

Reduced Burden of Disease and Improved Outcome of Patients with Rheumatoid Factor Positive Rheumatoid Arthritis Compared with Dropouts. A 10 Year Observational Study

JOHN DARMAWAN, JOHANNES J. RASKER, and HENDRI NURALIM

ABSTRACT.

Our objective was to determine outcome and burden of disease in a 10 year study of patients with rheumatoid factor positive rheumatoid arthritis (RF+ RA) compared with study dropouts. Three hundred and one consecutive subjects with disease duration of 3–255 months at presentation were enrolled. The acute (as measured by C-reactive protein, CRP) and chronic (by erythrocyte sedimentation rate, ESR) phases of RF+ RA were suppressed by pulse intravenous (IV) combination of low dose methylprednisolone (MPS) + cyclophosphamide (CYC) for 3 consecutive days and weekly intravenous methotrexate (MTX) with simultaneous oral cyclosporine (CSA) + mycophenolate mofetil (MPM). After achieving negative CRP and ESR < 40 mm/h, IV therapy was tapered and switched to oral low dose MTX+CSA+MPM until negative CRP titer and ESR < 25 mm/h (men < 15 mm) Westergren were achieved. American Rheumatism Association (ARA) functional classification measured disability. Dropouts did not complete the study for various reasons. At baseline, cases and dropouts were comparable in age and sex distribution, including mean age, disease duration, disease features, and associated conditions. Mortality in 274 cases was 2.9% versus 25.9% in dropouts. ARA functional class in cases decreased from 3.2 ± 0.7 to 1.4 ± 0.3 and in dropouts was 3.2 ± 0.6 at baseline versus 3.5 ± 0.5 at outcome. Disability of dropouts was significantly worse compared with cases. In dropouts, more associated conditions occurred than in cases. The burden of disease and outcomes were significantly worse in dropouts compared with cases. (J Rheumatol 2003;30 Suppl 67:50-53)

Key Indexing Terms:

RHEUMATOID FACTOR POSITIVE
RHEUMATOID ARTHRITIS
IMMUNOSUPPRESSANT
MORTALITY
OUTCOME
BURDEN OF DISEASE

From the WHO Collaborating Center, Community-Based Epidemiology, Prevention, and Treatment of Rheumatic Disease, Seroja Rheumatic Center, Semarang, Indonesia; and Department of Rheumatology, Medisch Spectrum Twente and Communication Studies, University Twente, Enschede, The Netherlands.

J. Darmawan, MD, PhD, Director; H. Nuralim, MD, WHO Collaborating Center, Community-Based Epidemiology, Prevention, and Treatment of Rheumatic Disease, Seroja Rheumatic Center; J.J. Rasker, MD, Department of Rheumatology, Medisch Spectrum Twente and Communication Studies, University Twente.

Address reprint requests to Dr. J. Darmawan, Seroja Rheumatic Center, Jalan Seroja Dalam 7, Semarang 50136, Indonesia.

Methotrexate (MTX)¹, cyclosporine (CSA)², and mycophenolate mofetil (MPM)³ are disease modifying antirheumatic drugs (DMARD). In the treatment of rheumatoid arthritis (RA), oral combination of MTX+CSA⁴+corticosteroid and pulse intravenous (IV) methylprednisolone (MPS) + cyclophosphamide (CYC)⁵ are effective. Single-drug therapy with a DMARD was not or was less effective in moderate or severe RA⁶.

The objective of our 10-year observational study was to describe outcome and calculate burden of disease in people with rheumatoid factor positive (RF+) RA treated with a combination of 4–5 immunosuppressants compared with those who withdrew from study (dropouts).

MATERIALS AND METHODS

The 301 consecutive new patients with RF+ RA between January 1984 and 1989 were enrolled in a 10-year observational study. RF+ RA was defined when a titer of RF latex > 640 and/or RF Waaler-Rose > 32 was present. Standard laboratory monitoring, in particular of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), was carried out at baseline and at followup to determine response to therapy and to monitor adverse effects.

