Mod Rheumatol (2006) 16:214–219
DOI 10.1007/s10165-006-0487-1

ORIGINAL ARTICLE

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Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study

Received: February 7, 2006 / Accepted: April 27, 2006

Abstract This report documents the results of a study performed to examine clinical use of mizoribine (MZR), using data from a large-scale prospective cohort study, IORRA (Institute of Rheumatology Rheumatoid Arthritis). The number of patients with RA entered in this study from October 2000 through October 2003 was 6238. Three hundred and six patients (4.9%) received MZR therapy. Mizoribine users who were taking methotrexate (MTX) (MTX–MZR group, $n = 94$) and over 70 years of age (elderly group, $n = 45$) were collected. Cumulative retention rates of MZR were calculated by Kaplan–Meier analysis. Median drug survival of MZR was 28 months for the poor responders to MTX and 43 months for the poor responders to MZR, with no significant difference between these groups. Cumulative retention rate of MZR in the elderly group did not show a significant difference compared to that in patients aged under 70 years. Ten patients (10.6%) in the MTX–MZR group and 10 patients (22.2%) in the elderly group experienced adverse effects of MZR. None of these adverse effects was serious. This study indicated that, although MZR has not been frequently prescribed for RA patients, it may be useful and relatively safe for patients who are poor responders to MTX as an additional regimen to MTX therapy as well as for elderly patients.

Key words Cohort study · Disease-modifying antirheumatic drug (DMARD) · Methotrexate (MTX) · Mizoribine (MZR) · Rheumatoid arthritis (RA)

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Introduction

Recent strategies in the treatment of rheumatoid arthritis (RA) have recommended that treatment with disease-modifying antirheumatic drugs (DMARDs) should be aggressively initiated at an early stage of disease to improve prognosis.[1,2] Approximately ten types of oral DMARDs are currently available in Japan, and of these, methotrexate (MTX) is commonly used for patients with RA.[3,4] Methotrexate, an inhibitor of folic acid metabolism with potent immunosuppressive activity, is currently approved in Japan only for "use in patients who have failed to respond to at least one DMARD." Nevertheless, dozens of years of usage and experience have proven the safety and efficacy of MTX. Among DMARDs approved in Japan, MTX is now being prescribed as first-line therapy in many cases of RA.[3,5] The rate of treatment continuation for patients taking MTX has been higher than for those taking other DMARDs. However, poor responders to MTX are often encountered,[3,4] and many physicians are unsure how to treat such patients.

Mizoribine (MZR) is an immunosuppressant that inhibits its nucleic acid metabolism and is a relatively safe DMARD.[6,7] Mizoribine was discovered in the culture broth of *Eupenicillium brefeldianum* isolated from soil from the island of Hachijo, Japan. This agent inhibits inosine monophosphate dehydrogenase, a rate-limiting enzyme in the de novo pathway of nucleic acid synthesis,[8,9] thereby inhibiting lymphocyte proliferation. In 1984, MZR was first approved for the treatment of graft rejection after kidney transplantation. Subsequently, it was also approved for the treatment of other diseases including lupus nephritis, RA, and primary nephrotic syndrome. It is currently marketed in China and Korea as well as in Japan. Two double-blind controlled clinical trials[7,10] have demonstrated the efficacy of MZR in the treatment of rheumatoid arthritis. Mizoribine is generally considered as a drug of second choice among DMARDs, but based on its mechanism of action and safety, it is often used in combination with other DMARDs.

This report documents the results of a study performed to analyze clinical use of MZR, including use in combina-

tion with MTX, using data from a prospective observational cohort study, IORRA (Institute of Rheumatology Rheumatoid Arthritis), that began in October 2000 at the Institute of Rheumatology, Tokyo Women's Medical University.[11,12] For this cohort, not only physician's assessments, patient's assessments, and laboratory data but also various types of patient information including disability index, disease activity, comorbidity, and medications used are collected from patient questionnaire sheets from approximately 5000 RA patients every 6 months.

