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Feature Article

Mizoribine as an effective combined maintenance therapy with prednisolone in child-onset systemic lupus erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is one of the major collagen diseases in childhood. However, the pathogenesis of this disease still remains unknown. The disease is known as a chronic inflammatory disease. Since oral and intravenous corticosteroid therapy has been introduced into the treatment of SLE, the prognosis of patients has improved significantly. However, it has now become clear that there are limitations in the effectiveness, as well as adverse reactions when corticosteroids therapy is administered for a long-term period. Therefore, we have been attempting to improve the maintenance therapy of child-onset SLE.
Methods: We have proposed and tested a new type of combination therapy using prednisolone (PSL) and mizoribine (MZR) in pediatric patients with SLE for maintenance therapy after the induction of remission.
Results: Our results showed that this combination therapy is more effective than the previous regimen. In addition, no significant side-effects were observed in our study.
Conclusion: This combination therapy is still not perfect. Efforts should be continued to establish an optimal therapy regimen for child-onset SLE.

Key words children, combination therapy, immunosuppressant, mizoribine, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is one of the major collagen diseases that occur in childhood.[1] Although the pathogenesis still remains unknown, SLE is now known to be a chronic inflammatory disease like other connective tissue diseases.[1] Therefore, before starting therapy it is important to accurately evaluate the patients in the identification of affected organs. We should also treat the patients with SLE as early and completely as possible to prevent a permanent destruction of organs. In addition, it is important for the patients to maintain in the remission mode of the disease for as long as possible. From the standpoint mentioned above, we have recently changed our therapy protocol for connective tissue diseases, particularly for child-onset SLE to improve the therapy for SLE.[2–4]

Since oral corticosteroids and intravenous (i.v.) methylprednisolone (mPSL) pulse therapy has been introduced in the treatment of patients with SLE, the prognosis of patients has significantly improved, particularly in patients with child-onset SLE.[1,5] However, it has become clear that there are limitations of the effectiveness, as well as adverse reactions to the corticosteroids in the treatment of SLE, especially child-onset SLE.[2,6] We have frequently experienced relapses of the disease activity[7,8] in the patients undergoing a tapering of the dosage of prednisolone (PSL), even after the induction of the disease remission. Therefore, we, along with others, have been trying to improve the maintenance therapy regimen for SLE.[2,6] We proposed a combination therapy in the treatment of child-onset SLE.[3,4] Namely, the combination of PSL and immunosuppressive drugs, such as mizoribine (MZR) was applied to improve the effectiveness, as well as to reduce the adverse reactions of corticosteroids. We previously reported that this combination therapy for child-onset SLE was useful as it reduced the total amount of PSL, as well as the frequency of relapse of the disease activity in the treatment of SLE.[4]

In this article, we introduce our data from patients with child-onset SLE with the combination therapy.[4] In addition, we also discuss other types of therapy including cyclophosphamide

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Table 1 Summary of the patients in this study – prednisolone group

Case No.	Sex	Age of disease onset (years)	CH50 (U/mL)	C3 (mg/mL)	C4 (mg/mL)	Urine protein†	Urine occult blood†	Anti-DNA Ab (IU/mL)	Renal biopsy§
1	F	8.3	14.7	52	5	3 +	3 +	1:80‡	III
2	F	12.0	17.1	46	7	1 +	negative	7	IVb
3	F	8.2	< 12.0	26	4	1 +	negative	110	II
4	F	14.7	< 12.0	25	3	1 +	3 +	> 120	IV
5	M	7.2	< 12.0	65	7	1 +	negative	1:80‡	IV
6	F	13.9	< 12.0	40	8	4 +	3 +	52	IVb

†Qualitative assay using the testape method. ‡Titer of anti-DNA antibody was expressed by a serum dilution. §World Health Organization classification of lupus nephritis; Ab, antibody; F, female; M, male. Modified from ref. no. 4.

