

April 04/11: The outcome of Wegener patients improved significantly

Key messages:

- Improved diagnosis and treatment reduce mortality and relapse rates of Wegener patients.
 - Comparing diagnosis in the last four decades, the interval between first symptoms and diagnosis was reduced from 8 to 4 months.
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Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades

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Background: Wegener's granulomatosis is a severe autoimmune disease leading to massive damage of organs or even death. The importance of an early but correct diagnosis is indispensable to induce counteractions in time.

Summary: Three cohorts of patients diagnosed in 1966 – 1993 (cohort 1), 1994 – 1998 (cohort 2) and 1999 – 2002 (cohort 3) were retrospectively assessed for clinical manifestations, therapy procedures, trends in therapy, mortality, and incidence of malignancies.

Unchanged: - Organ manifestations are similar.

- Cyclophosphamide (CYC) is still the most prescribed drug.
- No increased rate of malignancies

Changed: - Interval between first symptoms and diagnosis was reduced by half to 4 month.

- The median cumulative dose of CYC was significantly reduced.
- Declined standardized mortality ratios (SMR) with fewer deaths and decreased relapse rates.

Young males had a considerably higher SMR and more frequent renal manifestations compared to young females.

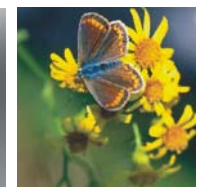
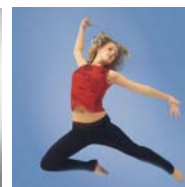
Conclusions: The decline in mortality is probably due to improved diagnostic and therapeutic procedures and increased awareness of WG, leading to earlier diagnosis, reduction in relapse rates, and lower cumulative CYC dose with fewer deaths related to therapy.

Shorter periods of remission induction and increasing intravenous administration of CYC account for a reduced cumulative CYC dose.

The decline in relapse rates is associated with the implementation of a regular maintenance therapy.

Comment: This study confirms the better outcome of Wegener patients during the last 40 years. And the development of better diagnostic tests, finding more Wegener patients and less controls positive is still going on. Phadia's highly sensitive and specific EliA PR3^S assay yields a good evidence for the determination of the disease.

The panel for detection ANCA-associated Vasculitis is complemented by the sensitive and specific EliA MPO^S assay.



Improved Outcome in 445 Patients With Wegener's Granulomatosis in a German Vasculitis Center Over Four Decades

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Objective. To determine the long-term outcome in patients with Wegener's granulomatosis (WG) over 4 decades in an academic hospital unit specializing in rheumatology.

Methods. We included 290 patients, divided them into 2 cohorts, and compared them with the historical cohort of 155 patients. Comparisons were retrospective regarding disease manifestations, therapy, mortality, and incidence of malignancies. The historical cohort (cohort 1) included 155 patients diagnosed between 1966 and 1993, cohort 2 included 123 patients diagnosed between 1994 and 1998, and cohort 3 included 167 patients diagnosed between 1999 and 2002.

Results. Over time, the interval between first symptoms and diagnosis was reduced by half (from 8 months to 4 months). Organ manifestations were similar in the 3 cohorts, and more than 80% of patients still required cyclophosphamide (CYC); however, the median cumulative dose was reduced significantly (from 67 gm in cohort 1 to 36 gm in cohort 2 and to 24 gm in cohort 3). The standardized mortality ratios (SMRs) declined (from 2.1 in cohort 1 to 1.41 in cohort 2 and to 1.03 in cohort 3), with fewer deaths related to WG

and/or therapy (86.4% in cohort 1, 76.9% in cohort 2, 50% in cohort 3), decreasing relapse rates (63.9% in cohort 1, 51.2% in cohort 2, 35.3% in cohort 3), and no increased rate of malignancies. Compared with young females, young males had a considerably higher SMR (8.87 [95% confidence interval 4.05–16.8]) and more frequent renal manifestations (54.4% versus 33.8%).

Conclusion. Mortality of WG patients declined over the last 4 decades, probably due to improved diagnostic and therapeutic procedures and increased awareness of WG, which led to earlier diagnosis and therapy, reduction in relapse rates, and lower cumulative CYC dose with fewer deaths related to therapy.

The outcome of Wegener's granulomatosis (WG) has improved dramatically over the last decades as a result of more sophisticated diagnostic procedures and therapy options (1). Increased mortality has been associated with older age (>50 years), kidney involvement (with impaired renal function), and pulmonary manifestations at diagnosis in several studies including our own "historical cohort" of 155 WG patients (2). While several studies reported in the 1990s demonstrated an increased mortality of WG patients compared with that in the general population (3–6), only a slight elevation of the standardized mortality ratios (SMRs) at 5 years (to 1.6) was reported for a recent Swedish population-based cohort of patients with WG and microscopic polyangiitis (MPA) diagnosed between 1978 and 2005 (7), and no increased SMR was reported for women age <60 years with various vasculitides in a study that assessed a population of patients with disease onset in the 1990s (8).

The improved outcome may be related to an earlier diagnosis as a result of an increased awareness of WG and to the implementation of activity- and stage-adapted therapy and less toxic treatment regimens since the 1980s, which were later assessed in studies by the

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European Vasculitis Study Group (EUVAS) (9–12) and which are now part of the recently published European League Against Rheumatism (EULAR) treatment recommendations (13). Regarding our originally investigated “historical” cohort of 155 patients followed up from 1966 to 1993 (2), all patients achieved at least a response; nonetheless, relapse rates were high (64%). Median survival was 21.7 years, with most deaths being related to WG or its therapy.

