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ORIGINAL ARTICLE

Methylprednisolone pulse plus mizoribine in children with Henoch–Schoenlein purpura nephritis

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Abstract We evaluated whether methylprednisolone and urokinase pulse therapy combined with mizoribine (MUPM) was effective in children with severe Henoch–Schoenlein purpura nephritis (HSPN). We studied 12 patients who had been diagnosed with HSPN of at least ISKDC type III. All patients were treated with MUPM. Clinical features, pathological findings, and prognosis were prospectively investigated. Ten patients (responders; nine with ISKDC grade IIIb and one with grade IVb) were treated with MUPM, whereas MUPM was discontinued due to the lack of response in two patients (non-responders; two with grade IVb). Among responders, urinary protein excretion had decreased significantly from 99.7±37.8 to 25.9±33.4 mg/m^2 per hour after 3 months of therapy. The acute index and tubulointerstitial scores decreased significantly from 5.8±1.5 and 3.8±0.6 at the first biopsy to 2.3±1.3 and 1.0±0.8 at the second biopsy, respectively. At the most recent follow-up, eight of the responders had normal urine, and two had minor urinary abnormalities. Non-responders demonstrated continued high levels of urinary protein excretion after 3 months of therapy, and MUPM was discontinued. Our study suggests that MUPM is effective in ameliorating the proteinuria and the histological severity of HSPN in patients with <50% crescents but is not so effective for HSPN in patients with >50% crescents.

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Introduction

Henoch–Schoenlein purpura (HSP) is an immunoglobulin (Ig)A-mediated immune-complex vasculitis that affects predominantly the skin, joints, gastrointestinal tract, and kidneys. It occurs most frequently in childhood, and its prognosis is mainly predicted by the severity of renal involvement. The proportion of patients reported to have renal involvement varies between 20% and 80%. The majority of children with Henoch–Schoenlein purpura nephritis (HSPN) present only with hematuria and/or low-grade proteinuria, or both, and have a good chance of recovery. However, patients with massive proteinuria at onset frequently have a progressive course [1–5].

As for the treatment of HSPN, there are some reports dealing with the use and efficacy of multiple combined agents, including cyclophosphamide and other immunosuppressive drugs [6–11]. However, one issue that needs to be addressed is the side effects of cyclophosphamide, which have necessitated the withdrawal of cyclophosphamide from the combination therapy due to problems such as anemia, leukopenia, alopecia, hemorrhagic cystitis, and hypogonadism [12].

Mizoribine (MZB) (Bredinin™, Asahi Kasei Pharma, Tokyo, Japan) is an antimetabolite that exerts an immunosuppressant effect by inhibiting lymphocyte proliferation [13]. It is effective for nephritic syndrome [14], lupus nephritis [15], and IgA nephropathy [16] and is characterized as a safe and well-tolerated drug. However, there have been no reports to date on the efficacy of MZB therapy for HSPN in childhood.

Here, we report the administration of MZB in place of cyclophosphamide as part of a combination therapy for severe childhood HSPN and evaluate the efficacy and safety of the regimen.

Materials and methods

The study was carried out under the auspices of the Human Experiments at Fukushima Medical University Hospital. Informed consent was obtained from all patients or their parents.

Patients

All patients presented at the Department of Pediatrics of Fukushima Medical University School of Medicine between January 2003 and December 2007 and were regarded as eligible for the study if they had been biopsied and were newly diagnosed to have HSPN of greater than ISKDC grade IIIb and if the following criteria were satisfied: (1) a diagnosis of HSP, made on the basis of major manifestations of the illness consisting of a purpuric rash and abdominal pain, without thrombocytopenia and with additional features, such as arthritis or nephritis, accepted as being consistent with the diagnosis, (2) under 15 years of age as of the start of therapy and follow-up, (3) no previous treatment with corticosteroids or immunosuppressive drugs, and (4) sufficient renal biopsy tissue available for histological evaluation (minimum of ten glomeruli).

On entry into the study, the medical histories were obtained for all patients, and all patients underwent a physical examination.

