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Feature Article

Role of mizoribine in renal transplantation

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Abstract Renal transplantation is the optimal form of therapy for children and adolescents with end-stage renal disease. Usually histocompatibility differences exist between donor and recipient, so it is necessary to modify or suppress the immune response to enable the recipient to accept a graft. Calcineurin inhibitors (CNI), which include cyclosporin (CsA) and tacrolimus (FK506), give many benefits on the outcome after renal transplantation, but have some toxic effects, especially nephrotoxicity. Therefore, inhibitors of purine synthesis revived as newer generation of more specific inhibitors, mizoribine (MZ) and mycophenolate mofetil (MMF). The Japanese pediatric renal transplantation clinical study group attempted to reduce and then discontinue steroid administration in combination with another three immunosuppressive drugs, CsA, MZ and anti-lymphocyte globurin (ALG). This study showed good clinical results. Mizoribine is an effective immunosuppressive drug in human renal transplantaton. However, it is not as popular as other inhibitors of purine synthesis, such as azathioprine (AZA) and MMF, because MZ has been used mainly in Japan and infrequently in other countries. However, MZ is a more useful immunosuppressive drug than AZA, when it is used in combination with CNI.

Key words child, immunosuppressant, mizoribine, purine metabolism, renal transplantation.

End-stage renal disease is currently considered not to be a lethal disease for children, because of excellent progress in renal replacement therapy, including dialysis therapy and renal transplantation. In particular, renal transplantation is the optimal form of therapy for children and adolescents with end-stage renal disease. There is now over 30 years of accumulated experience with renal transplantation in children.

Progress in histocompatibility matching, immunosuppressive management, peri- and postoperative care, and diagnosis and treatment of rejection have all contributed to improvement of patient survival and graft outcome in pediatric renal transplantation. When histocompatibility differences exist between donor and recipient, it is necessary to modify or suppress the immune response to enable the recipient to accept a graft.

Immunosuppressive therapy, in general, suppress all immune responses, including those to bacteria, fungi, viruses and even malignant tumors. Table 1 shows a classification of main immunosuppressive drugs, which are used for organ transplantation in humans. Currently, pharmacological immunosuppression is safer.

However, the progress of immunosuppressive therapy in renal transplantation needed many years of development.

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History of renal transplantation

In the 1950s when clinical renal transplantation began, sublethal total-body irradiation was employed. The outcome was not satisfactory to patients with end-stage renal disease at all.

In 1959, by using the anticancer drug 6-mercaptopurine (6-MP), Schwartz and Dameshek showed that pharmacologic immunosuppression was possible after transplantation, but clinically limited by the requirement for parenteral administration. Two years later, azathioprine (AZA), an orally absorbed analog of 6-MP, was synthesized in 1961 by Elion *et al*. In 1962, Murray and Calne started the clinical trial of AZA for the prevention of kidney allograft rejection in human, and successfully used it combined with prednisolone for human allograft transplantation.[1]

Operative procedures of renal transplantation was completed in the 1960s. Thereafter, AZA, an inhibitor of purine synthesis, was for two decades the keystone to immunosuppressive therapy in human renal transplantation. However, AZA can not specifically inhibit the de novo pathway of purine synthesis, which is the only pathway of purine synthesis in human lymphocytes. Therefore, AZA is named the first generation inhibitor of purine synthesis. Mizoribine (MZ) and mycophenolate mofetil (MMF) are specific inhibitors of the de novo pathway and they are called second generation inhibitors of purine synthesis.

Table 1 Classification of immunosuppressants

1. Inhibitors of nucleotide synthesis
Alkylating drug
Cyclophosphamide
Inhibitors of purine synthesis
1st generation:azathioprine (AZA)
2nd generation:mizoribine (MZ), mycophenolate mofetil (MMF)
Inhibitors of pyrimidine synthesis
Luflunomidel
2. Calcineurin inhibitors (CNI)
Cyclosporin (CsA)
Tacrolimus (FK506)
3. Blockade of IL-2 signal
Rapamycin (RAPA)
RAPA-RAD
4. Antibody to a surface member of lymphocytes polyclonal antibody
Anti-lymocyte globulin (ALG)
Antithymocyte globulin (ATG)
Monoclonal antibody
Anti CD3: OKT3
Anti I L-2 receptor(CID2 5)
Basiliximab
Daclizumab
5. Others
Glucocorticosteroids
prednisolone
methylprednisolone
A blocker of heat shock protein 70 (HSP70)
15-deoxyspergualin (DSG)

