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Original article

Prevalence and concordance of early and sustained remission assessed by various validated indices in the early arthritis "ESPOIR" cohort

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ABSTRACT

Objectives: To assess the prevalence of remission in early arthritis, to evaluate the concordance across different criteria sets in defining this state, and to look for predictive factors for early and sustained remission.

Methods: Patients from the ESPOIR cohort were followed-up every 6 months. We analysed early remission and sustained remission in 3 groups of patients: patients having rheumatoid arthritis (RA) according to 2010 ACR/EULAR criteria, undifferentiated arthritis (UA), and the whole cohort. Remission was defined according to ACR/EULAR criteria, 28 Joint Disease Activity Score (DAS28 < 2.6), and Simplified Disease Activity Index (SDAI ≤ 3.3). Agreement was evaluated by k-coefficient. Predictive factors for sustained remission at 1, 3 and 5 year in RA patients were analyzed.

Results: Eight hundred and nineteen patients were included. Early remission rates in the RA/UA/ESPOIR groups were observed in respectively 29.2% (181/682), 51.4% (55/123) and 32.7% (239/813) of patients by DAS28; 15.7%, 29.1% and 18% by SDAI; and 11.2%, 29.1% and 12.8% by ACR/EULAR criteria. Agreement between classifications of remission was low for DAS28 vs. ACR/EULAR (k = 0.44), high for SDAI vs. ACR/EULAR (k = 0.78), and moderate for SDAI vs. DAS28 (k = 0.54). Lower baseline disease activity scores, non-menopausal status and younger age were the best predictive factors for sustained remission, with consistent results across the 3 definitions of remission.

Conclusion: Our study showed that the rate of early and sustained remission in early arthritis is dependent on the definition used, with a variable degree of agreement across criteria sets, but with consistent predictive factors of favourable outcome in patients finally diagnosed with RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that is characterized by joint inflammation leading to joint destruction. This causes decreased functional capacity, work disability, and reduced quality of life [1]. Studies evaluating tight control and treat-to-target strategies advocate that remission should be reached as soon as possible and should ideally be maintained during the course of the disease [2,3]. Since a cure has not yet been established for rheumatoid arthritis (RA), the best achievable state in patients with RA is remission. However, the best way to define remission is still under debate. Categories of high, moderate, and low disease activity as well as remission have been identified for the most commonly used indices: the disease activity score using 28 joint counts (DAS28) [4], and Simplified Disease Activity Index (SDAI) [5]. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recently proposed new definitions of remission in RA for clinical trials, which could also be used as the primary outcome of clinical trials and real life practice [6,7]. Testing these new remission criteria in RA cohorts was encouraged to determine their practicality for daily use [6]. Recently, a validation of these criteria using the ESPOIR study showed that patients in ACR/EULAR remission in ESPOIR had a high rate of later radiographic and functional stability, and suggests that these definitions of remission are valid in clinical practice settings [8].

Better knowledge about prevalence and prognostic factors for remission might improve patient care according to their individual profile. Only a few studies have examined sustained remission in usual clinical settings [9–11]. In the literature, definitions of sustained remission in RA vary considerably in both measurement and duration, and whether discontinuation of antirheumatic treatment is a prerequisite remains also debated.

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The aim of this study was to assess the prevalence of remission during the initial follow-up of a cohort of patients with early inflammatory arthritis, to evaluate the concordance across different criteria sets in defining this state, and to look for predictive factors for early and sustained remission in RA patients.

2. Methods

2.1. Source data

The ESPOIR cohort is a nationwide prospective cohort study of adults in France conducted under the auspices of the French Society of Rheumatology [12]. The study was approved by the Institutional Review Board of the Montpellier University Hospital, which was the coordinating center. Prior to inclusion, written informed consent was obtained from each participant.

This cohort has included 813 patients with early arthritis between December 2002 and March 2005. Forteen participating investigational centres located across French territory had participated. Each center included a substantial number of patients, ranging from 35 to 83. In each of those centres, each staff physician as well as the private rheumatologists accustomed to refer patients were incited and reminded on a regular basis that patients were expected for inclusion in ESPOIR, and although no strict rule had been imposed, all efforts were made to systematically offer this opportunity to patients with early arthritis potentially fulfilling inclusion criteria.

