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A RANDOMIZED CLINICAL TRIAL OF IN-PATIENT MULTIDISCIPLINARY TREATMENT VERSUS ROUTINE OUT-PATIENT CARE IN ACTIVE RHEUMATOID ARTHRITIS

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SUMMARY

The aim of the present study was to compare the effects of in-patient multidisciplinary treatment with standard out-patient care in patients with active rheumatoid arthritis (RA). Eighty patients with active RA were randomized to receive 11 days of in-patient multidisciplinary treatment followed by standard out-patient care ($n = 39$), or to standard out-patient care only ($n = 41$). Patients were assessed at baseline, and after 2, 4, 12 and 52 weeks. In the in-patients, the improvement in variables of disease activity (weeks 2 and 4) and emotional status (weeks 4 and 12) was greater when compared with the out-patients ($P < 0.05$). The improvement in laboratory and functional measures did not differ between the groups. In the in-patient group, the percentage of patients responding to the American College of Rheumatology criteria for improvement was significantly greater at any time point during follow-up than in the out-patient group. A short period of in-patient multidisciplinary treatment for active RA has a direct beneficial effect on disease activity and emotional status with the favourable effect on disease activity remaining after 52 weeks.

KEY WORDS: Rheumatoid arthritis, Hospitalization, Multidisciplinary treatment, Rehabilitation, Outcome.

FOR several decades, a conservative treatment regimen was considered to be the basis of the management of patients with active rheumatoid arthritis (RA) [1–3]. This basic regimen consisted of medical treatment with salicylates, bed rest, joint splinting, exercise therapy, heat or cold therapy, occupational therapy and emotional support. The basic treatment of RA patients was traditionally carried out in an in-patient setting and could last up to several months. Initially, only observational studies provided evidence to support the advantages of hospitalization for multidisciplinary treatment [4–11]. In the past 20 yr, a few controlled studies have compared in-patient and out-patient management [12–17]. The results consistently favoured the patients cared for in the hospital, for periods even as short as 10–14 days. However, only one of these studies [16] used randomization and had an adequate number of patients and duration of follow-up period.

Over recent years, the number and duration of hospital admissions for flares of RA have decreased, following a general trend towards restriction of health care costs and keeping patients out of hospital. As the literature is not conclusive, the question remains whether hospitalization can make a valuable contribution to the management of RA patients with high disease activity.

The present study aimed to answer the following questions. (1) Does a short period of intensive in-patient multidisciplinary team care have advantages over the regular out-patient care for active RA in terms of disease activity, functional status and emotional status? (2) Does the treatment effect persist over length of time?

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PATIENTS AND METHODS

Study groups

All patients with active RA, requiring institution or change of disease-modifying anti-rheumatic drugs (DMARDs) and visiting the out-patient clinic of Leiden University Hospital, were eligible for the study. Inclusion criteria were as follows: fulfilment of the 1987 American Rheumatism Association criteria for definite RA [18], age 18–75 yr, at least three swollen joints, and at least two of the following three criteria: a modified Ritchie Articular Index [19] ≥ 9, duration of morning stiffness ≥ 45 min and an erythrocyte sedimentation rate (ESR) ≥ 28 mm/h.

Exclusion criteria were a previous hospitalization for multidisciplinary treatment, a medical need for immediate hospitalization, classification in American College of Rheumatology (ACR) functional class I or IV [20], the presence of other major sources of disability or severe joint damage primarily requiring surgical correction.

The study was approved by the Medical Ethics Committee and all patients gave informed consent after receiving written information about the purpose of the study.

Trial design

After enrolment into the study, the patients were assigned at random to receive in-patient

multidisciplinary treatment followed by routine out-patient care or to receive the routine out-patient care only. Random allocation was achieved by means of randomly assorted cards which were placed in sealed envelopes in blocks of 10, and performed for women and men separately. Apart from the patients who were randomized, a third group of patients was studied, comprising those patients who fulfilled the inclusion criteria, but refused random allocation. All clinical data of this patient group were collected according to the study protocol. This group will be further indicated as the 'non-allocated patient group'.

