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Is the Disease Course of Rheumatoid Arthritis Becoming Milder?

Time Trends Since 1985 in an Inception Cohort of Early Rheumatoid Arthritis

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Objective. **Based on comparisons of short-term cohort studies or cross-sectional samples of patients from different calendar times, it has been suggested that present patients with rheumatoid arthritis (RA) have a milder disease course compared with that of patients in past decades. This study was undertaken to investigate whether the course of disease activity and functional disability in patients with RA has become milder over the past several years.**

Methods. **We used the Nijmegen inception cohort of early RA, which included all patients with newly diagnosed RA who had attended the department of rheumatology at Radboud University Nijmegen Medical Centre since 1985. Patients were assessed for disease activity by the Disease Activity Score in 28 joints (DAS28) every 3 months and for functional disability by the Health Assessment Questionnaire (HAQ) disability index (DI) every 6 months. Within the total cohort, 4 subcohorts were defined, based on the date of inclusion of the patients (1985–1990, 1990–1995, 1995–2000, 2000–2005). To investigate whether the course of disease activity and functional disability (over time) was different between the subcohorts, longitudinal regression analysis (linear mixed models) was used, with the DAS28 and HAQ DI over time as outcome variables, respectively, and subcohort as the independent variable, correcting for baseline demographic and clinical characteristics. The treatment strategy was compared between the subcohorts.**

Results. **The DAS28 at baseline and over the first 5 years of disease was lower in the more recent subcohorts. The HAQ DI did not show improvement but instead a trend toward worsening functional disability. Using longitudinal regression it was shown that disease activity improved early in the disease course and stabilized thereafter, and that this improvement was greater in patients in the more recent subcohorts and in patients with a higher baseline DAS28. Initially, the HAQ DI also improved but stabilized thereafter, and this initial improvement was less pronounced in patients in the more recent subcohorts and was greater for patients with a higher baseline HAQ DI. The treatment strategy was more aggressive in the more recent subcohorts, as shown by a shorter duration from diagnosis to the start of treatment with prednisone or disease-modifying antirheumatic drugs (DMARDs), and a greater prevalence of DMARD therapy.**

Conclusion. **The course of disease activity in RA patients has become milder in more recent years. The reason for this improving trend remains to be elucidated, although the trend coincides with a more aggressive treatment strategy.**

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which mainly affects the joints. It is a heterogeneous disease, and the course can vary considerably from mild to very disabling. The course of this disease is not easily predicted (1). It has been suggested that the disease course has changed over the past decades. Observations from retrospective, population-based inception cohorts of RA patients and analyses of short-term cohort studies, randomized controlled trials, and cross-sectional samples of patients with RA from

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different times in different years suggest that the incidence of RA has decreased (2–4) and that RA is becoming a milder disease (5–12).

A number of reasons can be considered to help explain this trend. For instance, RA may be diagnosed and treated earlier, improving the prognosis of patients. Furthermore, changes in treatment strategy for RA have occurred over the past decades (13–17), and new drugs have been introduced (18–21), allowing RA to be treated more aggressively, which lessens disease activity and improves outcome. Also, the effects of RA may have changed due to environmental factors.

A further explanation for findings of less severe disease may be related to changes in the health care system or to study designs. For example, differences may be caused by changes in the diagnosis process for RA patients, or because more rheumatologists are available to provide disease-specific care. Therefore, patients with milder disease may also be seen by rheumatologists, whereas in the past such patients would not have been referred to a specialist. Furthermore, criteria for treating patients with disease-modifying antirheumatic drugs (DMARDs) and inclusion criteria for clinical studies may have changed over time (2,5–10,22,23).

In order to perform a valid study tracking changes in the course of RA over time, a prospective long-term inception cohort study in which patients are followed up from disease onset in a defined area using standardized inclusion criteria is needed. Patients should be assessed by uniformly trained assessors using standardized measurement instruments and assessment intervals, and assessments should be calibrated. Joint count assessments should be calibrated regularly to verify that the trained assessor performs the assessments according to consistent criteria. The information gathered regarding these time trends may also provide some insight into the effectiveness of treatment strategies and the etiology of the disease.

The purpose of this study was to investigate whether the course of RA disease activity and functional disability has improved over the past decades. Additionally, we investigated whether the treatment strategy for RA has become more aggressive in the past decades.

