EXTENDED REPORT

# Damage in the anca-associated vasculitides: long-term data from the European Vasculitis Study group (EUVAS) therapeutic trials

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## ABSTRACT

**Objectives** To describe short-term (up to 12 months) and long-term (up to 7 years) damage in patients with newly diagnosed antineutrophil-cytoplasm antibody-associated vasculitis (AAV).

**Methods** Data were combined from six European Vasculitis Study group trials (n=735). Long-term follow-up (LTFU) data available for patients from four trials (n=535). Damage accrued was quantified by the Vasculitis Damage Index (VDI). Sixteen damage items were defined a priori as being potentially treatment-related.

**Results** VDI data were available for 629 of 735 patients (85.6%) at baseline, at which time 217/629 (34.5%) had ≥1 item of damage and 32 (5.1%) ≥5 items, reflecting disease manifestations prior to diagnosis and trial enrolment. LTFU data were available for 467/535 (87.3%) at a mean of 7.3 years postdiagnosis. 302/535 patients (56.4%) had VDI data at LTFU, with 104/302 (34.4%) having ≥5 items and only 24 (7.9%) no items of damage. At 6 months and LTFU, the most frequent items were proteinuria, impaired glomerular filtration rate, hypertension, nasal crusting, hearing loss and peripheral neuropathy. The frequency of damage, including potentially treatment-related damage, rose over time (p<0.01). At LTFU, the most commonly reported items of treatment-related damage were hypertension (41.5%; 95% CI 35.6 to 47.4%), osteoporosis (14.1%; 9.9 to 18.2%), malignancy (12.6%; 8.6 to 16.6%), and diabetes (10.4%; 6.7 to 14.0%).

**Conclusions** In AAV, renal, otolaryngological and treatment-related (cardiovascular, disease, diabetes, osteoporosis and malignancy) damage increases over time, with around one-third of patients having ≥5 items of damage at a mean of 7 years postdiagnosis.

## INTRODUCTION

Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV).[1] These multisystem inflammatory diseases of the small blood vessels result in life-threatening or organ-threatening disease with an increased mortality ratio of 2.6 (95% CI 2.2 to 3.1).[2] Treatment with high-dose glucocorticoids and immunosuppressants is organ-saving and life-saving, but also toxic.[3] Therapy-associated adverse events account for almost 60% of deaths within the first year.[4] Relapses are common, occurring in 40%,[5] and chronic comorbidities, secondary to vasculitis or its treatment, such as cardiovascular disease, are also increased.[6 7]

The concept of damage infers irreversible aspects of disease which will not respond to escalation of immunosuppressive treatment,[8] in contrast with potentially reversible disease activity. The Vasculitis Damage Index (VDI)[9] is a validated checklist of 64 items, recording all damage from the onset of vasculitis, irrespective of whether it is caused by disease or treatment. The VDI is easy to use, with good test-retest repeatability and content validity,[8 9] and is predictive of future mortality.[10–12] Patients with systemic vasculitis, who have ≥5 recorded items of damage, have a 6.4-fold increase in mortality risk (95% CI 2.1 to 19).[10] The number of relapses is associated with an increase in VDI score[13 14] and early disease activity scores correlate moderately well with later VDI scores.[14 15] The VDI has been approved by the Outcome Measures in Rheumatology (OMERACT)[8] group and the European League Against Rheumatism (EULAR),[16] as the key outcome measure to record damage in AAV clinical trials.

The European Vasculitis Study Group (EUVAS) oversees multicentre randomised controlled trials (RCTs) in patients with GPA and MPA. Each complies with the European Community Study Group on Clinical Trials in Systemic Vasculitis (ECSYSVASTRIAL) guidelines, produced to standardise data collection tools, disease scoring and treatment regimens.[17] The VDI is scored at regular time points throughout each trial, providing prospectively recorded damage information.[17] A long-term follow-up (LTFU) questionnaire to collect patient outcomes has subsequently been completed by clinicians in four of these trials approximately 5 years after study completion.

Previous smaller studies including the Wegener's Granulomatosis Etanercept Trial (WGET)[18]; a UK series of systemic vasculitis patients[10]; and a Norwegian study of patients[13] have described cumulative damage, focusing on patients with GPA. The objective of this longitudinal observational study is to describe the type and extent of damage accrued by patients with GPA and MPA, and different ANCA subtypes, during the course of the EUVAS trials and over LTFU.

## PATIENTS AND METHODS

### Original trials

A total of 735 patients with newly diagnosed GPA and MPA were recruited between 1995 and 2009

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into six EUVAS RCTs[19–24] (table 1). Patients enrolled in CYCAZAREM, MEPEX, CYCLOPS, IMPROVE and RITUXVAS had moderate to severe renal involvement; those in NORAM none to mild.

The trials were performed in accordance with the 1964 Declaration of Helsinki and subsequent amendments; ethical approval was obtained by national and local ethics committees in accordance with national legislation. All patients had a diagnosis of GPA or MPA on adapted 1994 Chapel Hill disease definitions,[25] clinical presentation, positive ANCA serology and/or histology.[17] Patients with life-threatening pulmonary haemorrhage, coexistent autoimmune condition, malignancy, infection, pregnancy or aged <18 or >80 years were excluded.

### LTFU

The LTFU questionnaire was performed in accordance with the 1964 Declaration of Helsinki and subsequent amendments; ethical approval was obtained by national and local ethics committees as required. Details of 535 patients recruited to four trials (NORAM, CYCAZAREM, MEPEX, and CYCLOPS) were collected between September 2004 and January 2007, approximately 5 years after trial completion. Data collected included mortality, the VDI and glucocorticoid use.