In-patient treatment consisted of a fixed period of 11 days of hospitalization in a rheumatology clinic associated with the Leiden University Hospital shortly after study entry. The clinic is a referral centre with in-patient facilities for patients with rheumatic diseases from the district of Leiden (300 000 inhabitants) and surrounding districts (1 million inhabitants), and has 38 beds. Apart from primary nursing care, the treatment consisted of prescribed regimens of bed rest and a daily individual range of motion and muscle-strengthening exercise programme performed by the physical therapist. The occupational therapist provided information on the principles of joint protection, self-care, household and work activities. Joint splints, adaptive equipment and house adaptations were arranged for if necessary. The social worker discussed aspects related to coping with the disease and financial questions. Treatment goals and modalities were discussed during weekly multidisciplinary team conferences. In all study groups, DMARDs were introduced or changed shortly after study entry and during the whole study period non-steroidal anti-inflammatory drugs (NSAIDs) were optimized, intra-articular injections with corticosteroids were administered and DMARDs were changed if needed. During out-patient care, the prescription of drugs, paramedical treatment and splints was left to the attending physician at the out-patient clinic. In order to stay as close to daily practice as possible, no special attempts were made in either group to alter the treatment regimens normally employed in the out-patient setting.

Assessment methods

All patients were assessed at study entry, after 2 weeks (at discharge in the in-patient group), and at 4, 12 and 52 weeks. All assessments were done by the same physician (TPMV), who was not involved in the management of the patients, but could for practical reasons not be blinded to the patient's randomization status.

Measures of disease activity included the following. (1) The patient's estimation of severity of disease activity, pain and fatigue, all measured on a visual analogue scale (VAS). Morning stiffness was measured both by duration (minutes) and severity (VAS) [21]. (2) The physician's estimation of disease activity on a four-point scale, ranging from 0 = no disease activity to 3 = high disease activity. (3) The number of swollen joints; 20 joints were examined, including the temporomandibular joints, the sternoclavicular joints, the shoulders, elbows, wrists, knees and ankles. The proximal interphalangeal and metacarpophalangeal of each hand, and the metatarsophalangeal joints of each foot, were calculated as a single unit. (4) The modified Ritchie Articular Index [19], including the same joints plus the cervical spine and the hips (maximum possible score 69). (5) Laboratory investigations including ESR and C-reactive protein (CRP).

Functional status was assessed by (1) a Dutch version of the Health Assessment Questionnaire (HAQ) [22] and (2) grip strength, as measured with a Martin vigorimeter [23].

Emotional status was measured by the anxiety and depression items of the Dutch-Arthritis Impact Measurement Scales (AIMS) [24].

Radiographs of both hands, wrists and feet were made at study entry and after 52 weeks of follow-up. All radiographs were assessed according to the criteria of Kellgren [25] by an independent reader (A. Cats) (maximum possible number of affected joints 50; maximum erosion score 200).

Health care costs were calculated for in-patients by review of the comprehensive hospital charges at the rheumatology clinic at the time the study was conducted. The use of health care services during out-patient management in all groups was determined from medical records and patient interviews.

Statistical analysis

To calculate the sample size, the patient's estimation of pain as measured with a VAS was chosen as the primary outcome measure for the present trial. A difference of 30% between the in-patient and the out-patient group according to the improvement in the first 2 weeks was arbitrarily considered to be a clinically important difference for the present trial. Assuming no change in the out-patient group during the first 2 weeks, and using Student's two-tailed t-test of the difference between two means with $\alpha = 0.05$ and $\beta = 0.20$, a sample size of 36 in each group would be required to detect this difference.