Subjects and methods

Patients in the analysis were selected from among 6238 RA patients who had participated at least once during a three-year period from October 2000 to October 2003 in the prospective observational cohort study, IORRA, conducted in our institution. Three hundred and six patients (4.9%) received MZR therapy on the basis of IORRA. All patients were of Japanese origin and all had been diagnosed with RA according to the 1987 classification criteria of the American College of Rheumatology (formerly, the American Rheumatism Association)[13] during their clinical course.

Of the 306 MZR users, MZR users who were taking MTX (MTX–MZR group, $n = 94$) and over 70 years of age (elderly group, $n = 45$) were collected. These patients were carefully checked for regimens used based on medical records, and analyzed for cumulative retention rates of MZR using the Kaplan–Meier method. The MTX–MZR group was classified into the following five groups according to treatment regimen: group A, MZR added to MTX therapy for poor responders to MTX; group B, MTX added to MZR therapy for poor responders to MZR; group C, switched from MTX to MZR; group D, switched from MZR to MTX; and group E, started MZR and MTX concurrently. In addition, for each DMARD the mean age of RA patients at the time of use was calculated based on the IORRA database. Kaplan–Meier analysis was also used to compare the cumulative retention rate of MZR in patients aged over 70 years (elderly group) with that in those aged under 70 years. The log-rank test was performed to compare the survival curves of each group. The relevant MZR users were also examined for occurrence of adverse reactions, which were collected from the patients' self-report questionnaires, IORRA.

Results

Of the 6238 RA patients, 306 (4.9%) received MZR therapy during the 3-year period from October 2000 to October 2003. Among these patients, 94 (30.7%) were taking MTX (MTX–MZR group), who were classified as follows: 50 patients in group A, 24 in group B, 7 in group C, 4 in group D, and 9 in group E. Median drug survival of MZR was 28 months in group A, 56 months in group B, 15 months in group C, 2 months in group D, and 13 months in group E. Cumulative retention rate of MZR was thus highest in group B, poor responders to MZR for whom MTX was added, but lowest in group D, the poor responders to MZR switched to MTX (Fig. 1). In addition, data were analyzed for the combination of group A and group C patients whose cumulative retention rate of MZR may have been due to the efficacy of MZR (i.e., poor responders to MTX), as well as for the combination of group B and group D patients, the poor responders to MZR. Median drug survival of MZR was 28 months in group A and group C combined (poor responders to MTX) and 43 months in group B and group D combined (poor responders to MZR) (Fig. 2). There was no significant difference between these two groups, as determined by the log-rank test ($P = 0.33$).

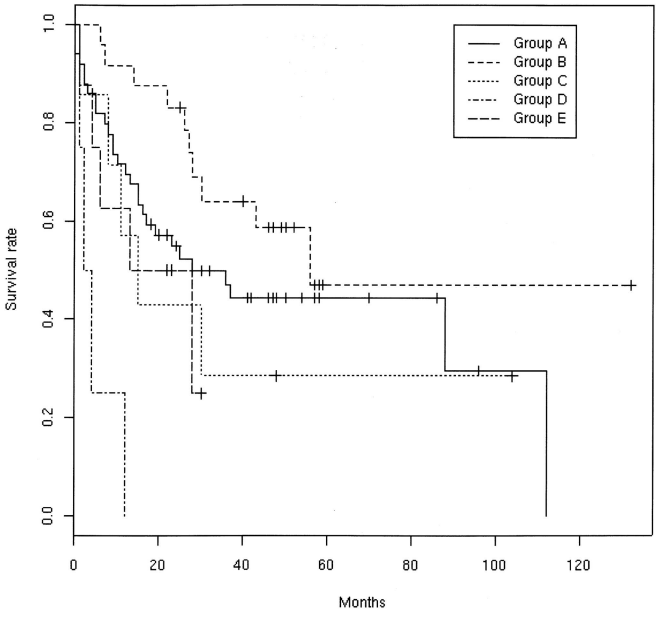

Fig. 1. Survival analysis of Mizoribine (MZR) treatment continuation in the five methotrexate (MTX)–MZR combination therapy groups. Cumulative retention rate of MZR was highest in group B, the poor responders to MZR for whom MTX was added, but lowest in group D, the poor responders to MZR switched to MTX

The mean age of MZR users was 58.8 years, which was the highest among DMARDs, and MZR had one of the highest user rates (17.4%) for elderly patients over 70 years of age (Table 1). Median drug survivals of MZR were 18 months and 30 months in patients aged over 70 years (elderly group) and those aged under 70 years, respectively, without significant difference between these two groups as determined by the log-rank test ($P = 0.39$) (Fig. 3).