We have followed a strict stage- and activity-adapted therapy regimen since the end of the 1980s (14–20), and we implemented a standardized patient education program in 1994 (21). In order to evaluate how clinical and translational research has improved patients’ outcome, we conducted a retrospective study of 290 patients to assess clinical manifestations, therapy procedures, trends in therapy, mortality, and incidence of malignancy in WG, and we compared the findings with those from our “historical” cohort of 155 patients (referred to herein as cohort 1).

PATIENTS AND METHODS

Vasculitis center and patients. All consecutive patients were assessed at the Vasculitis Center Schleswig-Holstein, Germany, which takes care of vasculitis patients from the catchment area (state of Schleswig-Holstein) but also serves as a tertiary referral center for the rest of Germany. All patients fulfilled the American College of Rheumatology 1990 criteria (22) and were divided into 2 entry cohorts according to the year of diagnosis (1994–1998 [cohort 2] and 1999–2002 [cohort 3]). Followup ended in March 2005.

Definition and assessment of disease stages and activity, extent of disease, and mortality. Patients had their medical records checked with regard to (first) disease manifestations, underwent standardized interviews regarding first symptoms attributable to WG, and underwent a physical examination and interdisciplinary clinical, laboratory, and technical examinations to assess disease activity, extent of disease, and therapy-related side effects (as described for the historical cohort [2]). “Localized disease” was defined as manifestations restricted to the upper and/or lower respiratory tract with no signs of clinical vasculitis (e.g., purpura, alveolar hemorrhage, or glomerulonephritis); “generalized disease” corresponded to systemic, clinical vasculitis with organ- and/or life-threatening manifestations. “Early systemic disease” has been distinguished from generalized disease since 1995 (23) and was defined as manifestations not restricted to the upper and/or lower respiratory tract but which are not yet organ- or life-threatening.

Complete remission was diagnosed when signs and symptoms of disease were fully absent, laboratory tests and technical examinations revealed no pathologic findings related to disease activity, and the glucocorticoid dose did not exceed 7.5 mg/day prednisolone. “Response” (formerly, partial remission) was defined as stabilization due to lack of progression or as improvement due to reduced disease activity with no

occurrence of new symptoms over at least 3 months. Relapse was consistent with recurrence of disease signs or symptoms after complete remission or “response” for at least 3 months. Extent of disease was determined by the Disease Extent Index (DEI) (24). All-cause mortality was documented. Deaths outside the center were assessed as reported by family, practitioner, and/or death certificate. Activity assessment using the Birmingham Vasculitis Activity Score (BVAS) was not included in the study, since the BVAS was introduced during the study period (25). Antineutrophil cytoplasmic antibodies (ANCA) were assessed as previously described, partly on sera that had been stored (2). ANCA titer was always interpreted in conjunction with the clinical picture to determine disease activity. A rise in ANCA titer without any other signs of disease activity was not considered a reason to step up therapy.

Treatment procedures. Treatment was adapted according to disease stage, extent of disease, and disease activity. Cyclophosphamide (CYC) (oral [2 mg/kg body weight/day] or pulse [15–20 mg/kg body weight every 3 weeks]) plus glucocorticoids (GCs) was used for remission induction in organ- or life-threatening “generalized disease.” Methotrexate (MTX) (0.3 mg/kg body weight/week) or CYC in conjunction with high-dose GCs (1 mg/kg/day prednisolone initially) was administered in “early systemic disease” according to the physician’s judgment. Patients with a high DEI (>7) or extensive pulmonary involvement (cavities >3 cm, infiltrates) were preferably treated with CYC and not MTX. All patients taking (oral and intravenous) CYC received uroprotection with mesna. In “localized disease,” trimethoprim/sulfamethoxazole (TMP/SMX; 2 × 960 mg/day), MTX, or CYC was used, depending on the severity of disease. After 3–12 months, patients were switched to maintenance therapy, which was continued for at least 12 months at full dose. In general, remission induction with CYC was performed for ≥6 months in the first cohort, whereas later on, we attempted to reduce periods of remission induction to 3 months.

We followed a strict principle of early GC reduction, starting 3–8 days after initiating prednisolone. Prednisolone was usually reduced to 15 mg/day after 2–3 months and to ≤7.5 mg/day when patients were switched to maintenance therapy with MTX, azathioprine (AZA; 2 mg/kg body weight/day), leflunomide (LEF; 20–30 mg/day), or TMP/SMX. GCs were stopped after >12 months of remission in patients until the end of the 1990s; subsequently, low-dose prednisolone (3–5 mg/day) was continued for maintenance. Since the year 2000, *Pneumocystis jiroveci* prophylaxis with TMP/SMX has been administered to all patients receiving the combination of GCs and CYC. Since 1994, all patients have been educated using a standardized training program (21) which consists of 5 different modules held by physicians, nurses, nutritionists, psychologists, and physiotherapists.

