Risk Factors Associated with Relapse in Japanese Patients with Microscopic Polyangiitis

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ABSTRACT. ***Objective.*** We retrospectively studied the risk factors associated with relapse during remission maintenance therapy for myeloperoxidase-antineutrophil cytoplasmic autoantibody (MPO-ANCA)-positive microscopic polyangiitis (MPA).

Methods. Sixty-two patients diagnosed with MPA according to the European Medicines Agency classification algorithm during a 2-year period from January 1, 2005, to December 31, 2006, and who achieved remission after the first remission-induction therapy, were examined (registration no. UMIN000001785).

Results. The patient group comprised 25 men and 37 women aged 70.0 ± 8.9 years. The mean observation period was 30.2 ± 15.9 months. The rate of relapse was 24.2% (15/62), and mean interval between remission and relapse was 16.9 ± 13.5 months. During maintenance therapy following remission, the risk of relapse increased when the reduction rate of prednisolone increased above 0.8 mg/month (OR 12.6, 95% CI 2.2–97.9). Proteinuria at the start of maintenance therapy (regression coefficient 1.991 ± 0.758, $p < 0.05$) and the change in red blood cell counts in urine during the period from the start of maintenance therapy to the final observation (regression coefficient 0.126 ± 0.040, $p < 0.01$) were identified as risk factors influencing the vasculitis damage index.

Conclusion. In Japan, relapse of MPO-ANCA-positive MPA may be associated with the reduction rate of oral prednisolone administration during maintenance therapy. (First Release Dec 15 2011; J Rheumatol 2012;39:545–51; doi:10.3899/jrheum.110705)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY
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Microscopic polyangiitis (MPA), the most prevalent small- to medium-vessel vasculitis in Japan, is mostly positive for myeloperoxidase-antineutrophil cytoplasmic autoantibody (MPO-ANCA). MPA has been reported to have a high relapse rate and requires longterm immunosuppressive treatment for relapse prevention[1,2,3]. Because MPA is prevalent among the elderly, longterm immunosuppressive treatment often causes side effects such as infection and bone complications. In Japan MPA is treated by an attending physician who follows the guidelines for remission maintenance therapy issued by the Intractable Vasculitis Investigative Research Team of the Ministry of Health, Labor and Welfare (Clinical manual for vasculitis, March 2002)[4]. In order to revise the current guidelines to make them evidence-based, it is necessary to elucidate the risk factors associated with the relapse of MPA and to prospectively investigate the efficacy of drugs used in remission maintenance therapy. We performed a retrospective cohort study to determine the incidence of relapse and the risk factors among patients with MPO-ANCA-positive MPA, and to investigate the factors that influence the vasculitis damage index (VDI).

MATERIALS AND METHODS

Patient selection and definitions. Our study enrolled Japanese patients who had been diagnosed with MPO-ANCA-positive MPA for the first time at collaborating institutions during a 2-year period from January 1, 2005, to December 31, 2006, and who achieved remission following the first remission-induction therapy. Diagnosis of MPA was made according to the European Medicines Agency (EMEA) classification algorithm[5]. Patients met the definition of primary systemic vasculitis, but were excluded if they had Churg-Strauss syndrome or granulomatosis with polyangiitis (Wegener's).

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Patients also presented with clinical features and histology compatible with small-vessel vasculitis, and had no surrogate markers for granulomatosis with polyangiitis (Wegener's). In cases with no histological findings of MPA, patients were diagnosed with MPA if they were positive against both ANCA and surrogate markers for renal vasculitis. Some of the ANCA-positive patients who presented with vasculitis-associated organ damage in the kidney only were diagnosed with renal limited MPA (renal limited vasculitis), and were included in our study.

Because this was a retrospective observational study, we followed the Ethical Guidelines for Epidemiologic Research issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare of Japan (registration no. UMIN000001785). We also obtained approval from the relevant Ethics Committees at the principal research facility and collaborative institutions.

