The Joint Vasculitis Registry in German-speaking countries (GeVas): subgroup analysis of 266 AAV patients

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Abstract

Objective

Prospective long-term observational data on the disease course of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were missing in Germany to date. Therefore, the Joint Vasculitis Registry in German-speaking countries (GeVas) has been established to follow the course of patients with AAV. The aim of this study is to present baseline data of patients with newly diagnosed and relapsing AAV enrolled in the GeVas registry.

Methods

GeVas is a prospective, web-based, multicentre, clinician-driven registry for the documentation of organ manifestations, damage, long-term outcomes, and therapy regimens in various types of vasculitis. Recruitment started in June 2019.

Results

Between June 2019 and October 2022, 266 patients with AAV were included in the GeVas registry: 173 (65%) with new-onset and 93 (35%) with relapsing AAV. One hundred and sixty-two (61%) patients were classified as granulomatosis with polyangiitis (GPA), 66 (25%) as microscopic polyangiitis (MPA), 36 (13%) as eosinophilic granulomatosis with polyangiitis (EGPA), and 2 (1%) as renal limited AAV. The median age was 59 years (51-70 years, IQR), 130 (51%) patients were female. Most patients were ANCA positive (177; 67%) and affected by general symptoms, pulmonary, ear nose throat (ENT), renal and neurological involvement. For induction of remission, the majority of patients received glucocorticoids (247, 93%) in combination with either rituximab (118, 45%) or cyclophosphamide (112, 42%).

Conclusion

Demographic characteristics are comparable to those in other European countries. Differences were found regarding ANCA status, frequencies of organ manifestations, and therapeutic regimens. The GeVas registry will allow longitudinal observations and prospective outcome measures in AAV.

Key words

antineutrophil-cytoplasmic antibody (ANCA), ANCA-associated vasculitis (AAV), GeVas Registry, prospective

See page 857 for the affiliations.

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic disorder characterised by necrotising vasculitis predominantly affecting small vessels. AAV comprises three distinct entities, specifically granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), which are characterised by overlapping as well as distinct clinical and pathological features and by differences with respect to their association with proteinase 3 (PR3)- and myeloperoxidase (MPO)-ANCA (1-3).

AAV is a rare disease with a worldwide regionally varying annual incidence between 20–50 per 1 million residents and a prevalence of 300–420 per 1 million residents (1, 4). In Germany, a recent analysis of insurance data indicates an annual incidence of GPA of 34 and MPA of 13 cases per 1 million population and a prevalence of GPA of 210 and of MPA of 46 cases per 1 million population (5). Data from a meta-analysis show that EGPA is markedly less common than GPA and MPA, with a median incidence of 1 new case per 1 million population per year and a prevalence of 12 per 1 million population in Europe (6).

Multiorgan involvement is common in AAV. Most patients with GPA and MPA are affected by respiratory tract and/or renal involvement culminating in the development of pulmonary-renal syndrome with organ- and life-threatening pulmonary capillarities and alveolar haemorrhage and rapidly-progressive glomerulonephritis. Due to the systemic nature of the underlying vasculitis, any organ can be involved. EGPA is exceptional in that it is characterised by asthma as well as blood and tissue eosinophilia (1). Peripheral nerves, paranasal sinuses and lung are the most frequently involved organs in EGPA (7).

Despite significant improvement of diagnosis and immunosuppressive therapy over the last years, AAV is still characterised by its chronic disease course, inherently frequent relapses and significant overall vasculitis- and therapy-associated morbidity and mortality, resulting in a substantial socioeconomic impact (1, 8-11). Moreover, there are regional differences regarding demographic data, phenotype, and outcome of AAV (12, 13). While GPA is predominant in the UK and central Europe, MPA is more common in Japan (12, 14, 15). Moreover, differences in age at manifestation and PR3-ANCA prevalence in GPA exist between Japan and the UK, indicating the influence of different genetic and environmental factors in AAV pathogenesis (12, 15).