Patients were followed up once a month during the study. At each follow-up visit, the patients were asked about their symptoms and were monitored for any side effects of the therapy. Clinical features, laboratory data, pretherapy and post-therapy pathological findings, and prognosis were prospectively investigated.

Treatment

Following diagnostic renal biopsy, the patients were treated with methylprednisolone and urokinase pulse therapy combined with mizoribine (MUPM). MUPM is a combination of "pulse" methylprednisolone, at 30 mg/kg per day i.v. bolus (maximum 1 g) for three consecutive days, and pulsed UK, at 5,000 u/kg/day i.v. bolus (maximum 180,000 u) for seven consecutive days, followed by daily oral prednisolone (1 mg/kg per day) for 6 months, along with MZB, antiplatelet agents (dipyridamole 5 mg/kg/day), and an anticoagulant (warfarin) for 24 months. MZB was given orally at a single dose of 5 mg/kg (maximum 150 mg) body wt per day for 24 months. Warfarin was given orally at a single morning dose of 1 mg (aged less than 7 years) or 2 mg (aged over 7 years) to maintain the Thrombotest at 30–50%.

Definitions

Hematuria was considered a positive finding if urinary microscopic examination showed five or more red blood cells per high power field, and macrohematuria was considered a positive finding if blood was visible to the naked eye [17]. Proteinuria was evaluated by 24-h quantitative measurements.

A responder was defined as a patient in whom proteinuria had decreased (by more than two thirds of urinary protein excretion at the onset), whereas a non-responder was defined as a patient in whom the proteinuria (at more than two thirds of urinary protein excretion at the onset) was still present at 3 months after treatment regimen.

The clinical status of each patient was classified as follows:

Normal: the patient was normal on physical examination, with normal urine and renal function.
Minor urinary abnormalities: the patient was normal on physical examination and had microscopic hematuria or proteinuria of less than 20 mg/m^2 per hour.
Persistent nephropathy: the patient had proteinuria of 20 mg/m^2 per hour or greater and 24-h creatinine clearance (24hCcr) of 60 ml/min per 1.73 m^2 or greater.
Renal insufficiency: the patient had 24hCcr of less than 60 ml/min per 1.73 m^2. (This category included patients who were on dialysis, who had received a transplanted or who had died).

Pathology

The first renal biopsies were performed initially in all patients, and the second biopsies were performed in the recovery phase (10.2±3.0 months after onset) in all patients in order to assess the efficacy of the therapy. Material for histological studies was fixed in 12% neutral formalin, embedded in paraffin, sliced at 2–3-μm thickness, and stained with hematoxylin and eosin or periodic acid–Schiff reagent. The specimens were assessed by light microscopy and immunofluorescence (IF). The mean (±SD) number of glomeruli found in the biopsy specimens was 24.6±10.3 (range 12–53).

The glomerular changes were graded according to the classification devised by the pathologists of the International Society of Kidney Disease in Children [12], as follows: I, minor glomerular abnormalities; II, pure mesangial proliferation [(a) focal, (b) diffuse]; III, minor

glomerular abnormalities or mesangial proliferation, with crescents in <50% of glomeruli [(a) focal, (b) diffuse mesangial proliferation]; IV, same as III but with crescents in 50–75% of glomeruli [(a) focal, (b) diffuse mesangial proliferation]; V, same as III but with crescents in >75% glomeruli [(a) focal, (b) diffuse mesangial proliferation]; VI, membranoproliferative-like lesions.

To compare biopsies, a histological scoring system was modified to evaluate acute and chronic changes. Acute changes included mesangial proliferation (grades 0–3, 0= normal, 1 = slight, 2 = moderate, 3 = severe), segmental necrosis with cellular crescent formation (scored according to the percentage of glomeruli involved, 0=0%, 1=1–20%, 2=20–50%, 3 = >50%), and interstitial edema with mononuclear cell infiltration (0–3). The acute index is the sum of the scores of those changes. Chronic renal injury was estimated by determining the number of glomeruli with fibrous crescents and segmental or global sclerosis. Each abnormality was scored on a scale of 0–3 according to the number of glomeruli involved, as for the scoring of acute crescent formation. In addition, the combination of tubular atrophy and interstitial fibrosis was graded on a scale of 0–3. The chronicity index is the sum of the scores of those chronic renal changes. Scoring was performed in a blinded fashion on specimens identified only by codes. Tubulointerstitial (TI) changes were clarified further according to TI scores described by Foster et al. [7].