PATIENTS AND METHODS

Patient cohort and assessments. To study time trends in the disease course of RA, we used the Nijmegen inception cohort of early RA (24). This inception cohort continuously includes all patients with newly diagnosed RA who have attended the rheumatology clinic at Radboud University Nijmegen Medical Centre since 1985. Cohort inclusion requirements included RA, diagnosed according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (25), of <1 year duration and no prior use of DMARDs or prednisone. The referral area of this hospital is roughly the greater Nijmegen area, covering a population of ~500,000. Patients are usually referred to the department by general practitioners, but the center also serves as a second- and third-opinion referral center. Assessments are made by trained research nurses using standard measurements at fixed intervals. Trained research nurses performed joint counts, using the Disease Activity Score in 28 joints (DAS28) (26), approximately once each year for the duration of the study. Reproducibility of these measures was found to be high (coefficient of variation <10% for the DAS28). This makes the cohort useful for studying time trends in the disease course.

Among other measurements, the 28-joint tender joint count (TJC) and swollen joint count (SJC), a visual analog scale (VAS) for well-being, a VAS for pain, and the erythrocyte sedimentation rate (ESR) were assessed every 3 months. The DAS28 was calculated from the TJC, SJC, the ESR, and the VAS well-being scores. The DAS28 is an index for disease activity with a range from 0 to 10 in which higher scores indicate higher disease activity. Every 6 months the Health Assessment Questionnaire (HAQ) disability index (DI) (27) was completed by the patients. HAQ DI values were partly based on an updated version of the HAQ DI (mainly for subcohort 3), which was somewhat different from the earlier version (28). For analysis, a "regressed" HAQ DI value was used, based on a regression formula relating the old version of the HAQ DI to the new one. HAQ DI values were calculated without correction for aids and devices. Age, sex, rheumatoid factor (RF) status, and the duration of symptoms were also documented at baseline.

As of January 2005, 525 patients were included in this inception cohort. Four subcohorts were defined within the total cohort, based on the date of inclusion of the patients. Patients included from January 1985 until January 1990 comprised cohort 1, patients included from January 1990 until January 1995 comprised cohort 2, patients included from January 1995 to January 2000 comprised cohort 3, and patients included from January 2000 to January 2005 comprised cohort 4.

Statistical analysis. Demographic and clinical characteristics of the patients at inclusion (age, sex, duration of symptoms before diagnosis, RF, ESR, TJC, SJC, VAS for well-being, VAS for pain, the DAS28, and the HAQ DI) were compared between the 4 subcohorts to determine whether differences were already present between the subcohorts at the time of diagnosis that could influence the disease course. To investigate whether there were differences in disease activity and functional disability over the course of the disease between the subcohorts, the DAS28 (and components), the HAQ DI at 5 years of followup, and the averaged HAQ DI and DAS28 (per patient over the first 5 years) were compared between the first 3 subcohorts. Comparisons were made using analysis of variance or chi-square tests when appropriate. If needed, variables were transformed (using the square root) to achieve a normal distribution.

Determination of whether there were differences in the course of disease activity and functional disability over time between the subcohorts was accomplished through longi-

Table 1. Patient demographics and clinical variables at baseline*

	Subcohort				
	1985–1990 (n = 167)	1990–1995 (n = 132)	1995–2000 (n = 114)	2000–2005 (n = 112)	*P*
Female sex, no. (%)	108 (65.1)	82 (62.1)	77 (67.5)	66 (58.9)	0.5524
RF positive, no. (%)	131 (78.9)	97 (74.1)	86 (76.1)	62 (67.4)	0.2288
Age, mean ± SD years	54.1 ± 14.4	55.5 ± 14.8	55.8 ± 14.9	57.3 ± 14.1	0.3763
Duration of symptoms, days	309 (144, 694)	233 (124, 437)	235 (123, 728)	212 (115, 523)	0.12
DAS28, mean ± SD	5.7 ± 1.2	5.4 ± 1.4	5.0 ± 1.5	4.8 ± 1.2	<0.0001
TJC	9 (5, 16)	8 (3, 15)	7 (4, 13)	5 (2, 11)	0.0296
SJC	12 (8, 17)	11 (6, 17)	10 (5, 13)	9 (6, 14)	0.0879
ESR, mm/hour	40.5 (22, 60)	34 (13.5, 49)	24.5 (9.5, 38.5)	19 (10, 34)	<0.0001
VAS well-being, mean ± SD	43.6 ± 24.9	49.2 ± 23.4	47.7 ± 23.8	49.2 ± 22.6	0.1816
VAS pain, mean ± SD	45.3 ± 21.9	48.3 ± 23.2	48.8 ± 22.1	47.6 ± 23.8	0.6340
HAQ DI	0.54 (0.2, 1.04)	0.54 (0.2, 1.49)	0.61 (0.3, 1.39)	0.91 (0.5, 1.68)	0.1959

