Ten-Year Radiographic Outcome in Patients with Rheumatoid Factor Positive Rheumatoid Arthritis Treated with Aggressive Immunosuppressive Combination Therapy

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ABSTRACT. We observed 10-year radiographic outcomes in patients with rheumatoid factor positive rheumatoid arthritis prospectively. Group I, II, and III comprised 87, 125, and 89 consecutive subjects with disease duration at presentation of less than 4, 4–24, and 25–255 months, respectively. Initial therapy was with combinations of pulse intravenous (IV) methylprednisolone (0–125 mg), cyclophosphamide (100–200 mg), methotrexate (MTX, 5–15 IV mg/week) and simultaneous oral cyclosporin A (CSA, 25 mg bid/tid). After disease was controlled IV therapy was tapered and switched to oral MTX + CSA. Outcomes from the Larsen Index and Erosive Joint Count were compared in cases and in dropouts with baseline and each other. Significant improvement in the Larsen Index and Erosive Joint Count was observed in Group I ($p < 0.0001$). In Group II and III the improvement or deterioration was not significant. The Larsen Index and Erosive Joint Count deteriorated significantly in the dropouts compared with baseline and cases ($p < 0.0001$). In conclusion, in early RA, in a Malayo-Polynesian patient sample, radiological progression could be halted with aggressive combination treatment. (J Rheumatol 2004;31 Suppl 69:66–69)

Key Indexing Terms:
RHEUMATOID FACTOR POSITIVE RHEUMATOID ARTHRITIS IMMUNOSUPPRESSANT
LARSEN INDEX EROSIVE JOINT COUNT FUNCTIONAL CLASS CLINICAL STUDY

Methotrexate (MTX)[1], cyclosporin A (CSA)[2], and mycophenolate mofetil (MMF)[3] are disease modifying antirheumatic drugs (DMARD). In the treatment of rheumatoid arthritis (RA) the oral combination of MTX + CSA[4] + corticosteroid and pulse intravenous (IV) methylprednisolone (MPS) + cyclophosphamide (CYC)[5] were effective. Single drug therapy with a DMARD was not effective or was less effective in moderate or severe RA[6].

The objective of our observational study was to describe 10-year radiographic outcomes in rheumatoid factor positive rheumatoid arthritis (RF+ RA) treated with a combination of 4 or 5 immunosuppressants.

MATERIALS AND METHODS

All new cases of RF+ RA seen between January 2, 1984, and January 2, 1989, a total of 301 cases, were included in the study. RF+ RA was defined when a titer of RF latex ≥ 640 and/or RF Waaler-Rose ≥ 32 was present. Categorization in Group I (N = 87), II (N = 125), and III (N = 89) was based on disease duration at presentation of < 4 months (very early), 4–24 months (early), and > 24 months (late), respectively. Standard laboratory monitoring was carried out for response to therapy and adverse effects of drugs.

Posterior-anterior hand and/or foot radiographs were taken at entry and every 6 months during the first 2 years and yearly thereafter. The same investigator (JD) evaluated all patients at the first and the last visit; radiographic films were read openly by the first and blindly by the third author. In case of differences of opinion these were discussed until agreement was reached. Erosions were graded by a Rau modified Larsen classification[7].

Titer of C-reactive protein (CRP)[8], erythrocyte sedimentation rate (ESR), symptoms, and signs of inflammation and response to therapy were guidelines to initial frequency and dosage of immunosuppressants (Table 1).

Subsequently, tapering of the frequency and dosage of immunosuppressants was based on improvement of laboratory indicators when clinical symptoms and signs had subsided. Negative CRP and normal ESR were maintained[9,10] until final evaluation.

Initial treatment was 3 consecutive-day pulse IV combination of MPS + CYC, weekly IV MTX[11], and simultaneous oral CSA to all patients (Table 1). Since 1994 MMF has been added to suppress flare[3]. All received oral folic acid 1 mg/day. The frequency, dose, and total number of subsequent pulses and oral administration varied in each subject depending on response and adverse effects. Once disease activity was controlled, the frequency of IV therapy was tapered from monthly to 3-monthly, and doses were tapered to a minimum. Subsequent treatment was switched to oral administration of MTX + CSA. When patient's disease was in remission taking oral drugs, MTX was tapered first, subsequently MMF, and finally CSA, to obtain disease remission without drug. Flares were immediately suppressed in similar fashion. Patient education, including joint protection, was emphasized[12].

By meticulous history taking, preventive measures were taken to mini-

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Table 1. Immunosuppressants in combination in the treatment of rheumatoid factor positive RA.