While several vasculitis registries have been established in Europe and USA, a registry in German-speaking countries has been missing so far. The Joint Vasculitis Registry in German-speaking countries (GeVas) was therefore founded to meet the need for registry-based data regarding AAV to support physicians and health cost carriers by providing high quality real-life data on disease manifestations and courses, treatment effectiveness, comorbidities, long-term patient outcomes and assessment of disease burden, and by serving as basis to identify needs for improving the structure of healthcare of patients with AAV (16, 17). GeVas has been established in 2019 to follow the course of patients with new onset or relapsing vasculitis (inception cohort). The GeVas registry allows for long-term follow-up of a substantial cohort of vasculitis patients in a multicentre setting, and for comparisons of phenotype, organ involvement and therapy of AAV in German-speaking countries *versus* other European countries and the United States of America (USA) (18-20, 16). In this study, we report on differences regarding female/male ratio, ANCA status, frequencies of organ manifestations, and therapeutic regimen found between the GeVas registry and other European and USA registries.

Patients and methods

Data source

GeVas is a prospective, web-based, multicentre, clinician-driven registry for the documentation of organ manifestations, damage, long-term outcomes, and therapy in various types of vasculitis in German-speaking countries (16). Recruitment of patients started in June 2019. By October 2022, 15 centres of which 10 rheumatological, 2

nephrological, 2 combined rheumatological-nephrological centres and one neurological centre have been initiated and have included patients. Meanwhile, 517 patients have been documented in the registry. The protocol, methodology, and status of this registry have been reported previously (16).

Ethics

The study was approved by the Ethics committee (EC) of the University of Lübeck (EC reference number: 16–306) and by the responsible EC of each of the participating centres. All patients gave written informed consent for the study. GeVas is registered in the German Clinical Trials Register (DRKS00011866).

Definitions and classification

Patients with newly diagnosed or relapsing AAV as defined by the 2012 revised International Chapel Hill Consensus Conference (CHCC) definitions, 1990 American College of Rheumatology (ACR) criteria and the MIRRA criteria for EGPA were included (3, 21, 22). Moreover, AAV was classified into the respective category using clinical surrogate endpoints following the European Medicines Agency (EMA) algorithm (23). The present study includes patients recruited through October 2022. The new ACR/EULAR criteria published in March 2022 were therefore not yet mandatory during this period (24-26).

Statistical analysis

Descriptive analyses were performed with SAS 9.4. Continuous variables are presented with number of observations, median and interquartile range (IQR). Categorical variables are reported as absolute and relative frequencies.

Results

Cohort and patient characteristics

Two hundred and sixty-six patients with either newly diagnosed AAV (n=173; 65%) or relapsing AAV (n=93; 35%) were enrolled in the GeVas registry between June 2019 and October 2022. Most patients were classified as granulomatosis with polyangiitis (GPA) (n=162; 61%), 66 patients as microscopic polyangiitis (MPA) (25%), 36 patients as eosinophilic granulomatosis with polyangiitis (EGPA) (13%), and 2 patients as renal limited AAV (1%). Both patients with renal limited AAV were attributed to MPA in the following (Table I). The median age was 59 (51-70, IQR) years (GPA: 59 (51-69, IQR), MPA: 64 (54-76, IQR), EGPA: 56 (48-63, IQR)). One hundred and thirty patients were female (51%) and 136 male (49%) (GPA: female: 77 (48%), male: 85 (52%); MPA: female: 34 (50%), male: 34 (50%); EGPA: female: 19 (53%), male: 17 (47%)) (Table I).

