The Joint Vasculitis Registry in German-speaking countries (GeVas): subgroup analysis of 195 GCA patients

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Abstract

Objective

Giant cell arteritis (GCA) is one of the most common forms of vasculitis. There is an abundance of studies which are conducted in a randomised controlled trial setting but limited with respect to cohort size and follow-up time. GeVas is the first large-scale registry for vasculitides in German-speaking countries that enables to evaluate this rare disease. Herein we focus on the subgroup of GCA patients including follow-up data up to one year.

Methods

GeVas is a prospective, web-based, multicentre registry for the documentation of organ manifestations, outcomes, and therapy regimens in vasculitides. Recruitment started in June 2019. By April 2023, 15 centres were initiated and have started to enrol patients.

Results

After 4 years, 195 GCA-patients were included in the registry, of which 64% were female and 36% were male. The average age was 76 years at the time of recruitment (IQR=69-82). Seventy-nine percent were included in the registry because of a newly diagnosed GCA and 21% because of a relapse. At the first assessment most of the patients (89%) described general symptoms. Thirty-one percent stated ocular symptoms. Cranial symptoms were documented in 78% of the cases. All patients were documented with immunosuppressive treatment at start, of whom 95% received prednisolone, 16% cyclophosphamide, 20% methotrexate, and 48% tocilizumab. After three months 62% and after one year 91% of the patients achieved remission.

Conclusion

Regarding demographics, clinical manifestations and diagnostics, our study showed a similar composition compared to other studies. However, our data differed in terms of treatment regimens.

Key words

giant cell arteritis, GeVas Registry, long-term outcome

See page 902 for the affiliations.

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Introduction

The most frequently diagnosed form of vasculitis in Germany is giant cell arteritis (GCA), with an incidence of 20 to 30 per 100,000 individuals >50 years of age (1).

The lifetime risk for women amounts to 1%, for men to 0.5% (2). GCA is characterised by a granulomatous inflammation with formation of giant cells of the vessel wall, predominantly by CD4+-T-lymphocytes and macrophage infiltrates (3). GCA mainly involves large- and medium-sized arteries, *e.g.*, the aorta and its larger intra- but mostly extra cranial branches like the extradural carotid or more commonly the vertebral arteries (4), resulting in a wide spectrum of clinical manifestations that are grouped into cranial symptoms, large vessel involvement, symptoms of polymyalgia rheumatica (PMR) and general symptoms such as fatigue and fever. PMR-like symptoms include proximal myalgia, morning stiffness, bursitis, and synovitis.

The clinical manifestations of GCA are characterised by neurological involvement, ischaemia due to occlusion of intracranial vessels or alternative branches of the aorta and visual disturbances up to loss of vision due to occlusion of the optic arteries. The most important long-term complication is the development of an aortic aneurysm (5).

With respect to therapy, different immunosuppressive therapeutic options exist with glucocorticoids (GC) being the basis of therapy, biologicals like tocilizumab or conventional synthetic DMARDs like methotrexate (6-8). In the past, corticosteroid-sparing therapy regimens have become increasingly important to minimise the side effects of long-term glucocorticoid therapy, with tocilizumab being the first drug approved in the EU (9-12).

Like most vasculitides, GCA is also characterised by chronicity and relapses, leading to significant overall morbidity and mortality (13). A significant number of studies have been driven by a retrospective and/or monocentric study design including small patient cohorts, which may be justified by the rarity of the disease (7, 13-17). The aim of the Joint Vasculitis Registry in German-speaking countries (GeVas) is to document patients who have been recently diagnosed with vasculitis or have changed their treatment due to a relapse (inception cohort) (16). The German-speaking countries include Germany, Austria and the German-speaking cantons of Switzerland. Because of the rarity of these diseases, GeVas allows a systematic and prospective documentation in German-speaking countries for the first time, thereby enabling a standardised documentation of disease outcomes under the supervision of physicians specialized in vasculitis patient care over an extended period. Of note, the present analysis refers to the subgroup of GCA and its characteristics (18).

Patients and methods

Data source

A detailed description of the GeVas registry, protocol and methodology has been published previously (18). Data entry is performed via a web-based electronic case report form (eCRF) in RDE-LIGHT (RDE = Remote Data Entry), which is based on HTML and Javascript. The eCRF was developed by the Clinical Trials Unit of the Medical Centre, University of Freiburg, Germany.

