Incidence of Extraarticular Rheumatoid Arthritis in Olmsted County, Minnesota, in 1995-2007 Versus 1985-1994: A Population-based Study

ELENA MYASOEDOVA, CYNTHIA S. CROWSON, CARL TURESSON, SHERINE E. GABRIEL, and ERIC L. MATTESON

ABSTRACT. ***Objective.*** To assess incidence and mortality effects of extraarticular rheumatoid arthritis (ExRA) in patients with incident RA in 1995-2007 compared to 1985-1994, in Olmsted County, Minnesota, USA.

Methods. Data on incident ExRA were abstracted from medical records of patients with RA — Olmsted County residents who first met the 1987 American College of Rheumatology criteria for RA between January 1, 1995, and December 31, 2007. Patients were followed until death, migration from Olmsted County, or December 31, 2008. ExRA were classified using the predefined criteria and compared to the corresponding 1985-1994 inception RA cohort (n = 147).

Results. The 1995-2007 cohort included 463 patients with RA followed for a mean of 6.3 years; mean age was 55.6 years, 69% were women, 67% were positive for rheumatoid factor (RF). The 10-year cumulative incidence of any ExRA (50.1%) and severe ExRA (6.7%) in the 1995-2007 cohort was similar to the 1985-1994 cohort (46.2% and 9.7%, respectively). The 10-year cumulative incidence of vasculitis, but not other features of ExRA, was significantly lower in the 1995-2007 cohort (0.6%) compared to the 1985-1994 cohort (3.6%). RF positivity, erosions/destructive changes, and use of methotrexate, other disease-modifying antirheumatic drugs and systemic corticosteroids were significantly associated with ExRA in the 1995-2007 cohort. ExRA was associated with mortality risk (HR 2.1, 95% CI 1.2, 3.7) in the 1995-2007 cohort. The decrease in mortality following ExRA in the 1995-2007 cohort versus the 1985-1994 cohort did not reach statistical significance (HR 0.6, 95% CI 0.3, 1.2, p = 0.16).

Conclusion. ExRA remains a common complication associated with increased mortality in RA. The occurrence of vasculitis appears to be decreasing in recent years. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.101133)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EXTRAARTICULAR MANIFESTATIONS
INCIDENCE MORTALITY RISK FACTORS

Extraarticular manifestations of rheumatoid arthritis (ExRA) occur in a substantial proportion of patients with RA (~40%) and are associated with particularly severe and disabling disease, frequent life-threatening comorbidities, and poor outcomes[1,2,3,4,5,6,7]. Some reports suggest that in recent years, RA may be becoming milder, with lower disease activity, less radiological progression, and lower rates of functional disability, which to a substantial degree is likely related to improved therapeutics[8,9,10,11]. Whether the epidemiological pattern of ExRA occurrence has changed in recent years has not been examined in population-based patient cohorts. To determine the recent trends in incidence and mortality of ExRA and the risk factors associated with occurrence of ExRA, we performed a longitudinal study on a population-based inception cohort of Olmsted County, Minnesota, residents first diagnosed with RA between January 1, 1995, and December 31, 2007. This study extended our previous observations of ExRA epidemiology from earlier decades (1955-1994)[7,12,13].

From the Department of Health Sciences Research and Department of Rheumatology, Skåne University Hospital, Malmö, Sweden; and Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Supported by a grant from the National Institutes of Health, NIAMS (R01 AR46849), and the Rochester Epidemiology Project (R01 AG034676 from the National Institute on Aging).

E. Myasoedova, MD, PhD; C.S. Crowson, MS, Department of Health Sciences Research; C. Turesson, MD, PhD, Department of Rheumatology, Skåne University Hospital; S.E. Gabriel, MD, MSc; E.L. Matteson, MD, MPH, Department of Health Sciences Research and Division of Rheumatology, Mayo Clinic College of Medicine.

Address correspondence to Dr. E.L. Matteson, Mayo Foundation, 200 First Street SW, Rochester, MN 55905. E-mail: matteson.eric@mayo.edu

Accepted for publication January 28, 2011.

MATERIALS AND METHODS

Study setting. The population of Olmsted County, Minnesota, is geographically defined with the majority of the population (65%–70%, according to the recent estimates) living in the city of Rochester. The availability of comprehensive medical records for all residents seeking medical care makes the population of Olmsted County an optimal resource for investigation of longitudinal trends in RA epidemiology and associated ExRA. The resources of the Rochester Epidemiology Project (REP) provide ready

access to the medical records of all Olmsted County residents from all inpatient and outpatient healthcare providers including the Mayo Clinic and its affiliated hospitals for the past 65 years. This system ensures virtually complete ascertainment of all clinically recognized cases of RA in patients residing in Olmsted County. The unique features and potential of the REP for population-based studies have been described[14,15].