The Birmingham Vasculitis Activity Score (BVAS2003) was used to evaluate disease activity[6]. For BVAS2003 scoring, we listed clinical features associated with active vasculitis that had newly appeared (new) or worsened (worse) in the past 4 weeks[6]. In the initial assessment, however, to avoid the possibility of eliminating symptoms and dysfunctions that had persisted for over a month, we decided to include all cases of vasculitis-associated disorder (persistent) that existed prior to therapy. In the second and final assessment, we listed those features identified as newly appeared or worsened during the previous 4 weeks. The VDI was used to score irreversible events persisting for at least 3 months[6,7], and the damage included events attributable to the vasculitis syndrome, complications of treatment, infection, or concurrent diseases.

Treatment following the diagnosis of MPA was categorized as remission-induction therapy and maintenance therapy[8,9]. In remission-induction therapy, corticosteroid (CS) treatment including methylprednisolone pulse treatment (500 mg or 1000 mg/day for 3 days) was performed. To evaluate the efficacy of oral CS, the dose was converted into that of prednisolone (PSL) using the simple equation of 5 mg PSL = 4 mg methylprednisolone. Cyclophosphamide (CYC) was administered orally or by intravenous infusion. Patients were considered to have undergone immunosuppressive treatment if they received CS treatment and/or immunosuppressants [azathioprine (AZA), methotrexate (MTX), mizoribine, and tacrolimus]. Depending on the disease activity of each patient, plasma exchange (PE) and/or intravenous immunoglobulin (IVIG) treatment were selected as supplementary treatment. Maintenance therapy was defined as all treatments started when a patient met the criteria of remission after remission-induction therapy.

We collected clinical records for patient information such as clinical imaging, laboratory data, treatment regimen, and complications during followup to determine whether each patient was in a state of remission or relapse. We considered that remission had been achieved when disease activity due to active vasculitis was not observed (BVAS2003 = 0) during 2 clinical evaluations performed more than 1 month apart[10]. Relapse was defined as the recurrence or new onset of disease activity (BVAS2003 ≥ 1)[10].

We also investigated infection, defined as a condition that required hospitalization (except for upper respiratory inflammation) and the administration of antibiotics, antiviral agents, or antifungal/mycotic medication (except for superficial trichophytosis).

Statistical analysis. We comparatively studied relapse rate, the main evaluation item in our study, until the final observation using the Cox proportional hazards model and the Kaplan-Meier method. The results were expressed with a p value and an OR with a 95% CI. The final observation for relapse patients was taken as the time of relapse, while the final observation for those who did not relapse was taken as the time of the last observation. For those who died of anything other than disease activity, their final observation was taken as time of death.

On the basis of data collected, univariate analysis was performed to determine potential risk factors for relapse. Among the potential risk factors, those that were considered clinically and statistically important were further analyzed using multivariate analysis to investigate their independence. With regard to the change in VDI, multiple linear regression analysis was performed to comparatively analyze the change in VDI by setting VDI at the time of final observation as the independent variable and the observed outcome as the dependent variable. Further, association analysis between relapse and the presence of MPO-ANCA at the start of maintenance therapy was performed. All statistical analysis was performed using the statistical language R (version 2.11.1)[11].

