ARD Online First, published on May 2, 2014 as 10.1136/annrheumdis-2013-204906

EXTENDED REPORT

Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes

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Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2013-204906).

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Received 12 November 2013
Revised 28 March 2014
Accepted 6 April 2014

To cite: Ruyssen-Witrand A, Guernec G, Nigon D, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2013-204906

ABSTRACT

Objectives Using data for patients with early rheumatoid arthritis (RA) from the ESPOIR cohort, we aimed to evaluate the impact of remission versus low disease activity (LDA) by the Simple Disease Activity Index (SDAI) at 1 year on 3-year structural damage assessed by the modified Sharp–van der Heijde total score (mTSS) and functional impairment assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI).

Methods We included 625 patients from the ESPOIR cohort who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA at baseline and had an SDAI score at 1 year. mTSS and HAQ-DI scores were compared at 3 years for patients with SDAI remission or LDA status at 1 year. A linear mixed model was used to assess the independent effect of SDAI status at 1 year on mTSS and HAQ-DI at 3 years.

Results Of the 625 patients included (mean (SD) age 48.5 (12.1) years; 491 (78.6%) were women), 121 (19.4%) were in SDAI remission and 223 (35.7%) in LDA at 1 year. The mean (SD) mTSS and HAQ-DI score at 3 years was 9.6 (9.2) and 0.23 (0.42), respectively, for patients in remission at 1 year and 15.8 (16.1) and 0.43 (0.52), respectively, for patients with LDA (both $p<0.05$). Multivariate analysis revealed an association of remission rather than LDA status at 1 year and reduced mTSS score ($p=0.005$) but not HAQ-DI score ($p=0.4$) at 3 years.

Conclusions Aiming for SDAI remission rather than LDA at 1 year leads to better radiographic outcomes at 3 years in early RA patients.

The prognosis of rheumatoid arthritis (RA) has greatly changed in the last two decades, with many new treatment options, including biological agents, leading to good control of disease activity and prevention of structural damage and long-term disability.[1–3] In parallel, the importance of early effective therapy and the implications of disease activity on function and joint destruction have led to 'tight control' and 'treat-to-target' therapeutic strategies.[4–9]

When initiating a new treatment, the target in the European League Against Rheumatism (EULAR) guidelines[10] is remission or low disease activity (LDA). Indeed, targeting remission is often associated with good functional outcome and reduced structural progression.[11] For many years, clinical remission was defined by a disease activity score in 28 joints (DAS28) ≤2.6,[12] which was widely used in clinical trial outcomes.[13] However, this score has been criticised because residual disease activity was frequently observed in patients with DAS28 remission.[14–16] Recently, the American College of Rheumatology (ACR) and EULAR proposed more stringent criteria for defining remission with Boolean criteria ≤3 or Simple Disease Activity Index (SDAI) ≤3.3.[17] However, the validation of such criteria for long-term outcomes, especially functional impairment and structural damage, is needed. These criteria have been proposed for clinical trials, but experts have suggested that they can be used for daily practice.

Several studies showed a low prevalence of clinical remission according to the EULAR definition in clinical trials or in routine practice, whereas targeting LDA is often easier with a large sample of patients.[18–20] Thus, aiming at LDA might be an alternative goal, and most studies have pooled patients in remission and LDA when assessing the association of disease activity and structural damage. Few studies have examined the difference between patients in remission and LDA in terms of long-term outcomes such as structural damage and functional impairment.

Using data for patients with early RA from the ESPOIR cohort, we aimed to evaluate the impact of achieving remission versus LDA comparing the SDAI, Clinical Disease Activity Index (CDAI) and DAS28 at 1 year on 3-year structural damage and functional impairment.

METHODS

Patients

This study used data from a large national, multicentre, longitudinal, prospective cohort of 813 patients with early arthritis in France, the Etude et Suivi des POlyarthrites Indifférenciées Récentes (ESPOIR) cohort. The characteristics of the cohort were described previously.[21] Briefly, 813 patients with early arthritis recruited in 14 clinical centres in France with arthritis duration <6 months and no prior treatment with disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids were included between 2002 and 2005. Patients underwent clinical, functional, biological and radiological assessments at baseline and at each visit. For the present study, we selected patients who fulfilled the

2010 ACR/EULAR criteria[22] for RA at least once within the first 3 years of follow-up and had an SDAI score at 1 year (n=625).

