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Remission and Low Disease Activity in Granulomatosis With Polyangiitis and Microscopic Polyangiitis: Prevalence and Impact on Damage Accrual

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Objective. To assess the prevalence and impact on damage accrual of different levels of disease activity in patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

Methods. Patients with GPA and MPA followed for ≥5 years in 2 different centers were included. Disease activity and damage were assessed using the Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI), respectively. Three levels of remission were defined: complete remission (BVAS = 0, negative for antineutrophil cytoplasmic antibody [ANCA], off treatment), clinical remission off therapy (CROffT; BVAS = 0, positive for ANCA), and clinical remission on therapy (CROnT; BVAS = 0, negative or positive for ANCA, glucocorticoids ≤5 mg/day and/or immunosuppressant). A low disease activity state (LDAS) was defined as 0 < BVAS ≤3, low-dose glucocorticoids (≤7.5 mg/day), and/or immunosuppressant. Remission or LDAS were defined as prolonged when lasting ≥2 consecutive years.

Results. A total of 167 patients were included: 128 (76.6%) with GPA, 39 (23.4%) with MPA, mean ± SD age 51.0 ± 16.7 years. During a 5-year follow-up, 10 patients (6.0%) achieved prolonged complete remission, 6 (3.6%) prolonged CROffT, 89 (53.3%) prolonged CROnT, 42 (25.1%) prolonged LDAS, and 20 (12.0%) never achieved LDAS. The VDI score at 5 years progressively worsened according to increasing levels of disease activity targets (complete remission, CROffT, CROnT, and LDAS). The mean ± SD 5-year VDI score was higher in patients not achieving prolonged remission compared to those who did (3.7 ± 2.0 versus 2.2 ± 1.9; $P < 0.0001$). By multivariate analysis, baseline ear, nose, and throat ($P = 0.006$), and lung involvement ($P = 0.047$) were negative predictors of prolonged remission.

Conclusion. More than 60% of patients with GPA/MPA achieved prolonged remission, which was associated with better long-term outcomes. In contrast, prolonged LDAS correlated with increased damage accrual and was not a sufficient treatment target.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) belong to antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV), a group of multisystemic disorders characterized by inflammation and necrosis of small vessels. Following initiation of high-dose glucocorticoids (GCs) and immunosuppressants, the prognosis of AAV patients significantly improved, with a dramatic reduction of overall mortality (1,2). Despite the occurrence of early acute mortality related to disease activity and/or treatment complications, AAV have become chronic-relapsing diseases, with significant morbidity secondary to damage accrual from previous disease activity, recurrent flares, and drug-related toxicity (3,4). Organ damage, as measured by the Vasculitis Damage Index (VDI) (5), has been used in many outcome studies (6,7), with close correlation with mortality rate (8).

Defining novel therapeutic goals to guide treatment and improve long-term outcomes of AAV is highly needed. A treat-to-target approach has been successfully applied to certain rheumatic disorders, such as rheumatoid arthritis, seronegative spondyloarthritis, and systemic lupus erythematous (SLE) (9–12). Indeed, remission and low disease activity state (LDAS) are regularly employed as clinical targets in the management of

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SIGNIFICANCE & INNOVATIONS

- This is the first study assessing the prevalence of different levels of remission and low disease activity state (LDAS) in patients with granulomatosis with polyangiitis and microscopic polyangiitis and their impact on damage accrual over time.
- More than 6 of 10 patients are able to achieve prolonged remission, which is associated with a better outcome in terms of damage accrual, compared to LDAS.
- Baseline organ involvement, particularly ear, nose, throat and lung involvement negatively affect the probability to attain prolonged remission during follow-up.
- Our study highlights the need for different disease activity levels to be tested in large cohorts to validate a treat-to-target approach in antineutrophil cytoplasmic antibody–associated vasculitides.

these patients (12,13). Conversely, a widely accepted definition of remission as a therapeutic target in AAV is lacking, as well as a definition of the effect of different disease activity levels on AAV outcomes. According to recommendations of the European Alliance of Associations for Rheumatology (EULAR)/European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) (14), treatment of AAV should be driven by the severity of organ involvement. Nevertheless, persistent, less severe disease manifestations can still be associated with significant morbidity and damage accrual over time (15). Therefore, a need exists for standardized definitions of remission and LDAS in AAV, which could enable a treat-to-target approach to be tested.

