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ORIGINAL ARTICLE

Long-Term Survival of Patients With Wegener's Granulomatosis

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Prior to the use of corticosteroids and cytotoxic protocols, untreated patients with Wegener's granulomatosis (WG) had a 1-year mortality between 50 and 80%. The advent of treatment has improved the dismal prognosis. This mortality abstract quantitates the improved but still poor survival in treated patients with WG. Over a 12-year follow-up, males had a mortality ratio of 255% and an excess death rate of 25. For females over a 15-year follow-up, the mortality ratio was 455% with an excess death rate of 32. In both sexes, mortality was highest in the early intervals.

AUTHOR'S SUBJECTS

Between June 1982 and December 1987, the authors collected data on 85 patients with WG from 25 rheumatology centers in the United States, Canada, and Mexico. Some participants were diagnosed prior to being enrolled in the study. The diagnosis of WG was based on criteria developed by the American College of Rheumatology and was uniform through all participating centers. The criteria used to classify WG were

- nasal or oral inflammation
- abnormal chest x-ray
- microhematuria or red cell casts in urine sediment
- granulomatous inflammation on biopsy (hemoptysis was used as a surrogate if biopsy data was unavailable).

The presence of 2 or more of the 4 criteria had a sensitivity of 88% and specificity of 92% for classifying a patient as having WG. The author's noted no apparent misclassification of the original disease diagnosis of WG.

Of the original 85 entrants (54 male, 31 female), 77, or 90.6% (48 male, 29 female), were available for review on June 30, 1993. Twenty-eight deaths were recorded (18 male, 10 fe-

Table 1. Expected Mortality of Males From Author's General Population

Year	P'	p'	q'	$\check{p}'$	$\check{q}'$
1	.990	.990	.010	—	—
2	.971	.981	.019	—	—
3	.951	.979	.021	—	—
4	.931	.979	.021	—	—
5	.922	.990	.010	—	—
1–5	.922	.922	—	.984	.016
6–10	.863	.936	—	.987	.013
11–12	.824	.955	—	.977	.023
1–12	.824	.824	—	.984	.016

Table 2. Observed Mortality of Males With Wegener's Granulomatosis

Year	P	p	q	$\check{p}$	$\check{q}$
1	.833	.833	.167	—	—
2	.833	1.0	0	—	—
3	.755	.906	.094	—	—
4	.706	.935	.065	—	—
5	.667	.945	.055	—	—
1–5	.667	.667	—	.922	.078
6–10	.608	.912	—	.982	.018
11–12	.608	1.0	—	1.0	0
1–12	.608	.608	—	.959	.041

male). Mean follow-up for the cohort was 7.1 years.

The authors gave no mean or median ages for the participants.

AUTHOR'S STATISTICAL METHODS

Patients known to be alive at the end of study on June 30, 1993, were censored as of that date. Time to death for patients lost to follow-up was censored at the date they were considered lost to follow-up. Survival curves were constructed for the general population and matched to WG cases for year of entry, age at entry, sex, race, and length of follow-up.

Expected survival probabilities for the general population were calculated on the basis of probabilities published by the National Center for Health Statistics in the United States and Statistics Canada. The 2 patients entered by the center in Mexico were lost to follow-up. Separate Kaplan-Meier survival curves were constructed for all patients and for males and females separately.

AUTHOR'S RESULTS

The overall mortality of WG greatly exceeded that of Canadian and United States general populations. The standardized mortality ratios for females were higher than for males but did not reach statistical significance ($P = 0.068$, two-sided t test). Factors associated with mortality included

- age at disease onset (younger worse)
- sex (female worse)
- duration (longer worse).

Diagnostic variables of increased mortality were an abnormal chest x-ray and granuloma formation on biopsy when entered with age at disease onset.

Three disease categories were compared: (1) upper respiratory tract and cranial structures including sinuses and / or nose and / or ears and / or eye and / or subglotic stenosis; (2) lower respiratory tract disease including pulmonary infiltrates, nodules, and hemoptysis; and (3) systemic disease with multiorgan involvement. There were 56 patients with renal disease, 41 with pulmonary disease, 24 with central nervous system disease, 15 with gastrointestinal disease, and 11 with cardiac involvement. Due to multisystem disease, the total exceeds the original number of entrants. Survival among the 3 categories was not significantly different. Patients in all 3 categories were at increased risk of death. Renal and pulmonary involvement were the most common organ-related causes of death. The most common overall cause of death was infection, likely secondary to immunosuppressive medications.