Study population and data collection. The study population comprised a retrospectively identified population-based incidence cohort of RA patients who were Olmsted County residents > 18 years of age and who first met the 1987 American College of Rheumatology (ACR) criteria for RA[16] between January 1, 1995, and December 31, 2007. The incidence date for RA was defined as the earliest date at which the patient fulfilled > 4 of the 1987 ACR criteria. The complete (inpatient and outpatient) medical records of this incident 1995-2007 cohort of patients were reviewed by one author (EM) using a structured protocol. ExRA were classified according to the criteria used in our previous studies[13] (Table 1). Manifestations of severe ExRA were defined according to the Malmö criteria[5] and included pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis. All questionable cases were additionally reviewed by coinvestigators supervised by the principal investigator (ELM) and confirmation or rejection of the case-status was accomplished based on the predefined criteria[5,13]. The accuracy and completeness of the data collection were confirmed by the principal investigator through independent review of a subsample of 80 medical records, with consistent results.

The patients were followed from the RA incidence date until death, migration from Olmsted County, or December 31, 2008. The date of ExRA incidence was recorded. The date of death was noted according to the death certificate. Data on potential risk factors for ExRA were abstracted from the medical records. The risk factors included age, sex, smoking status (current and ever) at RA incidence, body mass index (BMI) at RA incidence, positivity for rheumatoid factor (RF) and/or antinuclear antibody (ANA) at any time during the followup, erythrocyte sedimentation rate [ESR; highest ESR during the first year of RA and repeatedly high ESR values (≥ 3 ESR values of ≥ 60 mm/h with a minimum interval of 30 days between 2 measurements)], joint erosions/destructive changes at any time during the followup, and use of antirheumatic medications [methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs (DMARD), biologic response modifiers, and corticosteroids].

Statistical methods. The cumulative incidence of ExRA, adjusted for competing risk of death, was estimated at 10-year followup[17,18]. These methods are similar to the Kaplan-Meier method, with censoring of patients who are still alive at last followup. However, patients who die before experiencing ExRA are appropriately accounted for to avoid overestimation of the rate of

Table 1. Criteria for inclusion as extraarticular manifestations of rheumatoid arthritis. From: Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Ann Rheum Dis 2003;62:722-7, with permission from BMJ Publishing Group Ltd.[13]

1. Pericarditis	(A) Clinical judgment and exudation verified by echocardiography, if ultrasound not available (B) Clinical criteria (1 required): Typical pericardial pain, peripheral oedema, dyspnoea/orthopnoea, ascites, dysrythmia (heart rate > 140/min, atrial flutter/fibrillation, 2–3 degrees atrioventricular block, ventricular tachycardia) Objective criteria compatible with pericarditis (1 required) Physical examination Cardiac catheterisation findings Histological examination Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma
2. Pleuritis	Clinical judgment and exudation verified by x-ray examination Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma
3. Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (< 1.8×10^9/l) on two occasions Other causes improbable, such as drug side effect or infection
4. Major cutaneous vasculitis	Diagnostic biopsy or clinical judgment by dermatologist
5. Neuropathy	Clinical judgement by doctor and signs of polyneuropathy/mononeuropathy at electromyography/electroneurography
6. Scleritis, episcleritis or retinal vasculitis	Clinical judgment by ophthalmologist
7. Glomerulonephritis	Clinical judgment by nephrologist and positive biopsy
8. Vasculitis affecting other organs	Clinical judgment by organ specialist and biopsy compatible with vasculitis
9. Amyloidosis	Clinical judgment and positive biopsy from affected organ
10. Keratoconjunctivitis sicca	Clinical judgment Positive Rose-Bengal staining or result of Schirmer's test < 5 mm/min
11. Xerostomia	Clinical judgment Abnormal sialometry, sialography, salivary scintigraphy or salivary gland biopsy with lymphocytic infiltrate
12. Secondary Sjögren's syndrome	Two of three criteria: Keratoconjunctivitis sicca (see above); Xerostomia (see above); Serological evidence: rheumatoid factor, ANA, anti-Ro (SSA), anti-La (SSB) positive, or hypergammaglobulinaemia
13. Pulmonary fibrosis	Clinical judgment and Decreased vital capacity or carbon dioxide transfer factor by 15% from normal
14. Bronchiolitis obliterans organising pneumonia	Clinical judgment by pulmonologist
15. Cervical myelopathy	Clinical judgment Increased atlantoaxial movement — verified by x-ray examination
16. Subcutaneous rheumatoid nodules	Clinical judgment
17. Rheumatoid nodules in other locations	Positive biopsy