In this study, we evaluated the prevalence and impact of various levels of remission and LDAS in the context of GPA and MPA. The aim of our study was to assess the prevalence of remission and LDAS in patients affected by GPA and MPA and their relationship with subsequent damage accrual.

PATIENTS AND METHODS

Patients. We included consecutive patients affected by GPA and MPA according to the American College of Rheumatology criteria and/or Chapel Hill revised nomenclature (16,17), diagnosed in 2 European vasculitis clinics (University of Paris, France and University of Pavia, Italy) between June 1994 and June 2014 and followed up for ≥5 years. Patients with a diagnosis of eosinophilic GPA were excluded from this study. Ethical approval was obtained by the local ethics committee (Institutional Review Board Cochin) in accordance with national legislation. Each patient signed the informed consent for the use of clinical and laboratory data for study purposes. Patients were included if they attended at least 2 visits per year, no more than 6 months apart.

Data collection. Information collected at baseline included demographic characteristics (age, sex, date of symptom onset, and diagnosis), physiologic parameters (height, weight, and body mass index), comorbidities, ANCA specificity and AAV subtype, disease manifestations, laboratory findings (complete blood cell count, creatinine, albumin, C-reactive protein level), and type of immunosuppressants used for remission induction and maintenance.

Disease activity, definition of remission, and LDAS. Disease activity was assessed with the Birmingham Vasculitis Activity Score (BVAS; version 3) (18) at each visit. Remission and LDAS were classified in accordance with BVAS, ANCA status, and ongoing treatment (Table 1). Complete remission was defined as no disease activity (BVAS = 0) and negative ANCA (enzyme immunoassay, reference range 0–5 U/ml) in GC-free and immunosuppressant-free patients. Clinical remission off therapy (CROffT) was defined as no disease activity (BVAS = 0) and positive for ANCA (enzyme immunoassay) in GC-free and immunosuppressant-free patients; clinical remission on therapy (CROnT) as no disease activity (BVAS = 0) in patients with low-dose GCs (prednisone-equivalent dose ≤5 mg/day) and/or immunosuppressants, regardless of ANCA status. We defined LDAS as meeting all of the following conditions: 1) no or low disease activity (BVAS ≤3) with no activity in major organ systems; 2) no new disease activity compared with the previous assessment; 3) a current prednisone-equivalent dose ≤7.5 mg/day; and 4) a standard maintenance dose of immunosuppressants (Table 1).

Active disease was defined as BVAS score of >3, with new features of disease activity. Every level of disease activity was classified as prolonged when lasting more than 2 consecutive years. In case of relapsing-remitting disease, only the longest period of disease activity maintained during the follow-up period of 5 years was considered. Patients achieving prolonged complete remission, CROffT, or CROnT during the follow-up were defined as remitted patients; in contrast, patients who attained prolonged LDAS or those who never reached LDAS were defined as unremitted patients. Prolonged complete remission was distinguished from prolonged CROffT with the aim of evaluating the impact of ANCA and their subtypes on long-term outcomes in patients who achieved sustained remission after discontinuation of immunosuppressive treatment. Patients who met criteria for both CROnT and LDAS were classified as being only in prolonged CROnT. Achievement of the different levels of disease activity was evaluated every 6 months from diagnosis up to 5 years of follow-up for each patient. Any modification of the disease activity level occurring between each 6-month assessment time-point was recorded.

Definition of relapse and damage accrual. Relapse was defined by the reappearance or worsening of disease activity, with BVAS score of >0 and the need to increase GCs or modify

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Table 1. Definitions of remission and low disease activity state in GPA and MPA*

	Disease activity	New features of AAV activity	ANCA status	Prednisone dose	Immunosuppressants
Complete remission	BVAS = 0	No	No	No	No
Clinical remission off therapy	BVAS = 0	No	Yes	No	No
Clinical remission on therapy	BVAS = 0	No	Yes/no	≤5 mg/day	Yes
Low disease activity	0 ≤BVAS ≤3†	No	Yes/no	≤7.5 mg/day	Yes‡
Active disease	BVAS >3	Yes	Yes/no	Yes/no	Yes/no

* AAV = antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; BVAS = Birmingham Vasculitis Activity Score; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis.
† Including no activity in major organ systems.
‡ Requiring standard maintenance dose of immunosuppressant.

immunosuppressive treatment. Relapses were classified as major or minor in accordance with the presence or absence of life-threatening and/or organ-threatening manifestations. The proportion of patients with ≥1 major relapse was recorded at 2 years and 5 years. Damage accrual was measured at 2 years and 5 years using the VDI (5). Moreover, damage was categorized as related to vasculitis or its treatment.

