Open Journal of
Clinical & Medical
Case Reports

Volume 2 (2016)
Issue 15

ISSN 2379-1039

Successful Treatment of Elderly-Onset Minimal Change Nephrotic Syndrome by using Mizoribine

Tetsuhiko Yasuno*; Miyata Masaaki; Renya Watanabe; Aki Hamauchi; Kenji Ito; Yasuhiro Abe; Yoshie Sasatomi; Hitoshi Nakashima

***Tetsuhiko Yasuno, MD, PhD**
Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma Johhnan-ku, Fukuoka 814-0180, Japan
Email: yasuno9584@fukuoka-u.ac.jp

Abstract

There are many case reports of pediatric patients with nephrotic syndrome (NS) that responded to mizoribine (MZR) treatment; however, there are no previous reports of adult patients. We administered prednisolone (PSL) and MZR to a 65-year-old man with minimal change NS (MCNS). Once remission occurred, the doses of PSL and MZR were gradually tapered; combined treatment with 2 mg/day PSL plus 50 mg/day MZR maintained remission for three years. MZR alone (50 mg/day) was then administered. One year later, the patient developed recurrent NS and combined PSL and MZR treatment was initiated again; this produced rapid remission. This elderly patient with long-term treatment-dependent MCNS, therefore, showed a complete response to treatment by using MZR.

Keywords

nephrotic syndrome; mizoribine; MCNS

Introduction

Minimal change nephrotic syndrome (MCNS) accounts for 20% of nephrotic syndrome (NS)cases in patients aged 65 years or older. Membranous nephropathy (MN) is the main cause of NS, followed by MCNS. Patients with MN who are in their 60s and 70s account for 60% of all intractable NS cases [1]. Calcineurin inhibitors are used for the treatment of steroid-resistant NSand of steroid-dependent NS where steroids cannot be used effectively owing to adverse reactions; they are also used to treat frequently relapsing NS (FRNS), and other conditions. However, the use of cyclosporine A (CsA) to treat MCNS is not recommended for patients with renal dysfunction, hypertension, or glucose intolerance.

Mizoribine (MZR) is a purine synthesis antagonist that was developed in Japan. There are several reports of MZR administration to pediatric patients with FRNS. However, there are very few reports concerning the treatment of elderly patients with MCNS. Compared to CsA, MZR produces fewer adverse reactions, and this prompted us to investigate the use of combined steroid and MZR in elderly patients with MCNS.

Here, we describe an elderly patient with MCNS who was successfully treated using combined steroid and MZR therapy.

Case Presentation

The patient initially presented with NS at 62 years. He had marked lower-extremity edema. His urinary protein excretion was 17.9 g/day, and his serum albumin level was 1.8 g/dl. Kidney biopsy confirmed MCNS (Figure 1 and 2) and treatment with prednisolone (PSL) at 40 mg/day was initiated. After three days of 500mg methylprednisolone pulse therapy, treatment with a combination of MZR and PSL was initiated. MZR (150mg)was taken once a day in the morning. This treatment resulted in complete remission. The blood MZR concentration was 0.0 μg/dlat trough and 1.2 μg/m l4h after administration. The doses of PSL and MZR were gradually tapered subsequently and administration of 2 mg/day PSL and 50 mg/day MZR maintained remission for 3 years; finally, PSL was discontinued when the patient was 66 years of age. One year later, however, he developed recurrent NS and was treated with 30 mg/day PSL and 150 mg/day MZR. This treatment produced rapid and favorable effects (Figure 3).

Discussion

MZR selectively suppresses the *de novo* and salvage pathways of nucleotide synthesis, and this high selectivity has been reported to reduce the incidence of adverse reactions [2]. It also suppresses macrophage infiltration and inhibits chronic pathological changes in renal tissue [3, 4, 5, 6, 7]. Anti-proteinuric effects were also reported because of the maintenance of glomerular epithelial cell morphology [8, 9, 10, 11]. CsA is usually used to treat FRNS in adults; however, this therapy often impairs renal function and/or increases the severity of hypertension. For pediatric FRNS, MZR produced fewer adverse reactions than CsA and also significantly reduced relapse rates [12]. Furthermore, it has shown efficacy in the treatment of CsA-induced nephropathy [13, 14]. These pleiotropic effects in kidney disease and its immunosuppressant activity in elderly patients suggested that combination treatment with PSL and MZR may achieve remission more effectively than by treatment with PSL alone, which had failed to improve the condition of the patient described in the present study.

