





Clinical Manifestations and Long-Term Outcomes of Eosinophilic Granulomatosis With Polyangiitis in North America

Irena Doubelt,¹  David Cuthbertson,² Simon Carette,¹ Sharon A. Chung,³ Lindsay J. Forbess,⁴ Nader A. Khalidi,⁵ Curry L. Koenig,⁶ Carol Langford,⁷ Carol A. McAlear,⁸ Larry W. Moreland,⁹  Paul A. Monach,¹⁰  Philip Seo,¹¹ Ulrich Specks,¹² Robert F. Spiera,¹³  Jason M. Springer,¹⁴ Antoine G. Sreih,⁸ Kenneth J. Warrington,¹² Peter A. Merkel,⁸ Christian Pagnoux,¹ and for the Vasculitis Clinical Research Consortium

Objective. To describe clinical manifestations and outcomes in patients with eosinophilic granulomatosis with polyangiitis (EGPA) in North America.

Methods. Analysis of patients aged 18 years or older who fulfilled the 1990 American College of Rheumatology Classification Criteria for EGPA enrolled in the Vasculitis Clinical Research Consortium from 2003 to 2019. Main clinical characteristics, treatments, outcomes, and accumulated damage were studied.

Results. The cohort included 354 patients; 59% female; age at diagnosis of 50.0 (± 14) years; 39% were antineutrophil cytoplasm antibody (ANCA) positive. Time from diagnosis to last follow-up was 7.0 (± 6.2) years; 49.4% had one or more relapse. Patients positive for ANCA more commonly had neurological and kidney involvement when compared with patients negative for ANCA, who had more cardiac and lung manifestations. At last study visit, only 35 (12.6%) patients had been off all therapy for more than 2 years during their follow-up. The overall mortality rate was 4.0% and did not differ by ANCA status or cyclophosphamide use. Scores on the Vasculitis Damage Index (VDI) for 134 patients with two or more visits and more than 1 year of follow-up increased from 1.7 (± 1.8) at enrollment (3.7 [± 5.1] years after diagnosis) to 3.35 (± 2.1) at last follow-up (7.5 [± 5.8] years after diagnosis), mainly represented by chronic asthma (67.5%), peripheral neuropathy (49.6%), and chronic sinusitis (31.3%). Longer duration of glucocorticoid use and relapse were associated with higher VDI scores.

Conclusion. This analysis describes the many clinical manifestations and varied outcomes of EGPA and highlights the ongoing need to attain more sustained, long-term remission to limit the accrual of disease-related damage.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest of the antineutrophil cytoplasm antibody (ANCA)-associated vasculitides. The annual incidence is approximately 0.6/million to 3.4/million (1,2), with a prevalence of 2 million to 38/

million (2–4). It is often characterized by an initial prodromal phase with asthma and/or rhinosinusitis, progressing into eosinophilic infiltration of multiple organ systems and the development of systemic vasculitis (5,6).

A positive test for ANCA in EGPA is less common compared with granulomatosis with polyangiitis (GPA) or microscopic

The Vasculitis Clinical Research Consortium (VCRC) is part of the Rare Diseases Clinical Research Network, an initiative of the Office of Rare Diseases Research, National Center for Advancing Translational Science (NCATS). The VCRC is supported by funding from NCATS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (U54 AR057319), the National Center for Research Resources (U54 RR019497), and GlaxoSmithKline.

¹Irena Doubelt, MD, Simon Carette, MD, MPhil, Christian Pagnoux, MD, MSc, MPH: Vasculitis Clinic, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; ²David Cuthbertson, MS: Health Informatics Institute, University of South Florida, Tampa; ³Sharon A. Chung, MD, MAS: University of California, San Francisco; ⁴Lindsay J. Forbess, MD: Cedars Sinai Medical Center, Los Angeles, California; ⁵Nader A. Khalidi, MD: McMaster University and St. Joseph's Healthcare, Hamilton, Ontario, Canada; ⁶Curry L. Koenig, MD, MS: University of Utah Hospital, Salt Lake City; ⁷Carol Langford, MD, MHS: Cleveland Clinic, Cleveland, Ohio; ⁸Carol A. McAlear, MA,

Antoine G. Sreih, MD, Peter A. Merkel, MD, MPH: University of Pennsylvania, Philadelphia; ⁹Larry W. Moreland, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; ¹⁰Paul A. Monach, MD: Division of Rheumatology, Veterans Affairs Boston Healthcare System, Boston, Massachusetts; ¹¹Philip Seo, MD: Johns Hopkins University, Baltimore, Maryland; ¹²Ulrich Specks, MD, Kenneth J. Warrington, MD: Mayo Clinic College of Medicine and Science, Rochester, Minnesota; ¹³Robert F. Spiera, MD: Hospital for Special Surgery, New York, New York; ¹⁴Jason M. Springer, MD, MS: University of Kansas, Kansas City.