Statistical analysis. The association between different levels of remission and demographic and clinical variables was tested by logistic regression analysis. The following variables were considered in the univariate analysis: age at diagnosis, sex, diagnostic delay, BVAS at disease onset, AAV phenotype, ANCA specificity, type of organ involvement, number of relapses, and therapy including GCs and immunosuppressants. Factors associated with unremitted disease at univariate analysis (*P* less than 0.05) were entered into the multivariate model. Logistic regression (RStudio) was used to assess the relationship between baseline characteristics and the inability to attain prolonged remission during the follow-up. The impact of different levels of disease activity on time to first relapse was assessed by Cox regression analysis.

RESULTS

Demographic and clinical characteristics at baseline. Among 321 consecutive patients with newly diagnosed GPA and MPA, 167 patients (52.0%) fulfilled the inclusion criteria. Demographic characteristics, clinical features, and damage, according to different levels of disease activity, are summarized in Table 2. A total of 97 patients (58.1%) were women, mean ± SD age at diagnosis was 51.0 ± 16.7 years, and 128 patients (76.6%) and 39 patients (23.4%) had GPA and MPA, respectively. Eighty-six patients (51.5%) were positive for proteinase (PR3)–ANCA, and 48 patients (28.7%) were positive for myeloperoxidase-ANCA.

Remission-induction immunosuppressive treatment. At baseline, remission-induction therapy consisted of a combination of GCs and cyclophosphamide in 111 patients (66.5%), methotrexate in 23 (13.8%), rituximab (RTX) in 9 (5.4%), and azathioprine in 4 (2.4%). Twenty patients (12.0%) were treated with GCs alone, mainly due to MPA without poor prognostic factors.

Remission-maintenance immunosuppressive treatment. After remission-induction immunosuppressive treatment, in combination with GCs, 83 patients (49.7%) received additional maintenance treatment with azathioprine, 34 (20.4%) with methotrexate, 19 (11.4%) with RTX, and 13 (7.8%) with mycophenolate mofetil. Eighteen patients (10.8%) were treated with GCs alone.

Levels of disease activity during follow-up. During the 5-year follow-up, 10 patients (6.0%) achieved prolonged

Table 2. Demographic characteristics and clinical and laboratory features of patients with GPA and MPA included in the study*

Characteristic	All patients (n = 167)
Age, years	53.0 (43–64)
Female, no. (%)	97 (58.1)
Vasculitis subtype, no. (%)	
GPA	128 (76.6)
MPA	39 (23.4)
ANCA subtype, no. (%)	
Proteinase 3–ANCA	86 (51.5)
Myeloperoxidase-ANCA	48 (28.7)
Negative ANCA	28 (16.8)
Not available	5 (2.9)
Vasculitis features at diagnosis, no. (%)	
Ear, nose, and throat involvement	109 (65.3)
Constitutional symptoms	107 (64.1)
Lung involvement	92 (55.1)
Musculoskeletal involvement	85 (50.9)
Glomerulonephritis	76 (45.5)
Skin involvement	43 (25.7)
Peripheral neuropathy, no. (%)	37 (22.2)
Cardiac involvement	13 (7.8)
Central nervous system involvement	9 (5.4)
Gastrointestinal involvement	4 (2.4)
Birmingham Vasculitis Assessment Score	14 (9–21)
Laboratory features at diagnosis	
Serum creatinine, μmol/liter	82 (70–127)
Serum albumin, μmol/liter	3.3 (2.8–3.7)
C-reactive protein, mg/liter	80 (31–155)
Hemoglobin, gram/liter	115 (99–131)

* Values are the median (interquartile range) unless indicated otherwise. ANCA = antineutrophil cytoplasmic antibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis.

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complete remission, 6 (3.6%) achieved prolonged CROffT, and 89 (53.3%) achieved prolonged CROnT. Forty-two patients (25.1%) achieved prolonged LDAS. In contrast, 20 patients (12.0%) never achieved LDAS. Therefore, 105 patients (62.9%) were defined as remitted, while 62 (37.1%) were classified as unremitted. Stratification of patients in prolonged LDAS and those who never attained prolonged LDAS with respect to disease activity and GC dose during follow-up is shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24958.

