# Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in Japan: A Nationwide, Prospective Cohort Study

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***ABSTRACT. Objective.*** The aim was to elucidate the prognosis and risk factors associated with relapse during longterm remission maintenance therapy for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

***Methods.*** Patients with newly diagnosed AAV (n = 156) were registered in the Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides (RemIT-JAV) study, and among them, 83 patients who achieved remission were enrolled and followed up for 24 additional months in our nationwide, prospective cohort study (Co-RemIT-JAV; registration number UMIN 000006373). Patterns of maintenance therapy, effectiveness, and safety were evaluated from months 25 to 48 after the RemIT-JAV. The primary outcome measure was the rate of relapse. Secondary outcome measures included overall and renal survival, risk factors associated with relapse, and incidence rates of serious infections.

***Results.*** The patients comprised 35 men and 48 women aged 65.3 ± 12.6 years. Between months 25 and 48, the survival rate was 95% (79/83). Causes of death included 1 thyroid cancer, 1 infection, and 2 unknown reasons. Four patients had developed endstage renal disease (ESRD) by Month 24; 1 developed ESRD beyond Month 25. The relapse rate was 24% (20/83) from months 25 to 48. Multivariable analysis revealed that oral prednisolone ≤ 2.5 mg/day at Month 24 was a significant risk factor for relapse between months 25 and 48 (HR = 3.1, 95% CI 1.1–8.5).

***Conclusion.*** One-quarter of patients with AAV relapsed during maintenance therapy, and relapse was associated with the dose of oral prednisolone 24 months after the initiation of remission induction therapy in Japan. (First Release February 1 2018; J Rheumatol 2018;45:521–8; doi:10.3899/jrheum.170508)

*Key Indexing Terms*:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY RISK FACTORS CORTICOSTEROID
IMMUNOSUPPRESSIVE AGENTS REMISSION-MAINTENANCE THERAPY

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by inflammation and necrosis of small and medium blood vessels, with unknown etiology[1]. Most patients can achieve remission through treatment with high-dose glucocorticoids (GC) and concomitant cyclophosphamide (CYC) or rituximab (RTX) as remission-induction therapy[1,2]. Previously, the regimens for remission-maintenance therapy attracted strong attention from investigators because AAV requires longterm immunosuppressive treatment to prevent relapse, while at the same time preventing and minimizing adverse effects of GC and immunosuppressants, including infection, osteoporosis, cardiovascular diseases, and malignancies[1,2]. However, evidence on the effectiveness and safety of the treatment regimens are limited. Given this background, we previously implemented a retrospective cohort study to elucidate the incidence of relapse and associated risk factors among patients with myeloperoxidase (MPO)-ANCA–positive microscopic polyangiitis (MPA). We reported that the rate of relapse was as high as 24.2%, and the risk of relapse increased when the reduction rate of prednisolone (PSL) was > 0.8 mg/month[3].

In our study, we aimed to investigate current remission maintenance treatments and their effectiveness for overall survival, renal survival, and relapse. We also identified risk factors associated with relapse in Japanese patients with AAV who were prospectively enrolled and followed up for 24 months following the nationwide cohort study, Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides (RemIT-JAV)[4,5].

## MATERIALS AND METHODS

*Database*. We reported the methods of RemIT-JAV elsewhere[4,5]. Briefly, 156 consecutive patients with newly diagnosed AAV were enrolled from 22 tertiary care institutions from April 2009 to December 2010. The criteria for enrollment included a diagnosis of AAV made by the site investigators, fulfilling the criteria for primary systemic vasculitis proposed by the European Medicines Agency algorithm[6]. The site investigators excluded patients with malignancy, infection, drug-induced vasculitis, secondary vasculitis, other types of vasculitides, vasculitis mimics, sarcoidosis, and other nonvasculitis granulomatous disease. Our present study included patients who were followed up for 24 months until the end of the observation period of RemIT-JAV and provided additional informed consent to participate. Of the 156 patients registered in RemIT-JAV, 116 patients were followed up by Month 24. Other patients were lost to followup, or died during the RemIT-JAV study period. Thereafter, the following Co-RemIT-JAV was approved by 16 institutions among 22 that participated in the RemIT-JAV, resulting in further decrease in the number of enrolled patients in our study. Finally, 83 were eligible: 9 were classified with eosinophilic granulomatosis with polyangiitis (GPA), 23 with GPA, 40 with MPA, and 11 were unclassifiable. Our prospective cohort study of remission maintenance therapy in Japanese patients with AAV, which follows on from the RemIT-JAV, is referred to as the Co-RemIT-JAV study.

