THU0301 SAFETY FOLLOWING INITIATION OF RITUXIMAB IN GRANULOMATOSIS WITH POLYANGIITIS (GPA) OR MICROSCOPIC POLYANGIITIS (MPA): INTERIM ANALYSIS OF THE RITUXIMAB IN ANCA-ASSOCIATED VASCULITIS REGISTRY (RAVER)

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Background: Therapy-related serious adverse events (SAEs) are important causes of morbidity in patients with GPA or MPA. Long-term safety data of rituximab in GPA/MPA are limited.
Objectives: To characterize safety events in an observational registry of patients with GPA/MPA initiating rituximab.
Methods: This interim analysis of RaVeR, an ongoing open-label real-world study of adult patients with GPA or MPA initiating rituximab (dose/frequency determined by investigator), was conducted when 50% of patient-years (PY) were collected (July 2015). Safety events included serious infections (SI), infusion-related reactions (IRR), serious cardiac events, malignancies, and other serious events. Crude incidence rates (IR) and 95% CI were calculated. Trial registration number: NCT01613599
Results: 97 patients (291 PY) received rituximab, of whom 70% received rituximab retreatment. Median follow-up was 2.4 years. Overall, 91% of patients were ANCA-positive and 78% had GPA. 17 patients (17.5%) had a history of plasmapheresis or dialysis; 20 (20.6%) were receiving rituximab plus cyclophosphamide at baseline. 33 patients had 71 SAEs (32.4/100 PYs [95% CI: 25.32–40.89]). 11 patients had 20 SIs (9.13/100 PYs [95% CI: 5.58–14.10]). 9 patients (9.3%) experienced 13 serious cardiovascular (CV) events (5.93/100 PYs [95% CI: 3.16–10.15]), 12 of which were reported as unrelated to rituximab. Of the 13 CV events, 9 were atrial arrhythmias and most patients had associated renal or CV disease history. There were no serious IRRs or SAEs within 24 hours of rituximab infusion. There were 6 deaths (2.74/100 PYs [95% CI: 1.01–5.96]); causes of death included septic shock, interstitial lung disease, congestive heart failure, cardio-respiratory arrest and 2 deaths of unknown etiology. The severe disease flare rate was 5.94/100 PYs (95% CI: 3.16–10.15). Among patients who received rituximab retreatment, the IRs of SAEs (26.1/100 PYs) and SIs (7.29/100 PYs) were not increased compared with the overall cohort.

Table. Observed safety events of interest

	Number of events	IR per 100 PY (95% CI)
All SAEs	71 in 33 pts (34%)	32.42 (25.3 to 40.9)
Serious infections	20 in 11 pts (11%)	9.13 (5.58 to 14.1)
Serious cardiac events	13 in 9 pts (9%)	5.93 (3.16 to 10.15)
Serious vascular events	6 in 5 pts (5%)	2.74 (1.01 to 5.96)
Malignancies	2 in 2 pts (2%)	0.91 (0.11 to 3.30)

IR, incidence rate; PY, patient-year; SAE, serious adverse event.

Conclusions: In this interim analysis of patients with GPA/MPA treated with rituximab, SAEs were not increased compared with comparable cohorts of patients with renal involvement. Safety events did not increase with rituximab retreatment. These results are consistent with the known safety profile of rituximab and provide preliminary long-term, practice-level safety data for rituximab in GPA/MPA.
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THU0302 HISTOLOGY FINDINGS IN GIANT CELL ARTERITIS (GCA) AND THEIR RELATIONSHIP WITH THE ULTRASOUND RESULTS: ANALYSIS OF DATA FROM THE TABUL STUDY (TEMPORAL ARTERY BIOPSY VS ULTRASOUND IN DIAGNOSIS OF GIANT CELL ARTERITIS)