Statistical analysis. Continuous variables were reported as median values and ranges. For nonparametric comparison of continuous variables by calendar year of diagnosis, the Kruskal-Wallis test for 3 independent groups (1966–1993 versus 1994–1998 versus 1999–2002) and the Mann-Whitney test for 2 independent groups (1966–1993 versus 1994–1998) were performed. For the comparison of categorical variables (patients’ characteristics by calendar year of diagnosis), the chi-square test was used. For tests on cumulative characteristics, the diagnosis years from 1966 to 1993 were only compared with the diagnosis years from 1994 to 1998 because of the

Table 1. Clinical and demographic characteristics of the 3 cohorts*

	Cohort 1, 1966–1993 (n = 155)	Cohort 2, 1994–1998 (n = 123)	Cohort 3, 1999–2002 (n = 167)	P†
End of followup, date	3/31/1997	3/31/2005	5/31/2005	–
Followup, years	6.6 (0.3–27.2)	7.3 (0.1–11.1)	3.9 (0.2–6.2)	<0.001
Patients followed up >5 years, no. (%)	114 (73.5)	102 (82.9)	40 (24.0)	<0.001
Patients lost to followup/deceased, no. (%)	14 (9.0)	20 (16.3)	14 (8.4)	0.005
Male/female, no. (%)	76/79 (49.0/51.0)	62/61 (50.4/49.6)	85/82 (50.9/49.1)	0.943
Age at diagnosis, years	48 (12–73)	52 (17–77)	55 (16–85)	<0.001
Interval from first symptoms to diagnosis, months	8 (0–292)	5 (0–195)	4 (0–250)	0.007
Interval from diagnosis to first admission, months	2 (0–291)	2 (0–60)	2 (0–41)	0.602
cANCA positive, no. (%)‡	130 (83.9)	103 (83.7)	131 (78.4)	0.364
PR3 ANCA positive, no. (%)	130 (83.9)	100 (81.3)	129 (77.2)	0.316
pANCA/MPO ANCA positive, no. (%)‡	4 (2.6)	4 (3.3)	9 (5.4)	0.392
“Localized” WG, no. (%)§				
At onset	79 (51.0)	45 (36.6)	70 (41.9)	0.451
At diagnosis	24 (15.5)	17 (13.8)	18 (10.8)	0.048
Biopsy compatible with WG, no. (%)	139 (89.7)	97 (78.9)	117 (70.1)	<0.001
DEI				
At diagnosis	9 (2–19)	7 (2–15)	7 (2–17)	0.0025
Over whole disease course	11 (2–19)	11 (2–17)	9 (2–17)	0.013¶

* Except where indicated otherwise, values are the median (range). The interval from symptoms to diagnosis declined, as did the Disease Extent Index (DEI) at diagnosis and over the whole disease course. cANCA = cytoplasmic antineutrophil cytoplasmic antibody; PR3 ANCA = proteinase 3-specific ANCA; pANCA = perinuclear ANCA; MPO ANCA = myeloperoxidase-specific ANCA; WG = Wegener's granulomatosis.

† P values compared cohort 1 (diagnosed in 1966–1993), cohort 2 (diagnosed in 1994–1998), and cohort 3 (diagnosed in 1999–2002).

‡ For some patients, ANCA testing was not available at the time of diagnosis, but all patients underwent ANCA testing during followup.

§ Restricted to upper/lower respiratory tract.

¶ Cohort 1 versus cohort 2.

shorter followup period in the cohort of patients with disease diagnosed in the years from 1999 to 2002.

SMRs for overall mortality and cancer mortality and standardized incidence ratios (SIRs) were calculated on the basis of age, sex, and calendar-specific mortality rates in the former country of West Germany. PAMCOMP software (26) was used for analysis. We calculated 95% confidence intervals (95% CIs) for the SMR assuming a Poisson distribution. SMRs and SIRs refer to the total of cancer-attributable deaths and cancer incidence, respectively, in subgroups according to the years of diagnosis (3 categories: 1966–1993, 1994–1998, and 1999–2002). Patients ranged in age from 12.6 years to 85.4 years, with only 155 persons age \leq 45 years and 290 persons age >45 years. According to the distribution of age at diagnosis, 3 tertiles were used to build 3 age groups: age group 1 (148 patients [68 males and 80 females], median age 31.7 years [range 12.6–44.4 years]), age group 2 (149 patients [82 males and 67 females], median age 51.8 years [range 44.7–59.3 years]), and age group 3 (148 patients [73 males and 75 females], median age 65.1 years [range 59.6–85.4 years]).

For the SMR calculation, the official statistics processed by the German Cancer Research Center were used as reference data. Data from 2000–2004 were extrapolated to 2005–2009 to include the last year of observation. For the calculation of the SIR, data of the Saarland Cancer Registry (from 1970–2004) were used as a reference, while the calendar period of 1965–1969 was extrapolated backward from the calendar period of 1970–1974, and the calendar period of 2005–2009 was extrapolated forward from the calendar period of 2000–2004.