Tissues for IF assay were immediately fixed in OCT compound and frozen at −80°C until use for IF. IF assay was performed to detect IgG, IgA, IgM, C1q, C3, C4, and fibrinogen. The intensity of immunofluorescence was graded on a scale of 0–3, where 0 = negative, 1 = mild, 2 = moderate, and 3 = severe.

Statistics

Data are expressed as mean values ± SEM. Statistical analysis was performed on a Macintosh computer with a software package for statistical analysis (Stat View, Abacus Concepts, Berkeley, CA, USA). Several variables that were clearly not normal in their distribution were compared using non-parametric statistics such as the Mann–Whitney' test or Wilcoxon signed rank test. The renal survival rates were calculated using the life-table method (Kaplan–Meier). $P<0.05$ was considered significant.

Results

Twenty-eight patients were newly diagnosed with HSPN at the Department of Pediatrics, Fukushima Medical University School of Medicine between January 2003 and December 2007. Histological sections from these 28 patients were reviewed, and 18 patients were found to show HSPN greater than ISKDC grade IIIb. Twelve of these 18 children with greater than ISKDC grade IIIb met the criteria for inclusion in our trial. Nine patients had HSPN with ISKDC grade IIIb; three patients had HSPN with ISKDC grade IVb. Ten patients (responders) were treated with the treatment regimen, and second biopsies were performed, whereas the treatment regimen was discontinued in two patients (non-responders) due to a lack of response. The age at onset was 7.8±3.1 years, and the duration from onset was 3.1±1.1 years. The duration from onset to renal biopsy was 2.7±2.3 months, and the male-to-female ratio was 5:7. Baseline characteristics between the responder and non-responder patients are shown in Table 1. Patients with low values for 24hCcr tended to be non-responders.

Comparison of laboratory findings between the first renal biopsy and the most recent follow-up was shown (Table 2). At the first renal biopsy of patients in responders, hematuria was present in all patients in the responder group. Twenty-four-hour creatinine clearance had decreased in two patients and ranged from 49 to 54 ml/min per 1.73 m^2. The mean urinary protein excretion before the

Table 1 Baseline characteristics between responders and non-responders

	Responders	Non-responders
Age (years)	8.0±3.3	6.5±0.7
Gender (M/F)	4:6	1:1
The duration from onset to renal biopsy	2.9±2.5	2.0±0.0
Initial presentation		
Purpura	9	2
Arthralgia	0	0
Abdominal pain	7	2
Urinary protein excretion (mg/m^2/h)	92.1±34.3	138.0±41.2
Hematuria (macro)	8 (5)	2 (1)
Serum albumin (g/dl)	3.4±0.2	3.0±0.3
24 h Ccr (ml/min/1.73 m^2)	80.2±18.7	48.0±5.7

Table 2 Comparison of laboratory findings between the first renal biopsy and the most recent follow-up

	At the first renal biopsy	At the most recent follow-up	*P*
Urinary protein excretion (mg/m^2/h)	92.1±34.3	2.6±4.2	<0.001
Hematuria (macro)	10 (5)	2 (0)	<0.01
Serum albumin (g/dl)	3.4±0.2	4.0±0.3	<0.01
Serum creatinine (mg/dl)	0.39±0.05	0.35±0.04	<0.05
24 h Ccr (ml/min/1.73 m^2)	80.2±18.7	124.5±19.0	<0.001

initiation of therapy was 99.7±37.8 mg/m^2 per hour, but it decreased significantly (p<0.001) to 25.9±33.4 mg/m^2 per hour after 3 months of therapy. The change in the disappearance rate of proteinuria is shown in Fig. 1. In the non-responder group, 24hCcr had decreased in both patients, ranging from 44 to 52 ml/min per 1.73 m^2. The mean urinary protein excretion before the initiation of therapy was 137.5±41.2 mg/m^2 per hour and, after 3 months of therapy, remained at 104.8±24.1 mg/m^2 per hour, so that the treatment regimen was discontinued. At the most recent follow-up, urinary protein excretion had disappeared in the responder groups, and 24hCcr had returned to normal values in the two patients who had renal impairment at the initiation of therapy. The serum albumin levels were also within the normal range, and the incidences of hematuria and serum creatinine levels at most recent follow-up were lower than those at the first renal biopsy. At the latest follow-up, eight of the responders (80%) had normal urine, two (20%) had minor urinary abnormalities, and none of the ten had persistent nephropathy or renal insufficiency.