The maximum MZR blood concentration is achieved by 3–4 h after oral administration. The half-life of this compound is 2.2 h and 80% of the absorbed dose is excreted via the kidney [15]. Receiver operator curve analysis showed that a blood concentration of more than 1.1 μg/ml was required for efficacy against MN in a Japanese study. It has also been shown that a blood concentration level of more than 4 μg/ml induced adverse reactions such as gastritis, hepatic disorders, and thrombocytopenia [15]. Thrice-daily oral administration of 50 mg MZR was not sufficient to maintain a therapeutic blood concentration and we therefore administered 150mg MZR once a day. This form of administration may be important for efficacy [16].

Conclusion

In summary, we report an elderly patient with MCNS who was successfully treated using steroid and MZR combined therapy. MZR, taken once a day, could reduce side effects and provide an effective therapeutic approach.

Figures

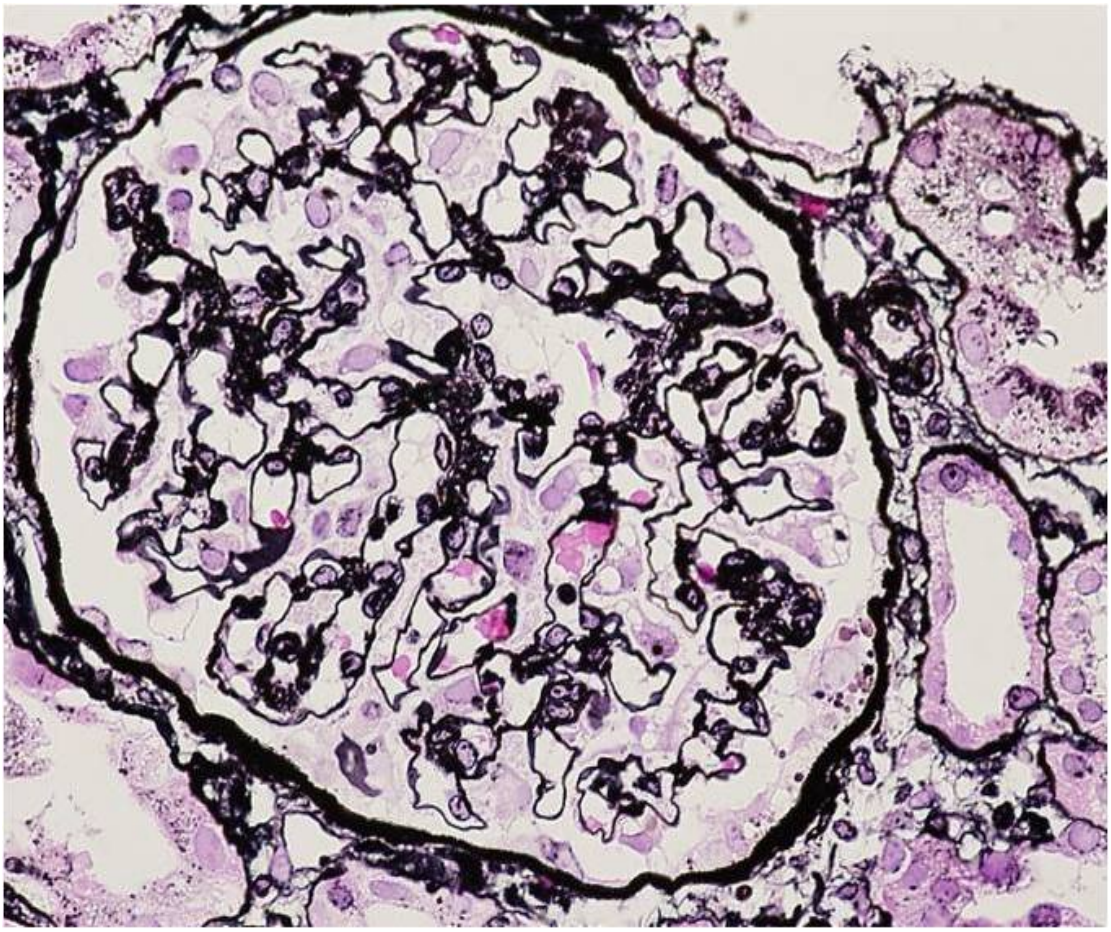

Figure 1: Light microscopy showing minor glomerular abnormalities (PAM stain).

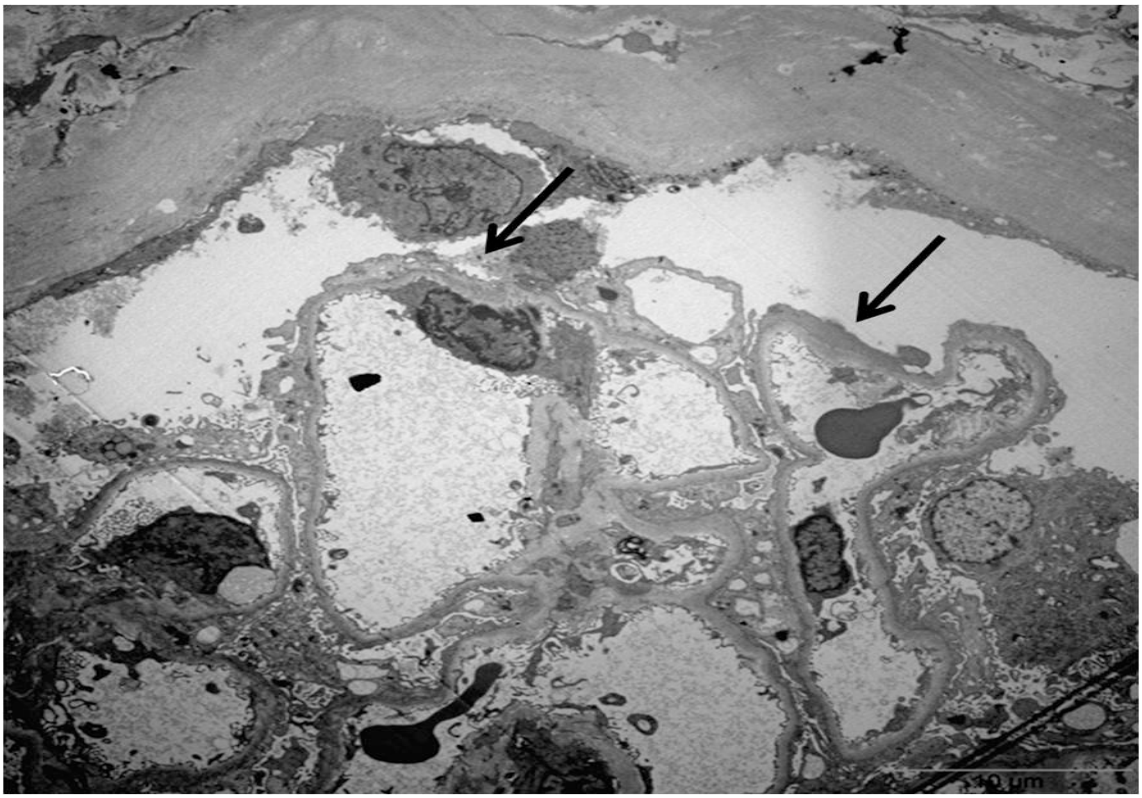

Figure 2: Electron microscopy revealing foot process fusion (black arrows).