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Background: Although temporal artery biopsy (TAB) has been the gold standard for diagnosis of GCA, ultrasound has superior sensitivity but lower specificity. Occasionally, histological evidence of inflammation is restricted to the *vasa vasorum*, the periadventitial small vessels, or both, which could limit the diagnostic sensitivity of ultrasound for GCA. Moreover, false positive ultrasound results have been described in patients with arteriosclerosis on histology.
Objectives: To compare histologic findings with ultrasound results from patients with suspected GCA included in the TABUL study (a multinational study to assess the relative performance of ultrasound and TAB for diagnosing GCA).
Methods: All patients with newly suspected GCA underwent an ultrasound of both temporal and axillary arteries, followed by a TAB, within 7 days of commencing glucocorticoid therapy. TAB pathological diagnoses were analysed and the different histologic features were compared with the ultrasound results using Chi-square or Fisher exact tests.
Results: Results for TAB and ultrasound were available in 388 patients (69% with a final clinician's diagnosis of GCA). An artery was definitely obtained in 363 (94%) TABs; the pathological diagnosis was GCA in 104 (29%) cases, arteriosclerosis in 35 (10%), normal in 203 (56%) and other conditions in 21 (6%). All TABs compatible with GCA also had a final clinician's diagnosis of GCA (73% with positive ultrasound). Table 1 shows that ultrasound positivity occurred more frequently in patients where the media was the predominant site of inflammation (p=0.01). The ultrasound result was positive in 9 (26%) cases where TAB was consistent with arteriosclerosis, 8 (89%) of whom had a final clinician's diagnosis of GCA. The ultrasound was positive in 64 (32%) cases where TAB was normal, 52 (81%) of whom had a final clinician's diagnosis of GCA.

Table 1: Relationship between the histologic features of patients with a TAB diagnosis of GCA and ultrasound results

Histologic features (n patients)	Ultrasound positive (n=76)	Ultrasound negative (n=28)	*p value*
Predominant site of inflammatory cellular infiltrate			
Predominant intima infiltrate (n=8)	7 (87.5%)	1 (12.5%)	*0.679*
Predominant IEL infiltrate (n=13)	10 (76.9%)	3 (23.1%)	*1.000*
Predominant media infiltrate (n=21)	20 (95.2%)	1 (4.8%)	*0.010*
Predominant adventitia infiltrate (n=19)	11 (57.9%)	8 (42.1%)	*0.099*
Predominant *vasa vasorum* infiltrate (n=4)	2 (50%)	2 (50%)	*0.293*
Predominant transmural infiltrate (n=39)	26 (66.7%)	13 (33.3%)	*0.254*
Histologic specific findings			
Presence of giant cells (n=74)	58 (78.4%)	16 (21.6%)	*0.056*
Presence of vessel complete occlusion (n=24)	17 (70.8%)	7 (29.2%)	*0.778*
Presence of IEL fragmentation (n=86)	61 (70.9%)	25 (30.1%)	*0.386*
Presence of intimal hyperplasia (n=91)	65 (71.4%)	26 (28.6%)	*0.506*

TAB = temporal artery biopsy; IEL= internal elastic lamina

Conclusions: Amongst patients with suspected GCA, ultrasound is more likely to be positive when histological inflammation is predominantly present in the intima-media. No significant correlation between histologic findings and negative ultrasound results was found, but the small number of cases with predominant *vasa vasorum* infiltrates in our cohort limited this analysis. There was only one false positive ultrasound in patients with arteriosclerosis on TAB.
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THU0303 CLINICAL FEATURES AND PROGNOSIS OF ANCA-ASSOCIATED VASCULITIS WITH RENAL INVOLVEMENT AT DIAGNOSIS

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Background: Kidneys are major organs targeted by antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Clinical manifestations, laboratory data, and prognosis of AAV with renal involvement at diagnosis are not elucidated.