Local institutional review boards approved the study, and written informed consent was obtained from all subjects.[21]

Clinical, biological and immunological data

Clinical data

All patients underwent a clinical examination at baseline and 6, 12, 18, 24 and 36 months. We collected data on demographic characteristics including age, gender, symptom duration, smoking habits, tender joint count in 28 joints, swollen joint count in 28 joints, patient global assessment on a Visual Analogue Scale (VAS), physician global assessment on a VAS at each visit as well as current treatment with DMARDs, biological DMARDs use and mean dose of glucocorticoids used.

Biological and immunological data

Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were measured at each visit. Titres of anti-CCP2 antibodies (anticitrullinated peptides antibodies (ACPA); ELISA, DiaSorin, France; positive >50 U/mL) were quantified at baseline in a central lab. Patients were classified as having no, low and high titres of ACPA by anti-CCP2 antibodies <50, 50–150 and >150 U/mL, respectively.

Disease activity assessment

Disease activity assessed by the SDAI[23] was calculated as follows: TJC28+SJC28+patient global VAS (cm)+physician global VAS (cm)+CRP (mg/dL). CDAI[24] was calculated as follows: TJC28+SJC28+patient global VAS (cm)+physician global VAS (cm). DAS28[25] was calculated as follows: $0.56\sqrt{(TJC28)}+0.28\sqrt{(SJC28)}+0.70\ln(ESR)+0.014$ (patient global VAS (mm)).

Clinical disease activity states were defined[26] as remission, SDAI≤3.3, CDAI≤2.8 or DAS28<2.6; LDA, SDAI 3.3–11, CDAI 2.8–10 or DAS28 2.6–3.2; and moderate or high disease activity, SDAI >11, CDAI >10 or DAS28 >3.2.

Functional impairment

Functional impairment was assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI) measured at baseline and at each visit (6, 12, 24 and 36 months). Only HAQ-DI at 3 years was used to assess the relationship between disease activity and functional impairment.

Radiography

Baseline and 3-year radiographs of the hands, wrists and feet were read by one rheumatologist (GT) who was aware of the temporal order and assessed by the modified Sharp–van der Heijde score.[27] The reader was blinded to patient identity, characteristics and treatment. The results were expressed as total Sharp score (mTSS). Intrareader correlation coefficient was 0.97; the smallest detectable change was about 1 point.[28] The details of the method of radiographs scoring are available in online supplementary material.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the sample. Continuous variables are presented as mean (SD) and categorical variables as number (percentage).

Missing data management

Starting from a dataset of 625 patients, 496 (79.4%) and 535 (85.6%) patients, with no missing information for the two outcomes of interest, remained for analysis of mTSS and HAQ-DI scores, respectively, at 3 years.

We managed the remaining missing data for data on glucocorticoids, DMARDs and biological DMARDs intake by assuming an MAR mechanism of missing data, with the multiple imputation method Multivariate Imputation by Chained Equation.[29 30] The details of the procedure are available in online supplementary material.

Univariate analyses

The primary objective of the study was to compare the mTSS and HAQ-DI scores at 3 years according to SDAI status at 6 months and 1 and 2 years. The mean mTSS and HAQ-DI score at 3 years was compared by SDAI status by z test at each assessment. The same analyses were performed for structural progression defined by the mTSS difference between baseline and 3 years. The same analyses were repeated taking into account the CDAI, then the DAS28 as disease activity scores and at 6 months and 1 and 2 years. The 3-year progression of mTSS by SDAI status at 6 months and 1 and 2 years was represented as a cumulative probability plot. Demographic and clinical characteristics as well as treatment at baseline, 6, 12, 18, 24 and 36 months were compared by SDAI status at 1 year by χ^2 test for dichotomous variables and z test for continuous variables.

Multivariate analysis

The multivariate model used was the linear mixed model proposed by Laird and Ware[31] with stepwise inclusion,[32] including SDAI status, glucocorticoids, DMARDs intake, biological agents intake, ACPA, smoking habits, baseline erosions, age and sex as covariables. The details of the model are available in online supplementary material.

The same procedure was used to model the HAQ-DI score at 3 years.

Furthermore, another time-dependent longitudinal mixed model was tested and detailed in the online supplementary material.

All analyses involved use of R software (nlme package).

