

Original

Comparison of the Therapeutic Effects on the Renal and Life Prognosis in ANCA-associated Nephritis

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Summary

ANCA-associated rapidly progressive glomerulonephritis has been treated with steroid pulse therapy (mPSL pulse), cyclophosphamide pulse therapy (IVCY), rituximab (RTX), and plasma exchange (PE), but the differences in renal and life outcomes are not fully understood. To determine the long-term prognostic impact of plasma exchange in ANCA-associated rapidly progressive glomerulonephritis, we conducted a retrospective observational study with stratification by treatment modality to determine the prognostic impact of plasma exchange in ANCA-associated rapidly progressive glomerulonephritis. Eighty patients with ANCA-associated glomerulonephritis who underwent renal biopsy at our hospital were divided into 5 groups, and the renal and life prognosis were evaluated. IVCY and RTX significantly improved renal survival compared with steroid therapy and PE. PE and PSL oral groups did not improve renal prognosis, but survived without death during the observation period. PE is introduced in patients requiring hemodialysis at biopsy to rapidly reduce ANCA levels with favorable life prognosis.

Key Words: ANCA, plasma exchange, steroid, cyclophosphamide, rituximab

Introduction

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic inflammatory disease that causes inflammation in small to medium-sized blood vessels throughout the body. These include microscopic polyangiitis (MPA), polyangiogranulomatosis (GPA), and eosinophilic polyangiitis granulomatosa (EGPA), all of which cause systemic vascular inflammation, resulting in organ damage such as rapidly progressive glomerulonephritis (RPGN), interstitial pneumonia, alveolar hemorrhage, neuritis, and gastroenteritis¹⁾. In particular, RPGN is often accompanied by cres-

cent formation in the renal tissue, and the prognosis and response to treatment are often estimated based on these findings and laboratory test results to determine a treatment plan. Treatment options include steroid pulse therapy, cyclophosphamide pulse therapy, rituximab, and plasma exchange. However, large amounts of steroids or immunosuppressive drugs often cause higher mortality due to their side effects and complications (e.g., infection). Therefore, there is no established treatment strategy, with strategies often varying between institutions and physicians, and the optimal treatment in terms of the renal and life prognosis is not fully understood²⁾.

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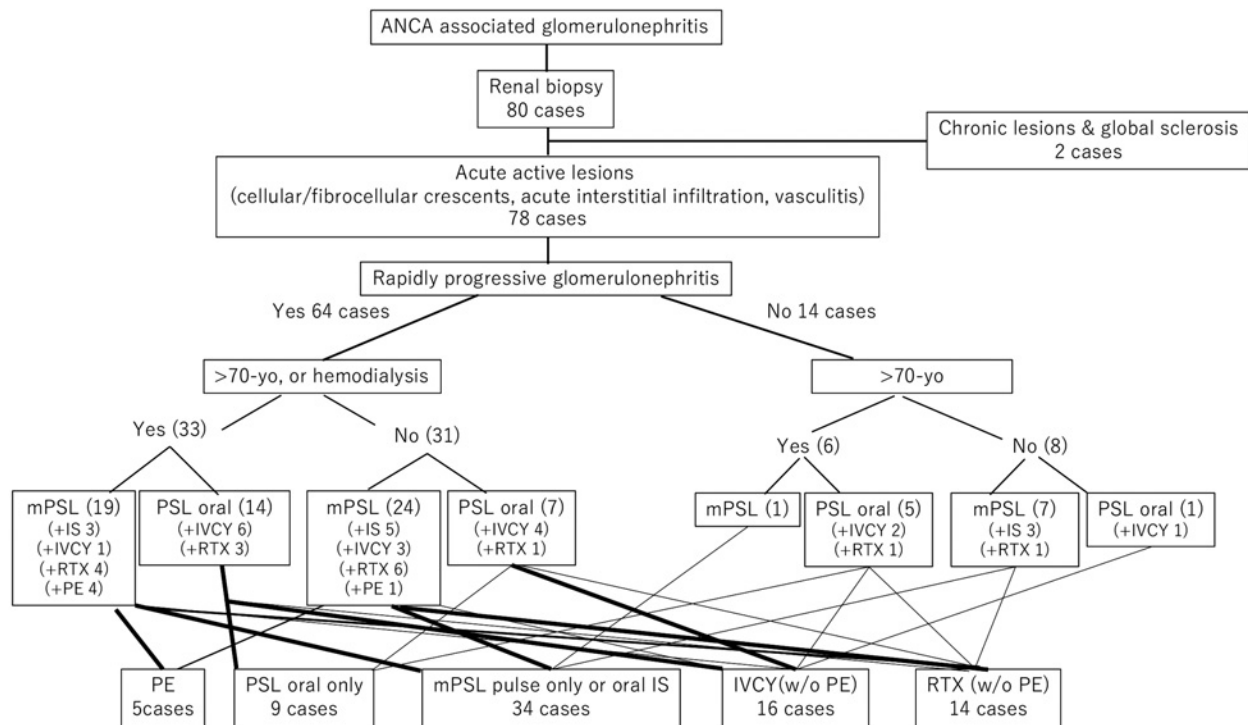