Disease features

At the time of enrolment most patients with AAV were affected by general symptoms (n=188, 71%). Pulmonary involvement was the most common organ manifestation (n=151, 57%), followed by involvement of ear, nose, and throat (ENT) (n=139, 52%), kidney (n=103, 39%), peripheral nervous system (PNS) (n=62, 23%), skin (n=41, 15%), central nervous system (CNS) (n=28, 11%), eye (n=27, 10%), heart (n=17, 6%), and gastrointestinal tract (GI) (n=15, 6%). In GPA, the most frequent organ manifestation was ENT involvement (n=105, 65%), followed by pulmonary involvement (n=95, 59%). Renal involvement was reported in 51 patients (31%). Other frequent organ manifestations concerned PNS (n=27, 17%), skin (n=23, 14%), and eyes (n=22, 13%). Patients with MPA most frequently presented with kidney (n=48, 71%) and pulmonary involvement (n=32, 48%), followed by PNS (n=19, 29%), CNS (n=11, 17%), skin (n=11, 17%), and ENT involvement (n=11, 17%). In EGPA, the most common organ manifestation was pulmonary involvement (n=24, 69%), followed by ENT (n=23, 66%), PNS (n=16, 46%), heart (n=9, 26%), skin (n=7, 20%), and GI involvement (n=6, 17%).

In terms of comorbidities at baseline, 95 (36%) of the patients suffered from hypertension, 38 (14%) had asthma, 32 (12%) atherosclerosis, 29 (11%) hyperlipidaemia, 28 (11%) chronic kidney disease, and 16 (6%) had diabetes. Sixteen (6%) had a history of malignancy. Demographic and clinical characteristics are listed in detail in Table I.

Disease activity

The median BVAS V3.0 at baseline was 7 (4–13, IQR) (GPA: 7 [4–12]; MPA: 9 [5.5–14]; EGPA: 7 [4–12]) and median VDI 1 (0–2, IQR) (GPA: 1 [0–2]; MPA: 0 [0–2]; EGPA: 0 [0–2]). Median CRP at baseline was 19 mg/l (4–81 mg/l, IQR), median eGFR 73 ml/min/1,73 m^2 (45–90 ml/min/1,73 m^2, IQR), and median creatinine 82 µmol/l (71–124 µmol/l, IQR). At the time of study enrolment 110 patients (42%) were PR3-ANCA positive [GPA: 108 (67%); MPA: 0 (0%); EGPA: 2 (6%)] and 67 patients (25%) were positive for MPO-ANCA (GPA: 5 (3%); MPA: 57 (84%); EGPA: 5 (14%) on in-house enzyme-linked immunosorbent assay (ELISA).

Treatment

For induction of remission, most patients received glucocorticoids (n=247, 93%) (GPA: n=149, 92%; MPA: n=62, 94%; EGPA: n=34, 97%) in combination with rituximab (n=118, 45%) or cyclophosphamide (n=112, 42%). Twenty-six patients (10%) received a combination therapy of rituximab and cyclophosphamide for remission induction (GPA: n=16, 10%; MPA: n=10, 15%, EGPA: n=0, 0%). Forty-six patients were treated with methotrexate (17%), 20 patients received azathioprine (8%), followed by leflunomide (n=8, 3%), mepolizumab (n=7, 3%), avacopan (n=6, 2%), and mycophenolate (n=4, 2%). Plasma exchange was applied in 9 patients (3%) (GPA: n=5, 3%; MPA: n=4, 6%; EGPA: n=0, 0%). In GPA, rituximab was administered for induction of remission in 83 patients (51%), whereas cyclophosphamide was applied in 58 patients (35%). Patients with MPA were treated with rituximab or cyclophosphamide with equal frequency (n=34, 51%). EGPA patients mostly received cyclophosphamide for induction of remission (n=19, 54%), followed by methotrexate (n=8, 23%). Moreover, 7 patients with EGPA (20%) were treated with mepolizumab for induction of remission. For supportive therapy, 237 patients were prescribed vitamin D (89%) and 192 patients obtained pneumocystis prophylaxis (72%). Management is further detailed in Table I.

Table I. Demographics and clinical characteristics of AAV patients enrolled in GeVas registry (06/2019 – 10/2022).