Radiographic films were read openly by the first and blindly by the third author and graded by Rau modified Larsen classification⁷. Any differences of opinion were discussed until agreement was reached.

The mean scores for associated conditions and for demographic, clinical, radiographic, and laboratory variables of the 301 subjects were recorded at baseline and at final visit in those who completed the therapy (cases) and in dropouts followed for comparison.

No oral CYC and MPS were prescribed. Subsequently, tapering of the frequency and dosage of immunosuppressants was determined according to improvement of CRP and ESR when clinical symptoms and signs had subsided⁸. A negative CRP and ESR < 25 mm/h was maintained^{9,10} until final evaluation.

Initial treatment was 3 consecutive daily pulse IV combinations of MPS (0–125 mg) + CYC (0–100 mg), and weekly IV MTX (5–10 mg) with simultaneous oral CSA (25 mg bid–tid) to all patients. MPM (250 mg bid–tid) was added to suppress resistant flares. The frequency, dosages, interval between successive pulses, and total number of pulses and oral administration varied in each individual depending on response and adverse effects.

After negative CRP and ESR < 40 mm/h (arbitrary) were reached, IV therapy was tapered step-by-step from 1- to 3-monthly intervals, and optimal therapeutic doses were reduced to minimum effective doses before termination of IV administration. Subsequently, treatment was switched to oral administration of MTX+CSA+MPM. When RF+ RA was in control under maintenance therapy (CuMT) oral MTX was tapered first, then MPM, and finally CSA if no flare occurred.

Disease in CuMT was present when under optimal and minimal effective dosages of immunosuppressants the mean values of the following core set endpoints were achieved and maintained for at least 1 year and 3 months: swollen and tender joint count < 0.5; CRP titer < 3 mmol/l; American Rheumatism Association functional class < 2; patient and physician global assessment > 4; visual analog scale < 10; ESR < 25 mm/h (men < 15 mm) Westergren; mean Larsen Index and Erosive Joint Count not significantly worse compared with baseline. A flare was defined when arthritis reappeared in > 1 joints with a CRP titer > 6 mg/l and/or ESR > 25 mm/h (men < 15 mm). Burden of disease covered disability and socioeconomic handicap.

Statistical analysis was performed using the software SPSS-PC Version 9.

RESULTS

Age and sex-specific distribution, the mean scores of clinical, radiological and laboratory variables, and associated conditions of the 274 cases and 27 dropouts at baseline were comparable ([Table 1](#), [Table 2](#)). The outcomes of these and associated conditions of the 274 cases and 27 dropouts at baseline were comparable ([Table 1](#), [Table 2](#)). The outcomes of these variables were significantly worse in the dropouts compared with the cases and baseline. The mean flare rate per patient over the period of 10 years was 0.612.

Table 1A. Comparison of demographic data and sex-specific distribution of 274 cases and 27 dropouts with rheumatoid factor positive rheumatoid arthritis.

	Cases		Dropouts	
	1st Visit, n = 274	Final Visit, n = 268	1st Visit, n = 27	Final Visit, n = 20
Mortality, %	—	2.2	—	25.9
Age range, yrs	17–78	27–88	19–76	29–86
Mean age, yrs, SD	33 ± 15.1	42 ± 17.4	32 ± 16.3	42 ± 16.9
Male: female ratio	1:3	1:3	1:3	1:3
Range of disease duration, mo	2–255	122–275	4–255	124–275

Mean disease duration, mo 46.9 ± 166.8 47.1 ± 167.2
 25.6 ± 67.7 17.8 ± 67.8

Table 1B. Demographic data by age group in cases compared with dropouts.