RESULTS

Patient characteristics and treatment outcomes. We collected 68 survey responses from 18 institutions during the survey period until January 2010 and evaluated them according to the EMEA algorithm. Results revealed 6 cases of granulomatosis with polyangiitis (Wegener's), which were excluded, leaving 62 cases to study further. The mean observation period was 30.2 ± 15.9 months. There were 25 men and 37 women, aged 70.0 ± 8.9 years. The tissue biopsy rate of the patients was 56.5% (35/62). Two elderly patients were treated conservatively during the initial remission-induction therapy. Of the 60 patients who underwent immunosuppressive treatment, 32 patients (53.3%) were treated with CS treatment alone (20–60 mg/day) and the other 28 (46.7%) were treated with CS treatment and an immunosuppressant (26 cases of CYC, 2 cases of MTX). Patients who received CYC in remission-induction therapy were considered to have potentially organ- or life-threatening disease activity (mean BVAS 10.0 ± 3.4), which mainly consisted of pulmonary involvement such as infiltrate and/or alveolar hemorrhage, rapidly progressive glomerulonephritis, and involvement of 2 or more organs. In addition, 2 cases (1 with CS and another with CS/CYC immunosuppressive treatment) received IVIG as combination treatment. PE was performed in 8 of the 60 cases. Six patients (9.7%) with endstage renal failure started dialysis treatment before the final observation. There were 2 deaths due to infection and 2 deaths due to cerebrovascular complication not caused by active vasculitis; those 4 cases were 6.5% of the total. There were 15 cases of relapse (relapse group), including 1 case in which immunosuppressive treatment was discontinued during maintenance therapy. In another case, the patient was receiving oral CYC immunosuppressive treatment alone after the discontinuation of oral CS treatment. Major relapses were hematuria/proteinuria in 3 cases, deterioration of kidney function accompanied with fever and hematuria in 2, alveolar hemorrhage and worsening of kidney function accompanied with hematuria/proteinuria in 2, pulmonary infiltrate in 1, headache and meningitis in 1, pleurisy, pulmonary infiltrate and kidney dysfunction accompanied with hematuria/proteinuria in 1, sensory peripheral neuropathy in 1, cutaneous abnormalities, mucous membranes/eye symptoms, pleurisy, pulmonary infiltrate and central nervous system involvement including meningitis, seizures, stroke, cranial nerve palsy and mononeuritis multiplex in 1, skin vasculitis, pulmonary infiltrate and headache in 1, and exacerbation of kidney function accompanied with hematuria/proteinuria in 1. Minor relapses were fever, myalgia, and weight loss in 1 case. Of the 47 cases that maintained remission (non-relapse group) throughout the maintenance therapy peri-

od, 44 patients were still receiving immunosuppressive treatment at the time of final observation, but the treatment had been discontinued in the other 3 patients.

Predictors of relapse. The relapse rate was 24.2% (15/62), and the mean duration between remission and relapse was 16.9 ± 13.5 months. In the relapse group, the period between initial remission-induction therapy and relapse was 21.6 ± 14.4. Cox proportional hazards model analysis of variables that influenced relapse frequency revealed a PSL reduction rate (mg/month) during maintenance therapy as a dependent variable ($p < 0.01$). We further calculated the threshold of the PSL reduction rate that had separated the risk of relapse (Table 1). The results revealed that when the PSL reduction rates were grouped into 1 above (fast group) and 1 below (slow group) the threshold of the PSL reduction rate (0.86 mg/month), the number of relapse cases was 12.6-fold (95% CI 2.2–97.9) higher in the fast group than in the slow group ($p < 0.01$). Figure 1 shows the estimated Kaplan-Meier survival curves for the whole cohort (A) and those based on the PSL reduction rate of 0.86 mg/month as the threshold (B).

Using the initially collected data, univariate analysis was also performed to determine potential risk factors for relapse. In addition to the observed factors, differences in the clinical laboratory test values obtained at the start of maintenance therapy and at the final observation were included in the analysis. The results showed that there were no significant quantitative or qualitative variables at the 5% significance level. At the 10% significance level, however, the level of immunoglobulin M at the start of maintenance therapy ($p = 0.093$) and the steroid reduction rate ($p = 0.085$) were selected as significant quantitative variables. The selected significant qualitative variables were the presence of chronic infection ($p = 0.056$), hematuria (qualitative) at the start of therapy ($p = 0.037$), and prophylactics to pneumocystic pneumonia at the start of therapy ($p = 0.042$). When we analyzed the data, excluding deaths as missing values, the PSL reduction rate became significant at around the 5% level ($p = 0.047$). When a logistic regression model was developed using the above variables, the PSL reduction rate was selected, similar to the case of Cox proportional hazards model analysis ($p = 0.026$).

