A Study of Multiple Causes of Death in Rheumatoid Arthritis

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ABSTRACT. Objective. To evaluate rheumatoid arthritis (RA)--related mortality in the state of São Paulo (Brazil).

Methods. Data from all death certificates (DC) from 1996 to 2010 were analyzed using a multiple cause-of-death method. We compared the results from 2 subperiods (1996-2000 and 2006-2010).

Results. We found 3955 DC related to RA — 27.6% with RA as the underlying cause of death (UCD) and 72.4% with RA as the nonunderlying cause of death (NUCD). Ninety percent of RA-related deaths occurred at age ≥ 50 years. The mean ages at death were 67.1 ± 13.3 and 67.9 ± 13 years for RA as the UCD and NUCD, respectively. The most frequent NUCD associated with RA were pneumonia, sepsis, renal failure, interstitial lung disease, and heart failure. In the last subperiod, there was an increase in infectious causes. When RA was an NUCD, we observed a decrease in the mean age at death for the last subperiod (p = 0.021). The most common UCD were circulatory and respiratory system diseases. Comparing the mean age at death between RA-related deaths and the general population when deaths occurred at ages beyond 50 years, the linear regression analysis showed a downward curve for RA-related death (p < 0.001 and r = -0.795), while for the general population, as expected, the curve had an upward pattern (p < 0.001 and r = 0.993).

Conclusion. Unexpectedly, RA-related deaths occurred at earlier ages in the more recent subperiod. Cardiovascular disease remained the most important cause, and infectious diseases are an increasing cause of death associated with RA, raising the question of whether infections were related to the more vigorous immunosuppressive treatment recommended by recent guidelines. (First Release October 15 2015; J Rheumatol 2015;42:2221–8; doi:10.3899/jrheum.150166)

Key Indexing Terms: RHEUMATOID ARTHRITIS MORTALITY CAUSES OF DEATH VITAL STATISTICS BRAZIL

Rheumatoid arthritis (RA) is the most common cause of chronic inflammatory arthritis and its prevalence is estimated at 0.5% to 1% of the adult population around the world1,2. In Brazil, there are no studies evaluating a representative sample of the whole population. Studies evaluating specific cities have shown a prevalence rate varying from 0.2 to 1%3,4.

RA can affect persons at any age, and prevalence rises with aging; it is highest in women older than 65 years. The estimated prevalence varies geographically, with the highest rates in northern Europe and North America1.

Despite the main clinical characteristic of articular involvement, other systems can be involved and are associated with worsening of life expectancy. Patients with RA have a higher frequency of comorbidities than those seen in the general population. These comorbidities are intrinsi-
Materials and methods

Geographic and demographic information. The state of São Paulo is located in the southeast region of Brazil and has an area of 248,222.8 km², slightly smaller than the United Kingdom. In 2010 it had a population of 41,262,199, distributed in 645 municipalities. São Paulo is the richest state of the federation and is responsible for 33.1% of the Brazilian gross domestic product.

Data source. We analyzed mortality data obtained from the São Paulo Data Analysis System Foundation (Fundação Sistema Estadual de Análise de Dados), the institution responsible for vital statistics in São Paulo.

In Brazil, the DC is established according to World Health Organization (WHO) recommendation and is composed of 2 parts: the first presents the sequence of events leading to death, with UCD stated on the last line, and the second part is composed of contributing causes of death. According to WHO, the UCD is defined as “...disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury.” All the causes of death written on the DC, with the exception of the UCD, were described as nonunderlying causes of death (NUCD). The term multiple causes of death refers to the set of all causes (underlying and nonunderlying).

We analyzed all DC data that had codes associated with RA, recognized as category M05 (seropositive RA) and subcategories M06.0 (seronegative RA), M06.1 (Still disease), M06.8 (other specified RA), and M06.9 (RA, unspecified) on any line of the DC, in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, in use in Brazil since 1996.

Mortality rates. We evaluated all DC data from 1996 to 2010 and calculated the crude annual mortality rate by age and sex, using demographic data provided by the Information Technology Department of The Brazilian Unified Health Care System (DATASUS; an organ of the Brazilian National Ministry of Health).

The age and sex-adjusted mortality rate was calculated by the direct method over the entire period and annually, using the Brazilian population in 2000 as reference. All mortality rates were calculated per million inhabitants.