The participating centres enter the corresponding routine data from the patients' medical records into the eCRF via a standard web browser. Data are being entered exclusively in pseudomised form, *i.e.* each patient is assigned a patient identification code in the registry prior to data entry. The patient identification code is assigned by the respective participating study centre and can only be decoded by the respective centre.

The eCRF is organised into specific sections (demographics, vasculitis entity, clinical characteristics, immunosuppressive treatment, etc.) that correspond to the list of outcomes and in which the respective parameters are recorded in a standardised form.

Due to the lack of current diagnostic criteria for classifying vasculitides and the pending results of the DCVAS study, the classification criteria that have been used in national and international stud-

ies are used to enrol patients in the registry. The following criteria were used: American College of Rheumatology classification criteria, Chapel Hill Consensus Conference nomenclature and definitions and the GIACTA Criteria (6, 19, 20). Because of the study design as a registry study, there is no limitation of the number of patients or the follow-up time.

Recruitment started in June 2019. By April 2023, 15 centres in Germany were initiated and have begun enrolling patients. Meanwhile, 195 patients with GCA have been documented in the registry (18).

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 classifications

The study is designed to enrol any patient who fulfils the criteria for a systemic or organ-limited vasculitis according to the Chapel Hill Consensus Conference, the 1990 American College of Rheumatology (ACR)-criteria or the GIACTA-criteria (20-22). Patients with a newly diagnosed GCA or who have changed their treatment due to a relapse in the last 6 months are included in the registry (inception cohort design). The newly designed criteria from the European League Against Rheumatism and the American College of Rheumatology from 2022 were not published at the time of the GeVas registry establishment (23, 24).

Statistical analysis

In advance, an analysis plan was prepared that specifies the goals of the interim analysis (18). This plan notes the definitions for the analysis population and the statistical methods.

For descriptive statistics, the arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and number of complete and missing observations are summarised. If possible, continuous data may be grouped into categories.

Categorical data is summarised by the total number of patients in each category and the number of missing values. Relative frequencies are represented by the total number as percentage (100x the number of patients divided by the total number of patients).

As the study design of the GeVas study is a registry study, an explicit distinction between primary and secondary outcomes is not made, but a list of equivalent outcomes has been defined as seen in Table I. The analysis reported in the present article focuses on describing baseline characteristics as well as 3-, 6- and 12-months follow-up data of the GCA subgroup within the GeVas registry.

Results

Cohort and patient characteristics

By April 2023 195 patients with GCA had been enrolled in the registry. Those patients were followed-up over a year. Due to different inclusion starting points, the patients are documented for different lengths of time in the follow-up, so that the number of patients decreases over the follow-up visits (First Assessment = 195; 3 months = 137; 6 months = 109; 12 months = 81). Most patients were included because of a newly diagnosed GCA (79%), twenty-one percent of the patients were included because of a relapse resulting in a change of treatment. Sixty-four percent of the patients were female and 36% were male. The median age was 76 years (IQR: 69–82). The oldest patient was 94 years old and the youngest was 53 years. Histological testing or imaging procedures can be used to confirm the diagnosis. While only 21% patients had a confirmatory biopsy (74% of patients without a performed biopsy), 83% of patients had positive imaging in the form of ultrasound, MRI, CT or PET (4% of patients without performed imaging).

Comorbidities

Various comorbidities can be reported in the GeVas registry: Arterial hypertension, diabetes, hyperlipidaemia, osteopenia and osteoporosis, congestive heart failure, cardiac arrythmia, coronary heart disease, stroke, peripheral arterial disease, chronic kidney disease and diverticulosis or diverticulitis. Regarding GCA, the first four in particular appear to be clinically relevant. 56% of the patients reported arterial hypertension, 15% diabetes, 15% hyperlipidaemia and 9% osteopenia/osteoporosis. After one year of observation, the proportion of the first three did not change a lot (53%; 15%; 18%). Otherwise, the percentage of osteoporosis increased by 9% to 18% (Table II).

Disease features

Most patients (89%) stated general symptoms including myalgia, fever, weight loss and fatigue at the first assessment.

Typical for GCA is an organ involvement of the eyes and/or the cranial system. At first assessment, 31% of the patients had an ocular involvement including blurred vision (5%), double vision (5%), amaurosis fugax/sudden visual loss (12%) or anterior ischaemic optic neuropathy (AION) (9%). After three months, 11% had an ocular involvement. After one year, eye involvement was stated in 4% of which most patients were affected by blurred vision.