* Except where indicated otherwise, values are the median (25th, 75th percentiles). RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; TJC = 28-joint tender joint count; SJC = 28-joint swollen joint count; ESR = erythrocyte sedimentation rate; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index.

tudinal regression analysis (a linear mixed model with a random intercept and a Gaussian link function). Outcome variables for the analyses were the DAS28 and HAQ DI over time, and subcohort and time (disease duration) were independent variables. Baseline clinical and demographic factors were also included in the model to correct for possible baseline differences between the subcohorts. Several interaction terms were tested within the model to determine whether the course of disease activity or functional disability over time (disease duration) was different between the subcohorts, and whether the effects on subcohorts were present for men and women, RF-positive and RF-negative patients, and older and younger patients, respectively (effect modification).

To investigate whether the treatment strategy became more aggressive in more recent years, the time lag between initiation of first-line drug treatment and the start of the first DMARD or prednisone was compared between the subcohorts. The percentage of time during which DMARD or prednisone therapy was received over the first 5 years was calculated for the cohort and subcohorts. If patients were receiving combination therapy, this time was counted for both drugs. The average number of DMARD/prednisone courses and methylprednisolone injections per patient and the number of patients receiving combination DMARD therapy in the different subcohorts over the first 5 years were calculated and compared. Since methotrexate (MTX) is commonly considered the preferred DMARD, and it was anticipated that there would be changes in dosing for MTX over time during treatment, the average maximum dose reached during the first 5 years was compared between the subcohorts. All analyses were performed with SAS version 8.0 (SAS Institute, Cary, NC).

RESULTS

Between January 1985 and January 1990, 167 patients were enrolled (subcohort 1). Subcohort 2 included 132 patients, subcohort 3 included 114 patients, and subcohort 4 included 112 patients. Over the first 5

Table 2. Status of the disease at 5 years and course of the disease over the first 5 years*

	Subcohort			
	1985–1990 (n = 115)	1990–1995 (n = 85)	1995–2000 (n = 73)	*P*
At 5 years				
DAS28, mean ± SD	3.7 ± 1.3	3.4 ± 1.4	3.2 ± 1.4	0.0140
HAQ	0.49 (0.28, 0.90)	0.44 (0.15, 1.1)	0.83 (0.26, 1,29)	0.4476
Over the first 5 years				
DAS28, mean ± SD	4.1 ± 1.0	3.9 ± 1.0	3.4 ± 1.3	<0.0001
TJC	3.9 (1.8, 7.1)	4.8 (2.8, 7.5)	2.5 (1.2, 4.8)	0.0145
SJC	6.8 (4.7, 9.5)	6.6 (4.6, 9.0)	4.2 (2.5, 6.2)	<0.0001
ESR, mm/hour	21.1 (13.6, 29.2)	13.7 (8.9, 23.5)	12.5 (6.5, 21.9)	0.0001
VAS well-being, mean ± SD	31.9 ± 16.0	36.7 ± 16.4	32.6 ± 18.2	0.1186
VAS pain, mean ± SD	32.3 ± 16.1	35.5 ± 15.1	33.9 ± 16.7	0.3493
HAQ	0.36 (0.17, 0.72)	0.41 (0.18, 0.77)	0.56 (0.23, 1.15)	0.1198

* The disease activity variables are averaged per patient over the first 5 years of disease. Except where indicated otherwise, values are median (25th, 75th percentiles). See Table 1 for definitions.

