Chapter 13

Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis

Results from two large early arthritis cohorts

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ABSTRACT

Objective Remission has become an attainable goal of rheumatoid arthritis (RA) treatment, especially since the advent of biological anti-rheumatic therapy. Because little is known about patients who achieve remission with conventional treatment, we used two large independent inception cohorts to study the prevalence and predictive factors for disease modifying anti-rheumatic drug (DMARD)-free sustained remission after treatment with conventional therapy.

Methods Remission was assessed in patients from the Leiden Early Arthritis Clinic (EAC, n=454) and the British Early RA study (ERAS, n=895) who fulfilled the 1987 ACR criteria for RA and were treated with conventional therapy. Sustained DMARD-free remission was defined as fulfilling the following criteria for at least one year: 1) no current DMARD-use, 2) no swollen joints and 3) classification as remission by the patient's rheumatologist. Predictive factors were identified by Cox regression analysis.

Results Sustained DMARD-free remission was achieved by 68/454 (15%) of patients in the EAC and 84/895 (9.4%) in the ERAS. Five factors were associated with sustained DMARD-free remission in both cohorts: acute onset, short symptom duration before inclusion, non-smoking, absence of IgM rheumatoid factor and of HLA shared epitope alleles. In the ERAS, low disease activity at baseline was also predictive of remission. Multivariate analyses revealed symptom duration and the absence of autoantibodies (anti-CCP2/RF) as independent predictors.

Conclusion Sustained DMARD-free remission in RA patients treated with conventional therapy is not uncommon. Symptom duration at presentation and the absence of autoantibodies are associated with sustained DMARD-free remission.

INTRODUCTION

Patients with rheumatoid arthritis (RA) vary considerably in terms of their disease course and outcome. The spectrum of possible disease outcomes extends from debilitating, destructive joint disease on one side, to remission, the most favorable outcome, on the other side [1]. Since the introduction of biological anti-rheumatic treatment, remission is increasingly being reported as a primary disease outcome of new therapeutic trials [2]. In addition to the potent suppression of disease activity which can be achieved with these novel treatment agents, the recent insight that early initiation of anti-rheumatic therapy leads to better long-term outcomes [3, 4], has led to a shift in the current goals of RA treatment towards aiming for remission.

When studying remission in RA, there are several aspects of remission which need to be taken into account and which are inconsistently defined and used in the literature. The first inconsistency involves the duration of the remission. Clinical trials frequently use a disease activity score (DAS)-based definition of remission which does not require a specified follow-up period, but can be fulfilled at one single point in time.

The second factor which needs to be taken into account is the use of anti-rheumatic treatment. Remission can be interpreted as either a state of minimal disease activity while using anti-rheumatic treatment, or as persistent resolution of the disease after discontinuation of therapy [5, 6]. The DAS-based remission criteria do not require remission to be drug-free, because they were intended to monitor treatment response in clinical trials [7, 8]. Remission rates as reported in clinical trials therefore often reflect the number of patients which achieve minimal disease activity while using novel therapeutic agents. Data on how often remission persists after discontinuation of treatment are scarce [9], though this may better reflect disease resolution.

A third aspect of remission studies is the type of treatment which was administered. Despite the fact that remission rates after treatment with new therapeutic agents are now often reported, there are few data on remission after treatment with conventional therapy such as non-steroidal anti-inflammatory drugs (NSAIDs) and non-biological disease modifying antirheumatic drug (DMARD) therapy. Such studies would however, allow a better interpretation of the remission rates reported by clinical trials of novel agents.

In this study, we investigated the prevalence and prognostic factors for sustained DMARD-free remission in two large, independent inception cohorts of RA patients treated with conventional therapy. In order to investigate remission as a definitive disease outcome, stringent criteria were used to define remission: the sustained absence of synovitis for at least one year after the discontinuation of therapy with DMARDs. This definition is an approximation of a definitive cure of the disease, and as such, is close to the meaning of remission as it is used for other diseases such as malignancies.

Investigating remission as a definitive disease outcome, resembling cure, is very important from a pathophysiological point of view. Knowledge of which clinical or immunological patient characteristics are associated with remission could fuel new hypotheses about the biological pathways involved in disease persistence and resolution, and would increase our understanding of the disease course of RA.