Patients' characteristics at study entry and the use of medical and paramedical services during follow-up were compared by Mann–Whitney U or Pearson χ^2 tests where appropriate. Differences between the groups according to changes from baseline at the different time points were analysed on an intention to treat basis, by multiple regression analysis, adjusting for small variations in baseline values and medical treatment. The ACR preliminary criteria for improvement [26] were used to define 'responders' and 'non-responders'. Patients were characterized as responders if they showed $\geqslant 20\%$ improvement in both tender and swollen joint count, plus $\geqslant 20\%$ improvement in three out of five other ACR core set measures: patient and physician global assessments, patient pain, disability (HAQ score) and an acute phase reactant (ESR).

TABLE III
Mean values of measures of disease activity, functional status and emotional status of 108 patients, randomly assigned to the in-patient group (IG) or the out-patient group (OG), and the results of the non-allocated patient group (NA) at study entry and during follow-up

		Week				
		0	2	4	12	52
Pain (VAS; 0–10)	IG	4.55	3.44*	3.36*	3.14	2.80
	OG	5.04	5.03	4.82	3.96	3.68
	NA	3.83	3.91	3.88	3.72	3.00
Disease activity patient (VAS; 0–10)	IG	5.67	4.06*	3.91*	3.32*	2.83*
	OG	6.17	5.57	5.29	4.54	4.21
	NA	5.27	4.47	4.70	3.82	2.81
Morning stiffness (VAS; 0–10)	IG	4.64	3.42*	3.04*	2.62*	2.35
	OG	4.56	4.81	4.43	3.85	3.07
	NA	3.05	2.81	2.65	2.60	1.96
Fatigue (VAS; 0–10)	IG	4.26	3.49*	3.61*	3.52	3.12
	OG	5.27	5.37	5.13	4.61	4.23
	NA	4.39	3.94	4.34	4.62	4.10
No. of swollen joints (0–20)	IG	8.9	8.2*	7.6*	7.6	6.2
	OG	9.3	10.2	10.0	8.6	7.8
	NA	8.8	8.3	8.3	7.2	6.1
Ritchie Articular Index (0–69)	IG	18.1	13.1*	15.0*	12.7	11.8
	OG	17.9	17.9	17.2	14.6	13.1
	NA	15.2	12.7	11.6	10.3	9.7
ESR (mm/h)	IG	53.4	47.8	52.1	42.4	36.1
	OG	61.4	57.5	58.4	53.9	44.7
	NA	50.3	49.3	46.0	36.4	29.9
CRP (mg/l)	IG	41.4	35.1	37.2	29.1	23.9
	OG	33.9	35.0	31.9	32.5	25.8
	NA	34.1	35.0	38.1	20.7	19.5
HAQ score (0–3)	IG	1.23	1.01	1.17	1.11	1.04
	OG	1.23	1.24	1.17	0.99	0.94
	NA	1.00	1.11	1.00	0.97	0.87
Grip strength (kPa)	IG	29.7	31.7*	33.4	35.9	40.3
	OG	26.9	24.9	26.9	33.2	34.8
	NA	39.5	39.8	42.5	46.2	45.0
Anxiety (0–10)	IG	4.35	4.15	3.56*	3.26*	3.69
	OG	4.42	4.08	4.05	4.20	3.55
	NA	3.95	4.06	4.05	3.31	3.46
Depression (0–10)	IG	3.52	3.16	2.93	2.41*	2.66
	OG	3.83	3.48	3.79	3.54	2.71
	NA	3.21	3.58	3.34	2.80	2.54

*$P < 0.05$, comparison of changes from baseline between in-patient and out-patient group, results adjusted for differences at baseline (multiple regression analysis).

patients found the protocol visits too troublesome. The non-allocated patients had fewer changes of DMARDs and NSAIDs, and fewer intra-articular injections, than the randomized patients during follow-up (see Table II). In none of the non-allocated patients was prednisone started. With respect to the clinical status at baseline, the non-allocated patients had less disease activity and a better functional and emotional status when compared to the total group of randomized patients (see Table III). However, only the differences according to the patient's assessment of morning stiffness, the Ritchie Articular Index and grip strength reached statistical significance ($P < 0.05$). The improvement in the patient's estimation of pain, the Ritchie Articular index, the HAQ score and the depression score at week 2, and the anxiety score at weeks 2 and 4, was significantly smaller in the non-allocated group when compared with the in-patient group ($P < 0.05$). The comparison between the non-allocated group and the out-patient group showed that the improvement in the number of swollen joints at weeks 2 and 4, and the improvement in the CRP at week 12, was greater in the non-allocated group than in the out-patient group ($P < 0.05$). Table V shows that in general non-allocated patients had a lower use of medical and paramedical services during follow-up in comparison with the in-patient and out-patient groups.