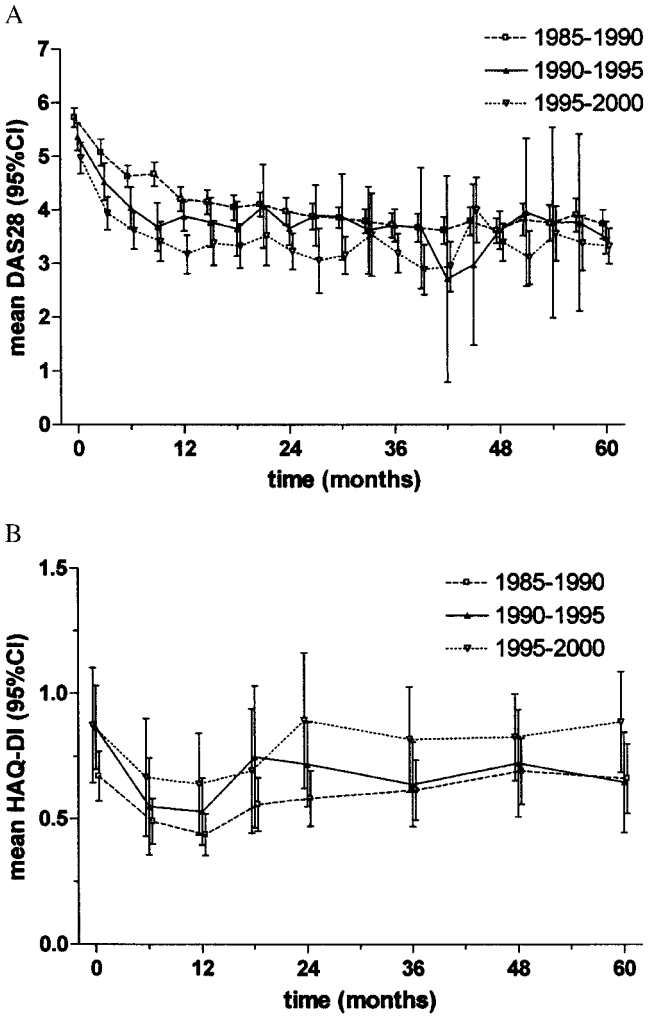

Figure 1. Disease Activity Score in 28 joints (DAS28) (**A**) and Health Assessment Questionnaire (HAQ) disability index (DI) (**B**) over the first 5 years of disease in subcohort 1 (1985–1990), subcohort 2 (1990–1995), and subcohort 3 (1995–2000). Values are the mean and 95% confidence interval (95% CI).

years, 21.3% of cohort 1, 24.2% of cohort 2, and 25.4% of patients in cohort 3 were lost to followup. Dropout rates were not significantly different between subcohorts, and the predominant reasons in all subcohorts were as follows: death (20–25%), voluntary withdrawal (20–30%), and voluntary withdrawal due to low disease activity (5–10%).

Table 1 presents the demographic and clinical characteristics of patients in the 4 subcohorts at baseline. No statistically significant differences in demographic characteristics between the subcohorts was demonstrated. However, the mean age of patients at the time of diagnosis appeared to increase over time, from 54.1 years in subcohort 1 to 57.3 years in subcohort 4, and the percentage of RF-positive patients decreased from 79% to 67%. Furthermore, the duration of symptoms before diagnosis decreased from a median of 309 days to a median of 212 days.

With regard to clinical characteristics, the DAS28 and all of its components, except for the VAS for well-being, decreased (improved) between 1985 and 2000. A trend toward an increase (worsening) in the VAS for well-being was found. The VAS pain index did not show a clear trend. The HAQ DI also worsened; this measure increased from a median of 0.54 in subcohort 1 to a median of 0.91 in subcohort 4; however, the difference was not statistically significant.

Table 2 presents the clinical characteristics of the patients at 5 years of disease duration, averaged over the first 5 years. Subcohort 4 is not shown in this table, since the patients in this subcohort did not have 5 years of followup. At 5 years, the DAS28 was lowest in subcohort 3, as compared with the older subcohorts. The median HAQ DI was again higher in the more recent subcohorts. The average disease activity over time per patient showed similar trends of improvement. The average DAS28 improved from 4.1 in the oldest subcohort to 3.4 in subcohort 3. Only the VAS for well-being and the VAS pain index did not show a clear trend. The average HAQ DI over time per patient increased (worsened) from a median of 0.36 in the oldest subcohort to a

Table 3. Results of longitudinal regression with DAS28 over time as the outcome variable*

Parameter	Coefficient	95% CI	*P*
Intercept	0.92	0.43, 1.40	0.0003
Time	0.05	0.03, 0.08	<0.0001
Time^2	−0.001	−0.001, 0.0002	0.0026
1995–2000 subcohort	−0.33	−0.06, 0.1	0.0136
1990–1995 subcohort	−0.13	−0.40, 0.13	0.3152
1985–1990 subcohort	–	–	–
DAS28 at baseline	0.77	0.69, 0.85	<0.0001
Time × DAS28 at baseline	−0.02	−0.03, 0.02	<0.0001
Time^2 × DAS28 at baseline	0.0003	0.0002, 0.0004	<0.0001
Time × 1995–2000 subcohort	−0.02	−0.03, 0.004	0.0135
Time × 1990–1995 subcohort	−0.001	−0.02, 0.01	0.9261
Time^2 × 1995–2000 subcohort	0.0004	0.0001, 0.0006	0.0018
Time^2 × 1990–1995 subcohort	0.0001	−0.0002, 0.0003	0.6089

* Time (disease duration in months) × Disease Activity Score in 28 joints (DAS28) at baseline and time^2 × DAS28 at baseline are the interaction terms of disease duration with disease activity at baseline. These interaction terms indicate that for patients with higher disease activity at baseline, the initial improvement in disease activity is larger. Time × subcohort and time^2 × subcohort are the interaction terms of disease duration with the subcohorts. These interaction terms indicate that for patients in the more recent subcohorts, the initial improvement in disease activity is larger. 95% CI = 95% confidence interval.