Adverse reactions reported by patients and regarded as related to MZR occurred in 37 (12.2%) of 304 patients treated during the 3-year study period (Table 2). The adverse reactions led to withdrawal of the drug in 15 patients (4.9%) (Table 2). Of 94 patients in the MTX–MZR group, 10 (10.6%) experienced adverse reactions. These adverse reactions included stomatitis in 4 patients, eczema/urticaria in 2, and glossitis, herpes zoster, heartburn, and headache in 1 patient each, and adverse reactions leading to discontinuation of the drug were observed in 5 of these patients. There

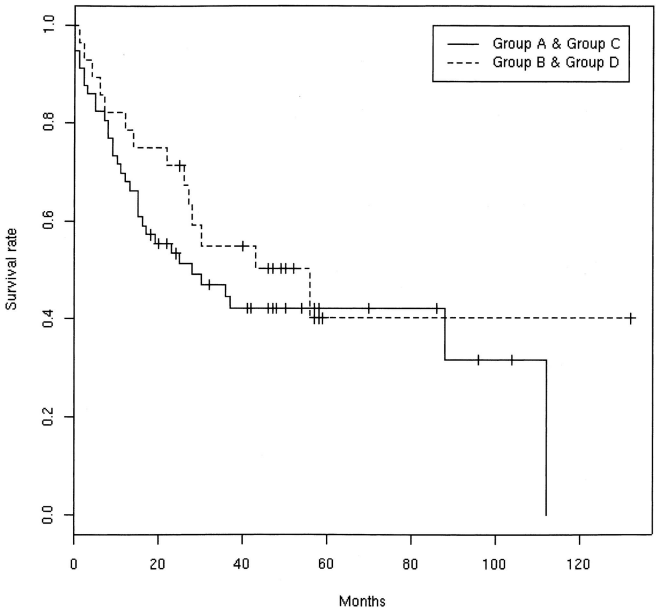

Fig. 2. Survival analysis of MZR treatment continuation in the groups of poor responders to MTX (groups A and C) and MZR (groups B and D). Median drug survival of MZR was 28 months for the poor responders to MTX and 43 months for the poor responders to MZR. There was no significant difference between these two groups, as determined by the log-rank test ($P = 0.33$)

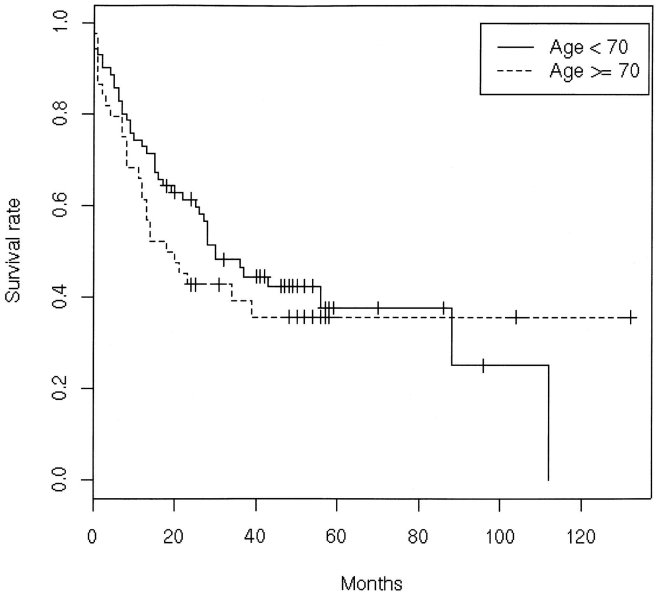

Fig. 3. Survival analysis of MZR treatment continuation in patients aged over 70 years (elderly group) and those aged under 70 years. Median drug survivals of MZR were 18 months and 30 months in patients aged over 70 years and those aged under 70 years, respectively, without significant difference between these two groups as determined by the log-rank test ($P = 0.39$)