PATIENT TREATMENT

Eighty-one of the 85 patients received corticosteroids. Fifty-four percent received cytotoxic therapy, usually cyclophosphamide or

Table 3. Comparative Mortality of Males With Wegener's Granulomatosis

	Mortality Ratio		Excess Death Rate	
Year	Interval (%) $(100q_i/q'_i)$	Annual Geometric Average (%) $100\ \breve{q}_i/\breve{q}_i'$	Interval $1000\ (q_i - q_i')$	Annual Geometric Average $1000\ (\breve{q}_i - \breve{q}_i')$
1	1670	—	157	—
2	0	—	0	—
3	450	—	73	—
4	310	—	44	—
5	550	—	45	—
1–5	—	490	—	62
6–10	—	140	—	5
11–12	—	0	—	0
1–12	—	255	—	25

Table 4. Expected Mortality of Females From Author's General Population

Year	P'	p'	q'	$\breve{p}'$	$\breve{q}'$
1	.992	.992	.008	—	—
2	.983	.991	.009	—	—
3	.975	.992	.008	—	—
4	.967	.992	.008	—	—
5	.958	.991	.009	—	—
1–5	.958	.958	—	.991	.009
6–10	.925	.966	—	.993	.007
11–15	.875	.946	—	.989	.011
0–15	.875	.875	—	.991	.009

Table 5. Observed Mortality of Females With Wegener's Granulomatosis

Year	P	p	q	$\breve{p}$	$\breve{q}$
1	.958	.958	.042	—	—
2	.892	.931	.069	—	—
3	.858	.962	.038	—	—
4	.858	1.0	0	—	—
5	.825	.962	.038	—	—
1–5	.825	.825	—	.962	.038
6–10	.667	.808	—	.958	.042
11–15	.533	.799	—	.956	.044
0–15	.533	.533	—	.959	.041

Table 6. Comparative Mortality of Females With Wegener's Granulomatosis

	Mortality Ratio		Excess Death Rates	
Year	Interval (%) $(100q_i/q'_i$	Annual Geometric Average (%) $(100\breve{q}_i/\breve{q}_i')$	Interval $1000(q_i - q_i')$	Annual Geometric Average $1000(\breve{q}_i - \breve{q}_i')$
1	525	—	34	—
2	770	—	60	—
3	475	—	30	—
4	0	—	0	—
5	420	—	29	—
1–5	—	420	—	29
6–10	—	600	—	35
11–15	—	400	—	33
1–15	—	455	—	32

azathioprine. At the time of follow-up, 77% of the survivors had inactive disease. Fifty-three of 77 survivors (69%) remained on corticosteroids and/or cytotoxic therapy during the study. Twenty-three percent remained on treatment 5½ years after the original study closed.

MORTALITY STATISTICAL ANALYSIS

The source publication contained 3 survival probability curves, including survival of all patients and males and females separately. Each curve illustrated the survival probability of patients with WG compared with the general population. The survival curves were enlarged 120% to facilitate measurement. Using calipers, the height of each 1-year interval was measured. The method of proportions was used to convert these measurements into percent survival. Reproduction and magnification of the survival curves can introduce distortions that affect calculations. Expected survival of females revealed minimal variation in yearly interval expected rates. For males, considerable variation was noted at the end of years 1 and 5. This was likely due to distortions in reproduction resulting in impreciseness of measuring points on the curves. Male expected rates were not graduated. This can affect the yearly intervals but has little impact on overall long-term results and conclusions. Cumulative and interval survivals were calculated to 3 decimal places. For expected and observed populations, cumulative survival (*P*), interval survival (*p*), and interval mortality (*q*) were determined for each successive 1-year interval. Annual geometric average mortality ($\check{q}$) and survival rates ($\check{p}$) were calculated for the cumulative 12-year interval for males and 15-year interval for females. Cumulative survivals were also calculated for durations 1–5, 6–10, and 11–12 years in males and 1–5, 6–10, and 11–15 years in females. Mortality ratio (MR) is the ratio of the observed interval mortality rate to the expected interval mortality rate. Ratios 0–199% are rounded to the nearest 1% and 200% and upward to the nearest 5%. Excess death rate (EDR) is the number of excess deaths per thousand individuals exposed to the risk of death per year. It is the difference between observed and expected deaths in an interval. EDR is rounded to the nearest whole number.

DISCUSSION

Survival in both males and females with WG is diminished in terms of elevated mortality ratios and excess death rates. Males over the 12-year observation had a mortality ratio of 255% and an excess death rate of 25. Survival was poorest in the first 5-year interval, with the mortality ratio elevated to 490% and an excess death rate of 62. In the next 5-year interval, these diminished to 140% and 5, respectively. No deaths were reported in years 11 and 12.

Experience for females was more adverse. Over the 15-year duration, the mortality ratio was 455% and excess death rate was 32. Five-year intervals 1–5 and 11–15 were similar, with mortality ratios about 400% and excess death rates about 30. The middle 5-year interval (6–10) revealed a mortality ratio of 600% and excess death rate of 35.

This analysis has several confounding variables. Referral bias must be considered in interpreting this data. All patients studied were referred to rheumatology centers and thus had more severe disease. The very high early mortality likely reflects the most ill patients being referred due to treatment failure in their primary care settings. The study enrolled patients from 1982 to 1987 and follow-up ended in 1993. With the development of newer medications and more aggressive treatment protocols, I would anticipate improved survival.

Over the duration of the study, 8 patients (9%) were lost to follow-up. Their effect if included in the final evaluation is unknown. Their baseline characteristics were the same as for those completing the study. Thus, their exclusion does not likely alter the results. Expected population mortality was determined from United States and Canadian general

populations. Insurance mortality is better than that of general populations. For underwriting, one should expect higher mortality ratios and excess death rates since expected mortality is lower. The overall effect of the admixture of general versus insurance populations, referral bias, and newer treatment is unknown. The former will make underwriting mortality more adverse. The latter two would likely make underwriting mortality less adverse.