## TRIAL ASSESSMENTS

### Baseline data

Baseline data recorded for each patient included age, gender, and laboratory measures. The ANCA type was recorded as myeloperoxidase ANCA (MPO-ANCA) when positive by MPO-ANCA ELISA or a perinuclear ANCA (pANCA) pattern on immunofluorescence microscopy; as proteinase 3 ANCA (PR3-ANCA) when positive by PR3-ANCA ELISA or a cytoplasmic ANCA (cANCA) pattern by indirect immunofluorescence microscopy.

## DISEASE ASSESSMENT

### Birmingham vasculitis activity score (BVAS V.2)[26]

The BVAS V.2 is a checklist of 66 items used to score vasculitis disease activity.[26] Total scores are calculated from the sum of all positive individual items. Data were collected prospectively within the trials at 0, 3, 6, and 12 months.

### VDI

The VDI is a validated checklist of 64 items divided into 11 categories,[9] 10 relating to specific organ systems and an 'other' category relating to potential treatment side effects.[11] An item of damage is only recorded if it occurred after the onset of vasculitis and is considered permanent, defined as present for more than 3 months. In the case of patients with established comorbidity, prior to vasculitis, this is only recorded if it has deteriorated significantly for at least 3 months since disease onset. There is no attribution to cause, so the VDI can capture the effects of disease or therapy. There is no weighting of items or reversibility. A VDI score ≥5 was used a priori to indicate severe damage, reflecting associations with mortality.[10] VDI data were collected prospectively at 0, 3, 6, 12 and 18 months and at LTFU.

### Early and late damage

Individual VDI items were used to describe early (6 months) and late (LTFU) damage. The 10 most frequently scored individual VDI items were determined at each time point based on all available VDI data.

### Treatment-related damage

Fifteen damage items were defined a priori as being potentially related to treatment, based on a previous list of treatment-related VDI items[11] (osteoporosis, diabetes, cataracts, atrophy and weakness, malignancy, gonadal failure, marrow failure, chemical cystitis, avascular necrosis), and items related to treatment or active disease: hypertension, angina/coronary artery disease, alopecia, cerebrovascular accident, myocardial infarction and mouth ulcers.

### Treatment received

Immunosuppressive treatment regimens are summarised in table 1. All patients underwent remission induction with cyclophosphamide, then switched to azathioprine maintenance, except those randomised to methotrexate induction in NORAM,[22] and Rituximab induction with no maintenance in RITUXVAS.[24] High-dose glucocorticoids and plasma exchange were allowable. Local investigators made treatment decisions post-trials. No data was available on cardiovascular risk factor management. The LTFU questionnaire recorded whether patients were on glucocorticoids at their last visit, and if they had received glucocorticoids within the following post-trial months: 13–18 (MEPEX only), 19–24, 25–36, 37–48 and 49–60. Total duration of glucocorticoid use was defined as months of glucocorticoid use within the original trial plus follow-up.

**Table 1** Summary of trial characteristics

| Trial | NORAM[22] | CYCAZAREM[19] | MEPEX[20] | CYCLOPS[21] | IMPROVE[23] | RITUXVAS[24] |
|---|---|---|---|---|---|---|
| Number of patients | 100 | 155 | 137 | 149 | 156 | 44 |
| Disease severity | Cr<150 μmol/L, no critical organ disease | Cr<500 μmol/L, no life threatening disease | Cr>500 μmol/L or requiring dialysis | Generalised disease with renal involvement but Cr<500 μmol/L | Any disease severity | Renal involvement |
| Treatment | Induction: methotrexate versus cyclophosphamide | Maintenance: cyclophosphamide versus azathioprine | Induction: adjunctive treatment for severe glomerulonephritis | Induction: daily oral versus pulsed cyclophosphamide | Maintenance: mycophenolate mofetil versus azathioprine | Induction: Rituximab versus cyclophosphamide |
| Date | 1995–2000 | 1995–2000 | 1995–2002 | 2000–2004 | 2002–2009 | 2006–2007 |
| Follow-up | 18 months (treatment for 12 months) | 18 months | 12 months | 18 months | Median of 39 months | 12 months |
| LTFU | Yes | Yes | Yes | Yes | No | No |

Cr, creatinine; LTFU, long-term follow-up questionnaire.



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## STATISTICAL METHODS

Data from the six trials were combined and analysed within SPSS V.20 and Stata V.9. Continuous variables are expressed as mean with SD or median with IQR; categorical variables as frequencies with percentages, all with 95% CIs.

Datasets for analysis were defined in terms of the VDI data provided; no imputation of missing data was performed. To maximise available VDI data and limit possibility of bias, three datasets were created: (1) patients with VDI data at 6 months, (2) patients with VDI data at LTFU, and (3) for comparison of VDI data across time, patients with data at baseline, 6 months, 12 months, and LTFU. The existence and extent of any non-response bias was estimated from comparisons of baseline data between responders and non-responders.

The statistical significance of differences between groups in terms of continuous data was determined from independent sample t tests or Mann–Whitney tests, and in terms of proportions using $\chi^2$ tests. Repeated measures analysis of variance was used to compare groups in terms of change in VDI scores over time. Statistical significance was taken at the 5% ($p<0.05$) level throughout.