Objectives: We compared clinical features of AAV with renal involvement with patients without renal involvement.
Methods: We conducted an observational study of 104 patients with AAV (12 eosinophilic granulomatosis with polyangiitis, 23 granulomatosis with polyangiitis (GPA), 66 microscopic polyangiitis, 3 renal limited vasculitis) between in 2008 to 2016 in Nagasaki University Hospital. Using medical records, we analyzed the patients' baseline variables, laboratory data, clinical symptoms, and therapeutic outcomes after treatments including episodes of relapses, initiations of dialysis, and death. Renal involvement was defined as the state with estimated glomerular filtration rate <60 mL/min/1.73 m^2 or microscopic hematuria (2+ or greater) which were not caused by renal diseases except for AAV.
Results: Sixty-nine patients had renal involvement. Patients with renal involvement group had higher median age at diagnosis than patients without renal involvement group (75 years vs. 66 years, $p<0.001$). Patients with renal involvement included fewer GPA patients compared to other AAV types. Patients with renal involvement had lower hemoglobin levels (10.3 g/dL vs. 12.3 g/dL) and lower platelet levels ($23.7x10^4/\mu L$ vs. $28.7x10^4/\mu L$). Patients with renal involvement had higher erythrocyte sedimentation rate (78mm/h vs. 20mm/h), MPO-ANCA titers (116 U/mL vs. 58 U/mL) and urine protein levels (0.81 g/gCr vs. 0.15 g/gCr). Patients with renal involvement had lower C3 levels, but CH50 and C4 levels did not differ between in two groups. There were no differences in treatments including doses of prednisolone and use of methylprednisolone pulse and cyclophosphamide between in two groups. Multivariable regression analysis revealed that age at diagnosis is the most significant explanatory variable to renal involvement. Nineteen percent of patients with renal involvement had initiations of dialysis. Multivariable analysis demonstrated estimated glomerular filtration rate at diagnosis is the most significant explanatory variable to initiations of dialysis (p=0.010). Receiver operating characteristic curve showed the cutoff level of estimated glomerular filtration rate to distinguish initiations of dialysis was 37mL/min/1.73 m^2 (sensitivity=79%, specificity=70%, area under the curve=0.80). Assessed by a log-rank test, overall survival rate did not differ between in two groups (p=0.29).
Conclusions: Patients with renal involvement had higher age at diagnosis. Patients with renal involvement included fewer GPA patients. Patients with renal involvement had lower C3 levels. Estimated glomerular filtration rate at diagnosis is the most significant explanatory variable to initiations of dialysis.
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THU0304 VASCULITIS PATIENTS ADMITTED TO INTENSIVE CARE UNIT: IMPLICATIONS FROM A SINGLE-CENTER RETROSPECTIVE STUDY

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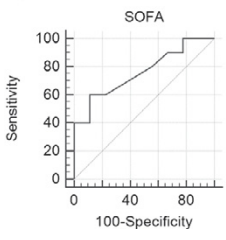
Background: Vasculitides are a heterogeneous group of disorders that are characterized by the inflammation of the vasculature vessels. Vasculitides may present as a life-threatening condition and cause higher rates of morbidity and mortality. There are few studies assessing the outcome and prognosis of patients with vasculitides admitted to the intensive care (ICU).
Objectives: To assess the outcome of vasculitides patients required admission to ICU and to identify factors associated with mortality
Methods: A retrospective study was carried out, including all patients who were diagnosed with vasculitides and admitted to the ICU of the Sheba Medical Center, Tel-Hashomer, throughout the years 2000–2014. Continuous variables were computed as mean±standard deviation, whilst categorical variables were recorded as percentages, where appropriate. Student's t-test and chi-squared analyses were performed for investigating the impact of the clinical variables on mortality.
Results: Twenty-five vasculitides patients admitted to the ICU were included in the present study (mean age 52±14y, sex ratio M/F: 12/13). The mortality rate among these patients was 48%. Leading causes for ICU admission were: infection (64%), vasculitides exacerbation (34%), and hemorrhage (16%). Variables significantly associated with mortality were: the use of Rituximab prior to admission ICU (p=0.039), involvement of the hemodynamic system (p=0.024), the SOFA score (p=0.041), blood infections during the first week at ICU (p=0.018) and persisting after the first week (p=0.007).