Of the 195 GCA-patients, 152 patients (78%) stated cranial symptoms. Most common were new onset headache (53%), tender temporal artery (20%), swollen temporal artery (14%), jaw claudication (33%) and scalp tenderness (16%). Additionally, 21% stated proximal myalgia, 5% morning stiffness and 1% proximal bursitis/synovitis. In the follow-up exam, after 3 months, still 23% are documented with cranial symptoms. Revisiting the patients after one year, 9% suffered from the symptom described above.

Treatment

All patients received an immunosuppressive therapy (100%) including GC therapy or DMARDs/Biologicals at the first visit. Ninety-five percent received glucocorticoid (GC) therapy. Of whom 56% received an i.v. pulse GC therapy followed by tapering; 2% a long-term oral GC therapy with *i.v.* pulses and

Table I. Outcome parameters of GCA patients enrolled in the GeVas registry 04/2023.

GeVas interim analysis	
Number [FA/3M/6M/12M]	Number; n
Demographics [FA]	Female; n (%) Male; n (%) Age (years); (median, [Min, Q1, Q3, Max, Std. Dev.])
Reason for inclusion [FA]	Newly diagnosed vasculitis; n (%) Relapse; n (%)
Criteria for diagnosis [FA]	CHCC 2012; n (%) ACR 1990; n (%) GIACTA; n (%) Clinical; n (%)
Biopsy [FA]	Positive biopsy; n (%) Negative biopsy; n (%) Not performed biopsy; n (%)
Imaging [FA]	Positive imaging; n (%) Negative imaging; n (%) Inconclusive imaging; n (%) Not performed imaging; n (%)
Comorbidities [FA/3M/6M/12M]	Arterial hypertension; n (%) Diabetes; n (%) Smoking; n (%) Hyperlipidaemia; n (%) Congestive heart failure; n (%) Atrial fibrillation; n (%) Coronary heart disease; n (%) Myocardial infarction; n (%) Stroke/TIA; n (%) pAVK; n (%) CKD; n (%) Osteopenia/Osteoporosis; n (%) Diverticulosis/Divertikulitis; n (%)
Clinical manifestation [FA/3M/6M/12M]	
General symptoms; n (%)	Fatigue, n (%) Fever >38°C; n (%) Myalgia; n (%) Weight loss >2kg in last 6 months; n (%)
Eyes; n (%)	Blurred vision; n (%) Double vision; n (%) Amaurosis fugax/sudden visual loss; n (%) Anterior ischaemic optic neuropathy AION; n (%)
Neurological / Cranial symptoms; n (%)	New-onset headache; n (%) Tender temporal artery; n (%) Swollen temporal symptoms; n (%) Jaw claudication; n (%) Scalp claudication; n (%) Proximal myalgia; n (%) Morning stiffness; n (%) Proximal bursitis/Synovitis; n (%)
Laboratory [FA/3M/6M/12M]	CRP; (median, [Min, Q1, Q3, Max, Std. Dev.]) ESR; (median, [Min, Q1, Q3, Max, Std. Dev.]) Leukocytes; (median, [Min, Q1, Q3, Max, Std. Dev.]) Thrombocytes; (median, [Min, Q1, Q3, Max, Std. Dev.])
Immunosuppressive therapy [FA/3M/6M/12M]	
Immunosuppressive therapy; n (%)	
Prednisolone; n (%)	i.v. pulse therapy followed by tapering; n (%) Long-term oral GC therapy i.v. pulses required (no tapering regime); n (%) Stable long term GC therapy without i.v. pulses; n (%) Prednisolone monotherapy; n (%)
DMARDs; n (%)	Azathioprine; n (%) Cyclophosphamide; n (%) Methotrexate; n (%)
Biological; n (%)	Tocilizumab; n (%)
Supportive therapy; n (%)	Vitamin D; n (%) Bisphosphonate; n (%) Pneumocystis prophylaxis; n (%)
Scores [FA/3M/6M/12M]	BVAS; (median, [Min, Q1, Q3, Max, Std. Dev.]) VDI; (median, [Min, Q1, Q3, Max, Std. Dev.])
Follow-up-disease activity [FA/3M/6M/12M]	Active disease; n (%) Remission; n (%) Response; n (%) Relapse-major; n (%) Relapse-minor; n (%) Refractory; n (%)

43% a long-term oral GC therapy without any need for *i.v.* pulses. Patients who received a stable long-term oral GC therapy had an initial median dose of prednisolone of 40mg (IQR=15;60). The first GC *i.v.* pulse dose was on median 125mg (IQR=95;250).