RESULTS

Characteristics of RA patients

Among the 813 patients with early RA included in ESPOIR cohort, 698 fulfilled the 2010 ACR/EULAR criteria within the first 3 years of follow-up and had more active disease at baseline, as was previously reported.[33] Among the 698 patients, 625 had SDAI data available at 1 year. The flow chart of the selection of patients is in online supplementary figure S1. The main baseline characteristics of patients fulfilling the 2010 ACR/EULAR criteria for RA in the ESPOIR cohort with available SDAI at 1 year (n=625) as well as the main 1- and 3-year characteristics of patients with available radiograph data (n=496) and HAQ-DI score (n=535) at 3 years are in table 1. All three samples had similar clinical characteristics.

The proportion of patients in remission versus LDA at 1 year was higher when using the DAS28 criterion rather than SDAI or CDAI criteria (see online supplementary table S1).

Association of baseline characteristics and SDAI remission or LDA status at 1 year

Patients in SDAI remission at 1 year were younger than those in SDAI LDA for those with both radiographs and HAQ-DI score at 3 years (p<0.0001). Furthermore, erosive disease at baseline was greater for patients with SDAI LDA than remission at 1 year for those with HAQ-DI data at 3 years (p=0.04) (table 2).

Table 1 Patient baseline and 1- and 3-year characteristics by radiographs and HAQ-DI score available at 3 years

Patient characteristics	All patients, n=625		Patients with radiographs at 3 years, n=496		Patients with HAQ-DI score at 3 years, n=535	
	No. observed		No. observed		No. observed	
Baseline characteristics						
Age, years, mean (SD)	625	48.5 (12.1)	496	48.8 (11.9)	535	48.6 (12.0)
Gender, female, number (%)	625	491 (78.6)	496	391 (78.8)	535	420 (78.5)
Symptom/disease duration*, months, mean (SD)	625	7.3 (8.6)	496	7.6 (9.0)	535	7.6 (9.0)
RF presence, number (%)	625	334 (53.4)	496	262 (52.8)	535	288 (53.8)
ACPA						
▶ Absence, number (%)	625	340 (54.4)	496	265 (53.4)	535	278. (52.0)
▶ Low titres, number (%)	625	47 (7.5)	496	40 (8.1)	535	43 (8.0)
▶ High titres, number (%)	625	238 (38.1)	496	191 (38.5)	535	214 (40.0)
Smokers, number (%)	625	301 (48.2)	496	238 (48.0)	535	255 (47.7)
mTSS, mean (SD)	594	5.3 (7.6)	496	5.6 (7.8)	517	5.6 (7.9)
HAQ-DI, mean (SD)	625	1.0 (0.7)	496	1.0 (0.7)	535	1.0 (0.7)
Patients with erosive disease, number (%)	594	215 (36.2)	496	175 (35.3)	517	182 (34)
1-year characteristics						
SDAI remission, number (%)	625	121 (19.4)	496	94 (19.0)	535	103 (19.3)
SDAI LDA, number (%)	625	223 (35.7)	496	178 (35.9)	535	198 (37.0)
SDAI MDA or HDA number (%)	625	281 (45.0)	496	224 (45.2)	535	234 (43.7)
Glucocorticoids use, number (%)	625	292 (46.7)	496	231 (46.6)	535	251 (46.9)
Cumulative glucocorticoids intake, mg, mean (SD)	621	1058 (1407)	494	1035 (1384)	533	1053 (1385)
DMARDs use, number (%)	625	516 (82.6)	496	411 (82.9)	535	445 (83.2)
Delay before first DMARDs intake†, months, mean (SD)	538	1.1 (1.9)	430	1.1 (1.9)	464	1.1 (1.9)
Biological DMARDs use, number (%)	625	42 (6.7)	496	35 (7.1)	535	38 (7.1)
3-year characteristics						
mTSS, mean (SD)	511	14.3 (14.9)	496	14.3 (14.9)	507	14.3 (14.9)
HAQ-DI, mean (SD)	535	0.5 (0.6)	492	0.5 (0.6)	535	0.5 (0.6)
Glucocorticoids use, number (%)	539	219 (35.0)	493	199 (40.1)	535	217 (40.6)
DMARDs use, number (%)	539	403 (74.8)	493	367 (74.4)	535	399 (74.6)
Biological DMARDs use, number (%)	539	75 (13.9)	493	70 (14.1)	535	75 (14.0)