	Age Groups						Total
	15–24	25–34	35–44	45–54	55–64	65+	
Cases							
Women	33	51	39	36	30	17	206
Men	11	17	13	12	10	5	68
Women + men	44	68	52	48	40	22	274
Mortality							
Women	—	—	—	—	2	3	5
Men	—	—	—	—	—	1	1
Women + men	—	—	—	—	—	—	6
Dropouts							
Women	3	6	3	3	3	2	20
Men	1	2	1	1	1	1	7
Women + men	4	8	4	4	4	3	27
Mortality							
Women	—	—	—	—	3	3	6
Men	—	—	—	—	—	1	1
Women + men	—	—	—	—	—	—	7

Table 2. Univariate analysis of the mean scores of clinical, disability, radiographic, laboratory variables, and associated conditions of 274 cases and 27 dropouts at baseline and last visit.

	Cases		Dropouts	
	1st Visit, n = 274	Final Visit, n = 268	1st Visit, n = 27	Final Visit, n = 20
Clinical and laboratory variables				
Mean swollen joint count	5.4 ± 2.2	0.2 ± 0.1	5.5 ± 2.2	17.4 ± 6.3
Mean tender joint count	4.5 ± 1.7	0.2 ± 0.1	4.5 ± 1.6	16.2 ± 6.5
Mean visual analog pain scale	53.5 ± 21.3	4.6 ± 1.8	52.9 ± 19.9	81.7 ± 31.4
Mean erosive joint count	3.2 ± 2.3	2.7 ± 2.1	3.3 ± 2.3	10.9 ± 8.3
Mean Larsen Index	2.3 ± 0.7	2.4 ± 0.6	2.1 ± 0.8	3.1 ± 0.8
Mean physician global assessment	1.7 ± 0.7	4.1 ± 0.9	1.6 ± 0.9	1.3 ± 0.4
Mean patient global assessment	1.9 ± 0.5	4.0 ± 0.9	2.0 ± 0.1	1.1 ± 0.1
Mean CRP titer, mmol/l	17.3 ± 5.7	0.3 ± 0.1	17.9 ± 6.0	39.8 ± 17.1
Mean ESR, mm/h	64.2 ± 26.8	16.2 ± 6.3	63.9 ± 23.9	87.5 ± 37.2
Functional class and burden of disease				
ARA functional class	3.2 ± 0.5	1.3 ± 0.2	2.4 ± 0.3	3.5 ± 0.5
Family support, %	15.0	0.0	14.8	100.0
Dependent self-care, %	9.9	0.0	11.1	40.0
Aided mobility, %	6.9	0.0	7.4	45.0
Wheelchair bound, %	1.1	1.1	0.0	45.0
Associated conditions and complications				
Skin disorders, %	1.5	3.7	3.7	80.0
Abnormal ALT, %	2.9	0.0	3.7	45.0
TIA and/or CVA, %	1.1	0.0	3.7	30.0
Hematemesis/melena, %	1.1	1.9	0.0	25.0
Renal disease, %	1.1	2.2	0.0	25.0
Ischemic hearth disease, %	0.7	0.7	0.0	20.0
Cataract, %	0.7	0.7	3.7	20.0
Diabetes mellitus, %	0.7	3.7	3.7	20.0
Hypertension, %	3.6	2.2	3.7	20.0
Osteoporotic vertebral fracture, %	5.5	7.4	0.0	15.0
Osteoporotic hip fracture, %	0.7	0.0	0.0	5.0

Femoral head osteonecrosis, %	0.4	0.0	0.0	11.1
Digital rheumatoid vasculitis, %	0.4	0.4	0.0	5.0

Twenty-one patients dropped out because of noncompliance to treatment and laboratory monitoring schedules, but not due to more severe or more resistant disease. Dropouts were due to direct adverse effects as follows: MTX 3 patients, CYC 2, and MPS 1.

Mortality in the cases was due to tuberculosis in 1, sepsis in 1, stroke in 2, malignancy in 1, and myocardial infarct in 1. In the dropouts, death was due to traffic accident in 1, myocardial infarction in 3, and cerebrovascular accident in 3. Death in both cases and dropouts occurred in the age group of > 55 years with disease duration of > 20 years at presentation. Due to immediate suppression of an early flare, all cases were in CuMT at the final visit.