occurrence of ExRA, which can occur if such subjects are simply censored. Incidence and mortality rates, as well as RA disease characteristics, were compared to those reported previously for the incident RA cases between January 1, 1985, and December 31, 1994, from the smaller source population (i.e., Rochester, Minnesota), followed through December 31, 2000[13]. RA disease characteristics were compared between the cohorts using chi-square and rank-sum tests. Cumulative incidence rates for the 2 cohorts (1995-2007 and 1985-1994) were compared using methods by Gray[19]. Kaplan-Meier methods were used to estimate mortality following ExRA occurrence and trends in occurrence of a second ExRA. Cox proportional hazards models were used to assess the association of ExRA with mortality, as well as to assess the association between the risk factors and development of ExRA, adjusting for age, sex, and calendar year of RA diagnosis. Time-dependent covariates were used to model risk factors that developed over time. Medication usage was coded as present on the day it was started and returned to absent following the stopping date. In the analysis of risk factors of second ExRA we included patients with a first ExRA, and the date of the first ExRA was the index timepoint for the analyses.

RESULTS

Patient characteristics. The study included 463 patients with incident RA in Olmsted County, Minnesota, in 1995-2007 compared to 147 patients with incident RA in 1985-1994. As expected, the mean (standard deviation) followup time for the 1995-2007 cohort was shorter than for the 1985-1994 cohort [6.3 (3.5) yrs; range 0–16 yrs vs 8.4 (3.8) yrs; range 0–14 yrs, respectively). Table 2 compares the characteristics of the 1995-2007 and the 1985-1994 incident RA cohorts. Age and sex were similar in both cohorts. The proportion of RF-positive patients was somewhat lower in the 1995-2007 cohort compared to the 1985-1994 cohort, but this difference did not reach statistical significance ($p = 0.12$). The proportion of ANA-positive patients in the 1995-2007 cohort was significantly lower than in the 1985-1994 cohort ($p < 0.001$). This is likely an artifact due to the changes in reference ranges and methods for the ANA testing over time. The highest ESR estimates in the first year after RA and the proportion of patients with repeatedly high ESR values (≥ 3 values ≥ 60 mm/h) were significantly lower in the 1995-2007 cohort compared to the 1985-1994 cohort ($p = 0.007$ and $p < 0.001$, respectively; Table 2).

The proportions of patients with radiographic joint erosions/destructive changes detected at some time during the followup period were similar in both cohorts. In the 1995-2007 cohort, 29% of patients had joint erosions/destructive changes during the first year after RA compared to 21% of patients in the 1985-1994 cohort ($p = 0.06$), which is likely due to the improved use of diagnostic imaging in recent years. The proportion of ever-smokers was lower in the 1995-2007 cohort ($p = 0.04$), but there were no differences in the proportions of current smokers between the cohorts. Obesity (BMI ≥ 30 kg/m^2) was significantly more common in the 1995-2007 versus the 1985-1994 cohort ($p < 0.001$; Table 2). Finally, the proportion of patients ever treated with methotrexate, hydroxychloroquine, and biologic response modifiers was significantly higher, and the proportion of patients on other DMARD was lower, in the 1995-2007 cohort versus the 1985-1994 cohort (Table 2). The use of corticosteroids was 81% in 1995-2007 compared to 74% in the 1985-1994 cohort ($p = 0.06$).

Table 2. Characteristics of patients with incident RA in the 1985–1994 cohort (Rochester, Minnesota residents) and 1995–2007 cohort (Olmsted County, containing Rochester, Minnesota, residents).

