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Could Accelerated Aging Explain the Excess Mortality in Seropositive Rheumatoid Arthritis Patients?

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Abstract

Objective—To determine whether the mortality pattern in seropositive RA patients is consistent with the concept of accelerated aging by comparing the observed mortality rates in RA to age accelerated mortality rates from the general population using statistical models.

Methods—A population-based inception cohort of seropositive RA patients (1987 ACR criteria) was assembled and followed for vital status until July 1, 2008. Expected mortality was obtained by applying the death rates of the general population to the age, sex and calendar year distribution of the RA population. Observed mortality was estimated using Kaplan-Meier methods. Acceleration factors were estimated for expected mortality using accelerated failure time models.

Results—A total of 755 seropositive RA patients (mean age of 55.6 years, 69% women) had a mean follow-up of 12.5 years during which 315 patients died. The expected median survival was age 82.4 years, whereas the median survival for the RA patients was age 76.7 years. The models suggest that, in terms of mortality rates, RA patients are effectively 2 years older at RA incidence, and thereafter age 11.4 effective years for each 10 years of calendar time.

Conclusion—The overall observed mortality experience of seropositive RA patients is consistent with the hypothesis of accelerated aging. The causes of accelerated aging in RA deserve further investigation.

Keywords

Rheumatoid arthritis; accelerated aging; mortality

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology affecting approximately 1% of the adult general population.(1) While it is known that rheumatoid arthritis (RA) patients, (especially seropositive RA patients) suffer from increased mortality, the mechanisms underlying this increase are unknown.(2) Inflammation and immune dysregulation are strongly implicated. Premature aging due to senescence of multiple systems, such as the immune, endocrine, cardiovascular, muscular and nervous systems, represents an attractive biological model that may, in part, explain the excess mortality observed in RA and other chronic diseases.

The aim of the current study was to determine whether the mortality pattern in seropositive RA patients is consistent with the concept of accelerated aging by comparing the observed mortality rates in RA to age accelerated mortality rates from the general population.

PATIENTS AND METHODS

The study population consisted of an inception cohort of all cases of seropositive RA first diagnosed between January 1, 1955 and January 1, 2008 age ≥ 18 years. Seronegative patients were not included in this study because, in our cohort, we did not observe increased mortality in this group when compared to the general population.(2) Cases before January 1, 1980 included only Rochester, MN residents, as previously described, whereas cases after January 1, 1980 included all Olmsted County residents(3). All cases fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA(4). Incidence date was defined as the first date of fulfillment of (four out of the seven) diagnostic criteria. All cases were followed longitudinally through their entire medical records until death or July 1, 2008. Using the resources of the Rochester Epidemiology Project(5), all patients (irrespective of residency status) were tracked nationally (using the National Death Index and other sources) to ascertain vital status.

To better understand the excess mortality in seropositive RA patients, the concept of accelerated aging was examined mathematically using accelerated failure time models. Accelerated failure time models have been infrequently used in clinical studies, though they are very common in the analysis of industrial reliability data.(6) The more familiar proportional hazards model assumes that risk factors increase the daily rate of events (or hazard), whereas the accelerated failure time models assume that risk factors change the time it takes to experience an event. In other words, the time to event accelerates, so the subjects 'age' more rapidly than their calendar age. A primary difference is that in the proportional hazards model, effects are instantaneous, whereas in the accelerated failure time model, damage accumulates over time. For example, insufficient oil for an automobile engine shaft causes the shaft to gradually and prematurely wear, resulting in shaft failure. The shaft failure can be seen as an instantaneous event, but is actually the result of accelerated wear or aging of the shaft caused by the risk factor of insufficient oil. In clinical research, the proportional hazards model has been very successful in acute settings, such as advanced cancer and early cardiac mortality, but its primacy in chronic diseases is far less certain. (7)

Under the model of 'accelerated aging', there are three different ways in which the aging of RA subjects might be affected. The first is extra years may have already accumulated at the time of RA incidence. This damage could have occurred as a slow accumulation or all at once (as a bolus), depending on the pathological mechanisms underlying the pre-clinical course of RA. The second is an acceleration of aging beginning at the time of RA incidence, e.g., each year of age after RA incidence is equivalent to 1.2 years effective aging without the disease. The third is a compound acceleration, where each year the acceleration is higher than the year before, analogous to compound interest. For example, the first year after RA incidence could be equivalent to 1.2 years effective aging while the 10th year after incidence could be 1.4 years effective aging.

