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ORIGINAL ARTICLE

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Long-term use of mizoribine in rheumatoid arthritis patients on hemodialysis

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Abstract Small doses of mizoribine (MZR) were administered to five rheumatoid arthritis (RA) patients on hemodialysis (HD). A maintenance dose of 25 mg or less was administered either once per day or once following HD. The Lansbury activity index improved in all patients. The blood concentrations of MZR before and after HD were 0.33–1.79 μg/ml and 0–0.93 μg/ml, respectively. Hence, the rate of elimination by HD ranged from 50.3% to 83.4%. As far as side effects were concerned, alopecia was seen in two patients, and one patient developed shingles. However, the severity of these symptoms was mild and, after discontinuing or reducing the dose of MZR for a certain period of time, we were able to continue its administration. These findings suggest that the long-term administration of MZR is a useful treatment for RA patients on HD.

Key words Disease-modifying antirheumatic drug · Hemodialysis · Mizoribine · Rheumatoid arthritis

Introduction

There are many problems associated with the administration of disease-modifying antirheumatic drugs (DMARDs) to rheumatoid arthritis (RA) patients on hemodialysis (HD). In this study, we obtained favorable results when mizoribine (MZR) was administered for more than 1 year.

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Materials and methods

The subjects were five RA patients (one man and four women), whose ages at the start of drug administration ranged from 51 to 72 years. All patients satisfied the American College of Rheumatology (ACR) criteria of symmetrical swelling or pain in at least three joints of the hand or fingers, and morning stiffness lasting at least 1 hour. These symptoms were present for at least 2 months. Three patients had had RA for less than 1 year, and the remaining two patients had had the disease for more than 10 years. The three patients who had had RA for less than 1 year developed RA following HD, and the two patients who had had RA for more than 10 years were put on HD after developing renal failure. Three patients had stage-1 RA, one had stage-3 RA, and one had stage-4 RA. In addition, one patient had class-1 RA, two had class-2 RA, and two had class-3 RA (Table 1). As far as the use of DMARDs was concerned, MZR was the first DMARD used for the patients who had had RA for less than 1 year. The two patients who had had RA for more than 10 years had taken many DMARDs prior to MZR. The disease activities of RA were evaluated by erythrocyte sedimentation rate (ESR), Lansbury activity index (LAI),[1] and rheumatoid factor (RF). MZR doses were determined by analyzing its blood concentration, clinical symptoms, and side effects. Since no pathological examinations were conducted, details concerning the nephropathy that had led to hemodialysis were not available. HD was performed three times a week, with each treatment lasting 4–4.5 h, while using dialyzers [(PS 1.3, PS 1.0 (KAWASUMI, Tokyo, Japan), or CLEE 1.2 (TERUMO, Tokyo, Japan)]. None of the patients was able to urinate without assistance.

Results

A maintenance dose of 25 mg or less of MZR was administered once per day or once following HD. A nonsteroidal anti-inflammatory drug (NSAID) was coadministered to

Table 1. Data on the five patients

	Case				
	1	2	3	4	5
Age (years)	72	58	51	70	51
Sex	F	F	M	F	F
RA					
Stage	I	I	I	IV	III
Class	1	2	2	3	3
Duration[a]					
RA	2M	7M	2M	30M	12Y
HD	9M	15Y	18Y	7Y	11M
Follow-up	4Y	3Y6M	2Y9M	1Y1M	1Y
Drugs (dose)					
MZR	25 mg/day	25 mg/HD	12.5 mg/HD	25 mg/HD	25 mg/HD
NSAIDs	(+)	(+)	(−)	(+)	(−)
PSL	(−)	(−)	5 mg/day	2.5 mg/day	5 mg/day
Before the administration of MZR					
LAI (%)	118	67	66	87	39
ESR (mm/h)	>140	89	140	77	41
RF	(−)	(−)	(±)	(+)	(+)
Present time					
LAI (%)	25	33	38	56	30
ESR (mm/h)	68	41	5	39	25
RF	(±)	(±)	(−)	(+)	(+)
Concentration of serum MZR					
Pre-HD (μg/ml)	1.55 ± 0.19	1.16 ± 0.14	0.36 ± 0.03	1.17 ± 0.25	0.83 ± 0.25
Post-HD (μg/ml)	0.77 ± 0.12	0.20 ± 0.09	0.11 ± 0.03	0.21 ± 0.10	0.33 ± 0.12
Elimination rate (%)	50.3	83.4	69.4	83.1	62.2
Side effects	alopecia	alopecia shingles	(−)	(−)	(−)