Our study was implemented in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Written informed consent was obtained from each patient, and the study protocol was approved by the ethics committees of each participating institution, including the medical ethics committee of Kanazawa University (approval number 1115). Co-RemIT-JAV was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000006373).

*Data collection*. Baseline data for each patient in Co-RemIT-JAV, corresponding to data at the end of RemIT-JAV (i.e., Month 24), included demographic information, comorbidities, laboratory data, Birmingham Vasculitis Activity Score (BVAS)[7], and chest imaging data. Patients were evaluated at 6, 12, 18, and 24 months after the start of Co-RemIT-JAV and at relapse. For clarity, we refer to these timepoints as months 30, 36, 42, and 48 from the baseline of the RemIT-JAV throughout this paper. The following data were collected: vital signs, BVAS, laboratory data, treatments, and adverse events. With regard to renal function, the estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR (ml/min/1.73m$^2$) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (if female, × 0.739)[8]. Organ involvement was defined according to the BVAS system. The Vasculitis Damage Index (VDI)[9] was evaluated at months 24, 30, 36, 42, and 48 from the RemIT-JAV baseline. No treatment protocol was provided because Co-RemIT-JAV was an observational study. The selection and dosage of immunosuppressive agents and GC were determined at the discretion of the attending physicians. Site investigators completed the electronic case reports for each patient and submitted them to the Co-RemiT-JAV data center at the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

*Outcomes*. The primary effectiveness outcome of our study was relapse rate. Relapse was defined as recurrence or new onset disease activity attributable to active vasculitis[10]. Remission was defined as BVAS 0 on 2 occasions > 1 month apart, according to the European League Against Rheumatism (EULAR) recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis[5,10]. Major relapse was defined as relapse with organ-threatening or life-threatening disease activity, and other relapses were classified as minor[5,10]. Secondary effectiveness outcomes included cumulative overall endstage renal disease (ESRD)-free and overall survival rates. ESRD was defined as dependence on dialysis or an irreversible increase in serum creatinine level > 5.6 mg/dl (500 μmol/l)[4]. GC other than PSL were converted to an equivalent dose of PSL.

The safety outcomes were type and incidence of serious adverse events and serious infections. Seriousness was defined based on an International Conference on Harmonization report[11]. Bacterial infections that required intravenous administration of antibiotics and opportunistic infections were regarded as serious. A diagnosis of infection was based on the attending physicians' diagnosis, using a comprehensive evaluation of physical, laboratory, and imaging findings.

*Statistical analysis*. In our study, we analyzed data collected at months 24, 30, 36, 42, and 48 from the RemIT-JAV baseline. Followup continued until the final visit, death, or Month 48 (whichever occurred first). Categorical variables were summarized by frequency and percentage, and compared using the chi-square test. Continuous variables were summarized by mean values and SD, and compared using Mann–Whitney U test between 2 groups. Overall survival and relapse-free survival rates were analyzed using the Kaplan–Meier method and log-rank test. A p value of $< 0.05$ was considered statistically significant between 2 categories.

Based on the data collected, the potential risk factors for relapse were identified by univariate analysis. Among the potential risk factors, those that were considered clinically and statistically important were further analyzed using multivariable analysis to investigate their significance. Here, we included the following variables as potential risk factors for relapse: age, sex, BVAS at Month 0, duration from Month 0 to remission, and VDI and dose of GC at Month 24 from the RemIT-JAV baseline. All statistical analyses were performed using the Statistical Package, version 23 (SPSS). No correction for multiple testing of patient characteristics was performed.