	AAV	GPA	MPA	EGPA
Number of patients, n (%)	266 (100)	162 (61)	68 (26)	36 (14)
Demographics				
Age (years), median [IQR]	59 [51-70]	59 [51-69]	64 [54-76]	56 [48-63]
Gender				
Male, n (%)	136 (49)	85 (52)	34 (50)	17 (47)
Female, n (%)	130 (51)	77 (48)	34 (50)	19 (53)
Reason for inclusion in the study				
Newly diagnosed vasculitis; n (%)	173 (65)	87 (54)	56 (82)	30 (83)
Relapse, n (%)	93 (35)	75 (46)	12 (18)	6 (17)
Relapse - major, n (%)	47 (18)	39 (24)	6 (9)	2 (6)
Relapse - minor, n (%)	46 (17)	36 (22)	6 (9)	4 (11)
Comorbidities				
Asthma	38 (14)	11 (7)	4 (6)	23 (66)
Diabetes, n (%)	16 (6)	10 (6)	5 (8)	1 (3)
Hypertension, n (%)	95 (36)	56 (35)	29 (44)	8 (23)
Hyperlipidaemia, n (%)	29 (11)	16 (10)	10 (15)	2 (6)
Atherosclerosis, n (%)	32 (12)	18 (11)	11 (17)	3 (9)
Chronic kidney disease, n (%)	28 (11)	16 (10)	10 (15)	2 (6)
Malignancy, n (%)	16 (6)	13 (8)	1 (2)	2 (6)
Organ involvement				
General symptoms, n (%)	188 (71)	122 (75)	42 (64)	23 (66)
ENT, n (%)	139 (52)	105 (65)	11 (17)	23 (66)
Lung/chest, n (%)	151 (57)	95 (59)	32 (48)	24 (69)
Renal, n (%)	103 (39)	51 (31)	48 (71)	4 (11)
Heart, n (%)	17 (6)	7 (4)	1 (2)	9 (26)
GI, n (%)	15 (6)	7 (4)	2 (3)	6 (17)
CNS, n (%)	28 (11)	16 (10)	11 (17)	1 (3)
PNS, n (%)	62 (23)	27 (17)	19 (29)	16 (46)
Skin, n (%)	41 (15)	23 (14)	11 (17)	7 (20)
Eye, n (%)	27 (10)	22 (14)	2 (3)	3 (9)
Laboratory tests				
PR3-ANCA, n (%)	110 (42)	108 (67)	0 (0)	2 (6)
MPO-ANCA, n (%)	67 (25)	5 (3)	57 (84)	5 (14)
eGFR (ml/min/1.73 m^2), median, [IQR]	73 [45-90]	75 [55-90]	50 [23-82]	90 [73-100]
Creatinine (µmol/l), median, [IQR]	82 [71-124]	80 [71-110]	100 [72-239]	77 [70-84]
Haematuria, n (%)	82 (31)	54 (33)	25 (38)	1 (3)
Proteinuria, n (%)	94 (35)	55 (34)	33 (50)	5 (14)
CRP (mg/l), median, [IQR]	19 [4-81]	25 [5-91]	16 [5-71]	6 [1-26]
Immunosuppressive treatment at baseline				
Prednisolone, n (%)	247 (93)	149 (92)	62 (94)	34 (97)
Avacopan, n (%)	6 (2)	2 (1)	4 (6)	0 (0)
Cyclophosphamide, n (%)	112 (42)	58 (36)	34 (52)	19 (54)
Rituximab, n (%)	118 (45)	83 (51)	34 (52)	0 (0)
Cyclophosphamide and rituximab, n (%)	26 (10)	16 (10)	10 (15)	0 (0)
Methotrexate, n (%)	46 (17)	34 (21)	4 (6)	8 (23)
Azathioprine, n (%)	20 (8)	13 (8)	5 (8)	2 (6)
Mycophenolate (mycophenolate mofetil or mycophenolic acid), n (%)	4 (2)	3 (2)	1 (2)	0 (0)
Leflunomide, n (%)	8 (3)	7 (4)	1 (2)	0 (0)
Mepolizumab, n (%)	7 (3)	0 (0)	0 (0)	7 (20)
Other immunosuppressive treatment, n (%)	7 (3)	4 (2)	2 (3)	1 (3)
Plasma exchange, n (%)	9 (3)	5 (3)	4 (6)	0 (0)
Comedication				
Pneumocystis prophylaxis, n (%)	192 (72)	116 (72)	52 (79)	22 (63)
Vitamin D, n (%)	237 (89)	148 (91)	59 (89)	28 (80)
BVAS, median, [IQR]	7 [4-13]	7 [4-12]	9 [5.5-14]	7 [4-12]
BVAS ≥12, n (%)	78 (30)	40 (25)	26 (41)	10 (29)
VDI, median, [IQR]	1 [0-2]	1 [0-2]	0 [0-2]	0 [0-2]

