EXTENDED REPORT

Joint surgery in the Utrecht Rheumatoid Arthritis Cohort: the effect of treatment strategy

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Objective: To investigate the prevalence and prognostic factors of joint surgery in a large cohort of patients with rheumatoid arthritis, whose treatment, clinical and radiographic data have been assessed at predefined points in time since disease onset.

Methods: Data on surgical interventions were retrospectively obtained from 482 patients with rheumatoid arthritis whose follow-up data for at least 2 years were available, including treatment and response to treatment during the first 2 years. Survival time until the first surgical intervention and until the first major surgical intervention was determined for the total study population by Kaplan–Meier survival curves. Three separate Cox regression analyses were carried out to determine which variables measured at baseline, during the first year and during the first 2 years were predictors for joint surgery.

Results: 27% of the patients underwent surgical interventions. Mean survival time until the first surgical intervention was 10.4 years. The percentage of patients with a surgical intervention was 10% lower in the group with response to treatment when compared with the non-response group. Next to a delayed start with disease-modifying antirheumatic drugs, fast radiographic progression during the first year and first 2 years was a predictor of joint surgery in the multivariate regression analyses.

Conclusion: Treatment with disease-modifying antirheumatic drugs immediately after diagnosis results in less joint surgery when compared with a delayed start. Furthermore, joint surgery is carried out more often in patients who do not respond to treatment.

Rheumatoid arthritis is a chronic disease characterised by its fluctuating course, and heterogeneity of disease activity and joint damage. At the moment, treatment of rheumatoid arthritis is characterised by early administration of (combinations) disease-modifying antirheumatic drugs (DMARDs).

Although the efficacy of treatment has improved during the past decade, a group of patients still require one or more surgical interventions. Joint surgery can be seen as an outcome measure, reflecting the unfavourable course of rheumatoid arthritis. Surgical interventions vary from minor interventions such as the removal of noduli and arthroscopy to major interventions such as total joint arthroplasty. A few studies investigated the prevalence of joint surgery. In a study population including 1600 patients, it was estimated that 25% of the patients undergo total joint arthroplasty within 23 years after disease onset.¹ In two other studies with follow-up durations of 5 and 10 years, joint surgery was carried out in 17% and 19% of the patients, respectively.^{2–3} The costs for surgical interventions are high and comprise a major part of the total direct costs.⁴ In our study on direct costs, we found that the mean (standard deviation (SD)) annual cost for surgery was €152 (2222) and that for hospitalisation was €391 (1602).⁵ The total costs of those patients (n=33) who underwent a surgical intervention were €93,383. Identification and modification of risk factors for joint surgery might postpone or prevent joint surgery and thus reduce these high costs related to rheumatoid arthritis.

In several studies, high erythrocyte sedimentation rate (ESR),^{1–3} functional disability,^{1–3–6} radiographic damage^{1–3} and long disease duration^{1–3} have been reported as risk factors for surgical interventions. Most often these variables were

assessed at diagnosis. However, patients with severe disease activity at baseline might respond well to treatment in the initial years after diagnosis, which could retard joint damage later on and, with that, surgical interventions. We already found that response to treatment is a predictor of remission, irrespective of treatment.⁷ Thus, the kind of treatment and response to treatment might also influence the chance of joint surgery later on and are therefore of interest in the prognostic analyses. Except for two studies,^{1–2} treatment has not been included in the prediction analyses as a possible prognostic factor for surgical interventions.

Two studies investigated the prognostic ability of variables with increasing observation time. Prediction of joint surgery improves with duration of observation time,^{1–2} because probably with longer observation time the effect of treatment is included indirectly. To determine the predictive ability of variables with increasing observation time, a cohort of patients whose data have been obtained since diagnosis is required. In the region of Utrecht, The Netherlands, we have followed patients with rheumatoid arthritis since disease onset and assessed several variables at predefined points in time. This inception cohort allows us to investigate the ability of treatment strategy and response to treatment, in addition to demographic characteristics and clinical and radiographic variables assessed at diagnosis and during the first 2 years after diagnosis, to predict the requirement of joint surgery later on.