METHODS

Patient population

The study population consisted of two cohorts: the Leiden Early Arthritis Clinic (EAC) and the British Early RA Study (ERAS).

The Leiden EAC is an inception cohort of patients with recent-onset arthritis (less than 2 years of complaints) that was initiated at the department of rheumatology of the Leiden University Medical Center in 1993 [10]. The present study included patients who fulfilled the 1987 revised ACR criteria for RA at baseline (n=369) or within the first year of follow-up (n=85), and who presented to the EAC between 1993 and 2002. The treatment strategy differed according to the inclusion period. Patients included between 1993 and 1995 were initially treated with analgesics and subsequently with chloroquine or sulfasalazine if they had persistent active disease. Between 1996 and 1998, patients who were included were promptly treated with chloroquine or sulfasalazine, while after 1998 the initial treatment strategy consisted of either methotrexate or sulfasalazine. Patients included in the EAC after January 2003 were not part of the current study because, due to their limited duration of follow-up, they only had a short period of time to achieve sustained DMARD-free remission, and therefore had a high risk of misclassification. These patients who presented after January 2003 did not differ markedly from the patients who were included earlier with regard to the rate and the predictive factors of sustained DMARD-free remission (data not shown), but they were not part of the present study because of the high risk of misclassification as mentioned above. Follow-up visits with standard clinical assessments were performed two weeks after the first presentation and yearly thereafter. Demographic characteristics, a 44 swollen joint count (SJC) and the modified Stanford Health Assessment Questionnaire (HAQ) were recorded at each visit. Laboratory evaluation consisted of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements, determination of IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide 2 antibodies (anti-CCP2). Furthermore, genotyping of the HLA-DRB1 region was performed to determine the number of RA-associated Shared Epitope (SE) alleles [11]. Radiographs of hand and feet were scored according to the Sharp-van der Heijde scoring method (SHS) [12].

To determine if the prevalence and predictive factors which were identified in the Leiden EAC cohort could be replicated, a second inception cohort was used: the ERAS. This cohort consists of RA patients who were recruited from 9 rheumatology departments in the UK from 1986 until 1996. During this period, consecutive patients who presented with RA according to the ACR criteria were included in the ERAS if their symptoms of RA had lasted less than 2 years and no second-line antirheumatic medication had been used. ERAS patients were treated according to the rheumatologist's preference, which generally entailed a short course of analgesics, followed by sequential monotherapy or combination therapy for more severe RA with methotrexate, sulfasalazine and hydroxychloroquine as favored drugs.

Baseline and yearly assessments comprised of the Ritchie articular index, a 44 SJC, the HAQ and measurements of ESR and IgM RF. Disease activity scores (DAS) were calculated according to the original formula [13]. In addition, HLA-DRB1 genotyping was performed. Radiographs of hand and feet were scored according to the Larsen scoring method [14]. In contrast to the EAC, measurements of CRP and anti-CCP were not performed in the ERAS.

Both in the ERAS and the EAC, a number of patients failed to complete follow-up: n=136 (23%) in the EAC and n=384 (30%) in the ERAS. The most common reasons in both cohorts were death, moving and withdrawal of consent. Because the definitive disease outcome (remission versus non-remission) could not be accurately determined for the deceased patients, the present report shows the results of the analyses without these patients. However, when the deceased patients were included in the non-remission group, the identified predictive factors did not change (data not shown). In total, 454 EAC patients and 895 ERAS patients were included in the present study.

Definition of remission

Sustained DMARD-free remission was defined according to the following three criteria: 1) no current use of DMARDs, 2) no swollen joints and 3) classification as DMARD-free remission by the patient's rheumatologist. Corticosteroids were considered to be equivalent to DMARDs for the present study, while NSAIDs did not qualify as DMARDs. Patients had to fulfill all three criteria in order to be diagnosed with remission. To ensure that remission was not temporary, but rather sustained and long-lasting, the absence of swollen joints had to have been observed by a rheumatologist for at least one year after discontinuation of DMARD-therapy. In both EAC and ERAS cohorts, all patients were seen approximately every four months by their rheumatologists, even when they had very low disease activity. In addition, standardized follow-up visits to collect data for the EAC and ERAS were performed annually. In the EAC, all patients with remission were discharged from the outpatient clinic after at least one year of observation after discontinuation of DMARDs in the absence of joint swelling. Most patients in the EAC who achieved remission were followed-up longer than the minimum requirement of one year; the median