Multiple causes of death. For all analyses, except mortality rate, we selected only DC data in which age at death was ≥ 20 years, to exclude juvenile idiopathic arthritis (< 16 yrs old) and to compare the age intervals of the general population, divided into 5-year intervals (e.g., 15-19 yrs).

When RA was described as UCD, we evaluated NUCD data described on the DC, and conversely, when RA was described as NUCD, we evaluated UCD data; we also estimated the observed/expected ratio (O/E ratio). O/E ratio is the ratio for 1 specific UCD associated with RA (observed) and the expected UCD data; we also estimated the observed/expected ratio (O/E ratio). O/E ratio is the ratio for 1 specific UCD associated with RA (observed) and the expected for the same UCD in the general population, allowing an estimate of whether the specific UCD is more (O/E ratio > 1) or less (O/E ratio < 1) frequent in RA-related deaths. If O/E ratio is equal to 1, it suggests a pattern similar to the general population. The O/E ratio was adjusted for sex and age.

Although we could not evaluate the treatment of patients, we decided to compare 2 specific subperiods (subperiod I: 1996-2000, and subperiod II: 2006-2010), which represent distinct approaches regarding treatments. In subperiod I, there were no patients using tumor necrosis factor inhibitors in Brazil. Meanwhile, in subperiod II, the treatment became more aggressive, with the intention of better controlling the inflammatory process. At that time, biologic therapy was made available by the public health system.

Similarly to Santo, et al., we used the expressions “death from” or “death due to” to refer to the UCD, whereas “deaths with a mention of” and “mortality related to” refer to a specific condition that could be UCD or NUCD.

For each data entry (RA as UCD or NUCD), we studied the following variables: sex distribution, age at death, the total number of causes listed per DC, and all described causes of death.

A subgroup of 166 DC were for cases submitted to autopsy and we compared the causes of death in the subgroup submitted to autopsy with the whole group of DC.

Results

For the entire period (1996–2010), 3,629,559 death certificates were issued in São Paulo state. The term RA was listed in 3955 DC, with 1095 (27.6%) as UCD and 2860 (72.4%) as NUCD. In 17 DC, the age at death was younger than 20 years (4 as UCD and 13 as NUCD). The annual mean of deaths with any mention of RA was 263.6. The female/male ratio was 3.3 for RA as UCD and 3.2 as NUCD (Table 1).

Figure 1 shows the distribution of RA-related deaths according to age ranges. Death was more common in females, and 90% of RA-related deaths occurred at older than 50 years.

The adjusted mortality rate for the entire period was 6.5 deaths/million inhabitants (Table 1), with highest values for females. In linear regression analysis, we did not find any trend over the period for females (p = 0.13 and R = –0.409) and males (p = 0.09 and R = –0.452).

The mean number of causes of death per DC with any mention of RA was 4.2 ± 1.2 for the entire period. We observed an increase in the number of RA-related entries over the years (3.9 ± 1.1 vs 4.4 ± 1.2, p < 0.001 for subperiod I and II, respectively).

RA as UCD. The mean age at death when RA was the UCD was 67.1 ± 13.3 years for the entire period (67.6 ± 13.2 for female vs 65.4 ± 13.6 for male, p = 0.021). There was no difference between subperiods.

The most important NUCD associated with RA were pneumonia (38.8%), sepsis (29.7%), renal failure (11.4%), interstitial lung disease (10.91%), and heart failure (9.1%). On subperiod comparison, subperiod II showed an increase in infectious causes (pneumonia and sepsis) and surgical operation with implant of artificial internal device, and a reduction in heart failure and stroke (Table 2).

RA as NUCD. The mean age at death when RA was the NUCD was 67.9 ± 13 years for the entire period (68.3 ± 13.1 for females vs 66.5 ± 12.5 for males, p = 0.001). Comparing subperiods, we observed a decrease in the mean age at death for the latter subperiod (68.4 ± 12.9 vs 67.1 ± 13.2 yrs; p = 0.021).
The most common UCD were circulatory (35.1%) and respiratory system diseases (21.8%). Among the circulatory system diseases, there was a predominance of the following categories: ischemic heart diseases (11.5%), cerebrovascular diseases (5.5%), and hypertensive diseases (4.2%).