IF findings showed that the amount of immunoglobulins, such as IgG, IgM, and complements of C1q and C4, did not differ between the first and second biopsies, but the amounts of IgA, C3, and fibrinogen at second renal biopsy were less than those observed at the first renal biopsy (p< 005) (Table 3). In responders, nine patients had had HSPN with ISKDC grade IIIb and one patient had HSPN with ISKDC grade IVb at the first biopsy. The acute index decreased significantly from 5.8±1.5 at the first biopsy to 2.3±1.3 at the second biopsy (p<0.001), TI score decreased significantly from 3.8±0.6 at the first biopsy to 1.0±0.8 at the second biopsy (p<0.001), and the chronicity index scores at the first biopsy were similar to those at the second biopsy (2.3±1.0 vs. 2.5±0.8) (Fig. 2). The percentages of glomeruli showing crescents at the first and second biopsies were 33.7±11.0% and 1.6±2.7%, respectively. At the second biopsy, eight patients had had HSPN with ISKDC grade IIa and two patients had HSPN with ISKDC grade IIIa. In non-responders, two patients had had HSPN with ISKDC grade IVb (Table 3).

As to comparison of the serum concentration of MZB, the serum concentrations of MZB (μg/ml) in responder and non-responders were 0.0±0.0 and 0.0±0.0 at C0, 0.7±0.2 and 0.7±0.1 at C1, 1.3±0.5 and 1.4±0.2 at C2, 1.4±0.6 and 1.6±0.3 at C3, and 1.1±0.5 and 1.2±0.1 at C4.

There were no differences in the serum concentrations of MZB at C0, C1, C2, C3, and C4 between responders and non-responders. As to side effects of the treatment, one patient developed mild glaucoma, but none of the patients presented any signs of mild growth retardation. Three patients developed hypertension, which was well controlled by treatment with nifedipine. Finally, one patient presented uricacidemia, which was well controlled by treatment with allopurinol. There were no patients with any signs of leukopenia, and the doses of anticoagulants used in the

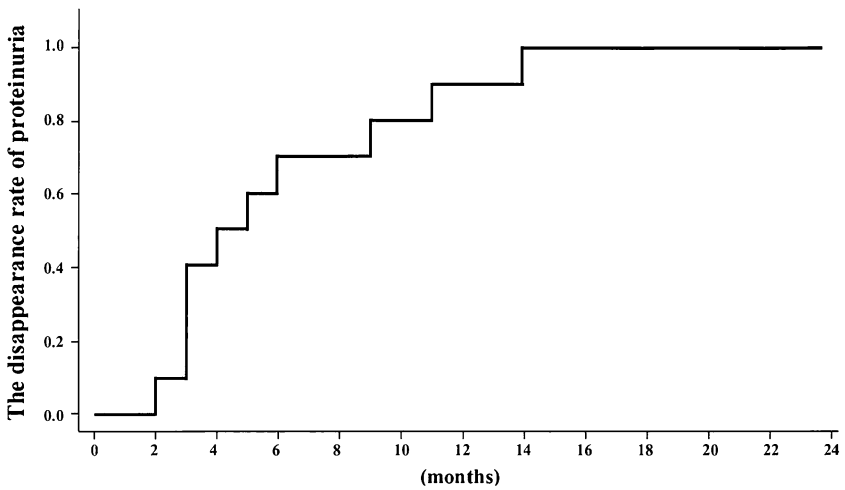

Fig. 1 The change in the disappearance rate of proteinuria

Table 3 Comparison of pathological findings between the first and second biopsies