## RESULTS

*Patient characteristics*. Patients comprised 35 men and 48 women aged 65 ± 13 years, and had a median followup of 24 months (3–24 mos). Select patient characteristics and treatments are summarized in Supplementary Table 1 (available with the online version of this article). Patients with MPA were older than those with GPA (69.1 vs 60.9 yrs). At the start of the Co-RemIT-JAV, corresponding to Month 24 of the RemIT-JAV, all enrolled patients remained in remission, although MPO-ANCA and proteinase (PR)3-ANCA positivity were observed in 25 and 3 patients, respectively. Mean eGFR was significantly lower in patients with MPA than in patients with GPA. Mean VDI score for all patients was 1.8 ± 1.5 at Month 24. Mean VDI score did not differ significantly between patients with MPA from those with GPA (Month 36 from RemIT-JAV baseline, 2.9 ± 1.8 and 2.5 ± 1.8, respectively, p = 0.31; Month 48, 3.1 ± 1.6 and 2.5 ± 1.9, respectively, p = 0.22; data not shown).

Regarding remission-maintenance therapy, 1 patient did not receive immunosuppressive treatment at Month 24 from the RemIT-JAV baseline. Of the 82 patients who received immunosuppressive treatment, 39 (47.6%) were treated with GC alone, 1 (1.2%) with methotrexate (MTX) alone, and the remaining 42 (51.2%) with GC and an immunosuppressant. The percentage of patients treated with GC and the doses did not differ between the 2 groups. At the final visit, 80 patients were still receiving immunosuppressive treatment, and treatment had been discontinued in the other 3 patients. The mean PSL dose of 6.2 ± 3.0 mg/day at Month 24 from the RemIT-JAV baseline was finally tapered to 5.8 ± 3.6 mg/day during the observation period.

*Relapse*. Of the 83 patients, 20 (24.1%) relapsed during the observation period, including 9 with MPA and 4 with GPA, and the mean duration between Month 24 from the RemIT-JAV baseline and relapse was 3.6 ± 6.8 months (Figure 1A). Of the 20 relapses, 4 were major and 16 were minor. There was no significant difference in relapse rate between patients with MPA and GPA (23% vs 17%, p = 0.69; Figure 1B). There was also no significant difference in relapse rate between MPO-ANCA–positive and proteinase 3 (PR3)-ANCA-positive patients (27% vs 11%, p = 0.43) at Month 48 from the RemIT-JAV baseline, although the former was higher.

*Overall and renal survival*. Four deaths were reported between months 25 and 48 (3 with MPA and 1 with GPA). Causes of death reported by site investigators were thyroid cancer (n = 1), infection (n = 1), and unknown (n = 2). Overall survival rate for all study patients is shown in Figure 2A. The overall survival rate did not differ between patients with MPA and GPA (p = 0.64, Figure 2B). Although 4 patients with MPA had developed ESRD by Month 24 and 1 had developed MPA by Month 30 from the RemIT-JAV baseline, overall eGFR was maintained in patients with MPA and GPA (Figure 3A and Figure 3B, respectively), and no additional cases of ESRD were reported between months 25 and 48.

*Predictors of relapse*. Univariate analysis was performed to determine potential risk factors for relapse. Data for the RemIT-JAV at baseline (i.e., Month 0) and at Month 24 were included in the analysis (Supplementary Table 2, available with the online version of this article). No variables attained the significance level of 0.05 except for PSL dose (mg/day) at Month 24 from the RemIT-JAV baseline (p = 0.05). At the significance level of 0.1, however, the levels of C-reactive protein (p = 0.06) and eGFR (p = 0.07) at Month 0 and eGFR at Month 24 from the RemIT-JAV baseline (p = 0.06) showed statistical significance. As significant categorical variables, infrequent use of CYC within the first 3 weeks of remission induction therapy (p = 0.07) was associated with relapse. Based on these results, we further evaluated the threshold of the PSL dose that could discriminate the risk of relapse using receiver-operating characteristic analysis. The results identified an optimal PSL dose cutoff point of 2.5 mg/day. According to the results of univariate analysis (Supplementary Table 3, available with the online version of this article), we calculated the HR of PSL as ≤ 2.5 mg/day using