Abbreviations: ACR, American College of Rheumatology; AUC, area under the curve; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; SRU, Utrecht Rheumatoid Arthritis Cohort; VAS, visual analogue scale

PATIENTS AND METHODS

From 1990 until 1998, all patients with a disease duration of <1 year, visiting one of the outpatient clinics of the Utrecht Rheumatoid Arthritis Cohort (SRU), The Netherlands, and fulfilling the revised 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis⁸ and who did not meet any of the exclusion criteria, were asked to participate in a clinical trial to compare the effects of two treatment strategies—that is, an early start with DMARDs versus a delayed start with DMARDs. In the first strategy group, patients were randomly assigned to one of the three following treatment arms at diagnosis: (1) the methotrexate arm; (2) the intramuscular gold arm; and (3) the hydroxy-chloroquine arm. In the delayed start with DMARD group, patients did not receive any DMARD immediately at diagnosis but started using DMARDs if necessary during follow-up. In this group patients started with non-steroidal anti-inflammatory drugs (NSAIDs), and therefore this group is hereafter referred to as the NSAID group. After 1994, all patients were randomised into one of the three treatment arms of the early start with DMARD group because planned interim analyses showed that this strategy was much more beneficial.^{9–11}

Clinical variables and radiographic damage

Patients included in one of the two strategy groups visited the outpatient clinic once every 3 months during the first 2 years and once every 6 months thereafter for assessment of disease activity.

At each outpatient visit, the following clinical variables were assessed: ESR (mm/h), pain on a visual analogue scale (VAS; mean score; 0–100 mm = worst score), VAS general well-being (0–100 mm = worst score), joint score according to the Thompson joint score (a weighted score including both swollen and tender joints, range 0–534¹²), duration of morning stiffness (0–720 min) and functional disability (Dutch Health Assessment Questionnaire¹³; 0–3 = worst score). At baseline and every year thereafter, radiographs of hands and feet were scored according to the Sharp–van der Heijde method (range 0–448).¹⁴ Differences in total scores of individual patients of >25% were discussed until agreement was reached. The intraclass correlation coefficient between two sets of scores was 0.98, indicating excellent agreement.¹⁵ Annual radiographic progression rate was calculated for the first year and for the first 2 years.

Surgical interventions

Patients' medical records were checked for any surgical intervention as a consequence of rheumatoid arthritis. All recorded surgical interventions were grouped into minor, intermediate and major interventions; also, the date of the procedures was recorded. Minor interventions were defined as arthroscopy, carpal tunnel decompression and rheumatoid nodule removal. Intermediate interventions included arthrodesis, synovectomy, and replacement or resection arthroplasty of the smaller joints of hands and feet. Major interventions included joint replacement of hip, knee, shoulder, elbow, ankle and wrist.

Statistical analyses

Descriptive statistical analyses were carried out for patients who remained in the cohort for at least 2 years. Baseline characteristics were compared between patients with a surgical intervention and patients without a surgical intervention using either the unpaired *t* test for continuous variables or the χ^2 test for categorical data, as appropriate. In this study, we also evaluated whether a response to treatment at 1 year or at 2 years resulted in less joint surgery later on. Response to treatment was achieved when a minimum of

three of four of the following criteria were met: morning stiffness ≤ 15 min, Thompson joint score ≤ 10 , VAS pain ≤ 10 mm and ESR ≤ 30 mm/h. Kaplan–Meier analyses were applied to determine the estimated mean (95% confidence interval (CI)) survival time from inclusion until the first surgical intervention or until the first major surgical intervention.

As follow-up duration was different for individual patients, univariate and multivariate Cox proportional regression analyses were carried out to determine demographic, clinical and radiographic prognostic factors, measured during the first 2 years, for surgical interventions. For both univariate and multivariate Cox regression analyses, three different analyses are reported. The first analysis uses only baseline data as covariates. The second analysis includes the area under the curve (AUC) standardised to time (during the first year) of all clinical variables, the radiographic progression rate during the first year and response to treatment measured at 1 year after diagnosis. The third analysis includes the AUC obtained during the first 2 years of all clinical variables, the radiographic progression rate during the first 2 years and response to treatment measured at 2 years after diagnosis. To calculate the AUC, missing data between two visits were imputed by the mean of the previous and the next score. For the multivariate Cox regression analyses, a forward procedure was applied and all variables were entered in order of significance level as obtained in the univariate analyses. In both the second and third analyses, age, sex, rheumatoid factor test assessed at diagnosis (positive *v* negative) and treatment strategy at diagnosis (NSAID group *v* DMARD group) were also included as covariates. All data were analysed using SPSS V.11.5.

RESULTS

Patients

Of the 590 patients who were randomised between 1990 and 1998 in the SRU, 482 patients had a follow-up duration of at least 2 years and medical records of these patients could be retrieved and were used in the present study. Table 1 shows the characteristics of the study population, assessed at disease onset. In all, 71% of the patients were women and 65% had a positive rheumatoid factor test at diagnosis. The average disease duration was 7.2 years (range 2–14 years) at the time of this study. No significant differences were found in baseline characteristics of the 482 evaluated patients and the other 108 non-evaluated patients of the original cohort, except that the non-evaluated patients were older (56 (SD 14) years *v* 61 (SD 15) years; *p* < 0.01).