AAV: antineutrophil-cytoplasmic antibody-associated vasculitis; ANCA: antineutrophil-cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; CNS: central nervous system; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear nose throat; GI: gastrointestinal; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PNS: peripheral nervous system; PR3: proteinase 3; VDI: Vasculitis Damage Index.

Discussion

Here, we present the first analysis of patients with AAV enrolled in the GeVas registry. In this paper, we aimed to characterize the demographics, clinical manifestations, and treatment for induction of remission in the GeVas registry at baseline. The basic demographic characteristics of our cohort in terms of age and gender ratio are consistent with those of other previously published large European AAV cohorts from the United Kingdom (UK), France, Spain, and Poland (12, 13, 18, 27-29). The male-to-female ratio in our cohort was approximately 1:1 for all AAV entities. A report from the Polish registry (POLVAS) showed a different male-to-female ratio of 1:2 for EGPA (18). Data from the Portuguese registry showed a male-to-female ratio which was also in favour of the female sex (1:1.6 for GPA, 1:3.4 for MPA, and 1:2.2 for EGPA) (20).

Depending on the AAV entity, the median age at manifestation is generally reported to be between 38 and 75 years (1). In that respect, patients with MPA tend to be older than GPA patients, whereas patients with EGPA are somewhat younger, respectively (1). Age distribution in our cohort was largely similar to recently published European studies. Patients with GPA in a Spanish study as well as in the Portuguese registry however were younger, even in comparison with the group of patients with EGPA (20, 27). In the Polish cohort, the median age of patients with GPA and EGPA was also slightly younger because children were included (18). By contrast, in a Japanese study, patients with GPA and MPA were slightly older at disease onset compared to European studies (12, 13).

Clinical manifestations of GPA and MPA patients included in the present analysis showed less frequent renal involvement in comparison with recent reports from Poland, Spain, Japan, the UK, and Ireland (12, 13, 18, 27, 30). This is potentially related to the predominance of rheumatology centres recruiting patients in our registry thus far. Intriguingly, the GPA cohort in our analysis showed a lower proportion of patients with ENT manifestations compared with studies from Poland, Spain,

Portugal, Japan, and the UK (12, 18, 20, 27). In the UK, less frequent PNS involvement is reported in MPA compared to our study (13). The reason for these differences between the cohorts with respect to ENT involvement in GPA and PNS in MPA remains speculative. In EGPA, we report a higher proportion of patients with cardiac manifestations in our patient population compared with a study from France, whereas renal involvement occurred less frequently (28). This might be related to the lower proportion of ANCA-positive EGPA patients in our cohort. Glomerulonephritis has been reported to occur more frequently in ANCA-positive EGPA, and cardiac involvement more often in ANCA-negative EGPA in a French study (31). Moreover, EGPA patients in our cohort suffered less frequently from pulmonary involvement compared with a French study (28). This could be explained by the fact that the French study included only patients with a new diagnosis of vasculitis and not patients with relapse as in our patient group. In our cohort, 110 (42%) patients were PR3-ANCA positive and 66 (25%) patients were MPO-ANCA positive on ELISA. Compared to our GPA patient group, PR3-ANCA was reported more frequently in the GPA cohorts from the UK, Poland, and Spain, and less frequently in Japan (12, 18, 27). Interestingly, the frequency of PR3-ANCA in our cohort is comparable to that of the Irish National Rare Kidney Disease (RKD) registry, although the proportion of patients with renal involvement is higher in the RKD registry due to the predominance of nephrology centres recruiting patients (30). MPO-ANCA on the other hand was found more frequently in patients with MPA in Japan and Spain, and less frequently in the UK compared to our cohort (13, 27). In EGPA, a higher prevalence for MPO-ANCA than in our cohort has been reported in studies from France, Spain as well as Poland (18, 27, 28). To what extent the lower impact of nephrology centres in the GeVas registry affects the reported ANCA frequencies compared with other registries is unclear, but may be resolved with recruitment of further nephrology centres for GeVas.