*Difference between onset of first joint pain and inclusion in the ESPOIR cohort.
†Difference between the date of inclusion in ESPOIR cohort and the first DMARDs intake.
p<0.05 values are shown in bold.
ACPA, anticitrullinated peptides antibodies, no, low and high titres of ACPA by anti-CCP2 antibodies definition was <50, 50–150 and >150 U/mL, respectively; DMARDs: disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; mTSS, modified Sharp–van der Heijde total score; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

Patients achieving SDAI remission or LDA at 1 year did not differ in mean delay to the first DMARD defined by the difference between first DMARD intake and first symptoms of the disease (14.9 vs 13.1 months, p=0.4 for patients with radiographs at 3 years and 14.9 vs 13.2 months, p=0.5, for those with HAQ-DI at 3 years); DMARDs use at 1 year (79.9% vs 80.9%, p=0.9, and 79.6% vs 81.3%, p=0.8, respectively); and biological DMARDs use at 1 year (18.0% vs 15.5%, p=0.4 and 18.3% vs 15.6%, p=0.5, respectively). Glucocorticoids use was higher but not significantly for patients with LDA than remission at 1 year (33.0% vs 43.8%, p=0.1, with radiographs at 3 years and 33.0% vs 44.9%, p=0.06, for those with HAQ-DI at 3 years).

Association of SDAI remission or LDA status at 6 months and 1 and 2 years and mTSS at 3 years and 3-year structural progression

We found no difference between patients in remission or LDA at 6 months in terms of mTSS at 3 years for all disease activity scores used (table 3). Structural damage by the mTSS at 3 years was lower for patients in SDAI remission than LDA at 1 year (mean mTSS: 9.6 vs 15.8, p=0.0007); this difference was also observed with use of the CDAI but not DAS28 at 1 year (table 3). Mean mTSS was lower at 3 years for patients in SDAI remission than LDA at 2 years (table 3, figure 1) by the SDAI or CDAI but not DAS28. Furthermore, mTSS progression was lower for patients in SDAI or CDAI remission than LDA at 1 or 2 years (table 3, figure 1).

Association of SDAI remission or LDA status at 1 year and functional status (HAQ-DI) at 3 years

Functional impairment assessed by HAQ-DI at 3 years was lower for patients in remission than with LDA at 6 months (table 4) with the SDAI, CDAI or DAS28. HAQ-DI was lower at 3 years for patients in SDAI remission than LDA at 1 year (mean HAQ-DI: 0.23 vs 0.43, p=0.0002, Mann–Whitney test); this difference was also observed with use of the CDAI and DAS28 at 1 year. Mean HAQ-DI at 3 years was lower for patients in remission than LDA at 2 years by the SDAI or CDAI but not DAS28 (table 4).

Factors predicting mTSS or HAQ-DI score at 3 years by SDAI remission or LDA status at 1 year

Association with 3-year mTSS

To adjust for potential confounders, we used a multivariate linear mixed model to predict log(mTSS) at 3 years by SDAI

Table 2 Baseline patient characteristics by SDAI remission or LDA at 1 year by radiographs and HAQ-DI score available at 3 years

	Patients with radiographs at 3 years, n=496					Patients with HAQ-DI at 3 years, n=535				
	Remission at 1 year n=94		LDA at 1 year n=178			Remission at 1 year n=103				
Patient characteristics	No. observed		No. observed		p Value	No. observed		No. observed	LDA at 1 year n=198	p Value
Baseline characteristics										
Age, years, mean (SD)	94	44.3 (11.9)	178	51.3 (11.3)	**<0.0001**	103	43.4 (12.0)	198	51.2 (11.2)	**<0.0001**
Gender, number of females (%)	94	74 (78.7)	178	134 (75.3)	0.6	103	83 (80.6)	198	147 (7.2)	0.3
Disease duration, months, mean (SD)	94	6.9 (8.3)	178	8.0 (9.5)	0.3	103	6.5 (8.0)	198	8.1 (9.5)	0.1
RF presence, number (%)	94	51 (54.3)	178	98 (55.1)	1.0	103	58 (56.3)	198	112 (56.6)	0.9
ACPA										
▶ Absence, number (%)	94	49 (52.1)	178	93 (52.2)	0.6	103	52 (50.5)	198	100 (50.5)	0.5
▶ Low titre, number (%)	94	12 (12.8)	178	16 (9.0)		103	13 (12.6)	198	17 (8.6)	
▶ High titre, number (%)	94	33 (35.1)	178	69 (38.8)		103	38 (36.9)	198	81 (40.9)	
Smokers, number (%)	94	47 (50)	178	79 (44)	0.5	103	51 (49.5)	198	89 (44.9)	0.5
mTSS, mean (SD)	94	4.2 (5.8)	178	6.5 (9.4)	0.47	101	4.2 (5.7)	188	6.5 (9.2)	0.0321
HAQ-DI, mean (SD)	94	0.8 (0.6)	178	0.9 (0.7)	0.2	103	0.9 (0.6)	198	0.9 (0.7)	0.5
Patients with erosive disease, number (%)	94	25 (26.6)	178	67 (37.6)	0.09	101	25 (24.3)	188	73 (36.9)	**0.04**