Surgical interventions

Overall, 130 (27%) patients underwent a total of 240 surgical interventions, with a maximum of five interventions per patient: one intervention, *n* = 65 (50%); two interventions, *n* = 39 (30%); three interventions, *n* = 15 (12%); four interventions, *n* = 3 (2%); and five interventions, *n* = 8 (6%). Of all surgical interventions, 17% was a minor intervention, 53% an intermediate intervention and 30% a major intervention. Of the 128 intermediate surgical interventions, the number of arthrodesis was 26 (20%), including 12 of the wrist or hand, 13 of the ankle or foot and 1 of the shoulder. In all, 48 patients underwent a total of 73 major surgical interventions; of these, the hip (51%) was the most frequently operated joint, followed by the knee (38%), the wrist (7%) and the shoulder (4%). The median (interquartile range) time from diagnosis to the first small intervention was 3.6 years (0.7–7.2), to the first intermediate intervention 4.7 years (2.2–6.4) and to the first major intervention 6.0 years (4.3–9.1). Table 1 shows the characteristics at diagnosis for the surgery group and the non-surgery group.

Table 1 Baseline characteristics for the total study population and separately for patients with and without any surgical intervention during follow-up

	Total group n = 482	Surgical intervention No (n = 352)	Yes (n = 130)	p Value
Age, years	56 (14)	56 (14)	54 (14)	0.407
Sex, % female	71	69	76	0.125
Rheumatoid factor, % positive	65	62	71	0.082
ESR, mm/h	40 (26)	39 (24)	43 (31)	0.055
Morning stiffness, min	110 (114)	107 (117)	105 (110)	0.937
General well-being on VAS, mm	50 (23)	49 (24)	50 (24)	0.333
Pain on VAS, mm	47 (26)	45 (26)	48 (26)	0.776
Thompson joint score	144 (96)	135 (91)	159 (104)	0.012
Functional disability, HAQ	1.3 (0.7)	1.3 (0.7)	1.4 (0.8)	0.415
Radiographic damage score	4.7 (7.2)	5 (7)	5 (7)	0.942
Treatment groups				
DMARD group	430 (89)	323 (92)	107 (82)	0.005
NSAID group	52 (11)	29 (8)	23 (18)	

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale. Data are mean (standard deviation) for continuous variables and percentages for categorical variables. Ranges for variables are as follows: ESR, 2–140 mm/h; morning stiffness, 0–720 min; general well-being on VAS, 0–100 mm = worst score; pain on VAS, 0–100 mm = worst score; joint score, Thompson joint score 0–534; functional disability, HAQ 0–3 = worst score; and radiological damage score, modified Sharp–van der Heijde score 0–448.

Survival analyses

Figure 1 shows the survival curve until the first surgical intervention of any kind and until the first major surgical intervention for the total study population since inclusion. The estimated mean (95% CI) survival time from inclusion until the first surgical intervention was 10.4 years (9.8 to 10.9) and that until the first major intervention was 12.5 years (12.1 to 12.9).

Treatment strategy and response to treatment

Forty five (87%) of the patients in the NSAID group started using DMARDs within the first 2 years after diagnosis after a mean (SD) disease duration of 10 (5) months. Figure 2 shows the Kaplan–Meier survival curve for both treatment strategy groups. Patients in the NSAID group had an increased risk for surgical interventions when compared with those in the DMARD group (log rank test $p = 0.036$).

At 1 year, 25% of patients in the NSAID group and 44% of patients in DMARD group showed a good response to treatment ($p = 0.012$). After 2 years these percentages were 48% and 47%, respectively ($p = 0.95$). The percentage of

Figure 1 Kaplan–Meier survival curve until the first surgical intervention (solid line) and until the first major surgical intervention (dotted line) since inclusion for the entire study population. At each 2-year interval, numbers indicate the remaining patients for follow-up.

Figure 2 Kaplan–Meier survival curve until the first surgical intervention for the disease-modifying antirheumatic drug (DMARD) group (solid line) and the non-steroidal anti-inflammatory drug (NSAID) group (dotted line). At each 2-year interval, numbers indicate the remaining patients for follow-up. Difference between treatment groups by log rank test = 0.036.

patients needing a surgical intervention in the entire cohort after the first year was higher (albeit not significant) in the non-response group than in the response group (30% v 23%; $p = 0.086$). At 2 years this result became significantly different (ie, 32% v 21%, respectively; $p = 0.012$).

