Mod Rheumatol (2008) 18:91–95
DOI 10.1007/s10165-007-0012-1

CASE REPORT

A case of lupus nephritis improved after appropriately adjusting the dosage of mizoribine

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Received: 11 May 2007 / Accepted: 20 September 2007 / Published online: 26 December 2007

Abstract A 29-year-old male presenting nephrotic syndrome and facial skin erythema was admitted to our hospital in September of 2000. We diagnosed him as having systemic lupus erythematosus (SLE) accompanied by lupus nephritis (WHO class V). The disease activity had decreased after treatment with methylprednisolone (m-PSL) pulse therapy, which was followed by oral PSL. Thereafter, when tapering the dosage from 60 to 30 mg/day, the lupus nephritis flared up and he was re-hospitalized in February of 2001. After successful retreatment with m-PSL pulse therapy followed by the tapering of the dosage from 60 to 30 mg/day, we used mizoribine (MZR) as a combination therapy. The lupus nephritis flared up again after tapering down to 17.5 mg/day of PSL. Then, we changed the MZR dosage from 150 mg/day in three divided daily doses to 200 mg/day in two divided daily doses. This modification increased the peak blood concentration (Cmax) of MZR from 0.63 to 1.55 μg/ml. At present, we have been able to successfully taper the dosage to 7.5 mg/day of oral PSL and the patient has achieved a state of remission without any side effects. Monitoring of the serum concentration of MZR is thus considered to be important for achieving effective therapy of SLE, especially for steroid-resistant lupus nephritis. If the serum concentration of MZR does not reach an effective level, then the dosage of MZR should be adjusted appropriately in order to maintain an adequate serum concentration of MZR.

Keywords Lupus nephritis · Mizoribine · Cmax

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Introduction

In systemic lupus erythematosus (SLE), the therapeutic measures for lupus nephritis are vitally important. Over the past two or three decades, owing to advancements in treatment methods, the renal prognosis and life expectancy of patients with lupus nephritis has improved [1] The survival of patients with lupus nephritis at 5, 15, 25 years were 84, 62, and 54%, respectively, and this survival rate has been steadily improving [1]. Immunosuppressive agents, such as cyclophosphamide or azathioprine, are more effective than corticosteroids alone in preventing the development of lupus nephritis [2, 3]. At present, intravenous cyclophosphamide pulse therapy in addition to steroid therapy is considered to be the most effective strategy [4]. Mizoribine (MZR; 4-carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate) is a novel immunosuppressive agent isolated from the culture media of Eupenicillum brefeldianum M-2166 in 1974 in Japan [5]. The immunosuppressive effect of MZR has been suggested to be due to the inhibition of DNA synthesis in S phase of the cell cycle [6]. It acts via the selective inhibition of inosine monophosphate dehydrogenase and guanosine monophosphate synthetase, thus resulting in the inhibition of T and B cell proliferation [7]. In addition to the efficacy and safety of MZR after renal transplantation,

recent studies have demonstrated the utility in the treatment of childhood nephritic syndrome, SLE, and IgA nephropathy [8]. The major side effect of MZR derived from its original mechanism is hyperuricemia with an incidence of about 10% [9]. Other remarkable adverse effects have not been previously reported. Yumura et al. [10] recently reported the effects of long-term treatment with MZR in patients with proliferative lupus nephritis. However, MZR is still not used as often as cyclophosphamide or cyclosporine, perhaps in part due to its relatively low efficacy. We herein report a case of lupus nephritis in which the administration of MZR was adjusted during the treatment course and successful results were thus obtained.

Case report

In August of 2000, a 29-year-old male was diagnosed with having nephrotic syndrome and was hospitalized at another hospital. He was also suspected of having a connective tissue disease due to the onset off facial skin erythema and the presence of positive antinuclear antibodies, and therefore he was admitted to our hospital in September of 2000.

Laboratory tests revealed an increased erythrocyte sedimentation rate of 62 mm in 1 h, a decreased white blood cell count of 3,860 μl^{-1}, and a lymphocyte count of 1,080 μl^{-1}. The level of total protein was 3.9 g/dl, albumin (Alb) 1.3 g/dl, urea nitrogen 54 mg/dl, creatinine 2.28 mg/dl, and total cholesterol 321 mg/dl. The levels of C3 (46 mg/dl), C4 (11.1 mg/dl) and CH50 (16.1 IU/ml) were low. Antinuclear antibodies were positive (1 in 640 dilution) with homogeneous and speckled patterns. The levels of anti-DNA antibodies, anti-Sm antibodies, and anti-U1 RNP antibodies were negative. A urinalysis showed significant proteinuria (13.3 g/day) together with hematuria, and hyaline and granular casts.