ACPA, anticitrullinated peptides antibodies; no, low and high titres of ACPA by anti-CCP2 antibodies definition was <50, 50–150 and >150 U/mL, respectively; HAQ-DI, Health Assessment Questionnaire Disability Index; LDA, low disease activity; mTSS, modified Sharp–van der Heijde total score; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.
p<0.05 values are shown in bold.

status at 1 year. The results for the final model are summarised in table 5.

SDAI status at 1 year was significantly associated with structural progression of mTSS at 3 years (p<0.001). The mean (SD) difference estimated with contrast method between SDAI remission and LDA at 1 year in log(mTSS) progression within 3 years was −0.427 (p=0.0015) and at 2 years 0.189 (p=0.0077). The other variables significantly associated with structural progression within 3 years were age, presence of baseline erosions and ACPA presence; biological DMARDs use at 6 months and 2 years were associated with a low risk of mTSS progression within 3 years (p=0.010 and p=0.059, respectively), as was glucocorticoids use at 18 months (p=0.009).

The time-dependent longitudinal mixed model gave similar results (see online supplementary table S2) and showed a significant difference between patients in SDAI remission at 1 year versus SDAI LDA in terms of structural mTSS progression within 3 years.

Association with 3-year HAQ-DI

On multivariate analysis, the association of SDAI status and HAQ-DI score did not remain significant (p=0.84, contrast method, data not shown).

DISCUSSION

According to the EULAR recommendations for RA,[10] treatment should aim at a target of remission or LDA in every patient. This aim should be reached at least 3–6 months after initiating the treatment and patients should be monitored every 1–3 months to adapt therapy to the target. The EULAR also proposed new

Table 3 Three-year mTSS and 3-year mTSS progression by remission or LDA in disease activity score at 6 months and 1 and 2 years

	3-year mTSS				3-year mTSS progression		
Disease activity measure/status	No. observed	Remission	LDA	p Value	Remission	LDA	p Value
Status at 6 months							
SDAI	218	14.2±14.8	14.0±14.3	0.9	9.1±11.1	8.1±9.9	0.5
CDAI	216	13.6±14.2	13.9±16	0.9	8.7±10.7	8.3±10.3	0.8
DAS28	220	13.4±13.4	14.5±15.7	0.6	7.9±10.0	8.7±10.4	0.6
Status at 1 year							
SDAI	272	9.6±9.2	15.8±16.1	**0.0007**	5.4±7.4	9.3±11.2	**0.003**
CDAI	266	9.5±9.1	15.6±15.6	**0.0006**	5.4±7.5	9.2±11.0	**0.003**
DAS28	272	12.8±12.6	15.3±16.8	0.2	7.5±9.1	8.7±11.3	0.3
Status at 2 years							
SDAI	305	12.2±12.9	15.8±14.6	**0.03**	6.6±8.2	10.6±11.8	**0.0009**
CDAI	309	11.9±12.5	15.9±14.7	**0.01**	6.6±7.9	10.5±11.9	**0.001**
DAS28	298	13.1±12.5	14.0±12.2	0.6	7.5±8.8	9.3±10.1	0.1

CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Index in 28 Joints; LDA, low disease activity; mTSS, modified Sharp–van der Heijde total score; SDAI, Simple Disease Activity Index.
p<0.05 values are shown in bold.