Patients were eligible for inclusion in the cohort if they had a definite clinical diagnosis of RA or a diagnosis of undifferentiated arthritis (UA) with a potential for progressing to RA. Thus, these patients had at least two swollen joints, present for more than 6 weeks but less than 6 months, and were naïve for DMARDs and corticosteroids at inclusion. The baseline clinical, immunological, and radiological features of the 813 included patients were published [13,14]. Diagnosis of RA was defined after 1 year of follow-up, according to 2010 ACR/EULAR criteria for RA.

2.2. Study design

The baseline assessment included a standardized interview, a general physical examination, and laboratory tests. Each patient was asked to undergo an evaluation by an office-based rheumatologist every 6 months for 2 years and once a year thereafter.

2.3. Outcome measurement

We analyzed early remission (at 6 months follow-up) in 3 different groups of patients: patients who were diagnosed as having RA according to 2010 ACR/EULAR criteria (RA) at month 12, undifferentiated arthritis (UA) after 1 year of follow-up, and the whole cohort.

The characteristics of patients, which included the swollen joint count (SJC), the tender joint count (TJC), patient's and evaluator's global assessments of disease activity (PGA and EGA, respectively) on a visual analog scale (in cm), smoking status, comorbidity, presence of extra-articular features, ESR, CRP, RF and HAQ were described and compared according to fulfilment or not of remission according to the following definitions:

- 28 Joint Disease Activity Score (DAS28 < 2.6) [4];
- Simplified Disease Activity Index (SDAI $\leq$ 3.3) [5];
- the 2011 ACR/EULAR Boolean remission criteria [6].

For this study, sustained remission at 1 year was defined by remission state in both 6 months- and 1 year visits; sustained remission at 3 years was defined by remission state in all consecutive 6 months-, 1- and 3-year visits; and sustained remission at 5 years was defined by remission state at all consecutive 6 months-, 1-, 3-, and 5-year time points.

2.4. Measurements

Clinical assessment included demographic data: age, gender, menopause, smoking status and comorbidities. Biochemical measurements included rheumatoid factor, anti-CCP antibody and C-reactive protein (CRP; mg/L) were also assessed.

2.5. Radiological data

Radiographs of the hands, wrists and feet in the postero-anterior view were performed for each patient at baseline, 6 and 12 months. Images were centralised and scored according to modified total Sharp score (mTSS) [15] by an experienced rheumatologist who was blinded to the patient's other data, in known chronological order. For each patient, an erosion score, a joint-narrowing score and a total radiographic score were assessed [16].

2.6. Statistical analysis

The statistical analysis was performed in three steps. Firstly, descriptive statistics were calculated for baseline characteristics in three groups of patients: patients who were diagnosed as having RA according to 2010 ACR/EULAR criteria (RA), undifferentiated arthritis (UA) after 1 year of follow-up, and the whole cohort. For variables that were normally distributed, the mean $\pm$ standard deviation (SD) was reported. For dichotomous variables, the number (%) of patients was listed relative to the total number of patients for whom information was available about the characteristic under investigation. Agreement across available criteria sets was evaluated by k-coefficient. In the second step, three logistic regression models using three definitions of the dependent variable "remission yes/no" were developed at 6 months, 1 year, 3 years and 5 years in the patients who were diagnosed as having RA according to 2010 ACR/EULAR criteria (RA) at 1 year. The first definition of remission was the DAS28 < 2.6. The second definition of remission used the ACR/EULAR remission criteria set. The third definition of remission was based on SDAI $\leq$ 3.3. Categorical variables were analysed using Chi-square or Fisher's tests, depending on sample size restrictions, and the odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Factors found to be significant to the $P < 0.15$ level in univariate analysis were included to the multivariate model. At last, characteristics of patients in DMARD-free sustained remission at 1 year, 3 years and 5 years according to DAS28 were calculated: For variables that were normally distributed, the mean $\pm$ SD was reported. For dichotomous variables, the number (%) of patients was listed relative to the total number of patients for whom information was available about the characteristic under investigation.

Statistical analyses were performed using SAS V.8.2. *P*-values < 0.05 were regarded as significant.

3. Results

3.1. Demographic, clinical and biological characteristics of the 3 groups of patients

Table 1 shows the baseline characteristics of the patients. The mean age was 48.5 $\pm$ 12.2 years, 46.5 $\pm$ 13.7, and 48.1 $\pm$ 12.6 for

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Table 1
Patients' characteristics at baseline.