time of observation after discontinuation of DMARDs in the absence of swollen joints was 2.5 years. Patients who had a recurrence of their arthritis after discharge, could easily return to the Leiden University Medical Center, the only referral center for Rheumatology in a health care region of approximately 400.000 inhabitants. The frequency of relapse was recorded and patients with relapse (n=6) were included in the non-remission group. In the ERAS, the majority of patients who had achieved remission continued to undergo their yearly assessments, which provided an opportunity to assess if there was continued absence of joint swelling.

Statistical analysis

Summary statistics were generated to investigate the prevalence of sustained DMARD-free remission and the baseline characteristics of remission and non-remission patients. Patients included in the ERAS had a longer average period of follow-up than patients in the EAC, due to the fact that the ERAS was initiated in 1986, while the EAC was started in 1993. To avoid skewing of the results due to the difference in follow-up time, the present analysis used data from the first 10 years of follow-up for all patients.

Baseline variables were assessed for their ability to predict remission by univariate and multivariate regression analysis. To take into account the difference in follow-up times among patients, analyses were performed by Cox regression analysis, after verification that the proportional hazards assumption was satisfied. In Cox regression models the dependent variable is the "time-to-event", which consisted of the time to remission for the remission patients, and the time to last follow-up (with a maximum of 10 years) for the non-remission patients. The time of remission was defined in the EAC as the date at which DMARDs were discontinued due to remission, and in the ERAS as the date of the first annual study visit when patients were in DMARD-free remission. The analysis was also performed with a later date defined as the time of remission (date described above plus one year), which led to similar results. This indicates that the predictive factors were stable regardless of the exact date used to define remission.

In order to investigate the predictive ability of baseline characteristics in univariate analysis, each variable was included as a covariate in a separate non-conditional Cox regression analysis. The results of the univariate analyses were subjected to correction for multiple testing by the Holm method [15]. Subsequently, multivariate Cox regression analysis was performed to identify significant independent predictors for achieving remission. As possible explanatory variables, all baseline variables with a p-value below 0.10 in univariate analysis were included in the model. A two-step modeling approach was performed which in the first step identified independent predictive variables by a backward step selection procedure that removed variables with a p-value greater than 0.10. To verify that the identified predictive variables were indeed independent predictors

for the entire cohort, they were then entered as covariates into a second multivariate Cox regression analysis (enter model).

If there is a highly significant correlation between two variables they cannot be entered into the same multivariate model, as this results in over-correction and annulment of the effect. In both cohorts, symptom duration and radiographic damage (as measured by SHS in the EAC and Larsen score in the ERAS) were highly correlated. Symptom duration was included in the multivariate models because a longer symptom duration most likely caused a higher radiological score and not vice versa. In the ERAS, the Ritchie articular index, SJC and DAS were highly correlated due to the fact that the DAS is a component measure consisting of amongst others, the Ritchie articular index and the SJC, and therefore the DAS was omitted from the multivariate model.

In the EAC, a number of cases (n<50) had missing values for baseline continuous variables, which would have resulted in their exclusion from the multivariate model. For these patients with missing values, multiple imputation analysis was performed using STATA with the *ice* and *mim* packages (StataCorp. 2007. Stata statistical software: Release 10. College Station, TX, USA). Multiple imputation was applied to the final Cox regression model identified through the preliminary variable selection step (predictive variables: symptom duration, CRP and anti-CCP). The full database was used to generate 25 imputations, each from 10 cycles and incorporating both survival and censoring information within the multiple imputation prediction equations. In the ERAS, the number of cases with missing variables was very limited and for that reason no imputation was performed.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 14.0, except for the multiple imputation. P-values below 0.05 were considered to be statistically significant, except for the results of univariate analysis for which subsequent correction for multiple testing was performed.