Variable	Period of RA Incidence 1985–1994 (n = 147)	1995–2007 (n = 463)	p
Age, mean ± SD, yrs	57.8 ± 16.4	55.6 ± 15.6	0.14
Female, n (%)	101 (69)	320 (69)	0.93
RF-positive, ever, n (%)	108 (73)	306 (67)	0.12
% tested for RF, ever	100	99	
ANA-positive, ever, n (%)	77 (60)	105 (26)	< 0.001
% tested for ANA, ever	88	86	
Highest ESR in the 1st year after RA incidence, mean ± SD mm/h	35.3 ± 25.1	30.0 ± 24.7	0.007
ESR ≥ 3 values ≥ 60 mm/h, n (%)	23 (16)	28 (6)	< 0.001
Joint erosions/destructive changes, n (%)			
Ever	66 (45)	229 (49)	0.33
In 1st year after RA incidence	31 (21)	134 (29)	0.06
% radiographed, ever	89	97	
Cigarette smoking, n (%)			
Ever	88 (60)	233 (50)	0.04
Current	27 (18)	80 (17)	0.76
Obesity (BMI ≥ 30 kg/m^2), n (%)			
Ever	37 (25)	237 (51)	< 0.001
In 1st year after RA incidence	32 (22)	218 (47)	< 0.001
Drug exposure, ever, n (%)			
Methotrexate	75 (51)	299 (65)	0.003
Hydroxychloroquine	72 (49)	295 (65)	0.002
Other DMARD	67 (46)	104 (23)	< 0.001
Biologic response modifiers	3 (2)	96 (21)	< 0.001
Corticosteroids	109 (74)	376 (81)	0.06

RA: rheumatoid arthritis; RF: rheumatoid factor; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate; BMI: body mass index; DMARD: disease-modifying antirheumatic drugs.

Incidence and mortality of ExRA. Among the 463 incident RA patients identified in the 1995-2007 period, 184 patients developed an incident ExRA (25 with severe ExRA) during the followup (Table 3). In the comparison cohort of 147 patients with incident RA in the 1985-1994 period, there were 64 patients with incident ExRA (13 with severe ExRA). The cumulative incidence for any ExRA in the 1995-2007 cohort was similar to the 1985-1994 cohort ($p = 0.88$) with the 10-year cumulative incidence of 50.1% versus 46.2%, respectively. The incidence of severe ExRA was also similar in the 1995-2007 cohort compared to the 1985-1994 cohort ($p = 0.51$), with 10-year cumulative incidence of 6.7% and 9.7%. Analyzing individual ExRA, the cumulative incidence of rheumatoid vasculitis (including major cutaneous vasculitis and internal organ vasculitis) was significantly lower in the 1995-2007 cohort versus 1985-1994 cohort ($p = 0.011$). In particular, the 10-year cumulative incidence of rheumatoid vasculitis decreased from 3.6% in the 1985-1994 cohort to 0.6% in the

Table 3. Cumulative incidence of extraarticular rheumatoid arthritis (ExRA) at 10-year followup after RA incidence in the 1985–1994 cohort (Rochester, Minnesota residents) and 1995–2007 cohort (Olmsted County, containing Rochester, Minnesota, residents).

Extraarticular Manifestation	Period of RA Incidence: 1985–1994 (n = 147) Number of Events*	1985–1994 (n = 147) 10-year Cumulative Incidence (%)	1995–2007 (n = 463) Number of Events*	1995–2007 (n = 463) 10-year Cumulative Incidence (%)
Any ExRA	64	46.2	184	50.1
Severe ExRA*	13	9.7	25	6.7
Pericarditis	2	2.0	8	2.6
Pleuritis	3	2.1	6	1.9
Felty's syndrome	0	0	2	0.5
Vasculitis**	5	3.6	2	0.6
Neuropathy	2	1.4	6	1.2
Mononeuropathy	0	0	2	0.2
Polyneuropathy	2	1.4	4	1.0
Scleritis	0	0	0	0
Episcleritis	1	0.7	3	0.7
Retinal vasculitis	0	0	0	0
Glomerulonephritis	0	0	0	0
Other ExRA	60	43.4	169	45.7
Amyloidosis	0	0	0	0
Keratoconjunctivitis sicca	16	12.2	74	20.4
Xerostomia	1	0.7	2	0.5
Sjögren's syndrome	13	9.7	38	9.6
Pulmonary fibrosis	9	6.6	15	5.0
Bronchiolitis obliterans	0	0	2	0.7
Organizing pneumonia	1	0	2	0.4
Cervical myelopathy	3	2.2	2	0.7
Subcutaneous nodules	43	31.2	110	31.2
Other nodules	0	0	1	0.2

* Malmö criteria[5]. ** Includes major cutaneous and internal organ vasculitis.