	At the first renal biopsy	At the second renal biopsy	*P*
Immunofluorescence findings			
IgG	0.2±0.3	0.1±0.2	NS
IgA	2.8±0.4	1.7±0.4	<0.001
IgM	0.1±0.3	0.0±0.0	NS
C1q	0.0±0.0	0.0±0.0	NS
C3	2.4±1.1	1.2±0.8	<0.01
C4	0.0±0.0	0.0±0.0	NS
Fibrinogen	2.4±0.7	1.0±0.6	<0.01
ISKDC classification			
II	0	8	<0.01
IIIa	0	2	NS
IIIb	9	0	<0.01
IVb	1	0	NS
Vb	0	0	NS

NS not significant

treatment regimen did not result in bleeding. Most of the side effects were mild and well controlled, and all were reversible.

Discussion

Our study suggests that MUPM significantly reduced urinary protein excretion and prevents any increase in crescentic and sclerosed glomeruli in responder patients with ISKDC grade IIIb and IVb; however, MUPM did not significantly reduce urinary protein excretion in non-responder patients with ISKDC grade IVb. At their most recent follow-ups, none of the responder patients treated with MUPM showed persistent nephropathy or renal insufficiency.

As for reports concerning the prognosis of HSPN, Counahan et al. reviewed 88 patients with HSPN and found that 15 of the 26 patients (58%) with at least grade IV and five of 38 (13%) without treatment had active renal disease, renal insufficiency, or both [5]. Yoshikawa et al. [18] reported that HSPN was a significant cause of childhood chronic renal failure, accounting for 16% of all children entering dialysis programs in Japan. The pathologic features that are valuable predictors of prognosis are histologic grade, especially the percentage of glomeruli with crescents, and higher chronicity indices [1, 2, 4, 5]. Therefore, it is necessary to assure that therapy for severe HSPN is adequate. Niaudet et al. [3] reported that methylprednisolone pulse therapy was effective in patients at risk of progression of their nephropathy, especially if it was started early during the course of the disease, before the crescents became fibrosed. Further, we have reported that methylprednisolone and urokinase pulse therapy plus cyclophosphamide was effective in preventing the progression of sclerotic changes in HSPN patients of at least grade

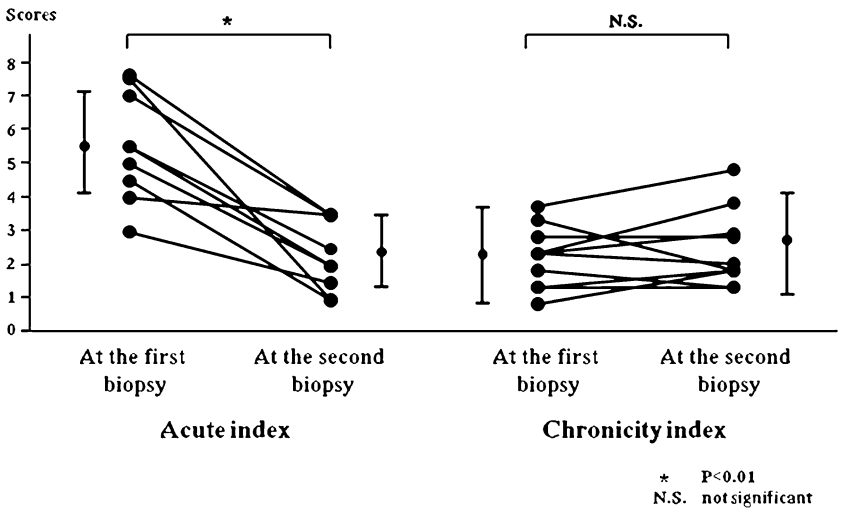

Fig. 2 Comparison of acute index and chronicity index between the first and second renal biopsies

IV [11]. In addition, Shin et al. reported that cyclosporine A (CyA) is effective in reducing proteinuria in HSPN [19].

However, one issue that needs to be addressed is the side effects associated with the use of cyclophosphamide, which has necessitated the withdrawal of cyclophosphamide from the combination therapy due to problems such as anemia, leukopenia, alopecia, hemorrhagic cystitis, and hypogonadism [12]. As to the side effects associated with CyA, hypertension, nephrotoxicity, hepatotoxicity, cardiotoxicity, and leukoencephalitis have all been observed [20].