Table 4. Results of longitudinal regression with HAQ-DI over time as the outcome variable*

Parameter	Coefficient	95% CI	*P*
Intercept	0.01	−0.09, 0.10	0.8996
Time	0.01	0.009, 0.02	<0.0001
Time^2	−0.0001	−0.0002, 0.0001	0.0018
1995–2000 subcohort	0.1	−0.08, 0.20	0.3931
1990–1995 subcohort	0.05	−0.07, 0.16	0.4305
1985–1990 subcohort	–	–	–
HAQ-DI at baseline	0.85	0.77, 0.94	<0.0001
Time × HAQ DI at baseline	−0.03	−0.03, 0.02	<0.0001
Time^2 × HAQ DI at baseline	0.0004	0.0003, 0.0005	<0.0001
Time × 1995–2000 subcohort	0.004	0.001, 0.006	0.0062
Time × 1990–1995 subcohort	−0.002	−0.005, 0.0003	0.0288

* Time (disease duration in months) × Health Assessment Questionnaire (HAQ) disability index (DI) at baseline and time^2 × HAQ DI at baseline are the interaction terms of disease duration with functional disability at baseline. These interaction terms indicate that for patients with higher functional disability at baseline, the initial improvement in functional disability is larger. Time × subcohort is the interaction term of disease duration with the subcohort. These interaction terms indicate that for patients in the more recent subcohorts, the initial improvement in functional disability is smaller in subcohort 3 as compared with subcohorts 1 and 2. 95% CI = 95% confidence interval.

median of 0.56 in subcohort 3, but this trend was not statistically significant.

Figure 1A shows the course of the DAS28 over time (disease duration) for the different subcohorts. It can be seen that over the course of disease in the most recent subcohort, the DAS28 was lower, as compared with scores in the older subcohorts. Table 3 shows that, using longitudinal regression, the DAS28 decreased (improved) from the time at diagnosis, and that this improvement stabilized over time (time and time^2). When the subcohort was added to the model as a variable, it was shown that subcohort 2 (1990–1995) and subcohort 3 (1995–2000) had a lower DAS28 over time as compared with the oldest subcohort. The initial improvement in DAS28 over time was found to be more pronounced in patients in the more recent subcohorts, as compared with the oldest subcohort and with patients who had higher baseline disease activity (the interaction terms of subcohort × time and subcohort × DAS28 at baseline). No further effect modification could be demonstrated. Female sex, older age, and RF positivity were associated with a higher DAS28 over time; however, they did not confound the relationship between subcohort and disease activity over time, and therefore these variables were removed from the final model.

Figure 1B shows the course of the HAQ DI over time (disease duration) for the different subcohorts. It can be seen that, over the course of the disease in the most recent subcohorts, the HAQ DI was higher (worse) than that in the older subcohorts.

Using longitudinal regression, an initial improvement in the HAQ DI, which later stabilized, was also found (Table 4). When adding the subcohorts to the model, it was found that subcohort 3 had significantly higher HAQ DI scores over time, as compared with subcohort 1 and subcohort 2. The initial improvement in the HAQ DI was found to be less in subcohort 3 as compared with the other subcohorts and more pronounced in patients with a higher HAQ DI at baseline. No further effect modification could be demonstrated. Female sex and older age were associated with a higher HAQ DI over time, although they did not confound the