The discovery of cyclosporin (CsA) in 1976 and its application to renal transplantation in 1978 was an important milestone. It is categorized to calcineurin inhibitor (CNI) and gives many benefits on the outcome after renal transplantation, but it has some toxic effects, especially nephrotoxicity. Its use is limited by the marked nephrotoxicity. Another CNI, tacrolimus (FK506), was discovered in 1987. Many clinical data using tacrolimus in organ transplantation showed good outcomes. Tacrolimus has also nephrotoxicity.

To reduce the side-effects of CNI, various immunosuppressive regimens have been recommended. Some immunosuppressive drugs may be combined with a decreased dose of CNI and steroid. Their additive drugs are inhibitors of purine-synthesis (AZA, MZ, MMF), rapamycin (RAPA) and others. Rapamycin is similar to tacrolimus in structure and targets the same binding protein (FK-binding protein, FKBP). However, its mode of action is distinctively different from tacrolimus. Rapamycin inhibits the response of lymphocytes to cytokines, whereas CNI block their production of cytokines. Its major side-effects are thrombocytopenia, leukopenia and hyperlipidemia. Figure 1 summarizes the points of their immunosuppressive effects along the T cell activation after the stimulation by alloantigens.

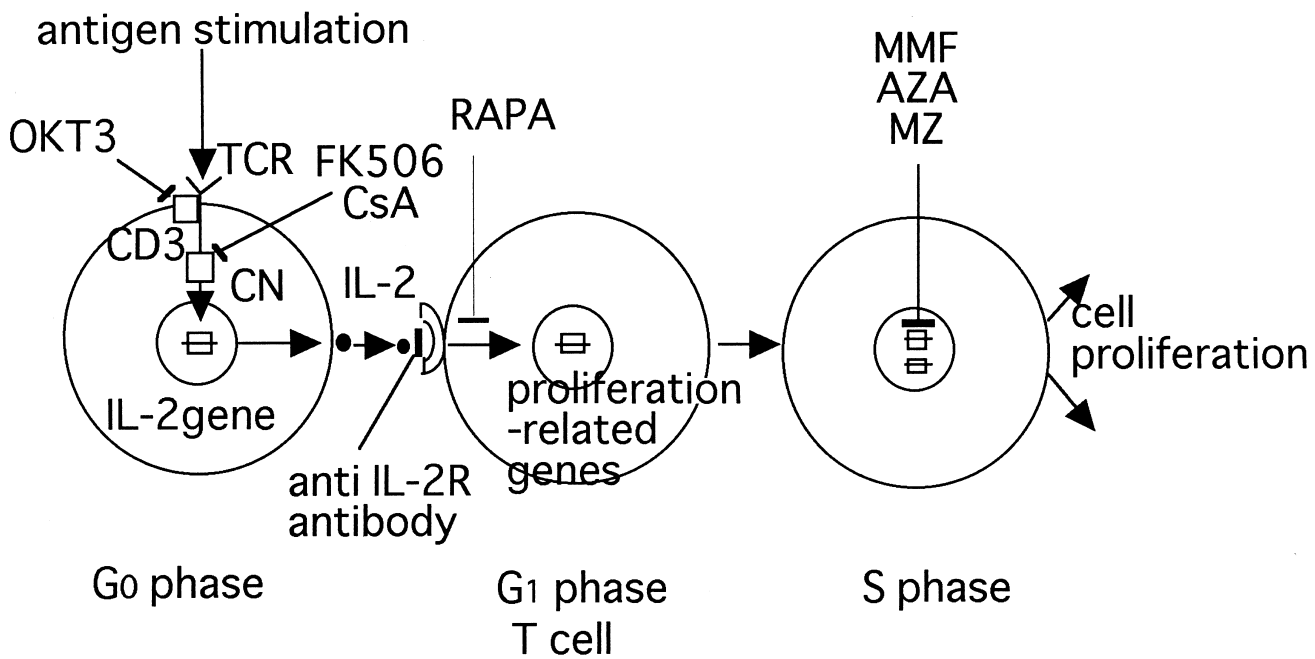

Fig. 1 Immunosuppressants and their mechanism (Otsuka, Hiroi, Senoh). AZA, azathioprine; CN, calcineurin; CsA, cyclosporin; FK056, tacrolimus; MMF, mycophenolate mofetil; MZ, mizoribine; OKT3, anti-CD3 antibody; RAPA, rapamycin.