Statistical Methods

Descriptive statistics (means, standard deviations, etc.) were used to summarize age at incidence date and length of follow-up. Observed mortality was estimated using Kaplan-Meier methods with age as the time-scale. Expected mortality was obtained by applying the death rates of the general population to the age, sex and calendar year distribution of the RA population.

The 3 parameters of interest (A, B and C) were estimated using maximum likelihood estimation techniques and the principles of accelerated failure time models.(6) In these models age was modeled as "effective age" = "actual age" + A + B*time + C/2 *time²,

where time is the time since RA incidence. Using this “effective age”, an “effective predicted mortality” was obtained for each subject from population mortality rates for individuals of that actual age and sex in the same calendar years. The models were fit using maximum likelihood, which attempts to minimize the differences between observed and predicted mortality at all time points (ages) simultaneously. The full model includes all 3 parameters: A is the amount of excess aging already present at RA incidence, B is the effective aging per year post RA incidence, and C is the increase in B by 10 years after RA incidence. Models including C without B, i.e. a quadratic term for time without a linear term, were not assessed. Models were compared to determine which parameters or combination of parameters best fit the excess mortality observed in the RA patients by using Chi-square tests to compare the likelihood of each of the nested models to the full model (containing all 3 parameters).

RESULTS

A total of 755 seropositive RA patients (mean age of 55.6 years, 69% women) had a mean follow-up of 12.5 years (total: 9428 person-years) during which 315 patients died. The expected median survival was age 82.4 years, whereas the estimated median survival was age 76.7 years for the RA patients (Figure 1).

Table 1 shows the results of fitting models for each of the parameters of accelerated aging (excess aging present at RA incidence [A], effective aging per year post RA incidence [B] and the compound acceleration post RA incidence [C]) individually and in combination. The full model (with all 3 parameters) reveals an excess aging of 2.4 years, an effective aging of 10.7 effective years for every 10 years, and a compound acceleration rate of 0.14 years every 10 years. This model demonstrates that the mortality experience of seropositive RA patients is similar to aging 2.4 additional years at RA incidence and subsequently aging 10.73 effective years during the first 10 years after RA incidence and 10.87 effective years during the second decade following RA incidence.

The model “A,B” without any compound acceleration is quite similar to the full model ($p=0.24$). It predicts seropositive RA patients age 2.0 additional years at RA incidence and an extra 1.4 years during each decade following RA incidence.

The models without excess aging present at RA incidence (models “B, C” and B alone) do not fit the data quite as well as the full model ($p=0.07$ and $p=0.05$, respectively). These models are similar to each other, predicting seropositive RA patients age at a constant and/or compounding acceleration with no excess aging at the time of RA incidence.

The model with only excess aging at RA incidence (A alone) was significantly worse than the full model ($p=0.006$). In other words, the assumption that seropositive RA patients have experienced excess aging at the time of RA incidence, but age normally thereafter is not consistent with the observed mortality experience of seropositive RA patients in our cohort.

These models were also examined for males and females separately, and for patients who developed seropositive RA at younger ages (age<55 years) and older ages separately. No differences were found in the estimates of accelerated aging in these various subsets (data not shown).

DISCUSSION

This study showed that the overall observed mortality experience of seropositive RA patients is consistent with the hypothesis of accelerated aging estimated using mathematical models. The best fitting models consistently showed effective aging of approximately 2

extra years at the time of RA incidence and additional aging of about 1 year for each 10 years of actual time thereafter. These models predict the aging of seropositive RA patients is influenced by both an excess aging that occurred sometime prior to RA incidence and an acceleration of aging, both of which are biologically plausible. The excess aging at RA incidence is consistent with the hypothesis that an inflammatory / immunological insult or injury precedes clinical presentation of RA, whereas the acceleration of aging is consistent with the concept of senescence of the immune or other subsystems of the body following the development of RA.