RESULTS

Prevalence of sustained DMARD-free remission

The baseline characteristics of the RA patients in the EAC and ERAS are shown in Table 1. On average, ERAS patients had a longer disease duration and a higher number of swollen joints at baseline, and were more often IgM RF and HLA SE allele positive than EAC patients.

Sustained DMARD-free remission was achieved by 68/454 = 15.0% of patients in the EAC and 84/895 = 9.4% of patients in the ERAS. The median time to remission was 43 months in both cohorts (interquartile range (IQR) EAC: 24-67, ERAS: 18-60) (Figure 1A). A subgroup analysis was performed to investigate if the prevalence of remission in the EAC would have been different if only the 369 patients who presented with RA at baseline

Table 1. Baseline characteristics of patients in both cohorts.

	EAC n=454	ERAS n=895
Period of inclusion	1993-2003	1986-1996
Age in years, mean (SD)	56 (16)	52 (13)
Female gender	69%	69%
Symptom duration in months, mean (SD)	6.4 (9)	8.3 (6)
44 swollen joint count, median (IQR)	8 (4-14)	14 (7-25)
IgM Rheumatoid factor positive	58%	63%
HLA SE positive	66%	72%
Sharp van der Heijde score, mean (SD)	8.0 (11)	NA
Larsen score, mean (SD)	NA	3.7 (9)

NA: not available

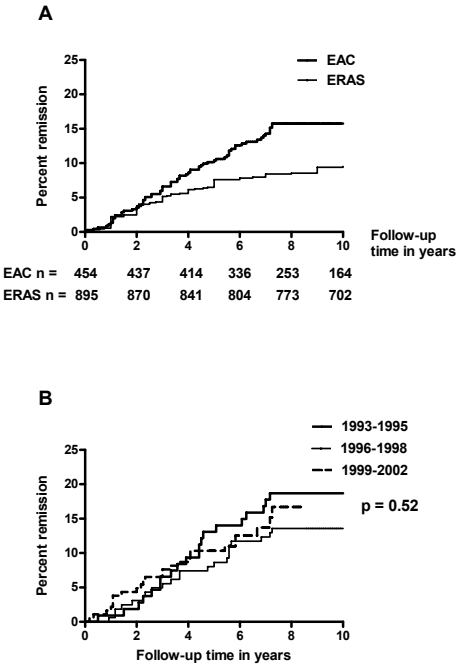

Figure 1: Kaplan-Meijer curves of the percentage of patients with sustained DMARD-free remission.
Figure: 1A: The y-axis depicts the percentage of patients who achieved remission. The x-axis reflects the follow-up time in years. Indicated below the x-axis is the number of patients available for analysis at each timepoint.
Figure 1B: Kaplan-Meijer curves of the percentage of patients in the EAC with sustained DMARD-free remission, stratified for period of inclusion. Differences between the different strata are non-significant: p-value log rank test across all strata: 0.52. The line representing the patients included from 1999 until 2002 terminates at 8 years of follow-up due to the fact that this was the maximum follow-up for patients in this stratum (data were collected in 2007).

had been included (leaving out the 85 patients who developed RA within the first year of follow-up). This revealed a similar prevalence of sustained DMARD-free remission as in the entire group: 14.9% (55/369).

The prevalence of remission steadily increased in the first part of the follow-up period until approximately seven years after inclusion, after which it remained relatively stable. To investigate if patients who were included at a later point in time and who had therefore been treated with a different treatment strategy had a higher chance of achieving remission, or achieved remission faster, analyses in both cohorts were stratified for inclusion period. This revealed that the rate of achieving remission did not differ between patients who were included in different inclusion periods (log rank test: p-value: 0.52) as shown for the EAC in Figure 1B. The same was true for patients who were included in different time periods in the ERAS (data not shown).

Univariate analysis

In order to investigate which baseline patient characteristics can predict sustained DMARD-free remission, univariate Cox regression analysis was performed. The following variables were associated with sustained DMARD-free remission in the EAC: symptom duration at baseline, smoking, CRP, RF IgM, anti-CCP2 antibodies, radiographic damage as measured by SHS, and HLA SE alleles (Table 2). A subgroup analysis of the 369 patients who presented with RA at baseline (without the 85 patients who developed RA within the first year of follow-up) again led to the same results. Of these identified factors, symptom duration at baseline, acute start of complaints, the presence of RF IgM, HLA SE alleles, and radiographic damage could be replicated in the ERAS (Figure 2).

