SURVIVAL FOLLOWING THE ONSET OF SCLERODERMA: RESULTS FROM A RETROSPECTIVE INCEPTION COHORT STUDY OF THE UK PATIENT POPULATION

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SUMMARY

Scleroderma is a multisystem disease which in many populations is reported to have a substantially reduced survival. One problem with many of the published studies is the inclusion of patients with differing lengths of disease at baseline, with the possibility of left censorship bias. The aim was to determine the survival and its predictors in a cohort of scleroderma patients with new onset of disease. All 283 new patients referred to one of the authors (CMB) who had a reported disease onset after 1 January 1982 were studied. Detailed clinical and laboratory information at baseline and at 1 yr were extracted from the structured records. Vital status as at 1 December 1993 was determined using the UK’s NHS Central Register. Expected numbers of deaths were obtained by applying local age and sex all-cause mortality rates. In total, there were 1871 person-years of follow-up with crude mortality rates of 3.9 and 2.6%/year, respectively, in males and females. The mortality rate remained approximately constant over the first 10 yr of follow-up. In comparison with expected survival, based on the age distribution of the cohort, there was an overall 4-fold increased mortality rate in this group which was higher in females (standardized mortality ratio (SMR) 4.6, 95% CI 3.2-6.2) than in males (SMR 3.2, 95% CI 1.8-5.0). Analysis of cause-specific mortality showed that 79% of the excess deaths were scleroderma related, but this proportion was substantially lower in males than in females (67% vs 83.9%). These data confirm the increased mortality rate associated with scleroderma, but these rates are lower than those reported from other centres. Females have a higher age-adjusted mortality which is reflected in the different pattern of mortality between the sexes.

KEY WORDS: Scleroderma, Mortality, Survival.

Scleroderma is a multisystem disorder whose course can vary from being a relatively benign condition involving the skin and peripheral vasculature to a rapidly progressive disease affecting internal organs with a consequent high mortality risk [1].

There have been a number of studies examining survival following presentation with scleroderma, with 5 yr survival rates varying between 34 and 73% [2]. In a further large multicentre study from the USA [3], 6 yr survival was ~57%, confirming the high mortality in this disorder. By contrast, a recent study from Canada showed a more optimistic view, with a 6 yr survival of 76% [4]. It also seems likely that patients with scleroderma do have an increased risk of unrelated deaths. In the US collaborative series, 42 out of the 131 deaths (32%) were said to be unrelated to scleroderma [3]. Similarly, in the Canadian series, only 27 of the 61 (44%) [4] were definitely related to the onset of the disease.

There are a number of problems in interpreting these reports. Firstly, given the rarity of the disease, most data come from centres with a specialist interest. Frequently, such patients are recruited well into the course of their disease and survival from presentation is subject to the problems of left censorship bias [5]. Insofar as those recruited into the cohort are not a full representative sample of all those who develop the disease. Secondly, it is difficult to interpret mortality rates in the absence of consideration of background population mortality. Scleroderma is a disease with a median age of onset of around 50 yr [6], and thus the age and sex distribution of the patient cohort will influence mortality experience given their different effects on background mortality risk. One recent Canadian study showed over a 4-fold increased mortality rate over an 11 yr period with no difference between males and females [7].

In this report, we review the mortality experience of a large cohort of patients referred to a single UK centre. We attempted to recruit a true inception cohort and determined survival following self-reported symptom onset rather than date of first attendance. The second objective was to estimate the increased mortality risk over and above the background population risk in both males and females, and also to determine how much of any excess mortality risk could be directly attributable to scleroderma per se and how much could be related to a heightened mortality risk from non-related causes.

PATIENTS AND METHODS

The patients recruited to the study were drawn from all patients referred to the scleroderma clinic service run by one of the authors (CMB) between 1982 and 1992. Patients were included in this analysis if their disease onset occurred after 1 January 1982, with disease onset defined as the self-reported date of first...
skin change. Patients who were first referred after 1982, but who had had a disease onset prior to this date, were excluded. All the patients included satisfied the preliminary ARA criteria for scleroderma [8]. Detailed clinical, laboratory and other relevant information was abstracted from the patients' records, much of which is held on a structured database. The patients were subdivided into limited and diffuse cutaneous forms using standard criteria [9].