Figure 1 Treatment groups and their combination therapies.

ANCA: antineutrophil cytoplasmic antibody, PSL: prednisolone, mPSL: methyl prednisolone pulse therapy, PE: plasma exchange, IVCY: intravenous cyclophosphamide, RTX: rituximab.

Plasma exchange is expected to be useful because it can remove ANCA without immunosuppression, but it is only indicated for patients with alveolar hemorrhage or anti-GBM antibodies. In this study, we compared the renal and life outcomes of different treatment modalities, and clarified the indications for plasma exchange and its usefulness.

Subjects and Methods

Eighty patients with ANCA-associated RPGN who underwent renal biopsy between 2001 and 2021 were included in the present study, including 70 cases of MPO-ANCA, 7 cases of PR3-ANCA, 1 case of MPO-ANCA + PR3-ANCA, and 2 cases of MPO-ANCA + positive anti-GBM antibody.

After excluding two patients who were not treated with steroids or immunosuppressive drugs, 78 patients were analyzed in this study. The mean age of the patients was 66 years (24-84 years), 38 patients were male and 42 patients were female. The patients were divided into 5 groups according to their treatments as shown in Fig. 1: the PSL pulse group ($n = 34$ [6 of whom were additionally treated with oral immunosup-

pressive drugs (IS)], the PSL oral group ($n = 9$), the PE group ($n = 5$), the IVCY group ($n = 16$), and the RTX group ($n = 14$). Treatment selection and its combination depended primarily on patient age, hemodialysis, and disease activity based on the Japanese Society of Nephrology guidelines for rapidly progressive glomerulonephritis^{3,4}. The rate of reduction of ANCA, rate of dialysis induction, time to dialysis induction, mortality rate, and hemodialysis-free renal survival rate were compared among these 5 groups. This is a single center study that was approved by the Clinical Research Ethics Committee of Dokkyo Medical University (No. R-2-1, R71-3J) and conducted in accordance with the Helsinki Declaration and Dokkyo Medical University Clinical Research Guidelines.

Statistics

Data are expressed as mean \pm SE. The clinical data at renal biopsy, one month after treatment and final observation was statistically compared among five treatment groups. The data of groups that showed a normal distribution were analyzed by a one-way analysis of variance followed by the Bonferroni post-test for

Table 1 Clinical data at the time of renal biopsy in each treatment groups

	mPSL pulse (n = 34)	PSL oral (n = 9)	PE (n = 5)	IVCY (n = 16)	RTX (n = 14)
Age	65 ± 2	72 ± 2	66 ± 6	68 ± 2	65 ± 4
Male:Female	18:16	4:5	2:3	7:9	7:7
Serum Cr (mg/dL)	3.37 ± 0.50	1.83 ± 0.45	4.61 ± 1.63	1.83 ± 0.41	1.89 ± 0.29
eGFR (mL/min/1.73 m ²)	27.2 ± 4.9	45.6 ± 14.2	19.2 ± 8.7	40.5 ± 6.1	34.1 ± 4.9
Proteinuria (g/gCr)	2.39 ± 0.32	0.98 ± 0.37*	1.90 ± 0.58	1.20 ± 0.28*	1.86 ± 0.40
Urinary RBC (/HPF)	68 ± 6	31 ± 10	59 ± 17	49 ± 8	58 ± 11
Urinary WBC (/HPF)	19 ± 5	15 ± 5	14 ± 3	13 ± 3	13 ± 4
ANCA titer	217 ± 40	206 ± 83	444 ± 270	396 ± 140	235 ± 61
MPA/GPA	32/2	8/1	4/1	14/0	11/3
Percent of cellular and fibrocellular crescent (%)	23 ± 3	14 ± 4	35 ± 11	31 ± 6	29 ± 7
Extrarenal involvement (%)					
Pulmonary	9	22	20	63	50
Ear nose and throat	0	0	0	6	14
Nervous system	0	33	0	13	7
Cardiovascular	6	0	0	0	0
Cutaneous	3	0	0	19	7
BVAS scores	14 ± 0.8	17 ± 1.3	14 ± 1	14 ± 1.4	15 ± 1.4