RESULTS

Patient characteristics. We recorded information about 123 patients with disease diagnosed between 1994 and 1998 (cohort 2) (followup of 7.3 years) and 167 patients with disease diagnosed between 1999 and 2002 (cohort 3) (followup of 4 years) and compared it with information about the 155 patients of the historical cohort (cohort 1) (followup of 6.6 years). The distribution of sex was comparable, whereas the median age at diagnosis increased significantly, from 48 years (range 12–73 years) in cohort 1 to 55 years (range 16–85 years) in cohort 3. The interval between first symptoms and diagnosis was reduced by half (from a median of 8 months [range 0–292 months] to a median of 4 months [range 0–250 months]) (Table 1). In cohorts 1, 2, and 3, histologic findings compatible with WG were seen in 64%, 57.7%, and 53% of patients, respectively, based on biopsy samples obtained from the upper respiratory tract; in 14.4%, 16.5%, and 17.1% of patients, respectively, based on biopsy samples obtained from the lower respiratory tract; and in 15.1%, 25.8%, and 23.1% of patients, respectively, based on biopsy samples obtained from the kidney. Table 1 summarizes the details of patient characteristics.

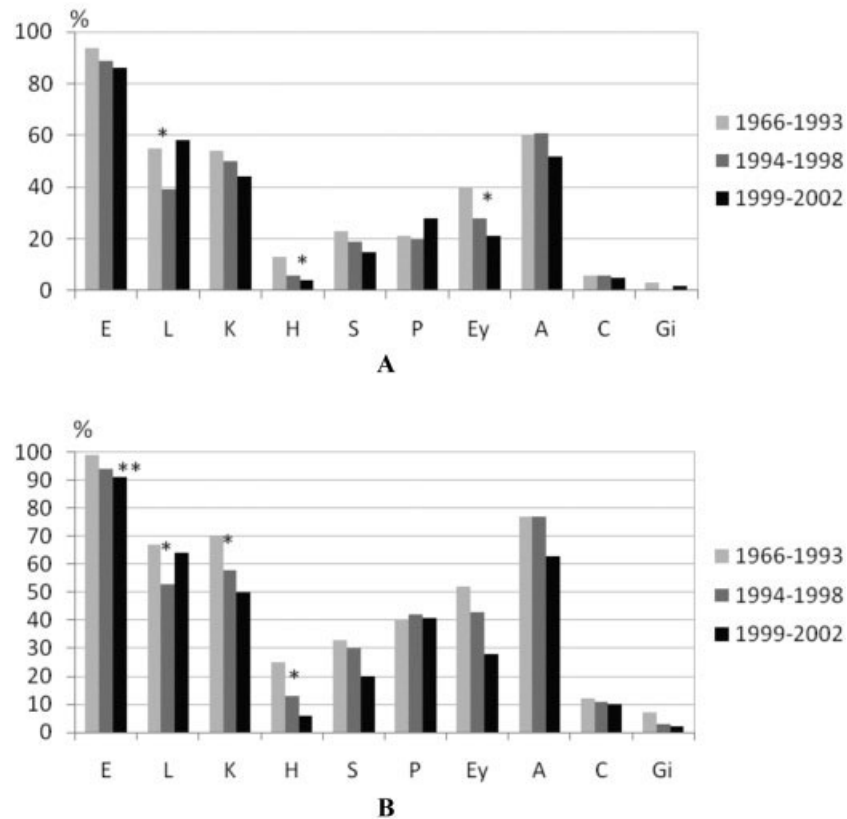


Figure 1. A, Percentage of organ manifestations at diagnosis in cohort 1 (diagnosed in 1966–1993), cohort 2 (diagnosed in 1994–1998), and cohort 3 (diagnosed in 1999–2002). The letters denote organ involvement: E = ear, nose, throat; L = lung; K = kidney; H = heart; S = skin; P = peripheral nervous system; Ey = eye; A = arthralgia/arthritis; C = central nervous system; Gi = gastrointestinal tract. In cohorts 1, 2, and 3, 51 of 155 patients (32.9%), 30 of 123 patients (24.4%), and 57 of 174 patients (32.8%), respectively, presented with impaired kidney function at diagnosis (creatinine clearance <70 ml/minute). In cohorts 1, 2, and 3, 8 patients (5.2%), 1 patient (0.8%), and 7 patients (4.2%), respectively, were dependent upon dialysis. **B,** Percentage of organ manifestations over the whole course of follow-up. In cohorts 1, 2, and 3, 108 patients (69.7%), 71 patients (57.8%), and 84 patients (50.3%), respectively, had kidney involvement over the whole course of follow-up, of whom 16 patients (14.81%), 5 patients (7.0%), and 2 patients (2.4%), respectively, were dependent upon dialysis at the end of follow-up. * = $P \leq 0.05$; ** = $P < 0.01$, cohort 1 versus cohort 2. No comparison was done between cohort 1 and cohort 3 or between cohort 2 and cohort 3.

Symptoms of disease manifestations at disease onset persisting for >3 months before diagnosis. At disease onset, ear, nose, throat (ENT) symptoms and arthralgia/arthritis appeared most frequently; however, these declined over time (75.5% of patients in cohort 1 had ENT symptoms compared with 49.6% of patients in cohort 2 and 53.3% of patients in cohort 3 [$P < 0.001$ for cohort 1 versus cohort 2]; 43.2% of patients in cohort 1 had arthralgia/arthritis compared with 19.5% of patients in cohort 2 and 16.2% of patients in cohort 3 [$P < 0.001$ for cohort 1 versus cohort 2]). Moreover, there was a significant decline of symptoms related to organ mani-

festations of the lung and kidney (25.8% of patients in cohort 1 had lung symptoms compared with 4.8% of patients in cohort 2 and 4.9% of patients in cohort 3 [$P < 0.001$ for cohort 1 versus cohort 2]; 14.2% of patients in cohort 1 had symptoms related to kidney disease compared with 0.8% of patients in cohort 2 and 0.6% of patients in cohort 3 [$P < 0.001$ for cohort 1 versus cohort 2]).