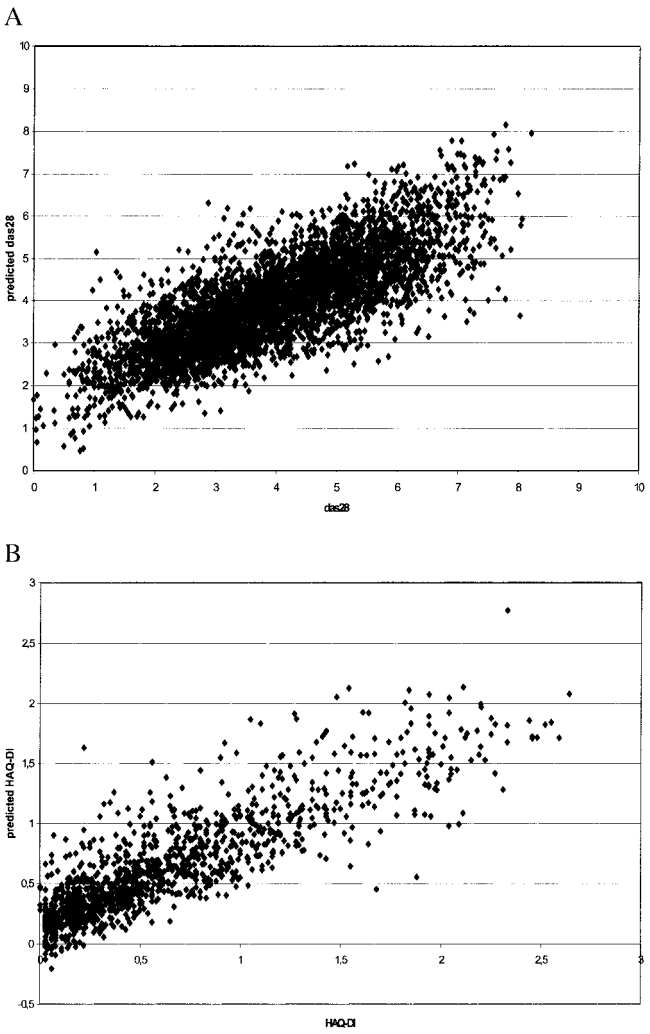

Figure 2. Observed versus expected values for the DAS28 (**A**) and the HAQ DI (**B**). See Figure 1 for definitions.

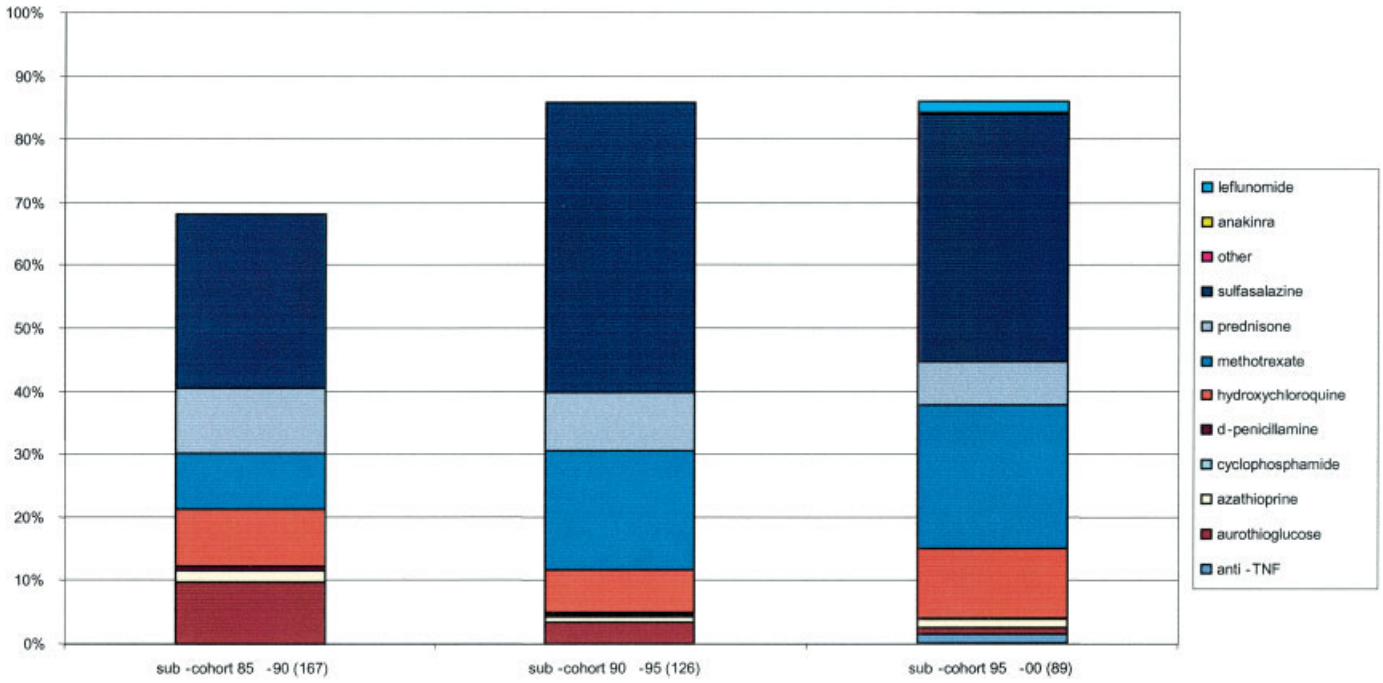

Figure 3. Percentage of time receiving disease-modifying antirheumatic drug (DMARD) and prednisone therapy, and distribution of drugs used in the first 5 years of rheumatoid arthritis treatment. Percentage of time was calculated as the percentage of the total time spent receiving DMARD therapy within the subcohorts. Values in parentheses are n values. Anti-TNF = anti–tumor necrosis factor.

association between subcohort and HAQ DI over time, and were therefore removed from the final model.