*P < 0.05 vs. PSL pulse. mPSL: methyl prednisolone, PSL: prednisolone, PE: plasma exchange, IVCY: intravenous cyclophosphamide, RTX: rituximab, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, BVAS: Birmingham Vasculitis Activity Scores.

comparisons between groups. A Kruskal-Wallis non-parametric analysis followed by Steel-Dwass multiplex comparison was performed for the analysis of non-normally distributed data. An age- and sex-adjusted Cox biohazard analysis was performed to identify independent risk factors for renal and life prognosis. The comparison of renal and life survival was performed by a Kaplan-Meier analysis and the difference among groups was analyzed with the log-rank test. Statistical analyses were performed using SSRI software version 1.02 (Social Survey Research Information Co., Ltd. Tokyo, Japan) and p values of < 0.05 were considered statistically significant.

Results

There was no significant difference in age among the treatment groups, but the PSL oral group was slightly older, with a mean age of 72 years; the PE group had relatively higher serum creatinine at biopsy, with 40% of these patients introduced to hemodialysis soon after renal biopsy (Table 1). The IVCY group was selected for patients with relatively mild renal dysfunction (Cr 1.83 ± 0.41 mg/dL) because of the difficulty of

dose-adjustment of IVCY when renal function declined. The percentage of cellular and fibrocellular crescents in the IVCY group was second only to that in the PE group, although the difference was not statistically significant (Table 1). Involvement of extrarenal organs such as lung, skin, and otolaryngeal lesions was more common in the IVCY and RTX groups, but the Birmingham Vasculitis Activity Score (BVAS) was not statistically different among the five groups (Table 1).

The possible risk factors for renal prognosis were eGFR and proteinuria at the time of renal biopsy, but not ANCA titers (Table 2). A possible risk factor for life prognosis was eGFR, but treatment group was not a significantly independent risk factor (Table 2).

The PE and IVCY groups had high ANCA levels at the time of renal biopsy, which rapidly decreased after the start of treatment. The RTX group had high ANCA levels in the first month of treatment with no immediate effect, but eventually decreased to an average of 10 U/mL. The PE group had the highest serum creatinine levels at the time of renal biopsy, and in some cases the improvement in ANCA titer rapidly allowed temporary withdrawal from dialysis, but reintro-

Table 2 Age- and sex-adjusted Cox biohazard analysis of the risk factors for renal and life prognosis

Risk factors for renal survival	Hazard ratio	95% CI	p value	Risk factors for life survival	Hazard ratio	95% CI	p value
eGFR at renal biopsy	0.861	0.782-0.948	0.0024	Treatment (mPSL1, PSLoral2, PE3, IVCY4, RTX5)	1.560	0.96-2.54	0.072
proteinuria at biopsy	1.423	1.108-1.826	0.0057	eGFR at renal biopsy	0.892	0.81-0.98	0.017
ANCA titer at biopsy	1.001	0.999-1.003	0.0781				

CI: confidence interval, mPSL: methyl prednisolone, PSL: prednisolone, PE: plasma exchange, IVCY: intravenous cyclophosphamide, RTX: rituximab.