Baseline variable	ESPOIR cohort group (n = 813)	RA group (n = 682)	UA group (n = 123)
Age (years), (mean [SD])	48.1(12.6)	48.5 (12.2)	46.5 (13.7)
Women, n (%)	624 (76.8)	533 (78.2)	85 (69.1)
Menopause, n (%)	285 (45.7)	249 (46.8)	34 (40.0)
RF positivity, n (%)	372 (45.8)	371 (54.4)	1 (0.82)
Anti-CCP antibody, n (%)	315 (38.8)	315 (46.2)	0 (0.0)
DAS28, n (%)			
< 2.6	21 (2.63)	8 (1.20)	13 (10.7)
Between 2.6 and 3.2	40 (5.01)	21 (3.14)	18 (14.8)
Between 3.2 and 5.1	346 (43.3)	269 (40.2)	71 (58.2)
> 5.1	392 (49.1)	371 (55.5)	20 (16.4)
Erosive disease, n (%)	262 (34.0)	237 (36.7)	21 (17.7)
Active smokers, n (%)	183 (47.2)	148 (45.1)	33 (56.9)
CRP > 10 mg/L, n (%)	376 (46.3)	321 (47.1)	53 (43.4)
Comorbidity, n (%)	333 (41.0)	281 (41.2)	50 (40.7)

RA: rheumatoid arthritis according to 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria; UA: undifferentiated arthritis; SD: standard deviation; RF: rheumatoid factor; Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or haematuria) or current cancer.

patients who were diagnosed as having RA after 1 year of follow-up, UA and the whole cohort, respectively. Among the RA patients, 371 (55,5%) had high disease activity at baseline (DAS28 > 5.1) vs. 392 (49.5%) of the whole cohort and 20 (16.4%) of the UA.

3.2. Remission rate at 6 months follow-up visit according to the 3 definitions in the 3 groups of the patients

Early remissions in the RA patients, UA and the whole cohort were observed in respectively 29.2%, 51.4% and 32.7% of patients by DAS28, 15.6%, 29.1% and 18.0% by SDAI, and 11.2, 20.9% and 12.7% by ACR/EULAR remission criteria (Supplementary material, Fig. S1).

3.3. Agreement across classifications in remission by the different remission criteria in the ESPOIR cohort

The agreement between classifications in remission at 1 year by k-statistics was moderate for SDAI vs. DAS28 (k = 0.54 [CI95%] [0.48–0.61]), low for DAS28 vs. ACR/EULAR remission criteria (k = 0.44 [CI95%] [0.38–0.51]), and high for ACR/EULAR remission criteria vs. SDAI (k = 0.78 [CI95%] [0.72–0.84]) (Supplementary material, Fig. S2).

3.4. Predictive variables of sustained remission according to DAS28

Univariate analysis showed that the patients who fulfilled remission criteria at 1 year were younger had lower baseline DAS28, more often absence of associated comorbidity and were more likely to be in non-menopausal status for females. Lower baseline disease activity scores (DAS28 < 5.1), non-menopausal status and younger age (< 50 years) were factors associated with sustained remission at 3 and 5 years (Table 2).

Stepwise logistic regression analysis of predictive factors revealed that lower baseline disease activity scores (DAS28 < 5.1) and younger age (< 50 years) were the best predictive factors for sustained remission at 1 year. A younger age (< 50 years) was again an independent predictive factor of the sustained remission at 3 and 5 years (Table 3).

3.5. Predictive variables of sustained remission according to 2011 ACR/EULAR remission criteria

Univariate analysis showed that lower baseline disease activity scores (DAS28 < 5.1), non-menopausal status and younger age (< 50 years) were associated factors for sustained remission at 1 and 3 years. A lower baseline disease activity score was also associated with remission at 5 years, although only a trend to statistical significance could be observed (P = 0.053) (Table 4).

Stepwise logistic regression analysis of predictive factors revealed that lower baseline disease activity scores (DAS28 < 5.1), and younger age (< 50 years) were the best predictive factors for sustained remission at 1 year (Table 3). None of them had any significant association with sustained remission at 3 and 5 years.

Table 2
Factors associated with sustained remission according to DAS28 for RA patients (univariate analyses).