The patient was diagnosed with SLE according to the 1997 American College of Rheumatology revised criteria for classification of SLE, based on the presence of facial skin erythema, proteinuria, leukopenia, and positive antinuclear antibodies. A renal biopsy was performed and a histological examination established a diagnosis of lupus nephritis (WHO class V). He received methylprednisolone (m-PSL) pulse therapy (1 g, 3 days) followed by 60 mg/day of oral prednisolone (PSL), which increased the white blood cell count, C3, C4, CH50, and Alb, decreased urea nitrogen and creatinine, and resulted in a complete resolution of the proteinuria. The dose of oral PSL was decreased to 40 mg/day and he was discharged in November of 2000.

Lupus nephritis flared up while the dose of oral PSL was decreased to 30 mg/day and he was re-hospitalized in February of 2001. He received m-PSL pulse therapy again followed by 60 mg/day of oral PSL, which resulted in a complete resolution of the proteinuria. In September of 2001, 150 mg/day in three divided daily of MZR that was an only immunosuppressive agent indicated for lupus nephritis was added to 30 mg/day of PSL, and he was discharged (Fig. 1).

Lupus nephritis flared up again while the dose of oral PSL was decreased to 12.5 mg/day, which thus resulted in a complete resolution of the proteinuria by dose up to 20 mg/day in May 2003 (Fig. 2). The blood MZR concentration 2 h after its oral administration was 0.63 μg/ml on 150 mg/day in three divided daily. Therefore, the method of use of MZR was changed to 200 mg/day in two divided daily doses in order to obtain high blood MZR concentration before tapering the oral PSL to 15 mg/day in April 2004. The blood MZR concentration 2 h after its oral administration was 1.55 μg/ml on 200 mg/day in two divided daily does. The dose of PSL was tapered to 7.5 mg/day, and lupus nephritis did not flare up again and no side effects were observed (Fig. 3).

Discussion

In a clinical setting, MZR has been thought to be a relatively mild immunosuppressant with a low degree of clinical toxicity [11, 12]. Subsequently, peak blood concentrations ranging from 3.0 to 6.0 μg/ml of MZR have been reported to be required to effectively inhibit the human mixed lymphocyte reaction [13]. Regarding the blood levels of MZR, during regular oral use, i.e., administration at 3 mg/kg per day in three divided daily doses, the peak levels of the drug are around 0.5 μg/ml [8]. In this context, Honda [14] reported that large doses of MZR of more than 5 mg/kg might be effective in patients with steroid-resistant nephrotic syndrome. It was also reported that 300 mg/day of MZR divided into three daily doses were effective in a pediatric case of lupus nephritis [15]. In this case, the first peak serum level of MZR was 0.70 μg/ml, the second was 1.64 μg/ml, and the third was 1.11 μg/ml, respectively. Tanaka et al. speculated that oral pulse therapy might produce sufficiently high peak MZR blood concentrations to prevent immune cells from exiting the G1 phase and entering the S phase by blocking T cell proliferation [16]. There is also an opinion that the clinical effect of MZR would be insufficient unless its peak blood level reaches 0.8–1.0 μg/ml [17]. In our patient, the peak blood concentration (Cmax) of MZR was 0.63 μg/ml on 150 mg/day in three divided daily doses. To obtain sufficiently high peak MZR blood concentrations, we changed MZR of 150 mg/day in three divided daily doses to 200 mg/day in two divided daily