In addition, univariate analysis in the ERAS revealed several other predictive variables (44 SJC, Ritchie articular index, HAQ and DAS4, Table 3). A sub-analysis in the ERAS on

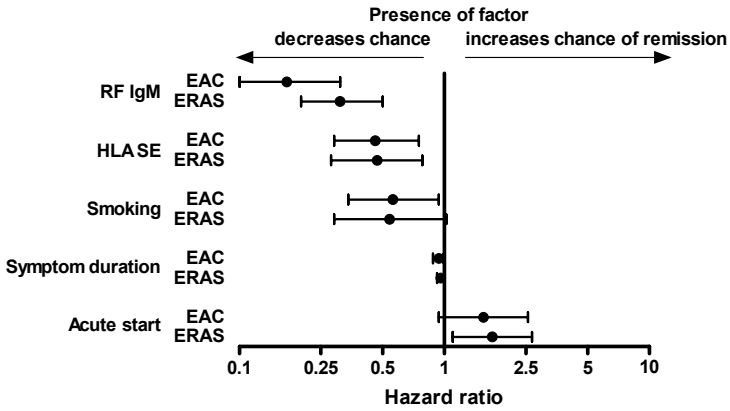

Figure 2: Predictors for sustained DMARD-free remission identified in both cohorts.
Depicted are the hazard ratio's with 95% confidence intervals.

Table 2. EAC univariate analysis: baseline characteristics of patients who did and did not achieve sustained DMARD-free remission.

Patient characteristic †	Remission n=68	No remission n=386	Hazard Ratio ‡	95% CI #	P *
Age in yrs, mean (SD)	59 (17)	56 (16)	1.02	0.99-1.03	0.067
Female gender, n (%)	50 (74%)	262 (68%)	1.28	0.74-2.19	0.38
Symptom duration at baseline in months, median (IQR)	3 (1-6)	5 (2-9)	0.94	0.88-0.99	**0.021**
mean (SD)	4.6 (5)	6.7 (9)			
Smoking, n (%)	22 (33%)	175 (47%)	0.56	0.34-0.94	**0.028**
Family history positive for RA, n (%)	12 (19%)	111 (31%)	0.55	0.30-1.04	0.064
Absence of comorbidities, n (%)	43 (64%)	233 (63%)	0.98	0.59-1.61	0.92
Acute start of complaints, n (%)	43 (64%)	192 (53%)	1.55	0.94-2.56	0.084
Start of complaints in small joints, n (%)	38 (57%)	175 (47%)	1.48	0.91-2.40	0.11
Symmetrical start of complaints, n (%)	46 (72%)	239 (67%)	1.24	0.72-2.14	0.44
44 Swollen joint count, median (IQR) §	8.0 (4-12.5)	8.0 (4-14)	1.00	0.96-1.04	0.82
mean (SD)	9.6 (7)	9.8 (7)			
HAQ, median (IQR)	1.1 (0.6-1.6)	1.0 (0.5-1.5)	1.06	0.74-1.52	0.76
mean (SD)	1.1 (0.7)	1.1 (0.7)			
ESR in mm/h, mean (SD)	38 (25)	44 (28)	0.99	0.98-1.00	0.14
CRP in mg/l, median (IQR)	17 (8-31)	20 (9-45)	0.99	0.98-1.00	**0.039**
mean (SD)	24 (24)	35 (40)			
RF IgM positive, n (%)	14 (21%)	247 (64%)	0.17	0.10-0.31	**<0.001***
Anti-CCP2 positive, n (%)	8 (13%)	236 (66%)	0.09	0.04-0.18	**<0.001***
SHS, median (IQR) ¶	3 (1-8)	5 (2-11)	0.95	0.90-0.99	**0.026**
mean (SD)	5 (6)	9 (12)			
HLA SE positive, n (%)	33 (50%)	247 (69%)	0.46	0.29-0.75	**0.002***

† For variables which were normally distributed, mean and standard deviation (SD) are reported. For non-normally distributed variables, median and interquartile range (IQR) are reported and also the mean and standard deviation since Cox regression uses parametric analysis. For dichotomous variables, the number and the percentage of patients are listed, relative to the total number of patients for whom information about the characteristic under investigation was available.