	Sustained remission at 1 year			Sustained remission at 3 years			Sustained remission at 5 years		
	Yes n (%)	No n (%)	P-value	Yes n (%)	No n (%)	P-value	Yes n (%)	No n (%)	P-value
Age > 50 years	40 (36.0)	261 (56.2)	< 0.001	19 (33.9)	236 (56.8)	0.001	14 (37.8)	192 (56.3)	0.03
Women, n (%)	84 (75.6)	362 (78.1)	0.59	41 (73.2)	326 (78.5)	0.36	29 (78.3)	268 (78.5)	0.97
Menopause, n (%)	23 (27.3)	184 (50.8)	< 0.001	10 (24.3)	166 (50.9)	0.001	8 (27.5)	135 (50.3)	0.01
RF positivity, n (%)	66 (59.4)	249 (53.6)	0.27	27 (48.2)	233 (56.1)	0.26	17 (45.9)	202 (59.2)	0.11
Anti-CCP, n (%)	56 (50.4)	217 (46.7)	0.48	24 (42.8)	211 (50.8)	0.26	16 (43.2)	180 (52.7)	0.26
DAS28, n (%)									
< 2.6	4 (3.7)	3 (0.6)		2 (3.6)	4 (0.9)		2 (5.4)	4 (1.2)	
2.6–3.2	7 (6.5)	11 (2.4)	< 0.001	4 (7.2)	11 (2.7)	0.02	2 (5.4)	12 (3.6)	0.03
3.3–5.1	55 (51.4)	173 (37.7)		27 (49.1)	157 (38.6)		20 (54.1)	130 (39.1)	
> 5.1	41 (38.3)	271 (59.1)		22 (40.0)	234 (57.6)		13 (35.1)	187 (56.1)	
Erosion SHS, n (%)	37 (34.5)	167 (37.7)	0.54	15 (28.3)	149 (36.9)	0.21	13 (36.1)	127 (38.4)	0.78
Smoking, n (%)	22 (39.2)	96 (43.4)	0.57	11 (36.6)	88 (45.1)	0.38	6 (28.5)	73 (45.3)	0.14
CRP positivity, n (%)	54 (48.6)	212 (45.6)	0.57	28 (50.0)	192 (46.2)	0.59	17 (45.9)	161 (47.2)	0.88
Comorbidity, n (%)	34 (30.6)	205 (44.1)	0.01	18 (32.1)	181 (43.6)	0.10	14 (37.8)	139 (40.7)	0.73

Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or haematuria) or current cancer; Erosion SHS: Erosion Sharp-van der Heidjde score.

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Table 3
Stepwise logistic regression analysis of predictive factors of sustained remission according to three definitions for RA patients.

	Persistent remission (year)	Variables in the model	OR	CI (95%)
Remission defined by DAS28	1	Age* DAS28*	0.45	0.29–0.71
		<2.6	1	
		Between 2.6 and 3.2	0.67	0.11
		Between 3.3 and 5.1	0.29	0.06
		>5.1	0.15	0.03
	3	Age*	0.40	0.22–0.72
	5	Age*	0.46	0.23–0.94
Remission defined by 2011 ACR/EULAR remission criteria	1	Age* DAS28*	0.33	0.15–0.72
		<2.6	1	
		Between 2.6 and 3.2	1.40	0.19–1.02
		Between 3.3 and 5.1	0.21	0.03–1.22
		>5.1	0.15	0.02–0.88
	3	–		
	5	–		
Remission defined by SDAI	1	Age* DAS28	0.35	0.17–0.70
		<2.6	1	
		Between 2.6 and 3.2	1.52	0.20–11.11
		Between 3.3 and 5.1	0.33	0.06–1.88
		>5.1	0.18	0.03–1.07
	3	DAS28*		
		<2.6	1	
		Between 2.6 and 3.2	0.62	0.07–4.95
		Between 3.3 and 5.1	0.08	0.01–0.51
		>5.1	0.07	0.01–0.43
	5	–		

RA: rheumatoid arthritis; DAS28: 28 Joint Disease Activity Score; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; SDAI: Simplified Disease Activity Index; OR: odds ratios; 95% CI: 95% confidence intervals. After adjusting on age, gender, rheumatoid factor, ACPA, DAS28, erosions, tobacco, CRP > 10 mg/L, and comorbidities; factors found to be significant to the $P < 0.15$ level in univariate analysis were included to the multivariate model.
* $P < 0.05$.