1995-2007 cohort, although the numbers of incident cases of vasculitis were small in both cohorts. The 10-year cumulative incidence of keratoconjunctivitis sicca in the 1995-2007 cohort was 20.4% compared to 12.2% in the 1985-1994 cohort (p = 0.12). There were no substantial changes in the occurrence of other individual ExRA in the 1995-2007 cohort versus the 1985-1994 cohort.

Similar to the 1985-1994 cohort, the most common ExRA in the 1995-2007 cohort were subcutaneous nodules, keratoconjunctivitis sicca, and Sjögren's syndrome (Table 3). There were no cases of scleritis, retinal vasculitis, glomerulonephritis, or amyloidosis in either 1995-2007 cohort or 1985-1994 cohort. Occurrence of a second ExRA appeared to be similar in the 2 cohorts, with 10-year cumulative incidence of 37.5% in the 1995-2007 cohort and 36.6% in the 1985-1994 cohort. Trends in occurrence of a second ExRA subsequent to the first ExRA were similar in both cohorts (data not shown).

In the 1995-2007 cohort, ExRA was a significant predictor of premature mortality (HR 2.1, 95% CI 1.2, 3.7) adjusting for age, sex, and calendar year. Neither severe ExRA nor the development of a second ExRA conferred a greater mortality risk than occurrence of any one ExRA (HR 2.2, 95% CI 0.8, 6.2 and HR 0.5, 95% CI 0.2, 1.5, respectively). During the followup, 53 deaths occurred per 2956 person-years of observation in the 1995-2007 cohort. Figure 1 shows mortality trends after occurrence of any ExRA in 1995-2007 versus 1985-1994 cohorts. Survival curves diverged during the first year after occurrence of ExRA and remained separated during the following years. However, the difference in mortality following ExRA in the 1995-2007 cohort versus 1985-1994 cohort did not reach statistical significance (HR 0.6, 95% CI 0.3, 1.2, p = 0.16). Although the mortality risk after the occurrence of severe ExRA was nearly halved in the 1995-2007 cohort compared with the 1985-1994 cohort, this difference was not statistically significant (HR 0.5, 95% CI 0.1, 1.7, p = 0.25).

Risk factors associated with occurrence of ExRA. To determine the effects of occurrence of ExRA in recent years, we analyzed the associations of potential risk factors with incidence of ExRA in the 1995-2007 cohort (Table 4). RF positivity, joint erosions/destructive changes, and use of methotrexate, other DMARD and systemic corticosteroids were found to be significantly associated with the occurrence of any ExRA. Use of biologic response modifiers and systemic corticosteroids was significantly associated with severe ExRA. Male sex, current smoking, RF positivity, joint erosions/destructive changes, and use of methotrexate,

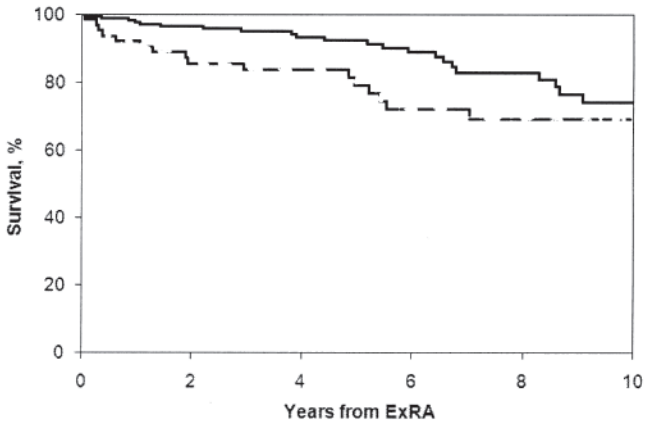

Figure 1. Mortality after any extraarticular rheumatoid arthritis (ExRA) manifestation in patients with incident RA in the 1985-1994 decade (broken line) compared to patients with incident RA in the 1995-2007 period (solid line); p = 0.16, adjusted for age and sex.

other DMARD and biologic response modifiers were significantly associated with the development of rheumatoid nodules. Use of biologic response modifiers was significantly associated with the occurrence of a second ExRA (HR 2.3, 95% CI 1.1, 4.9). None of the other risk factors, nor subcutaneous nodules as the first ExRA, was significantly associated with the occurrence of a second ExRA. Following additional adjustment for characteristics of RA activity and severity (i.e., ≥ 3 ESR values of ≥ 60 mm/h, RF positivity, and presence of erosions/destructive changes on radiographs), the strength of some of these associations was slightly weakened (Table 4).