Organ manifestations and extent of disease at diagnosis according to age and sex. Only the frequency of lung, heart, and eye involvement changed significantly over time (Figure 1A). The median DEI at diagnosis

Table 2. Therapy regimen and outcomes in the 3 cohorts*

	Cohort 1, 1966–1993 (n = 155)	Cohort 2, 1994–1998 (n = 123)	Cohort 3, 1999–2002 (n = 167)	P†
Therapy regimen				
CYC	142 (91.6)	110 (89.4)	142 (85.0)	0.154
Cumulative dose, median (range) gm	67 (0–378)	36 (0–200)	24 (0–136)	<0.001‡
MTX, induction	8 (5.2)	32 (26)	33 (19.8)	<0.001
MTX, maintenance	37 (23.9)	63 (51.2)	71 (42.5)	<0.001
AZA, maintenance	16 (10.3)	51 (41.5)	50 (29.9)	<0.001
LEF, maintenance	1 (0.6)	35 (28.5)	47 (28.1)	<0.001
TNF antagonists	0 (0.0)	5 (4.1)	26 (15.6)	<0.001
Rituximab	0 (0.0)	1 (0.8)	6 (3.6)	0.026
Outcome				
Complete remission	83 (53.5)	86 (69.9)	123 (73.7)	<0.001§
Worsening	0 (0.0)	1 (0.8)	0 (0.0)	–
“Response” (stabilization/improvement)	72 (46.5)	36 (29.3)	44 (26.3)	–
Relapse	99 (63.9)	63 (51.2)	59 (35.3)	0.028‡
Relapse in those with >5 years of followup	86/112 (76.8)	59/102 (57.8)	20/40 (50)	–
Malignancy	8 (5.2)	2 (1.6)	8 (4.8)	0.233
MDS	11 (7.1)	12 (9.8)	7 (4.2)	0.171
CYC-induced cystitis	17 (11.0)	13 (10.6)	10 (6.0)	0.228
Infections	41 (26)	31 (25.2)	33 (19.8)	0.326

* Except where indicated otherwise, values are the number (%) of patients. CYC = cyclophosphamide; MTX = methotrexate; AZA = azathioprine; LEF = leflunomide; TNF = tumor necrosis factor; MDS = myelodysplastic syndrome.

† Cohort 1 (diagnosed in 1966–1993) versus cohort 3 (diagnosed in 1999–2002).

‡ Cohort 1 versus cohort 2 (diagnosed in 1994–1998).

§ Versus “response” (stabilization/improvement).

decreased from 9 in cohort 1 to 7 in cohort 3 (Table 1). In cohorts 1, 2, and 3, 83 of 155 patients (54%), 61 of 123 patients (50%), and 74 of 167 patients (44%), respectively, presented with renal involvement (with or without renal impairment) (see Figure 1A). When kidney involvement was stratified according to sex, males presented with kidney involvement more frequently than females (57.8% versus 40.1%; $P < 0.001$). The median DEI at diagnosis and over the whole disease course was higher in males (at diagnosis, 9 [range 2–17]; over the whole disease course, 11 [range 2–17]) than in females (at diagnosis, 7 [range 2–9]; over the whole disease course, 9 [range 2–19]).

When we stratified the sexes into 3 different age groups (group 1, median age 31.7 years [n = 148]; group 2, median age 51.8 years [n = 149]; group 3, median age 65.1 years [n = 148]), young males presented significantly more often than young females with kidney manifestations at diagnosis (54.4% versus 33.8%; $P = 0.011$) and had a higher mean DEI at diagnosis (7 [range 2–19] versus 5 [range 2–19]; $P = 0.019$) and over the whole course of followup (11 [range 2–17] versus 9 [range 2–19]; $P = 0.001$). The median time to diagnosis after the occurrence of first symptoms was 6 months (range 0–250 months) for young males and 11 months (range 0–195 months) for young females ($P = 0.47$).

In the group of middle-aged patients (67 females

and 82 males), there was no significant difference in the percentage of patients with kidney involvement (56.1% of males versus 40.3% of females; $P = 0.055$) or in the percentage of patients presenting with impaired renal function (30.5% of males versus 25.4% of females; $P = 0.124$). However, the median DEI at diagnosis (9 [range

Table 3. Results for overall mortality described by SMR with respect to all patients and cohorts, according to year of diagnosis*

	Sample size	Deaths	SMR (95% CI)
All cohorts			
Males	223	30	1.8 (1.22–2.58)
Females	222	13	1.23 (0.66–2.11)
All	445	43	1.58 (1.14–2.13)
Cohort 1 (1966–1993)			
Males	76	12	2.0 (1.03–3.49)
Females	79	10	2.34 (1.12–4.31)
All	155	22	2.1 (1.34–3.25)
Cohort 2 (1994–1998)			
Males	62	10	1.7 (0.81–3.12)
Females	61	3	0.93 (0.19–2.73)
All	123	13	1.41 (0.75–2.42)
Cohort 3 (1999–2002)			
Males	85	8	1.7 (0.73–3.34)
Females†	82	0	–
All	167	8	1.03 (0.44–2.03)

* SMR = standardized mortality ratio; 95% CI = 95% confidence interval.

