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ORIGINAL ARTICLE

Life expectancies of Japanese patients with rheumatoid arthritis: a review of deaths over a 20-year period

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Abstract We investigated trends in life expectancy in rheumatoid arthritis (RA) patients, reviewing records for 286 patients (204 female, 82 male) who had died over the past 20 years. The average age at death was 68.8 years before 1990, increasing to 72.1 years after 2001. Trends in disease modifying anti-rheumatic drugs (DMARDs) saw gold preparations (45.2%) predominate before 1990, sulphydryl donor agents (53.6%) from 1991 to 2000, then methotrexate (43.0%) after 2001. The most common causes of death were infectious diseases up to 1995, rheumatic disease 1996–2000, and cardiovascular events and malignancies after 2001. Major advances in surgical interventions, such as joint replacement surgery, occurred after 1990. Surgical intervention followed by a period of rehabilitation maintained a favourable level of activities of daily living (ADLs), The requirements for favourable life expectancy are control of RA inflammation and maintenance of a favourable level of ADLs. Although recently developed DMARDs and biological agents show promise, caution is required to avoid serious adverse reactions. Optimum care of patients with RA will require preventive measures and early intervention for infections and rheumatic diseases, as well as for lifestyle diseases, osteoporosis and malignancies.

Keywords Activities of daily living · Disease modifying anti-rheumatic drug · Life expectancy · Rheumatoid arthritis

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Introduction

Life expectancies for rheumatoid arthritis (RA) patients are 10 years less than for other adults [1–3]. The most common cause of death of Western RA patients is cardiovascular disease, including cerebrovascular disease (43%), followed by malignancies (13%) and infection (13%) [1]. The main causes of death for Japanese RA patients include the three major causes of death in the Japanese population, namely malignancies, cerebrovascular disease, and cardiovascular disease, as well as infections and rheumatic diseases such as rheumatoid lung disease and secondary amyloidosis [1]. Persistently high levels of rheumatic inflammation lead to progressive articular destruction, impairing activities of daily living (ADLs) [4]. Complications of RA, such as infections, are also more common in patients with impaired ADLs due to RA. Major advances in the treatment of RA have occurred in the past 10 years, in pharmacotherapy comprising disease modifying anti-rheumatic drugs (DMARDs) and biological agents, and surgical interventions such as joint replacement surgery. These advances in treatment enable us to control rheumatic inflammation, making it relatively easy to maintain reasonable level of ADLs. As a result, we can expect improved long-term prognoses for RA patients, both in terms of functional prognosis and life expectancy. In this study, we investigated trends in life expectancy and deaths in RA patients in

the Japanese population, according to the year of their deaths, and examined the implications for future therapeutic regimens.

Subjects and methods

The subjects were 286 RA patients treated at the participating institutions over the past 25 years, continuously for a period of 1–23 years (average 7 years), who subsequently died. The average age of onset of RA was 57.1 years (range 25–87 years). There were 82 men and 204 women, slightly more men than the prevalence in the general population [3]. The Larsen grades [5] of the wrist radiographs at the commencement of treatment were grade I in 64 subjects, grade II in 46, grade III in 95, grade IV in 58, with 23 showing mutilans type grade V showing resorptive bone destruction of the wrist. Subjects were subdivided into four groups according to the times of their deaths: between January 1981 and December 1990 (group I) for 62 subjects; between January 1991 and December 1995 (group II) for 74; between January 1996 and December 2000 (group III) for 64; and between January 2001 and December 2005 (group IV) for 86. We examined demographic data, treatments with the emphasis on pharmacotherapy and surgical procedures, clinical courses and causes of death, and compared these parameters between groups.

Results

DMARDs used and changes in ADLs

The authors employed step-wise administration of DMARDs, in the order gold agents, sulphydryl compounds, and then immunosuppressant agents [4, 6]. The DMARDs used in the final stages (Fig. 1) were predominantly gold agents (45.2%) and D-penicillamine (40.3%) in group I. D-Penicillamine (31.1%) and bucillamine (22.5%) were most used during the 1990s, with steadily increasing use of sulphasalazine and methotrexate (19.6%) over this decade. In group IV, methotrexate (43.0%) and other immunosuppressant agents accounted for over half of all DMARD prescriptions. Concomitant use of prednisolone was seen in 52.8% of all subjects, tending to increase in recent years.

