1; methylpredonisolone (Medrol), mg/kg/day the day before transplantation, 2 mg/kg/day for 4 post-transplantation days, 1.4 mg/kg/day 5 up 7 days after, and thereafter gradually reduced to 0.25 mg/kg/day, and Mi, 2-3 mg/kg/day for 2 pre-transplantation days, and thereafter as indicated in Table 1. Local

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Table 1. Administration Method for Azathioprine and Mizoribine in the early Post-transplantation Stage

Peripheral blood leukocyte ($/mm^3$)	Azathioprine (mg/day)	Mizoribine (mg/day)
<3000	0	0
3001~4000	25	50
4001~5000	50	50
5001~6500	75	50
6501~9000	100	50
9001<	125	50

graft irradiation was given in a dose of 150 rad 3 to 4 times in the early postoperative stage. When acute rejection occurred, Solu-Medrol was intravenously dripped for 2 to 3 days; Medrol was administered in doses of 1.0-2.0 mg/kg/day for 3 days, 0.75-1.0 mg/kg/day for the subsequent 3 days, and then 0.5-0.75 mg/kg/day for 6 days, and thereafter gradually reduced, and both Az and Mi, as indicated in Table 1.

Table 2. Acute Rejection Which Occurred Within 3 Months After Transplantation

Case	Age	Sex	Donor	Matching	After transplantation		
					Within 1 nmo th	From 1 until 3 months	outcome at 3 months
LD 33	25	F_a	P_c	C	1	0	well functioning
LD 35	18	F	P	A	0	0	death (fulminant hepatitis)
LD 36	40	M_b	S_d	A	0	0	well functioning
LD 37	26	M	P	D	1	0	well functioning
LD 38	32	M	P	C	0	1	well functioning
LD 39	31	M	S	D	0	0	well functioning
LD 40	30	M	P	C	1	0	well functioning
LD 41	28	M	S	D	1	0	well functioning
LD 42	30	F	P	C	2	0	well functioning
LD 43	22	F	P	C	0	1	well functioning
LD 44	34	M	P	C	0	0	well functioning
LD 45	29	M	P	D	2	2	graft loss (oxalosis) and death
LD 46	29	F	P	D	0	0	well functioning
LD 47	20	F	P	C	0	0	well functioning
LD 48	29	M	S	D	0	0	well functioning
LD 49	26	F	P	D	0	0	well functioning
LD 50	37	M	S	E	1	3	well functioning

F_a : female M_b : male P_c : parent S_d : sibling

RESULTS

I. Rejection preventing effect

1) Acute rejection preventing effect

Acute rejection in the early post-transplantation stage was observed 16 time in 9 of 17 patients. 7 of the 9 recoverd without deterioration of graft function and one who died from fulminant hepatitis had a graft functioning well.

2) Chronic rejection preventing effect

Of 15 patients who had recieved Mi for more than 15 months starting before transplantation, serum creatinine levels were examined (Table 3). In 3 of 15 patients, serum creatinine increased by 0.3 mg/dl or more; one of 3 patients lost graft function owing to chronic rejection. In 12 of 15 patients, no elevation of the serum creatinine level was found.

Serum creatinine level was also examined in patients surving for one years or more after transplantion on Mi administered in place of Az because of the adverse reactions of Az, and those recieving Mi in addtion to St and Az for other reasons (Table 4). In one of 8 patients, serum creatinine increased by 0.3 mg /dl or more; this was interpreted as being due to the chronic rejection having occurred before medication. In 7 of 8 patients, there was no elevation in the serum creatinine level. It is of interest that serum creatinine did not

Table 3. Changes in Serum Creatinine Levels of Patients Who Had Been Administered Mizoribin From Pre-transplantation