**Table 2** Demographic and clinical characteristics at baseline for all patients, for those in trials currently providing long-term follow-up (LTFU) data, and in terms of whether or not Vasculitis Damage Index (VDI) data were present at LTFU

| | All patients (n=735) | Patients eligible for LTFU (n=535) | Patients with VDI data at LTFU (n=302) | Patients without VDI data at LTFU (n=233) | p Value |
|---|---|---|---|---|---|
| Diagnosis, n (%) (n=735) | | | | | |
| Microscopic polyangiitis (MPA) | 332 (45.2) | 254 (47.5) | 135 (44.7) | 119 (51.1) | |
| Granulomatosis with polyangiitis (GPA) | 403 (54.8) | 281 (52.5) | 167 (55.3%) | 114 (48.9) | 0.169* |
| Sex, n (%) (n=735) | | | | | |
| Male | 415 (56.5) | 288 (53.8) | 154 (51.0) | 134 (57.5) | |
| Female | 320 (43.5) | 247 (46.2) | 148 (49.0) | 99 (42.5) | 0.158* |
| Age, years, mean (SD) (n=735) | 57.6 (14.4) | 57.7 (14.3) | 56.8 (14.6) | 58.9 (13.9) | 0.093† |
| Trial, n (%) (n=735) | | | | | |
| NORAM | 95 (12.9) | 95 (17.8) | 55 (18.2) | 40 (17.2) | |
| CYCAZAREM | 155 (21.1) | 155 (29.0) | 84 (27.8) | 71 (30.5) | |
| MEPEX | 137 (18.6) | 137 (25.6) | 61 (20.2) | 76 (32.6) | |
| CYCLOPS | 148 (20.1) | 148 (27.7) | 102 (33.8) | 46 (19.7) | 0.001* |
| IMPROVE | 156 (21.2) | 0 | 0 | 0 | |
| RITUXIVAS | 44 (6.0) | 0 | 0 | 0 | |
| Serum creatinine (μmol/L) median (IQR) (n=729) | 192 (98.7 to 440) | 203 (96.8 to 498) | 176 (91.4 to 413.3) | 257 (100 to 613.5) | 0.002‡ |
| Haemoglobin g/dL median (IQR) (n=728) | 9.9 (9.7 to 11.5) | 9.8 (8.6 to 11.5) | 9.9 (8.7 to 11.6) | 9.6 (8.45 to 11.4) | 0.065‡ |
| WBC $10^9$/L median (IQR) (n=728) | 11.0 (8.6 to 14.4) | 10.8 (8.4 to 13.7) | 10.7 (8.3 to 13.6) | 11.1 (8.45 to 14.2) | 0.549‡ |
| Platelets $10^9$/L median (IQR) (n=728) | 366 (281 to 490 | 364 (276 to 482) | 361 (272.5 to 490 | 367 (286.5 to 474) | 0.975‡ |
| CRP mg/L median (IQR) (n=726) | 54 (16 to 120) | 54 (18 to 118) | 51 (16.8 to 112.3) | 63 (18.2 to 133.5) | 0.296‡ |
| ESR mm/h median (IQR) (n=571) | 80 (44 to 102) | 91 (58 to 125) | 85 (46 to 117.8) | 100 (68.5 to 150) | 0.001‡ |
| ANCA ELISA only, n (%) (n=704) | | | | | |
| MPO | 243 (34.5) | 174 (32.5) | 95 (31.5) | 79 (33.9) | |
| PR3 | 394 (56.0) | 286 (53.5) | 170 (56.3) | 116 (49.8) | |
| Double positive | 16 (2.3) | 16 (3.0) | 6 (2.0) | 10 (4.3) | |
| Negative | 51 (7.2) | 51 (9.5%) | 30 (9.9) | 21 (9.0) | 0.040* |
| ANCA ELISA or IIF, n (%) (n=723) | | | | | |
| MPO | 277 (38.3) | 205 (38.3) | 110 (36.4) | 95 (40.8) | |
| PR3 | 411 (56.8) | 288 (53.8) | 172 (57.0) | 116 (49.8) | |
| Double positive | 16 (2.2) | 16 (3.0) | 6 (2.0) | 10 (4.3) | |
| Negative | 19 (2.6) | 18 (3.4) | 13 (4.3) | 5 (2.1) | 0.015* |
| BVAS score, median (IQR) (n=685) | 16 (10 to 23) | 17 (12 to 23) | 16.5 (12 to 23) | 17 (11.5 to 23) | 0.967‡ |
| BVAS quartiles, n (%) (n=685) | | | | | |
| 0–10 | 174 (25.4) | 111 (20.7) | 57 (18.9) | 54 (23.2) | |
| 11–16 | 170 (24.8) | 152 (28.4) | 94 (31.1) | 58 (24.9) | |
| 17–23 | 179 (26.1) | 152 (28.4) | 87 (28.8) | 65 (27.9) | |
| 24+ | 162 (23.7) | 120 (22.4) | 64 (21.2) | 56 (24.0) | 0.323* |
| Total VDI scores, n (%) (n=629) | | | | | |
| 0 | 412 (65.5) | 350 (71.7) | 223 (74.3) | 127 (67.6) | |
| 1–2 | 133 (21.1) | 88 (18.0) | 50 (16.7) | 38 (20.2) | |
| 3–4 | 52 (8.3) | 32 (6.6) | 19 (6.3) | 13 (6.9) | |
| >=5 | 32 (5.09) | 18 (3.7) | 8 (2.7) | 10 (5.3) | 0.283* |

Data are shown as n (%), mean (SD), or median with IQR.
*Pearson test ($\chi^2$).
††t Test.
‡Mann-Whitney U test.
ANCA, antineutrophil cytoplasm antibody; BVAS, Birmingham vasculitis activity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.