Dr. Pagnoux reports receiving fees for serving on advisory boards from ChemoCentryx, GlaxoSmithKline, Sanofi, and Hoffman-La Roche; he also reports receiving lecture fees and research grant support from Hoffman-La Roche and GlaxoSmithKline. Peter A. Merkel reports receiving funds in the past 2 years for consulting from AbbVie, AstraZeneca, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, CSL Behring, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx,

SIGNIFICANCE & INNOVATIONS

- This is a detailed analysis of the largest North American cohort of patients with eosinophilic granulomatosis with polyangiitis (EGPA).
- Clinical manifestations of EGPA, but not relapse rates or death, differed on the basis of antineutrophil cytoplasm antibody status.
- Although mortality in this cohort was low compared with that of previously reported cohorts, the relapse rate and accumulation of damage from EGPA and its treatment was high.
- Greater damage in patients with EGPA was associated with longer duration of glucocorticoid use and history of relapse.

polyangiitis (MPA). When positive, it most commonly has a perinuclear pattern on indirect immunofluorescence, with specificity for antibodies directed against myeloperoxidase (MPO), as tested by ELISA (4,7). Most series of EGPA from 1985 to 2010 described that ANCA-positive patients typically had more features or surrogates of vasculitis, such as glomerulonephritis or mononeuritis multiplex, and more frequent weight loss, myalgias, or arthralgias (8–11). Alternatively, patients without detectable ANCA were more prone to develop cardiac disease and eosinophilic pulmonary infiltrates (8,9,11,12). Higher mortality with lower risk of relapse has also been suggested in some, but not all (4), of the former ANCA-negative EGPA cohorts (10,12).

Therapy with glucocorticoids (GCs) and additional immunosuppressants in severe cases (13) have gradually transformed the prognosis of patients with EGPA. Survival rates have improved to more than 90% at 5 years (14–16). However, these therapies are frequently used at large doses and/or for long durations, mainly because of persistent asthma. Thus, patients remain at high risk for adverse effects, infections, and premature mortality, especially in the first year after diagnosis (17). Substantial damage may accrue during the disease course, and long-term outcomes in EGPA are limited.

The purpose of this study was to describe the main clinical characteristics, treatment patterns, outcomes, and longitudinal damage in a North American cohort of patients with EGPA.

PATIENTS AND METHODS

Study population. Eligible patients with EGPA were enrolled from 2003 to 2019 in the Vasculitis Clinical Research Consortium (VCRC) longitudinal study (LS) (NCT00315380) or the VCRC One-Time DNA (OT) (NCT01241305) study

across eight United States and two Canadian sites. Patients were at least 18 years old at the date of enrollment and fulfilled the 1990 American College of Rheumatology Classification Criteria for EGPA (5). Enrollment occurred at the time of diagnosis or any time during the course of their disease (flare or remission). The observational, prospective LS collected clinical and laboratory information quarterly to annually on the basis of patient preference and availabilities. The OT study was a one-time collection of clinical data and DNA. Visits for both studies involved the completion of standardized forms that collected information on patient demographics, disease characteristics, relapse(s) prior to enrollment, and, for LS only, treatments received, relapses after enrollment, and damage.

Disease relapse was based on physician-expert clinical judgement and defined as an increase in disease activity, attested by an increase in the Birmingham Vasculitis Activity Score, requiring a dose increase, initiation, or reinstatement of GCs and/or any immunosuppressive drug.

Studied outcomes. Main demographics, time of onset of asthma to diagnosis, main organ involvement at diagnosis and during follow-up, ANCA status, and, for LS only, type of treatments received since diagnosis and cumulative duration of GC use were analyzed. ANCA-positive status was defined as history of any positive tests by immunofluorescence and/or ELISA.

Analyzed outcomes included relapse(s), longitudinal damage, and, for LS only, deaths. Longitudinal damage was assessed using the Vasculitis Damage Index (VDI), which is scored as the sum of any of the 64 items identified by the investigator (18), and analyzed at enrollment (if diagnosis was made >3 months prior to enrollment) and subsequently at 1, 3, 5, and 7 years after diagnosis (\pm 6 months). The VDI score at the last study visit at least 1 year from the date of diagnosis was compared with the VDI score at enrollment.

Statistical analyses. Qualitative and categorical variables were analyzed and reported as count (percentage) and compared using χ^2 test or Fisher's exact test, as appropriate. Quantitative variables were computed calculating the mean \pm SD or median with interquartile range (IQR) and compared using Student's *t* test or one-way ANOVA. Patient variables and outcomes (sex, clinical manifestations, relapse, death, and "off GC and immunosuppressant therapy") were documented and compared according to ANCA status and receipt of cyclophosphamide (CYC). Multivariate Poisson regression analysis was used to analyze predetermined, independent associations with VDI at last follow-up (for the LS

Insmed, Janssen, Kiniksa, Kyverna, Magenta, Novartis, Pfizer, Sparrow, Takeda, and Talaris; for research support from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx; and royalties from UpToDate.

Address correspondence to Christian Pagnoux, Vasculitis Clinic, Mount Sinai Hospital, 60 Murray Street, Suite 2-220, Box 8, Toronto, Ontario, M5T 3L9, Canada. Email: christian.pagnoux@sinahealth.ca.

Submitted for publication February 22, 2021; accepted in revised form March 29, 2021.

patients with ≥ 2 visits and ≥ 1 -year postdiagnosis follow-up) and age, sex, ANCA status, history of ever using CYC, duration of GC use, or history of relapse.