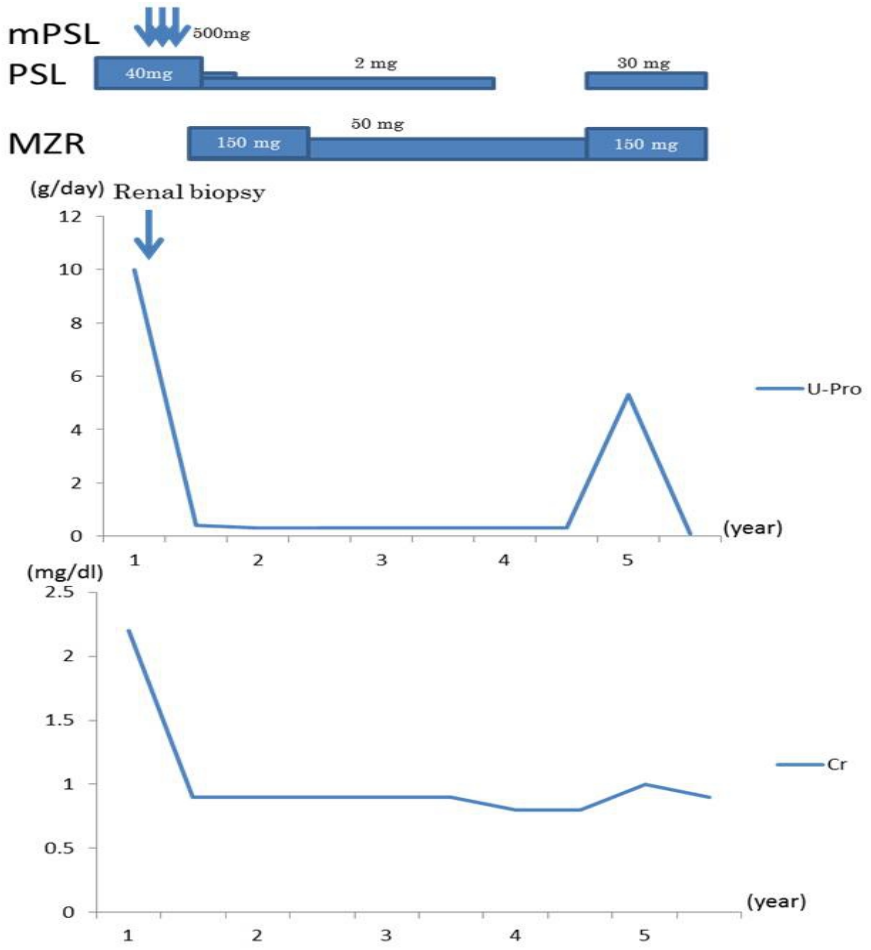

Figure 3: Clinical course

References

1. Yokoyama H, Sugiyama H, Narita I, Saito T, Yamagata K, Nishio S, Fujimoto S,Mori N, Yuzawa Y, Okuda S, Maruyama S, Sato H, Ueda Y, Makino H, Matsuo S. Outcomes of primary nephrotic syndrome in elderly Japanese: retrospective analysis of the Japan Renal Biopsy Registry (J-RBR). Clin Exp Nephrol. 2015;19(3):496–505.

2. Kawasaki Y. Mizoribine: a new approach in the treatment of renal disease. Clin Dev Immunol. 2009; 2009:681482.

3. Sato N, Shiraiwa K, Kai K, Watanabe A, Ogawa S, Kobayashi Y, Yamagishi-Imai H, Utsunomiya Y, Mitarai T. Mizoribine ameliorates the tubulointerstitial fibrosis of obstructive nephropathy. Nephron. 2001; 89(2):177–85.

4. Ikezumi Y, Suzuki T, Karasawa T, Kawachi H, Nikolic-Paterson DJ, Uchiyama M. Use of mizoribine as a rescue drug for steroid-resistant pediatric IgAnephropathy. Pediatr Nephrol. 2008; 23(4):645–50.