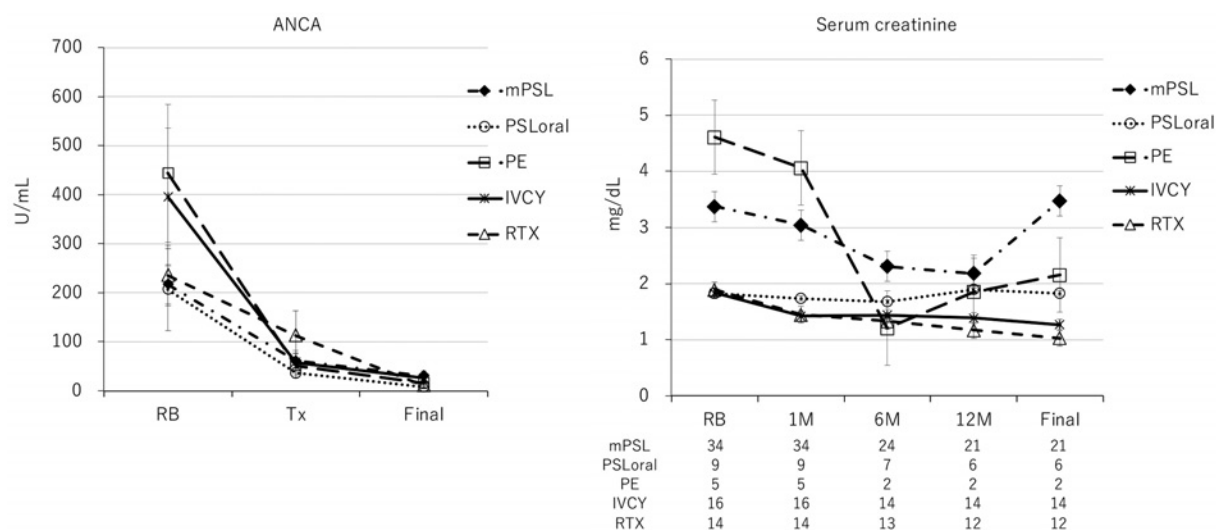


Figure 2 ANCA titers and serum creatinine levels at renal biopsy, after 1 month (1M), 6 months (6M) and 12 months (12M) of treatment and at the final observation in each treatment group, including methyl prednisolone pulse therapy group (mPSL), oral prednisolone group (PSLoral), plasma exchange group (PE), intravenous cyclophosphamide group (IVCY), and rituximab treatment group (RTX).

duction was also common (Fig. 2).

The mPSL pulse group also had high serum creatinine levels second to that in the PE group at the time of renal biopsy, and in many cases, creatinine levels temporarily improved after treatment but in some cases it rose again. The IVCY, RTX, and PSL oral groups had an average serum creatinine level of < 2 mg/dl at the time of renal biopsy, and the IVCY and RTX groups showed improvement in serum creatinine levels after treatment (Fig. 2).

Cumulative mortality was higher in the RTX and IVCY groups within 48 months (Fig. 3); these deaths were mainly due to infection and malignancy (Table 3). The PE and PSL oral groups had the best life prognosis with no deaths until 120 months (Fig. 3).

For renal survival, 80% of patients in the PE group

received dialysis within 36 months. Fifty percent of patients in the PSL oral group and 30% in the mPSL pulse group underwent dialysis within 90 months. Only 10% of patients in the RTX and no patients in the IVCY group had introduced hemodialysis until 90 months (Fig. 4).

Renal survival and life survival were compared with and without each mPSL pulse, IS, RTX, or PE therapy to determine the effect of each treatment in the five groups of patients receiving the combination therapy (Fig. 5). Renal prognosis was significantly better in the IS group, which included IVCY, oral cyclosporine A, mizoribine, and cyclophosphamide. However, mPSL pulse therapy was associated with worse renal and life outcomes than no mPSL pulse therapy, because these therapies were selected in severely advanced cases.