DISCUSSION

A negative CRP and ESR < 25 mm/h (men < 15 mm)^{9,10} were maintained until the end of the study. This was achieved longterm with minimum effective dose of 1–2 immunosuppressants. Rare flares during the period of 10 years were immediately suppressed. Joint protection may have helped in the prevention of new erosions and inhibition of deterioration of existing erosions¹¹. Halting progression of existing erosions has prevented further joint destruction, ankylosis, joint deformities, and worsening of disability¹².

Mortality in the dropouts is higher due to uncontrolled progression of disease and worsening of the associated conditions including atherosclerotic events and due to abuse of prednisone and/or nonsteroidal antiinflammatory drugs. However, the direct and indirect association of RF+ RA with mortality is difficult to determine. A real control group would be required to get a true picture of the natural course of the disease when treated in the traditional way, but in our opinion this is ethically unacceptable. Cases would have fared comparably to the dropouts if autoimmune inflammation had not been totally suppressed.

Hemorrhagic cystitis is not recorded due to the low dose and relative short period of IV CYC exposure. We have not prescribed oral CYC¹³ and MPS¹⁴ because of significantly more frequent and more severe adverse effects compared with pulse IV CYC+MPS. The burden of disease in terms of disability and socioeconomic handicap was higher in dropouts than in the cases, as may be expected.

The following circumstances made the conversion of burden of disease into US dollars impossible: indirect costs of lost earnings and career, complicated by high unemployment, by disguised and parttime employment in a developing country; fluctuating monetary exchange rate with US dollars from month to month; unrecorded nonmedical, alternative, and self-medication; lack of rheumatic care registries; low-

income patients' lack of health insurance and social security; lack of a national rheumatic disease control program; and unquantifiable psychological suffering of the patient.

To conclude, in our study of rheumatoid arthritis the burden of disease and the outcomes were significantly worse in study dropouts compared with baseline scores and with the follow up scores of cases.

REFERENCES

1. Kremer JM. Safety, efficacy, and mortality in a longterm cohort of patients with rheumatoid arthritis taking methotrexate. Followup after a mean of 13.3 years. *Arthritis Rheum* 1997;40:984-5. [[MEDLINE](#)]
2. Pasero G, Priolo F, Marubini E, et al. Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporine A. *Arthritis Rheum* 1996;39:1006-15. [[MEDLINE](#)]
3. Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin Exp Rheumatol* 1993;11 Suppl 8:S117-9.
4. Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporin and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;333:137-41. [[MEDLINE](#)]
5. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. *Am J Med* 1984;76:377-84. [[MEDLINE](#)]
6. Calguneri M, Pay S, Caliskaner Z, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1999;17:699-704. [[MEDLINE](#)]
7. Rau R, Schleuser B, Herborn G, Karger T. Longterm treatment of destructive rheumatoid arthritis with methotrexate. *J Rheumatol* 1997;24:1881-9. [[MEDLINE](#)]
8. Devlin J, Gough A, Huissoon A, et al. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with outcome. *J Rheumatol* 1997;24:9-13. [[MEDLINE](#)]
9. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Dessop JD. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43:1473-7. [[MEDLINE](#)]
10. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. *J Rheumatol* 1997;24:20-7. [[MEDLINE](#)]

11. Hammond A, Freeman K. One-year outcomes of a randomized controlled trial of an educational-behavioural joint protection programme for people with rheumatoid arthritis. *Rheumatology* 2001;40:1044-51. [[MEDLINE](#)]

12. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000;43:22-9. [[MEDLINE](#)]

13. Haubitz M, Schellong S, Gobel U, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998;41:1835-44. [[MEDLINE](#)]

14. Petri M, Zonana-Nacach A, Barr S, Magder L. Damage in systemic lupus erythematosus is dependent on dose and mode of delivery of corticosteroid [abstract]. *Arthritis Rheum* 1999;42 Suppl:S97.