Chronic Comorbidity in Patients with Early Rheumatoid Arthritis: A Descriptive Study

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ABSTRACT. ***Objective.*** To study the presence of chronic coexisting diseases in patients with rheumatoid arthritis (RA) and its effect on RA treatment, disease course, and outcome during the first years of the disease.

Methods. From January 1985 to December 1990, 186 patients with recent onset RA were enrolled in a prospective longitudinal study. Between January 1991 and November 1992 patients were interviewed on the basis of a comorbidity questionnaire. For analysis the diseases were coded according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) medical diagnoses. Disease activity during the period of followup was measured by the Disease Activity Score. Outcome in terms of physical disability (Health Assessment Questionnaire) and radiological damage (Sharp's modified version) over 3 and 6 year periods was determined.

Results. In the group of 186 patients, with mean disease duration of 4.3 years at January 1991, 50 patients (27%) reported at least one chronic coexisting disease. The most frequently reported coexisting diseases were of cardiovascular (29%), respiratory (18%), or dermatological (11%) origin. For the major part (66%) chronic coexisting diseases were already present before onset of RA. No statistically significant differences in use of disease modifying antirheumatic drugs or corticosteroids were observed between RA patients with and without chronic coexisting diseases. No statistically significant differences were found in disease activity or in outcome in terms of physical disability and radiological damage over 3 and 6 year periods between the 2 groups with RA.

Conclusion. The results showed that about 27% of patients with RA in this inception cohort had at least one chronic coexisting disease. Treatment, disease course, and outcome did not differ between patients with and without chronic coexisting diseases during the first years of the disease. (J Rheumatol 2001;28:1511–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS COMORBIDITY DISEASE ACTIVITY SCORE
DISEASE MODIFYING ANTIRHEUMATIC DRUGS OUTCOME

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic inflammation of synovial joints as the most prominent feature, often resulting in decreased functional capacity. Next to joint involvement, many other factors influence the general condition of the patient with RA, such as extraarticular features, drug side effects, or the presence of coexisting diseases. These coexisting diseases can vary from minor, sometimes self-limiting diseases like flu, urinary tract infection, etc., to life threatening diseases like myocardial infarction or cancer. A problem in studying coexisting diseases is that no exact definition of "comorbidity" used as a collective noun for comorbid conditions, co-disease, coexisting disease, and unrelated diseases is available. In this study "comorbidity" in RA has been defined as coexisting diseases not related to RA or the use of drugs.

When using the Medline database search linking "rheumatoid arthritis," "comorbidity," or "co-existing," a small number of studies is found in which coexisting diseases in RA are studied as the main objective[1-3]. These studies show that RA is associated with a high prevalence of coexisting diseases[1-3]. In other diseases like cancer and psychiatric syndromes, it has been shown that the presence of coexisting diseases was correlated with increased mortality and decreased response to medical therapy, and under treatment of the less serious unrelated disorder[4-11]. In RA the presence of coexisting diseases has been suggested to influence measures of RA outcome such as physical function[1,11]. As no information is available with respect to the influence of chronic coexisting diseases on disease course, treatment, and outcome in terms of radiographic damage,

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we evaluated this influence in an inception cohort of patients with RA during the first years of the disease.

MATERIALS AND METHODS

Starting January 1985, all consecutive patients attending the University Medical Centre Nijmegen with recent onset RA (diagnosis < 1 year at study entry) according to the American Rheumatism Association criteria (ARA, 1987) who had not previously received second-line antirheumatic drugs were asked to participate in a longterm prospective cohort study.

