Incidence and predictors of severe extra-articular disease manifestations in an early rheumatoid arthritis inception cohort

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There are limited data on extra-articular disease from the long-term follow-up of rheumatoid arthritis inception studies. In the Lund early rheumatoid arthritis prospective study[1] consecutive patients with definite rheumatoid arthritis (symptom duration <24 months) were included from 1985 to 1989 [N = 183; 116 women, 67 men; mean age 51.2 (SD 12.4) years; mean duration of symptoms 11.1 (SD 6.1) months]. Patients with active disease were offered treatment with disease-modifying antirheumatic drugs throughout the study according to general clinical practice, which changed during the study period.

For the present study, a retrospective survey of all medical records was used to identify severe extra-articular manifestations according to predefined criteria.[2] The total time of follow-up, censoring patients at death, loss to follow-up or 31 December 2004, and the cumulative incidence rate of severe extra-articular manifestations was calculated. Autoantibodies were analysed in stored samples.[1] Baseline serum concentrations of complement factors C3 and C4 were determined in fresh samples by electroimmunoassay,[3] and the results were presented as a percentage of the reference levels.

The mean follow-up was 15.4 years (SD 3.9). Four patients who fulfilled the criteria for severe extra-articular disease manifestations (pleuritis, N = 3; Felty's syndrome, N = 1) before inclusion were excluded from the present analysis. Twenty-two patients (12.3%) with the onset of severe extra-articular disease after inclusion were identified (table 1), corresponding to a cumulative incidence rate of 0.8/100 person-years at risk. This figure is slightly lower than the estimate from the community-based sample from Rochester, Minnesota,[4] where incident cases of rheumatoid arthritis have been surveyed since the 1950s.

Patients who later developed severe extra-articular disease had similar baseline C-reactive protein, erythrocyte sedimentation rate and Health Assessment Questionnaire scores at inclusion, compared with rheumatoid arthritis controls (table 2). By contrast, complement levels were lower in the severe extra-articular disease group, in particular C4 (table 2). Patients with severe extra-articular manifestations tended to be more likely to have had a positive rheumatoid factor (table 2).

Our results indicate that severe extra-articular manifestations still occur in a substantial proportion of patients. Some recent studies indicate a decrease in the incidence of rheumatoid arthritis-associated vasculitis.[5 6] The present sample is not sufficient to compare the incidence rate of vasculitis or other individual extra-articular manifestations specifically with other studies.

The median time from the diagnosis of rheumatoid arthritis to the onset of severe extra-articular disease was longer than that reported previously.[7] The use of early disease-modifying antirheumatic drug treatment of active disease may have delayed the onset of severe extra-articular manifestations compared with older studies. It is possible that early treatment with methotrexate, which was not part of our protocol in the 1980s and early 1990s, may further delay or prevent severe extra-articular disease.

Although C4 levels were generally within the normal range, higher levels, comparable with those seen in rheumatoid arthritis controls, would have been expected in extra-articular rheumatoid arthritis patients as complement levels tend to increase with systemic inflammation.[8] Our results are therefore compatible with early complement activation related to immune complex formation, which may be particularly important in vasculitis.[9 10] The pathogenesis of extra-articular manifestations requires further study.

Table 1 Incident severe extra-articular manifestations according to predefined criteria, identified in a structured retrospective survey

	N (%)	RA duration (years) at ExRA onset (median; range)
Pericarditis	3 (1.7)	13.6 (11.9–17.9)
Pleuritis	6 (3.3)	11.9 (0.1–16.4)
Felty's syndrome	2 (1.1)	8.6 (1.8–15.5)
Interstitial lung disease	5 (2.8)	12.9 (8.3–13.9)
Glomerulonephritis	3 (1.7)	6.2 (2.2–8.4)
Peripheral neuropathy	5 (2.8)	5.2 (3.7–15.8)
Scleritis	1 (0.6)	7.2
Episcleritis	3 (1.7)	14.3 (14.0–15.8)
Major cutaneous vasculitis	3 (1.7)	6.9 (2.2–8.6)
Other major organ vasculitis*	1 (0.6)	5.4
Any severe ExRA manifestation	22 (12.3)	10.7 (0.1–16.4)

ExRA, extra-articular rheumatoid arthritis; RA, rheumatoid arthritis.
*One case of nasal necrotising vasculitis, occurring together with mononeuropathy and cutaneous vasculitis, but without other signs of Wegener's granulomatosis.

Table 2 Baseline data* for patients developing extra-articular disease versus non-extra-articular rheumatoid arthritis patients

	ExRA	Non-ExRA	
N	22	157	p
Age; years (mean; SD)	48.4 (10.2)	51.9 (12.7)	0.21
Male/female (N)	8/14	56/100	0.89
Current smoker	10 (50%)	41 (36%)	0.22
Ever smoker	15 (75%)	70 (61%)	0.23
IgM RF positive	19 (90%)	116 (76%)	0.25
IgA RF positive	20 (95%)	115 (79%)	0.05
IgG RF positive	18 (86%)	97 (64%)	0.05
ANA positive	10 (45%)	65 (41%)	0.72
Anti-CCP positive	19 (90%)	118 (79%)	0.25
CRP, mg/l (median; IQR)	5 (0–61)	15 (0–42)	0.88
ESR, mm/h (mean; SD)	40.8 (32.5)	35.2 (27.0)	0.38
Complement (mean; SD)	10.9 (3.4)	12.0 (3.8)	0.22
C3, % of normal (mean; SD)	114.2 (11.6)	120.7 (27.3)	0.11
C4, % of normal (mean; SD)	106.1 (25.0)	129.6 (39.5)	0.03
HAQ, mean; SD	0.94 (0.65)	0.92 (0.59)	0.89

ANA, Antinuclear antibody; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ExRA, extra-articular rheumatoid arthritis; HAQ, Health Assessment Questionnaire; IQR, interquartile range; RF, rheumatoid factor.
*Missing data for smoking (two with ExRA and 42 non-ExRA patients), C3 and C4 (seven with ExRA and 37 non-ExRA patients), IgM RF, IgA RF, IgG RF and anti-CCP (one with ExRA, six non-ExRA patients).

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The use of the tumour necrosis factor antagonist infliximab in heart transplant recipients: two case reports

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Inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), have been implicated in the pathophysiology of heart failure, leading to the hypothesis that TNF inhibition might improve the symptoms of patients with moderate-to-severe cardiac symptoms. Recent data from the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) pilot study, however, suggested that infliximab, a chimeric monoclonal antibody against TNF-α, not only failed to produce clinical benefits, but given at higher doses (10 mg/kg) was associated with a worsening of cardiac symptoms. Conversely, two large-scale trials, RECOVER and RENAISSANCE, examined the effects of infliximab and etanercept in over 2000 patients with heart failure, finding no increased risk of mortality or morbidity.[1] We describe two case reports of patients who received TNF antagonist therapy after heart transplant for heart failure. The patients had a previous history of rheumatoid arthritis, diabetes mellitus, and hypertension, as well as other conditions, including hypercholesterolemia, psoriasis and colon cancer (case 1, Hispanic man, 58 years old) and peripheral vascular disease (case 2, African-American woman, 63 years old). The use TNF antagonist therapy after heart transplant was of concern, in light of the ATTACH study results, as well as the lack of data regarding tumour recurrence in patients on TNF antagonists.