† No deaths occurred during the time of observation.

2–17] versus 7 [range 2–13]; $P = 0.031$) and over the whole course of followup (11 [range 2–17] versus 9 [range 2–15]; $P = 0.021$) was higher in males (data not shown). In elderly patients (75 females and 73 males), renal manifestations (63% versus 46.7%; $P = 0.046$) and impaired kidney function at diagnosis (50.7% versus 30.7%; $P = 0.045$) were found significantly more often in males than in females; however, the difference was not as significant as that in the group of young patients. Furthermore, the median DEI at diagnosis was higher in elderly males (9 [range 2–17] versus 7 [range 2–15]; $P = 0.011$), but this difference was not maintained over the whole course of disease (9 [range 2–17] versus 9 [range 1–17]; $P = 0.233$).

Organ manifestations over the whole course of followup. For organ manifestations over the whole course of followup, only cohorts 1 and 2 were compared, since they had equal intervals of followup. The frequency of ENT manifestations declined significantly (from 99.4% to 93.0%; $P = 0.006$). There were significant declines in frequency of involvement of the kidney (from 69.7% to 57.8%; $P = 0.032$), lung (from 66.5% to 52.8%; $P = 0.021$), and heart (from 25.2% to 13%; $P = 0.011$), whereas the frequency of other organ manifestations did not change significantly (Figure 1B). The median DEI over the whole course of followup declined from 11 in cohort 1 to 9 in cohort 3 ($P = 0.013$ for cohort 1 versus cohort 2) (Table 1). The frequency of end-stage renal disease (ESRD) at the end of followup declined from 10.3% in cohort 1 to 4.1% in cohort 2. In cohort 3, 1.2% of patients were dependent upon dialysis at the end of followup.

Therapy strategies and treatment-related morbidity. More than 80% of patients required CYC during followup. The proportion of patients receiving pulse CYC increased from 4.5% in cohort 1 to 30% in cohort 2. The cumulative CYC dose per patient was reduced significantly from 67 gm in cohort 1 to 36 gm in cohort 2 and to 24 gm in cohort 3 ($P < 0.001$ for cohort 1 versus cohort 2); however, followup was shorter in the last cohort. Likewise, CYC-related side effects such as CYC-induced cystitis and myelodysplastic syndrome as well as infections declined; however, these changes were not significant (Table 2). In cohorts 1, 2, and 3, *P jiroveci* pneumonia occurred in 1, 0, and 3 patients, respectively. Mortality due to WG and immunosuppressive therapy declined from 86.4% in cohort 1 to 76.9% in cohort 2 ($P = 0.008$) and to 50% in cohort 3. The changes in therapy procedures and treatment-related morbidity are shown in Table 2.

Table 4. Results for overall mortality described by SMR with respect to age groups of patients at the time of diagnosis*

	Sample size	Deaths	SMR (95% CI)
Age group 1			
Males	68	9	8.87 (4.05–16.8)
Females†	80	0	–
All	148	9	5.77 (2.6–10.95)
Age group 2			
Males	82	9	1.74 (0.80–3.31)
Females	67	4	2.36 (0.63–6.03)
All	149	13	1.90 (1.01–3.24)
Age group 3			
Males	73	12	1.15 (0.59–2.01)
Females	75	9	1.08 (0.49–2.05)
All	148	21	1.12 (0.69–1.71)

* Age group 1 had a median age of 31.7 years (range 12.6–44.4 years), age group 2 had a median age of 51.8 years (range 44.7–59.3 years), and age group 3 had a median age of 65.1 years (range 59.6–85.4 years). See Table 3 for definitions.

† No deaths occurred during the time of observation.

Remission, “response” (stabilization or improvement), and relapse (Table 2). The frequency of complete remission increased from 53.5% in cohort 1 to 73.7% in cohort 3, leading to a reduction from 46.5% to 26.3% in the percentage of patients achieving a “response” ($P < 0.001$ for complete remission versus “response” [stabilization/improvement]). Relapse rates declined from 63.9% in cohort 1 to 51.2% in cohort 2, with followup over 7 years ($P = 0.028$). In cohort 3, the relapse rate decreased further to 35.3%, yet the followup period was shorter (4 years).

Age- and sex-associated deaths and SMR. Mortality declined steadily, including deaths related to WG or therapy (Table 3). Taking all 3 cohorts together, there was a significantly elevated SMR of 1.58 (95% CI 1.14–2.134), which was due to an increased SMR in males of 1.8 (95% CI 1.22–2.58) rather than the SMR of 1.23 (95% CI 0.66–2.11) in females. Cohort 1 showed an increased SMR of 2.1 (95% CI 1.34–3.25), whereas a significantly elevated SMR could not be found in cohort 2 (SMR 1.41 [95% CI 0.75–2.42]) or cohort 3 (SMR 1.03 [95% CI 0.44–2.03]) (Table 3). In cohorts 2 and 3, the SMR in males was still increased (to 1.7 [95% CI 0.81–3.12] in cohort 2 and to 1.7 [95% CI 0.73–3.34] in cohort 3), and deaths were more frequent in males than in females (10 versus 3 in cohort 2 and 8 versus 0 in cohort 3). A stratification according to age and sex (Table 4) yielded a significantly elevated SMR of 5.77 (95% CI 2.6–10.95) for young patients, which was due to an elevated SMR of 8.87 (95% CI 4.05–16.8) in young males (there were no deaths in young females). There was no increased SMR in the groups of middle-aged and

elderly patients (SMR 1.9 [95% CI 1.01–3.24] and SMR 1.12 [95% CI 0.69–1.71], respectively). Mortality was significantly lower in patients who received high cumulative doses of CYC (mortality hazard ratio for ≤ 20 gm, 3.01 [95% CI 1.24–6.77]; for >20 gm to 50 gm, 1.05 [95% CI 0.45–2.44]; for >50 gm, 1).