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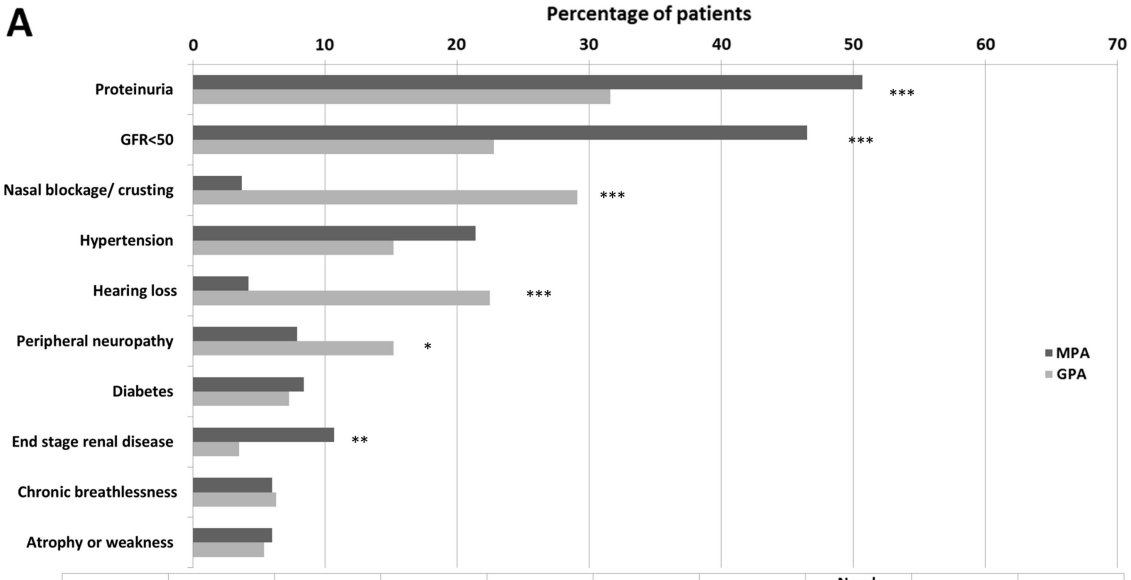
## RESULTS

### Demographic and clinical characteristics at baseline

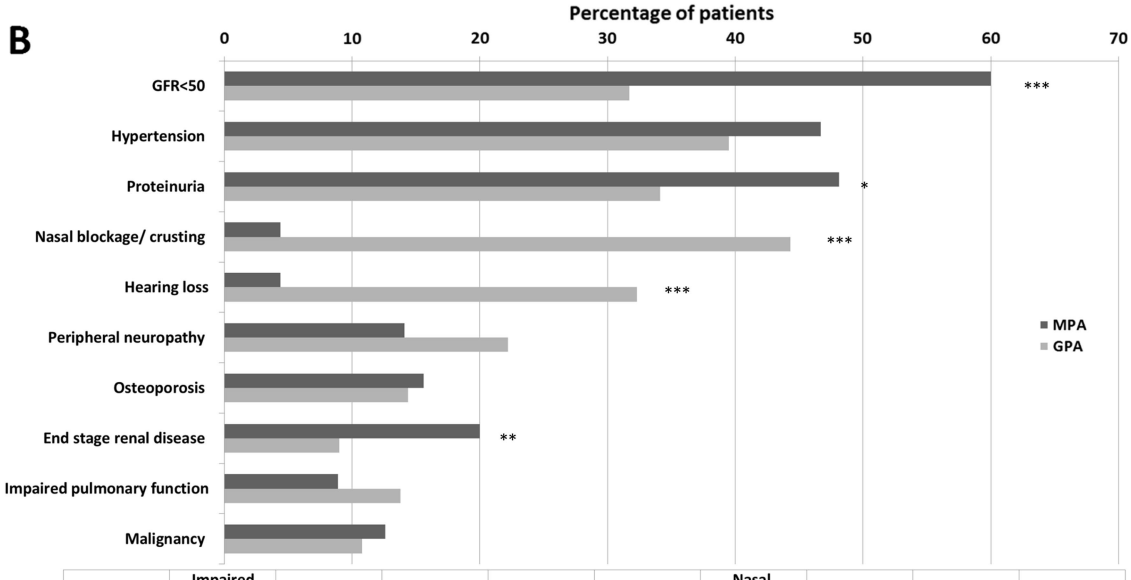
Seven hundred and thirty-five patients with a mean age of 57.6 (SD 14.4) years, 415 (56.7%) male, participated in the six trials (table 2). Over half (54.8%) had GPA. On ANCA subtyping, 411 (56.8%) were PR3-ANCA and 277 (38.3%) MPO-ANCA. The median baseline creatinine was 192 μmol/L (IQR 98.7 to 440) and median total BVAS score 16 (IQR 10–23).

### Data completeness at LTFU

Four hundred and sixty-seven patients (87.3% of the 535) had data at LTFU, with a mean of 87 months (7.3 years; SD 26.4 months) follow-up. Of these 467, 302 (64.7%; 56.4% of the 535) had VDI data at LTFU and had been followed for a mean of 85 months (7.1 years; SD 25.1 months). Baseline demographics of those with and without VDI data at LTFU are shown in table 2. Patients with no VDI data had higher serum




| | Atrophy or weakness | Chronic breathlessness | End stage renal disease | Diabetes | Peripheral neuropathy | Hearing loss | Hypertension | Nasal blockage/ crusting | GFR<50 | Proteinuria |
|---|---|---|---|---|---|---|---|---|---|---|
| MPA | 6 | 6 | 10.7 | 8.4 | 7.9 | 4.2 | 21.4 | 3.7 | 46.5 | 50.7 |
| GPA | 5.4 | 6.3 | 3.5 | 7.3 | 15.2 | 22.5 | 15.2 | 29.1 | 22.8 | 31.6 |




| | Malignancy | Impaired pulmonary function | End stage renal disease | Osteoporosis | Peripheral neuropathy | Hearing loss | Nasal blockage/ crusting | Proteinuria | Hypertension | GFR<50 |
|---|---|---|---|---|---|---|---|---|---|---|
| MPA | 12.6 | 8.9 | 20 | 15.6 | 14.1 | 4.4 | 4.4 | 48.1 | 46.7 | 60 |
| GPA | 10.8 | 13.8 | 9 | 14.4 | 22.2 | 32.3 | 44.3 | 34.1 | 39.5 | 31.7 |