Table 2 Summary of the patients in this study – prednisolone plus mizoribine group

Case No.	Sex	Age of disease onset (years)	CH50 (U/mL)	C3 (mg/mL)	C4 (mg/mL)	Urine protein†	Urine occult blood†	Anti-DNA Ab (IU/mL)	Renal biopsy§
1	F	11.3	< 12.0	20	7	3 +	3 +	103	IIb
2	F	14.0	12.4	25	3	3 +	3 +	3.2	IVc
3	F	14.4	15.1	40	6	1 +	negative	2000	IVc
4	F	17.1	15.4	40	7	1 +	2 +	1200	IIIb
5	F	12.0	9.7	17	4	1 +	1 +	350	IVb
6	F	14.1	22.9	40	15	3 +	1 +	1:1280‡	IVb
7	F	12.6	12.2	27	6	3 +	3 +	1100	IV

†Qualitative assay using the testape method. ‡Titer of anti-DNA antibody was expressed by a serum dilution. §World Health Organization classification of lupus nephritis; Ab, antibody; F, female; M, male. Modified from ref. no. 4.

(CY) pulse therapy, which was developed and recently used in the treatment of child-onset SLE.[9–14]

Study of the short- to middle-term outcomes with combination therapy

Intravenous mPSL pulse therapy has been shown to be more effective than oral PSL therapy alone in the initial treatment of the pediatric patients with SLE to reduce the disease activity.[2,5] However, the efficacy of this mPSL pulse therapy does not always continue as long as expected.[2] As a result, we often experienced patients who underwent the therapy, particularly severe cases, and showed a relapse of the disease activity, even with oral PSL therapy.[2,6] Therefore, we have been trying to develop a new therapy after the induction of the disease remission by i.v. mPSL pulse therapy for child-onset SLE. Namely, we proposed a combination therapy with PSL and immunosuppressants.[3,4] We now expect this therapy to have a higher efficacy and less adverse effects than the previous ones. The immunosuppressants selected for this combination therapy was MZR because of its low frequency of adverse reactions.[15–17]

Objective and methods

The object of this study was to evaluate the usefulness of combination therapy in pediatric patients with SLE.[4] The subjects of this study consisted of 13 cases (one boy and 12 girls) of child-onset SLE with nephritis, who were treated in our department from the beginning of the disease onset in 1983 to 1995 (Tables 1,2). All subjects were initially treated with one to three courses of i.v. mPSL pulse therapy (15 mg/kg per day, three successive days). After a remission of the disease the subjects were treated either with PSL alone (PSL group, six cases) or with PSL + MZR (PSL + MZR group, seven cases) for the maintenance therapy.

The average age of the patients in the PSL group (one boy and five girls) was 10.3 years (ranging from 8 to 14 years), while that of the PSL + MZR group was 13.4 years (ranging from 11 to 17 years). Renal biopsies of the patients of each group performed at the onset of the disease were classified according to World Health Organization (WHO) classification of lupus nephritis.[18] One patient was Class II, another Class III and five patients were Class IV in the PSL + MZR group.

Four cases in the PSL + MZR group were also treated with CY (one case with oral administration and three with

i.v. administration) before starting the combination therapy because of their severe nephritis (WHO classification, IIIb <) determined by renal biopsy specimens. For recent cases we chose only the combination therapy as a maintenance therapy in child-onset SLE due to the superior effectiveness. Therefore, their treatments in patients of the PSL group were treated from 1983 to 1990, in contrast to those in the PSL + MZR group who were treated from 1991 to 1995. The dosage of PSL in the PSL group was 30 mg/day and that in PSL + MZR group was 15–20 mg/day, while the dosage of MZR was 150–200 mg/day.

We compared the clinical symptoms, laboratory data, frequency of the relapse of the disease, total amount of corticosteroids, and adverse effects in the two groups for a 2-year time period after starting the treatment. For assessing the total amount of corticosteroids we calculated and converted the amount of corticosteroids into that for PSL. In this study we considered the relapse of the disease activity in the patients by detecting continuous low serum levels of CH50 values (< 25.0 U/mL) for more than 5 weeks.