Table 4
Factors associated with sustained remission according to 2011 ACR/EULAR sustained remission criteria for RA patients (univariate analyses).

	Sustained remission at 1 year			Sustained remission at 3 years			Sustained remission at 5 years		
	Yes *n* (%)	No *n* (%)	*P*-value	Yes *n* (%)	No *n* (%)	*P*-value	Yes*n* (%)	No *n* (%)	*P*-value
Age > 50 years	11 (30.5)	304 (53.8)	0.006	3 (23.1)	265 (54.4)	0.02	1 (20.0)	234 (54.9)	0.18
Women, *n* (%)	30 (83.3)	440 (77.8)	0.44	11 (84.6)	380 (78.1)	0.74	1 (20.0)	92 (21.6)	1
Menopause, *n* (%)	6 (20.0)	216 (49.1)	0.002	1 (9.1)	186 (48.9)	0.001	0 (0.0)	163 (48.8)	0.12
RF positivity, *n* (%)	24 (66.6)	304 (53.8)	0.13	7 (53.8)	272 (55.8)	0.88	3 (60.0)	250 (58.6)	1
Anti-CCP, *n* (%)	19 (52.7)	265 (46.9)	0.49	5 (38.1)	246 (50.5)	0.39	3 (60.0)	227 (53.3)	1
DAS28, *n* (%)									
<2.6	2 (5.7)	5 (0.9)		1 (7.7)	5 (1.1)		1 (20.0)	5 (1.2)	
2.6–3.2	5 (14.2)	15 (2.7)	<0.001	2 (15.4)	15 (3.1)	0.01	0 (0.0)	17 (4.1)	0.05
3.3–5.1	15 (42.8)	226 (40.6)		4 (30.7)	193 (40.4)		2 (40.0)	167 (39.9)	
>5.1	13 (37.1)	310 (55.7)		6 (46.1)	264 (55.3)		2 (40.0)	229 (54.7)	
Erosion SHS, *n* (%)	11 (31.4)	203 (37.5)	0.46	4 (30.7)	173 (36.6)	0.77	1 (20.0)	156 (37.8)	0.65
Smoking, *n* (%)	9 (42.8)	115 (42.7)	0.99	4 (44.4)	97 (42.2)	1	1 (25.0)	85 (41.7)	0.64
CRP positivity, *n* (%)	16 (44.4)	259 (45.8)	0.87	5 (38.4)	226 (46.4)	0.57	1 (20.0)	197 (46.2)	0.38
Comorbidity, *n* (%)	11 (30.5)	238 (42.1)	0.17	3 (23.1)	208 (42.7)	0.15	1 (20.0)	183 (42.9)	0.39

RF: rheumatoid factor; Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or haematuria) or current cancer; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; DAS28: 28 Joint Disease Activity Score; CRP: C-reactive protein; Erosion SHS: Erosion Sharp-van der Heidjde score.

3.6. Predictive variables of sustained remission according to SDAI

For sustained remission at 1 year, univariate analysis showed that lower baseline disease activity scores (DAS28 < 5.1), rheumatoid factors positivity, non-menopausal status and younger age (< 50 years) were factors associated with sustained remission at 1 and 3 years. A lower baseline disease activity score was associated with remission at 5 years (Table 5).

Stepwise logistic regression analysis of predictive factors revealed that lower baseline disease activity scores (DAS28 < 5.1), and younger age (< 50 years) were the best predictive factors for sustained remission at 1 year. Only a low baseline score was associated with sustained remission at 3 years. No factor was predictive of sustained remission at 5 years (Table 3).

3.7. Stepwise logistic regression analysis of predictive factors of early remission

Lower baseline disease activity scores (DAS28 < 5.1), absence of associated comorbidity, younger age (< 50 years) and the presence of rheumatoid factor were the best predictive factors according to

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Table 5
Factors associated with sustained remission according to SDAI for RA patients (univariate analyses).