[a] M, months; Y, years
RA, rheumatoid arthritis; HD, hemodialysis; MZR, mizoribine; NSAIDs, nonsteroidal anti-inflammatory drugs; PSL, prednisolone; LAI, Lansbury activity index; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

three patients. A steroid drug was administered to three patients (Table 1). LAI scores showed improvements in every patient 2–3 months after the start of MZR administration (Fig. 1). Similar degrees of improvement were seen in ESR and CRP (Fig. 2). In addition, RFs were not exacerbated following MZR administration in any patient. Although no severe side effects such as hepatic dysfunction or bone-marrow hypofunction were observed, two patients developed alopecia. In one of these patients, the alopecia was alleviated by temporarily discontinuing the use of the drug, and in the other patient, a dose reduction was sufficient to alleviate the condition. Furthermore, one patient had shingles, but this condition was alleviated by temporarily discontinuing the use of the drug. In these patients, MZR administration was later resumed, and no other notable problems have since been detected. At a dose of 25 mg/day, the blood concentration of MZR ranged from 1.27 to 1.79 μg/ml before HD, and from 0.57 to 0.93 μg/ml after HD. At a dose of 25 mg/HD, the blood concentration of MZR ranged from 0.58 to 1.29 μg/ml before HD and from 0 to 0.49 μg/ml after HD, and at a dose of 12.5 mg/HD, it ranged from 0.33 to 0.40 μg/ml before HD and from 0.09 to 0.14 μg/ml after HD. Hence, the rate of elimination by HD ranged from 50.3% to 83.4%. Nevertheless, the blood concentration of MZR did not exceed 2 μg/ml in any patient (Fig. 3).

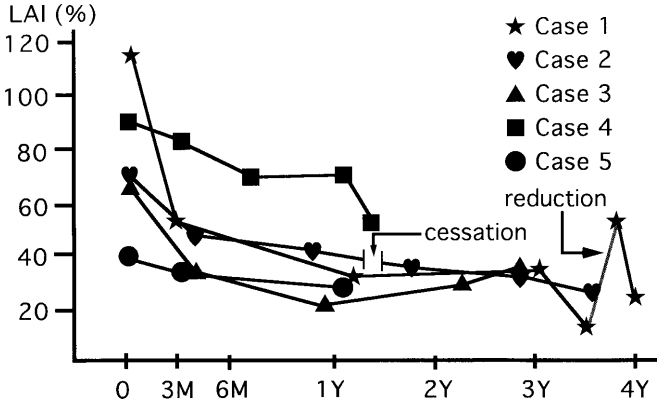

Fig. 1. Lansbury activity index (*LAI*)

Case report

A 72-year-old woman was put on HD in April 1995 owing to chronic renal failure. Starting in December 1995, arthritis appeared in both of her hands and her fingers. She was first examined in January 1996. At the initial examination, arthritis was found to be present in both wrists, metacarpo-