In addition to GC therapy, most patients received a disease-modifying anti-rheumatic drug (DMARD) or biological therapy. Nineteen percent of patients received GC therapy only. The most frequent conventional DMARDs and biologics to induce remission were tocilizumab (TCZ), methotrexate (MTX) and cyclophosphamide (CYC). TCZ was used in 93 patients (48%) and MTX in 39 patients (20%). Azathioprine was used in 3 patients (1.5%) and leflunomide in 1 patient (0.5%). CYC was used in 31 patients (16%). As supportive therapy, Vitamin D was prescribed to 91%, bisphosphonates to 3% and *pneumocystis jiroveci* prophylaxis (PjP) to 53% of the patients.

After one year, 77% of the patients still received GC therapy, most of them in form of a stable long-term oral GC therapy without i.v. pulses with a dose of 5 mg (IQR=4,75;5,25). Further details on immunosuppressive therapy in the follow-up are included in the following analyses. Only 5% of the patients received a *pneumocystis jiroveci* prophylaxis. The number of patients receiving Vitamin D or bisphosphonates did not change.

Adverse events were documented in 18% including gastrointestinal symptoms (5%), neurological symptoms (1.5%), cardiovascular symptoms (1.5%), infections (5%) and cytopenia (1.5%) (Table III).

Disease activity

The definitions of the different states of disease activity are stated in Table IV.

At start, 100% of the patients had active disease, of which a part of patients had their first manifestation of GCA, and the other part had a relapse. After three months 7% of the patients were still documented with an active disease, 22% with a response to immunosuppressive therapy, 62% were in remission (defined as an absence of disease activity under a prednisolone dose of

Table II. Demographics and clinical characteristics of GCA patients enrolled in the GeVas registry (06/2019-04/2023).