**Figure 1** Frequency of the 10 most common Vasculitis Damage Index (VDI) items by clinical subtype. (A) At 6 months (n=531; 215 MPA, 316 granulomatosis with polyangiitis (GPA)); (B) At long-term follow-up (LTFU) (n=302; 135 microscopic polyangiitis (MPA), 167 GPA). Frequency of the three items significantly associated with antineutrophil cytoplasm antibody (ANCA) serology; (C) At 6 months (n=529; 181 myeloperoxidase (MPO), 319 PR3, 14 MPO and PR3, 15 negative); (D) At LTFU (n=301; 110 MPO, 172 PR3, 6 MPO and PR3, 13 negative). *p<0.05; **p<0.01; ***p<0.001;****p<0.0001.



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creatinine and erythrocyte sedimentation rate (ESR) at baseline than patients with VDI data (both p<0.01). There was a higher frequency of patients with VDI data at LTFU from the CYCLOPS trial (p<0.01).

### Mortality

By LTFU, 133 patients had died, 46 (15.2%) of those with VDI data at LTFU (ie, after their last clinic attendance) (n=302), and 87 (37.3%) of those without (n=233). Fifty-one per cent of MEPEX patients had died (70/137), 17.4% (27/155) from CYCAZAREM, 16.9% (25/148) from CYCLOPS and 11.6% (11/95) from NORAM (overall $\chi^2$=69.1, df=3, p<0.001). Cause of death was available for 84 patients, and attributed to vasculitis in 16 (19.0%), immunosuppression in 24 (28.6%) and sepsis in 31 (36.5%), with no differences between trials.

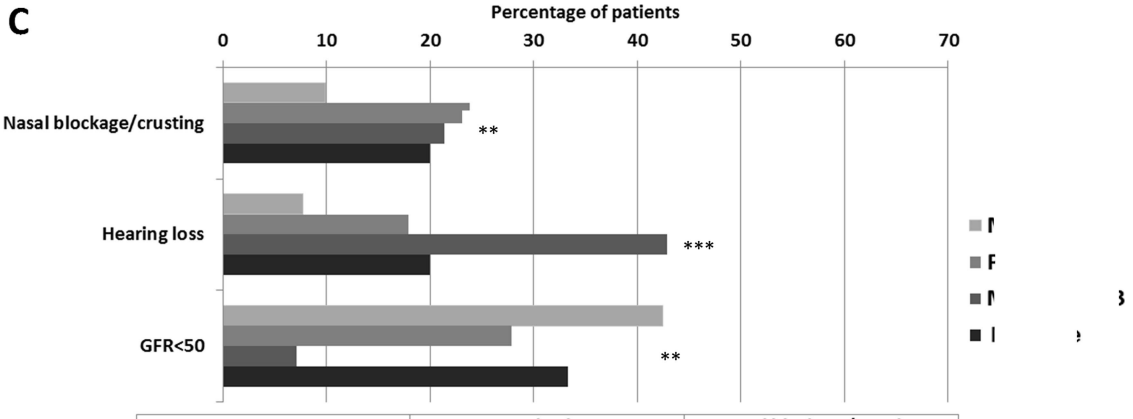
### Glucocorticoid use

Almost 300 patients (n=296; 63.4% of the 467, 55.3% of the 535) had data on glucocorticoid use. Within these, 139/291 (47.8%) were on glucocorticoids at their last visit, with the mean length of glucocorticoid use being 40.4 months (SD 16.7; median 36.0, IQ range 2 to 60). Eighty-three patients (28.0%) used glucocorticoids for 60 months, 64 (21.6%) 37–54 months, 103 (34.8%) 19–36 months, and 46 (15.5%) 1–18 months.

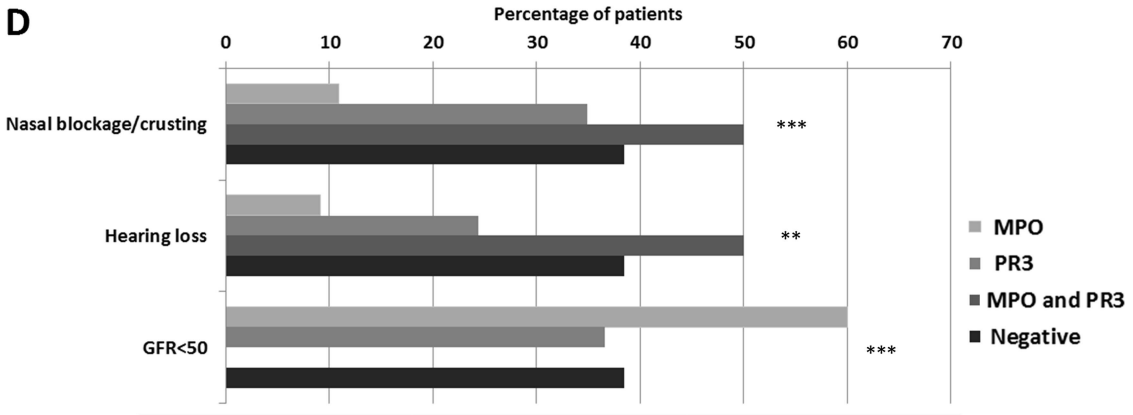
### Early and late damage

Assessment of early damage was based on 531 patients (72.2% of the 735) with VDI data at 6 months (n=215 MPA, n=316 GPA); assessment of late damage on 302 patients (56.4% of the 535) with VDI data at LTFU (n=135 MPA, n=167 GPA).