Cancer incidence and cancer mortality. Eighteen malignancies were documented in 445 patients, of which 6 led to death. All patients dying of cancer were male. One malignancy of the lung, 1 of the colon, 1 each of the uterus, prostate, and testes, 1 leiomyosarcoma of the lung, 3 nonmelanotic skin cancers, 1 melanoma of the uvea, 4 bladder carcinomas, and 1 adenocarcinoma of unknown primary origin accounted for 15 solid malignancies. Three patients had leukemia/lymphoma. In the 3 cohorts together, there was neither an increased incidence of cancer (SIR in all patients 0.82 [95% CI 0.45–1.38], SIR in males 1.12 [95% CI 0.56–2.01], SIR in females 0.41 [95% CI 0.08–1.21]) nor increased cancer mortality (SMR in all patients 0.65 [95% CI 0.24–1.43], SMR in males 1.10 [95% CI 0.4–2.4], no deaths in females) compared with the general population.

DISCUSSION

Former outcome studies on WG delineated high mortality rates and treatment-related morbidity (2,27). In order to improve outcome, we started to apply and to improve disease stage- and disease activity-adapted therapy regimens continually since the 1980s, some of which were assessed later in EUVAS clinical trials and are part of standard care today, as recently reported in the EULAR recommendations (13). The implementation of a stage- and activity-adapted treatment is probably the main reason for a stepwise improvement in the outcomes of the 3 cohorts.

The presented findings of a declining mortality rate in WG over time are consistent with recent population-based studies by Stratta et al, who demonstrated that survival in patients with various vasculitides approached that of the general population after 1993, mainly in women age <60 years (8), and Eriksson et al, who showed an improved 5-year survival rate when comparing 2 cohorts of patients with WG/MPA diagnosed before and after 1996 (SMRs of 2.5 and 1.6, respectively) (7). We demonstrated that improvement of therapeutic procedures not only had a substantial effect on the reduction of therapy-related morbidity and mortality, but also led to a decline in relapse rates and an increase in rates of complete remission.

Remarkably, $\sim 80\%$ of patients in all cohorts of our study still required CYC for the induction of remis-

sion. However, the drastic reduction in the cumulative CYC dose found by Eriksson et al and Villa-Forte et al (7,28) was confirmed by the present study. Shorter periods of remission induction (3 months instead of 6 months) and increasing intravenous administration of CYC (from 4.5% of patients in cohort 1 to 30% of patients in cohort 2) account for a reduced cumulative CYC dose. CYC-sparing therapy regimens for remission induction, such as TMP/SMX or MTX (15,17–20), were already used in the 1980s; MTX was already used for remission induction in nearly one-third of cohort 2 patients with less severe disease and in nearly half of the patients in all cohorts during the disease course.

The decline in relapse rates (from 63.9% to 51.2% and 35.3%) is associated with the implementation of a regular maintenance therapy that was introduced in the 1990s (at the beginning of followup of cohort 2). MTX was the main medication used for remission maintenance for approximately half of all patients in cohort 2, when a maintenance therapy was applied at all. Then AZA and LEF were increasingly administered due to evidence from new studies (9,13,29). Furthermore, the decline in relapse rates may also be related to the retaining of low-dose prednisone (3–5 mg/day) since the end of the 1990s.

Interestingly, in spite of shortened remission induction with CYC and lower cumulative CYC doses, the rates of complete remission also increased (from 53.5% to 69.9% and 73.7%). The rate of full remission in cohort 3 is similar to that in other studies of data acquired during the same time period (7,8). Contrary to the findings in the present study, Eriksson et al (7) found no decrease in relapse rates in a cohort diagnosed before and after 1996, although relapse rates were similar to those in our study ($\sim 40\%$, followup periods of 18 years and 9 years, respectively).

Apart from the disease itself, therapy-related side effects, such as infections, hemorrhagic cystitis, and malignancy, represent a major cause of death in WG (3,5,27). We found a lower rate of infections in cohorts 1, 2, and 3 (14.2%, 25.2%, and 19.8%, respectively) compared with that in other studies (46% serious infections and 32% nonserious infections [5,27]), and our rate of infections remained relatively stable over time, which may have resulted from the practice of early and stringent GC reduction. We found a low rate of *P jiroveci* pneumonia in all cohorts, even before the introduction of prophylaxis in 2000; however, in spite of prophylaxis, we could not totally prevent the occurrence of *P jiroveci* pneumonia. The administration of mesna to all patients receiving CYC may account for the low rate of hemorrhagic cystitis (6–11%) in our cohorts compared with

that in others (30–34). An increased incidence of malignancies and mortality from malignancies in WG, as suggested by previous reports (6,32–36), was not found in the present study, which may also be partly explained by the strict use of mesna to avoid bladder cancer. However, the average followup period in our study was substantially shorter than the followup periods in other cohorts, and our data should be interpreted with caution.