Statistics

For the statistical analysis we employed the Fisher's *t*-test to compare the total amount of PSL in two groups. Differences with a *P*-value of < 0.05 were considered to be statistically significant.

Results

Frequency of the relapse of the disease activity

The frequency of the relapse of the disease activity in PSL group ranged from one to three times in all six patients (average 1.8 times). In the PSL + MZR group there was no relapse at all during the study period of 2 years. In the PSL group the total number of relapses was eight times based on the continuous low levels of serum CH50 values. Three out of the eight relapses were also followed by a deterioration in the proteinuria and hematuria in those patients.

Total amount of steroids

We calculated the total amount of corticosteroids administered to the patients in the two groups during the 2-year study period. The average of total amount of PSL was 20 440 mg (14 953–25 964 mg) in the PSL group, and 14 335 mg (7421–19 858 mg) in the PSL + MZR group (Fig. 1). A significant decrease was observed in the total amount of corticosteroid in PSL + MZR group ($P < 0.05$).

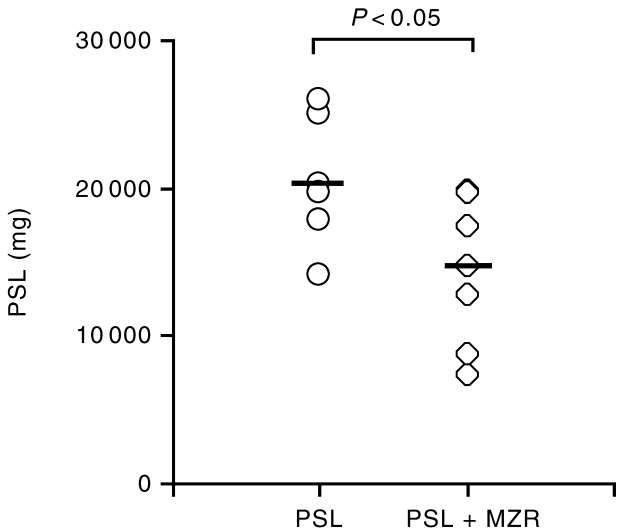

Fig. 1 Total cumulative dosage of prednisolone (PSL) in the patients. The amount of steroids was calculated in the patients of two groups for 2 years from starting the therapy. It was converted and expressed as the amount of PSL. There was a significant decrease (30% reduction) in the PSL + mizoribine (MZR) group ($P < 0.05$). The bar represents the mean cumulative dosage of total PSL in each group.

Adverse reactions

There were two cases of herpes zoster in each group during this study period. However, no other adverse reactions were observed in either group except for one case with mild liver dysfunction in the PSL + MZR group. However, it was a transient mild liver dysfunction and soon disappeared without any need to discontinue the therapy. There was also no cases of hairloss, bone marrow suppression, amenorrhea, hemorrhagic cystitis or renal dysfunction in this study.

Regarding developmental disturbances in height, in the PSL group the predicted height of the patients at the onset of the disease reached 95.6% during the 2-year study period. However, in the PSL + MZR group it reached to 99.8%, even though the average age in this group was older than in the other group. However, we compared the bodyweight of the patients in both groups to that of the aged-matched standard at the end of the study period. In the PSL group, three out of six patients gained an excessive amount of bodyweight, in contrast no patient was overweight in the PSL + MZR group.