The vital status (i.e. dead or alive) of each patient as at 31 December 1993 was determined. For many of these patients, this could be ascertained from review of their clinical records, i.e. the patient had definitely died prior to that date or was still attending the clinic. For the remainder, confirmatory information was obtained from the National Health Service Central Register (NHSCR) which is able to provide information on whether a subject is dead or alive, and if the former, the date of death. Copies of death certificates were obtained for all deceased patients.

The death certificates were inspected by two reviewers and the cause of death decided by consensus attributed to either scleroderma or a non-related cause. For the purposes of this analysis, scleroderma-related death was based on the underlying cause of death on the death certificate being due to a clinically coherent consequence of scleroderma or that scleroderma itself was mentioned as the actual underlying cause. Thus, any death attributed to pulmonary fibrosis was labelled as scleroderma related. Scleroderma-related deaths were further subdivided into groups based on the organ system primarily responsible; mainly lung, renal, heart, bowel and 'not otherwise specified'. The unrelated deaths were also subdivided into main groups of causes, these being ischaemic heart disease, cerebral vascular disease, respiratory infection, cancer, trauma and others.

Analysis

The age–sex-specific mortality rates from all causes were calculated. This was achieved by dividing the number of observed deaths over the 12 yr period (1982–1993 inclusive) by the number of person-years at risk in each sex group. Kaplan–Meier survival curves of the cohort were plotted and these were compared with the expected survival experience of the local general population. For this purpose, as the majority of the patients in the study were resident at first visit in the South East of England, the South East mortality rates published by the Office of Population Censuses & Surveys [10] were used. The number of observed and expected deaths in males and females was calculated (the expected being based on the age and sex distribution of the patients), and standardized mortality ratios (SMRs) together with their 95% confidence intervals derived. The number of excess deaths in both males and females was then calculated by subtracting the expected from the observed numbers of deaths. The excess deaths were then further subdivided into those that could be attributed and unattributed to scleroderma.

### RESULTS

In all, 283 patients were recruited to the study, 65 were male and 218 were female. The mean age at entry was 46 yr (s.d. 14 yr). Of these, 54% had limited cutaneous disease and 46% had diffuse cutaneous disease.

There were 55 deaths in total during this period, 17 in males and 38 in females. The main causes of death are shown in Table I. The predominant cause of scleroderma-related death was due to lung involvement and, not surprisingly, the major cause of unrelated death was ischaemic heart disease.

The crude mortality experience for the cohort is shown in Table II. There was an average annual mortality rate in the entire patient group of 3%/year and, as expected, given the higher background population mortality experience in males, the rate was higher in males than in females. When the causes of deaths were classified as being related or unrelated, it can be seen that most of the increased male mortality is due to the unrelated causes of death. The observed and expected survival curves for the patients are shown in Fig. 1. There were a total of 1871 person-years of follow-up, with a mean follow-up time of 6.6 yr. The 5 yr survival in the patient group was 87% compared with an expected rate of 98%. At 10 yr, the respective figures were 75 and 94%. Standardized mortality ratios are shown in Table III. For all causes of death, there was a 4-fold increased mortality and this was higher
in females than in males. In other words, the relative risk of dying for a female following the onset of scleroderma compared to her baseline population risk is higher than that for males. When data only from unrelated causes were examined, it can be seen as a 60% excess mortality. There is no difference in the SMR between males and females for unrelated causes of deaths. Based on these data, the numbers of excess deaths in both groups were calculated (Table IV). As can be seen, overall there were 42 excess deaths, 12 in males and 30 in females. One-fifth of the excess deaths could not be attributed to a scleroderma-related cause, but this proportion was higher in males (33%) than in females (17%).