Predictors of unremitted disease. Characteristics of remitted and unremitted patients during the 5-year follow-up are shown in Table 3. We analyzed features associated with failure to achieve and maintain prolonged remission. In this univariate model, inability to achieve prolonged remission was statistically associated with younger age ($P = 0.01$), GPA diagnosis ($P = 0.0003$), positive PR3-ANCA result ($P = 0.006$), and ear, nose and throat ($P < 0.0001$) and lung involvement ($P = 0.036$). In contrast, no difference was observed in terms of major organ manifestations and disease activity at disease onset. No statistical association was observed between prolonged remission and specific maintenance immunosuppressive treatment. In multivariate analysis using logistic regression, only ear, nose, and throat (odds ratio [OR] 3.72 [95% confidence interval (95% CI) 1.451–9.554], $P = 0.006$) and lung (OR 2.12 [95% CI 1.010–4.434], $P = 0.047$) involvement were independently associated with the inability to achieve prolonged remission during follow-up (Table 4).

Impact of disease activity on damage accrual. At 5 years, the mean ± SD VDI total score was 2.7 ± 2.0. The mean ± SD VDI score related to AAV items was higher compared to VDI score related to treatment items (2.0 ± 1.7 versus 0.7 ± 1.0, respectively). The mean ± SD VDI score at 5 years in patients with prolonged complete remission, CROffT, CROnT, LDAS, or those who never attained LDAS was 1.6 ± 1.2, 1.8 ± 1.7, 2.3 ± 1.9, 3.8 ± 1.9, and 3.3 ± 2.0, respectively (Figure 1).

The relationship between different levels of prolonged disease activity and organ damage accrual at 5 years was assessed. No statistically significant difference in terms of damage accrual at

Table 3. Univariate analysis of features associated with unremitted disease*

Characteristic	Remitted (n = 105)	Unremitted (n = 62)	*P*
Age, years	55.0 (44–67)	49.0 (36–59)	0.01†
Female, no. (%)	59 (56.2)	38 (61.3)	0.63
Vasculitis subtype, no. (%)			0.0003†
GPA	71 (67.6)	57 (91.9)	–
MPA	34 (32.4)	5 (8.1)	–
ANCA subtype, no. (%)			0.006†
Proteinase 3–ANCA	49 (46.7)	37 (59.7)	–
Myeloperoxidase-ANCA	39 (37.1)	9 (14.5)	–
Vasculitis features, no. (%)			
Constitutional symptoms	66 (62.9)	41 (66.1)	0.74
Ear, nose, and throat involvement	57 (54.3)	52 (83.9)	<0.0001†
Lung involvement	51 (48.6)	41 (66.1)	0.036†
Musculoskeletal involvement	54 (51.4)	31 (50.0)	0.87
Glomerulonephritis	51 (48.6)	25 (40.3)	0.34
Skin involvement	28 (26.7)	15 (24.2)	0.85
Peripheral neuropathy	26 (24.8)	11 (17.7)	0.34
Cardiac involvement	10 (9.5)	3 (4.8)	0.38
Central nervous system involvement	6 (5.7)	3 (4.8)	0.99
Birmingham Vasculitis Activity Score	15 (9–22)	14 (9–20)	0.66
Laboratory features			
Serum creatinine, μmol/liter	86 (71–142)	79 (63–100)	0.06
Serum albumin, μmol/liter	3.3 (2.7–3.8)	3.4 (3.0–3.7)	0.48
C-reactive protein, mg/liter	84 (32–154)	77 (18–181)	0.88
Hemoglobin, gram/liter	115 (97–131)	115 (99–128)	0.99
Damage accrual, mean ± SD			
VDI score at 2 years	1.74 ± 1.62	2.84 ± 1.86	<0.0001†
VDI score at 5 years	2.19 ± 1.88	3.65 ± 1.98	<0.0001†
Maintenance treatment, no. (%)			
Rituximab	15 (14.3)	4 (6.5)	0.13
Azathioprine	52 (49.5)	31 (50.0)	0.95
Methotrexate	19 (18.1)	15 (24.2)	0.35
Mycophenolate mofetil	5 (4.8)	8 (12.9)	0.06

* Values are the median (interquartile range) unless indicated otherwise. ANCA = antineutrophil cytoplasmic antibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; VDI = Vasculitis Damage Index.
† Statistically significant.