Factors influencing change in the VDI. We compared the VDI of patients between the relapse (3.7 ± 2.1) and non-relapse (3.0 ± 2.1) groups and found no significant difference. In contrast, there was a significant difference in the VDI of the relapse (5.6 ± 5.1) and non-relapse (3.5 ± 2.5) group at the final observation ($p < 0.05$). Multiple regression analysis was performed to identify the variables that influence VDI at final observation. We applied the Kruskal-Wallis test to determine the initial variables to be used in the analysis for extracting qualitative and quantitative variables (Table 2). Variables showing significance were the outcome (relapse) at the final observation ($p < 0.01$), the presence of proteinuria at the start of maintenance therapy ($p < 0.001$), the presence of hematuria (qualitative) at the start of maintenance therapy ($p = 0.03$), CS treatment at the start of remission-induction therapy ($p = 0.04$), degree of BVAS change ($p < 0.01$), and change in the number of red blood cells in urine ($p < 0.01$). When the severity of proteinuria (qualitative) and hematuria (qualitative) was scored using –, 1+, 2+, and 3+ as quantitative variables, and multiple linear regression analysis was performed to account for the interaction between explanatory variables, the variables selected by the analysis were proteinuria at the start of maintenance therapy (regression coefficient 1.991 ± 0.758, $p < 0.05$) and the change in the number of red blood cells in urine (regression coefficient 0.126 ± 0.040, $p < 0.01$; Table 3).

Analysis of the presence of MPO-ANCA during maintenance therapy. We analyzed the association between relapse and the presence of MPO-ANCA at the start of maintenance therapy. The results showed that the frequency of MPO-ANCA in the non-relapse group was 44.7% (21/47), whereas in the relapse group it was 66.7% (10/15). There was no statistically significant association between relapse and the presence of MPO-ANCA at the start of maintenance therapy ($p = 0.24$).

DISCUSSION

We conducted an observation study of Japanese patients with MPO-ANCA-positive MPA, and the results revealed the risk factors for relapse during remission maintenance therapy and the factors influencing chronic lesions. The rate of relapse, which was the main evaluation item in our study, was 24.2%, and the duration between remission and relapse was 16.9 months. The reduction rate of CS correlated with relapse, showing a higher incidence of relapse when the rate was > 0.86 mg/month. Further, chronic lesions, which were expressed by the VDI, correlated with the presence of proteinuria at the start of maintenance therapy and an increase in the red blood cells in urine during maintenance therapy.

In our study, 24% of the MPO-ANCA-positive patients with MPA who had initially achieved remission after the first treatment relapsed. The rate of relapse was within the range of 8%–38% of that reported in Europe and the United States[12,13,14,15,16,17]. The duration between the start of mainte-

Table 1. Corticosteroid (CS) reduction rate (mg/month) and association with relapse.

	Relapse				
	No	Yes	OR (95% CI)	p	Threshold
Reduction rate of CS (mg/month)					
Slow	35	3	12.606 (2.177–97.878)	0.0012	0.8633
Fast	6	7			