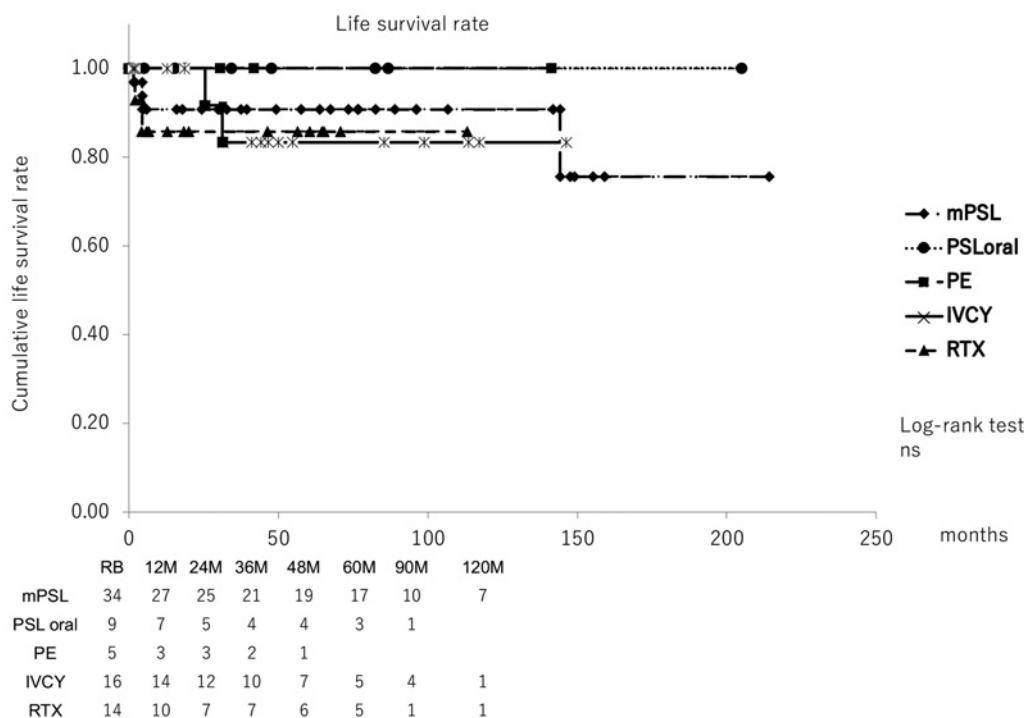


Figure 3 Kaplan-Meier life survival rate after diagnosis of ANCA-associated vasculitis in each treatment group, including methyl prednisolone pulse therapy group (mPSL), oral prednisolone group (PSLoral), plasma exchange group (PE), intravenous cyclophosphamide group (IVCY), and rituximab treatment group (RTX). The long-rank analysis showed no statistical difference with $p = 0.76$.

Table 3 Life survival and causes of death in each group

	mPSL pulse (n = 34)	PSL oral (n = 9)	PE (n = 5)	IVCY (n = 16)	RTX (n = 14)
Mean (median) observation period (months), min-max	68 (61) 1-214	55 (34) 1-205	44 (31) 3-141	56 (45) 1-146	39 (33) 2-113
Percentage of death (%)	11.8	0	0	12.5	14.3
Infection	2	0	0	1	2
Malignancy	1	0	0	1	0
Cardiovascular diseases	1	0	0	0	0

mPSL: methyl prednisolone, PSL: prednisolone, PE: plasma exchange, IVCY: intravenous cyclophosphamide, RTX: rituximab.

PE therapy was selected for patients with poor renal prognosis requiring hemodialysis, but the life prognosis with PE therapy did not show mortality until 150 months (Fig. 5).

Discussion

The IVCY or PE group had high ANCA levels before treatment, but ANCA levels could be rapidly reduced by treatment, and the rate of dialysis induction

was zero in the IVCY group. It has been reported that ANCA directly activates neutrophils, which adhere to and penetrate blood vessels and release various inflammatory mediators and stimulating factors⁵. Therefore, it is thought that the combination of immunosuppressive agents and plasma exchange can better suppress inflammation than steroids alone, and plasma exchange can directly eliminate ANCA, thereby inhibiting the progression of renal tissue inflammation and fibrosis.