	GCA			
	First Assessment	3 months	6 months	12 months
Number of patients	195	137	109	81
Demographics (n=195)				
Age (years); median [IQR-range; Min; Max]	76 [69-82; 53; 94]			
Gender (n=195)				
Male; n (%)	70 (35.9)			
Female; n (%)	125 (64.1)			
Reason for inclusion in the study (n=190, data missing=5)				
Newly diagnosed vasculitis; n (%)	150 (78.9)			
Relapse; n (%)	40 (21.1)			
Criteria used for diagnosis (n=195)				
CHCC 2012; n (%)	101 (51.8)			
ACR 1990; n (%)	108 (55.4)			
GIACTA; n (%)	87 (44.6)			
Clinical; n (%)	124 (63.6)			
Biopsy (n=157; data missing=38)				
Positive biopsy; n (%)	33 (21.0)			
Negative biopsy; n (%)	8 (5.1)			
Not performed biopsy; n (%)	116 (73.9)			
Imaging (n=180; data missing=15)				
Positive imaging; n (%)	150 (83.3)			
Negative imaging; n (%)	22 (12.2)			
Inconclusive imaging; n (%)	1 (0.6)			
Not performed imaging; n (%)	7 (3.9)			
Comorbidities (n=195) (n=133; data missing=4) (n=107; data missing=2) (n=79 data missing=2)				
Diabetes; n (%)	29 (14.9)	22 (16.5)	20 (18.7)	12 (15.2)
Hypertension; n (%)	109 (55.9)	65 (48.9)	56 (52.3)	42 (53.2)
Hyperlipidaemia; n (%)	30 (15.4)	23 (17.3)	17 (15.9)	14 (17.7)
Osteoporosis/Osteopenia n (%)	18 (9.2)	15 (11.3)	9 (8.4)	14 (17.7)
Organ involvement (n=195) (n=133, data missing=4) (n=107, data missing=2) (n=79, data missing=2)				
General symptoms; n (%)	174 (89,2)	46 (34.6)	32 (29.9)	17 (21.5)
Eyes; n (%)	61 (31.2)	15 (11.3)	13 (12.1)	3 (3.8)
AION; n (%)	17 (8.7)	2 (1.5)	1 (0.9)	0 (0.0)
Blurred vision; n (%)	10 (5.1)	2 (1.5)	1 (0.9)	1 (1.3)
Double vision	10 (5.1)	1 (0.8)	2 (1.9)	0 (0.0)
Amaurosis fugax/ Sudden visual loss; n (%)	23 (11.8)	2 (1.5)	1 (0.9)	0 (0.0)
Neurological / Cranial symptoms; n (%)	152 (77.9)	31 (23.3)	20 (18.7)	7 (8.9)
New-onset headache; n (%)	104 (53.3)	5 (3.8)	4 (3.7)	2 (2.5)
Tender temporal artery; n (%)	38 (19.5)	2 (1.5)	0 (0.0)	1 (1.3)
Swollen temporal symptoms; n (%)	27 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)
Jaw claudication; n (%)	65 (33.3)	7 (5.3)	2 (1.9)	2 (2.5)
Scalp claudication; n (%)	31 (15.9)	2 (1.5)	1 (0.9)	0 (0.0)
Proximal myalgia; n (%)	40 (20.5)	5 (3.8)	1 (0.9)	1 (1.3)
Morning stiffness; n (%)	9 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)
Proximal bursitis/Synovitis; n (%)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease activity (n=178, data missing=17) (n=122; data missing=15) (n=98; data missing=11) (n=68; data missing=13)				
Active disease, n (%)	178 (100)	9 (7.4)	0 (0.0)	0 (0)
Remission; n (%)	0 (0)	75 (61.5)	85 (86.7)	62 (91.2)
Response; n (%)	0 (0)	27 (22.1)	5 (5.1)	0 (0.0)
Relapse minor; n (%)	0 (0)	4 (3.3)	3 (3.1)	5 (7.4)
Relapse major; n (%)	0 (0)	3 (2.5)	1 (1.0)	0 (0.0)
Refractory; n (%)	0 (0)	4 (3.3)	4 (4.1)	1 (1.5)
Immunosuppressive treatment (n=195) (n=133, data missing=4) (n=106; missing data=3) (n=79, data missing=2)				
Immunosuppressive treatment; n (%)	195 (100)	133 (100)	106 (100)	79 (100)
Prednisolone; n (%)	185 (94.9)	121 (91.0)	92 (86.8)	61 (77.2)
i.v. Pulse GC therapy followed by tapering; n (%)	109 (55.9)			
Long-term oral GC therapy i.v. pulses required (no tapering regime); n (%)	4 (2.1)			
Stable long-term oral GC therapy without i.v. pulses; n (%)	84 (43.1)			
Prednisolone dose of long-term oral therapy in mg; median, [IQR]	40 [15;60]	10 [5;15]	5 [4;9,25]	5 [4,75;5,25]
Prednisolone dose of i.v. pulse; median, [IQR]	125 [95;250]			
Prednisolone monotherapy; n (%)	37 (19.0)	13 (9.8)	6 (5.7)	5 (6.3)
Azathioprine; n (%)	3 (1.5)	yet not available		
Cyclophosphamide; n (%)	31 (15.9)	yet not available		
Methotrexate; n (%)	39 (20.0)	yet not available		
Leflunomide; n (%)	1 (0.5)	yet not available		
Tocilizumab; n (%)	93 (47.7)	yet not available		
Supportive therapy; n (%)	188 (96.4)	128 (96.2)	97 (91.5)	74 (93.7)
Vitamin D; n (%)	177 (90.8)	122 (91.7)	90 (84.9)	70 (88.6)
Bisphosphonates; n (%)	6 (3.1)	4 (3.0)	4 (3.8)	3 (3.8)
Pneumocystis prophylaxis; n (%)	104 (53.3)	46 (34.6)	14 (13.2)	4 (5.1)

Table III. Adverse events.

Adverse events (n=195)	
Overall adverse events; n (%)	35 (17.9)
General symptoms; n (%)	3 (1.5)
Gastrointestinal symptoms; n (%)	10 (5.1)
Neurological symptoms; n (%)	3 (1.5)
Cardiovascular symptoms; n (%)	3 (1.5)
Infections (pneumonia, urinary tract infections, Zoster etc.); n (%)	9 (4.6)
Thrombocytopenia; n (%)	2 (1.0)
Leukopenia; n (%)	1 (0.5)
Others; n (%	4 (2.1)

Table V. Definition of different states of disease activity.

