Multiple extra-articular manifestations are associated with poor survival in patients with rheumatoid arthritis

C Turesson, R L McClelland, T J H Christianson, E L Matteson

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Rheumatoid arthritis is associated with an increased mortality compared with the general population.¹ Disability² and severe extra-articular rheumatoid arthritis (ExRA) manifestations³ predict mortality in patients with rheumatoid arthritis. In a previous study of a community-based sample of patients with rheumatoid arthritis, we showed that ExRA was a strong predictor of mortality, whereas the survival of patients with rheumatoid arthritis without severe ExRA was not largely different from the background population.⁴ We have now studied the effect of multiple ExRA manifestations on mortality.

Using the resources of the Rochester Epidemiology Project, all patients with rheumatoid arthritis residing in Rochester, Minnesota, with a disease onset between 1 January 1955 and 31 December 1994 were identified (n = 609;⁵ table 1). A structured review of all medical records from all care providers in the area was carried out and ExRA manifestations were identified and classified according to predefined criteria, as previously described.⁶ Severe ExRA manifestations included pericarditis, pleuritis, vasculitis, peripheral neuropathy, Felty's syndrome, glomerulonephritis and scleritis or episcleritis. Patients were followed up from the time of rheumatoid arthritis diagnosis until death, loss to follow-up or 31 December 2000.

Cox proportional hazards were used to assess the effect on mortality of ExRA, as well as the effect on mortality of new ExRA manifestations, controlling for the presence of previously existing ExRA. ExRA manifestations were modelled as time-dependent covariates and the models were adjusted for age, sex, smoking at diagnosis of rheumatoid arthritis, body mass index (BMI (weight (kg)/height² (m²))) at diagnosis and rheumatoid factor.

ExRA manifestations occurred in 260 (42.7%) patients during a median follow-up of 11.8 years. ExRA was associated with increased mortality in the fully adjusted model (p < 0.001; table 2). Additional ExRA manifestations occurred in 121 patients and further increased the risk of death (adjusted hazards ratio (HR) 1.91; 95% confidence interval (95% CI) 1.36 to 2.69). Onset of a first severe ExRA

Table 2 Effect of ExRA manifestations on mortality in patients with rheumatoid arthritis

	HR*	95% CI
First ExRA manifestation (any)	2.20	1.73 to 2.82
Second ExRA manifestation (any, controlling for first)	1.91	1.36 to 2.69
First severe ExRA manifestation†	4.45	3.29 to 6.00
Second severe ExRA manifestation (controlling for first)	1.70	0.90 to 3.19
Rheumatoid nodules after severe ExRA manifestation‡	1.60	1.21 to 2.12
Pulmonary fibrosis after severe ExRA manifestation‡	1.83	1.10 to 3.04

ExRA, extra-articular rheumatoid arthritis.

*The separate models were adjusted for age, sex, rheumatoid factor positivity at disease onset, smoking at disease onset and body mass index.

†Severe ExRA was defined according to the Malmö criteria.⁶

‡This model was adjusted for the presence of severe ExRA.

manifestation (n = 82) was particularly associated with premature mortality (adjusted HR 4.45; 95% CI 3.29 to 6.00). In patients with severe ExRA, the occurrence of a second severe ExRA manifestation (n = 17) further increased the risk of death (table 2), and the development of rheumatoid nodules (p = 0.001) or pulmonary fibrosis (p = 0.019) in patients with previously identified severe ExRA contributed significantly to increased mortality in adjusted models (table 2).

We found that the presence of multiple ExRA manifestations is associated with an increased overall mortality in rheumatoid arthritis. This is not explained by potential confounding factors such as smoking, rheumatoid factors and BMI. Smoking and rheumatoid factors are associated with increased comorbidity and mortality and are considered predictors of ExRA.⁶ Low BMI, presumably related to disease severity, is associated with increased mortality in patients with rheumatoid arthritis.⁷ However, the association between multiple ExRA manifestations and mortality remained significant in multivariate models adjusted for these factors.

Patients with severe ExRA have an increased risk of severe infections⁸ and cardiovascular disease.⁹ The role of rheumatoid arthritis-associated pathomechanisms in comorbidities needs to be studied further. We suggest that the extent of systemic involvement is a major determinant of survival in patients with rheumatoid arthritis.

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Authors' affiliations

C Turesson, Department of Rheumatology, Malmö University Hospital, Malmö, Sweden

E L Matteson, Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Table 1 Clinical characteristics of the rheumatoid arthritis cohort

Male sex, n (%)	164 (26.9)
Age at diagnosis, mean (SD)	58.0 (15.1)
RF positive at diagnosis, n (%)	185 (30.4)
Smokers at diagnosis, n (%)	317 (55.2)
BMI at diagnosis, mean (SD) (kg/m ²)	25.6 (4.9)
Any ExRA manifestation, n (%)†	260 (42.7)
Severe ExRA manifestation, n (%)†	82 (13.5)
Rheumatoid nodules, n (%)‡	183 (30.0)
Pulmonary fibrosis, n (%)‡	36 (5.9)

BMI, body mass index; ExRA, extra-articular rheumatoid arthritis; RF, rheumatoid factor.