Unspecified organism pneumonia was the main cause of death in respiratory system diseases (9.4%), followed by chronic lower respiratory diseases (6.4%) and other interstitial pulmonary diseases (2.4%).

In the last subperiod, there was an increase of neoplasm, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, diseases of the nervous system, other interstitial pulmonary diseases, diseases of the musculoskeletal system and connective tissue, and unspecified site urinary tract infection. We also observed a decrease in diseases of the respiratory system, unspecified cerebral infarction, and renal failure (Table 3).

The O/E ratio was higher than 1 for sepsis, systemic mycosis, Cushing syndrome, chronic obstructive pulmonary disease, pneumonia, decubitus ulcer, pyogenenic arthritis, and renal failure during the entire period.

Despite O/E = 1 for tuberculosis, considering both sexes and the entire period, we observed O/E higher than 1 (2.16; 95% CI 1.25-3.71) for women, without differences between subperiods. Table 4 shows the O/E ratio for the entire period and for subperiods.

We compared the mean age at death between RA-related deaths and in the general population, considering only deaths at age ≥ 50 years. Linear regression analysis showed a downward curve for RA-related deaths (p < 0.001 and r = –0.795) while for the general population, as expected, there was an upward pattern (p < 0.001 and R = 0.993; Figure 2).

Concerning the subgroup submitted to autopsy, we found 65 DC considering RA as a UCD, and in this subgroup, pneumonia and sepsis were the 2 most frequent causes of death, similar to what we found in the whole group. The percentage of death associated with pneumonia was even a little higher in the subgroup submitted to autopsy. In contrast, the percentage of sepsis was higher in the whole group (data not shown). We also found 101 DC considering RA as an NUCD, and in this subgroup the frequency of UCD was also similar to the whole group (data not shown).
DISCUSSION
Considering that guidelines reinforce the necessity of tight control with early and aggressive treatment to control the inflammatory process and prevent articular destruction, as well as to reduce extraarticular involvement in RA, we studied certain aspects concerning RA-related death, using the multiple-cause-of-death method and analyzing 2 specific subperiods.

With this method, we could increase the number of studied DC 3.6-fold, considering that a majority of RA-related deaths were described as NUCD.

In our present study, after evaluating 15 years (1996-2010) of mortality data from DC (n = 3955) issued in the state of São Paulo, we found that RA-related deaths represent 0.1% of deaths in the state. Ziadé, et al, using the same method, evaluated 32 years (1970-2002) in France and found RA mentioned in 0.22% of DC. This difference could be due to lower prevalence of RA in São Paulo state, underreporting, or both.

Circulatory system diseases were the most frequent cause of death when RA was the NUCD (1001 DC). Considering RA as the UCD, these causes were less frequent.
that the descriptor physician would recognize the most severe disease as the main cause of death, neglecting other chronic diseases. For example, when a patient with RA dies with myocardial infarction (MI), the physician would describe MI as the UCD a majority of the time, sometimes neglecting to describe RA. The O/E ratio was equal to 1, as observed by Ziadé, et al18 and reported in the literature review by Symmons and Gabriel19. Generally, as described by other authors5,20,21, cardiovascular disease (CVD) remained the most important cause of death in RA in our study.

Despite its overall low frequency in the DC, stroke was less often described in the second subperiod as UCD or NUCD with RA. This could suggest that better treatment was associated with decreasing stroke in the last subperiod. However, the O/E ratio was lower than 1 for both subperiods, and that could be due to underreporting.

Similarly to the findings of Sihvonen, et al, the most frequent infections described in RA-related deaths were pneumonia and sepsis20, which were in our study the main related causes of death when RA was UCD, for the entire period. The increased frequency for the last subperiod could be a result of more aggressive therapy leading to infections and deaths or a shift in the pattern of description. When RA was considered NUCD, death was due to infections (pneumonia and sepsis) in just 12% of DC data, Comparing the subperiods, pneumonia was less reported in the latter; likely because of the physician having understood that infection was a result of RA or its therapy; thus, RA was considered as a UCD. The O/E ratio for the entire studied period was > 1 for pneumonia and sepsis, suggesting that in general, infections and RA were related.