In terms of treatment, most patients in our cohort received glucocorticoids in combination with either rituximab or cyclophosphamide for the induction of remission. A recently published study based on data from the RISE registry from USA aiming to characterise AAV treatment patterns showed that cyclophosphamide was used in only 4% of the patients for induction treatment (19). Rituximab (31%) in combination with glucocorticoids was the most frequently administered therapy for the induction of remission in the subgroup of patients identified as possibly having new or relapsing disease in the USA cohort, followed by methotrexate (19%) (19). In our cohort, rituximab (44%) had been used more commonly for remission induction compared to the USA, the Portuguese, and the Irish registry (19, 20, 30). Cyclophosphamide had been more frequently administered (42%) in our study compared to the RISE registry, but less frequently than in the Irish RKD registry (19, 30). The clear-cut trend towards the preferential use of rituximab over cyclophosphamide in combination with glucocorticoids shown in the RISE registry reflects USA practice and is in line with the conditional recommendation of the ACR/VF guideline for the induction of remission in GPA and MPA (19, 32). However, the RISE and GeVas registries display considerable conceptual and design differences, with the former being a practice-based registry potentially including patients with less severe AAV and a smaller subgroup of possibly having new or relapsing disease (18%) (19), and the latter being an inception cohort exclusively including patients with new or relapsing AAV and thus, possibly a somewhat larger subgroup of patients with severe AAV. A direct comparison of patient groups in both registries is not possible based on the limited published data given in the RISE registry (19). Moreover, the combination of rituximab and cyclophosphamide with glucocorticoid according to the RITUXVAS trial regimen may have been used in patients with severe renal AAV more commonly in Germany compared to the USA (33). In our cohort, 26 (10%) of the patients received a combination therapy of rituximab and cyclophosphamide for remission induction. The issue of whether a combination of rituximab and cyclophosphamide with glucocorticoid is more effective than rituximab alone with glucocorticoid for the induction of remission in severe renal and/or pulmonary AAV has not been resolved and is subject to further study (ENDURRANCE trial, NCT03942887).

Plasma exchange was adjunctively applied in 9 (3%) of the patients with GPA and MPA. This low frequency may also reflect practice potentially related to the predominance of rheumatology centres over nephrology centres in the GeVas registry so far. In this cohort, methotrexate, azathioprine, leflunomide, and mycophenolate were infrequently administered possibly due to the inception design recruiting patients with new or relapsing AAV predominantly in clinical centres rather than practices. Accordingly, a substantial proportion of patients suffered from organ- or life-threatening AAV (BVAS ^{3} 12: 30%). The oral C5a receptor inhibitor avacopan was administered in 2% of the patients with GPA and MPA in our study. Avacopan has been approved for the treatment of severe active GPA and MPA in Europe in January 2022. The market launch in Germany was in February 2022. As outlined above, the present study considered patients recruited through October 2022. Notably, mepolizumab was used for the induction of remission in 7 (20%) of the patients with EGPA.

In conclusion, in this study, we present baseline observational data on patients with AAV enrolled in the GeVas registry with the aim to support physicians and health cost carriers by providing high quality real-life data on the disease course of AAV in German-speaking countries and by serving as basis to identify needs for improving the structure of healthcare of patients with AAV. Demographic characteristics are comparable to those in other European countries. Differences were found regarding ANCA status, frequencies of various organ manifestations and therapeutic regimen. The GeVas registry will provide an important source for longitudinal observation and prospective outcome measures in AAV.