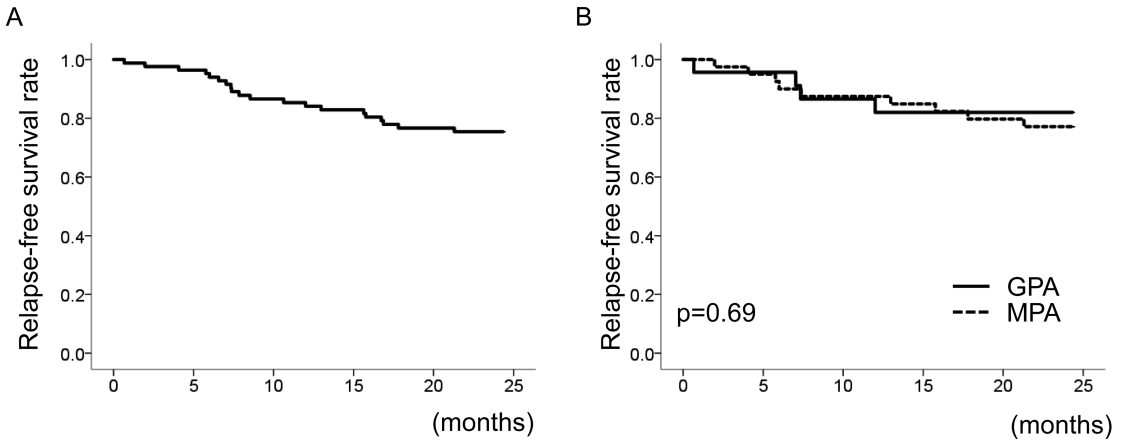


*Figure 1*. Cumulated relapse-free survival rates from months 24 to 48 from the RemIT-JAV baseline in (A) all patients; and (B) subtypes of AAV. AAV: antineutrophil cytoplasmic antibody-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RemIT-JAV: Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides; ANCA: antineutrophil cytoplasmic antibody.

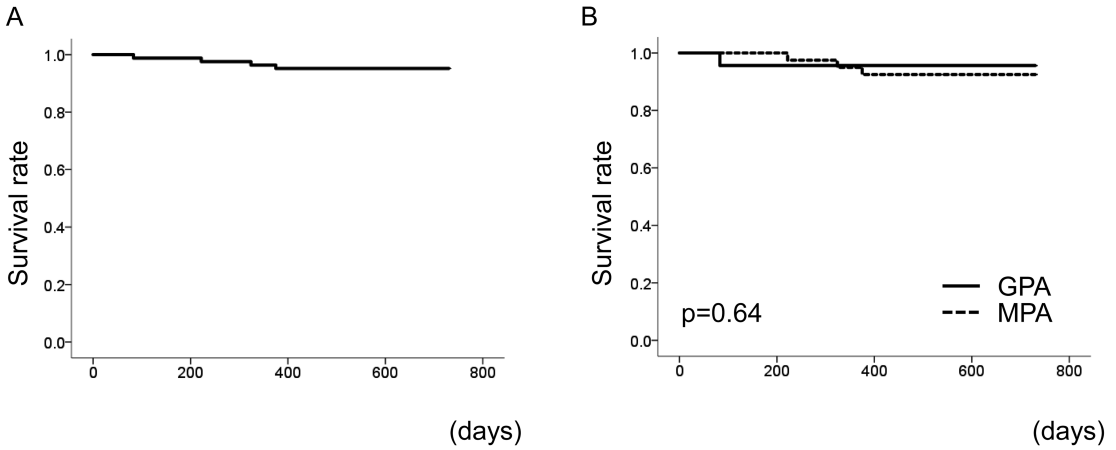


*Figure 2*. Cumulative overall survival rates among (A) all study patients; and (B) subtypes of AAV. AAV: antineutrophil cytoplasmic antibody-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