Renal failure was the third most common NUCD due to RA. Otherwise, when renal failure was the UCD, there was a significant decrease for the last subperiod. This could be due to the decrease in the use of nonsteroidal antiinflammatory drugs and the reduction in the frequency of amyloidosis [for entire period of study: 5 and 1 death(s) when RA was described as UCD and NUCD, respectively]. Despite this, the O/E was > 1. Corroborating this was the Hickson, et al study22, which stated that patients with RA are more likely to develop reduced kidney function than persons without RA.

According to Bongartz, et al, in a population-based study, patients with RA have a higher risk of developing interstitial lung disease (ILD) than the general population and generally have a worse survival rate compared with RA patients without ILD23. Among risk factors to develop RA-related ILD, male sex is one of the greatest23,24. In our study, we found that ILD was an important cause of death, which had a significant increase of description as UCD (RA as NUCD) in the second subperiod. In addition, the O/E ratio was > 1, suggesting that the death was associated with ILD.
with the highest levels for men (for entire period, O/E 16.98; 95% CI 11.16-25.82).

For neoplasm, as expected, when RA was a UCD, we observed a lower frequency of descriptions. This was likely due to neoplasm being considered as the main cause of death, and similar to what we observed for CVD, RA was forgotten. When RA was the NUCD, described neoplasms remained few; however, there was an increased level for the last subperiod. This was similar to the study by Ziadé, et al18, with O/E < 1 for neoplasms. In our study, lymphoma and prostatic cancer had O/E ratio = 1. Considering that lymphoproliferative disorder risk was associated with RA25, we would expect higher frequencies, which were not observed. This again brings up the possibility of underreporting in RA-related deaths.

Despite the expectation of higher frequency of tubercu-

Table 4. Observed/expected ratios for underlying causes of death in rheumatoid arthritis (RA), adjusted for age, by time periods, state of São Paulo, Brazil.

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<tr>
<td>Tuberculosis</td>
<td>1.08 (0.66–1.76) [16]</td>
<td>0.5 (0.16–1.55) [03]</td>
<td>1.37 (0.56–3.29) [05]</td>
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<td>Sepsis</td>
<td>3.45 (2.74–4.33) [74]</td>
<td>4.04 (2.73–5.98) [25]</td>
<td>2.98 (1.95–4.58) [22]</td>
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<tr>
<td>Mycoses*</td>
<td>8.29 (4.44–15.43) [10]</td>
<td>8.05 (2.58–25.06) [03]</td>
<td>11.14 (4.16–29.82) [10]</td>
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<tr>
<td>Neoplasms</td>
<td>0.3 (0.25–0.34) [143]</td>
<td>0.23 (0.15–0.32) [30]</td>
<td>0.37 (0.29–0.47) [66]</td>
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<tr>
<td>Malignant neoplasm of stomach</td>
<td>0.2 (0.1–0.39) [9]</td>
<td>0.15 (0.03–0.58) [02]</td>
<td>0.21 (0.06–0.66) [03]</td>
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<tr>
<td>Malignant neoplasm of bronchus and lung</td>
<td>0.32 (0.2–0.5) [19]</td>
<td>0.19 (0.06–0.59) [03]</td>
<td>0.46 (0.24–0.85) [10]</td>
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<tr>
<td>Lymphoma</td>
<td>0.7 (0.36–1.35) [9]</td>
<td>0.84 (0.26–2.59) [03]</td>
<td>0.89 (0.33–2.36) [04]</td>
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<td>Diabetes</td>
<td>1.04 (0.86–1.25) [111]</td>
<td>1.05 (0.74–1.49) [32]</td>
<td>1.05 (0.77–1.43) [40]</td>
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<tr>
<td>Cushing syndrome</td>
<td>133.37 (52.88–336.3) [5]</td>
<td>96.04 (12.56–734.15) [01]</td>
<td>67.79 (9.05–507.85) [01]</td>
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<td>Diseases of the circulatory system</td>
<td>1.07 (1.0–1.13) [1001]</td>
<td>1.14 (1.02–1.27) [328]</td>
<td>1.08 (0.96–1.16) [336]</td>
</tr>
<tr>
<td>Acute myocardial infarction, unspecified</td>
<td>0.94 (0.82–1.07) [218]</td>
<td>0.97 (0.76–1.22) [69]</td>
<td>1.01 (0.81–1.26) [78]</td>
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<tr>
<td>Heart failure</td>
<td>1.07 (1.07–1.32) [88]</td>
<td>1.01 (0.70–1.43) [30]</td>
<td>1.05 (0.71–1.54) [26]</td>
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<td>Stroke**</td>
<td>0.61 (0.48–0.75) [76]</td>
<td>0.67 (0.47–0.94) [33]</td>
<td>0.47 (0.29–0.74) [18]</td>
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<tr>
<td>Pneumonia</td>
<td>1.74 (1.54–1.96) [269]</td>
<td>2.86 (2.36–3.44) [109]</td>
<td>0.13 (0.06–0.25) [08]</td>
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<tr>
<td>Chronic obstructive respiratory diseases***</td>
<td>1.56 (1.34–1.81) [169]</td>
<td>1.43 (1.06–1.90) [46]</td>
<td>1.87 (1.45–2.36) [66]</td>
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<td>Digestive ulcer****</td>
<td>3.11 (2.23–4.33) [35]</td>
<td>2.96 (1.64–5.35) [11]</td>
<td>2.61 (1.35–5.02) [9]</td>
</tr>
<tr>
<td>Pyogenic arthritis</td>
<td>49.55 (31.31–78.42) [19]</td>
<td>22.50 (5.55–91.07) [02]</td>
<td>61.02 (29.99–124.01) [08]</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.87 (1.42–2.45) [53]</td>
<td>3.39 (2.35–4.87) [29]</td>
<td>1.91 (1.2–3.02) [18]</td>
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Numbers in parentheses are 95% CI. Numbers in brackets refer to observed number of the specific underlying causes of death and mention of RA. * Mycoses, except dermatophytosis (B35) and other superficial mycoses (B36). **Cerebral infarction (I63) and Stroke, not specified as hemorrhage or infarction (I64). *** Block chronic lower respiratory diseases (J40–J47), except Asthma (J45), Status asthmaticus (J46) and Bronchiectasis (J47). ****Digestive ulcer (K25–K28): Gastric ulcer (K25), Duodenal ulcer (K26), Peptic ulcer — site unspecified (K27), and Gastrojejunal ulcer (K28).
loss, mainly in the last subperiod, we found O/E > 1, just for females in the entire period. Considering that most studies show association between tuberculosis and RA26, we can speculate the underreporting of tuberculosis in RA-related deaths.