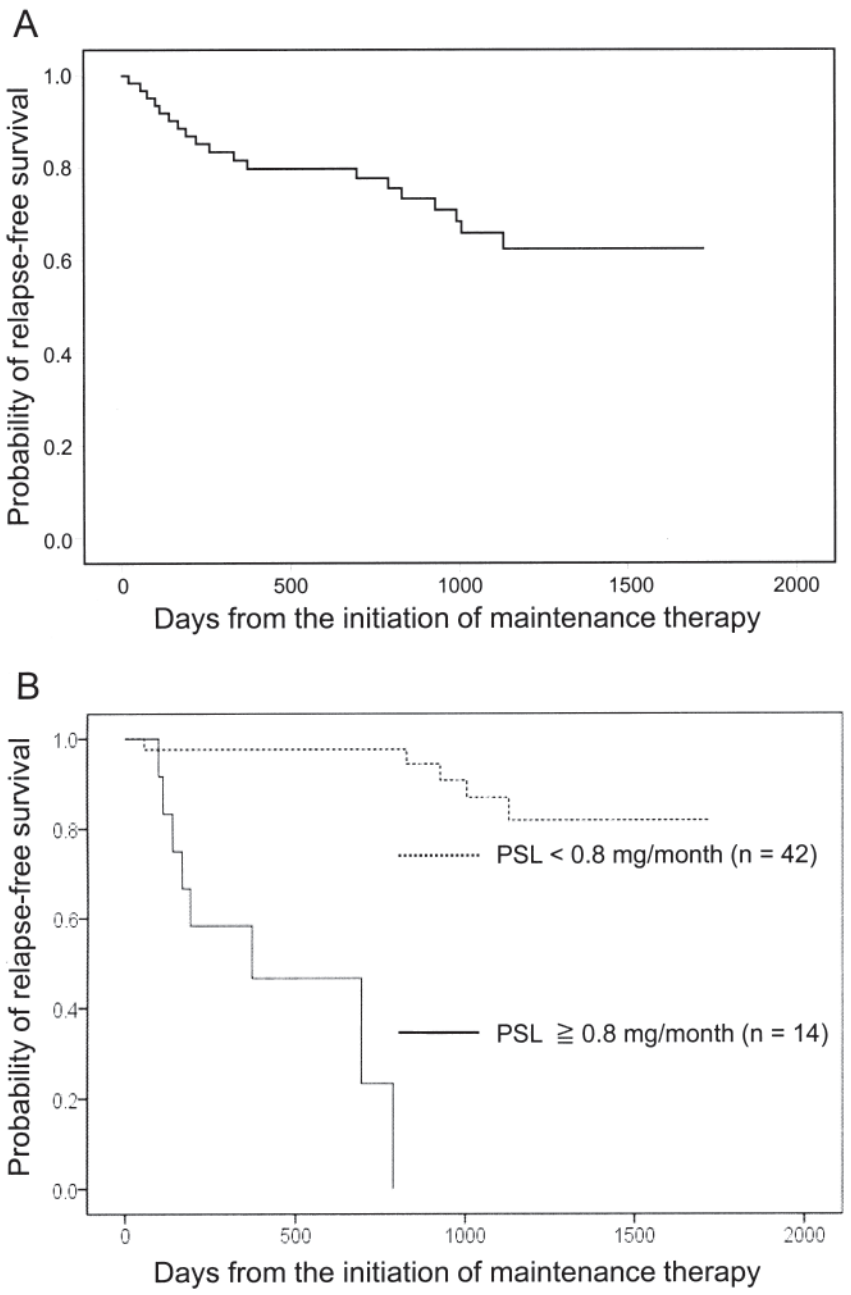

Figure 1. A. Survival without relapse for the whole cohort during maintenance therapy. B. Relapse-free survival rate associated with the reduction rate of oral corticosteroid during maintenance therapy. PSL: prednisolone.

nance therapy after achieving remission and the time when relapse occurred was 16.9 months. The period between the initial remission-induction therapy and relapse was 21.6 months, and this is similar to the mean period (22.5–43 months) that had been reported in Europe and the United States[13,14,16].

We found that the reduction rate of CS correlated with relapse with a threshold of 0.86 mg/month. Upper respiratory tract and pulmonary lesions and positive serology for ANCA against proteinase-3 (PR3-ANCA-positive) have been reported as risk factors for ANCA-associated vasculitis in Europe and the United States[2,3]. The rate of relapse is barely influenced by concurrent administration of CYC and the period of administration, concurrent administration of AZA, or PE[2,13]. A reduction of oral CS is advised during 1-month remission-induction therapy for ANCA-associated vasculitis, following the evidence-based guidelines of the British Society for Rheumatology/British Health Professionals in Rheumatology

Table 2. Univariate analysis of factors influencing the change in vasculitis damage index value. Quantitative variables were evaluated using Kruskal-Wallis analysis. Quantitative variables were evaluated using a correlation coefficient. Change of values was obtained by subtracting the value at the start of maintenance therapy from the value at the final observation.

	p
Qualitative variables	
Condition at final observation (relapse)	0.0088
Presence of proteinuria (qualitative) at the start of maintenance therapy	0.0002
Presence of hematuria (qualitative) at the start of maintenance therapy	0.0301
Use of steroid	0.0390
Quantitative variables	
Change in BVAS	0.0039
Change in number of red blood cells in urine	0.0028

BVAS: Birmingham Vasculitis Activity Score.

Table 3. Regression analysis of factors influencing the change in vasculitis damage index values. Severity of proteinuria (qualitative) expressed as a qualitative variable using –, 1+, 2+, or 3+. Change of values was obtained by subtracting the value at the start of maintenance therapy from the value at the final observation.