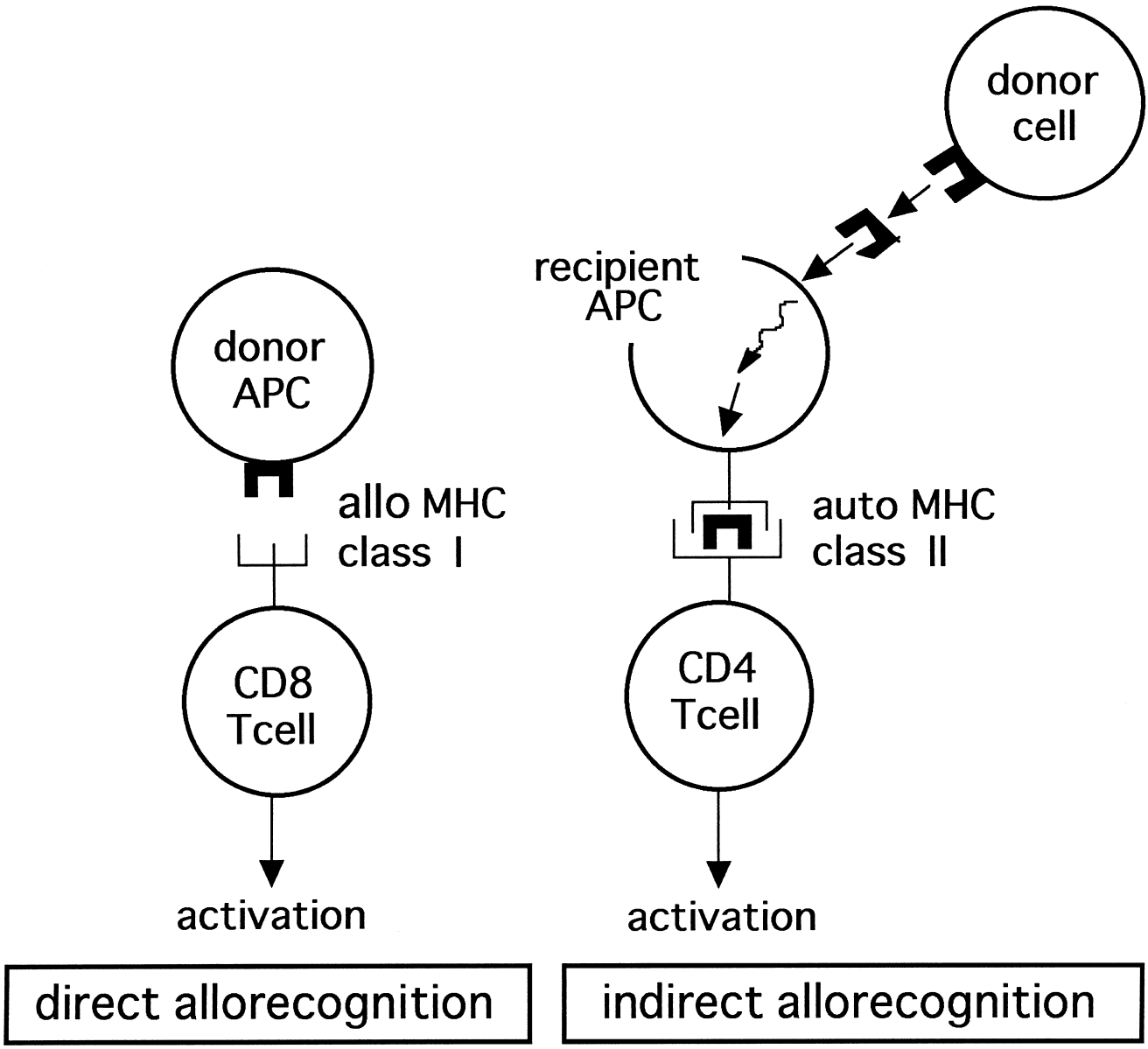

Fig. 2 Pathways of alloantigen recognition by recipient T cell. APC, antigen-presenting cell; MCH, major histocompatibility complex.