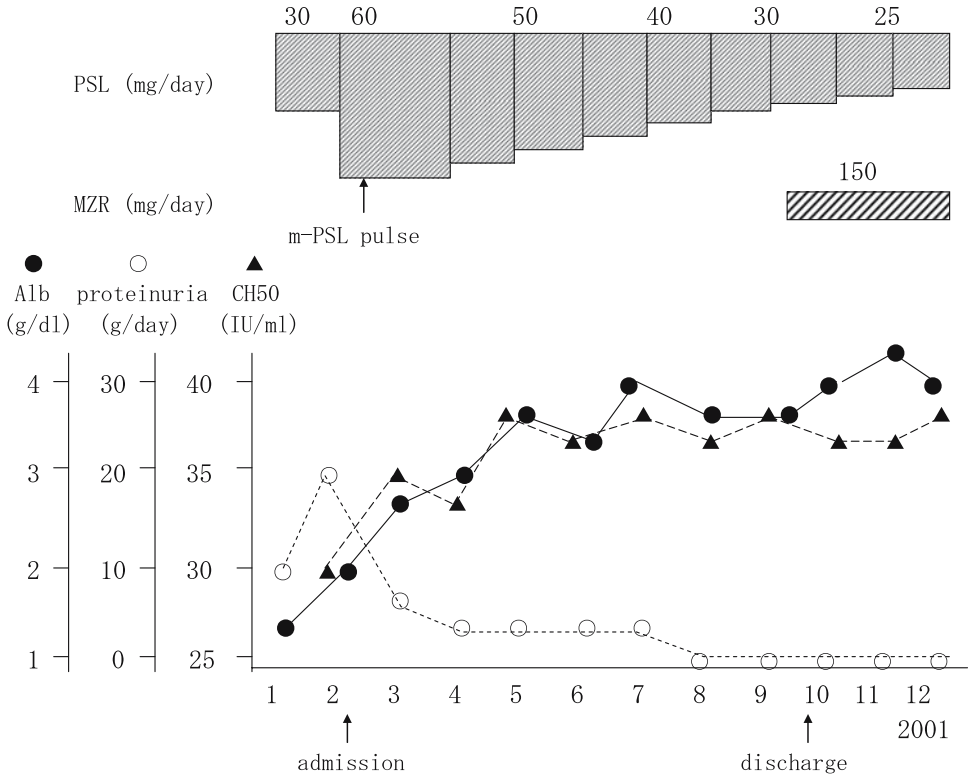

Fig. 1 Clinical course of CH50, Alb, proteinuria in 2001. Lupus nephritis flared up while the dose of oral PSL was decreased to 30 mg/day and then the patient was re-hospitalized in February of 2001. m-PSL pulse therapy again followed by 60 mg/day of oral PSL increased CH50 and Alb, thus resulting in a complete resolution of the proteinuria. In September of 2001, 150 mg/day in three divided daily of MZR was added to 30 mg/day of PSL, and he was then discharged

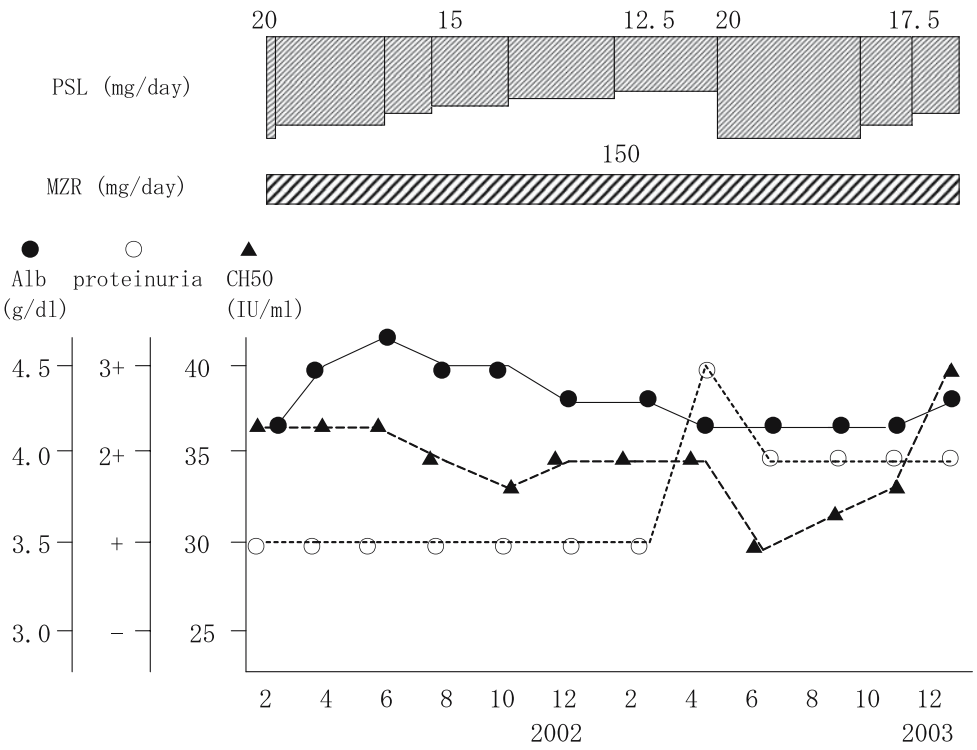

Fig. 2 Clinical course of CH50, Alb, proteinuria in 2002, 2003. Lupus nephritis flared up again while the dose of oral PSL was decreased to 12.5 mg/day in April 2003. The dose of PSL was increased to 20 mg/day which thus resulted in an increase of CH50 and a decrease of proteinuria

doses, and thereafter the Cmax of MZR was 1.55 μg/ml, namely higher than 1.0 μg/ml.