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Table 4. Multivariate analysis: predictive factors of unremitted disease during follow-up*

Characteristic	OR (CI 95%)	*P*
Age at diagnosis	0.99 (0.964–1.006)	0.17
Ear, nose and throat involvement	3.72 (1.451–9.554)	0.006†
Lung involvement	2.12 (1.010–4.434)	0.047†
Vasculitis subtype	0.69 (0.189–2.540)	0.58
Proteinase 3–ANCA	2.08 (0.798–5.420)	0.13
Myeloperoxidase-ANCA	0.63 (0.225–1.738)	0.37

* 95% CI = 95% confidence interval; ANCA = antineutrophil cytoplasmic antibody; OR = odds ratio.
† Statistically significant.

5 years was observed between patients in prolonged CROffT and those in prolonged CROnT (mean ± SD VDI score 1.8 ± 1.7 versus 2.3 ± 1.9; $P = 0.3$). On the other hand, patients in prolonged LDAS (mean ± SD VDI score 3.8 ± 1.9 versus 1.8 ± 1.7 in patients with prolonged CROffT; $P < 0.0001$) or those who never achieved LDAS (mean ± SD VDI score 3.3 ± 2.0 versus 1.8 ± 1.7 in patients with prolonged CROffT; $P = 0.001$) accrued significantly more damage. Considering only prolonged complete remission and CROffT, achieving complete remission did not show any benefit on damage accrual over time. Likewise, no difference in terms of mean VDI score at 5 years was noted between patients achieving prolonged LDAS compared to patients who spent no time in LDAS ($P = 0.99$) (Figure 1). Patients with unremitted disease had a higher mean ± SD VDI score both at 2 years (2.8 ± 1.9 versus 1.7 ± 1.6 in remitted patients; $P < 0.0001$) and at 5 years (3.7 ± 2.0 versus 2.2 ± 1.9 in remitted patients; $P < 0.0001$). At 5 years, the mean ± SD VDI score related to AAV items in patients in prolonged complete remission, CROffT, CROnT, LDAS, or those who never achieved LDAS was 1.1 ± 0.7, 1.2 ± 1.6, 1.5 ± 1.6, 3.0 ± 1.5, and 2.9 ± 1.9, respectively. Disease-related damage accrual was similar among patients in prolonged complete remission, CROffT, and CROnT ($P = 0.4$) and between patients in prolonged LDAS and those who spent no time in LDAS ($P = 0.8$). Conversely, in patients in prolonged LDAS and those who never attained LDAS, the disease-related VDI score was significantly higher compared to patients in prolonged CROnT (prolonged LDAS: mean ± SD 3.0 ± 1.5 versus 1.5 ± 1.6, respectively; $P < 0.0001$; never attained LDAS: 2.9 ± 1.9 versus 1.5 ± 1.6, respectively; $P = 0.0009$). At 5 years, the mean ± SD VDI score related to treatment items in patients with prolonged complete remission, CROffT, CROnT, LDAS, or those who failed to achieve LDAS was 0.5 ± 0.8, 0.7 ± 0.8, 0.8 ± 1.0, 0.8 ± 1.2, and 0.4 ± 0.7, respectively. Treatment-related damage accrual at 5 years was not influenced by the level of disease activity.

Due to the small sample size of patients in prolonged complete remission and CROffT, damage accrual was reassessed after grouping these 2 populations in a single entity. Patients in prolonged complete remission/CROffT presented with similar mean VDI score and mean disease-related VDI score at 5 years compared to patients in prolonged CROnT (mean ± SD VDI score 1.7 ± 1.4 versus 2.3 ± 1.9; $P = 0.23$; mean ± SD disease-related VDI score 1.1 ± 1.1 versus 1.5 ± 1.6; $P = 0.34$). Conversely, the mean VDI score and mean disease-related VDI score at 5 years were significantly lower in patients in prolonged complete remission/CROffT when compared both to patients in prolonged LDAS (mean ± SD VDI score 1.7 ± 1.4 versus 3.8 ± 1.9; $P = 0.0002$; mean ± SD disease-related VDI score 1.1 ± 1.1 versus 3.0 ± 1.5; $P < 0.0001$) and to those who never achieved LDAS (mean ± SD VDI score 1.7 ± 1.4 versus 3.3 ± 2.0; $P = 0.01$; mean ± SD disease-related VDI score 1.1 ± 1.1 versus 2.9 ± 1.9; $P = 0.002$) (Figure 1). The aggregation of the 2 populations into a single category did not affect treatment-related VDI score at 5 years. A sensitivity analysis performed after exclusion of 20 patients treated with GCs alone did not show significant differences in the distribution of different levels of disease activity during follow-up nor in terms of damage accrual at 2 years and at 5 years (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24958).