Statistically significant differences were defined if *P* values were less than 0.05. Statistical analyses were performed using Stata Software, version 12 (StataCorp).

Ethics. The protocols for the LS and OT study were approved by each local hospital research ethics board committees at all participating sites, and the research was performed in accordance with the Declaration of Helsinki. All subjects provided written consent for their participation prior to enrollment.

RESULTS

Demographic and clinical characteristics at enrollment. The study included 354 patients (277 LS; 77 OT); the male/female ratio was 145 (41%)/209 (59%); 309 (87.3%) patients were white, 20 (5.6%) were Asian, and 7 (2.0%) were Black or African American. The mean age at diagnosis and enrollment was 50.0 (± 14.2) and 53.5 (± 13.6) years, respectively; most patients (350 [98.8%]) were diagnosed after 18 years of age.

Prior to the diagnosis of EGPA, asthma was recorded for 246 (69.5%) patients for a mean of 8.6 (± 12.2) years; 329 (92.9%) patients were eventually diagnosed with asthma during follow-up. An ANCA status was available for 316 patients; 123 (38.9%) were positive, and the remainder (193 [61.1%]) were negative. Of those who tested positive for ANCA, MPO-ANCA (with reported specificity by ELISA) was positive in 104 patients (84.6%), proteinase-3-ANCA was positive in 11 patients (8.9%), and atypical ANCA was positive in five patients (4.1%). Main manifestations at diagnosis and at any time over the course of follow-up (until last study visit) are listed in Table 1 and compared with previously published large cohorts (>50 patients) in Table 2.

Treatments. In the LS, 115 (41.5%) patients received CYC at some point in their disease, 145 (52.3%) received azathioprine, 109 (39.4%) received methotrexate, and 25 (9%) received mycophenolate mofetil. Rituximab was used at some time in the disease course in 29 (10.5%) patients, and mepolizumab was used at some time in 25 (9.0%) patients. The median cumulative duration of GC use was 12.0 (IQR = 9) months.

At the last study visit, 35 (12.6%) patients had been off systemic GCs and immunosuppressant medications for more than 2 years during their follow-up. A total of 113 (40.8%) patients were off GC therapy only for more than 2 years since study enrollment.

Relapses and deaths. Fifty percent of patients in the cohort experienced at least one relapse since diagnosis. Of those followed longitudinally in the LS for 7.6 (± 5.9) years, 99 (35.7%) experienced at least one relapse after enrollment. Characteristics of these relapses, as recorded by the investigators, included

Table 1. Cumulative clinical manifestations of 354 patients with eosinophilic granulomatosis with polyangiitis at diagnosis and during follow-up

Clinical Manifestations	At Diagnosis	By the Time of Last Follow-Up
Constitutional symptoms, n (%)	207 (58.5)	290 (81.9)
Weight loss	83 (23.4)	106 (29.9)
Fatigue	178 (50.2)	256 (72.3)
Arthralgias	93 (26.3)	140 (39.5)
Myalgias	64 (18.1)	91 (25.7)
Ear/nose/throat, n (%)	201 (56.8)	292 (82.5)
Nasal polyposis	123 (34.7)	177 (50.0)
Sinus involvement	188 (53.1)	273 (77.1)
Lung, n (%)	196 (55.4)	296 (83.6)
Asthma	246 (69.5)	329 (92.9)
Pulmonary infiltrates	138 (38.9)	205 (57.9)
Alveolar hemorrhage	12 (3.4)	21 (5.9)
Nodules or cavities	23 (6.5)	43 (12.1)
Pleural effusion	24 (6.8)	35 (9.9)
Cutaneous, n (%)	68 (19.2)	106 (29.9)
Purpura	54 (15.3)	88 (24.9)
Ulcer(s)	8 (2.3)	14 (4.0)
Gangrene	3 (0.8)	4 (1.1)
Nodules	15 (4.2)	26 (7.3)
Neurological, n (%)	151 (42.7)	214 (60.5)
Stroke	2 (0.6)	5 (1.4)
Sensory neuropathy	126 (35.6)	181 (51.1)
Mononeuritis multiplex	81 (22.9)	116 (32.8)
Cardiac, n (%)	51 (14.4)	75 (21.2)
Pericarditis	22 (6.2)	35 (9.9)
Myocarditis	42 (11.9)	57 (16.1)
Gastrointestinal, n (%)	11 (3.1)	22 (6.2)
Colitis	6 (1.7)	15 (4.2)
Mesenteric ischemia	5 (1.4)	7 (2.0)
Renal, n (%)	16 (4.5)	36 (10.2)
Proteinuria	13 (3.7)	22 (6.2)
Hematuria	13 (3.7)	29 (8.2)
Elevated serum creatinine	10 (2.8)	18 (5.1)
Number of clinical manifestations, mean (SD) ^a	5.5 (2.4)	6.6 (2.3)

^a Data from patients within Vasculitis Clinical Research Consortium longitudinal study only (n = 27).

active asthma only (17%), ear/nose/throat (ENT) only (21%), active asthma and ENT (18%), other lung disease (14%), cardiac (9%), skin manifestations (8%), and/or neuropathy (18%).