‡ The hazard ratio, which is the effect measure generated by Cox regression analysis, can be interpreted similar to an odds ratio, meaning that a higher hazard ratio signifies a higher chance of remission.

95% CI denotes the 95% confidence interval.

* p-values below 0.05 are printed in bold. Asterisks indicate p-values significant after correction for multiple testing by the Holm method.

§ Ritchie articular index and DAS were not reported in the EAC.

¶ SHS denotes the Sharp van der Heijde score for radiographic damage.

Table 3. ERAS univariate analysis: baseline characteristics of patients who did and did not achieve sustained DMARD-free remission.

Patient characteristic	Remission n=84	No remission n=811	Hazard Ratio	95% CI	P *
Age in yrs, mean (SD)	51 (16)	52 (13)	1.00	0.98-1.01	0.58
Female gender, n (%)	53 (63%)	560 (69%)	0.78	0.50-1.22	0.28
Symptom duration at baseline in months, median (IQR) **mean (SD)**	6.0 (3-9) 7.0 (5)	7.0 (4-12) 8.5 (6)	0.96	0.92-1.00	**0.038**
Smoking, n (%)	13 (28%)	268 (42%)	0.54	0.29-1.02	0.059
Family history positive for RA, n (%)	20 (24%)	211 (26%)	0.87	0.53-1.44	0.59
BMI, mean (SD)	25 (4)	26 (5)	0.98	0.93-1.04	0.54
Acute start of complaints, n (%)	51 (61%)	383 (48%)	1.71	1.10-2.67	**0.017***
Start of complaints in small joints, n (%)	25 (30%)	204 (25%)	1.27	0.80-2.04	0.31
Symmetrical start of complaints, n (%)	63 (81%)	615 (78%)	1.18	0.67-2.07	0.56
44 Swollen joint count, median (IQR) § **mean (SD)**	9.5 (4-21) 13 (12)	15 (7-26) 17 (13)	0.97	0.95-0.99	**0.005***
Ritchie articular index, median (IQR) **mean (SD)**	4.0 (2-12) 6.5 (6)	10 (5-17) 13 (11)	0.91	0.88-0.95	**<0.001***
HAQ, median (IQR) **mean (SD)**	0.6 (0.1-1.1) 0.8 (0.7)	1.0 (0.5-1.6) 1.1 (0.7)	0.51	0.36-0.71	**<0.001***
ESR in mm/h, mean (SD) †	36 (30)	40 (27)	0.99	0.99-1.0	0.21
RF IgM positive, n (%)	29 (36%)	520 (66%)	0.31	0.20-0.50	**<0.001***
DAS4, mean (SD)	3.3 (1)	4.3 (2)	0.65	0.55-0.76	**<0.001***
Larsen score, median (IQR) **mean (SD)**	0.0 (0-2) 1.7 (3)	0.0 (0-4) 3.9 (9)	0.94	0.88-1.00	**0.050**
HLA SE positive, n (%)	34 (56%)	440 (74%)	0.47	0.28-0.78	**0.003***

* p-values below 0.05 are printed in bold. Asterisks indicate p-values significant after correction for multiple testing by the Holm method.
† CRP and anti-CCP2 were not measured in the ERAS.

the effect of current or past smoking as compared to never smoking as the reference group, revealed that current smoking was associated with the lowest chance of achieving remission (hazard ratio (HR) with 95% confidence interval (CI): 0.27 (0.08-0.87)), followed by past smoking (HR (95%CI): 0.78 (0.39-1.58)). In both EAC and ERAS, there was not a significant gene dose effect of the HLA SE alleles.

To correct for multiple testing, the Holm method was applied which revealed that in both cohorts, autoantibody status, presence of the HLA SE alleles and, in the ERAS, the Ritchie articular index, 44 SJC, DAS and HAQ at baseline were significant predictors of remission.