A VDI score of ≥3 and ≥5 at 5 years was found in 81 patients (49.0%) and 27 patients (16.2%) in our cohort, respectively.

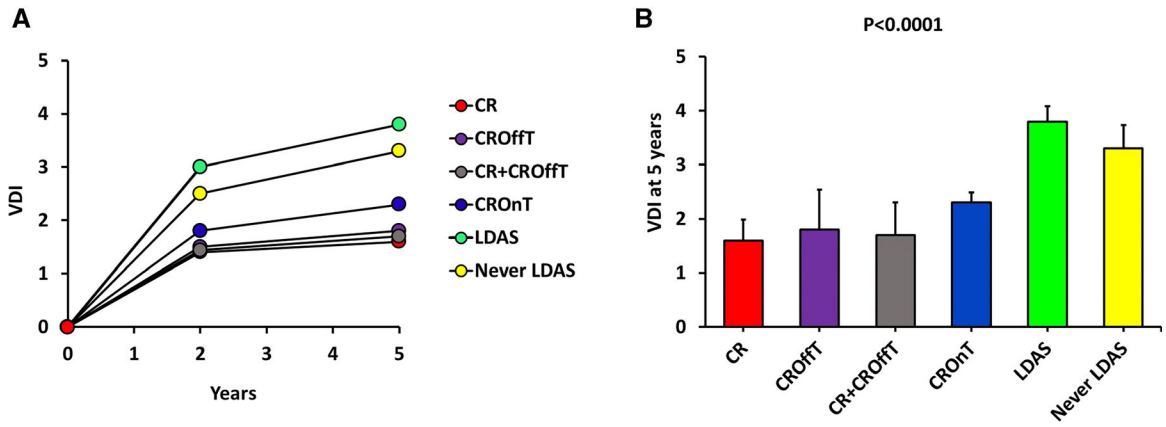

Figure 1. Mean Vasculitis Damage Index (VDI) score at 5 years. CR = complete remission; CROffT = complete remission off therapy; CROnT = complete remission on therapy; LDAS = low disease activity state.

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VDI score of ≥3 at 5 years was reached by 45 of 62 unremitted patients (72.6%), whereas only 36 of 105 remitted patients (34.3%) had a VDI score of ≥3 at 5 years (OR 5.07 [95% CI 2.53–9.84], $P < 0.0001$) (Figure 2). Similarly, 17 of 62 unremitted patients (27.4%) reached a VDI score of ≥5 at 5 years, as compared with 10 of 105 remitted patients (9.5%) (OR 3.59 [95% CI 1.52–8.46], $P = 0.0025$) (Figure 2). Among remitted patients, a comparable proportion of patients in prolonged complete remission, CROffT, and CROnT achieved a VDI score ≥3 (20%, 16.7%, and 37.1%, respectively; $P > 0.3$) and a VDI score ≥5 (0%, 16.7%, and 10.1%, respectively; $P > 0.2$).

Risk of major relapse according to disease activity. At 5 years, 57 patients developed at least 1 major relapse, which occurred more commonly in GPA compared with MPA patients (39.1% versus 17.9%; $P = 0.01$). The proportion of patients in prolonged complete remission, CROffT, CROnT, LDAS, and those who never achieved prolonged LDAS developing ≥1 major relapse was 30% (3 of 10), 30% (2 of 6), 24.7% (22 of 89), 35.7% (15 of 42), and 75% (15 of 20), respectively. No significant difference was observed between patients in prolonged LDAS, complete remission, CROffT, and CROnT.