Definite improvements in ADLs were seen a number of subjects with DMARD therapy and surgical interventions, accompanied by appropriate rehabilitation. At commencement of treatment, 89 subjects (31.1%) were unable to walk, and 70 (24.5%) were only able to walk indoors. A history of surgery [7, 8] (cervical spine, hip or knee) was seen in 50.7% of subjects. At the time of greatest

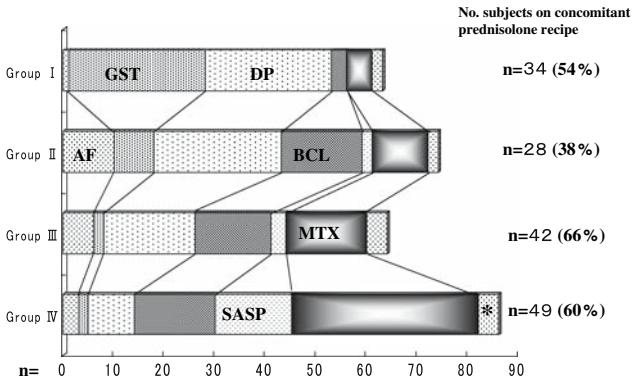

Fig. 1 DMARDs used in the final stages. Gold sodium thiomalate (*GST*), auranofin (*AF*), D-penicillamine (*DP*), bucillamine (*BCL*), sulphasalazine (*SASP*) and methotrexate (*MTX*). *Asterisks* other immunosuppressive agents

improvement in ADLs, the effects of the most recent operation were shown in 145 subjects (50.7%). ADLs were well maintained in all but 22 subjects (264 subjects, 92.3%) able to walk, and 214 (74.8%) able to walk outdoors. Long-term follow-up saw walking ability decline again in a number of subjects, however. Prior to the onset of the concomitant conditions or complications that led to their deaths, 82 subjects (28.7%) were only able to walk indoors, and 46 (16.1%) were unable to walk. A decline in ADLs was seen in 83 subjects (29.0%) in comparison with the time of maximum improvement in ADLs.

Systemic conditions and subjects' demographic characteristics stratified for year of death

We collated only systemic conditions that had been treated. Extra-articular rheumatic diseases were seen in the form of renal failure in 60 subjects (20%), with renal amyloidosis confirmed histopathologically in 21 (7.3%). Rheumatoid lung disease, principally pulmonary fibrosis, was seen in 35 subjects (12.2%), and vasculitis or other collagen disease in 15 (5.2%). Lifestyle diseases were seen in the form of hypertension in 106 subjects (37.1%), diabetes mellitus in 28 (9.8%), cardiovascular disease including myocardial infarction and angina pectoris in 28 (9.8%), and cerebrovascular disease in 20 (7.0%). Although extra-articular rheumatoid diseases tended to decrease from the late 1990s onwards, lifestyle diseases increased over time, with diabetes (14.0%) and cerebrovascular disease (23.3%) in particular markedly more prevalent in group IV.

The subjects' demographic factors according to group are given in Table 1. The ratio of men to women was rather higher than that in the general population, and particularly high in group IV. The average age of onset of RA was 57.1 years, with no difference between groups. The mean

Table 1 Subjects' demographic factors by group

Factor	Group I ($n = 62$)	Group II ($n = 74$)	Group III ($n = 64$)	Group IV ($n = 86$)
Gender: male/female	16/46	16/58	16/48	32/52
Age at disease onset; mean ± SD (years)	56.3 ± 6.3	58.5 ± 9.7	56.5 ± 9.3	56.8 ± 7.9
Disease duration; mean ± SD (years)	11.5 ± 4.9	13.2 ± 6.1**	13.8 ± 4.9*	15.5 ± 6.6**
Age at death; mean ± SD (years)	68.8 ± 7.1	71.2 ± 8.0**	71.6 ± 6.5*	73.0 ± 6.1**
Male	67.2 ± 5.9	69.3 ± 5.6	69.8 ± 5.3	71.3 ± 6.2
Female	69.4 ± 7.3	72.7 ± 6.3	72.9 ± 7.1	74.8 ± 6.5

** $P < 0.01$, * $P < 0.05$ in comparison with next group

duration between disease onset and death was 11.5 years in group I, significantly increased to 15.5 years in group IV. The average age at time of death also increased significantly with time, from 68.8 years in group I to 73.0 years in group IV. Comparison of the average age at time of death between men and women revealed a 4.1 year increase in average life expectancy for men, and 5.4 years for women, between group I and group IV.