Transplantation immunology

Medawar *et al.* showed that sensitized lymphocytes, but not serum could adoptively transfer rejection. The principal target of the immune response is the major histocompatibility complex (MHC) molecule on the graft, and recognition of allo-MHC by recipient T cells is the major event that triggers rejection. T cells of the recipient recognize alloantigen by at least two distinct pathways (Fig. 2).

In the direct pathway, relevant elements of foreign human leukocyte antigen (HLA) molecules are presented by donor antigen presenting cells (APC). This pathway accounts for the cytotoxic $CD8^+$ T cell response, which plays a major role in early allograft rejection. In the indirect pathway of allorecognition, self-APC present processed donor MHC along with self-restriction elements. The $CD4^+$ T-helper cells activated by the indirect pathway initiate additional effector mechanisms of rejection including delayed-type hypersensitivity responses, cell-mediated toxicity, and alloantibody production. Taken together these two pathways of alloantigen recognition constitute a signal, which is one of the three signals proposed for T cell activation.

This interaction between the alloantigen and CD3-T cell receptor (TCR) initiates signal transduction leading to a

cascade of events that results in activation of enzyme calcineurin, a calcium-calmodulin-dependent phosphatase, which plays a key role in the activation of DNA binding factors required for interleukin 2 (IL-2) gene transcription. The second signal for T-cell activation is provided by the interaction between accessory or costimulatory molecule-ligand pairs on APC and T cells. Provision of signal one without signal two induces anergy in T cells, a state of unresponsiveness even with appropriate signals.

The other important function of a costimulatory pathway is prevention of apoptosis or programmed cell death. The costimulatory pathways are multiple and redundant with B-7 and CD28, and CD40 and CD40 ligand among the more important. Signal three is provided by signals which flow from engagement of the cytokine IL-2 of its receptor after IL-2 receptor gene expression and induction of the expression of other cytokines culminating in release of the constitutive inhibition to cell-cycle activation, cell division, and full expression of cyclin function.

Mizoribine and other inhibitors of purine synthesis

Purine is the main material of DNA and RNA. Therefore, the inhibition of purine synthesis causes important effects on cell proliferaton and functions, especially on immune systems including lymphocytes. Figure 3 shows the outline of purine metabolism and the mechanisms of some inhibitors.

Azathioprine, a prodrug of 6-MP, was a first effective drug in clinical renal transplantation in 1962, and was for two decades the keystone to immunosuppressive therapy in humans. It is metabolized to active compounds, 6-MP and then thioisonic monophosphate (TIMP). These act as purine antagonists and impair synthesis of DNA and RNA by blocking synthesis of adenosine monophosphate (AMP) and guanosine monophosphate (GMP), resulting in a blockade of cell proliferation.[2] The drug, 6-MP inhibits an enzyme, hypoxanthine-guanine phosphoribosyltransferase. It is a key enzyme in salvage pathway of purine synthesis, which is a recycle process of degenarative products from nucleic acids. Thioisonic monophosphate can be incorporated directly into nucleic acids and leads to chromosome breaks. The most important side-effects of AZA are dose-related bone marrow toxicity and liver toxicity. Other side-effects include pancreatitis, alopecia, nausea, vomiting and increased risk of infection and neoplasia. Azathioprine has been used as immunosuppressive therapy in human renal transplantation for 40 years, but is now being challenged by the newer generation of more specific inhibitors of de novo purine synthesis, such as MZ and MMF.