5. Tanaka H, Oki E, Tsuruga K, Aizawa-Yashiro T, Ito Y, Sato N, Kawasaki Y,Suzuki J. Mizoribine attenuates renal injury and macrophage infiltration inpatients with severe lupus nephritis. Clin Rheumatol. 2010; 29(9):1049–54.

6. Ikezumi Y, Suzuki T, Karasawa T, Hasegawa H, Kawachi H, Nikolic-Paterson DJ, Uchiyama M. Contrasting effects of steroids and mizoribine on macrophage activation and glomerular lesions in rat thy-1 mesangial proliferative glomerulonephritis. Am J Nephrol. 2010; 31(3):273–82.

7. Aizawa T, Imaizumi T, Tsuruga K, Watanabe S, Chiba Y, Matsumiya T, Yoshida H, Tanaka H. Mizoribine selectively attenuates monocyte chemoattractant protein-1 roduction in cultured human glomerular mesangial cell: a possible benefit of its use in the treatment of lupus nephritis. Nephrology (Carlton). 2014; 19(1):47–52.

8. Nakajo A, Khoshnoodi J, Takenaka H, Hagiwara E, Watanabe T, Kawakami H,Kurayama R, Sekine Y, Bessho F, Takahashi S, Swiatecka-Urban A, Tryggvason K, Yan K. Mizoribine corrects defective nephrin biogenesis by restoring intracellular energy balance. J Am Soc Nephrol. 2007; 18(9):2554–64.

9. Takeuchi S, Hiromura K, Tomioka M, Takahashi S, Sakairi T, Maeshima A, Kaneko Y, Kuroiwa T, Nojima Y. The immunosuppressive drug mizoribine directly prevents podocyte injury in puromycin aminonucleoside nephrosis. Nephron Exp Nephrol. 2010; 116(1):e3–10.

10. Shibasaki T, Matsuda H, Gomi H, Usui M, Ishimoto F, Sakai O. Mizoribine reduces urinary protein excretion in rats given puromycin aminonucleoside. Am J Nephrol. 1996; 16(2):167–72.

11. Fujita T, Shimizu C, Ito K, Fuke Y, Satomura A, Matsumoto K. Anti-proteinuric effect of mizoribine monotherapy in three patients with membranous nephropathy. Clin Nephrol. 2010; 74(1):81–2.

12. Yoshioka K, Ohashi Y, Sakai T, Ito H, Yoshikawa N, Nakamura H, Tanizawa T, Wada H, Maki S. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. Kidney Int. 2000; 58(1):317–24.

13. Hara S, Umino D, Someya T, Fujinaga S, Ohtomo Y, Murakami H, Shimizu T. Protective effects of mizoribine on cyclosporine A nephropathy in rats. Pediatr Res. 2009; 66(5):524–7.

14. Hirose C, Aizawa T, Watanabe S, Tsuruga K, Ito E, Tanaka H. Efficacy of long-term multidrug therapy in a patient with focal segmental glomerulosclerosis. Pediatr Int. 2014; 56(1):129–30.

15. Kawasaki Y. Mizoribine: a new approach in the treatment of renal disease. Clin Dev Immunol. 2009; 2009:681482.

16. Doi T, Masaki T, Shiraki N, Kawai T, Yorioka N. Oral mizoribine pulse therapy for steroid-dependent focal segmental glomerulosclerosis. ClinNephrol. 2008; 69(6):433–5.

Manuscript Information: Received: June 25, 2016; Accepted: August 10, 2016; Published: August 13, 2016

Authors Information: Tetsuhiko Yasuno*; Miyata Masaaki; Renya Watanabe; Aki Hamauchi; Kenji Ito; Yasuhiro Abe; Yoshie Sasatomi; Hitoshi Nakashima
Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, Japan

Citation: Yasuno T, Masaaki M, Watanabe R, Hamauchi A, Ito K, Abe Y, et al.. Successful treatment of elderly-onset minimal change nephrotic syndrome by using mizoribine. Open J Clin Med Case Rep. 2016; 1150

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**

For reprints & other information, contact editorial office at **info@jclinmedcasereports.com**