	Sustained remission at 1 year			Sustained remission at 3 years			Sustained remission at 5 years		
	Yes *n* (%)	No *n* (%)	*P*-value	Yes *n* (%)	No *n* (%)	*P*-value	Yes *n* (%)	No *n* (%)	*P*-value
Age > 50 years	14 (29.7)	290 (54.1)	0.001	5 (27.7)	246 (54.2)	0.02	4 (33.3)	210 (53.8)	0.16
Women, *n* (%)	39 (82.9)	412 (76.8)	0.33	16 (88.8)	349 (76.8)	0.38	10 (83.3)	304 (77.9)	1.00
Menopause, *n* (%)	9 (23.1)	203 (49.2)	0.001	3 (18.7)	174 (49.8)	0.01	2 (20.0)	147 (48.3)	0.11
RF positivity, *n* (%)	32 (68.1)	284 (52.9)	0.04	11 (61.1)	249 (54.8)	0.60	7 (58.3)	221 (56.6)	0.90
Anti-CCP, *n* (%)	27 (57.4)	247 (46.1)	0.13	7 (38.8)	230 (50.6)	0.32	5 (41.6)	203 (52.1)	0.47
DAS28, *n* (%)									
< 2.6	2 (4.4)	5 (0.9)		2 (11.1)	5 (1.1)		2 (16.6)	5 (1.3)	
2.6–3.2	5 (11.1)	13 (2.4)	< 0.001	3 (16.6)	12 (2.7)	< 0.001	1 (8.3)	14 (3.6)	< 0.001
3.3–5.1	22 (48.8)	209 (39.5)		6 (33.3)	182 (40.9)		4 (33.3)	152 (39.7)	
> 5.1	16 (35.5)	302 (57.1)		7 (38.8)	246 (55.3)		5 (41.6)	212 (55.3)	
Erosion SHS, *n* (%)	15 (32.6)	194 (37.8)	0.48	6 (33.3)	163 (36.8)	0.75	3 (25.0)	143 (37.8)	0.54
Smoking, *n* (%)	12 (44.4)	108 (42.0)	0.81	5 (45.4)	91 (42.7)	1.00	2 (28.5)	80 (43.0)	0.70
CRP positivity, *n* (%)	19 (40.4)	250 (46.6)	0.41	7 (38.8)	210 (46.2)	0.53	5 (41.6)	181 (46.4)	0.74
Comorbidity, *n* (%)	14 (29.7)	229 (42.7)	0.08	5 (27.7)	195 (42.9)	0.20	4 (33.3)	164 (42.0)	0.54

RF: rheumatoid factor; Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or haematuria) or current cancer; SDAI: Simplified Disease Activity Index; DAS28: 28 Joint Disease Activity Score; CRP: C-reactive protein; Erosion SHS: Erosion Sharp-van der Heidjde score.

Table 6
Stepwise logistic regression analysis of predictive factors of early remission according to three definitions for RA patients.

	Remission at 6 months*n* (%)	Variables in the model	OR	CI (95%)
Remission defined by DAS28[a]	181 (29.2)	DAS28*		
		< 2.6	1	
		Between 2.6 and 3.2	0.15	0.01
		Between 3.3 and 5.1	0.08	0.01
		> 5.1	0.04	0.01
		Comorbidity*	0.61	0.42
Remission defined by 2011 ACR/EULAR remission criteria[a]	71 (11.2)	Age*	0.43	0.25–0.75
Remission defined by SDAI[a]	98 (15.6)	Age*	0.50	0.32–0.81
		RF*	1.69	1.06–2.67

RF: rheumatoid factor; Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or haematuria) or current cancer; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; DAS28: 28 Joint Disease Activity Score; SDAI: Simplified Disease Activity Index; OR: odds ratios; 95% CI: 95% confidence intervals; CRP: C-reactive protein. *$P < 0.05$.

[a] After adjusting on age, gender, rheumatoid factor, ACPA, Anti-CCP, DAS28, erosions, tobacco, CRP > 10 mg/L, and comorbidities; factors found to be significant to the $P < 0.15$ level in univariate analysis were included to the multivariate model.

DAS28 score, 2011 ACR/EULAR remission criteria and SDAI, respectively (Table 6).

3.8. Characteristics of patients in DMARD-free sustained remission at 1 year, 3 years and 5 years in the whole cohort

Forty-six patients were in DMARD-free sustained remission at 1 year, 30 patients at 3 years and 25 patients at 5 years in the whole cohort. Fifty percent (23) of patient in sustained remission at 1 year however met 2010 ACR/EULAR criteria for RA, 60% (18) at 3 years and 56% (14) patients at 5 years.