	Definitions of states of disease activity
Active disease	Any symptom attributable to active vasculitis, irrespective of treatment
Response	Relevant reduction of disease activity and absence of new manifestations
Remission	Absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy. Prednisolone should be a at a dose of 10mg/day or less.
Relapse minor	Re-occurrence or new onset of disease activity (neither organ- nor life-threatening)
Relapse major	Re-occurrence or new onset of disease activity (organ- or life-threatening)
Refractory disease	Lack of response, defined as 50% reduction in disease activity score, after >6 weeks of treatment or Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score list after >12 weeks of treatment

Table V. Subgroup analysis of patients who relapsed during the year of observation (relapse cohort) and those who did not (remission cohort).

	Remission cohort (n=179)	Relapse cohort (n=16)
Organ involvement (n=179/ n=16)		
Eyes; n (%)	59 (33.0)	2 (12.5)
AION; n (%)	15 (8.4)	2 (12.5)
Blurred vision; n (%)	10 (5.6)	0 (0.0)
Double vision	9 (5.0)	1 (6.3)
Amaurosis fugax/ Sudden visual loss; n (%)	21 (11.7)	2 (12.5)
Neurological / Cranial symptoms; n (%)	138 (77.1)	14 (87.5)
New-onset headache; n (%)	93 (52.0)	11 (68.8)
Tender temporal artery; n (%)	32 (17.9)	6 (43.0)
Swollen temporal symptoms; n (%)	24 (13.4)	3 (18.8)
Jaw claudication; n (%)	56 (31.3)	9 (56.3)
Scalp claudication; n (%)	28 (15.6)	3 (18.8)
Immunosuppressive treatment (n=179/ n=16)		
Immunosuppressive treatment	179 (100)	16 (100)
Prednisolone; n (%)	170 (95.0)	15 (93.8)
Prednisolone dose of i.v. pulse; median, [IQR]	125 [100;250]	100 [70;187,5]
Azathioprine; n (%)	3 (1.7)	0 (0.0)
Cyclophosphamide; n (%)	26 (14.5)	5 (31.25)
Methotrexate; n (%)	37 (20.7)	2 (12.5)
Leflunomide; n (%)	1 (0.6)	0 (0)
Tocilizumab; n (%)	88 (49.2)	5 (31.25)

10mg per day or less), 3% had refractory disease and 6% had a relapse. After one year of follow-up, 91% of the patients were in remission. Only 2% were refractory and 7% had a relapse. During the follow-up, sixteen participating patients, regardless of the reason for inclusion in the study, relapsed after already having achieved remission. The average time to relapse was 6.5 months. Comparing patients who experienced a relapse during follow-up with those who remained in remission, minor differences between organ manifestations and therapy regimens could be observed, like a more severe clinical manifestation at study inclusion or a lower prednisolone dose at baseline as seen in Table V.

Discussion

The GeVas registry is a registry for patients diagnosed with vasculitis that aims to capture all relevant data in clinical practice according to a standardised approach. It offers the possibility to improve the quality of clinical care of these diseases and to systematically characterise the clinical course of vasculitides as recorded by different specialised centres in Germany.

The GeVas registry acts as a data documentation system at a tri-national level with the potential to link to other national and international databases as in FAIRVASC (25). As of the current status, another eight European vasculitis registries have been established: United Kingdom and Ireland (UKIVAS) (26), Ireland (RKD) (27), France (FVSG Registry) (28), Spain (REVAS, ARTESER) (29, 30, 31), Poland (POLVAS Registry) (32, 33), Norway (NorVas), Czech Republic (Czech Registry of AAV) (34) and Greece (Greek Registry of AAV) (35), from which some of them are predominantly addressing AAV. In addition, the development of a vasculitis registry is on the research agenda in many other European countries (*e.g.* the Swiss SCQM (https://www.scqm.ch/), the Netherlands and Italy (36).

In this article we present data from GCA patients enrolled in the GeVas registry. The focus is on analysing data on demographics, clinical manifestations, and treatment regimens at baseline and during follow-up. This is the first evaluation of primary data to uncover potential care problems, to evaluate new treatment concepts that have not yet been sufficiently investigated in randomised trials and to generate further research hypotheses.

The demographic parameters at the time of inclusion in the study correspond to the demographics in other studies or

registries (37). As in other studies, a higher incidence is seen in women and in patients with higher age (1). The gender ratio of GCA patients, in the GeVas registry, was approximately 1:2 (male/female-ratio). The median age was 76 years with a interquartile range from 69 years to 82 years, which corresponds to the age range of other cohorts such as the Portuguese registry (33). Of note, we have not documented a patient with GCA under the age of 50 years which complies to the actual studies (1, 9).