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Competing interests
R. Bergner has acted as consultant of VIFOR, GSK, and has received personal fees for lectures from Abbvie, BMS, Chugai, GSK, Galapagos, MSD, Novartis, Roche, outside the submitted work.
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References
1. KITCHING AR, ANDERS HJ, BASU N *et al.*: ANCA-associated vasculitis. *Nat Rev Dis Primers* 2020; 6(1): 71. https://doi.org/10.1038/s41572-020-0204-y
2. ALBA MA, JENNETTE JC, HU Y *et al.*: Relevance of combined clinicopathologic phenotype and antineutrophil cytoplasmic autoantibody serotype in the diagnosis of antineutrophil cytoplasmic autoantibody vasculitis. *Kidney Int Rep* 2022; 7(12): 2676-90. https://doi.org/10.1016/j.ekir.2022.09.011
3. JENNETTE JC, FALK RJ, BACON PA *et al.*: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1): 1-11. https://doi.org/10.1002/art.37715
4. BANERJEE S, GRAYSON PC: Vasculitis around the world: epidemiologic insights into causality and a need for global partnerships. *J Rheumatol* 2017; 44(2): 136-9. https://doi.org/10.3899/jrheum.161468.
5. HELLMICH B, LAMPRECHT P, SPEARPOINT P *et al.*: New insights into the epidemiology of ANCA-associated vasculitides in Germany: results from a claims data study. *Rheumatology* (Oxford) 2021; 60(10): 4868-73. https://doi.org/10.1093/rheumatology/keaa924
6. JAKES RW, KWON N, NORDSTROM B *et al.*: Burden of illness associated with eosinophilic granulomatosis with polyangiitis: a systematic literature review and meta-analysis. *Clin Rheumatol* 2021; 40(12): 4829-36. https://doi.org/10.1007/s10067-021-05783-8
7. FURUTA S, IWAMOTO T, NAKAJIMA H: Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int* 2019; 68(4): 430-6. https://doi.org/10.1016/j.alit.2019.06.004
8. TAN JA, DEHGHAN N, CHEN W, XIE H, ESDAILE JM, AVINA-ZUBIETA JA: Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. *Ann Rheum Dis* 2017; 76(9): 1566-74. https://doi.org/10.1136/annrheumdis-2016-210942
9. WALLACE ZS, FU X, HARKNESS T, STONE JH, ZHANG Y, CHOI H: All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. *Rheu-*