Multivariate analysis

To investigate which of the patient characteristics were independent predictors for remission, multivariate Cox regression analysis was performed by a two-step modeling approach. Table 4 shows the results of the multivariate analysis for both cohorts. Three variables were found to be independent predictors of sustained DMARD-free remission in the EAC, two of which were significant ($p<0.05$): baseline CRP and anti-CCP status. In the ERAS, these two characteristics were not available but autoantibody status in the form of IgM RF was the most significant predictive variable. Symptom duration showed a trend towards significance in the EAC ($p=0.07$), while significantly associated with remission in the ERAS ($p=0.029$).

Table 4. Multivariate analysis: independent predictors for achieving sustained DMARD-free remission.

Cohort	Patient characteristic	Hazard Ratio	95% CI	P
EAC	Symptom duration in months	0.95	0.90-1.00	0.07
	CRP in mg/l	0.99	0.98-1.0	0.040
	Anti-CCP2	0.09	0.04-0.20	<0.001
ERAS	Symptom duration in months	0.94	0.89-0.99	0.029
	Acute start of complaints	2.03	1.15-3.59	0.015
	Ritchie articular index	0.92	0.88-0.97	0.001
	HAQ	0.66	0.44-0.99	0.044
	RF IgM	0.28	0.16-0.49	<0.001
	HLA SE	0.44	0.26-0.73	0.002

The fact that CRP and anti-CCP status were not available in the ERAS, made it difficult to assess to what extent the results of the ERAS replicated the findings in the EAC. The multivariate analysis of the EAC was therefore also performed after exclusion of these variables. This analysis revealed the following independent predictive variables (HR, 95%CI): symptom duration (0.96, 0.91-1.01), IgM RF (0.19, 0.11-0.35) and HLA SE alleles (0.59, 0.36-0.96). These three factors were also identified as independent predictors in the ERAS cohort, which therefore provides a complete replication of the data of the EAC.

Radiological progression

Although the present study aimed to find baseline characteristics predictive of achieving sustained DMARD-free remission, the rate of joint destruction during follow-up was also compared in the remission versus the non-remission group in the EAC. The remission patients had a lower level of joint damage with a median SHS (with IQR) after 1, 3 and 5 years of follow-up of 4 (1-9), 6 (1-14) and 6 (3-15), compared to the median SHS of the non-remission patients of 11 (5-24), 20 (9-39) and 26 (12-50).

Remission defined according to the ACR criteria

To determine whether the results would have been different if remission had been defined as specified by the ACR criteria, this definition was also applied to the EAC. Remission according to the ACR criteria was achieved by 97/454 (21.4%) of patients, including all of the 68 patients who achieved sustained, DMARD-free remission. The additional 29 patients were still using DMARDs at the time when they fulfilled the ACR remission criteria. Investigation of which baseline factors were predictive of achieving remission as defined by the ACR criteria revealed almost completely the same predictive factors (data not shown).

DISCUSSION

The present study investigated the prevalence and predictive factors for sustained DMARD-free remission in RA patients treated with conventional therapy. The long-term follow-up data from the Dutch EAC and the British ERAS cohorts revealed that sustained DMARD-free remission occurs in 9 to 15% of RA patients. Furthermore, sustained DMARD-free remission can be predicted by several clinical variables at first presentation which are routinely assessed in outpatient clinic. Most predictive characteristics which were identified in the EAC could be replicated in the ERAS. In this study, sustained DMARD-free was defined in its most stringent form which closely resembles a cure of the disease. The present findings therefore provide important new insights with regards to disease resolution and the factors underlying this process.

Notably, the frequency of sustained DMARD-free remission was roughly comparable in the ERAS and the EAC cohort, being 9.4 and 15% respectively. The finding that the prevalence was somewhat lower in the ERAS may be due to the fact that patients in the ERAS had a longer symptom duration at presentation, higher 44 SJC and were more often IgM RF positive and HLA SE positive than patients included in the EAC. These factors were found to be independently associated with a smaller chance of achieving remission in both cohorts, and are known to be associated with a severe disease course. This indicates that the patients included in the ERAS were less prone to achieve sustained DMARD-free remission than patients in the EAC.