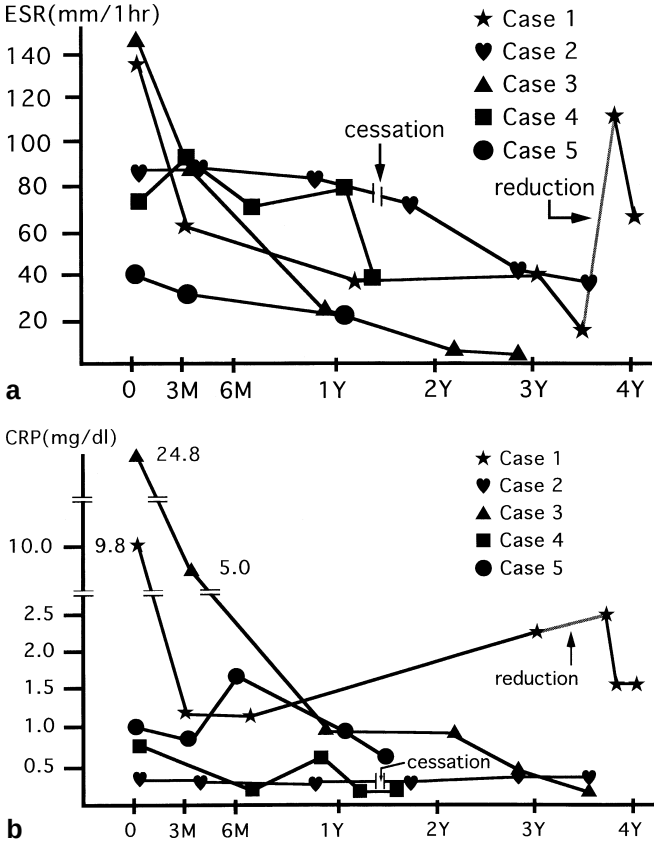

Fig. 2. **a** Erythrocyte sedimentation rate (*ESR*). **b** C-reactive protein (*CRP*)

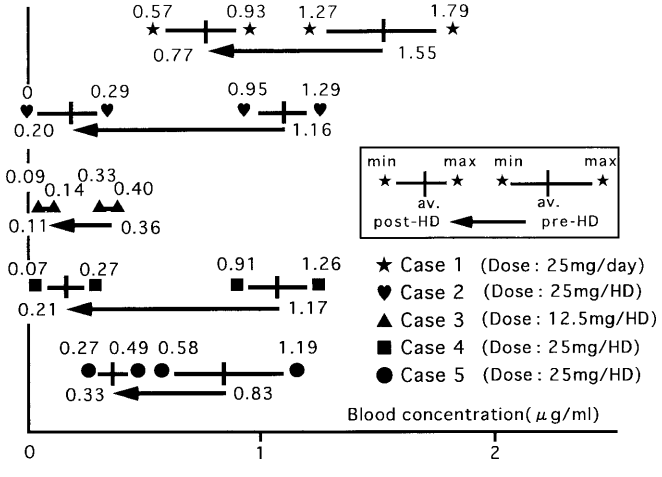

Fig. 3. Blood concentration of mizoribine before and after hemodialysis

phalangeal (MCP) joints, and proximal interphalangeal (PIP) joints in a symmetrical manner, and morning stiffness lasted for 12 h. The results of various tests showed that CRP and ESR were elevated to 9.8 mg/dl and 145 mm/h, respectively. However, the patient was RF-negative, and a radiographic examination showed no signs of joint destruction. According to ACR criteria, the patient was diagnosed as

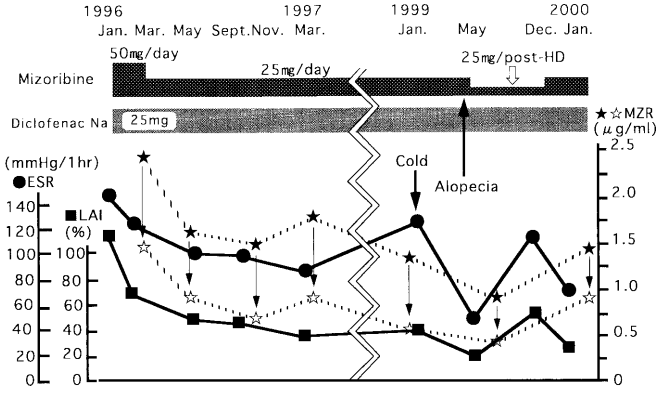

Fig. 4. Clinical course of case 1, who was a 72-year-old female with rheumatoid arthritis (RA) (stage I, class 1). HD was started in March 1995, and RA started in July 1995. *Solid stars*, blood concentration of MZR before HD; *open stars*, blood concentration of MZR after HD. *HD*, hemodialysis; *MZR*, mizoribine; *LAI*, Lansbury activity index; *ESR*, erythrocyte sedimentation rate

having rheumatoid arthritis (stage 1 and class 1). As the LAI was high at 118%, the use of a DMARD was considered. Because the patient was on HD, only 50 mg/day of MZR was administered initially, but the blood concentration of this drug was high before and after HD (2.41 and 1.35 μg/ml, respectively). As we were concerned about side effects, the drug dose was reduced to 25 mg/day. Thereafter, the blood concentration of MZR generally stabilized at 1.53–1.73 μg/ml before HD, and 0.60–0.87 μg/ml after HD. The average elimination rate was 50.3%. Improvements in clinical symptoms were noticeable approximately 2 months after the start of drug administration, and symptoms associated with arthritis disappeared in approximately 1 year and 6 months after the start of drug administration. After 3 years and 3 months of drug treatment, ESR decreased to 43 mm/h, and LAI improved to 18%. Nonetheless, the patient began to lose her hair at this time. Accordingly, 25 mg MZR was administered after HD starting in May 1999, and the patient's alopecia was alleviated, but RA activity gradually increased. Administration of 25 mg/day MZR was restarted in December 1999 and RA activity subsided. No alopecia has been detected since then (Fig. 4).