Another reason for an improved outcome may be an increased awareness of ANCA-associated vasculitides and their manifestations. Typical symptoms of WG due to lung and kidney manifestations were recognized earlier and diagnosed within 3 months in cohort 3. Furthermore, the interval from first symptoms to diagnosis declined from 8 months in cohort 1 to 4 months in cohort 3, which resulted in a reduced extent of disease at diagnosis. With regard to organ manifestations at diagnosis, the present study showed frequencies of organ involvement similar to those in the 2 population-based studies from Scandinavia (37,38) and confirmed the findings of Takala et al (38) regarding (nearly) unchanged organ manifestations at diagnosis and a rise in mean age at diagnosis. Furthermore, a declining interval from occurrence of symptoms to diagnosis has also been found by Eriksson et al (7) and Takala et al (38).

Third, a reduction in ESRD, which has been shown to be associated with increased mortality in numerous studies (1), may contribute to a decline in mortality, which is certainly a consequence of earlier diagnosis and therapy, improved care, and increased awareness. In general, renal outcome and mortality related to renal disease are difficult to compare between studies due to heterogeneous study populations (patients with WG and/or MPA) and to a selection bias regarding patients with (severe) renal involvement in studies carried out by nephrology units. We found a reduction in renal manifestations at diagnosis and over time as well as a reduction in ESRD at the end of followup in spite of similar rates of ESRD at diagnosis (in cohorts 1 and 3), although data from cohort 3 need to be interpreted with caution since the followup of this cohort was shorter. The trend toward a decline in ESRD in a cohort of patients with WG and MPA diagnosed before and after 1996 was confirmed by Eriksson et al (7). The reduction in renal manifestations and the decline in ESRD are probably related to earlier diagnosis and earlier introduction of therapy. Fourth, a standardized patient education program introduced in 1994 may also have played a part in improved outcome, since preliminary data demonstrated an increase in patients' knowledge regarding the disease and its therapy after

standardized training (21), even if we still lack formal proof of an improved outcome for educated vasculitis patients.

Young patients still displayed a considerably elevated SMR (5.77), which was exclusively due to deaths of male patients, probably as a consequence of a higher frequency of kidney involvement (including impaired renal function) at diagnosis and a higher DEI at diagnosis than that in young females. Interestingly, this was not associated with a delayed diagnosis of WG in young males.

The strength of this study lies in its standardized, interdisciplinary patient care and diagnostic and stage- and activity-adapted therapeutic procedures according to evidence and consensus of experts, including standardized patient education. Since this study was carried out at a rheumatology unit, disease manifestations and outcome are reflected without the selection bias of a nephrology unit. A weakness of the study is that our rheumatology center represents, at least in part, a tertiary referral center for patients who do not live in the catchment area. We do see patients with severe disease from the catchment area, but we also treat patients referred from far away who may have received treatment elsewhere during episodes of severe disease activity. Since patients were recruited not only from the catchment area, this study does not represent a true population-based study. However, major findings of this study, such as a decline in SMR and a rise in age at first diagnosis, are in line with those of recent population-based studies (8,34).

In conclusion, this retrospective monocentric study provides evidence for a decline in mortality which is probably due to improved diagnostic and therapeutic procedures and increased awareness of WG, leading to earlier diagnosis, reduction in relapse rates, and lower cumulative CYC dose with fewer deaths related to therapy. CYC remains a mainstay of therapy, and relapse is still a major issue in WG.

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. Dr. Reinhold-Keller 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. Holle, Gross, Latza, Reinhold-Keller. **Acquisition of data.** Holle, Nölle, Ambrosch, Heller, Reinhold-Keller. **Analysis and interpretation of data.** Holle, Gross, Latza, Ambrosch, Heller, Fertmann, Reinhold-Keller.

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Clinical Images: Divergent patterns of joint remodeling following effective urate-lowering therapy in tophaceous gout



The patient, a 35-year-old man, presented with severe tophaceous gout and hyperuricemia (10.2 mg/dl), despite receiving combination treatment with allopurinol (300 mg daily) and benzbromarone (100 mg daily). He had a history of renal transplantation and was treated with cyclosporine; his serum creatinine level was 2.07 mg/dl. During a prolonged hospital admission in 2007 for treatment of an infected tophus affecting the calf, monthly administration of rasburicase (1) was initiated, leading to normalization of the serum urate levels (3.8–6.0 mg/dl) and a gradual reduction in tophus size. Baseline radiography showed large gouty erosions, particularly affecting the left middle finger proximal interphalangeal (PIP) joint and the right first metatarsophalangeal (MTP) joint (**arrows** in left panels of **A** and **B**). After 2 years of treatment with rasburicase, repeat radiography in 2009 showed some regression in the soft tissue masses and divergent patterns of joint remodeling at different sites, with collapse and telescoping of the left middle finger PIP joint, and new bone formation with ankylosis at the right first MTP joint (**arrows** in right panels of **A** and **B**). Osteoblast-mediated bone resorption and enhanced osteoclastogenesis have previously been implicated in the pathogenesis of bone erosion in chronic tophaceous gout (2,3). These images suggest that resorption of tophi may alter these cellular processes in contrasting ways, leading to different patterns of bone remodeling.

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