Figure 1. Receiver Operating Characteristic (ROC) analysis of the predictive power of the Sequential Organ Failure Assessment (SOFA) score, in predicting the mortality of vasculitis patients admitted at intensity care unit (ICU), in terms of sensitivity and specificity.



Conclusions: Our study confirms the high mortality rate among vasculitides patients and mainly among those requiring admission to ICU. SOFA score and pre-admission treatment with rituximab have been found to be predictive of mortality.
Disclosure of Interest: None declared
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THU0305 EPIDEMIOLOGY OF ANCA-ASSOCIATED VASCULITIS IN NORTHERN NORWAY

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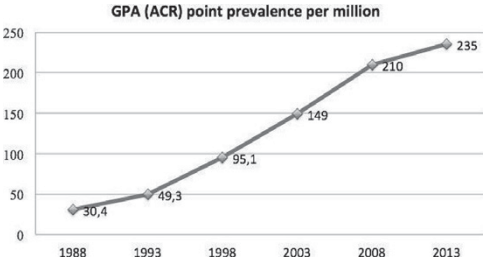
Background: The ANCA-associated vasculitides (AAV) have increased in prevalence since the 1980s, with granulomatosis with polyangiitis (GPA) being most prevalent in Caucasian population in circumpolar areas. This was also shown in a study on GPA in northern Norway between 1984 and 1998, which further showed an increasing incidence [1].
Objectives: The present study aimed to investigate the subsequent 15-year period in the same region, now including all the AAVs.
Methods: The study area has 11 hospitals, no private specialist in rheumatology or nephrology, and an adult population of 371 928. We retrospectively searched all hospital databases, using ICD-10 codes potentially compatible with AAV. Patients diagnosed with AAV from 1999 through 2013 according to the European Medicines Agency (EMEA) algorithm, and for GPA also the subgroup fulfilling the American College of Rheumatology (ACR) 1990 criteria, were included. For prevalence data, patients residing in the area, but with AAV diagnosis prior to 1999, were included too.
Results: Using the EMEA algorithm, 90 incident cases were classified as GPA, 39 as microscopic polyangiitis (MPA) and 14 as eosinophilic granulomatosis with polyangiitis (EGPA). Within the GPA group, 78 patients also met the ACR criteria. The results for incidence and prevalence are given in Table 1:

		Annual incidence/million				Point prevalence at 31. Dec		
		1999–2003	2004–2008	2009–2013	Total period	2003	2008	2013
ACR	GPA	11,4	16,7	12,5	13,6	149	210	235
EMEA	GPA	11,4	19,9	15,7	15,8	149	226	261
EMEA	MPA	2,7	6,5	11,0	6,8	10,8	31,9	63,3
EMEA	EGPA	2,7	2,7	1,6	2,3	13,5	18,6	30,4
EMEA	All AAV	16,8	29,0	28,2	24,9	173	276	354



Conclusions: The GPA incidence and prevalence in this study are the highest reported. Though the incidence has stabilized, prevalence is still increasing, albeit at a decelerating rate (Graph 1). Moreover, the total AAV prevalence doubled in the last 10 years, exceeding previous estimates. Incidence of MPA and EGPA are both within the range found elsewhere. But the MPA incidence appears to be rising reminiscent of GPA before the turn of the century.
References:
[1] Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis Rheum. 2000;43(11):2481–2487.
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THU0306 PREVALENCE AND CHARACTERISTICS OF NEUROPATHY IN PATIENTS WITH ANCA ASSOCIATED VASCULITIDES: DATA FROM THE DCVAS STUDY

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Background: Epidemiological data on vasculitic neuropathy (VN) in ANCA associated vasculitides (AAV) are scarce and controversial. The Diagnostic and