Discussion

We have been trying to establish a desirable therapy for the patients with child-onset SLE, however, no definitive regimen has yet been established. We have introduced mPSL pulse therapy in the treatment of pediatric patients with

SLE.[2,5] As expected, this new treatment regimen strongly decreased the disease activity of the patient than the ordinary PSL therapy. In addition, with this therapy we could achieve a relatively easier and quicker remission of the disease in most patients, except for severe cases, than in those treated with the previous therapy.[2,5] This mPSL pulse therapy also helped to shorten the duration of hospitalization in these patients. However, even with pulse therapy we could not completely avoid the adverse effects of PSL over long-term treatment periods in patients with child-onset SLE, particularly the disturbances of height and obesity.[2] Therefore, a new therapy with either less adverse effects or none at all is still needed. With this background, we proposed the combined therapy with PSL and immunosuppressants to achieve the long-term remission of the disease and to reduce the adverse effects of the drugs.[3,4]

The immunosuppressants in the treatment of SLE,[19–21] CY,[9–12] azathioprine (AZP),[22] methotrexate (MTX)[23,24] and MZR[3,4,15] were used. Recently, cyclosporin A (CyA)[25,25] and tacrolimus[26] were also used in the treatment of intractable cases with SLE. However, a high frequency of adverse effects with these drugs, has also been pointed out, namely, bone marrow suppression and hemorrhagic cystitis with CY,[27] bone marrow suppression and liver dysfunction with AZP, and liver dysfunction and interstitial pneumonia with MTX. Nephrotoxicity and liver dysfunction are well known side-effects after treatment with CyA and tacrolimus. However, MZR has been reported to be less toxic.[15–17] Therefore, we chose MZR as a drug of the combination therapy.

Mizoribine is a nucleoside of the imidazole class, purified from a culture medium of the mold *Penicillium* species and is established as an immunosuppressant in Japan.[15,28,29] This belongs to the same category as AZP in immunosuppressants. However, strictly speaking the mechanism of this drug is not the same as that of AZP. This compound is not taken up by nucleic acids in the cell. This drug has a milder immunosuppressive effect, but a less adverse effect than AZP does. As an immunosuppressant, MZR has been approved in Japan for the prevention of rejection in renal transplantation,[16] for lupus nephritis,[3,4] rheumatoid arthritis[30] and nephrotic syndrome.[31] There were few reports in which MZR was shown to be useful in patients with other rheumatic disorders such as juvenile dermatomyositis and/or polymyositis.[32] However, we feel from our experience that MZR, by itself, has not enough ability to induce a remission of the disease activity in the child-onset SLE patients with more than a moderate disease severity.

However, mecophenolate mofetil (MMF) was purified from *Penicillium* species and was developed independently, which is quite a similar drug to MZR in terms of its structure and properties. It has anticancer, antiviral, antifungal and antibacterial properties. In addition, MMF has been used clinically in the treatment of psoriasis, rheumatoid arthritis[33] and SLE,[34,35] as well as in preventing rejection after renal transplantation.[36,37]

We studied the usefulness of the combined therapy with PSL and MZR in pediatric patients with SLE as a maintenance therapy in combination with mPSL pulse therapy.[3,4] Comparing this therapy to PSL alone, we demonstrated that the combination therapy of PSL + MZR had some advantages in the first 2-year period after starting the therapy. There was no relapse of the disease in the PSL + MZR group, but in the PSL group there was during this period. As a result, this combination therapy resulted in a decrease in the total amount of a cumulative dosage of PSL in the PSL + MZR group.[4]

This type of combination therapy has also been used to induce remission in patients with juvenile rheumatoid arthritis (JRA).[38,39] In the treatment of JRA, MTX, aspirin and PSL were used. This was also developed for achieving a sufficient anti-inflammatory effect with a small dosage of each drug. It also resulted in a reduction of the adverse effects in comparison to treatment with a large dosage of a single drug. With this combination therapy we could induce a remission of the disease earlier than with the previous regimens in the treatment of patients with JRA. However, this therapy was not effective in around 10% of the patients with polyarticular type of JRA.[39] As a result, this combination therapy is still not a perfect treatment for JRA and still needs to be improved. In addition, we should continue to search for an optimal therapy for JRA without any adverse effects.