The immunosuppressive potency of MZR is observed on both cell-mediated and humoral immune reactions [18, 19]. It suppresses in vitro lymphoproliferative reactions to Pokeweed mitogen, phytohemagglutinin and concanavalin A [18], while inhibiting hemagglutinin production by suppressing IgM production in mice [19]. Kamata et al. described the prevention of glomerulopathy by reducing anti-DNA antibody synthesis in New Zealand black/white

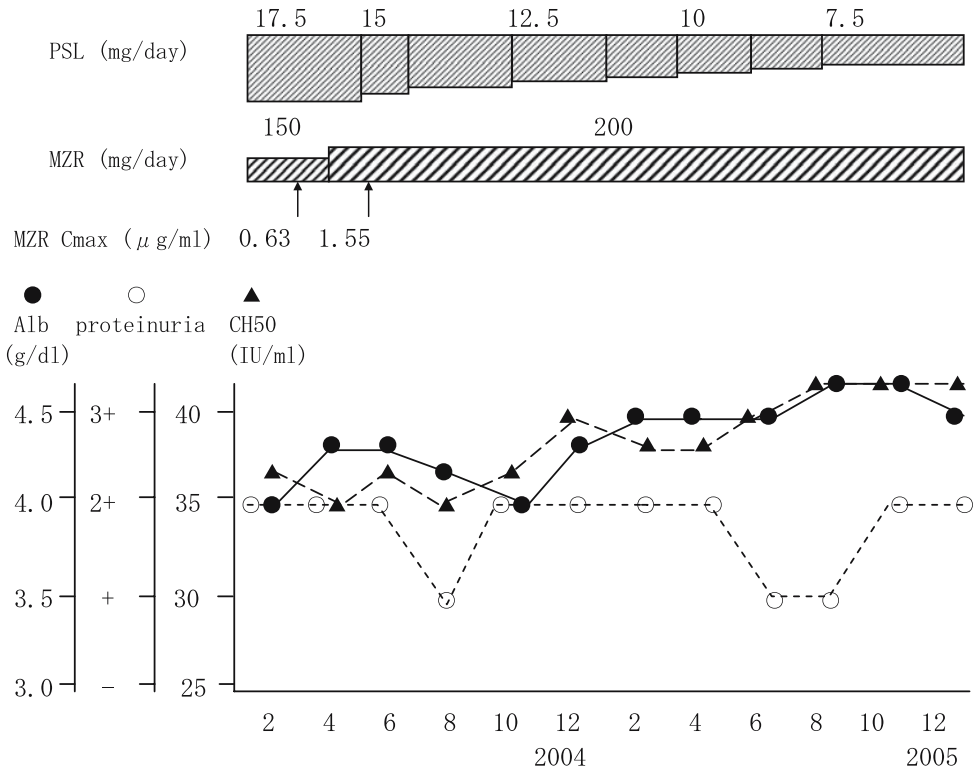

Fig. 3 Clinical course of CH50, Alb, proteinuria in 2004, 2005. In March of 2004 Cmax of MZR was 0.63 μg/ml on 150 mg/day in three divided daily doses. After changing the doses to 200 mg/day in two divided daily doses, the Cmax of MZR was 1.55 μg/ml in May of 2004. In August of 2005, the dose of PSL was tapered to 7.5 mg/day, and lupus nephritis did not again flare up

F1 hybrid mice [20]. In addition to its immunosuppressive effects, MZR inhibits cultured mesangial proliferation more significantly than other agents, such as corticosteroid, cyclophosphamide and cyclosporin A [21].

It has recently been reported that 14-3-3 proteins are MZR-binding proteins. 14-3-3 proteins interact with many proteins involved in cellular signaling, including the glucocorticoid receptor (GR). The interaction between 14-3-3 proteins and GR may enhance the transcriptional activity of the receptor, thus suggesting a steroid-sparing effect of MZR. Takahashi et al. [22] showed that MZR affected the conformation of 14-3-3 proteins and enhanced the interaction of GR and 14-3-3 proteins dose dependently in vitro. MZR also has a stimulatory effect on the transcriptional activation by the GR. These findings therefore suggest that one mechanism for the therapeutic effect of MZR could be the regulation of GR function via 14-3-3 proteins. MZR could augment the steroid effect, which also having a steroid sparing mechanism since a lower dose of steroid would have the same effect [13, 22]. Therefore, our oral MZR therapy may have made it possible to taper PSL, thus preventing a relapse of lupus nephritis according to this mechanism.

In conclusion, our results suggest that oral MZR therapy is effective in patients with steroid-resistant lupus nephritis. This report highlights the importance of monitoring the serum concentration of MZR. If the serum concentration of MZR does not reach an effective level, then the dosage of MZR should be adjusted appropriately. The adjustment of the MZR dosage is therefore considered important for obtaining effective therapy for the treatment of steroid-resistant lupus nephritis. We suggest that monitoring the serum concentration is essential for maintaining an adequate dosage of MZR. Although the effectiveness of MZR appeared gradually, no significant adverse effects, including bone marrow suppression, were observed in this case. It is necessary to further evaluate the efficacy of oral MZR therapy in long-term follow-up studies.

Acknowledgments We are grateful to Asahikasei Pharmaceutical Company for measuring the blood MZR concentration.

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