Eleven (4%) patients in the LS died after a mean of 4.7 (± 2.5) years after diagnosis (two from myocardial infarctions, one from an intestinal perforation, one from metastatic cancer, and seven from unknown causes). Only three of these deaths (two myocardial infarctions and one intestinal perforation) were deemed as possibly related to EGPA, as per the patient's physician-investigator.

Clinical presentation and outcomes according to ANCA status and receipt of CYC. The main clinical manifestations occurring during the disease course were compared according to the ANCA status and use of CYC (Table 3). ANCA-positive patients had significantly more neurologic and renal manifestations

Table 2. Comparison of clinical manifestations in previously published main series, large EGPA cohorts (>50 patients) with those in our VCRC study

Main Series Cohort	Nation(s)	Cohort Size, n	Age at Diagnosis, Mean, yr	Follow-Up Duration, mean	Laboratory Results ANCA+, %	Frequency of Organ/System Involvement or Manifestation, %								
						Asthma	Pulmonary Nonasthma (Infiltrates)	ENT	Skin	Heart	PNS	CNS	GI	Renal
Guillevin, 1999 (31)	France	96	48	-	20/42 (48)	100	-(38)	61	51	-	78	8	33	26
Keogh, 2003 (4)	United States	91	49	2.3 yr ^a	22/30 (73)	99	58 (-)	74	57	-	76	11	31	25
Sinico, 2005 (11)	Italy	93	52	-	35/93 (38)	96	51 (-)	77	53	16	65	14	22	27
Sable-Fourtassou 2005, (9)	France, Belgium, Latvia, and the United Kingdom	112	52	34 mo	43/112 (38)	100	-(65)	77	52	35	72	9	32	16
Samson, 2013 (16)	France, Belgium, and the United Kingdom	118	52	81 mo	48/118 (41)	94	-(60)	75	48	38	74	5	29	27
Moosig, 2013 (25)	Germany	150	49	53 mo	45/150 (30)	93	61 (58)	93	49	47	77	15	29	19
Healy, 2013 (12)	United States	93	-	-	38/93 (41)	100	66 (65)	63	68	28	52	13	17	17
Comarmond, 2013 (10)	France	383	50	67 mo	108/348 (31)	91	91 (39)	48	40	-	51	5	23	22
Sokolowska, 2014 (32)	Poland	50	41	^b ANCA+55mo/ANCA-75 mo	15/50 (30)	100	100 (98)	98	68	54	-	2	34	20
Cottin, 2017 (8)	France	157	49	7.4 yr	48/157 (30)	100	- (-)	-	-	-	-	-	-	21
VCRC, 2021	Canada and United States	354	50	7.6 yr	123/316 (39)	93	-(58)	83	30	21	58	5	6	10

ANCA, antineutrophil cytoplasm antibody; CNS, central nervous system; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ears, nose, and throat; GI, gastrointestinal; PNS, peripheral nervous system; VCRC, Vasculitis Clinical Research Consortium.

^a Median.

^b Duration of EGPA.

Table 3. Main characteristics and clinical manifestations over the course of the disease of 354 patients with EGPA according to ANCA status and use of CYC

Main Characteristic/Manifestation	All (N = 354) ^a	ANCA Positive (n = 123) ^a	ANCA Negative (n = 193) ^a	P Value ^a	All (N = 277) ^b	Use of CYC (n = 115) ^b	No Use of CYC (n = 162) ^b	P Value ^b
Female sex, n (%)	189 (59.8)	61 (49.6%)	128 (66.3)	<0.01	157 (56.7)	52 (45.2)	105 (64.8)	<0.01
ANCA positive, n (%)	-	-	-	-	98 (40.2)	46 (45.5)	52 (36.4)	0.15
Constitutional symptoms, n (%)	265 (83.9)	107 (87.0)	158 (81.9)	0.23	231 (83.4)	99 (86.1)	132 (81.5)	0.31
Ear/nose/throat, n (%)	264 (83.5)	98 (79.7)	166 (86.0)	0.14	226 (81.6)	90 (78.3)	136 (84.0)	0.23
Lung, n (%)	263 (83.2)	93 (75.6)	170 (88.1)	<0.01	232 (83.8)	89 (77.4)	143 (88.3)	0.02
Cardiac, n (%)	63 (19.9)	16 (13.0)	47 (24.4)	0.01	66 (23.8)	38 (33.0)	28 (17.3)	<0.01
Neurological, n (%)	199 (63.0)	90 (72.2)	109 (56.5)	<0.01	171 (61.7)	85 (73.9)	86 (53.1)	<0.01
Renal, n (%)	31 (9.8)	20 (16.3)	11 (5.7)	<0.01	26 (9.4)	15 (13.0)	11 (6.8)	0.08
Gastrointestinal, n (%)	20 (6.3)	4 (3.3)	16 (8.3)	0.07	18 (6.5)	8 (7.0)	10 (6.2)	0.79
Cutaneous, n (%)	94 (29.8)	41 (33.3)	53 (27.5)	0.27	89 (32.1)	39 (33.9)	50 (30.9)	0.59
Relapse, n (%)	158 (50.0) ^c	64 (52.0)	94 (48.7)	0.56	174 (62.8)	66 (57.4)	108 (66.7)	0.12
Cyclophosphamide use, n (%)	101 (41.4)	46 (46.9)	55 (37.7)	0.15	-	-	-	-
Off GCs and immunosuppressant(s), ^c n (%)	31 (9.8)	15 (12.2)	16 (8.3)	0.33	35 (12.6)	13 (11.3)	22 (13.6)	0.71

ANCA, antineutrophil cytoplasm antibody; CYC, cyclophosphamide; EGPA, EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid.