The most frequently recorded items of damage at 6 months and LTFU overlapped (figures 1A,B). Three of the six most frequent items of damage were renal: proteinuria, GFR<50 mL/min and hypertension. Proteinuria and GFR<50 mL/min were more common in MPA; nasal crusting, hearing loss and peripheral neuropathy more common in GPA. In terms of ANCA subtype, at 6 months and LTFU patients with PR3 versus MPO antibodies were significantly more likely to have hearing loss, nasal crusting and less likely to have GFR<50 mL/min (figure 1C,D). Of the 32 patients with ≥5 VDI items at baseline,




| | GFR<50 | Hearing loss | Nasal blockage/crusting |
|---|---|---|---|
| MPO | 42.5 | 7.7 | 9.9 |
| PR3 | 27.9 | 17.9 | 23.8 |
| MPO and PR3 | 7.1 | 42.9 | 21.4 |
| Negative | 33.3 | 20 | 20 |




| | GFR<50 | Hearing loss | Nasal blockage/crusting |
|---|---|---|---|
| MPO | 60 | 9.1 | 10.9 |
| PR3 | 36.6 | 24.4 | 34.9 |
| MPO and PR3 | 0 | 50 | 50 |
| Negative | 38.5 | 38.5 | 38.5 |

**Figure 1 (Continued)**



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25 (78.1%) were positive for PR3 antibody and only five (15.6%) for MPO; by 6 months this difference had disappeared.

Among the 302 patients with VDI data at LTFU, the majority (n=48, 87%) of the 55 patients from NORAM (entry criteria: creatinine<150μmol/L) had no renal-related VDI items at LTFU; this differed from the 61 MEPEX patients (entry criteria: creatinine >500 μmol/L or required dialysis), 95% (n=58) of whom had acquired at least one renal-related item ($\chi^2$ p<0.0001).

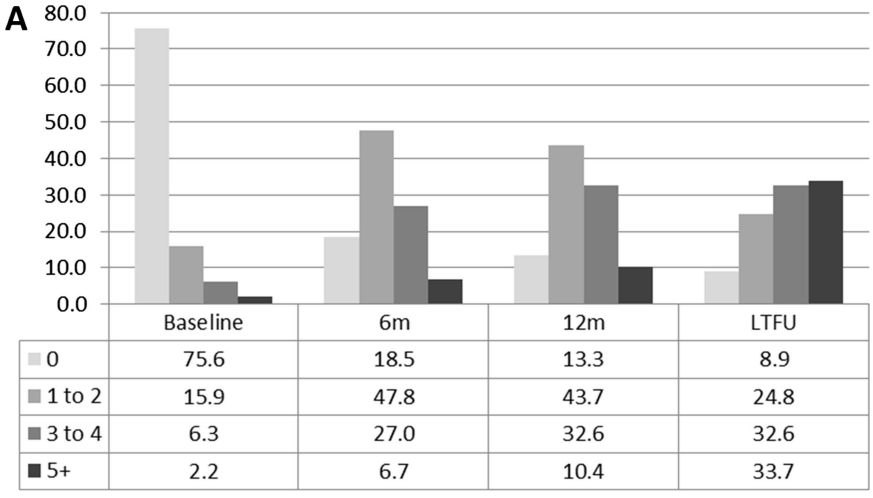
### Damage over time

Mean (SD) total VDI scores in the 270 patients with data at baseline, 6, 12 months and LTFU increased from 0.57 (1.31) at baseline, to 2.00 (1.71) at 6 months, 2.45 (2.02) at 12 months, and 2.66 (1.75) at LTFU, the number of patients with ≥1 VDI item increasing from 66 (24.4%) at baseline, to 220 (81.5%) at 6 months, 234 (86.7%) at 12 months, and 246 (91.1%) at LTFU (figure 2A). The numbers of patients with ≥5 VDI items were 6 (2.2%) at baseline, 18 (6.7%) at 6 months, 28 (10.4%) at 12 months, and 91 (33.7%) at LTFU (figure 2A).

There was no difference over time between patients with MPA and GPA in terms of total VDI score (mean 2.15 vs 2.26, respectively, repeated measures ANOVA p=0.58), although scores at baseline were lower in MPA patients (mean 0.38 vs 0.73, M-W test p=0.014) with 83% having no damage compared with 70% of GPA patients ($\chi^2$p=0.014) (figure 1A). Total VDI scores differed over time between patients in the four trials (p=0.036), with differences at each time point (p<0.001) and a significant interaction between time and trial (p<0.001) (figure 2B). Correlations between total BVAS scores at baseline and VDI scores at 6 months (r=0.139, p=0.001) and LTFU (r=0.139, p=0.016), were low; between simultaneous BVAS and VDI scores there was either no (6 months r=0.025, p=0.606) or low correlation (12 months r=0.131, p=0.008).