The clinical manifestations focused on the eyes and the cranial system. Ocular involvement was observed in every third case in our cohort. A complete visual, respectively a partial visual loss is documented in 12% which is noticeably less than reported in other studies (1, 33). We saw a significant decrease in the percentage of patients suffering from ocular involvement after 3 months. After one year only 4% of patients suffered from ocular involvement. Cranial symptoms on the other hand, were documented in 78%. Moreover, after one year 9% of the patients still suffered from proximal myalgia and cranial symptoms like headache and jaw claudication. The GeVas registry show a significantly less severe clinical manifestation as in other studies (38). The less severe clinical manifestations could indicate rapid diagnosis and treatment in Germany. In a study published in 2020 by Muratore *et al*., significant differences in disease severity and onset could be differentiated between an Italian and US cohort, although the glucocorticoid dose did not differ substantially at the start. A genetic, geographical and environmental factor-related component must therefore be considered (39).

Following the latest studies regarding the use of imaging and/or temporal artery biopsy, most of the patients were diagnosed without a histopathological confirmation (40, 41). A biopsy was performed in 26% of the cases with a positive result in 80% of the cases. A positive imaging was found in 83% in the GeVas patients. Only in 4% of the cases an imaging was not performed. Our study confirms the shift towards imaging techniques and away from histologic confirmation.

Comorbidities were documented over a year. In the first assessment 15% had diabetes, 56% arterial hypertension and 15% hyperlipidaemia (Table II). The first two of these comorbidities did not increase in prevalence during the first year in our cohort. The part of hyperlipidaemia increased to 18%. There is much evidence that systemic inflammation provides a proatherogenic effect by inducing dyslipidaemia. This should lead to the evaluation of an effective cardioprotective treatment, as the risk of cardiovascular events is known to be increased in GCA patients. Additionally, there was an increase in osteoporosis, which can be attributed to the glucocorticoid therapy. It was striking that 9% had osteoporosis in the beginning and 18% after one year, but only 3% (4% after 12 months) of the patients were treated with bisphosphonates. The number of osteoporosis cases is not indicated by a change in therapy in the follow-up data, indicating that an equal proportion are treated with bisphosphonates at the first visit as at 12 months, so appropriate therapy should have been initiated earlier.

Regarding the immunosuppressive therapy, the documented patients mainly received prednisolone in combination with TCZ, MTX or CYC for remission induction. Only every fifth patient is treated with a GC therapy only. Other drugs such as secukinumab or Jak inhibitors have so far been used less frequently but will most likely be used more frequently in the future.

It is very striking that after one year, more than 77% of patients still receive a glucocorticoid therapy, contrary to the recommendations in the current guidelines which recommend termination of therapy after one year in remission. However, it needs to be mentioned that the median dose was 10 mg after 3 months (IQR=5;15) and only 5 mg after a year (IQR=4,75;5,25). Current evidence suggests that a slow tapering regime is associated with a lower risk of relapses, but with a higher incidence of side effects, like osteoporosis and diabetes (42). In the GIACTA study, it was proven that a reduction of the glucocorticoid therapy can be started early and can be stopped after half a year. Nevertheless, using this regimen, only 50% of patients remained in remission at one year (6). The GUSTO and PET-VAS study proved that ultra-short prednisolone therapy with subsequent TCZ therapy is also possible (43, 44). Another study by Unizony *et al*. confirmed that an 8-week tapering of GC followed by TCZ is possible for remission induction in GCA patients (45). However, further studies to evaluate possible ischaemia risks and risks of relapses are still needed so that no definitive recommendation can yet be made (44). As far as the high proportion of GC therapy after one year is concerned, this could be due to a relatively high proportion of patients reporting general symptoms, which could lead to the continuation of a minimal GC dose. Other parameters that could explain the continuation of GC therapy, such as a high CRP value, could no longer be detected after one year. With continued GC therapy, an increase in GC-associated side effects such as osteoporosis and hyperlipidaemia were observed in our study like described above. The sufficient initiation of a specific therapy was not carried out adequately in our study. In summary, attention should be paid to an earlier reduction of GC therapy and proper side effect management. The data from the subsequent follow-up must be analyse to estimate the final treatment duration.