Although mycophenolic acid (MPA) was first isolated more than 100 years ago and was found to be a substance

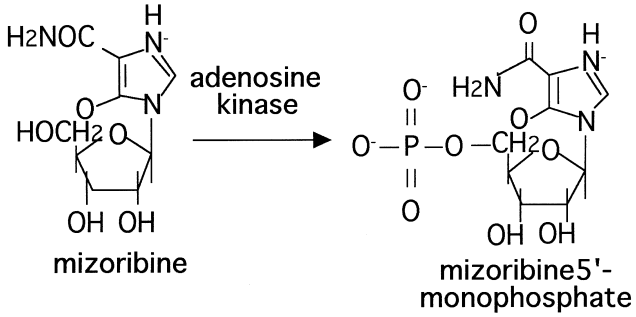

Fig. 3 Structure and activation of mizoribine.

with weak antibacterial activity, its immunosuppressive capacities were recognized much later. Mycophenolate mofetil is a prodrug of MPA. It interrupts the S phase of the cell cycle as AZA. Mycophenolic acid specifically inhibits the rate-limiting enzyme, inosine monophophate (IMP) dehydrogenase, in the de novo pathway of purine biosynthesis. Because T and B cells almost exclusively use the de novo pathway, MPA specifically inhibits the action of these lymphocytes. It also prevents the glycosylation of adhesion molecules that are involved in the attachment and infiltration of lymphocytes. Mycophenolate mofetil may improve long-term results after renal transplantation because early acute rejections have a detrimental influence on late graft survival and because MMF inhibits proliferation of smooth muscle cells in experimental models. There is no nephrotoxicity, hepatotoxicity, or neurotoxicity in MMF-treated patients. The side-effect profile of MMF includes gastrointestinal discomfort, diarrhea, leukopenia and thrombocytopenia.[3]

Another potent inhibitor of IMP dehydrogenase is MZ, 4-carbamoyl-1-β-D-ribofurano-syhmidazolium-5-olate (Fig. 3), which was isolated from the culuture media of *Eupenicillium brefeldianum* in 1974 in Japan. This agent is an imidazole nucleoside and has immunosuppressive effects *in vivo*. Mizoribine passes a cell membrane according to the gradient of its concentration. Then, MZ is phosphorylated by adenosine kinase (Fig. 3) and converted into its active form, MZ-5'-phosphate (MZ-5P). This activated form affects the synthesis of nucleic acids by inhibition of IMP dehydrogenase or both IMP dehydrogenase and GMP synthetase, (Fig. 4) the latter is not inhibited by MPA or MMF. The immunosuppressive effect of MZ has been suggested to be due to inhibition of DNA synthesis in the S stage of the cell cycle.[4] Mizoribine has been approved in Japan and used for maintenance immunosuppressive therapy after renal transplantation, and for lupus nephritis and rheumatoid arthritis. It has been shown to be less toxic than AZA. Because of a predominant renal metabolism, overimmunosuppression and adverse effects, it should be avoided by adapting the dose to the glomerular filtration rate and by monitoring MZ plasma trough level.