Trends in causes of death

The most common direct cause of death was infection, in 109 subjects (38.1%), followed by rheumatic disease in 63 (22.0%), cardiovascular disease in 52 (18.2%), cerebrovascular disease in 28 (9.8%), malignancy in 52 (8.7%), and other in nine (3.1%). By far the most common infection was pneumonia, accounting for the deaths of 102 subjects, followed by meningitis in four, and septicaemia in three. Rheumatoid lung disease accounted for the majority of rheumatic disease, pulmonary fibrosis in 29 subjects, and pleurisy in seven. Renal failure was the cause of death in 24 subjects, in most cases against a background of RA-associated nephritis or amyloidosis, and general debility in three. Cardiovascular disease took the form of myocardial infarction in 35 subjects, heart failure in 13, with two cases each of arrhythmia and ruptured aortic aneurysm. Cerebrovascular disease causing death comprised 13 cases of cerebral infarction, 12 of cerebral haemorrhage, and three of subarachnoid haemorrhage.

Trends in causes of death according to group are shown in Fig. 2. Infections accounted for almost half of deaths up until the mid-1990s (groups I and II), and declined thereafter. Rheumatic disease, including rheumatoid lung disease and chronic renal failure, increased until the late 1990s (group III), causing one-third of deaths in that group, but declined after 2001 (group IV). Cardiovascular disease, cerebrovascular disease and malignancy all increased throughout the study period, accounting for more than half of all deaths after 2001 (group IV). Examining the causes of death in group IV according to gender, we see that infections, rheumatoid disease and cerebrovascular disease were common in women ($n = 52$), and cardiovascular disease and malignancy in men ($n = 32$).

The 25 deaths due to malignancy comprised four cases of lymphoma, one of leukaemia, and 20 of cancer of parenchymatous organs. Until the early 1990s, gastric cancer was the most common, with five cases, but, from the late 1990s onwards, cancers involving various organs, namely lung, breast, oesophagus, liver, colon and prostate, were seen. The other recorded causes of death were three cases of gastrointestinal bleeding, two of liver cirrhosis and pancytopenia, and one each of ileus, peritonitis and drug-induced pneumonitis. The three deaths from gastrointestinal bleeding were all caused by non-steroidal anti-inflammatory drugs (NSAIDs), and the two cases of pancytopenia and the case of pneumonitis were also caused by DMARDs, all of these occurring no later than the early 1990s.

Infection was somewhat more common in subjects with advanced disease. Rheumatoid lung disease was a major cause of death in subjects with early disease, whereas chronic renal failure was particularly common in subjects with mutilans type RA. Death due to malignancy was common in subjects with early disease, less common in

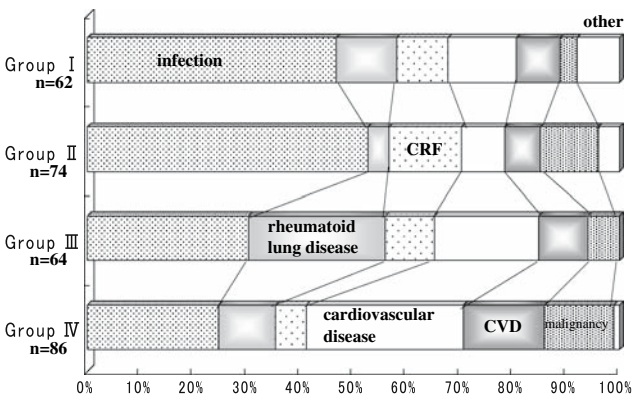

Fig. 2 Causes of death according to group. *CRF* chronic renal failure, *CVD* cerebrovascular disease

advanced disease, and unknown in those with mutilans type.