Discussion

There are many problems associated with the selection and administration of drugs in terms of their effectiveness and safety in RA patients on HD. In particular, when drugs that are excreted through the kidneys are to be administered, those that can easily be eliminated by HD are used in smaller doses, as the kidneys cannot excrete them naturally. Bucillamine, D-penicillamine, and Actarit are among these drugs, and there have been reports that RA was responsive to them in small doses.[2–5] Furthermore, one report documented that when a small amount of methotrexate (2.5 mg/week) was administered to RA patients on HD, a severe side effect (acute pancytopenia) developed.[6] Therefore,

caution should be exercised when administering DMARDs or immunosuppressive agents to RA patients on HD.

MZR is a purine metabolism antagonist that suppresses humoral and cellular immunity and the proliferation of lymphocytes. This drug is widely used to suppress rejection following renal transplantation, and to suppress the immune system in RA patients in Japan. Since MZR is excreted via the kidney, renal function is important. We therefore started administration at a low dose, and determined the appropriate dose by monitoring the blood concentration. In patients with normal renal function, the blood concentration of MZR does not exceed 2 μg/ml, and the incidence of side effects is low.[7] When MZR is administered to patients following renal transplantation, the blood concentration sometimes exceeds 4 μg/ml, thus increasing the risk of severe side effects such as bone-marrow dysfunction. It has also been reported that less clinically significant side effects, such as alopecia, have been observed when the blood concentration of this drug was 2.73 μg/ml.[8] As a result, we monitored the blood concentration of MZR to keep it below 2 μg/ml.

Initially, we administered MZR at a dose of 50 mg/day, then the blood concentration was above 2 μg/ml at 2.41 μg/ml. As a result, the dose was reduced to 25 mg/day, and the blood concentration fell to 1.27–1.79 μg/ml. Subsequently, less than 25 mg MZR was administered once per day or once following HD. The blood concentration of MZR did not exceed 2 μg/ml, and the patients experienced no severe side effects such as bone-marrow dysfunction. However, two patients developed a mild side effect (alopecia). In one of these patients, the alopecia was alleviated by temporarily discontinuing the use of the drug, and in the other patient a dose reduction was sufficient to alleviate the condition. Currently, MZR is being administered to these patients with no problems.

RA is a chronic disease, and its treatment requires a long period of time. Therefore, the effectiveness and safety of the long-term administration of DMARDs and immunosuppressive agents are important issues. The subjects of the present study were five patients who received a DMARD for more than 1 year. Improvements in symptoms in every patient were seen with less than 25 mg/day MZR, and despite the fact that MZR had been administered for more than 4 years in one patient, the symptoms remained favorable. It is difficult to compare the results of different studies in a simple way, but the results of the present study (less than 25 mg/day MZR) were more favorable than those of studies in which 150–300 mg/day MZR was administered to RA patients without nephropathy (improvement rate 50%–60%).[9,10] There have been no studies of the lowest possible level of MZR and its effectiveness in the treatment of RA, but in one study in which MZR was administered following kidney transplantation, when the lower level of MZR dropped below certain levels its immunosuppressive effects decreased rapidly.[8] In the present cases, the blood concentration of MZR before HD was maintained to some degree, which enhanced the clinical effects.

The relationship between the blood concentration of MZR and the side effects was also analyzed. In our patients, the blood concentration of this drug was kept below 2 μg/ml, and the rate of elimination by HD ranged from 50% to 80%. These figures are similar to those (50%–60%) obtained in previous studies,[5,11] and were maintained for as long as 4 years of administration. These findings show that MZR is less likely to accumulate in the body, suggesting that this drug could be used safely in the future. Therefore, MZR is a useful drug for RA patients on HD, and can safely be administered for an extended period.

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