4. Discussion

Early remission rates in the RA/UA/ESPOIR groups were observed in one third approximately of RA patients by DAS28; and in one fifth of patients by SDAI and ACR/EULAR criteria. Occurrence of remission at all time points was lowest for the ACR/EULAR clinical trial criteria, making it the most stringent remission definition. Baseline low disease activity, pre-menopausal status and younger age predicted the clinical remission.

Our results echo the work of others, demonstrating higher response rates when DAS28 < 2.6 is used and lower responses when index-based definitions or ACR/EULAR variants are applied [17,18].

Among the various remission criteria the most stringent ones appeared to be the SDAI since patients in SDAI remission had the lowest mean residual joint counts and joint count ranges. Previous studies show that the percentages of patients classified in remission were significantly greater with DAS28 (15% and 42.7%) than with SDAI (11% and 33.5%, $P < 0.01$) [19,20]. Indeed, similarly as what was defined within the Boolean definition of ACR/EULAR remission, a patient cannot be regarded in a state of disease remission if more than one joint is found to be either tender or swollen at clinical examination. With DAS28 definition on the other hand, the weighted parts of tender and swollen joint counts in the formula deriving the final activity score allow a theoretically high number of residual abnormal joints (i.e. either tender or swollen at physical examination), provided that other components of the composite score are sufficiently low to result in a globally low score. Indeed, a patient can be considered in disease remission according to DAS28, even though > 20/28 joints are reported swollen by the physician [21]. It should however be emphasised here that this theoretic situation is actually very unlikely in clinical practice, since combining such a high number of inflammatory

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joints with a health state considered as very satisfactory (extremely low disease activity by the patient self assessment) and normal acute phase reactants values is a very outlying, if not impossible, situation. The low stringency of the DAS28 remission criteria, especially in relation to residual joint counts, has already been addressed in previous studies [22,23] and is also apparent from the difference between the proportions of patients with a single visit in remission and that of patients in sustained remission [24].

We showed that the higher the baseline disease activity (as assessed by DAS28), the more limited the chance to achieve remission, with a consistent association whatever the definition of remission was chosen. We also found that the older the patient, the less likely to achieve remission with the three definitions.

Gossec et al. [25] found that patients who had baseline DAS of < 4 or a Ritchie Articular Index of < 17 were more likely to achieve remission at 3 years of follow-up. Vázquez et al. [26] confirmed this finding when using a DAS28 < 5.1 in several models. Forslind et al. [27] found that patients with a high baseline DAS28 were less likely to achieve remission at any time points of assessment. Age has also been shown to be a significant predictor of remission [28]. Burmester et al. (the ReAct trial) [29] found that the older the patient, the less likely to achieve remission up to 3 years of follow-up. However, this result was not confirmed by other anti-TNF studies [20,22] and the FIN-RACo study [30]. This is in line with our results. In the ReAct trial [23], patients having more than one comorbidity were less likely to achieve remission, whereas Hyrich et al. failed to demonstrate a significant association between comorbidity and remission in both etanercept- and infliximab-treated patients [31]. In our report, ACPA and comorbidity were identified as predictors of early and sustained remission.

The strengths of our study are that we have a large sample size, good long-term follow-up and we compared the most widely used composite indices for RA and recently published ACR/EULAR remission criteria at different time points in a cohort of patients with early inflammatory arthritis. The limitations of our study are that the treatment changes over time are not taken into account and that despite the major efforts made to optimize collection of data, several variables remained unknown and thus limited the number of patients with required data completed to conduct the planned analyses.

However, our study population was the ESPOIR cohort, which is a prospective observational study. Patients had never previously undergone treatment with a disease-modifying antirheumatic drug (DMARD) or steroids. In clinical trials, inclusion and exclusion criteria require studying a pre-selected group of patients, often greatly differing from patients seen in usual clinical practice. In contrast, observational studies usually include unselected patients, irrespective of their disease activity, underlying comorbidity or therapy, and the data generated, therefore, reflect routine care situations. The second highlight of the study is that for the first time, we have shown that predictors of remission are similar, irrespective of the definition that was applied.