a Cox proportional hazards model with backward elimination for covariates of age, sex, BVAS at Month 0, duration from Month 0 to remission, and VDI at Month 24 from the RemIT-JAV baseline. Only PSL ≤ 2.5 mg/day at Month 24 after starting remission induction therapy remained in the model, and the HR of relapse was 3.1 (95% CI 1.1–8.5; $p < 0.05$). Beta-coefficients for the univariate analysis of candidate predictors were shown in Supplementary Table 4 (available with the online version of this article). The estimated Kaplan–Meier survival curves stratified by PSL dose revealed that the patients treated with PSL > 2.5 mg/day at Month 24 from the RemIT-JAV baseline showed a significantly improved relapse-free survival rate than those treated with PSL ≤ 2.5 mg/day (Figure 4). Although the mean VDI score of patients treated with PSL at > 2.5 mg/day was higher than that of those treated with PSL at ≤ 2.5 mg/day at Month 24 from the RemIT-JAV baseline (Supplementary Table 3), the difference was not significant thereafter (Month 36 = 2.6 ± 1.8 and 2.2 ± 1.5 and Month 48 = 2.7 ± 1.6 and 2.3 ± 1.7, respectively; data not shown).

*Serious infections and other adverse events*. Between months 25 and 48 from the RemIT-JAV baseline, 14 serious infections in 14 patients (16.9%) were reported. The incidence rate of serious infections was 8.8/100 patient-years. The most frequent site of serious infection was the respiratory system (6 events), followed by the endocardium, subcutaneous tissue, paranasal and oral cavity, pancreatic cyst, and central venous catheter (1 event each). Patients with serious infections were older at disease onset and were more frequently treated with CYC between months 0 and 24 than those without (Supplementary Table 5, available with the online version of this article).

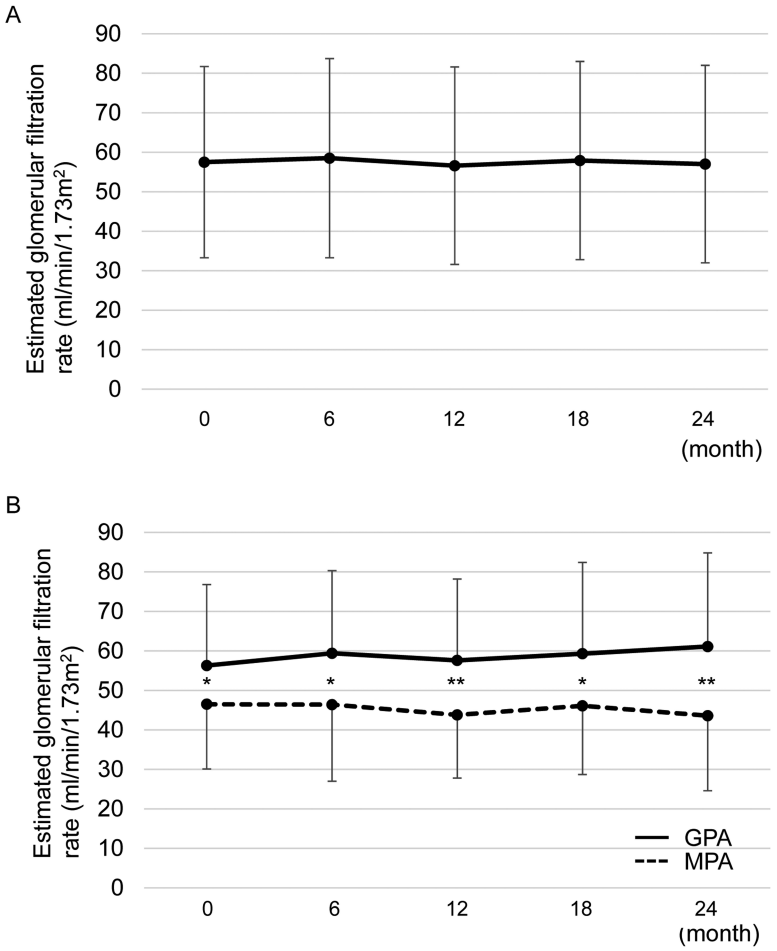


*Figure 3*. Change in eGFR observed from months 24 to 48 from the RemIT-JAV baseline (A) in all patients without ESRD; and (B) in patients with GPA and MPA. Vertical bars represent SD. *p < 0.05 and **p < 0.01 between the 2 groups. eGFR: estimated glomerular filtration rate; ESRD: endstage renal disease; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RemIT-JAV: Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides; ANCA: antineutrophil cytoplasmic antibody.

Other adverse events reported between months 25 to 48 from the RemIT-JAV baseline are shown in Supplementary Table 6 (available with the online version of this article), according to a PSL dose above or below 2.5 mg/day at Month 24.