TABLE IV
The number (percentage) of patients responding to the ACR criteria for clinical improvement during follow-up in 108 RA patients, randomly assigned to the in-patient group (IG) or the out-patient group (OG), and the results of the non-allocated patient group (NA)

	Week			
	2	4	12	52
IG	6 (15.3)*	7 (17.9)*	10 (25.6)*	18 (46.1)*
OG	0 (0)	0 (0)	3 (7.6)	9 (23.1)
NA	1 (3.7)	0 (0)	2 (7.7)	7 (26.9)

*$P < 0.05$, in-patient group compared with out-patient group (χ^2 test).

TABLE V
The use of medical and paramedical services and the introduction of adaptive equipment between 2 and 52 weeks after study entry in 104 patients† with active RA

	In-patient group ($n = 39$)	Out-patient group ($n = 39$)	Non-allocated patients ($n = 26$)
No. of office visits (mean; S.D.)	5.3 (2.4)	6.7 (5.4)	5.2** (2.3)
No. of laboratory investigations (mean; S.D.)	349 (152)	382 (238)	253** (150)
No. of radiographs (mean; S.D.)	1.1 (2.4)	1.6* (2.1)	1.0 (1.3)
No. of patients with a hospitalization for			
Active RA	3‡	4	1
Complications of RA or therapy	0	2‡	0
Orthopaedic surgery	2	0	2
No. of patients having one or more contacts with a			
Physical therapist	39	30*	15**
Occupational therapist	4	8	3
Social worker	4	9	3
District nurse	2	6	4
No. of patients with one or more			
Home adaptations	18	9*	2**
Orthopaedic shoe adaptations	14	7	2**
Splints of wrists and/or knees	34	9*	2**
Walking aids introduced	3	1	2
Wheeled mobility aids introduced	1	2	3

†Two patients in the out-patient group and two patients in the non-allocated group dropped out during the first year of follow-up.
‡One patient hospitalized within 3 months after study entry.
*$P < 0.05$, out-patient versus in-patient group (Mann–Whitney U or Pearson χ^2 test).
**$P < 0.05$, non-allocated versus in-patient group (physical therapy, splints, shoe and home adaptations), versus out-patient group (no. of office visits) or both (no. of laboratory investigations) (Mann–Whitney U or Pearson χ^2 test).

DISCUSSION

The results of the present study suggest that in patients with active RA, a short period of hospitalization in a rheumatology clinic with multidisciplinary team care has a beneficial effect with respect to disease activity and emotional status. The positive effect is maximal during the first month after admission. Over the whole follow-up period of 1 yr, the effect of hospitalization on disease activity remained, whereas the effect on emotional status diminished. No effect of hospitalization on measures of functional status was seen.

It is already known from several studies that hospitalization has a beneficial effect in patients with active RA [4–17]. Of the studies with a randomized design [12, 16, 17], one had a sufficient number of patients and a follow-up period of >6 months [16] and can therefore be compared with the results of the present trial. In that study, 71 female patients with active RA in whom out-patient management had failed were randomized to an average period of 16 days of in-patient treatment in a rheumatic disease unit, or to out-patient treatment. The primary outcome measure in that study was a composite score, the 'Pooled Index', comprising the active joint count, grip strength, duration of morning stiffness, ESR and change in functional capacity. At weeks 7, 19 and 35, the Pooled Index was significantly better in the in-patient group when compared with the out-patient group. The present study showed that the favourable effect of in-patient treatment on disease activity was maintained until 52 weeks of follow-up.