The O/E ratio for chronic obstructive pulmonary disease was > 1 for both subperiods, corroborating the Nannini, et al study27.

With more aggressive therapy and better disease control, we should see an increase in life expectancy. But we observed a decrease in the mean age at RA-related deaths, mainly since 2003. This was an opposite trend compared to the general population of São Paulo state. This result was completely different from what was observed in France18, where the mean age at death rose. One possible explanation can be the socioeconomic difference between populations, including healthcare access. The observation of increased infections in the second subperiod suggests that more aggressive treatment of RA in the more recent years could be associated with risk of earlier death in a population with higher risk of infections and the difficulty of accessing early treatment of this complication.

Mortality statistics present 2 limitations regarding the DC: quantitative and qualitative. Regarding DC number, in São Paulo state there is almost 100% coverage, with adequate reporting of deaths28,29. Concerning DC quality in São Paulo state during the period 1996 to 2007, only 6.4% of cases had ill-defined causes7. Another variable of DC quality is the number of causes mentioned per DC; in our study it was 4.2 for the entire period for any mention of RA.

The strength of our study was the coverage of DC throughout the state of São Paulo, allowing the inclusion of all deaths that occurred in different local healthcare areas, reducing selection bias. Further, the long period of study permitted comparisons between subperiods, when different therapeutic guidelines were followed.

The cause of deaths found in the subgroup submitted to autopsy were similar to those described in the whole group, reinforcing the reliability of our study.

Because we used DC-sourced data for this study, some limitations were intrinsically related to the method, such as underreporting and inadequate DC description.

An unexpected early occurrence of RA-related deaths in the state of São Paulo was found. CVD remained an important cause of death in RA, justifying a judicious followup and treatment of CV risk factors. Infectious diseases are an important cause of death in patients with RA, raising the question of whether infections are related to more vigorous immunosuppressive treatment, as recommended by recent guidelines.

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