Intravenous CY pulse therapy

Cyclophosphamide is a highly toxic drug, however, i.v. CY pulse therapy (500–1000 mg/M^2 per month) is now considered to be the therapy of choice in SLE patients with severe nephritis and central nervous system (CNS) lupus.[9–14] Even in pediatric SLE cases we also use this therapy consisting of a combination of PSL and immunosuppressant. The regimen of i.v. CY pulse therapy is as follows: seven monthly pulses of CY followed by a pulse every 3 months thereafter. In comparison to mPSL pulse therapy the immunosuppressive effects of i.v. CY pulse therapy seems to be stronger and last longer, although it takes time to show its effectiveness and has more adverse effects.[27] In addition, in our experience, the oral administration of CY has more adverse effects than i.v. CY pulse therapy under conditions of sufficient fluid administration to avoid hemorrhagic cystitis.

Furthermore, it is important to note that relapses frequently occur in patients with this therapy after finishing the protocol. The modified protocol to reduce the frequency of the relapse of disease activity in the patients with SLE is now used. Namely, we continue i.v. pulse therapy after 2 years, as

well as the combination therapy of PSL and immunosuppressants in the most severe cases. However, we also need to evaluate the long-term adverse reactions, such as malignancy and gonadal dysfunction in patients receiving this therapy.[27]

Plasmapheresis and adsorption

Recently, a new device has been developed which can effectively remove effectively autoantibodies and unknown materials from the blood of patients with SLE.[41–45] Although the effectiveness of this treatment itself was limited and did not last long, this therapy is now known to be useful following the combination with immunosuppressive drugs in patients with severe SLE. To apply this therapy, limitations remain regarding the special equipments and special staff members needed to set up and operate the machine, as well as the high financial costs. Therefore, this therapy is only available at specifically equipped hospitals. In addition, as a large amount of blood is required, patients with small body sizes are not indicated. This therapy is useful, however, several adverse events are associated with this treatment, such as hypotension, hypertension, blood loss, bleeding tendency, thrombosis and infection.[45] We should thus select this treatment for severe cases of SLE, particularly at an induction phase of disease remission.

Combination of plasmapheresis and i.v. CY pulse therapy

Euler *et al.*[11] reported on the effectiveness of the combination therapy of plasmapheresis and pulse CY in patients with severe SLE, particularly, lupus nephritis with WHO class IV and CNS lupus. Certainly, this combination therapy was effective regarding its immunosuppressive effects.[9,11,46] However, this is not a perfect therapy. Therefore, this protocol was modified to continue the treatment of the patients with SLE to reduce a relapse of the disease activity. We now select this therapy for the patients with severe SLE in an induction phase of the disease's remission, particularly the complication of antiphospholipid antibody syndrome and a high titer of autoantibodies.[9] Based on our experience we had a good response with this therapy.

Although this therapy is effective for the treatment of patients with severe SLE, this is still not a perfect therapy for SLE. Therefore, we should carefully select the patients for this therapy. As mentioned above, there are several adverse effects and problems associated with i.v. CY pulse therapy[27] and plasmapheresis.[46]

Conclusion

In this article we discussed the drug therapy for SLE, and demonstrated that the combination therapy of PSL and immunosuppressants including MZR was an effective therapy for SLE at the remission phase of the disease. Furthermore, it is thought that the synchronization therapy of i.v. CY pulse and plasmapheresis is the most powerful immunosuppressive therapy available at present, especially regarding patients with severe SLE for the induction of disease remission. However, these therapies are still not perfect regimens. Therefore, we should continue to improve the therapy for pediatric patients with SLE in order to achieve a high quality of life over a long-term period.

Finally, we are still searching for an optimal therapy for SLE. We therefore must pay careful attention to such patients, while clearly educating both the patients and their parents about the disease. In addition, to analyze the effectiveness of new therapies for pediatric patients with SLE the number of the patients at one facility is too small in Japan. Therefore, we hope that the Association of Pediatric Rheumatology in Japan can arrange for the clinical trials to establish new and improved therapeutic regimens for the rheumatic diseases in near future.

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