According to functional capacity, the present and former studies could not demonstrate a difference between the groups, except for a greater improvement of grip strength in the in-patient group.

A beneficial effect of in-patient treatment on measures of emotional status was demonstrated in the present study. In a former study [14], it was shown that at 1 yr, in-patients still showed a significant improvement according to mental health measures compared with control patients, whereas in the present study the difference between the two groups diminished during follow-up.

It remains unclear to what extent the individual multidisciplinary treatment components contribute to the positive effect of in-patient treatment. Medical treatment, including optimizing NSAIDs and the administration of intra-articular injections with corticosteroids, cannot explain the positive effect of in-patient treatment in the present study, as the results remained after adjustment for differences in medication and intra-articular injections during the first 2 weeks. In earlier years, the positive effect of in-patient treatment was merely attributed to physical rest, including bed rest and joint-splinting regimens [1–3]. A few studies have evaluated different bed-rest regimens for active RA during hospitalization [11, 27, 28]; however, none of them showed a substantial benefit of prolonged bed rest or complete immobilization over less restricted programmes. Apart from physical rest, the beneficial effect of in-patient treatment may be a total result of the comprehensive care supplied by a multidisciplinary treatment team, not only aiming at a decrease in disease activity, but also at an improvement in the patient's ability to cope with the disease. The permanent education and emotional support by all team members, adapting the home and work situation by education of relatives and employers, and providing adaptive devices at home or at work when needed, may make it easier to live with the disease. Apart from the multidisciplinary team care, treating patients in an in-patient setting may have additional therapeutic value compared with day care. Temporarily being away from the daily concerns of home and work may relieve the burden of pain, limitation and disability. This topic was addressed in two studies in which a structured in-patient programme was compared with a similar day-care programme. Helewa *et al.* [16] demonstrated the superiority of in-patient treatment compared with an intensive

out-patient programme, whereas Lambert *et al.* [17] found a comparable clinical improvement in both groups. However, the total number of hospital treatment days was not described for the out-patient group [16] or differed between the two groups because day patients spent part of the programme at home [17]. As the results are not conclusive, the additional effect of in-patient treatment needs further assessment in the future.

The present study was not primarily designed to evaluate the cost-effectiveness of in-patient treatment. It is suggested that the difference between the costs of in-patient and out-patient therapy can be mainly attributed to hospital charges during in-patient treatment, as during follow-up little differences between the two groups were found [15, 16]. Patients who are hospitalized for a flare of RA are not in need of intensive medical and nursing care, so the extent of medical equipment and nursing staff can be limited. In the present study, per diem hospital charges in the rheumatology clinic were only ~40% of the costs in a general hospital. By treating patients in an in-patient setting, transport costs are saved. Further evaluation of the cost-effectiveness of in-patient versus out-patient treatment is needed.

In the present study, 28 of 108 eligible patients (26%) refused hospitalization. We are not informed about such patients in other studies. Half of the non-randomized patients refused hospitalization because they felt too well. This is confirmed by the baseline data, showing that patients who refused randomization had less active disease, and a better functional and emotional status, than the total group of randomized patients. Although during the first weeks of follow-up the improvement in some measures of disease activity and emotional status was greater in the in-patient group when compared with the non-allocated patients, the differences between the non-allocated group and the in-patients were small. The use of medical and paramedical services was relatively low in the non-allocated group. It is not clear whether this group of patients had a greater ability to cope with the physical and emotional stress of a relapse of the disease than patients who were motivated for hospitalization.

Over the last decades, the frequency and duration of hospitalization for active RA have decreased rapidly, following the general tendency to keep people out of hospital and limit health care costs. The present study showed that a short period of hospitalization was more effective than standard out-patient care. How in-patient multidisciplinary team care relates to a similar day-care programme with respect to clinical effectiveness and economic costs has still to be assessed.

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