On the other hand, MZB (4-carbamoyl-β-D-ribofuranosylimidazolium-5-olate) is an immunosuppressive agent with an imidazole nucleoside that was first isolated from the culture medium of *Eupenicillium brefeldianum* in Japan. The immunosuppressive effect of MZB has been reported to be due to the inhibition of DNA synthesis in the S phase of the cell cycle. Because of its relative lack of toxicity, MZB has frequently been used during the past decade instead of azathioprine as a component of immunosuppressive drug regimens [12], and MZB is currently being used to treat renal transplantation patients [21], IgA nephropathy [16], lupus erythematosus [15], and childhood nephrotic syndrome (NS) [14]. We have also reported that prednisolone and mizoribine therapy is effective for those patients with the risk of progression of IgAN [16].

In this study, MUPM significantly reduced urinary protein excretion and prevented any increase in crescentic and sclerosed glomeruli in responder patients with ISKDC grade IIIb and IVb; it did not, however, significantly reduce urinary protein excretion in two non-responder patients with ISKDC grade IVb. At their most recent follow-up, none of the responder patients treated with MUPM showed persistent nephropathy or renal insufficiency. These findings suggested that MUPM is effective in ameliorating the proteinuria and histological severity of HSPN patients with <50% crescents, though it is not so effective for HSPN patients with >50% crescents.

We previously have reported that methylprednisolone and urokinase pulse therapy was effective in HSPN patients with at least grade IIIb, though some of the patients nevertheless progressed and developed increased sclerotic lesions [10]. The results of this study suggested that MUPM might prevent any increase in sclerosed glomeruli in responder HSPN patients with ISKDC grade IIIb, though it was not effective for HSPN patients with >50% crescents. Thus, MUPM may not be adequate for the treatment of patients with severe HSPN with 50% crescents, and methylprednisolone and urokinase pulse therapy plus cyclophosphamide or CyA and plasmapheresis might be preferred for their treatment.

The rationale for using MUPM in responder HSPN patients is that corticosteroids and immunosuppressive agents reduce IgA production and minimize the abnormal immune response and inflammatory events following glomerular IgA deposition. Warfarin and dilazep dihydrochloride are used to inhibit the mediators of glomerular damage [16]. As to the side effects, most of the side effects were mild and well controlled, and all were reversible. Severe side effects attributable to the treatment regimen were relatively rare, and prednisolone and MZB therapy was well and safely tolerated by all patients.

The peak blood level of MZB, during regular MZB therapy, is 3 mg/kg daily in three divisions; the peak levels of MZB have been reported to be approximately 0.5 μg/ml [15]. It has been reported that MZB concentrations effective enough to inhibit the human mixed-lymphocyte reaction require peak blood concentrations ranging between 3.0 and 6.0 μg/ml [22]. We used MZB as a single dose per day in order to elevate the concentration of MZB. Some recent studies have assessed the efficacy of oral MZB pulse therapy for severe lupus nephritis [23], steroid-resistant NS [24], and frequently relapsing steroid-dependent NS [25]. Ohtomo et al. reported that MZB pulse therapy (a single dose per day) in frequently relapsing steroid-dependent nephritic syndrome patients who are dependent on CyA treatment appears to be effective in reducing CyA exposure as well as in decreasing the frequency of relapses [25]. We evaluated the concentration of MZB when MZB was given orally in a single dose of 5 mg/kg body weight each day and found that the peak serum concentration of MZB was 1.3–2.1 μg/ml. If the concentration of MZB is elevated, MUPM may be more effective for severe HSPN with >50% crescents.

In conclusion, our study suggests that MUPM was effective in ameliorating the proteinuria and histological severity of HSPN patients with <50% crescents, though MUPM was not so effective for HSPN patients with >50% crescents. However, it is difficult to draw clear conclusions from this study, since few patients were examined and the period of observation was short. Hence, further studies of this therapy in children with severe HSPN are needed.

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Disclosures None.

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