Table 1. Mean age of subjects and percentage of subjects over 70 years of age for each DMARD

DMARD	Mean age of subjects (years)	Percentage of subjects over 70 years of age
Methotrexate	57.1	14.3
Bucillamine	56.1	15.3
Sulfasalazine	56.4	15.0
D-Penicillamine	57.8	16.5
Sodium aurothiomalate	56.2	14.6
Actarit	56.7	15.9
Auranofin	57.0	17.6
Mizoribine	58.8	17.4

DMARD, disease-modifying antirheumatic drug

Table 2. Adverse effects of mizoribine (MZR) among 304 rheumatoid arthritis patients during the 3-year study term determined using a self-report questionnaire

Adverse effect with MZR	No. of patients reporting	No. of patients discontinuing MZR due to adverse effect
Stomatitis	8	3
Skin rash	7	4
Epigastralgia	6	3
Heartburn	5	1
Herpes zoster	3	–
Dizziness	2	2
Skin itch	2	–
Liver dysfunction	1	1
Glossitis	1	1
Nausea	1	–
Headache	1	–
Total (%)	37 (12.2%)	15 (4.9%)

Table 3. Adverse effects with mizoribine in the MTX–MZR group and the elderly group during the 3-year study term determined using a self-report questionnaire

	Adverse effect with MZR	No. of patients	No. of patients discontinuing MZR due to adverse effect
MTX–MZR group (94 patients)	Stomatitis	4	2
	Skin rash	2	2
	Glossitis	1	1
	Herpes zoster	1	–
	Heartburn	1	–
	Headache	1	–
	Total (%)	10 (10.6%)	5 (5.3%)
Elderly group (45 patients)	Heartburn	3	1
	Epigastralgia	2	2
	Skin rash	2	1
	Herpes zoster	2	–
	Stomatitis	1	–
	Total (%)	10 (22.2%)	4 (8.9%)

None of the patients had severe adverse effects requiring hospitalization in either group
MZR, mizoribine; MTX, methotrexate

was no serious adverse reaction that required hospitalization (Table 3). Ten patients (22.2%) in the elderly group had adverse reactions (Table 3). The adverse reactions included heartburn in 3 patients, gastric pain, eczema/urticaria, and herpes zoster in 2 patients each, and stomatitis in 1 patient, and the reactions observed in 4 patients (8.9%) led to withdrawal of the drug. Of these adverse reactions, gastrointestinal disorders were common, but none were serious.

Discussion

This study was designed to examine the usefulness of MZR by analyzing data from a cohort study of RA patients. Of patients who received MZR, 30.7% were given MTX concomitantly or before or after taking MZR. Median drug survival of MZR was 28 months for the poor responders to MTX and 43 months for the poor responders to MZR (Fig. 2), with no significant difference between these groups, indicating that drug continuation rate was relatively well maintained in both. One report has noted that duration of treatment with a specific drug reflects the efficacy of the drug.[14] Taking this point into account, the above result suggests the usefulness of MZR when added for poor responders to MTX, as well as the usefulness of MTX when added for poor responders to MZR. Mizoribine antagonistically inhibits the purine synthesis system, and subsequently decreases intracellular guanosine monophosphate, thereby inhibiting cell growth.[15,16] Methotrexate, on the other hand, binds to dihydrofolate reductase during folic acid metabolism, and interferes with synthesis of the reduced form and the function of thymidylate synthetase, and thereby largely inhibits the pyrimidine synthesis system.[5] It is therefore generally presumed that concurrent use of MZR and MTX yields more potent inhibition of nucleic acid synthesis. Furthermore, in examining the effects of MTX and MZR, which inhibit bone marrow cell differentiation to osteoclasts, Yoshida found differences in the types of cells vulnerable to effects of the individual antimetabolites, and demonstrated the effectiveness of concurrent use of the two drugs.[17]

Reports on MZR concomitantly used with other drugs are summarized in Table 4.[7,18–25] Usefulness of MZR has been demonstrated for addition to nonresponders to DMARDs such as bucillamine and for intermittent concomitant use with MTX. As shown in Table 4, MZR is considered readily usable with other DMARDs in clinical practice for the treatment of RA, since it has a mechanism of action distinct from those of other DMARDs and has exhibited no drug interaction.