DISCUSSION

These data confirm the substantially increased mortality risk associated with the onset of scleroderma in both males and females. By comparing these rates to the expected mortality in the underlying population, it has been demonstrated that the female increase is greater than that for males. This difference needs to be confirmed in other similarly designed studies. Our data, however, are very similar to the recently published Canadian study adopting a similar analytical approach. That study reported SMRs of 4.2 and 4.8 for males and females, respectively [7]. Others [11] have suggested that the prognosis is poorer amongst males, but after adjustment for the baseline population risk in this gender, males probably have a better outcome. Almost half of the scleroderma-related deaths were due to lung disease, in contrast to the multicentre American study where only 20% of deaths were due to this cause [3]. In that study, 40% of scleroderma-related deaths were of renal origin, compared to <10% in the current series. This might represent one or both of the following phenomena. First, that the American series was more heavily selected to those with serious disease.
Secondly, there is the strong possibility that the improvement in the treatment of hypertensive renal crisis in scleroderma by the use of ACE inhibitors has substantially improved the mortality outcome: the patients in the US series were recruited between 1973 and 1977, and in the current series the date of recruitment was \( \sim 10 \) yr later. By contrast, in the Canadian study, of the 27 related deaths almost 60% were due to pulmonary disease compared with approximately a quarter due to renal disease [4].

Some of the excess mortality cannot be directly attributed to scleroderma, although there are insufficient numbers to make a definitive statement as to which particular causes of unrelated death were increased. It was interesting to note that the excess mortality due to unrelated deaths accounted for perhaps 33% of all deaths in male patients. In a number of studies [12–14], an excess number of deaths in patients with scleroderma from all forms of cancer, particularly epithelial cancers, have been reported. In this series, only one death was due to cancer and indeed this proportion is substantially smaller than one would expect from the general population experience. It is clearly difficult to know why there should be such a disparity in the results and it thus seems an unlikely hypothesis that scleroderma protects against the development of cancer. Other studies have also shown a high proportion of deaths in patients with scleroderma unrelated to the disease. Indeed, in Barnett et al.’s series [15] of 177 patients, less than half the deaths were related to the disease.

There are clearly a number of methodological issues involved in interpreting and comparing the data between studies. In the current study, we attempted to exclude those people with a disease onset before January 1982, given the possibility that they might be a biased group, either representing those who had survived long enough to be included into the study or, conversely, those whose disease had remained so severe that they needed to have continued attendance. It is perhaps not surprising, therefore, that the survival rates quoted in the current study are apparently better than those of other published work [2–4]. For example, in the US collaborative study, entry occurred at \( \sim 6 \) yr after the appearance of first symptoms. It should be recognized, however, that scleroderma can be a most insidious disease and dating the onset of the disease, even by the patient, is subject to considerable error; though perhaps in biological terms, it is more important to try and estimate the date than use the somewhat arbitrary date of first attendance at clinic.

Virtually all survival studies that have been published have relied on patients attending specialist centres. It seems intuitively likely that such patients will represent the more severe end of the spectrum and patients with limited disease without internal organ involvement may be more likely to be managed in a general medical setting. Unfortunately, it is not a practical proposition to recruit a true population cohort of newly diagnosed scleroderma cases, but this selection factor must be borne in mind in interpreting the results of this and other studies.

There are always difficulties in ascribing deaths accurately, either to be related or unrelated to scleroderma. Some entries on the death certificates were easily categorized, e.g. cancer and ischaemic heart disease, but for other mentions on death certificates, such as bronchopneumonia, the allocation is more hazardous. For example, in those with severe underlying lung disease, it is likely that bronchopneumonia might be the immediate antecedent cause of death. If the link is not recognized by the physician caring for the patient in their final illness, misclassification of the actual cause of death may result. Further, recent work has suggested an association between scleroderma and large-vessel disease [16]. This suggests that some of the excess deaths from coronary artery disease might have been related to scleroderma. Data from rheumatoid arthritis [17] have shown the tremendous problems in using such data to allocate an accurate cause of death, although for a disease like scleroderma, particularly when major internal organ involvement is involved, it might be somewhat easier.

There have been very few other studies of mortality in scleroderma in UK cohorts. In one study of 67 subjects, followed up to 1970, there was a 73% 5 yr survival with a 50% survival at 10 yr [18]. By contrast, in another study of 84 patients, 10 yr survival was 74% [19]. In neither study is there any comment on the increase in mortality compared with general population expectations.

In summary, these data demonstrate a 4-fold increase in mortality among patients with scleroderma attending a specialist centre compared with background population rates, with the relative increase greater in females. Scleroderma-related lung disease is the most important cause of death in this group of patients. There is also a small, but important, increase in deaths from apparently unrelated causes with no obvious predilection for any specific cause. This increase in unrelated deaths is proportionately more important in males. We have not been able to verify, in this study, results from other groups showing an increase in cancer mortality.

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REFERENCES