Finally, our study showed that the rate of early (6 months) and sustained remission in a cohort of early inflammatory arthritis is dependent on the definition used, with a variable degree of agreement across criteria sets, but with consistent predictive factors of favourable outcome in patients finally diagnosed with RA: younger age, lower baseline DAS28 and non-menopausal status. Fewer patients meet more stringent definitions of remission, and we would need to be an awareness that menopausal status, older age, and higher initial disease activity are associated with a lower odds of achieving sustained remission.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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This manuscript has been read and approved by all the authors and they have given necessary attention to ensure the integrity of the work. We guarantee that the manuscript will not be published elsewhere without the consent of the copyright holders. We declare that we have seen and approved the final version of manuscript.

We declare that we participated at the study as following: C. Lukas and B. Combe conceived the study and supervised its design, execution, and analysis and participated in the drafting and critical review of the manuscript. I. Hmamouchi and N. Rincheval did data management and statistical analyses. All other authors' participated in critical revision of the manuscript. I. Hmamouchi wrote the paper with input from all investigators.

Appendix A. Supplementary material

Supplementary material (Figs. S1–S2) associated with this article can be found, in the online version, at doi:10.1016/j.jbspin.2014.02.007.

References

[1] Sokka T. Long-term outcomes of rheumatoid arthritis. Current Opin Rheumatol 2009;21:284–90.
[2] Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis 2010;69:638–43.
[3] Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
[4] Prevoo ML, van THof MA, van Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
[5] Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23:100–8.
[6] Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
[7] Shahouri SH, Michaud K, Mikuls TR, et al. Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. Arthritis Rheum 2011;63:3204–15.
[8] Zhang B, Combe B, Rincheval N, et al. Validation of ACR/EULAR definition of remission in rheumatoid arthritis from RA practice: the ESPOIR cohort. Arthritis Res Ther 2012;14:R156.
[9] Jayakumar K, Norton S, Dixey J, et al. Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology 2012;51:169–75.
[10] Svensson B, Andersson ML, Bala SV, et al. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open 2013;3:e003554.

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[11] Prince FH, Bykerk VP, Shadick NA, et al. Sustained rheumatoid arthritis remission is uncommon in clinical practice. Arthritis Res Ther 2012;14:R68.
[12] Combe B, Benessiano J, Berenbaum F, et al. ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74:440–5.
[13] Lukas C, Combe B, Ravaud P, et al. Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: data from the *étude et suivi des polyarthrites indifférenciées récentes* (study and follow-up of early undifferentiated polyarthritis). Arthritis Rheum 2011;63:1804–11.
[14] Devauchelle-Pensec V, Josseaume T, Samjee I, et al. Ability of oblique foot radiographs to detect erosions in early arthritis: results in the ESPOIR cohort. Arthritis Rheum 2008;59:1729–34.
[15] van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
[16] Mouterde G, Lukas C, Logeart I, et al. Predictors of radiographic progression in the ESPOIR cohort: the season of first symptoms may influence the short-term outcome in early arthritis. Ann Rheum Dis 2011;70:1251–6.
[17] Klarenbeek NB, Koevoets R, van der Heijde DM, et al. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815–21.
[18] Mäkinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. Clin Exp Rheumatol 2006;24 [S-22-8].
[19] Khanna D, Oh M, Furst DE, et al. Evaluation of the preliminary definitions of minimal disease activity and remission in an early seropositive rheumatoid arthritis cohort. Arthritis Rheum 2007;57:440–7.
[20] Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. Rheumatology 2007;46:975–9.
[21] Landewe R, van der Heijde DM, Voskuyl A, et al. Condensed 28-joint counts jeopardise the construct validity of DAS28 remission: a comparison with the original DAS. Arthritis Rheum 2004;50:S457.
[22] Makinen H, Kautiainen H, Hannonen P, et al. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 2005;64:1410–3.
[23] van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis 2005;64:1582–7.
[24] Ometto F, Botsios C, Raffeiner B, et al. Methods used to assess remission and low disease activity in rheumatoid arthritis. Autoimmun Rev 2010;9:161–4.
[25] Gossec L, Dougados M, Goupille P, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis 2004;63:675–80.
[26] Vázquez I, Graell E, Gratacós J, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheumatol 2007;25:231–8.
[27] Forslind K, Hafström I, Ahlmén M, et al. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007;66:46–52.
[28] Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. Rheumatol 2007;34:1670–3.
[29] Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology 2007;46:1191–9.
[30] Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.
[31] Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:1786–94.

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