Most patients were treated with TCZ (48%) followed by MTX (20%). The METOGiA study is investigating MTX compared to TCZ. The study is ongoing but not yet completed and the results are eagerly awaited (46). The efficacy and effectiveness of TCZ were confirmed in randomised double-blind studies (6, 7, 47). There are currently no long-term studies, particularly on the question of when to stop medication, so the GeVas registry may offer a valuable opportunity to provide clues to this question. A meta-analysis showed that MTX both significantly reduced the risk of relapse and that it has a glucocorticoid-sparing effect (7). It is worth mentioning, that only TCZ, but not MTX is licensed in Germany for the treatment of GCA.

Yet, there is not much data available for CYC for therapy in GCA patients. Clinical practice has shown that it can

be used especially in patients with high glucocorticoid requirement or in patients where other treatments have failed or were not tolerated (2, 10). CYC was efficient in a case series with 31 patients with severe refractory GCA (8). It is important to note that the guidelines do not recommend CYC as first line therapy due to a lack of evidence from studies (9, 12).

In our study, 16% of patients were treated with CYC. Those patients seemed to have a more severe organ involvement at beginning or a refractory disease complicated by extensive pan-aortitis and stenosing large artery involvement including intracranial artery involvement. It is not possible to make a definitive statement on treatment performance within this study design. Further results on therapy in the follow-up are not considered here and are included in the subsequent analyses.

Adverse events were seen in 35 cases. Only 9 patients (5%) suffered under infections due to immunosuppressive therapy, which could be due to well-executed infection prophylaxis and vaccination programme.

In terms of overall therapeutic efficacy, 62% of the patients entered remission after three months and 91% after one year. In conclusion, patients in the registry were successfully treated. In the follow-up, 16 patients (8%) suffered a relapse after sustaining remission (Table V). An analysis of the data revealed that a more severe clinical manifestation at baseline increased the risk of relapse. In particular, patients who reported an AION, vision loss or had a more severe cranial involvement were more likely to relapse. It was also noticeable that the patients who suffered a relapse had a lower selected prednisolone dose at the start. The data may indicate that the induction therapeutic dose should have been picked higher to prevent a relapse. As described above, the data are not considered significant because of the relatively small size of the relapse cohort. Further analyses are required and will be performed in the future.

The main weakness of the study is related to the study design. Data have not been collected in a randomised controlled setting. Categorical variables were mainly used with only one selection option for the variable to match, so that a non-occurrence cannot be formally distinguished from missing data. To increase statistical reliability, patients with contradictory entries were excluded from the statistical analysis, which then appear under data missing. In addition, a dedicated analysis of the data set was carried out to add transferable data points, for example: A patient is not listed as taking GC but has documented a daily GC dose. Thus, additional monitoring like a query system and mandatory entries during the further course are planned. By Nevertheless, because of the simplified documentation system, we guarantee a high level of input consistency and a real representation of the clinical care of GCA patients can be created based on this registry study. Due to the high willingness of our colleagues to enter data, we assume that our data will have a practicable statistical value. After 4 years, 15 centres are participating in the registry, so we expect more vasculitis centres to participate, both inpatient and outpatient.

In summary, GeVas allows a systematically and prospectively documentation for the first time in German-speaking countries, thereby enabling the standardised documentation of disease outcomes under the supervision of physicians specialised in vasculitis patient care over an extended period.

The demographic characteristics of our patient cohort are comparable to other European registry studies. Differences can be found in terms of organ involvement and therapy regimen. Overall, there is less organ involvement, which may be due to early diagnosis and therapy initiation in Germany compared to other countries. There was also a significantly higher proportion of patients receiving CYC therapy and a prolonged glucocorticoid therapy. Further analyses are needed to define the optimal treatment duration, glucocorticoid-reduction regimen, and strategies to reduce or terminate immunosuppressive therapy.

After four years of enrolling patients in the registry, the GeVas registry prospectively monitors a substantial cohort of patients, allowing analysis of a large data set.

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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.

J.P. Bremer has acted as consultant of Galapagos, and has received personal fees for lectures from UCB Pharma, Chugai, Celgene, Abbvie, Janssen, Galapagos, Lilly, Sanovi-Aventis, Novartis, AstraZeneca, GSK, Roche.

B. Hellmich has received personal fees for lectures or advisory services from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, InflaRx, GSK, Pfizer, Phadia, MSD, Roche, Novartis and Vifor outside the submitted work.

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N. Venhoff has received personal fees for lectures and/or advisory services from Chugai and Novartis, and has pending patent application on the use of secukinumab in GCA; he has received grant/research support from John- Grube Research Award 2021.

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