## DISCUSSION

We conducted a prospective cohort study of Japanese patients with AAV, and the results revealed the relapse rate, risk factors for relapse, and overall and renal prognosis during remission maintenance therapy of AAV. The relapse rate, which was the primary endpoint of our study, was 24.1%, and the mean duration from Month 24 from the RemIT-JAV baseline to relapse was 3.6 months. The GC dose at Month 24 of RemIT-JAV was associated with relapse, with longer relapse-free survival observed in patients treated with PSL > 2.5 mg/day than in those treated with PSL ≤ 2.5 mg/day.

In this Japanese cohort, Co-RemIT-JAV, about 50% of the enrolled patients were diagnosed as MPA-positive for MPO-ANCA, which is in contrast to patients with AAV in Western countries, who are characterized by a predominance of PR3-ANCA and GPA[12]. In the preceding observational study (RemIT-JAV), the mean maximum daily dose of PSL was 41 mg/day for MPA and 40 mg/day for GPA. Within 3 weeks of starting remission induction therapy, 31% of patients with MPA and 60% of patients with GPA were treated with CYC[5]. Almost all patients were treated with low-dose GC, and only half received concomitant immunosuppressive agents at Month 24 from the RemIT-JAV baseline. These patients continued to receive low-dose GC at their last visit in the Co-RemIT-JAV study. This practice differs from that recommended by the EULAR/European Renal Association (ERA)-European Dialysis and Transplant Association (EDTA) guidelines and the British Society for

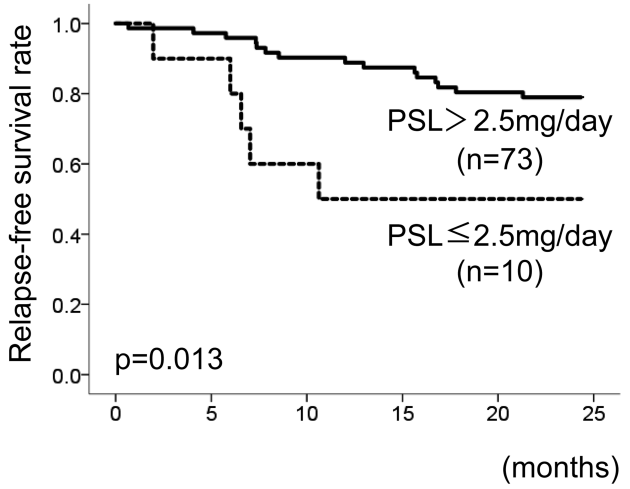


*Figure 4*. Cumulated relapse-free survival rates from months 24 to 48 from the RemIT-JAV baseline according to GC dose at Month 24. GC: glucocorticoid; PSL: prednisolone; RemIT-JAV: Remission Induction Therapy in Japanese patients with ANCA-associated Vasculitides; ANCA: antineutrophil cytoplasmic antibody.

Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines, in which treatment with concomitant use of either azathioprine, MTX, mycophenolate mofetil, or RTX with low-dose GC is recommended as remission maintenance therapy[1,2]. In particular, the percentages of patients who received immunosuppressive agents in our present study are lower than the rates reported in Western observational studies, in which 64-82% of patients were treated with an immunosuppressant plus GC for remission-maintenance therapy[13,14,15,16]. In previous studies, CYC is not commonly administered in Japan for MPA, because these patients often present with progressive renal impairment at an advanced age and are considered at high risk of severe infections[13,17,18]. Despite the differences in types and doses of immunosuppressive agents between Western countries and Japan, most Japanese patients with AAV continued to receive immunosuppression therapy for ≥ 4 years, as recommended by the EULAR/ERA-EDTA, and the BSR and BHPR guidelines[1,2].

In our present study, 24% of patients with AAV relapsed during remission maintenance therapy. The rate of relapse was within the range of 15–46% as reported in Europe and the United States[19,20,21,22], and similar to that observed in our previous retrospective study[3]. The high relapse rates observed in the European studies were associated with discontinuation of the study drugs or oral GC[21,22]. Therefore, as recommended by the latest guidelines from Western countries, remission maintenance therapy for AAV should be continued for ≥ 24 months, and in some cases for up to 5 years, once disease remission is achieved[1,2].