	Dose	Frequency	Maximum Dose
Pulse IV			
Methylprednisolone	0.00*–500 mg/day	3 consecutive days	1000 mg/week
Methotrexate	5–10 mg/week	once weekly	15 mg/week
Cyclophosphamide	1–5 mg/kg BW	3 consecutive days	< 500 mg/week
Oral therapy			
Methotrexate	5–10 mg/week	once weekly	15 mg/week
Cyclosporin A	1–2 mg/kg BW/day	daily	3 mg/kg BW/day
Mycophenolate mofetil**	250 mg bid	daily	250 mg tid

* Those with diabetes mellitus and intolerant gastrointestinal tract did not receive IV MPS. ** only since 1994.

mize gastrointestinal (GI) adverse effects. Patients with a history of gastroduodenal ulcers and irritation due to nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids were given oral and/or IV H2 antagonists and/or proton pump inhibitors simultaneously with the intravenous MPS + CYC and the weekly IV MTX. Patients at high risk for GI bleeds (history of melena and/or hematemesis) were not administered IV MPS.

In those with latent diabetes mellitus (DM), IV MPS was given only in 1–3 initial dosages while fasting, and 2 hours after meals blood glucose levels were closely watched. In patients with existing DM, no IV MPS was administered. These preventive measures may have minimized the appearance of new cases of DM and exacerbation of existing DM.

When radiographs of hand and foot joints showed localized osteopenia and/or osteoporosis, 7.5–15 mg clodronic acid (a biphosphonate) IV was additionally given in every IV session to prevent exacerbation of existing and/or the appearance of new osteoporosis[13].

No CYC or MPS was prescribed orally as side effects may be more severe than with IV administration. Compared with oral daily MPS, the moon face of intermittent IV MPS was not prominent[14]. In a few sensitive patients serum potassium and/or calcium dropped to abnormal low levels after a few IV MPS infusions. This was treated with IV modified Ringer's solution.

Controlled disease was defined as the following core set endpoints achieved for at least 3 months while receiving optimal dosages of immunosuppressants: mean swollen and tender joint count < 0.5; CRP titer < 0.5 mmol/l; mean American Rheumatism Association Functional Class < 2; mean patient and physician global assessment 4 or 5 (1 = worst; 2 = bad; 3 = moderate; 4 = good; 5 = excellent); mean visual analog pain scale < 10; mean ESR < 25 mm/h Westergren (men < 15 mm); and mean Larsen Index and Erosive Joint Count not significantly worse.

Remission taking oral drugs or remission without drug was defined as: when receiving minimal doses of 1–2 immunosuppressants, respectively, or without drug, the above core set endpoints were maintained for at least 1 year.

Flare was defined as: the reappearance of arthritis in ≥ 1 joints with a CRP titer > 6 mg/l and/or ESR of > 25 mm/h (men > 15 mm).

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

RESULTS

All patients were from the upper or higher middle class. More than 40% were ethnic Han and less than 60% were Malayo-Polynesian. Mixed Han and Malayo-Polynesian racial background could not be excluded. Male and female ratio was 1:3. Age ranges in years [mean age at presentation ± standard deviation (SD)] were: Group I 17–63 (28 ± 11.9), Group II 24–72 (29 ± 12.5), Group III 31–78 (41 ± 21.8), Groups I, II, III 17–78 (33.7 ± 15.4), and dropouts 18–76 (32 ± 15.5). NSAID and/or paracetamol and/or tramadol were given on demand for symptomatic relief of pain in the initial weeks before immunosuppressants attained therapeutic effect.

Twenty-seven patients dropped out because of noncompliance to treatment and laboratory testing, but not due to more severe or more resistant disease (Table 2).

The p value of the difference for improvement of the Larsen Index between the first and final visit: Group I < 0.0001, Group II > 0.05, Group III > 0.05, Groups I, II, III > 0.05; and for deterioration in dropouts < 0.0001 (Table 2). For improvement in the difference of the erosive joint count between the first and final visit the p value was: Group I < 0.0001, Group II > 0.05, Group III > 0.05, Group I, II, III > 0.05, and for deterioration in the dropouts < 0.0001.

The most frequent adverse effects of combination of low dose immunosuppressants were mild GI complaints (55.5%). Hematologic adverse effects were rare, comprising one case of leukopenia of 900/cc due to MTX and 1 case of 500/cc due to CYC. This was established after temporary suspension of all immunosuppressants and rechallenge agent by agent to identify the causal agent. Leukopenia was quickly overcome in a relatively short time with IV filgrastim. When a flare occurred several years later, rechallenge with a pulse IV combination of MPS + MTX + CYC with MTX of 5 mg/week and CYC 50 mg per pulse over a period of several weeks did not reinduce these adverse hematological effects and treatment still showed efficacy.

DISCUSSION

A relatively brief intervention by pulse IV low dosages of MPS + MTX + CYC that suppresses CRP and ESR to their normal values, and which were further maintained by oral immunosuppressant(s), resulted in longterm structural benefits in patients with RF+ RA[15]. The shorter the period between disease onset and initiation of therapy, the shorter the cumulative treatment period to remission with oral drugs and remission without drugs in patients with RF+ RA (Table 2)[16]. It is possible for grade ≤ 1 erosions in very early RF+ RA to heal and the disease to achieve longterm control without drug, provided flare is immediately suppressed.