Prognostic factors for surgical interventions

Table 2 shows the results of the three univariate analyses comprising variables obtained at baseline, during the first year and during the first 2 years. For all three analyses, high Thompson joint score and high ESR were prognostic factors for joint surgery, and the prognostic ability became stronger in time. Not baseline, but functional disability and radiographic progression measured during the first year and during the first 2 years were significant prognostic risk factors for joint surgery. A response to treatment, both at 1 and 2 years, was associated with less surgery. Except for

Table 2 Results of three univariate Cox regression analyses to determine prognostic factors of joint surgery, using data obtained at diagnosis, during the first year and during the first 2 years

	Baseline			First year			First 2 years		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Sex, female v male	1.435	0.963 to 2.139	0.076	NA	NA	NA	NA	NA	NA
Age, years	1.000	0.988 to 1.013	0.982	NA	NA	NA	NA	NA	NA
Randomisation, NSAID group v DMARD group	1.620	1.029 to 2.553	0.037	NA	NA	NA	NA	NA	NA
Response to treatment, no v yes	NA	NA	NA	1.459	1.018 to 2.092	0.040	1.612	1.130 to 2.299	0.008
RF, positive v negative	1.244	0.849 to 1.823	0.263	NA	NA	NA	NA	NA	NA
ESR, mm/h	1.008	1.002 to 1.015	0.013	1.012	1.005 to 1.019	0.001	1.014	1.006 to 1.022	0.001
Joint score, Thompson joint score	1.002	1.001 to 1.004	0.004	1.003	1.001 to 1.005	0.001	1.004	1.002 to 1.007	0.000
Pain on VAS, mm	1.002	0.995 to 1.008	0.592	1.009	1.000 to 1.017	0.045	1.010	1.001 to 1.019	0.025
General well-being on VAS, mm	0.997	0.990 to 1.004	0.431	1.008	0.998 to 1.018	0.104	1.011	1.001 to 1.021	0.031
Morning stiffness, min	1.000	0.999 to 1.002	0.575	1.002	1.000 to 1.004	0.096	1.002	1.000 to 1.004	0.093
Radiographic damage, Sharp-van der Heijde	1.004	0.979 to 1.029	0.771	1.017	1.006 to 1.027	0.002	1.031	1.015 to 1.047	0.000
Functional disability, HAQ	1.145	0.910 to 1.441	0.248	1.393	1.068 to 1.816	0.014	1.448	1.107 to 1.896	0.007

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; VAS, visual analogue scale.

For each clinical variable (ESR, Thompson joint score, pain on VAS, general well-being on VAS, morning stiffness and functional disability), three separate univariate Cox regression analyses were carried out, including (1) baseline values; (2) values obtained during the first year (AUC standardised to time; AUC first year); and (3) values obtained during the first 2 years (AUC 2 years).

Only sex (female v male), age, randomisation (NSAID v DMARD) and RF (positive v negative) were included in the baseline analyses.

Only response to treatment (no response v response) was determined at 1 and at 2 years after diagnosis.

Radiographic damage was determined at baseline, and radiographic progression was measured during the first year and during the first 2 years. The number of available radiographs for patients in the DMARD group and the NSAID group were, respectively: at baseline (328 (93%) v 120 (92%)); for radiographic progression over the first year (326 (93%) v 120 (92%)); and for radiographic progression during the first 2 years (317 (90%) v 118 (91%)).

morning stiffness, all variables measured over 2 years were associated with joint surgery.

Table 3 shows the results of the three multivariate Cox regression analyses. An early start with DMARDs decreases the risk for surgical interventions when compared with a delayed start with DMARDs after controlling for all other clinical and demographic variables in the three time-dependent analyses. In addition, fast radiographic progression, either during the first year or during the first 2 years, increases the risk for joint surgery. When analysing the association between clinical, radiographic and demographic characteristics obtained during the first year with a large surgical intervention, we found less prognostic factors than when including all surgical interventions; these were at baseline, ESR and Thompson joint score; during the first year, ESR, radiographic progression and functional disability; and during the first 2 years, ESR, Thompson joint score, functional disability and radiographic progression. In the multivariate analyses, Thompson joint score at baseline and ESR measured over the first and first 2 years were the only prognostic factors associated with a large surgical intervention.

DISCUSSION

The percentage of patients needing a surgical intervention in the SRU was 27% and that of patients needing a major

surgical intervention was 10%. Estimated mean survival time until the first surgical intervention was about 10 years. These data are in line with those of other studies, of which one was also carried out in an inception cohort,² which resembled our cohort.