*Data available from 606 patients.

†At any time during follow-up.

‡Severe ExRA was defined according to the Malmö criteria.⁶

R L McClelland, T Christianson, Department of Health Sciences Research, Mayo Clinic College of Medicine

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Correspondence to: C Turesson, Department of Rheumatology, Malmö University Hospital, 205 02 Malmö, Sweden; turesson.carl@mayo.edu

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Tumour necrosis factor α blockade and the risk of vasculitis

M De Bandt, B Saint-Marcoux, on behalf of the CRI (Club Rhumatismes et Inflammation)

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We report on a French national retrospective survey, showing 39 cases of biopsy-proved drug-induced vasculitis in patients treated with tumour necrosis factor (TNF) blockers for inflammatory arthritis, conducted among 1200 rheumatology and internal medicine practitioners registered on our website (<http://www.CRI-net.com>) between December 2004 and March 2005.

As, in France, the prescription for TNF blockers is limited to the hospitals, all the units using biologicals were contacted. The study included all patients ever known to have developed a vasculitic-like illness when under treatment with TNF blockers, and not only those who developed vasculitis during the 3-month study period.

Patients had longstanding destructive rheumatoid arthritis, spondylitis or juvenile chronic arthritis (JCA). Table 1 lists the main characteristics and treatments. Patients developed localised (29 cases) or systemic vasculitis (10 cases). None had a special risk factor for vasculitis (hepatitis C infection, cryoglobulinaemia, etc). All patients received the usual TNF-blocker doses; 10 also had a disease-modifying antirheumatic drug (mostly methotrexate).

Clinical manifestations were skin lesions in 33 patients (purpuric or necrotic rash, papules, nodules, livedo, etc), manifestation in the peripheral nervous system in 11

(1 mononeuritis; 3 mononeuritis multiplex; 7 sensory neuropathy), kidney disease in 7 (3 haematuria; 7 proteinuria; 1 renal insufficiency), abnormalities of the central nervous system in 3 (retinal thrombosis, epilepsy and cognitive defect), serositis in 4 (2 pleurisy; 2 pericarditis), myocarditis, vasculitis of the gallbladder and lung in 1 each.

In all, 29 patients had 1 documented organ disease (mostly skin), 7 patients had 2 (skin and kidney, skin and nerve, nerve and kidney) and 3 patients had 3 or more.

Histological proof was obtained in 27 (23 rheumatoid arthritis; 3 spondylitis; 1 JCA). Multiple biopsies (skin, nerve, muscle, kidney and bronchus) showed 13 leukocytoclastic vasculitis of the skin, 7 necrotising vasculitis (medium or small size vessels), 2 extravascular necrotising granuloma, 2 dermal inflammatory infiltrates and 3 extracapillary glomerulonephritis.

Immunological abnormalities before treatment were antinuclear antibody in 11 patients with rheumatoid arthritis (2 with anti-Sjögren's syndrome and 1 with spondylitis). After onset of vasculitis, we observed high levels of antinuclear antibody in 23 patients (4 with anti-DNA antibodies); anticardiolipin antibodies in 2; hypocomplementaemia in 7; perinuclear antineutrophil cytoplasmic antibody in 5; and cryoglobulinaemia in 6.

TNF blockers were discontinued in 33 of 39 patients. A remission was observed in 18 without any other treatment. Steroids and immunosuppressors were required in 15 cases. In 6 of 39 patients (with isolated skin manifestations), treatment was resumed but the manifestations slowly abated. One patient died. In 12 patients, TNF blockers were started again, owing to flare of arthritis, either with the same ($n=4$) or with another molecule ($n=8$); in 6 patients, a flare of vasculitis was observed.

A few cases of vasculitis in patients receiving treatment with TNF blockers have been published in the literature^{1–9}—mostly leukocytoclastic vasculitis. Our experience is different, with cases of necrotising vasculitis of medium-sized vessels or extravascular granulomas. We observed multiorgan disease not limited to the skin, with a high frequency of kidney and nerve manifestations occurring in patients with spondylarthritis, JCA or seronegative rheumatoid arthritis—diseases not usually associated with vasculitis. The imputability of TNF

Table 1 Main characteristics of 39 patients

Women (n)	32
Mean disease duration (years)	14.1 (7.1)
Mean age at onset of vasculitis (years)	51.6 (11.3)
Sero-positive RA (n)	30
Sero-negative RA (n)	4
JCA (seen in adulthood)	2
Spondylitis	2
Psoriatic arthritis (mainly axial)	1
Previous DMARDs	4.4 (2)
Etanercept	21
Infliximab	15
Adalimumab	2
Other TNF inhibitor	1
Mean treatment duration (months)	9.6 (13)

DMARD, disease-modifying antirheumatic drug; JCA, juvenile chronic arthritis; RA, rheumatoid arthritis; TNF, tumour necrosis factor.