Discussion

Life expectancies for rheumatoid arthritis (RA) patients are reported by many researchers to be less than for other adults [1–3, 9]. Infections and rheumatic disease are particularly important causes of death in RA patients [1, 2]. Articular destruction of multiple joints is the cause of ADL impairment, and patients with impaired ADLs are more susceptible to infections and rheumatic diseases. DMARDs that suppress RA inflammation, and biological agents that have recently become available [10], play an important part in the treatment of RA. Joint replacement surgery is also useful in patients' regaining and maintaining a satisfactory level of ADLs. Major advances in the treatment of RA, in pharmacotherapy and in surgical interventions, have occurred in the past 10 years, accompanied by changes in life expectancies and causes of death for RA patients.

Until 1990, the only DMARDs covered by medical insurance were gold agents and D-penicillamine. A number of new DMARDs, such as bucillamine and sulphasalazine, became available for use in the 1990s, and methotrexate was finally approved in 1999. Several other new immunosuppressive agents have become available since 2000, and the first biological agents came on the market in 2002. It is accordingly now relatively easy to control RA inflammation, even in patients with RA refractory to multiple DMARDs. Control of RA inflammation and suppression of disease activity not only preserves joint function [11] but, as a result, also maintains a favourable life expectancy [12]. Since the introduction of DMARD therapy with methotrexate as the anchor drug [13], not only functional prognoses, as measured by ADLs, but also life expectancies have definitely improved for RA patients [14]. This may have also had some effect on the changes seen in the causes of deaths in this patient group.

Surgical intervention followed by a period of rehabilitation maintained a favourable level of ADLs, with 92.3% able to walk postoperatively. Long-term follow-up saw walking ability decline again, however, particularly in subjects who died, with a decline in ADLs seen in 29.0% prior to their death. Up to the early 1990s, the causes of this decline in ADLs were destruction of other joints, complications of arthroplasty [8, 15], and cervical spine lesions [16, 17]. Surgical advances saw less ADL decline due to complications of arthroplasty from the late 1990s on [18], and osteoporotic compression fractures of the thoracolumbar spine, cerebrovascular disease and heart/respiratory failure became the main causes of a decline in ADLs. In particular, preventive measures are required for osteoporosis, as it causes thoracolumbar vertebral compression fractures as well as periprosthetic fractures following arthroplasty. Lifestyle diseases such as hypertension, diabetes mellitus and hyperlipidaemia must not be ignored as the causes of cerebrovascular disease and cardiovascular disease. In order to maintain favourable levels of ADLs, and prevent a decline in ADLs that can hasten death [12], the prevention, early detection and aggressive treatment of osteoporosis and lifestyle diseases will be even more important in the future.

The average life expectancies for Japanese adults [19] in 2000 were 77.8 years for men, and 84.6 years for women, an increase of 1.8 years for men and 2.8 years for women over the corresponding expectancies in 1990. RA patients in 2000 have a life expectancy that is 5.7 years shorter than that of the general population for men, and 9.8 years shorter for women, but the increase since 1990 has been marked, and they have come much closer to the general population. This increase can be attributed to advances in the treatment of RA.

The three most common overall causes of death were infection, followed by rheumatic disease and cardiovascular/cerebrovascular incidents. Past reports from Western countries placed cardiovascular disease, including cerebrovascular disease, as the most common cause of death in RA patients [1, 2, 12, 20–22], whereas Japanese reports consistently place infections as the number one cause of death [3, 9, 23–25]. Although deaths due to infection have declined steadily over the study period, continued vigilance is required in this area. Rheumatic diseases are highly specific to RA patients. Rheumatic diseases have become less common as a cause of death since 2000, although rheumatoid lung disease is an important cause of death in the relatively early stages of RA [26]. Vasculitis [25, 27, 28] and secondary amyloidosis [29] are more common in the late stages of RA in patients with highly active disease and, if not treated appropriately, can lead to death from chronic renal failure or general debility. Since 2000, infections and rheumatoid diseases have declined, and cerebrovascular disease, cardiovascular disease and malignancies have markedly increased, as the cause of death. The causes of death in RA patients are tending to converge with those for the general population, and this trend is likely to become stronger in the future. Maintenance of a favourable life expectancy in RA patients will require prevention, early detection and aggressive treatment of lifestyle diseases, including malignancies. Japanese adults undergo regular health checks for lifestyle diseases, and these could be applied to RA patients in modified form. Deaths due to adverse reactions to DMARDs or other drugs have decreased dramatically, but

caution is needed with adverse reactions to the new immunosuppressants and biological agents that have recently become available for use.

Conflict of interest There are no potential conflicts of interest.

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