In Figures 2A and B, the observed DAS28 and HAQ DI scores are plotted against the expected scores according to the models, demonstrating that the models had a reasonable fit. The treatment strategy appeared more aggressive in more recent subcohorts. The initiation of DMARD or prednisone therapy occurred in the first 3 months of treatment in 80.8%, 82.9%, and 85.5% of patients in the oldest to the most recent cohort, respectively. The DMARDs of first choice were most often sulfasalazine (SSZ) and MTX. Among patients in the oldest to the most recent subcohort, 59.8%, 82.1%, and 75.6%, respectively, started treatment with SSZ, and 2.4%, 8.6%, and 9.8%, respectively, started with MTX. Aurothioglucose and hydroxychloroquine were less frequently used as first DMARDs. The average number of DMARD courses increased from 2.7 to 3.1, and the number of methylprednisolone injections increased from 47 injections in 179 patients (26.3%) to 156 injections in 89 patients (175%) in the oldest and most recent cohorts, respectively. The percentage of time patients received DMARD/prednisone therapy over the first 5 years of disease increased from 69.9% to 86.5%.

Figure 3 shows the percentage of time (calculated as the percentage of total time of DMARD therapy) during the first 5 years of the disease per DMARD per subcohort. It can be seen that use of SSZ remained high, that use of MTX increased, and that use of hydroxychloroquine and aurothioglucose decreased. In subcohorts 1, 2, and 3, respectively, 16 patients (10.4%), 34 patients (28.1%), and 25 patients (24%) were treated with combination DMARD therapy. For MTX, the mean maximum dose reached over the first 5 years increased from 12.2 (SD 5.7) in the oldest subcohort to 14.6 (SD 6.5) in subcohort 3.

DISCUSSION

This study showed that the course of disease activity in patients with rheumatoid arthritis has been milder in more recent years. This trend coincides with a more aggressive treatment strategy. Patients included in an inception cohort of patients with early RA that started in 1985, as well as patients included more recently, were compared. It was found that patients included more recently had lower disease activity at baseline as well as over the first 5 years of their disease. Moreover, it was found that the course of disease activity in relation to disease duration was more favorable, i.e., a

steeper decrease in disease activity from the time of diagnosis was found. However, the HAQ DI at baseline and over time was not lower in patients enrolled later in the study, and even showed a worsening trend. This trend seems to contradict the improving course of disease activity in the more recent subcohorts.

This contradictory result may be partly a distinction between measures of physical examination, laboratory results, and patient-assessed outcomes, which can be influenced by internal standards or attitudes of patients (29). If current patients have higher "internal standards" or demands concerning their health and physical functioning, this may influence their response to subjective self-assessed measures and does not influence the measures of physical examination or laboratory results. This is also consistent with the fact that we did not observe a trend toward improvement in the other self-assessed measures, i.e., the VAS well-being and pain indexes. Also, disease activity as assessed by patients on a VAS did not show a decrease in patients included more recently. The physician-assessed disease activity on a VAS showed a decrease, although this measure was obtained only in the second to the fourth subcohorts (data not shown).

The degree of disease activity at baseline and the more favorable course of disease activity coincide with trends toward a shorter duration of symptoms at the time of cohort inclusion and the use of a more aggressive treatment strategy. The more aggressive treatment strategy was demonstrated by a shorter lag time before the start of DMARD and prednisone treatment, a longer duration of DMARD and prednisone treatment, and a shift in the type of DMARDs used as well as in the more frequent use of combination therapy and corticosteroids.

With regard to milder disease activity, our results are in accordance with findings of several studies comparing cross-sectional samples or clinical trials from different years (5–12). In these studies, patients were not followed up from disease onset, and an extended course of disease activity within a single long-term inception cohort was not investigated.

Our results concerning functional disability contrast with those in a study by Krishnan and Fries, who observed a decrease in average functional disability from 1977 to 1998 (10). This difference might partly be explained by the differing time frame of the study, as compared with our more recent inception cohort. Furthermore, differences in followup of patients may have confounded their results. Heiberg et al (11) also found that a set of health status measures, including the HAQ, improved between a cross-sectional sample of patients from the Oslo RA registry in 1994 and a cross-sectional sample of patients from this registry in 2001; however, the patients in the 2 groups partially overlapped, complicating interpretation of the results (22).

