Influence of demographic and clinical factors on the mortality rate of a rheumatoid arthritis cohort: A 20-year survival study ☆

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ABSTRACT

Objectives: To describe the mortality rate (MR) and standardized MR (SMR) of an incident cohort of rheumatoid arthritis (RA) patients followed up for 20 years, and to analyze the influence on morality risk of different demographic and clinical variables, including radiographic joint damage.
Methods: Retrospective longitudinal study that included 2271 RA patients attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain), enrolled from January 1994 to February 2013 and followed up from RA diagnosis to patients' death or September 2013. Disability and disease activity were measured as the averaged value of the Heath Assessment Questionnaire and the erythrocyte sedimentation rate, respectively, of the first 2 years after RA diagnosis. Radiographic joint damage of hands and wrists was assessed with the Sharp/van der Heijde score. Indirect SMRs with a 95% of confidence interval (95% CI) were calculated. Cox bivariate and multivariate regression models were performed to assess risk factors for death.
Results: A total of 431 patients died (19%) during the observation time (18,482 person-years), resulting in a MR of 23 subjects per 1000 patient-years [95% CI: 21–26]. SMR was 1.89 (1.72–2.08). In the multivariate analysis, men, older age at diagnosis, the presence of rheumatoid factor, higher number of hospital admissions, greater disease activity, and greater radiographic joint damage were independently associated with greater mortality risk.
Conclusions: RA patients have an excess mortality compared with the general population. Radiological joint damage and early disease activity are independent mortality risk factors. A tighter control at early stages may be necessary to reduce mortality.

Introduction

Rheumatoid arthritis (RA) is a complex chronic inflammatory disease characterized by heterogeneous manifestations, progression, and outcome. This condition is associated with an increased mortality risk and a reduced life expectancy of about 3–10 years compared with the general population [1,2]. Although the management of RA has experienced a substantial improvement over the last 15 years, mortality rates (MR) have remained fairly constant throughout time [3].

Different sociodemographic and disease-related factors, such as older age, male gender, higher levels of surrogate markers of inflammation, and occurrence of extra-articular manifestations, have been associated with a higher mortality risk [4].

Several studies have analyzed the mortality risk factors in Caucasian population, mostly of northern population ancestry. However, only two previous studies have been published in Spanish population: Martínez et al. [5], with less than 200 patients enrolled from a tertiary center from Madrid, followed up for 9 years before the introduction of tight control and biological therapy, and in which mortality risk factors were not studied. Additionally, Carmona et al. [6] analyzed the effect of biological treatment in mortality using two cohorts of Spanish patients, one

treated with anti-TNF therapy (789 patients, followed up from 2001 to 2006) and one treated with classic disease modifying anti-rheumatic drugs (789 patients followed up from 1999 to 2005).

The objective of our study was to describe the MR and standardized mortality rate (SMR) of an incident cohort of RA patients collected from a tertiary center, followed up to 20 years. Additionally, we wanted to analyze the role in mortality risk of different demographic and clinical variables, including radiographic joint damage.

Material and methods

Patients

The *Hospital Clinico San Carlos* RA cohort (HCSC-RAC) is a day-to-day clinical practice cohort that includes subjects that have received a clinical diagnosis of RA by their usual rheumatologist. From the early 1990s it was implemented in our outpatient clinic a system to record all the rheumatologic diagnoses that our patients receive in each visit during follow-up (using ICD9/10 codes). Diagnoses were stored in a relational database and from 2006 are being stored in a departmental electronic health record (Medi-LOG [7]). Based on these diagnoses we have developed an algorithm that allows us to include or exclude patients from the RA cohort.

We have included in the HCSC-RAC those patients that (a) are attending or have attended the rheumatology outpatient clinic of the *Hospital Clínico San Carlos* (Madrid, Spain), with at least two registered visits, (b) have received any ICD9 and/or ICD10 codes for RA by their usual rheumatologist (714, 714.1, 446.8, M05.3+, M06.9, M06.0, M05, M05.9, M06.2, M05.1+, M06.3, M05.8, M06, M06.8, M05.0, and M05.2), at least in two consecutive visits, (c) were 16 years old or older at symptoms onset, and (d) RA diagnosis was established from January 1, 1994 to February 15, 2013. In the case that the patient also receives a diagnosis of other autoimmune disease, such as inflammatory bowel disease (555.90, 556.00, 555, M07.4, M07.5, M07.6, K50, K50.0, K50.1, and K51.0), psoriasis or psoriatic arthritis (696, L40, L40.5, and M07), systemic lupus erythematosus (695.40, 710.00, 972.50, and M32), scleroderma (701.00, 710.10, 710.50, and M34), juvenile idiopathic arthritis (714.3, 714.5, M09, and M08), ankylosing spondylitis (720.00, 720.20, 720.80, 720.90, M45, and M46), either before being diagnosed of RA or after being included in the RA cohort, his/her clinical record is reviewed by a rheumatologist (LA or LRR) that decide if the patient is included or excluded from the cohort, based on clinical, laboratory and treatment data.