In this study, we found that treatment with conventional DMARDs prevents surgery later on. This finding is in contrast with an older study in which treatment effect was investigated, and the use of DMARDs increased the risk for total joint replacement.¹ This contrast can be explained by the randomisation of patients to the DMARD group in our cohort irrespective of disease activity and the non-random design of the other study in which supposedly patients who did worse were treated with DMARDs—in other words, bias by indication. In general, it is to be expected that this effect of treatment on joint surgery will be more pronounced for the newer more intensive treatment strategies, including treatment with biologicals, as it has already been shown that radiographic progression is for a major part inhibited or even halted by intensive treatment strategies.^{16–23} In line with our previous findings that a good response to treatment predicts remission,⁷ in the present study the response to treatment reduced the risk for joint surgery.

In univariate regression analyses the number and the predictive power of individual clinical variables became larger with longer observation time. Demographic factors were not

Table 3 Final models of three separate multivariate Cox regression analyses with increasing observation time to determine prognostic factors of joint surgery using data obtained at diagnosis, during the first year and during the first 2 years

	Baseline			First year			First 2 years		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Randomisation, NSAID group v DMARD group	1.748	1.094 to 2.793	0.020	1.881	1.180 to 2.998	0.008	1.938	1.200 to 3.130	0.007
Joint score, Thompson joint score	1.002	1.000 to 1.004	0.014						
Radiographic progression, Sharp-van der Heijde				1.018	1.006 to 1.030	0.003	1.035	1.017 to 1.053	<0.001

DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

A total of 438 patients were included in these analyses, as baseline radiographic or rheumatoid factor data were missing for 44 patients.

predictive for joint surgery. High ESR and joint score were the only two clinical variables, which were identified as prognostic factors with increasing observation time in all three analyses. Both these clinical variables have also been found to predict joint surgery in many other studies¹⁻⁶ and are also indicators for the development of radiographic damage.²⁴⁻²⁵ Not radiographic damage at baseline, as seen in other studies,^{1,2} but annual radiographic progression rate was a prognostic risk factor for surgical interventions in our study. Functional disability has often been found to be a predictor of an unfavourable outcome measure such as joint replacement,^{1-3,6} mortality²⁶⁻²⁷ and work disability.²⁸ In this study, functional disability was associated with joint surgery only in the univariate analyses, but it was excluded from the final model in the multivariate analyses by treatment and by radiographic progression during the first 2 years. Unfortunately, we did not have data on human leucocyte antigen status, which was also found to be a predictor of joint surgery in previous studies.²⁻²⁹⁻³⁰

There might be some shortcomings in this study, especially with respect to collecting data on joint surgery. Some patients might have undergone joint surgery in another institution. To deal with this problem, all rheumatologists checked the list of interventions of their patients and, in addition, telephone calls were made to a random sample ($n = 30 = 5\%$) of all patients. Data retrieved from the medical records seemed reliable. Another bias might be the underlying reason for joint surgery. Primary osteoarthritis could have been an additional cause for joint surgery, but whether this was the primary indication for joint surgery could not always be confirmed from the medical record. In another inception report it was shown that after controlling for primary osteoarthritis age at onset became a weaker prognostic factor, whereas associations with variables of disease activity and joint surgery became stronger.² Another drawback of the study might have been the discrepancy in follow-up time between the DMARD group (mean 7.1 years) and the NSAID group (8.4 years) because after 1994 all patients were randomised into one of the three treatment arms of the early start with DMARD group. However, when including data of only those patients who had been randomised between 1990 and 1994, the difference in percentage surgery between the NSAID and the DMARD groups remained significant (log rank test; $p = 0.017$). Although all patients with recent onset of rheumatoid arthritis fulfilling the revised ACR criteria for rheumatoid arthritis had been asked to participate in the study on the effects of an early start with DMARDs versus a delayed start with DMARDs between 1990 and 1998, we included only those patients who were willing to participate in the randomised trial in this study in order to determine the effect of treatment. The non-randomised ($n = 62$) group did not, however, differ from the randomised group with respect to percentage of patients (18%) undergoing surgical interventions (data not shown), and therefore the results of this study are representative of a population with rheumatoid arthritis fulfilling the ACR criteria and visiting an outpatient clinic in The Netherlands.

In conclusion, in our study 27% of 482 patients underwent joint surgery, of whom 10% had a large joint replacement after a mean disease duration of 7.2 years. Treatment with DMARDs immediately after diagnosis results in less joint surgery when compared with a delayed start. Other factors consistently predictive of joint surgery were ESR and joint score measured at baseline, and the annual radiographic progression rate. Furthermore, patients responding to treatment during the first 2 years need less surgery later on compared with patients not responding. This suggests that early intensive treatment can prevent joint surgery later on.

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