Our study showed that GC dose at Month 24 from the RemIT-JAV baseline was associated with relapse. Previous studies identified risk factors for relapse, such as upper respiratory tract and pulmonary lesions, and positive serology for PR3-ANCA[15,23,24]. Early cessation of maintenance therapy is also associated with an increased risk of relapse[25,26]. A metaanalysis of 13 studies involving 983 participants showed that continuation of GC is associated with reduced incidence of relapse compared with withdrawal (14% vs 43%)[27]. While the EULAR/ERA-EDTA, BSR, and BHPR guidelines recommend that remission-maintenance therapy for AAV be continued for ≥ 24 months following induction of sustained remission based on available evidence, a detailed regimen for the reduction of GC has not been described in their latest versions[1,2]. The PSL dose of 2.5 mg/day at Month 24 from the RemIT-JAV baseline corresponds to the dose recommended by the European Vasculitis Study Group at 18 months from the start of treatment in an oral corticosteroid-dosing regimen[28]. This difference of 6 months may reflect the lower frequency of concomitant use of immunosuppressive agents for remission maintenance therapy in Japan (51%) compared with Western countries. A previous longterm analysis of the WEGENT Trial reported that at the last update (median followup time 11.9 yrs), 46% of the patients were still taking GC (5.0–7.0 mg/day)[29]. While significant variability in GC dosing during remission-maintenance therapy may be accompanied with selection bias, and therefore have to be interpreted carefully, the GC dose obtained in our current study could be a minimum reference dose for the prevention of relapse during maintenance therapy in AAV.

The incidence rate of serious infections in our present study was higher than that found in previous studies from European countries (5-7%)[21,22,26]. While continuation of low-dose GC may be associated with fewer relapses, as mentioned, patients who were treated with CYC between months 0 and 24 from the RemIT-JAV baseline had a higher risk of subsequent severe infection, as assessed by univariate analysis. We could not perform multivariable analysis because of the small number of serious infections in our present study. Of note, there may be important differences including in severity of renal impairment in patients treated with or without CYC. It is also likely that there is a bias in that treating physicians choose to use CYC in patients with more severe disease. Our observational cohort study cannot elucidate these issues. Nonetheless, prudent assessment of the risks and benefits of longterm treatment with GC and concomitant immunosuppressive agents, especially regarding infection in older patients, is required in current practice. Optimal duration and dose of maintenance therapy should be investigated in future studies.

In our study, VDI scores were generally stable and there were no cases of ESRD between months 25 and 48 from the RemIT-JAV baseline. This finding is comparable with previous studies[19,22]. High VDI scores during remission were associated with relapse and infections[30]. In our present study, there was no statistical association between VDI score at

Month 24 and subsequent relapse or severe infection. Because there was a low incidence of relapse and serious infection, the association between progressive damage, relapse, and infection should be clarified in a larger cohort.

Our study has several limitations. First, the preceding study, RemIT-JAV, included 156 patients, but only 83 were eligible for this Co-RemIT-JAV study. We cannot exclude the possibility of selection bias. Second, institutional bias should be considered because our study involved university and tertiary hospitals in Japan. Third, we could not perform stratified analysis and sufficient multivariable analysis of the outcomes because of the small sample size. Also, we could not perform sufficient comparisons between the MPO-ANCA–positive and PR3-ANCA–positive patient groups because of the small number of PR3-ANCA–positive patients in this cohort. This problem will be addressed in the future by combining data from our study and another large-scale cohort study of Japanese patients with AAV that is currently under way. Fourth, our effectiveness data, including factors associated with relapse, may have been affected by indication bias because the treatments were determined at the discretion of the attending physicians. Despite these limitations, our prospective 24-month cohort study provided useful information on remission maintenance therapy in AAV.

Most of the Japanese patients with AAV received treatment with low-dose GC and half received immunosuppressants 24 months after the initiation of remission induction therapy. A PSL dose of ≤ 2.5 mg/day at that time was associated with later relapse, and the overall rate of relapse was 24%. Further studies are needed to optimize maintenance therapy for Japanese patients with AAV.


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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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