All patients were followed in a standardized way. Patients were treated by different rheumatologists, and were seen every 3 months by specially trained research nurses. At baseline IgM rheumatoid factor (by ELISA, normal < 10 IU/ml) and shared epitope status were determined. At every visit quantitative clinical and laboratory data were collected, comprising the Ritchie Articular Index (RAI), the number of tender joints, number of swollen joints, and erythrocyte sedimentation rate (ESR Westergren). Patients completed a Health Assessment Questionnaire (HAQ) every 6 months[12,13]. Anterior-posterior radiographs of hands and feet were obtained every 6 months during the first 3 years, and every 3 years thereafter, and the number of erosions and joint space narrowing were scored with a modified version of the Sharp method[14]. The maximal scores for joint space narrowing and erosions were summed to obtain the total score (ranging from 0 to 448). These radiographs were scored by one observer, without knowledge of clinical and laboratory data, in chronological order per patient. The use of disease modifying antirheumatic drugs (DMARD), corticosteroids, and nonsteroidal antiinflammatory drugs (NSAID) was recorded as to start and stopping date[15,16]. By January 1, 1991, 186 patients had entered the longterm prospective followup study, with a mean period of followup then of 4.3 years. These patients were included in the assessment of chronic coexisting diseases in RA. Assessment of the coexisting diseases was performed from January 1991 to November 1992. Outcome in terms of physical disability (HAQ) and radiological damage (Sharp score) over 3 and 6 year periods was recorded for these patients. As patients were included from January 1985 to January 1, 1991, outcome data of the patients from January 1988 to January 1, 1997, were used. The data gathering schedule is illustrated in Figure 1.

Assessment of coexisting diseases. From January 1991 to November 1992 all patients from the cohort were interviewed on the basis of a comorbidity questionnaire at every visit. Patients were asked if they had a specific coexisting disease, if they had been consulting a physician for this coexisting disease, and if they were being treated. In addition, patients were questioned for coexisting diseases existing before onset of the RA. Thereafter 2 research physicians reabstracted the medical records. When inconsistency was found between the patient questionnaire and the medical records, one senior staff member involved in the treatment of most of these patients was asked to resolve it. After this validation procedure, diseases were coded according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) medical diagnoses.

As no exact definition of "chronic coexisting diseases" is available at present, determination whether a specific symptom is attributable to an extraarticular manifestation of RA, to a drug side effect, or to a completely unrelated illness remains difficult. In this study the generally accepted extraarticular manifestations of RA were followed[17,18]. In case of uncertainty it was discussed by the research physicians and the staff member before the staff member classified it as a chronic coexisting disease or not[17,18]. The same procedure was followed when it was doubtful whether a certain disease was attributable to a drug side effect or not. No grading of severity of the different coexisting diseases was done. Patients were considered as having a chronic coexisting disease if this specific disease lasted for more than 6 weeks.

In addition, a Medline database search was performed from January 1981 to August 2000 using the MeSH headings "rheumatoid arthritis" and "comorbidity/co-disease/coexisting or unrelated disease." From this database, search studies in which coexisting diseases were one of the main objectives were selected and summarized[1-3,11,18-22].

Statistics. For univariate comparison of baseline characteristics, use of medication, area under the curve for the Disease Activity Score (DAS)[15,23] over the period of followup, and outcome variables of the 2 groups of patients, we used Mann-Whitney tests, Student's t tests, and chi-square tests for contingency tables. The use of DMARD or corticosteroids was calculated as percentage of the time patients had been treated with DMARD or corticosteroids during the period of followup.

RESULTS

In total 1288 questionnaires were completed by the 186 patients. Inconsistencies between the questionnaires and medical records were observed in less than 10%; these were resolved by the senior staff member. Five chronic coexisting diseases remained doubtful thereafter: 3 possible drug induced diseases, including a possible prednisone induced diabetes and 2 patients with possible DMARD induced hypertension, and 2 possible extraarticular features of the disease, including a cardiac and dermatological disease. For these diseases the most likely classification was considered, looking at predisposing factors like age.

Of the total group of 186 patients, 50 patients (27%) reported a chronic coexisting disease, of whom 19 patients (10%) reported two, 7 patients (4%) three, and 2 patients (1%) four chronic coexisting diseases. The baseline charac-

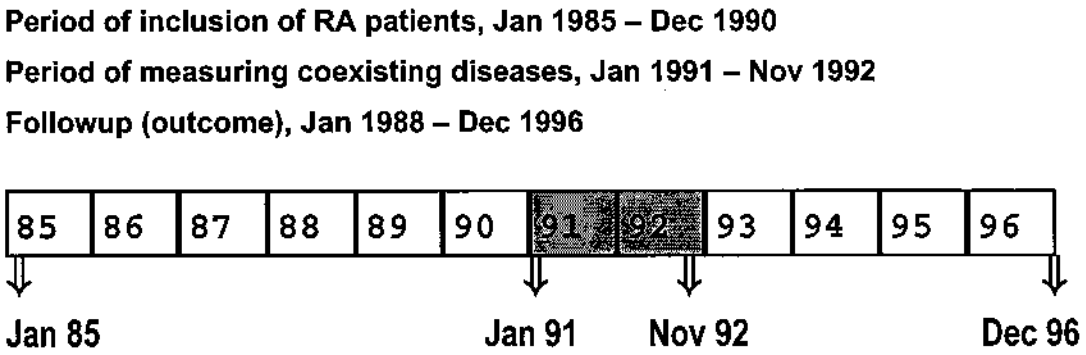

Figure 1. Inception cohort characteristics (period of inclusion, measurement of coexisting diseases, and followup).