Table 2. Clinical data, Larsen grades, and outcome of treatment of 301 patients with rheumatoid factor positive RA, including dropouts.

Group	I	II	III	Total	Dropouts
Disease duration at start, mo	< 4	4–24	> 24		
No. at 1st visit	87	125	89	301	—
Disease duration at start, mo, mean ± SD	3.1 ± 1.2	13.2 ± 4.3	137.5 ± 42.2	44.8 ± 14.7	48.5 ± 17.9
Treatment period to remission on oral drugs, mo, mean ± SD	9.2 ± 2.7	25.3 ± 9.1	76.6 ± 24.4	34.5 ± 11.1	—
Treatment period to TFC, mo, mean ± SD	21.7 ± 7.8	67.5 ± 21.7	—	—	—
Baseline mean Larsen Index	0.1 ± 0.0	3.1 ± 1.0	3.3 ± 0.6	2.4 ± 0.5	2.3 ± 0.7
Outcome mean Larsen Index	0.0 ± 0.0	3.0 ± 1.0	3.4 ± 0.5	2.4 ± 0.3	3.5 ± 0.5
Baseline mean Erosive Joint Count	0.1 ± 0.0	1.6 ± 0.3	8.4 ± 2.2	3.2 ± 0.9	3.1 ± 1.1
Outcome mean Erosive Joint Count	0.0 ± 0.0	1.5 ± 0.2	7.3 ± 2.1	2.7 ± 1.4	15.2 ± 6.2
Dropouts	4	10	7	21	—
Withdrawals	1	3	2	6	—
Mortality in cases	1	2	3	6	7–
No. at final evaluation	81	110	77	268	20
No. of patients without erosion in TFC	72	25	—	97	—
No. of patients without erosion in remission on oral drugs	9	—	—	9	—
No. of patients with Larsen Gr 1 in remission on oral drugs	—	5	—	5	—
No. of patients with Larsen Gr > 2 in remission on/off oral drugs*	—	80	77	157	—
No. of flares	21.4	70.0	69.3	160.7	—

* In remission on/off oral drugs: when under minimal doses of 1–2 immunosuppressants or without drug, the core set endpoints were maintained for at least 1 year i.e., erosions were not worse compared to baseline.

Early and late RF+ RA with grade ≥ 2 erosions can be controlled and kept under control longterm without significant deterioration of overall Larsen Index and Erosive Joint Count (Table 2). Joint protection and administration of IV bisphosphonates when required may have helped in the prevention of new erosions in Group I and inhibition of deterioration of existing erosion in Group II and Group III[13]. Disease duration[17] and grades of erosion[18] determine longterm outcome of the combination therapy with immunosuppressants.

The quick and dramatic relief of pain, reversal of morbidity, and functional recovery in very early and early RF+ RA by pulse IV combination of MPS + MTX + CYC was impressive to the patients and their families. This has prevented the development of new erosions in very early disease.

It may be expected that cases maintained in remission with oral drugs and remission without drugs would have had a similar course as dropouts if autoimmune inflammation had not been totally suppressed.

The expression and general course of RA in ethnic Han and Malayo-Polynesian subjects appears to be milder than in series in Europe[19]. Justification for early aggressive and intensive administration of combination of low dose selective immunosuppressants is based on the following considerations: up to 100% of RA patients will ultimately suffer from erosions[18]; RA morbidity can be reversed when treated early[16]; in our cohort patients with grade ≥ 2 erosions cannot obtain remission without drug; reduction of mean Larsen Index and mean Erosive Joint Count was insignificant in Groups II and III at the end of the study compared with baseline, indicating that the progression of the disease could be halted; but these are significantly increased in the dropouts compared with baseline and the cases; in RA the autoimmune inflammation is at its peak at disease onset and is most responsive to treatment; the outcome of disability is determined by the duration of disease before it becomes irreversible; patients in very early and early disease are in general relatively well, particularly regarding GI tolerance to drugs.

Longterm maintenance therapy with immunosuppressants was justified, as zero inflammation (negative CRP and normal ESR)[8,9] inhibited disease-induced new and/or exacerbation of existing erosions. Most probably due to the low dose immunosuppressants, hematological adverse effects were rare. Cystitis was not recorded due to the low dose of CYC applied. Oral CYC and MPS were not prescribed because of more frequent and severe adverse effects compared with pulse IV CYC + MPS[14]. This is based on previous anecdotal experience, which was later confirmed by Haubitz, *et al*[20] and Petri, *et al*[14] in vasculitis and systemic lupus erythematosus, when more frequent and more severe adverse effects were encountered compared with pulse IV administration of MPS + CYC. Similar

adverse effects of daily oral CYC + MPS can be expected in patients with RF+ RA.

CONCLUSION

In early RA, in a Malayo-Polynesian patient sample, radiological progression could be halted with aggressive combination treatment.

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