^a Data from patients within known ANCA status.

^b Data from patients within Vasculitis Clinical Research Consortium longitudinal study only.

^c For >2 consecutive years at any time during follow-up after the diagnosis of EGPA within Vasculitis Clinical Research Consortium longitudinal study only.

Table 4. VDI scores in patients with eosinophilic granulomatosis with polyangiitis at enrollment and 1, 3, 5, and 7 years after diagnosis and last follow-up

Time After Diagnosis	N	Years After Diagnosis	VDI (SD)
Enrollment, >3 months	291	4.2 (±5.4)	2.57 (±2.1)
1 year (±6 months)	103	1.0 (±0.3)	2.46 (±2.2)
3 years (±6 months)	83	3.0 (±0.3)	2.71 (±1.9)
5 years (±6 months)	47	5.0 (±0.2)	2.85 (±1.9)
7 years (±6 months)	37	7.0 (±0.3)	2.65 (±2.1)
Patients in LS with ≥2 visits and ≥1 year follow-up after diagnosis			
At enrollment	134 ^a	3.7 (±5.1)	1.68 (±1.8)
Last follow-up, >1 year	134	7.5 (±5.8)	3.35 (±2.1)

LS, longitudinal study; VDI, Vasculitis Damage Index.
^a Twenty-four patients had enrollment visit less than 3 months after diagnosis and were given VDI of 0.

but were less likely to have lung or cardiac manifestations compared with ANCA-negative patients, who were also more likely to be female. Relapses and deaths did not differ on the basis of ANCA status.

Receipt of CYC was significantly associated with cardiac and neurologic manifestations, whereas women and those with lung involvement were less likely to have received CYC. Women who received CYC were 51.0 (14.9) years of age at diagnosis versus 47.1 (14.3) for those who did not (*P* = 0.12); a similar proportion

of women who received CYC were less than 50 years old (24/51 [47.1%]) compared with those who did not (55/105 [52.4%]; *P* = 0.53). Relapses and deaths did not differ on the basis of use or lack of use of CYC.

Damage. VDI scores at enrollment for all patients and for those with a VDI score at both enrollment and at last follow-up visit (postdiagnosis follow-up >1-year in the LS) are illustrated in Table 4, with a detailed distribution of VDI score over time in Supplementary Figure 1. The most frequent VDI items present at the last follow-up visit (if ≥1-year follow-up after diagnosis) for the patients in the LS and those in the OT are shown in Figure 1. The top five VDI items (chronic asthma, peripheral neuropathy, chronic sinusitis, nasal blockade/chronic discharge/crusting, and osteoporosis/vertebral collapse) at last follow-up visit were the top five VDI items at enrollment.

A total of 134 patients in the LS had two or more visits and 1-year or more follow-up after diagnosis. For these patients, mean age at diagnosis was 48.8 (±14.3) years (women [*n* = 76], 46.9 [±14.3] years; men [*n* = 58], 51.4 [±13.9] years), and the mean follow-up period from diagnosis was 6.2 (±6.9) years. Multivariate analysis of last VDI scores in these 134 patients (Table 5) demonstrated the following variables as being associated with a higher last VDI score in the unadjusted model: male sex (mean VDI score of 3.7 [±2.3] in male patients versus 3.1 [±1.9] in female patients;