Results of other studies (11–16) are in general accordance with our findings concerning medication and referral time. Kremers et al (13) observed that the time to initiation of DMARD therapy decreased, and that age and various disease characteristics were associated with the initiation of DMARD therapy and the number of DMARD regimens used. Ward (14) found, using data from the National Ambulatory Medical Care Surveys, that the use of DMARDs (mainly MTX) increased between 1980 and 1995. However, this trend was not observed for RA patient visits reported by physicians who were not rheumatologists.

In the above-mentioned studies, as in the present study, the newest drugs (mainly the tumor necrosis factor–blocking agents and leflunomide) were used only marginally (during the first 5 years). In our study they were used only in the most recent subcohort (subcohort 3). It should be noted, however, that our medication database was complete only through May 2004; therefore, for part of subcohort 3, no 5-year medication data could be included in our calculations.

Concerning progression of joint damage, Sokka et al (9) reported a decrease in the 5-year progression of joint damage, as scored on the Larsen scale (30), from the 1983–1985 cohort to the 1988–89 cohort to the 1995–1996 cohort. The cohorts were from 3 separate studies performed at 1 rheumatology center; 2 of the studies were randomized controlled trials (1 of DMARD therapy and 1 of an exercise program) with differing inclusion criteria. As the authors state, the reasons for their observations may include improved therapy, milder disease, and patient selection.

A study using data from a California state hospitalization database showed that the rates of hospitalization for rheumatoid vasculitis or splenectomy associated with Felty's syndrome have decreased over the past 19 years. This also indicates a more favorable disease course. Furthermore, a recent decrease in the rates of primary total knee arthroplasty, but no decrease in the frequency of cervical spine surgery, was found (8). These results might reflect a less severe course of RA in more recent years, but changing indications or selection might also play a role. Furthermore, Holte et al (31) found that the number of patients with RA receiving disability pensions was decreased as compared with the population receiving disability pensions in general, which might also reflect a milder course of disease.

There are some drawbacks to our study. First, HAQ DI values were partly (mainly for subcohort 3) based on a "regressed" HAQ DI, using a regression formula that related the old version of the HAQ DI to the new one. The regression formula was based on a group that was sufficiently large to estimate a valid regression formula, and correlation was high ($r = 0.91$) (26). When we investigated average HAQ DI values over calendar time (at specific time points), it was found that this average fluctuated before as well as after introduction of the new HAQ DI, and that no deviation from a linear trend of increasing HAQ DI could be demonstrated. This indicates that the relatively large increase in the HAQ DI in subcohort 3, as compared with subcohorts 1 and 2, is at least partly based on random fluctuation and not on confounding by the HAQ DI.

Although it was our intention to follow up the patients from the Nijmegen inception cohort of early RA indefinitely, patients withdrew during the followup period. If dropouts were selective and differed between the compared subcohorts, this may have confounded our results. Fortunately, the main reasons for withdrawal were the same in all subcohorts. In survival analyses, the dropout rate for all reasons did not differ between the subcohorts, nor did the main reasons for withdrawal differ. We do not believe, therefore, that selective dropout confounded the results of our analyses. Also, selective dropout would probably result in more severe disease in the more recent subcohorts, because patients who drop out are expected to have milder disease. The longitudinal regression analysis, using the data from only the patients with complete data, did result in virtually the same results (not shown), as compared with the use of all available data, which suggests that the losses to followup were not selective.

All patients in this study were from the same center, and the inclusion criteria and the methods of assessment were constant over time. However, over time the referral area may have decreased somewhat, due to a higher number of rheumatologists in the area, but we do not believe that this has affected inclusion of a select group of patients with regard to disease status, and therefore we do not believe the results were influenced. A countrywide and/or worldwide trend toward earlier referral of arthritis patients to rheumatologists in general may have occurred over time, which may partly explain the lower disease activity over time. This might also partly explain the somewhat lower number of patients enrolled in the more recent years, since more patients are being treated earlier, before their disease meets ACR criteria, which would therefore exclude them from the present study. However, other reasons for these variations cannot be ruled out.

In conclusion, our results indicate that patients with early RA presenting in recent years have less severe disease activity at presentation as well as a more favorable disease course, compared with patients in earlier years. However, this trend is not evidenced by the patient-assessed measures of disease activity or functional disability, and based on these measures may even appear to be the opposite. This trend coincides with a tendency toward a shorter duration of symptoms at the time of diagnosis and more aggressive use of DMARD therapy over the course of disease.

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