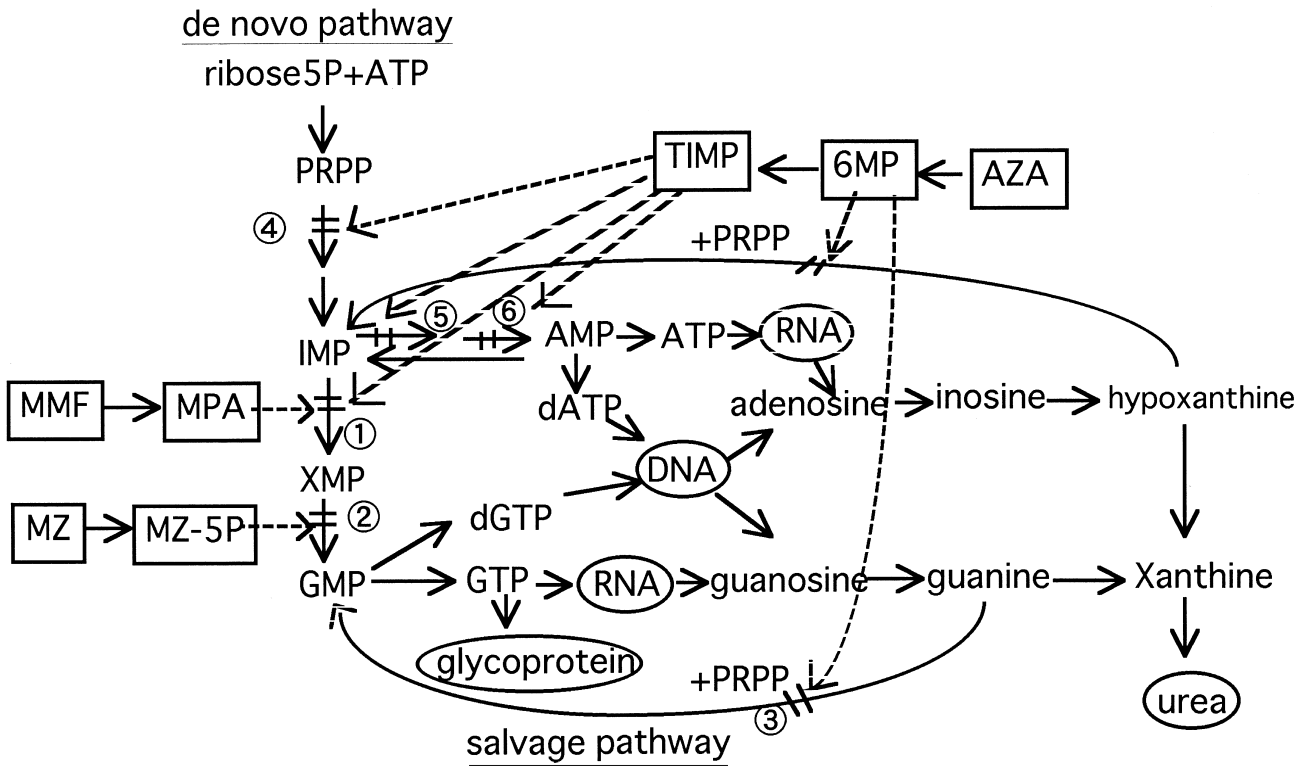

Fig. 4 Pathway of purine metabolism. AZA, azathioprine; IMP, inosine monophosphate; 6MP, 6-mercaptopurine; MZ, mizoribine; MZ-50, MZ-5'monophosphate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PRPP, phosphoribosyl pyrophosphate; TIMP, thioisonic monophosphate; XMP, xanthine monophosphate.

For now, at least in transplantation, AZA has widely been replaced by MMF or MZ. Most studies on MZ come from Japan, so, MMF is more popular worldwide than MZ. However, the mechanism of immunosuppressive action of MZ is almost identical with MMF. However, there is a significant difference on administration dose, which is usually 2–3 g per day (almost 50 mg/kg per day) in MMF and is much smaller, 2–4 mg/kg per day. The recommended dose of MZ is (1–) 2 mg/kg per day. Mizoribine is not metabolized and 100% of absorbed dose exists as the active form until excreted from urine, however, MMF is rapidly metabolized into inactive form through liver, and active MMF is usually only 2–3% of absorbed MMF. A much higher dose of MZ could be administered to obtain a more potent immunosuppressive effect.[5]

Results of human renal transplantation

There are only a few English papers about MZ therapy in human renal transplantation, because this agent was discovered and is mainly used in Japan.[5–9]

Tanabe *et al*.[5] compared two immunosuppressive protocols in renal transplantation. One is MZ therapy combined with methlprednisolone (MPL) and CsA (MZ group), another is AZA therapy combined with MPL and CsA (AZA group). Administration of AZA at a dose of 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. Administration of MZ, at a dose of 4–5 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. The dose schedule of CsA and MPL is the same in two groups. Administration of MLP was started on the day of transplantation at a dose of 125–500 mg/kg and reduced to a maintenance dose of 8 mg/day by the fourth month. Oral administration of CsA, 8–10 mg/kg per day, was started 2 days before transplantation.

Between January 1988 and April 1989, 116 patients were entered into the prospective long-term (10 years) trial and allocated into two groups at random. Both groups (MZ group and AZA group) consisted of 58 patients. There is no significant difference between the two groups in terms of recipient sex, donor sex, donor source (such as living and cadaveric donors), donor age, human leukocyte antigen-locus A, locus B, locus DR (HLA-AB) DR mismatches, and blood group ABO-compatibility.