Characteristics of the patients in this study for whom MZR was selected included the highest mean age among all DMARDs used and a long-term MZR usage rate of nearly 40% in elderly patients aged over 70 years (elderly group). This suggests that physicians select MZR as a drug for elderly patients in the treatment of RA. It was reported by Kashiwazaki et al.[6] that elderly patients aged over 60 years accounted for 50.2% (230/458 patients) of patients treated in a post-marketing clinical study of MZR. In a subsequent long-term extended study,[26] patients were stratified into an elderly patient group and a non-elderly patient group to compare therapeutic response to MZR, and no difference in usefulness was found between the two groups. According to a report by Urano et al.,[27] the response rate early after onset for elderly patients with RA was 46.2% (6/13 patients), and those who received MZR for not less than 12 months accounted for 53.8% (7/13 patients) of these elderly patients. These results are generally consistent with the findings of this study that median drug survival of MZR was 18 months in the elderly group. These findings suggest that MZR is relatively easy to use in elderly patients.

Table 4. Reports of effects of additional combination therapy with mizoribine in Japanese patients with rheumatoid arthritis refractory to treatment with other DMARDs

First author[Ref.]	Year	No. of RA patients	DMARDs	Duration	Efficacy (%)	Adverse effects
Mori[23]	1995	33	BUC (not shown) + MZR 100–150 mg/day	6 months	51.5	Skin rash: 1
Shiokawa[7]	1996	13	DMARDs (GST, BUC, MTX, D-Pen) + MZR 100–150 mg/day	24 weeks	33.0	None
Kikuchi[20]	1997	12	BUC 100–300 mg/day + MZR 75–150 mg/day	≥6 months	66.7	Abdominal discomfort: 1; Liver dysfunction: 1
Azuma[18]	1997	13	DMARDs (not shown) + MZR 50–300 mg/day	≥4 months	30.8	Diarrhea: 1; Irregularity in menstruation: 1
Kosakai[22]	1997	2	ACT 300 mg + MZR 75 mg	≥4 months	100.0	None
Tokuda[24]	1998	9	MTX ≥7.5 mg/week + MZR 300 mg/day (once a week)	12 weeks	55.5	Malignant lymphoma: 2
Ueki[25]	1999	10	BUC 200 mg/day + MZR 200 mg/day	≥10 months	80.0	None
Inoue[19]	1999	19	(GST 10 mg/week or AF 6 mg/day) + MZR 50–100 mg/day	12 months	66.6	Skin rash: 1; Nausea: 1; Constipation: 1; Liver dysfunction: 1
Kohriyama[21]	2003	15	MTX 6 mg/week + MZR 300 mg/day (twice a week)	24 weeks	33.0	Mild nausea: 1

BUC, bucillamine; GST, sodium aurothiomalate; D-Pen, D-penicillamine; ACT, actarit; AF, auranofin

Mizoribine has been documented to be a relatively safe drug not associated with significant adverse reactions.[6,7,26] In the present study, adverse reactions occurred with an approximate incidence of 10%–20% when MZR was administered in the MTX–MZR group or the elderly group, and the adverse reactions observed were of the types previously reported. This suggests that MZR is a DMARD that can be used with relative safety. Concomitant use of MZR with other DMARDs and its frequent prescription to elderly patients suggests that MZR is selected for its safety profile. However, although this study revealed no serious adverse effects of MZR, the dosage of MZR should be taken into account when MZR is administered to patients with renal dysfunction, especially to elderly patients, because it has been reported that the half-life span in the blood of MZR is approximately doubled in a patient whose creatinine clearance is under 40 ml/min.[28] In conclusion, this study indicated that, although MZR has not been frequently prescribed for RA patients, it may be used with relative safety in addition to MTX therapy in poor responders to MTX and elderly patients.

Acknowledgments This study was supported by a consortium of 33 pharmaceutical companies for the large observational cohort study of RA in our institute.

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