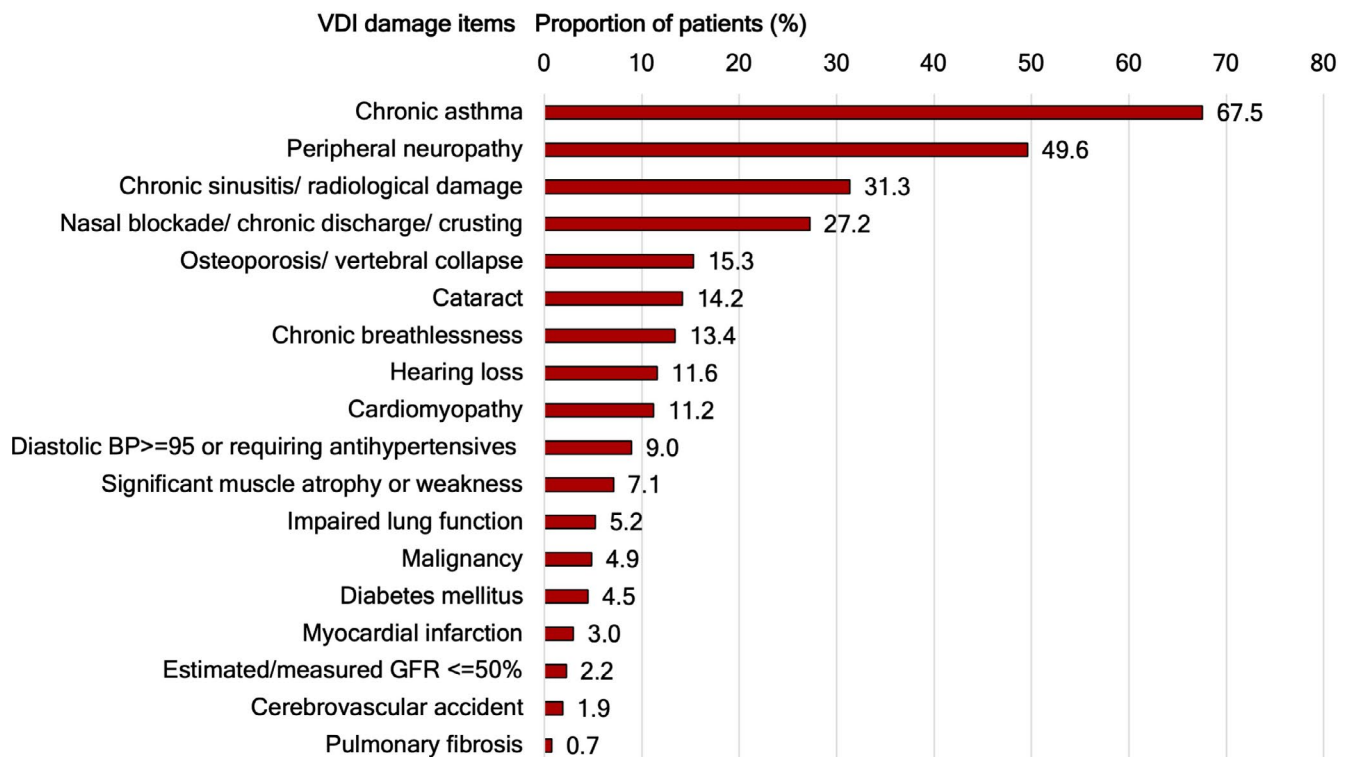


Figure 1. Main items of damage at last follow-up visit for all patients with patients with eosinophilic granulomatosis with polyangiitis and ≥1 year of follow-up after diagnosis (*n* = 268) in the Vasculitis Clinical Research Consortium. GFR, glomerular filtration rate; VDI, Vasculitis Damage Index.

Table 5. Factors associated with higher Vasculitis Damage Index score at last follow-up visit in the 134 patients with eosinophilic granulomatosis with polyangiitis

Parameter	N (%)	Last VDI Score, Mean (\pm SD)	IRR/OR ^b	95% CI	P value	OR/IRR	95% CI	P Value
			Unadjusted			Adjusted for the Duration of Follow-Up		
Duration of follow-up from diagnosis, mean (\pm SD), yr	7.45 (5.8)	-	1.0133	0.9931-1.0338	0.20	-	-	-
Age, mean (\pm SD), yr	48.8 (14.3)	-	1.0063	0.9979-1.0147	0.14	1.0094	1.0015-1.0174	0.02
Sex	-	-	1.2771	1.0306-1.5826	0.03	1.1589	0.9279-1.4475	0.19
Male	58 (43.3)	3.67 (2.32)	-	-	-	-	-	-
Female	76 (56.7)	3.11 (1.94)	-	-	-	-	-	-
ANCA Status (n=126) ^a	-	-	1.0785	0.8635-1.3469	0.51	1.0610	0.8490-1.3260	0.60
Positive	57 (45.2)	3.60 (2.39)	-	-	-	-	-	-
Negative	69 (54.8)	3.14 (1.97)	-	-	-	-	-	-
Use of CYC (ever)	-	-	1.1563	0.9260-1.4439	0.20	1.1789	0.9425-1.4746	0.15
Yes	58 (43.3)	3.62 (2.40)	-	-	-	-	-	-
No	76 (56.7)	3.14 (1.87)	-	-	-	-	-	-
Duration of GC use, mean (\pm SD), mo	12.0 (15.7)	-	1.0050	1.0025-1.0075	<0.01	1.0030	1.0001-1.0058	0.04
Relapse history	-	-	1.2948	1.0102-1.6597	0.04	1.3660	1.0819-1.7247	0.01
Yes	99 (73.9)	3.62 (2.23)	-	-	-	-	-	-
No	35 (26.1)	2.60 (1.61)	-	-	-	-	-	-

ANCA, antineutrophil cytoplasm antibody; CI, confidence interval; CYC, cyclophosphamide; GC, glucocorticoid; IRR, incidence rate ratio; OR, odds ratio; VDI, Vasculitis Damage Index.

Results are from a multivariate Poisson regression analysis of from patients in the Vasculitis Clinical Research Consortium longitudinal study with two or more study visits and 1 or more year of follow-up after diagnosis.

^a ANCA testing not done or results not available for eight patients.

^b IRR (Poisson equivalent of OR).