DISCUSSION

Systemic disease has a major impact on morbidity and mortality in RA. This retrospective population-based cohort study reveals that the occurrence of ExRA overall (including any ExRA and severe ExRA) in the 1995-2007 RA incidence cohort was similar to that in the 1985-1994 RA incidence cohort from the same population base. While not significantly affecting the major trends in the incidence of ExRA, the pattern of occurrence of some individual manifestations of ExRA (in particular, rheumatoid vasculitis and perhaps keratoconjunctivitis sicca) appears to be changing. Concordantly, the decline in the occurrence of rheumatoid vasculitis after 1995 has been described in some clinic-based studies[20,21]. The decline in prevalence of serious ExRA including vasculitis from 1985 to 2006 among US veterans also suggests evolving changes in epidemiology of some ExRA[22].

The use of more aggressive treatment strategies includ-

Table 4. Risk factors associated with occurrence of extraarticular rheumatoid arthritis (ExRA) in patients with incident RA in 1995–2007 period. Statistically significant associations (p < 0.05) are shown in bold type.

Variable	Any ExRA HR (95% CI)	Severe ExRA HR (95% CI)	Rheumatoid Nodules HR (95% CI)
Age (per 10-year increase)	1.0 (0.9, 1.1)	0.9 (0.7, 1.2)	1.0 (0.9, 1.1)
Male sex	1.2 (0.8, 1.6)	1.3 (0.5, 3.0)	**1.5 (1.01, 2.2)**
Cigarette smoking			
Ever	0.9 (0.7, 1.3)	1.0 (0.4, 2.3)	1.2 (0.8, 1.8)
Current	1.2 (0.8, 1.8)	1.6 (0.6, 4.1)	**1.6 (1.01, 2.4)**
BMI (per 1kg/m^2 increase)	1.0 (0.98, 1.03)	0.98 (0.9, 1.05)	1.02 (0.99, 1.05)
RF positivity	**2.2 (1.5, 3.3)**	0.8 (0.3, 2.0)	**4.5 (2.4, 8.2)**
ANA positivity	1.3 (0.9, 1.8)	1.7 (0.7, 4.2)	1.0 (0.6, 1.7)
ESR ≥ 3 values ≥ 60 mm/h	1.5 (0.6, 3.7)	3.2 (0.7, 14.9)	1.6 (0.6, 4.5)
Highest ESR in the 1st year of RA (per 10 mm/h increase)	1.0 (0.96, 1.1)	1.1 (0.9, 1.2)	1.0 (0.97, 1.1)
Erosions/destructive changes on radiographs	**2.2 (1.6, 3.0)**	1.1 (0.5, 2.7)	**2.8 (1.9, 4.2)**
Medication usage			
Methotrexate	**1.5 (1.1, 2.2)**	0.7 (0.3, 1.9)	**1.9 (1.3, 2.9)**
Hydroxychloroquine	1.3 (0.93, 1.8)	0.6 (0.2, 1.7)	1.2 (0.8, 1.9)
Other DMARD	**2.6 (1.6, 4.3)**	1.9 (0.5, 6.8)	**2.5 (1.4, 4.6)**
Biologic response modifiers	1.9 (0.99, 3.5)	**4.0 (1.4, 11.5)**	**2.2 (1.1, 4.4)**
Corticosteroids (systemic)	**1.4 (1.03, 2.0)**	**3.8 (1.5, 10.0)**	1.1 (0.8, 1.7)
Medication usage, adjusted*			
Methotrexate	1.2 (0.9, 1.8)	0.6 (0.2, 1.7)	1.5 (0.98, 2.3)
Hydroxychloroquine	1.3 (0.94, 1.9)	0.8 (0.3, 2.3)	1.3 (0.8, 2.0)
Other DMARD	**2.4 (1.4, 4.0)**	1.5 (0.4, 5.5)	**2.4 (1.3, 4.5)**
Biologic response modifiers	1.6 (0.8, 3.1)	**3.1 (1.04, 9.5)**	1.8 (0.9, 3.7)
Corticosteroids (systemic)	1.3 (0.96, 1.9)	**3.5 (1.3, 9.1)**	1.1 (0.7, 1.6)

* Adjusted for ESR ≥ 3 values ≥ 60 mm/h, RF positivity, erosions/destructive changes on radiographs. BMI: body mass index; RF: rheumatoid factor; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs.