Time to relapse according to disease activity. In a survival analysis aiming at evaluating the influence of different levels of disease activity on time to relapse, a shorter time to first relapse was observed in patients in prolonged LDAS and those who spent no time in prolonged LDAS compared to patients with prolonged remitted disease (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24958). These findings were confirmed in a Cox regression analysis after adjustment for age, sex, ANCA status, and organ involvement (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24958). Conversely, no statistically significant difference was observed among patients in prolonged complete remission, CROffT, and CROnT (see Supplementary Figure 1).

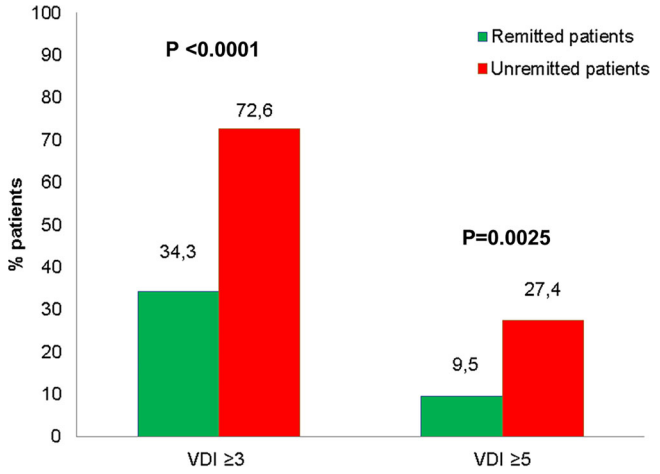

Figure 2. Mean Vasculitis Damage Index (VDI) score of ≥2 and ≥5 at 5 years. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24958/abstract.

DISCUSSION

In our study, we evaluated for the first time in AAV the prevalence of different levels of remission and LDAS and their impact on 5-year outcome in 2 different European cohorts of patients affected by GPA and MPA. In our cohort, patients who experienced prolonged remission accrued significantly less damage at 5 years compared to patients unable to achieve prolonged remission. Prolonged complete remission and CROffT were rarely achieved, occurring in only 6.0% and 3.6% of 167 patients, respectively. Conversely, the proportion of patients achieving prolonged CROnT and LDAS was higher, 53.3% and 25.1%, respectively. The optimal duration of remission-maintenance immunosuppressive treatment after achieving clinical remission is still a matter of debate. EULAR/ERA-EDTA recommendations suggest continuing immunosuppressants for at least 24 months after the induction of sustained remission (14). Recent evidence is suggesting that longer maintenance treatment duration is associated with better outcomes (19,20). However, the ideal duration of sustained remission that would influence long-term outcomes is still unknown. In our study, remission was defined as prolonged when lasting at least 2 consecutive years.

Even though any length of prolonged remission is discretionary, this cutoff was considered clinically relevant, providing a long time period for damage accrual and thus allowing for detection of differences between remitted and unremitted disease. At 5 years, the mean ± SD VDI score was 2.7 ± 2.0, mainly due to disease-related items (2.0 ± 1.7) rather than treatment-related items (0.7 ± 1.0). The disease-related VDI score was higher in patients with prolonged LDAS and in those who never achieved LDAS as compared with patients in prolonged CROnT, suggesting that damage accrual is more related to periods of poor control of disease activity than to treatment-related morbidity. Among remitted patients, the VDI score at 5 years was similar between patients in complete remission and CROffT; likewise, no difference was noted in terms of damage accrual when comparing patients in CROffT and patients in CROnT. Based on these findings, we can hypothesize that the sustained achievement of any level of remission, regardless of the continuation of long-term immunosuppressive treatment, might potentially represent an optimal target to achieve better outcomes.

Damage accrual over time was similar in persistently ANCA-positive and ANCA-negative patients who achieved prolonged remission after discontinuation of immunosuppression; however, the small sample size of the 2 subgroups does not allow drawing definitive conclusions on the impact of ANCA on long-term outcomes. Although the aggregation of the 2 subgroups of patients in prolonged complete remission and CROffT did not influence the results of our analysis, the predictive role of