Table 2 Protocol for immunosuppressive therapy after renal transplantation in children

	Cyclosporin	Methylprednisolone (mg/m^2)	Mizoribine (mg/m^2)	Anti-lymphocyte globulin (mg/m^2)
– 1 day	8–12 mg/kg	10	50	
Transplantation Trough level (ng/mL)		500	100	500
Week 1	200	40	100	500
Week 2	200	30	100	500
Week 3	200	20	100	
Week 4	200	16	100	
Week 5	200	12	100	
Week 6	200	10	100	
Week 7	200	8	100	
Week 8	100	6	100	
Week 9	100	4	100	
Alternate-day therapy, then withdrawal was attempted				

In the MZ group, 1-, 5- and 9-year-old patients survival rate was 98, 93, and 88%, respectively, and in the AZA group, it was 97, 95, and 83%, respectively. In the MZ group, 1-, 5- and 9-year-old graft-survival rate was 90, 73, and 58%, respectively, and in the AZA group, it was 93, 73, and 52%, respectively. There was no significant difference between the two groups in terms of the graft and patient survival. The incidence of acute rejection was 56.9% in both groups. However, since MZ showed much fewer adverse effects, no patients treated with MZ convered to AZA, whereas 27.6% of the patients treated with AZA were forced to change to MZ for adverse effects.

Although there was no significant difference in terms of patient and graft survival and graft survival and the incidence of rejection episodes, MZ showed much fewer adverse effects than AZA. Therefore, MZ seems to be a much more useful immunosuppressive agent for renal transplantation than AZA. Another new immunosuppressive drug, MMF, was proved to be much more effective than AZA. It has almost an identical mechanism of action with MZ, which inhibits IMP dehydrogenase, a key enzyme of the de novo pathway of purine synthesis. They speculated a significant difference of administration dose might cause this difference, the dose of MMF is usually 2–3 g per day, which is almost 50 mg/kg per day, whereas the dose of MZ was much smaller, 4 mg/kg per day.

The Japanese pediatric renal transplantation clinical study group conducted a multicenter prospective study, in which we attempted to reduce and then discontinue steroid administration in combination with another three immunosuppressive drugs, CsA, MZ and anti-lymphocyte globurin (ALG).[6] A total of 52 children (51 living-related donor transplants and one cadaver donor transplant), of whom the epiphysis was not closed yet, were included in the study and underwent renal transplantation at four hospitals between 1989 and 1993. Thirty children received continuous ambulatory peritoneal dialysis, 20 received hemodialysis before transplantation and two were transplanted preemptively.

The living-related donor was the HLA one haplo-identical parent in all cases.

The immunosuppressive therapy was started with CsA, MZ, MPL and ALG. Methlprednisolone was reduced to alternate-day treatment more than 6 months after transplantation, and withdrawn, if possible. Our protocol for immunosuppressive therapy after renal transplantation in children is summarized in Table 2. The daily dose of CsA was divided into two doses. The whole-blood trough level of CsA was maintained at 200 ng/mL, as determined by monoclonal antibody radioimmunoassay or fluorescent polarization immunoassay, thereafter reduced to 100 ng/mL (maintenance level) at the seventh postoperative week. Recently, we adjusted the whole-blood trough level of CsA at 250–300 ng/mL for the first 4 weeks after renal transplantation. Methlprednisolone was administered 500 mg/m^2 intravenously during the operation and then a daily dose of 40 mg/m^2 orally the next day after operation, which was gradually reduced every week. When the dose was decreased to 4 mg/m^2, alternate-day treatment was started, but this was discontinued in patients with stable graft function after informed consent was obtained. Mizoribine was started on the day before transplantation and continued at a dose of 100 mg/m^2 orally postoperatively. For 2 weeks, ALG was administered 500 mg/m^2 intravenously.

After renal transplantation, patients were followed-up for 4 years on average. None of the patients died during this period, and graft survived in 49 cases, which yields a patient survival rate of 100% and a graft survival of 94.2%. Steroid withdrawal was successful in seven patients (13.5%). The graft function was lost 15–29 months after transplantation in three of these patients. The causes of graft loss were acute rejection in two cases and recurrence of crescentic glomerulonephritis in one. At the last observation, 20 patients were receiving MPL daily and 22 were receiving MPL on alterate days.