$P = 0.03$), duration of use of GCs (increase of the VDI score by 0.5% for each additional month of GC use; $P < 0.01$), and relapse (mean VDI score of 3.6 [\pm 2.2] with a history of relapse versus 2.6 [\pm 1.6] with no relapse; $P = 0.03$). In the multivariate analysis adjusted for the duration of follow-up since diagnosis (Table 5), age (increase of VDI score by 0.6% for each additional year; $P = 0.02$) rather than sex was associated with higher VDI scores, along with the duration of GC and relapse history.

DISCUSSION

This is a detailed analysis of the largest North American cohort of patients with EGPA followed longitudinally. It confirms the varied nature of EGPA, with several clinical manifestations differing on the basis of ANCA status, and demonstrates the good survival rate in this disease despite high rates of relapse and extensive use of GCs. Although patients had periods off GCs, only a minority of patients were off all therapy for more than 2 years. Damage was common, with higher VDI scores in older patients, those with longer duration of GC use, and those with a history of disease relapse.

Comparisons of the current cohort with prior reports of large cohorts yield some interesting observations (Table 2). Asthma, nasal and sinus involvement, fatigue, pulmonary infiltrates, and sensory neuropathy were the most common manifestations at the time of EGPA diagnosis in the current cohort and continued to predominate throughout the course of the disease. These findings

are consistent with most previous reports, though higher rates of neurological (55-93%) and cutaneous (40-52%) manifestations have been previously reported. This may be due to environmental or genetic influences related to country of origin and/or ethnic backgrounds or more delayed diagnoses when more complications had developed (9,10,19-21).

Positive ANCA status was associated with a higher likelihood of neurological and kidney involvement compared with a negative ANCA status. Patients who were ANCA negative had more heart and lung involvement, a finding reported in several other cohorts (8,10,19,20). The overall mortality rate was 4%. In previous European and Asian cohorts from 1957 to 2014 with a similar mean duration of follow-up, mortality rates were 7% to 14%, although this improved in most recent reports (10,12,22-25). Similar to the current study, most other studies also reported no difference in death rates based on ANCA status (8,9,19,20,23), although one study reported more deaths in ANCA-negative cohorts, presumably because of more frequent cardiac manifestations (10). Earlier recognition of the disease and its life-threatening manifestations and improved available therapies for EGPA and cardiac disease may have contributed to the current findings, with a gradual shift in the causes of death from cardiac to other complications, especially treatment-related ones, such as infections.

Relapses are frequent in EGPA. However, studies of EGPA include inconsistent definitions of relapse, especially as to whether eosinophilic asthma or exacerbations of sinus polyposis should be considered as evidence of a relapse or analyzed separately.

Of the patients enrolled in the LS study, 35.7% had a relapse recorded after enrollment as assessed by the VCRC investigators, all of whom are quite familiar with the evaluation of patients with vasculitis. Half of relapses consisted only of asthma and/or exacerbations of ENT disease, which led to a change in, or the addition of, an immunosuppressive agent.

Data on damage in EGPA are scarce, at least when compared with data on GPA and MPA (26–29). Early identification of patients more at risk of damage and better management of the latter remain important unmet needs. In this cohort of patients with EGPA, higher VDI scores at the last visit were seen in patients who experienced a relapse and/or had longer durations of use of GCs, suggesting that long-term GC use may be associated with a detrimental impact or may be a marker of severity of disease (26,30). As male patients were 10 years older at diagnosis than female patients, the respective impact of male sex or older age at diagnosis for accrued damage is more complex, with varying results for these two parameters in the model after adjustment for duration of follow-up. Asthma and neuropathy were the leading damage items among the patients with EGPA, which also identifies another major need for better treatments for these specific manifestations and collaborative, multispecialty studies.

This study has many strengths and some limitations to consider. It reports on a large cohort involving multiple centers across the United States and Canada, thereby capturing a wide range of patients with EGPA and varying degrees of disease severity. Characteristics of this cohort's disease may be more complex because of referral bias to an academic center. The follow-up period exceeded 5 years on average, and the data collection was standardized. However, the LS is not an inception cohort, and enrollment of patients at any time of disease activity may have led to some recall bias or incomplete capture of subtler disease characteristics at the time of diagnosis. The most severely affected patients, who may die early in the course of their disease, may not have been captured. Underestimation of death in our cohort is also possible, as there is no linkage with national death registries and patients can be lost to follow-up. There remain challenges in defining relapse in EGPA and integrating asthma exacerbations and sinonasal manifestations in measures of disease activity. Using the VDI to assess asthma showed practical limitations given that chronic asthma was listed in the VDI in only 67.5% of the patients despite more than 90% of the cohort having had a diagnosis of asthma and only a few having been able to sustainably stop GC and immunosuppressant use.