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persistent ANCA positivity after treatment discontinuation needs to be further assessed in larger cohorts. On the other hand, considering only unremitted patients, achieving prolonged LDAS had no benefit compared to spending no time in LDAS. These data suggest that, in contrast to other rheumatic diseases, such as SLE, where low-grade disease activity has been demonstrated to be an adequate goal in a treat-to-target approach (21), allowing a persistent state of LDAS does not seem to be a favorable target in AAV. Ear, nose, and throat and lung involvement were independent negative predictive factors of unremitted disease at 5 years. Notably, major organ involvement at disease onset was not associated with the inability to achieve prolonged disease remission during follow-up. In a recent retrospective analysis from the French Vasculitis Study Group restricted to GPA patients, sustained remission off therapy at 5 years significantly correlated with a cyclophosphamide-based induction regimen and with RTX-based maintenance treatment (22). In our population, no statistical association was observed between any level of prolonged remission and specific immunosuppressants administered for remission induction or maintenance, as if the achievement of a specific state of disease activity, regardless of the treatment strategy used, is the most important determinant of future outcomes. Although the number of patients receiving RTX may have been limited by the 5-year follow-up duration, this low number strengthened the reliability of the applied definitions assessing prolonged states of disease activity and their association with long-term outcomes.

Despite a higher VDI score at 5 years in patients in prolonged LDAS as compared with those in prolonged CROnT, the proportion of patients with at least 1 major relapse during follow-up was comparable between the 2 groups, raising the hypothesis that residual persistent disease activity could contribute to damage accrual over time, regardless of the occurrence of severe relapses. Moreover, patients in prolonged LDAS had a shorter time to first relapse compared to patients with any level of prolonged remission; these findings suggest that, for patients with MPA and GPA, prolonged disease remission, rather than prolonged LDAS, should be considered as the optimal target to achieve during follow-up.

Higher damage accrual in unremitted patients compared to remitted patients might be explained by 2 potential interpretations. First, patients in prolonged LDAS or those who spent no time in LDAS presented more frequently with a mild relapsing-remitting course of disease with frequent exacerbations limited to the upper and/or lower airways, requiring low-dose GCs. Second, significant damage accrual and morbidity in these patients may also reflect, to a lesser extent, long-lasting GC treatment, even when used at low doses. In a previous study, Robson and colleagues evaluated short-term and long-term damage accrual in patients affected by AAV from different European trials (15). In this large analysis, which included patients with a mean follow-up of 7.3 years, damage progressively rose over time, with only 7.9% of patients showing no items of damage at the end of follow-up, whereas 34.4% developed ≥5 items, which is known to correlate with increased mortality (8). In our study, VDI scores ≥3 and ≥5 were recorded in 49.0% and 16.2% of patients, respectively, whereas only 10.8% of patients did not develop any damage features at 5 years from diagnosis. Compared to remitted patients, a significantly higher proportion of unremitted patients reached a VDI score ≥5 at 5 years (27.4% versus 9.5%).

Our study has a number of strengths. We assessed for the first time the prevalence of different levels of remission and LDAS and their effect on damage accrual in patients affected by GPA and MPA. Moreover, our population included patients from 2 different European cohorts, regularly followed for a 5-year period by the same teams of physicians. Nevertheless, our study has some limitations, including the retrospective nature of the collected data. The definition of remission and LDAS proposed in our study has not yet been validated and will need to be tested on different independent cohorts of patients. Furthermore, the proportion of patients treated with evolving therapeutic regimens, especially RTX, is limited, and the impact of RTX on the different levels of disease activity reached and on long-term outcomes will have to be further assessed; finally, we did not evaluate the impact of different durations of prolonged remission and LDAS on damage accrual over time.

More than 60% of GPA and MPA patients were able to achieve prolonged remission during follow-up. Ear, nose, and throat and lung involvement were the main independent predictors of unremitted disease. Achievement of any level of prolonged remission was associated with a better outcome in terms of damage accrual at 2-year and 5-year follow-up. In contrast, LDAS as defined by the present study does not seem to be an adequate target in the management of GPA and MPA. A treat-to-target approach in AAV, aiming at sustained remission, seems to be critical to prevent damage burden, and prolonged remission proved to be a useful surrogate marker to guarantee better outcomes. We suggest that future clinical trials and long-term cohort studies incorporate such disease activity definitions as optimal goals of AAV management.

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 submitted for publication. Dr. Delvino 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.

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Acquisition of data. Delvino, Sardanelli, Monti, Cohen, Puéchal, Mouthon, Montecucco, Guillevin, Terrier.

Analysis and interpretation of data. Delvino, Sardanelli, Monti, Cohen, Puéchal, Mouthon, Montecucco, Guillevin, Terrier.

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