ing increased usage of DMARD and biologic response modifiers in the 1995-2007 cohort versus the 1985-1994 cohort may be one of the possible factors affecting the pattern of occurrence of ExRA in recent years. While the use of advanced therapeutic regimens could have an influence on decrease in the occurrence of some ExRA (e.g., rheumatoid vasculitis)[23,24], these benefits could be counteracted by increased risk of other ExRA events (e.g., rheumatoid lung disease and rheumatoid nodules) associated with use of antirheumatic medication[25,26,27]. Indeed, the use of some antirheumatic medications was associated with increased risk of occurrence of ExRA in our study, and these associations were only slightly attenuated after the adjustment for available characteristics of RA activity and severity (i.e., repeatedly high ESR, RF positivity, and presence of erosions/destructive changes). These potential risks of antirheumatic therapies with respect to occurrence of ExRA may therefore, to some extent, explain the lack of a significant decrease in the occurrence of certain ExRA in the era of improved therapeutics.

Non-treatment-related changes in RA disease patterns toward milder disease in recent decades could also influence the occurrence of ExRA, particularly the decrease in vasculitis[5,8,9,10,11]. Concordantly, we found significantly lower ESR and marginally lower proportion of RF-positive patients in 1995-2007 versus 1985-1994. However, despite a suggested decrease in RA activity over time, the presence of active and severe RA in our study (i.e., RF positivity and joint erosions/destructive changes) continued to confer a significantly increased risk for ExRA similar to that of the earlier years[28,29]. This suggests that patients with advanced RF-positive RA remain a high-risk group for the development of ExRA, thus contributing to the sustained burden of ExRA.

Increased awareness of ExRA and improved diagnostic techniques could be another potential explanation for the lack of decline in the occurrence of some ExRA and the suggested marginal increase in keratoconjunctivitis sicca in 1995-2007 versus 1985-1994. The influence of some other factors, including environmental factors (e.g., smoking, obesity) cannot be excluded. There was a significant decrease in the obesity rates in the 1995-2007 versus the 1985-1994 cohort, but BMI did not appear to have a substantial influence on the occurrence of ExRA in our study. The effects of smoking may be greater on the occurrence of some manifestations (e.g., rheumatoid nodules) than on other subsets of ExRA. Similar to previous decades, during the 1995-2007 period, ExRA conferred a significant mortality risk[4]. However, in contrast to our previous findings[7], the mortality risk associated with severe ExRA and second ExRA manifestations was not greater than that of any ExRA. The decrease in the occurrence of vasculitis, previously shown to have a major influence on mortality, and better control of RA activity in recent years may be a possible explanation[7,30]. While not achieving statistical significance, an estimated 40% decrease in mortality risk after any ExRA and 50% decrease in mortality risk after severe ExRA in the 1995-2007 cohort versus the 1985-1994 cohort may be a promising sign for improvement in survival following ExRA in the future. However, this requires further study.

The major strengths of this study include its community-based longitudinal design, use of a comprehensive medical records linkage system, with complete medical information for each patient, and the use of the same classification for ExRA as in our previous studies. The comparative analysis of characteristics of successive RA incidence cohorts from the same underlying population further strengthens the results.

Our study has several potential limitations. The retrospective design necessarily means that only information available from medical records was considered and that only those events that came to medical attention were included for analysis. However, availability of complete medical records from all healthcare providers in the area is likely to minimize this weakness, as these REP records include the majority of clinically important ExRA events. Inherent to retrospective data is the possibility of misclassification of ExRA manifestations. However, independent review of the cases by several investigators-rheumatologists based on the uniform case definition and a structured protocol consistently used in other studies we have performed with this resource likely reduced misinterpretation of the data.

The mean followup was 6.3 years in the 1995-2007 cohort compared to 8.4 years in the 1985-1994 cohort. This difference is unlikely to have affected the analysis because our methods appropriately account for the length of followup. There was a possibility of limited power due to the small number of some specific ExRA events and limited number of deaths. The number of RA patients in the 1995-2007 cohort was significantly higher than in the 1985-1994 cohort. The reason for this is that, in contrast to previous studies enrolling residents of the city of Rochester, this study involved RA patients from a larger geographical area (Olmsted County), which includes the city of Rochester. In fact, there have been no dramatic changes in RA incidence in Olmsted County during the study period. Rather, there was a modest increase in RA incidence among women recently[31], which is unlikely to affect the results of this study. In an observational study of this kind it is difficult to draw firm conclusions about any causal relationships between potential risk factors (particularly antirheumatic treatment) and occurrence of ExRA. Thus, further efforts including prospective controlled studies are needed to investigate associations between drug exposure and ExRA. Finally, we cannot exclude the possibility that more attention was paid to recording ExRA in the clinic in recent years, but we have no data to support this.