### Treatment related damage

At LTFU, potentially treatment-related VDI items were reported for two-thirds of patients (n=201, 66.6%, of the 302 patients with data at LTFU; n=177, 65.6%, of the 270 with complete




| | Baseline | 6m | 12m | LTFU |
|---|---|---|---|---|
| 0 | 75.6 | 18.5 | 13.3 | 8.9 |
| 1 to 2 | 15.9 | 47.8 | 43.7 | 24.8 |
| 3 to 4 | 6.3 | 27.0 | 32.6 | 32.6 |
| 5+ | 2.2 | 6.7 | 10.4 | 33.7 |

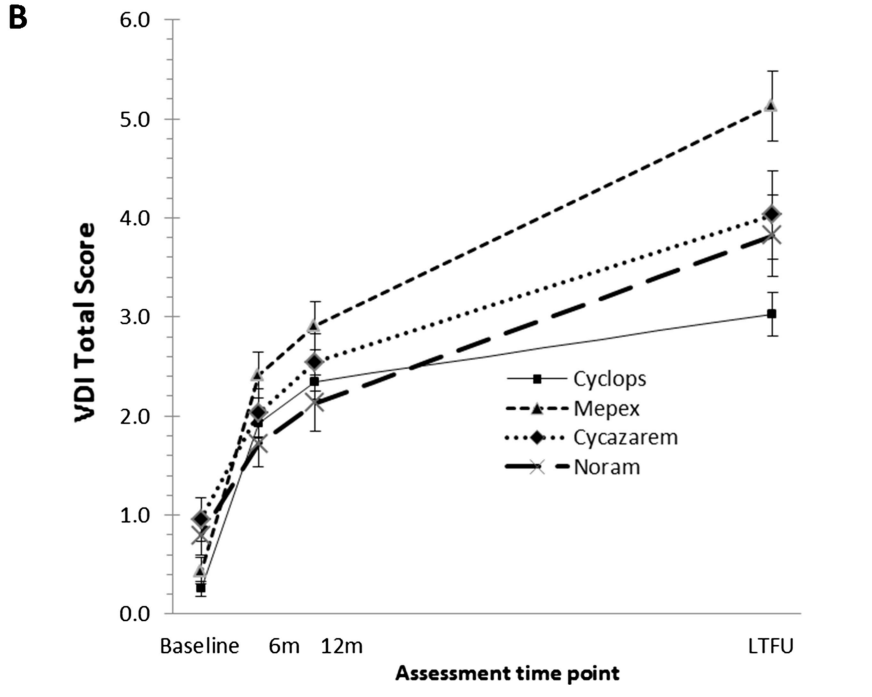



**Figure 2** (A) Percentage of patients in Vasculitis Damage Index (VDI) score groups at baseline, 6 months, 12 months and long-term follow-up (patients with data at all four assessments, n=270); (B) Total VDI scores over time by trial for n=270 patients with valid data at all assessments (Cyclops n=101; Mepex n=46; Cycazarem n=70; Noram n=53).



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**Table 3** Frequency, n (%), of Vasculitis Damage Index (VDI) items related to treatment over course of long-term follow-up (LTFU) for n=270 patients with VDI scores at baseline, six, 12 months and LTFU

| VDI Item | Baseline (%) | 6/12 (%) | 12/12 (%) | LTFU (%) | % Change at LTFU from baseline (95% CI) |
|---|---|---|---|---|---|
| Hypertension† | 13 (4.8) | 46 (17.0) | 60 (22.2) | 112 (41.5) | +36.7 (30.8 to 42.5)*** |
| Osteoporosis‡ | 0 | 4 (1.5) | 12 (4.4) | 38 (14.1) | +14.1 (9.9 to 18.2)*** |
| Malignancy§ | 0 | 0 | 1 (0.4) | 34 (12.6) | +12.6 (8.6 to 16.6)*** |
| Diabetes¶ | 3 (1.1) | 17 (6.3) | 22 (8.1) | 28 (10.4) | +9.3 (5.8 to 12.7)*** |
| Angina/bypass†† | 2 (0.7) | 3 (1.1) | 4 (1.5) | 22 (8.1) | +7.4 (4.3 to 10.6)*** |
| Cataract‡‡ | 2 (0.7) | 5 (1.9) | 8 (3.0) | 25 (9.3) | +8.5 (5.2 to 11.9)*** |
| Atrophy or weakness§§ | 5 (1.9) | 14 (5.2) | 16 (5.9) | 20 (7.4) | +5.6 (2.6 to 8.5)*** |
| Alopecia¶¶ | 0 | 11 (4.1) | 19 (7.0) | 23 (8.5) | +8.5 (5.2 to 11.9)*** |
| Cerebrovascular accident††† | 0 | 1 (0.4%) | 1 (0.4) | 10 (3.7) | +3.7 (1.4 to 6.0)** |
| Myocardial infarction‡‡‡ | 1 (0.4) | 4 (1.5) | 5 (1.9) | 12 (4.4) | +4.1 (1.7 to 6.4)** |
| Gonadal failure§§§ | 2 (0.7) | 6 (2.2) | 8 (3.0) | 11 (4.1) | +3.3 (1.2 to 5.5)** |
| Marrow failure¶¶¶ | 1 (0.4) | 4 (1.5) | 6 (2.2) | 8 (3.0) | +2.6 (0.7 to 4.5)** |
| Mouth ulcers†††† | 2 (0.7) | 4 (1.5) | 4 (1.5) | 4 (1.5) | +0.7 (−0.3 to 1.8) |
| Chemical cystitis‡‡‡‡ | 0 | 0 | 0 | 2 (0.7) | +0.7 (−0.3 to 1.8) |
| Avascular necrosis§§§§ | 0 | 0 | 1 (0.4) | 2 (0.7) | +0.7 (−0.3 to 1.8) |
| Osteomyelitis¶¶¶¶ | 0 | 0 | 0 | 2 (0.7) | +0.7 (−0.3 to 1.8) |