Case	3 months after transplantation				15 months after transplantation			
	St (mg/day)	Az (mg/day)	Mi (mg/day)	S-Cr (mg/dl)	St (mg/day)	Az (mg/day)	Mi(mg/day)	S-Cr(mg/dl)
LD 33	24	0	125	1.6	12	0	125	1.5
LD 36	24	17	100	1.9	8	12.5	50	1.6
LD 37	28	50	50	1.5	12	50	50	1.3
LD 38	24	50	50	1.9	12	100	0	1.5
LD 39	20	150	50	1.7	12	100	0	1.8
LD 40	22	25	50	1.1	15	0	0	1.1
LD 41	22	100	50	1.2	12	50	50	1.2
LD 42	10	0	0	1.7	15	0	50	1.4
LD 43	15	50	25	1.5	18	50	25	5.7
LD 44	16	50	100	2.5	rejected			
LD 46	20	0	25	0.9	12	0	25	1.1
LD 47	20	100	50	1.2	20	100	50	1.3
LD 48	26	100	50	1.2	20	100	0	2.3
LD 49	24	100	50	1.2	8	25	50	0.8
LD 50	26	125	25	2.4	16	100	50	2.2

Table 4. Changes in Serum Creatinine Level of the Patients Who Was Administered Mizoribine After Transplantation

Case	Reason of administration	Before administration			12 months after the begining of administration			
		St (mg/day)	Az (mg/day)	S-Cr (mg/dl)	St (mg/day)	Az (mg/day)	Mi (mg/day)	S-Cr (mg/dl)
LD 16	liver function disorder	8	88	1.7	8	75	25	1.5
LD 17	chronic rejection	20	100	5.1	20	100	12.5	5.8
LD 21	liver function disorder	18	0	2.0	12	0	75	1.7
LD 22	reduction of steroid	16	50	1.9	8	50	75	1.4
CD 2	liver function disorder	10	50	2.1	10	0	50	1.9
LD 26	liver function disorder	18	50	3.0	12	0	50	2.4
LD 27	liver function disorder	20	0	1.5	16	0	100	1.5
LD 30	liver function disorder leukocytepenia	12	50	1.9	6	25	100	2.0(9 m)

increase despite reduced dosage of St in 4 cases in which administration of Az was not allowed.

These results may indicate that Mi produces an effect fully preventing acute or chronic rejection not only with St plus Az, but also with St alone.

II. Side effects

In 9 of the 17 patients who begun to recieve Mi pre-operatively, GPT increased(by 100 U/L or more). One of the 9 patients died from fulminant hepatitis. In 4 of them, GPT increased only transiently and thereafter returned to normal range. Of the remaining 4, GPT levels were 100-300 U/L. The incidence and degree of liver function disorder after concomitant administration of St, Az and Mi were very similar to those after administration of St plus Az. Of the 8 patients who begun to receive Mi post-operatively, all the GPT levels were below 100 U/L; this may explain little hepatotoxicity of Mi itself.

In many cases of treatment with St, Az and Mi, there was no prominent decreasing-tendency in peripheral blood leukocyte counts. As shown in Table 1, even cases of decreased peripheral blood leukocytes were favorably treated with 50 mg/day of Mi. Thus, bone marrow depression due to Mi seems to be mild.

Since we used Mi, the frequency of infections

has not increased, nor have malignant tumors developed.

These results show that 50 mg/day of Mi caused little adverse reactions.

DISCUSSION

Mi, an imidazole analogue nucleotide, is said to exert an immunosuppressive action through inhibiting GMP synthesis in immunoresponsible cells[3]. An animal experiment showed that renal transplantation was successfully achieved with the aid of Mi administered in considerably massive doses of 5 mg/kg/day or more[5]. In humans, however, lesser doses seemed to be enough[4]. We also obtained satisfactory results with Mi in a relatively small dose of 1 mg/kg/day.

The administration method of Mi appears to vary among medical facilities, from concurrent use with St[1] to concomitant use with St plus Az[6]. We administered a relatively small dose of Mi concomitantly with St plus Az, and realized that such a method of administration produced a sufficient immunosuppressive effects with lesser side effects.

Since Az is likely to reduced peripheral blood leukocyte counts and/or to cause liver function disorders, not a few cases exist in which only St is accepted as an immunosuppressive agent. In such cases, reduction of the dosage of St is apt to cause rejection. However, delayed reduction for fear of the occurrence of rejection will give rise to more frequent occurrence of complications due to adverse reactions of St. In the present study, we proved mildness of the side effects of Mi, and satisfactory prevention of the occurrence of rejection in the concurrent use with St and Mi.

Conclusively, it was suggested that Mi could be administered as a safe and effective immunosuppressive drug and could contribute to the improvement of results of renal transplantation.

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