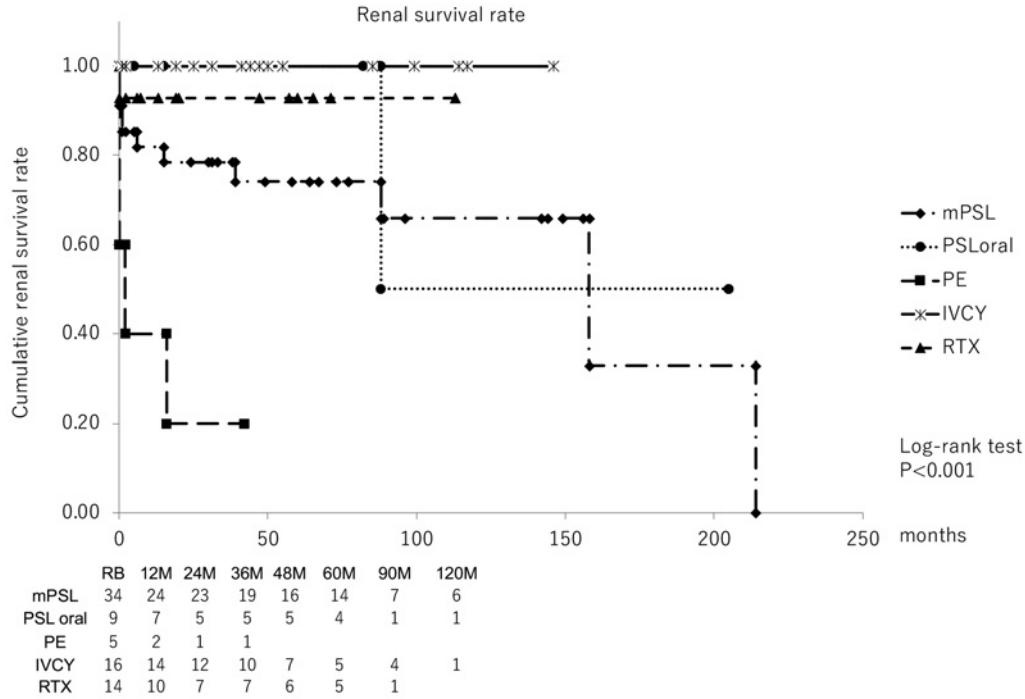


Figure 4 Kaplan-Meier renal survival rate after diagnosis of ANCA-associated vasculitis in each treatment group, including methyl prednisolone pulse therapy group (mPSL), oral prednisolone group (PSLoral), plasma exchange group (PE), intravenous cyclophosphamide group (IVCY), and rituximab treatment group (RTX). The long-rank analysis showed significant difference with $p = 0.001$.