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teristics of these patients with and without an unrelated chronic co-disease are presented in Table 1. No significant differences in baseline characteristics between the 2 groups of patients were observed. Table 2 shows the distribution of the coexisting diseases (number and categories). The most reported coexisting chronic diseases appeared to be of cardiovascular (29%), respiratory (18%), or dermatological (11%) origin. In the cardiovascular category, hypertension (16%) and angina pectoris (9%) were the most frequently reported chronic coexisting diseases. The most frequently reported coexisting diseases in the pulmonary category were chronic obstructive pulmonary disease (10%) and pneumonia (5%). Table 3 illustrates whether these chronic coexisting diseases developed before or after onset of RA. The majority of the chronic coexisting diseases (66%) existed for more than 5 years before the diagnosis of RA — this was the case for respiratory diseases in particular, 15 out of 16 patients.

No statistically significant differences in use of DMARD or corticosteroids were observed between RA patients with and without a chronic coexisting disease (Table 4). Table 5 gives the mean DAS, functional disability (HAQ), and radiographic damage of the 2 groups after 3 and 6 years' followup. No statistically significant differences were found for these variables between the 2 groups of patients with RA.

The characteristics of the studies that evaluated coexisting diseases in patients with arthritis are summarized in Table 6. In the Medline search from January 1981 to August 2000, 67 articles were found using the MeSH headings "rheumatoid arthritis" and "comorbidity/co-disease/coexisting or unrelated disease." In 2 of these studies the extent and nature of coexisting diseases was examined in a well defined population of patients with RA[2,3], but the presence

Table 1. Baseline characteristics of the study population.

	No Chronic Coexisting Diseases, n = 136	Chronic Coexisting Diseases, n = 50	p
Age, mean (SD), yrs	53.7 (14.4)	56.3 (13.4)	0.28
Male, %	36.3	40.0	0.64
IgM RF+, %	76.5	77.7	0.79
DAS, mean (SD)	4.32 (1.1)	4.00 (1.2)	0.14
HAQ, mean (SD)	0.69 (0.07)	0.72 (0.08)	0.65
SE, %	69.0	76.0	0.10

DAS: Disease Activity Score, HAQ: Health Assessment Questionnaire, SE: shared epitope.

Table 2. Distribution of chronic coexisting diseases.

Disease	N	% of Total Number of Coexisting Diseases
Hypertension	14	16
Angina pectoris	8	9
Other cardiovascular	4	4
Lung disease	16	18
Dermatosis	10	11
Eye disease	6	7
Kidney disease	5	6
Cancer	5	6
Gastrointestinal	5	6
Diabetes	5	6
Peripheral venous	4	4
Psychiatric	4	4
Hypothyroidism	2	2
Neurological	1	1
Total	89	

Table 3. Chronic coexisting diseases in relation to onset of RA.

	Before Onset Patients, n	% of Total Coexisting Diseases	After Onset Patients, n	% of Total Coexisting Diseases
Hypertension	4	4	10	12
Angina pectoris	3	3	5	6
Other cardiovascular	3	3	1	1
Lung disease	15	17	1	1
Dermatosis	5	6	5	6
Eye disease	6	7	0	0
Kidney disease	5	6	0	0
Cancer	5	6	0	0
Gastrointestinal	5	6	0	0
Diabetes	3	3	2	2
Peripheral venous	4	4	0	0
Psychiatric	0	0	4	4
Hypothyroidism	0	0	2	2
Neurological	1	1	0	0
Total	59	66	30	34

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Table 4. Use of DMARD* and corticosteroids.