**p<0.01; ***p<0.001 LTFU versus zero (paired z test and Wilcoxon test).
†Diastolic blood pressure >95 mm Hg or requiring antihypertensive medications.
‡Presence of osteoporotic fractures or vertebral collapse.
§Any malignancy confirmed by histology, excluding dysplasias.
¶Any type of diabetes requiring therapy.
††A compatible history and ECG changes.
‡‡Lens opacity in either eye documented by ophthalmoscopy.
§§Significant muscle atrophy or weakness, not attributable to a cerebrovascular accident.
¶¶Major chronic hair loss with or without scars, documented clinically.
†††Cerebrovascular accident resulting in focal findings such as paresis, weakness, etc.
‡‡‡Compatible history confirmed at least by ECG changes or cardiac enzyme elevation.
§§§Premature secondary amenorrhoea or azoospermia.
¶¶¶Leucopenia (white cell count <4000/μL), or thrombocytopenia (platelets <140) or anaemia (haemoglobin <10) preferably confirmed by marrow aspiration.
††††recurrent crops or persistent mouth ulcers requiring therapy.
‡‡‡‡Persistent haematuria or shrunken bladder.
§§§§Necrotic areas of bone due to lack of blood supply shown up on X-ray.
¶¶¶¶Documented clinically, confirmed by X-ray and/or culture.

follow-up data) with 92/302 (30.5%; 81/270, 30.0%) having one item of damage, and 52/302 (17.2%; 45/270, 16.7%) ≥3.

The frequency of these items among the 270 patients over the course of follow-up is shown in table 3. At LTFU, the most commonly reported items were hypertension, osteoporosis, malignancy and diabetes (table 3).

## DISCUSSION

This well-defined cohort of European patients with newly diagnosed GPA and MPA has extended follow-up of 7.1 years[17] and is the first study of damage to include patients with GPA and MPA. At baseline, 34.5% had ≥1 item of damage and 5.1% ≥5 items. Of note, a VDI damage item is scored if present for ≥3 months since the onset of any vasculitis symptom, so can predate diagnosis and trial enrolment. Damage accumulates early; by 6 months 82% have ≥1 item. Renal and cardiovascular items are most frequent overall; more MPA patients had proteinuria and GFR<50 mL/min, while otolaryngological damage was seen more frequently in GPA patients. Damage related to glucocorticoid treatment, including diabetes, osteoporosis and cataracts also rose, implying that immunosuppressive regimens are yet to be optimised. In terms of ANCA serology, PR3 positive patients had a greater frequency of high levels of baseline damage than those with MPA, and were specifically more likely to have otolaryngological damage. Patients with MPO-positive serology had a higher frequency of impaired renal function than those with PR3 positivity; these trends are broadly similar to those between GPA and MPA, when patients are classified according to clinical and histopathological features.[25]

Total one-year damage in this study is comparable to that described previously.[10 13 18 27] The frequency of individual damage items at 1 year, however, is higher than in the WGET trial in which items were only scored as present if constant for six rather than 3 months, and in which reversibility was also allowed.[18] The increased rate of cardiovascular damage seen in this cohort is in keeping with the previously described increased observed to expected ratio for ischaemic heart disease of 1.9 (95% CI 1.4 to 2.4).[6] A major limitation of this study is that there is no comparison of damage accrued with the numbers expected in the background population; there is also no data on management of cardiovascular risk factors. Malignancies recorded rose over LTFU; although types are not recorded in the VDI, this information is available from the LTFU questionnaire.[28]

Other limitations are that patients were recruited to clinical trials; elderly patients, those with lung haemorrhage at diagnosis and those with fatal disease were excluded. There may also be a bias in the LTFU data: patients with no VDI data at LTFU had higher baseline serum creatinine, and higher ESR than patients with VDI data (all p<0.01) suggesting that sicker patients were less likely to provide long-term data. The frequency of damage may therefore be under-represented. Additionally, the VDI may not adequately capture the range of damage seen in ANCA-associated vasculitis,[14] and may underestimate damage accrued if clinicians do not carry items over between each assessment. Lastly, this study provides a description of glucocorticoid



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duration but without dosages; cumulative months of a daily dose of prednisolone >20 mg/day are associated with increasing VDI scores (β=0.5 (95% CI 0.3 to 0.8), p<0.001).[13]

In conclusion, this study highlights the extent of damage seen over an average of 7 years in the ANCA-associated vasculitides, specifically in terms of potentially treatment-related damage, such as cardiovascular outcomes, diabetes, osteoporosis and malignancy. Damage should, therefore, continue to be an important outcome in AAV clinical trials and long-term cohort studies,[8] with use of the VDI as a primary outcome measure. Such focus may potentially aid refinement of therapeutic regimens and limit long-term damage,[29] with possible benefits in terms of associated mortality.[10]

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**Competing Interests** JR has received payment for lectures from Nordic Pharma, a consultancy for vasculitis disease assessment training from GlaxoSmithKline and a travel bursary from Chugai Pharma. AM has received a travel bursary from Laboratoire Francais de Biotechnologie (LFB). RL has received a consultancy for vasculitis disease assessment training with Nordic Pharma, Chemocentryx, Human Genome Science and GlaxoSmithKline and money to his institution from Nordic Pharma for an administrator to assist in disease assessment training in vasculitis. HD, RS, OF, LH, PH, DJ, and KW have no potential conflicts of interest.

**Ethics approval** This study was conducted with the approval of the West Midlands Multicentre Research Ethics Committee (ref: MREC/98/7/37).

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