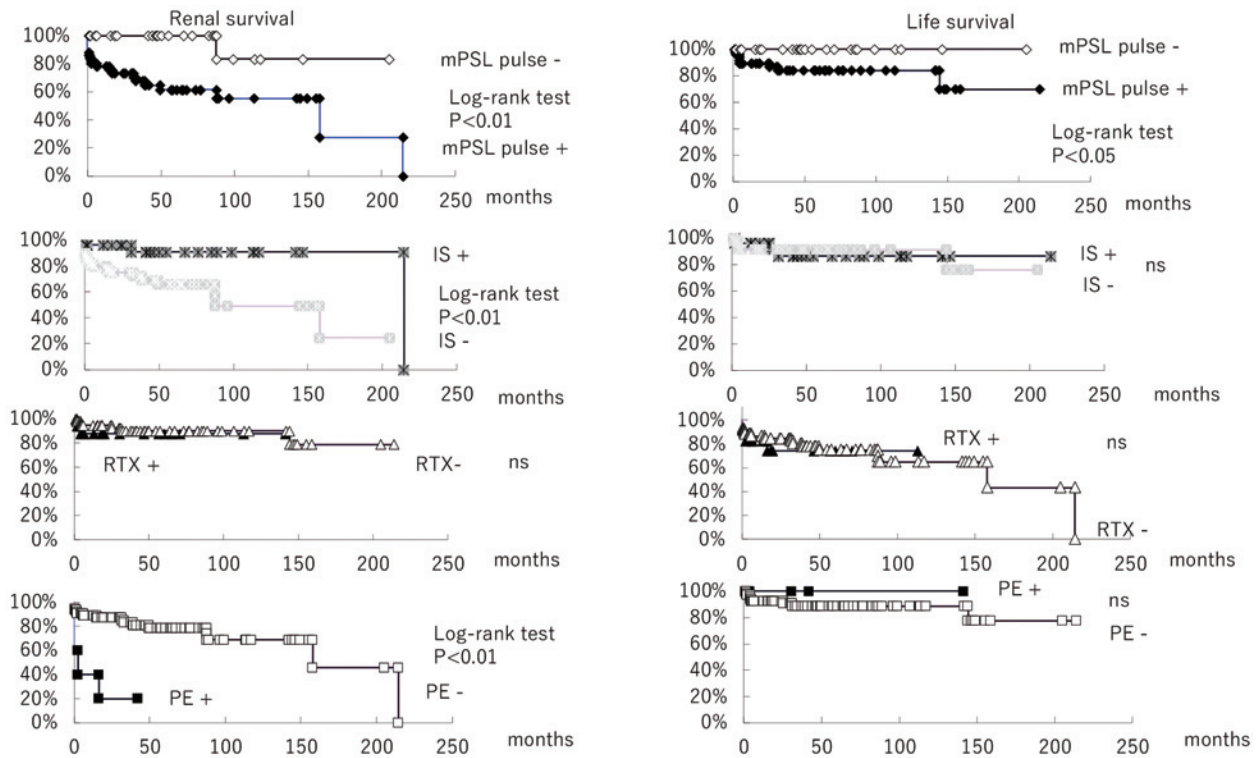


Figure 5 Kaplan-Meier renal and life survival rate of ANCA-associated vasculitis with or without methyl prednisolone pulse therapy (mPSL), immunosuppressant (IS), rituximab treatment group (RTX), or plasma exchange group (PE).

Studies have reported that plasma exchange was effective in patients with vasculitis and severe renal dysfunction⁶ and that the combination of steroids, cyclophosphamide, and PE reduced mortality⁷. In the present study, treatment with PE also led to improvement of renal function and a temporary withdrawal from dialysis with the early phase and no induction of hemodialysis was achieved in the IVCY groups.

Oral PSL was selected for older patients with fewer active crescents. Approximately 40% of them patients were introduced to dialysis, however, the life expectancy of the PSL oral group was better than that of other treatment groups and these patients survived more than 200 months. The PE group had significantly higher serum creatinine levels at renal biopsy, which was associated with the most active crescent formation, and some patients in the PE group were already introduced to hemodialysis at the time of biopsy. Even after temporary withdrawal from dialysis, most patients in the PE group were reintroduced to hemodialysis. The life expectancy was the best with the PSL oral group, but the RTX and IVCY groups had higher mortality rates than the other treatment modalities. Infection associated with immunosuppression was the main cause of death in patients with ANCA-associated vasculitis, and the risk was higher in proportion to the cumulative dose of immunosuppressive drugs and the intensity of immunosuppression⁸; the risk of infection was similar for newer immunosuppressive drugs such as RTX^{9,10}. The PSL oral group could temporarily reduce ANCA but could not sufficiently suppress ANCA production, which may explain the higher incidence of dialysis induction in comparison to the immunosuppressive group. However, in terms of long-term life prognosis, the risk of infection in the PSL oral group was lower than that in the immunosuppressive group; thus, the life prognosis was better.

A randomized trial in severe ANCA-associated vasculitis with eGFR < 50 mL/min/1.73 m² found that the use of plasma exchange did not reduce the incidence of death or end-stage kidney disease¹¹.

A meta-analysis of patients with ANCA-associated vasculitis treated with plasma exchange versus steroid pulse alone found no significant differences in mortality, complete remission, or adverse events¹². However, the results of the present study suggest that the com-

ination of immunosuppressive drugs and plasma exchange may improve the life prognosis of patients with severe disease who require dialysis on admission by rapidly reducing ANCA and preventing exacerbations in the acute phase, and by reducing the risk of infection in the chronic phase.

Limitations

This is a retrospective observational study that observed patients with ANCA-associated glomerulonephritis over 200 months. However, there are limitations such as the selection of treatment methods and their combinations, and the number of patients in each group is not large enough, especially in the PE group. Recurrence was observed during long-term observation of treatments with steroids and immunosuppressants, and doses were increased/decreased. The number and intervals of IVCY, RTX, and PE are different for each patient. These changes in treatment content affect renal function and prognosis, but evaluation was difficult. A randomized prospective study using the same fixed treatment protocol is required to accurately assess the efficacy of each treatment.

Conclusion

Plasma exchange performed via a jugular catheter in patients requiring hemodialysis induction at renal biopsy did not improve renal prognosis compared with the IVCY and RTX groups, but was safe with a favorable life prognosis.

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Author Contribution

Conception and design of the study, AT; acquisition and analysis of data, SY, AT; drafting the manuscript or figures, SY; writing—review and editing, AT; visualization, AT; supervision, AT; project administration, AT; funding acquisition, AT. All authors have read and agreed to the published version of the manuscript.

Disclosure Statement

The authors declare no conflicts of interest in association with the present study.

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