In the 1995-2007 RA incidence cohort, ExRA were com-

mon and the incidence of ExRA remained similar to that of the 1985-1994 RA incidence cohort. However, there was a significant decrease in the incidence of vasculitis, suggesting that the pattern of occurrence of some individual ExRA manifestations may be changing in recent years. Markers of RA severity and drug exposure were significantly associated with ExRA development recently. ExRA manifestations remain a significant predictor of mortality. Improved control of RA and milder disease currently may contribute to the decrease in the incidence of vasculitis, while some other factors, including some disease and treatment-related effects, may counteract these beneficial changes, contributing to the lack of improvement in the overall occurrence and mortality of ExRA. Given the possibility of confounding by indication in this observational study, assessment of the full effects of treatment on disease expression is a matter of ongoing research.

REFERENCES

1. Calguneri M, Ureten K, Akif Ozturk M, Onat AM, Ertenli I, Kiraz S, et al. Extra-articular manifestations of rheumatoid arthritis: results of a university hospital of 526 patients in Turkey. Clin Exp Rheumatol 2006;24:305-8.
2. Carmona L, Gonzalez-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis 2003;62:897-900.
3. Cimmino MA, Salvarani C, Macchioni P, Montecucco C, Fossaluzza V, Mascia MT, et al. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. Rheumatol Int 2000;19:213-7.
4. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54-8.
5. Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. Rheumatology 1999;38:668-74.
6. Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Ann Rheum Dis 2004;63:952-5.
7. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62-7.
8. Odegard S, Kvien TK, Uhlig T. Incidence of clinically important 10-year health status and disease activity levels in population-based cohorts with rheumatoid arthritis. J Rheumatol 2008;35:54-60.
9. Pincus T, Sokka T, Kautiainen H. Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. Arthritis Rheum 2005;52:1009-19.
10. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N, et al. Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. Ann Rheum Dis 2008;67:1153-8.
11. Welsing PM, Fransen J, van Riel PL. Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. Arthritis Rheum 2005;52:2616-24.
12. Turesson C, McClelland RL, Christianson TJ, Matteson EL. No decrease over time in the incidence of vasculitis or other extraarticular manifestations in rheumatoid arthritis: results from a community-based study. Arthritis Rheum 2004;50:3729-31.
13. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 2003;62:722-7.
14. Maradit Kremers H, Crowson CS, Gabriel SE. Rochester Epidemiology Project: a unique resource for research in the rheumatic diseases. Rheum Dis Clin North Am 2004;30:819-34, vii.
15. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996;71:266-74.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
17. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. Ann Stat 1978;6:534-5.
18. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley; 2002.
19. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
20. Ward MM. Decreases in rates of hospitalizations for manifestations of severe rheumatoid arthritis, 1983-2001. Arthritis Rheum 2004;50:1122-31.
21. Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? Rheumatology 2004;43:920-3.
22. Bartels CM, Bell CL, Shinki K, Rosenthal A, Bridges AJ. Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years. Rheumatology 2010;49:1670-5.
23. Hellmann M, Jung N, Owczarczyk K, Hallek M, Rubbert A. Successful treatment of rheumatoid vasculitis-associated cutaneous ulcers using rituximab in two patients with rheumatoid arthritis. Rheumatology 2008;47:929-30.
24. Puechal X, Miceli-Richard C, Mejjad O, Lafforgue P, Marcelli C, Solau-Gervais E, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis 2008;67:880-4.
25. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol 2007;36:172-8.
26. Lindsay K, Melsom R, Jacob BK, Mestry N. Acute progression of interstitial lung disease: a complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment. Rheumatology 2006;45:1048-9.
27. Williams FM, Cohen PR, Arnett FC. Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. J Am Acad Dermatol 1998;39:359-62.
28. Turesson C, Eberhardt K, Jacobsson LT, Lindqvist E. Incidence and predictors of severe extra-articular disease manifestations in an early rheumatoid arthritis inception cohort. Ann Rheum Dis 2007;66:1543-4.
29. Nyhall-Wahlin BM, Petersson IF, Nilsson JA, Jacobsson LT, Turesson C. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. Rheumatology 2009;48:416-20.
30. Erhardt CC, Mumford PA, Venables PJ, Maini RN. Factors predicting a poor life prognosis in rheumatoid arthritis: an eight year prospective study. Ann Rheum Dis 1989;48:7-13.
31. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 2010;62:1576-82.