Previous studies on remission in patients treated with conventional therapy have also reported remission rates between 10 and 20% [1, 16-19]. However, remission was not defined as a sustained disease outcome in these previous investigations, but rather as an episodic phenomenon. In the present study, the long-term follow-up data from the EAC and ERAS cohorts enabled us to investigate remission as a definite disease outcome, which most closely resembles a cure of the disease.

The possibility that treatment differences between the EAC and the ERAS may have affected the prevalence of remission cannot be entirely excluded. However, in the EAC, stratification for inclusion period (reflecting different treatment strategies) showed comparable remission rates for the three inclusion periods. This indicates that changes in treatment strategy during the course of the study did not have a major effect on the prevalence of sustained DMARD-free remission. Furthermore, in order to exclude the possibility that patients who achieved remission had been treated more stringently, a detailed investigation of medication use was performed in both cohorts. This revealed that the patients who achieved remission had not been treated more stringently, but rather tended to have been treated less aggressively, e.g. with NSAIDs only (in approximately 25% of patients) or with less potent DMARDs (data not shown). In both cohorts, patients who had been treated with DMARDs had a significantly lower chance of ever achieving remission (EAC: HR (with 95% CI) =0.12 (0.07-0.21), ERAS: HR=0.08 (0.05-0.12)). This suggests that the rheumatologists deemed the remission patients to have less severe disease which did not need to be treated with DMARDs. This is in line with the other results of the univariate analysis, which reveal that remission patients had less radiological damage (in the EAC and ERAS) and lower swollen joint counts, Ritchie articular index and HAQ (in the ERAS) at baseline. The effect of ever using DMARDs was not included in the multivariate models because the aim of the analysis was to identify baseline characteristics of the patients which were predictive of remission.

One may consider the observed prevalence of remission (9-15%) to be surprisingly high, leading to the question whether these patients "really" had RA. However, all patients fulfilled the 1987 ACR criteria for RA; a set of criteria that is not perfect, but is nonetheless the most frequently applied. In addition, remission was achieved after a median of 3.5 years, indicating that patients had a chronic polyarthritis for this lengthy period. Finally, the majority of remission patients had radiological joint destruction (although less severe than in the non-remission group); a hallmark which is considered characteristic for RA.

The current study identified several predictive factors for sustained DMARD-free remission. Autoantibody status, HLA SE alleles, smoking, an acute onset of complaints and the symptom duration before inclusion, were found to be predictive in both cohorts. The findings on the association between the absence of autoantibodies and remission are in line with prior reports that have documented a strong association between autoantibody status (IgM RF and anti-CCP2) and the rate of joint destruction in RA [20-22]. The current observations illustrate that these autoantibodies are also important persistency factors.

The majority of predictive factors identified in the EAC could be replicated in the ERAS, particularly when the same baseline characteristics were included in the multivariate models. The ERAS then provided a perfect replication of the results of the EAC. There were also some differences between the two cohorts with regard to the predictive factors which were identified. In the ERAS, disease activity at baseline, as reflected by the Ritchie

articular index, 44 SJC, DAS and HAQ, was inversely associated with achieving remission, while in the EAC, the 44 SJC and HAQ were not associated with remission. Part of this difference may be attributable to the on average higher disease activity in the ERAS at baseline (as apparent from the higher 44 SJC) and accompanying larger range of values, which lends more power to the ERAS to find an association between disease activity at baseline and definite disease outcome.

Interestingly, several factors which were recently described to predict remission after treatment with anti-TNF therapy such as age, gender and comorbidity could not be replicated in the present study [23, 24]. This could very well be the result of the different definitions of remission which were used. In these reports, remission was defined as a DAS below 1.6 or DAS28 below 2.6 during treatment, and it is therefore conceivable that the factors which were identified predict treatment response, rather than long-term disease resolution [25]. The difference in predictive factors emphasizes that low disease activity during treatment is different from remission which persists after discontinuation of anti-rheumatic therapy.

In conclusion, 9-15% of RA patients treated with conventional therapy achieved sustained DMARD-free remission. Several factors which can easily be determined in clinical practice such as symptom duration before presentation and the absence of IgM RF and anti-CCP antibodies are consistently associated with sustained DMARD-free remission. In light of our findings that RA can resolve in approximately one-tenth of patients, additional studies are warranted to further elucidate the underlying mechanisms.

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