RA patients are followed in routine clinical visits with their usual rheumatologist or specialized nurse, scheduled on demand based on disease activity, response and tolerance to treatment, and occurrence of adverse events. In parallel, evaluation visits are performed at baseline (when RA is diagnosed) and annually thereafter. In these visits demographic, clinical and laboratory data are collected by a trained health professional evaluator [including 28 painful and swollen joint counts, patient visual assessment scale for disease activity and global health, health assessment questionnaire (HAQ), and erythrocyte sedimentation rate (ESR)], and stored in Medi-LOG.

Regarding x-rays, they were performed when requested by the patient's rheumatologist when he/she deemed necessary and not as part of any protocol. In all, 52.7% of the x-rays were performed at baseline, 11% in the first 2 years after RA diagnosis, 17.3% between 2 and 5 years, 13.7% between 5 and 10 years, and 5% between 10 and 20 years after RA diagnosis.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the HCSC Ethics Committee.

Variables

Our main variable was all-cause mortality. Information regarding the date of death was obtained from the INDEF (*Índice Nacional de Defunciones,* Spanish for "National Mortality Index" http://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/IND_TipoDifusion.htm), a national register depending on the Spanish Ministry of Health that records all deaths in the Spanish territory, regardless the nationality of the deceased. Follow-up time was considered until September 2013, the time when mortality data was collected from the INDEF. No data regarding cause of death is registered in this registry.

Radiographic joint damage was assessed using the Sharp/van der Heijde score (SHS) of hands and wrists [8]. Reading was performed by one observer (JIC) who did not have access to the clinical data of the patients. Intraobserver reliability, measured with the intra-class correlation coefficient (ICC) was assessed by twice reading 20% of the radiographies, 1 year apart. The ICCs with 95% confidence interval (CI) for total SHS was 0.99 (0.99–0.99).

As surrogate measures of severity during the early course of the disease, we used the median value of the Health Assessment Questionnaire (HAQ) [9] and of the ESR that were performed at RA diagnosis, 1 and 2 years after. We used averaged values over time instead of baseline measurements, because it has been shown that the formers increase the predictive ability of such variables [10]. In the event that the patient died in the first 2 years after disease diagnosis, we used the averaged value of the available HAQ and ESR determinations. Other variables included in the analysis were gender, age at RA diagnosis, the elapsed time from RA diagnosis to x-ray, year at RA diagnosis, nationality, presence of RF, presence of anti-citrullinated peptide antibodies (ACPA), treatment with biological therapy, and number of hospital admissions during follow-up (regardless the cause).

ACPA detection tests and treatment with biological therapy were not available during part or the whole follow-up of some patients, and therefore they did not have the chance to be treated with such medication or to be tested for ACPA—the former became available in our center in October 2006 and the use of biological drugs started in January 2000. We accounted for this situation in two complementary ways, first, we divided the follow-up time in successive periods delineated by the previously referred dates and the date when the first biological therapy was prescribed, in case the patient was treated with biological drugs. Second, we introduced new categories on the variables ACPA positivity, and biological treatment—in the former, "no test available" (for those follow-up time intervals that ended before October 15, 2006), "ACPA presence," "ACPA absence," and "No test performed" (for those follow-up time intervals that started on October 15, 2006 or later). For biological drug treatment, "no biological drug available" (for those follow-up time intervals that ended before January 1, 2000), "Biological drug not prescribed" (for those follow-up time intervals from January 1, 2000 to the date the first biological drug was prescribed, patient's death or September 10, 2013), and "Biological drug prescribed" (for those follow-up time intervals from the date the first biological drug was prescribed to patient's death or September 10, 2013).

Statistical analysis

Continuous variables were described using median and interquartile range (IQR). Dichotomous and categorical variables were described using proportions. SHS was log transformed to