matology (Oxford) 2020; 59(9): 2308-15. https://doi.org/10.1093/rheumatology/kez589
10. QUARTUCCIO L, TREPPO E, VALENT F, DE VITA S: Healthcare and economic burden of ANCA-associated vasculitis in Italy: an integrated analysis from clinical and administrative databases. *Intern Emerg Med* 2021; 16(3): 581-9. https://doi.org/10.1007/s11739-020-02431-y
11. SÁNCHEZ ÁLAMO B, MOI L, BAJEMA I *et al*.: Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 2023; 38(7): 1655-65. https://doi.org/10.1093/ndt/gfac320
12. FURUTA S, CHAUDHRY AN, ARIMURA Y *et al*.: Comparison of the phenotype and outcome of granulomatosis with polyangiitis between UK and Japanese cohorts. *J Rheumatol* 2017; 44(2): 216-22. https://dx.doi.org/10.3899/jrheum.160005
13. FURUTA S, CHAUDHRY AN, HAMANO Y *et al*.: Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. *J Rheumatol* 2014; 41(2): 325-33. https://doi.org/10.3899/jrheum.130602
14. FUJIMOTO S, WATTS RA, KOBAYASHI S *et al*.: Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology* (Oxford) 2011; 50(10): 1916-20. https://doi.org/10.1093/rheumatology/ker205
15. NAIDU G, MISRA DP, RATHI M, SHARMA A: Is granulomatosis with polyangiitis in Asia different from the West? *Int J Rheum Dis* 2019; 22 Suppl 1: 90-94. https://doi.org/10.1111/1756-185x.13398
16. IKING-KONERT C, WALLMEIER P, ARNOLD S *et al*.: The Joint Vasculitis Registry in German-speaking countries (GeVas) - a prospective, multicenter registry for the follow-up of long-term outcomes in vasculitis. *BMC Rheumatol* 2021; 5(1): 40. https://doi.org/10.1186/s41927-021-00206-2
17. POP B, FETICA B, BLAGA ML *et al*.: The role of medical registries, potential applications and limitations. *Med Pharm Rep* 2019; 92(1): 7-14. https://doi.org/10.15386/cjmed-1015
18. WÓJCIK K, WAWRZYCKA-ADAMCZYK K, WŁUDARCZYK A *et al*.: Clinical characteristics of Polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. *Clin Rheumatol* 2019; 38(9): 2553-63. https://doi.org/10.1007/s10067-019-04538-w
19. WALLACE ZS, YUN H, CURTIS JR, CHEN L, STONE JH, CHOI HK: ANCA-associated vasculitis management in the United States: data from the Rheumatology Informatics System for Effectiveness (RISE) Registry. *J Rheumatol* 2021; 48(7): 1060-1064. https://dx.doi.org/10.3899/jrheum.201330
20. PONTE C, KHMELINSKII N, TEIXEIRA V *et al*.: Reuma.pt/vasculitis - the Portuguese vasculitis registry. *Orphanet J Rare Dis* 2020; 15(1): 110. https://doi.org/10.1186/s13023-020-01381-0
21. MASI AT, HUNDER GG, LIE JT *et al*.: The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; 33(8): 1094-100. https://doi.org/10.1002/art.1780330806
22. WECHSLER ME, AKUTHOTA P, JAYNE D *et al*.: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376(20): 1921-32. https://doi.org/10.1056/nejmoa1702079
23. WATTS R, LANE S, HANSLIK T *et al*.: Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66(2): 222-7. https://doi.org/10.1136/ard.2006.054593
24. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81(3): 315-20. https://doi.org/10.1136/annrheumdis-2021-221795
25. SUPPIAH R, ROBSON JC, GRAYSON PC *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81(3): 321-6. https://doi.org/10.1136/annrheumdis-2021-221796
26. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. *Ann Rheum Dis* 2022; 81(3): 309-14. https://doi.org/10.1136/annrheumdis-2021-221794
27. SOLANS-LAQUÉ R, FRAILE G, RODRIGUEZ-CARBALLEIRA M *et al*.: Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. *Medicine* (Baltimore) 2017; 96(8): e6083. https://doi.org/10.1097/md.0000000000006083
28. COMARMOND C, PAGNOUX C, KHELLAF M *et al*.: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013; 65(1): 270-81. https://doi.org/10.1002/art.37721
29. GUILLEVIN L, PAGNOUX C, SEROR R, MAHR A, MOUTHON L, TOUMELIN PL: The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90(1): 19-27. https://doi.org/10.1097/md.0b013e318205a4c6
30. SCOTT J, AN RÍOGH EN, AL NOKHATHA S *et al*.: ANCA-associated vasculitis in Ireland: a multi-centre national cohort study. *HRB Open Res* 2022; 5: 80. https://doi.org/10.12688/hrbopenres.13651.1
31. SABLÉ-FOURTASSOU R, COHEN P, MAHR A *et al*.: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005; 143(9): 632-8. https://doi.org/10.7326/0003-4819-143-9-200511010-00006
32. CHUNG SA, LANGFORD CA, MAZ M *et al*.: 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Rheumatol* 2021; 73(8): 1366-83. https://doi.org/10.1002/art.41773
33. JONES RB, TERVAERT JW, HAUSER T *et al*.: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363(3): 211-20. https://doi.org/10.1056/nejmoa0909169