	No Chronic Coexisting Diseases, n = 136	Chronic Coexisting Diseases, n = 50	p
DMARD duration, mean % of followup time (SEM)	77 (3)	70 (9)	0.29**
Number of DMARD taken, mean number during followup time (SEM)	2.8 (0.2)	2.8 (0.7)	0.91**
Use of steroids, number of patients (%)	31 (23)	10 (20)	0.68***
Steroid duration, mean % of followup time (SEM)	34 (16)	48 (12)	0.46**

*DMARD include sulfasalazine, methotrexate, gold, penicillamine, antimalarials, and cyclosporine. **Wilcoxon test. ***Chi-square test.

Table 5. Disease activity and outcome (functional disability and radiographic damage). Data are mean (SD).

	No Chronic Coexisting Diseases, n = 136	Chronic Coexisting Diseases, n = 50	p*
DAS	2.8 (0.09)	2.7 (0.08)	0.51
HAQ, t = 3 years	0.56 (0.44)	0.57 (0.41)	0.82
HAQ, t = 6 years	0.62 (0.43)	0.68 (0.44)	0.47
Radiographic damage, t = 3 years	7.24 (3.31)	7.14 (3.10)	0.86
Radiographic damage, t = 6 years	8.70 (3.92)	8.64 (3.13)	0.93

DAS: Disease Activity Score, area under the curve during period of followup (weighted mean). HAQ: Health Assessment Questionnaire.
*Mann-Whitney-, Student t, or chi-square test after square root transformation.

of diseases coexisting with RA could be derived from a small number of other studies as well[1,11,18-22].

DISCUSSION

Due to the high mean age at disease onset of patients with RA and the lifelong character of the disease, it is likely that patients are at increased risk of other coexisting diseases. However, searching Medline for "rheumatoid arthritis and comorbidity or coexisting diseases" yields only 2 studies in which this issue was the main objective[2,3]. To our knowledge our study is the first to report the extent and influence of chronic coexisting diseases on disease course in RA patients followed prospectively, although this was only for a short period.

This study clearly indicates the high frequency of chronic diseases coexisting with RA — 27% of patients reported at least one chronic coexisting disease. Hypertension, the most frequently reported chronic unrelated coexisting cardiovascular disease, was diagnosed after the onset of RA in the majority of the patients (70%). This is in contrast with chronic obstructive pulmonary diseases, which were already present before onset of RA in 95% of the patients. The 2 studies that focused on the extent of coexisting diseases in patients with arthritis[2,3] showed higher frequencies of coexisting diseases than we found. In Gabriel, *et al*, 57.6% of patients with RA developed at least one coexisting disease during followup[3]. The Charlson Comorbidity Index and the Index of Co-Existent Diseases (ICED) were used to assess the presence of coexisting diseases. The excess of coexisting diseases observed in that study might be explained by the different way of registering coexisting diseases, as the excess was partly caused by the registration of adverse reactions to NSAID. Another reason for the excess of coexisting diseases might be the older study population in that study — a higher rate of congestive heart failure and dementia was observed in comparison with the control population[3]. In the study of Berkanovic as well, a high percentage (54%) of diseases coexisting in RA was found[2]. That study had a cross sectional design and data on the presence of coexisting diseases were derived from telephone interviews with RA patients. In both studies no differentiation was made between chronic and nonchronic coexisting diseases[2,3], and patients had longer disease duration, which might also explain the high prevalence of coexisting diseases in comparison with our findings.

We also compared the frequency of coexisting diseases in

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Table 6. Characteristics of studies reporting on coexisting diseases in patients with arthritis.