In summary, this first report of a large multicentric cohort of patients with EGPA in North America confirms the highly varied nature of EGPA and some differences in manifestations based on ANCA status. It also demonstrates that overall survival in EGPA has continued to improve over the past decades but relapse rates and the burden from both disease and therapies continue to be high. Only a minority of patients were able to stop GC and immunosuppressant therapy, further highlighting the need for more effective

and individualized treatments. Apart from randomized controlled trials, the continuation of longitudinal cohort studies in EGPA, including this one, is crucial, with regular refinements in the data collection process. Enhanced data collection, taking into account the findings and limitations of this first report, will help further study the long-term effectiveness of newer treatments and their impact on the many manifestations of this rare disease and its damage.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Cuthbertson, Drs. Doubelt, Merkel, and Pagnoux had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Doubelt, Cuthbertson, Carette, Chung, Forbess, Khalidi, Koenig, Langford, McAlear, Moreland, Monach, Seo, Specks, Spiera, Springer, Sreih, Warrington, Merkel, Pagnoux.

Acquisition of data. Doubelt, Cuthbertson, Carette, Chung, Forbess, Khalidi, Koenig, Langford, McAlear, Moreland, Monach, Seo, Specks, Spiera, Springer, Sreih, Warrington, Merkel, Pagnoux.

Analysis and interpretation of data. Doubelt, Cuthbertson, Merkel, Pagnoux.

REFERENCES

1. Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000;43:414–9.
2. Romero-Gomez C, Aguilar-Garcia JA, Garcia-de-Lucas MD, Cotos-Canca R, Olalla-Sierra J, Garcia-Alegria JJ, et al. Epidemiological study of primary systemic vasculitides among adults in southern Spain and review of the main epidemiological studies. *Clin Exp Rheumatol* 2015;33 Suppl 89:11–8.
3. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? [Review]. *Best Pract Res Clin Rheumatol* 2005;19:191–207.
4. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med* 2003;115:284–90.
5. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;33:1094–100.
6. Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. *Curr Opin Rheumatol* 2007;19:25–32.
7. Pagnoux C, Guillevin L. Churg-Strauss syndrome: evidence for disease subtypes? [Review]. *Curr Opin Rheumatol* 2010;22:21–8.
8. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Autoimmun Rev* 2017;16:1–9.
9. Sable-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;143:632–8.
10. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, 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;65:270–81.

11. Sinico RA, di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005;52:2926–35.
12. Healy B, Bibby S, Steele R, Weatherall M, Nelson H, Beasley R. Antineutrophil cytoplasmic autoantibodies and myeloperoxidase autoantibodies in clinical expression of Churg-Strauss syndrome. *J Allergy Clin Immunol* 2013;131:571–6.
13. Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Expert Rev Clin Immunol* 2016;12:1059–67.
14. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488–98.
15. Jardel S, Puechal X, le Quellec A, Pagnoux C, Hamidou M, Maurier F, et al. Mortality in systemic necrotizing vasculitides: a retrospective analysis of the French Vasculitis Study Group registry. *Autoimmun Rev* 2018;17:653–9.
16. Samson M, Puechal X, Devilliers H, Ribl C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. *J Autoimmun* 2013;43:60–9.
17. Little MA, Nightingale P, Verburgh CA, Hauser T, de Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2010;69:1036–43.
18. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009;68:1827–32.
19. Sada KE, Amano K, Uehara R, Yamamura M, Arimura Y, Nakamura Y, et al. A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan. *Mod Rheumatol* 2014;24:640–4.
20. Baldini C, Della Rossa A, Grossi S, Catarsi E, Talarico R, d'Ascanio A, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 38 patients from a single Italian centre. *Reumatismo* 2009;61:118–24. In Italian.
21. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* 2011;90:19–27.
22. Durel CA, Berthiller J, Caboni S, Jayne D, Ninet J, Hot A. Long-term followup of a multicenter cohort of 101 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Arthritis Care Res* 2016;68:374–87.
23. Solans-Laque R, Fraile G, Rodriguez-Carballeira M, Caminal L, Castillo MJ, Martinez-Valle F, 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* 2017;96:e6083.
24. Kim MY, Sohn KH, Song WJ, Park HW, Cho SH, Min KU, et al. Clinical features and prognostic factors of Churg-Strauss syndrome. *Korean J Intern Med* 2014;29:85–95.
25. Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis* 2013;72:1011–7.
26. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. *Ann Rheum Dis* 2015;74:177–84.
27. Itabashi M, Takei T, Moriyama T, Shiohira S, Shimizu A, Tsuruta Y, et al. Long-term damage assessment in patients with microscopic polyangiitis and renal-limited vasculitis using the Vasculitis Damage Index. *Mod Rheumatol* 2014;24:112–9.
28. Koldingsnes W, Nossent JC. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. *J Rheumatol* 2003;30:80–8.
29. Suppiah R, Flossman O, Mukhtyar C, Alberici F, Baslund B, Brown D, et al. Measurement of damage in systemic vasculitis: a comparison of the Vasculitis Damage Index with the Combined Damage Assessment Index. *Ann Rheum Dis* 2011;70:80–5.
30. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. *Rheumatology* 2015;54:471–81.
31. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine* 1999;78:26–37.
32. Sokolowska BM, Szczekliak WK, Wludarczyk AA, Kuczia PP, Jakiela BA, Gasior JA, et al. ANCA-positive and ANCA-negative phenotypes of eosinophilic granulomatosis with polyangiitis (EGPA): outcome and long-term follow-up of 50 patients from a single Polish center. *Clin Exp Rheumatol* 2014;32 Suppl 82:41–7.