Concering graft function, creatinine clearance was 50 mL/min per $1.73m^2$ or higher in 43 patients, 25–50 mL/min per

1.73m^2 in four patients, and 25 mL/min pre m^2 or less in two patients.

Acute rejection was noted 67 times in 39 patients, including the cases of late onset. The first episodes of acute rejection was observed within 1 month in 19 patients (36.5%), within 3 months in 34 patients (65.4%), and within 6 months in 36 patients (69.2%). Alternate-day treatment with MPL was attempted 37 times in 33 patients. However, clinical acute rejection occurred in only one patient 61 months after alternate-day treatment was started. The patient with acute rejection had stable graft function subsequently. Chronic rejection developed in three patients from 3 to 41 months after the start of alternate-day treatment. The dose alternate-day MPL at the onset of rejection was 5.3 ± 1.5 mg (5.5 ± 1.7 mg/m^2) per day, which was equal of that (5.5 ± 2.2 mg (5.0 ± 2.1 mg/m^2) per day) given to the 19 patients who did not develop rejection 32.7 ± 13.3 months after the start of alternate-day treatment.

As for the patients in whom withdrawal of MPL was possible, MPL was discontinued 38.3 ± 9.3 months after transplantation, including the period of alternate-day treatment 12.9 ± 10.4 (2–30) months at a dose of 3.6 ± 1.3 mg (1.9–6.3 mg/m^2) per day. At the time of the report, an average of 16.7 months have passed since discontinuance of MPL, but no findings indicative of rejection were observed. Withdrawal of MPL was attempted 10 times in nine patients. Acute rejection was noted in three patients 1–13 months after withdrawal. Daily administration of MPL was resumed in two patients after they were administered a high dose of MPL by bolus injection, and graft function remained favorable. One patient experienced subclinical rejection 6 months after the initiation of alternate-day treatment with MPL, and acute rejection 3 months after discontinuance of MPL, but graft function stabilized once treatment with MPL at the maintenance dose in combination with AZA was resumed. In the patients who developed acute rejection after withdrawal of NTL, no significant differences were noted from patients in whom withdrawal of MPL was possible, in terms of the number of acute rejection episodes, alternate-day treatment duration, MPL dosage before withdrawal and time elapsed after transplantation.

Infectious diseases attributed to immunosuppressive therapy included six cases of cytomegalovirus (CMV) infection which occurred 5–10 weeks after transplantation.

The condition developed into pneumonia in one patient. Five of these six patients had shown acute rejection within 1 month after transplantation. The other patient with CMV infection, one patient with herpes zoster (second postoperative week), and three patients with labial herpes (more than 1 year postoperatively) did not present acute rejection within 1 month after transplantation.

Neuroblastoma and malignant lymphoma were noted in one patient each. At the time of this report, surgical therapy and chemotherapy have been completed for the former and the latter is under chemotherapy. The graft is functioning in both patients.

Persistent hepatic damage, as indicated by serum alanine aminotransferase and serum aspartate aminotransferase levels of 50 U/L or higher for more than 4 months, was noted in only one patient who had hepatitis C.

Since MZ has fewer adverse effects than AZA and has synergic actions with CsA, MZ has been used in immunosuppressive therapy combined with CsA after renal transplantation in recent years.

According to statistical data on immunosuppressive therapy, excluding steroids, for both children and adults compiled by the Japan Society for Transplantation, the 10-year graft survival rates of grafts from living donors using CsA and AZA (339 patients) and CsA and MZ (114 patients) were 65.1% and 72.8%, respectively, while those of grafts from cadaver donors using CsA and AZA (96 patients) and CSA and MZ (87 patients) were 60.2% and 71.0%, respectively, indicating the clinical efficacy of MZ.

Conclusion

Mizoribine is an effective immunosuppressive drug in human renal transplantaton. However, it is not as popular as other inhibitors of purine synthesis, such as AZA and MAW, because MZ has been used mainly in Japan and not so much used in other countries. However, MZ is a more useful immunosuppressive drug than AZA, when it is used in combination with CNI (CsA, tacrolimus). If MZ is used in a higher dosage, it is expected to be as effective as MMF, because both drugs have almost the same mechanism of action. Recently, a textbook and reviews refered MZ briefly as an useful immunosuppressive drug in human renal transplantation.[2,10,11]

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