Study	Design	Country	Patients (n), disease duration (yrs), and controls	Definition of Coexisting Diseases	Coexisting Diseases	Effects	Conclusion
Gabriel[3,19,20]	Prevalence cohort from population based data resource	USA	450 RA, 11.1 yrs, 891 sex and age matched controls	Charlson comorbidity index and ICED	Congestive heart failure 17%, myocard infarction 14%, dementia 12%	Trend to increased mortality in RA even after adjusting for comorbidity	RA predictor of rise in comorbidity from one year to the next
Berkanovic[2]	Longitudinal study, phone interviews	USA	288 RA, RA > 1 yr. Total population, by the SOA	List adapted from the AIMS	Hypertension 22%, stomach blood disease 12%	Functional status assessment in RA biased by comorbidity	20% of patients severe chronic comorbidity
Turesson[18]	Retrospective cohort study	Sweden	489 RA, 15.4 yrs, general population	Previously established criteria for exRA	Incidence exRA 7.9%, independent of stage of RA	Patients with exRA have greater mortality	Serositis and cutaneous vasculitis predominant exRA
Newcomer[22]	Cross sectional	USA	72 RA, 15.4 yrs, 75 controls without arthritis	Taxonomy described by Feinstein and Kaplan[23a] and CI	Control patients more comorbidities than RA (44 vs 25%)	RA patients worse lower extremity strength than control patients	Low extremity strength affected by comorbidity
Verbrugge[11]	Cross sectional	USA	Definition RA not mentioned. General population, > 55 yrs, no controls	13 chronic conditions using SOA	High blood pressure 21%, hearing impairment 14%	Chronic conditions have more effect on disabilty than age	Disability arises with increasing number of chronic conditions
Schellevis[21]	Longitudinal prevalence study of chronic diseases in general practice	Netherlands	64 OA, duration not mentioned, Dutch National Survey of General Practice	"Point prevalent concurrence" of the specific disease	Hypertension and chronic nonspecific lung disease (no percentages)	OA more comorbidities than other chronic disease	Chronic disease is a risk to have a 2nd or 3rd disease
Capell[1]	Longitudinal cohort study	UK	123 RA, from disease onset to 10 yrs followup, no controls	Not mentioned	Sepsis 45%, peptic ulceration 36%	Not mentioned	Not mentioned

ICED: Index of Co-existent Diseases, AIMS: Arthritis Impact Measurement Scales, CI: Comorbidity Index by Charlson, exRA: extraarticular manifestations of RA, SOA: Supplement on Aging to the 1984 National Health Interview survey, OA: osteoarthritis.

RA patients with data derived from a large database of a group of general physicians reporting on coexisting diseases in the same area as our outpatient clinic. The extent of coexisting diseases in 5 chronic diseases, including hypertension, chronic ischemic heart disease, diabetes mellitus, chronic nonspecific lung disease, and osteoarthritis, was described[21]. Patients with one of these 5 most common chronic diseases appeared to have a significantly higher frequency of chronic coexisting diseases, in particular patients older than 65 years, than patients without one of these 5 diseases. It was concluded that patients more frequently have more than one chronic disease, known as clustering, than could be expected by chance from the prevalence of the disease in the general population in that area[21]. Osteoarthritis was the disease with the highest rate of coexisting diseases. The percentage of chronic coexisting diseases in these patients was 27.8% (age < 65 years) and 32.8% (> 65 years), which seems comparable with the findings in our RA population. However, we note that the study population[21] differs with respect to age, definition and measurement of coexisting disease, and character of the disease (inflammatory versus degenerative) compared to our study population.

Many studies have confirmed the importance of assessment of coexisting diseases because of the influence on the other unrelated chronic disease[1,2,7,9,24,25]. Redelmeier, *et al* observed that the unrelated diseases can easily be neglected if the "primary" disease consumes attention[10]. We looked for effects of the chronic unrelated coexisting disease on the

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"primary" chronic disease, i.e., RA. We hypothesized that the polypharmacy of RA patients with chronic coexisting diseases might have an influence on the treatment given for RA and thus on the outcome measures. However, no differences in antirheumatic treatment, disease course, functional disability, or radiographic damage were observed between RA patients with and without chronic coexisting diseases in the first years of the disease.

Other studies have reported that the presence of coexisting diseases can act as an important confounder in outcomes research in both arthritis and other diseases[10,11,26–30]. Verbrugge, *et al*[11] reported a clear relationship between both the occurrence and the number of coexisting diseases and disability, measured both cross sectionally and longitudinally. In our study no differences were seen in functional disability (HAQ) and radiographic damage, 2 generally accepted measures of outcome in RA[31,32], between RA patients with and without chronic unrelated coexisting diseases. This is in contrast with the findings of Verbrugge, *et al*, but in that study another questionnaire measuring functional disability (both physical and social) was used and the patients were much older at study start[11].

We found the presence of chronic unrelated coexisting diseases is common in patients with RA. In the first years of disease, chronic coexisting diseases do not seem to influence the pharmacotherapy, disease activity, or outcome. To enable comparison between studies concerning coexisting diseases ("comorbidity") in RA, we strongly suggest development of a uniform measure of coexisting diseases. This measure should minimally include the severity of the specific coexisting disease. In addition, distinction should be made between RA related (extraarticular manifestations and drug side effects), and non-RA related, coexisting diseases.

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