Variables	p
Condition at final observation (relapse)	0.1117
Presence of proteinuria (qualitative) at the start of maintenance therapy	0.0029
Change in BVAS	0.7715
Change in number of red blood cells in urine	0.0035

BVAS: Birmingham Vasculitis Activity Score.

and the recommendation of the European League Against Rheumatism[8,9]. Recently, a metaanalysis of the association between relapse and the period of CS administration in patients with ANCA-associated vasculitis was performed using 13 randomized controlled trials and cohort studies[18]. The results of 1 particular group (n = 517, including 91 MPA cases) that had a gradual reduction followed by discontinuation of CS in 12 months after the initiation of treatment showed that the rate of relapse was 48%. However, the rate was merely 14% in another group (n = 288, including 133 MPA cases) in which PSL was gradually reduced to 5–7.5 mg/day or 5 mg/day by the end of a 12- or 22-month period, respectively, after the initiation of treatment.

Nonetheless, the influence of oral CS on relapse of MPA during maintenance therapy has never been studied. In general, the reduction of oral PSL is performed within 3 months after the start of remission-induction therapy and the dosage is maintained at a low level[8,9,12]. It is necessary to note that the clinical interpretation of the mean reduction rate of CS is expressed as the difference in the CS dose between the time of initiation of maintenance therapy and final evaluation, divided by the observation period. Despite this limitation, the results of our study will provide useful information for the development and enforcement of an oral CS reduction regimen for MPA remission maintenance therapy.

Although previous studies have reported an association between relapse and PR3-ANCA[2,3], association analysis in our study did not reveal a significant association between relapse and the presence of MPO-ANCA at the start of maintenance therapy. On the other hand, the association between relapse and change in MPO-ANCA values has been controversial[19,20]. Monitoring of ANCA values has been reported to be a useful indicator of relapse because, when the ANCA value increased 4-fold during remission of ANCA-associated vasculitis, enhancement of immunosuppressive therapy led to a reduction of the relapse rate[19]. Another study of relapse cases in which ANCA-associated vasculitis was accompanied by an increase in ANCA values reported that an increase in the ANCA value preceded relapse in 51% of cases[20]. In Europe and the United States, ANCA values were reported to be an unreliable predictor of relapse[15]. Because MPO-ANCA measurement kits used in our study varied from institution to institution, we were unable to determine the association between MPO-ANCA values and relapse. However, the results of the supplemental logistic regression model showed that there was a tendency toward relapse in patients who were positive against MPO-ANCA at the final observation compared with those who were negative (OR 28.8, 95% CI 0.986–839.8, p = 0.051). The results above suggest that continuous observation of MPO-ANCA values is needed to clarify the relationship between MPO-ANCA values and relapse.

The severity of proteinuria at the start of maintenance therapy and the change in red blood cell counts in urine during maintenance therapy, as revealed by urinalysis, were important factors influencing VDI, the indicator of vasculitis and chronic lesion. VDI in ANCA-associated vasculitis was shown to already be 1.3 on average at the start of maintenance therapy and this value increased to 2.5 in 18 months after the initiation of the therapy[12]. However, the factors influencing the VDI were not studied in detail. Multiple regression analysis revealed that proteinuria above 1 g/day was the only factor associated with increased incidence of death due to MPA[13]. The presence of compromised renal function at the time of diagnosis has also been reported as a marker for poor prognosis of MPA[21]. Proteinuria is an independent risk factor for endstage renal failure and cardiovascular disease (cardio-renal syndrome), and it has been known to be closely associated with patient survival[22,23]. For these reasons, management of proteinuria during maintenance therapy for a patient with MPA is extremely important with respect to quality of life and improved prognosis of patients with chronic vasculitis.

Our study has several limitations. First, patients enrolled in the study were retrospectively analyzed based on clinical records. Therefore, the possibility exists that information bias may be present due to missing values in statistical analysis.

Second, selection bias, for example, by not enrolling patients who died before the investigation period, may also affect the results. Third, the followup period was relatively short. Therefore, more relapses may occur over time. Despite these limitations, it is still critical to evaluate longterm observation studies in multiple centers to further understand predictors of disease outcome associated with increased morbidity.

Our study concerning remission maintenance therapy using CS and immunosuppressants showed that the rate of relapse remains high and increases in accord with the reduction rate of CS during remission maintenance therapy. Additional prospective cohort studies should be performed to establish a detailed CS administration regimen for safe and effective longterm remission maintenance therapy.

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APPENDIX

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