Aging processes involve changes in multiple subsystems, including immune and endocrine networks, among others.(8) Indeed, the hypothesis of accelerated aging is supported by a considerable body of literature on accelerated immune system aging, or immunosenescence, at a cellular level in RA.(9–16) Several studies on human T cells and in RA patients support this concept of cellular immunosenescence. For instance, in studies of human T cells, CD28-null T cells have been shown to emerge more rapidly with prolonged exposure to tumor necrosis factor alpha (TNF α), an inflammatory cytokine important in the disease phenotype of RA. (9) These CD28-null T cells are functionally active, long-lived oligoclonal lymphocytes with shortened telomeres, indicating extensive replication consistent with cells approaching the end stages of senescence. (10–13) Of interest is that telomere shortening, such as that seen in the CD28-null T cells of patients with RA, has been associated somewhat paradoxically with both defective immunocompetence (as seen in virus-specific T cells of patients with persistent infection) as well as susceptibility to autoimmune disease. (14) Critical telomere shortening could explain the sudden contraction of the T-cell repertoire that occurs between ages 65 and 75,(15) which also seems to correlate with the notion that aging is a risk factor for autoimmunity, as many autoimmune diseases do occur in the elderly and when the immune system is functionally declining. (16)

Simultaneous study of molecular components of senescence and statistics of mortality in RA could provide valuable insights into the clinical course of accelerated aging in RA and elucidating mechanisms that play key roles in the aging process. This was a clinical study and no data were available on molecular regulators and pathways previously implicated in in vitro and in vivo studies. The unique strengths of this study are the longitudinal follow-up of a large population-based inception cohort of patients with RA for up to 50 years, and the application of mathematical models rarely utilized in healthcare, although common in industrial reliability, to illustrate how mortality in patients with RA is consistent with the biological understanding of senescence. Study limitations include defining RA incidence based on fulfillment of ACR criteria, which does not accurately reflect the biological onset of the disease. While this is a standard approach, compelling evidence suggests biological changes, such as seropositivity, often occur years earlier than clinical manifestation of RA. Therefore, this study is unable to determine over what period of time prior to RA incidence the patients have accrued the additional aging present at the time of RA incidence. Our findings need to be replicated in other longitudinal RA cohorts to assess whether the aging parameters are consistent.

In conclusion, seropositive RA patients' mortality is consistent with accelerated aging of approximately 2 extra years at the time of RA incidence and about 1.4 extra years for each decade of actual time thereafter. Our study adds a unique dimension to the theory of immunosenescence by demonstrating, using mathematical models, that accelerated aging may explain the excess mortality in seropositive RA at the population level as well as at the cellular level. Our results support further scientific investigation into the underlying mechanisms of accelerated aging in RA and novel therapies for RA, e.g., targeting altered costimulatory pathways of senescent T cells in RA synovium and/or reconstitution of the T-

cell repertoire of senescent T cells. Such studies could also have broader implications regarding the mechanisms of aging in the general population.

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Figure 1. Overall survival of 755 seropositive RA patients vs. age. Observed, expected and fitted (using the full model) curves are shown.

Table 1
Comparison of different models of accelerated aging for seropositive rheumatoid arthritis patients

Model*	Description of model	Excess aging (in years) present at RA incidence (A)	Constant acceleration per 10 years (B*10)	Compound acceleration per 10 years (C)	Effective aging first 10 years after RA	Effective aging next 10 years after RA	p-value (vs. full model)
A, B, C (full)	Excess aging at RA incidence, constant and compound acceleration thereafter	2.4	10.73	0.14	2.4+10.73	10.87	reference
A, B	Excess aging at RA incidence and constant acceleration thereafter (no compound acceleration)	2.0	11.4	0	2.0+11.4	11.4	0.24
B, C	Constant and compound acceleration after RA incidence (no excess aging at RA incidence)	0	12.10	0.01	12.10	12.11	0.07
B	Constant acceleration after RA incidence only	0	11.8	0	11.8	11.8	0.05
A	Excess aging at RA incidence only	4.5	1	0	4.5+10	10	0.006
Null	No excess aging at RA incidence, no constant or compound acceleration thereafter	0	1	0	10	10	<0.001

* A is the amount of excess aging already present at RA incidence. B is a constant rate, i.e. the rate of effective aging does not change over time. C is the compound acceleration which represents the increase in B by 10 years after incidence, i.e. the rate of effective aging increases over time.