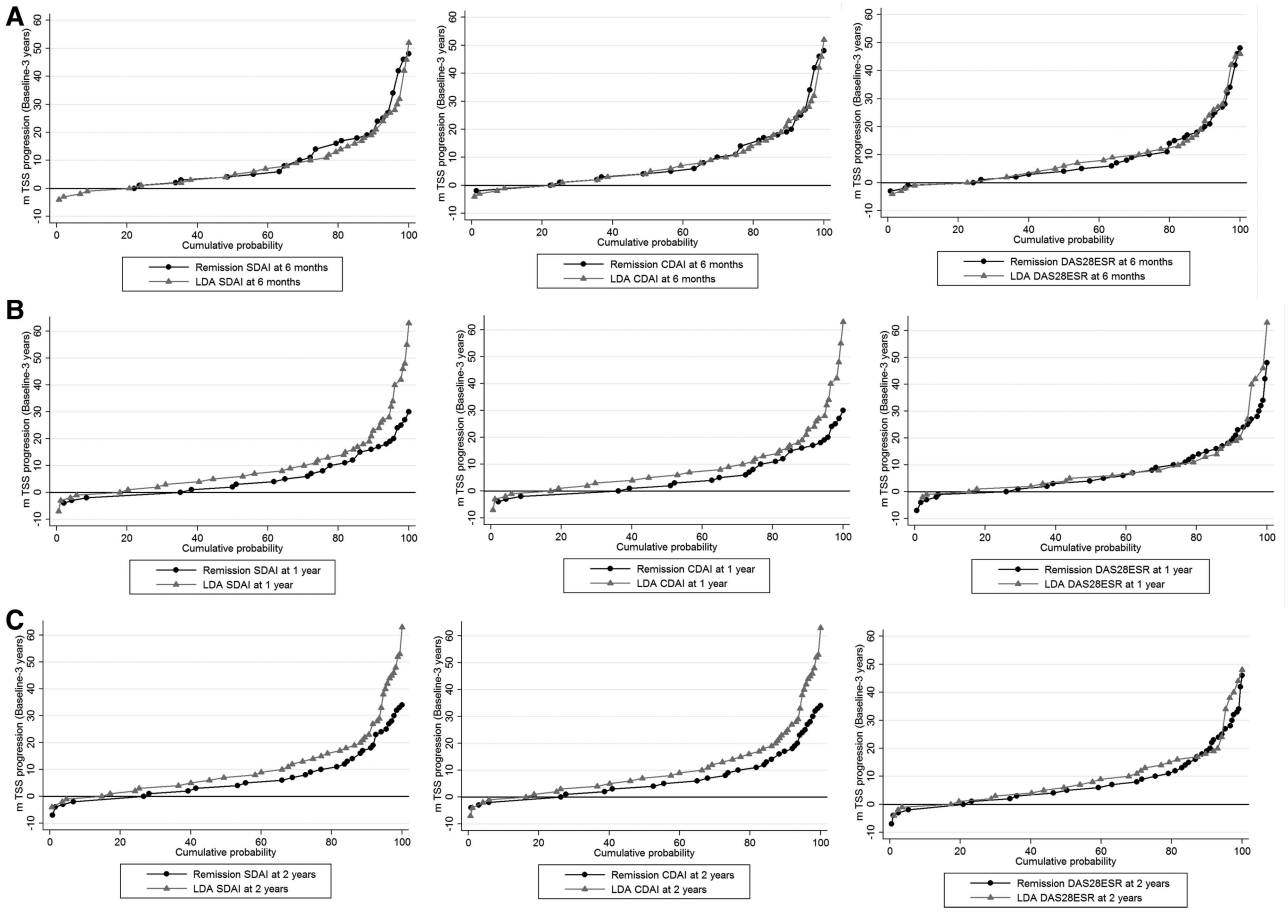

Figure 1 Cumulative probability plots of the progression of mTSS within 3 years according to Simple Disease Activity Index (SDAI) status (remission vs low disease activity (LDA)) at 6 months (A), 1 year (B) and 2 years (C). mTSS, modified Sharp–van der Heijde total score; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Scale in 28 Joints.

criteria for the definition of remission,[17] including the use of SDAI or Boolean criteria. In our study, we found no significant difference in structural damage by the mTSS at 3 years between patients with SDAI remission or LDA at 6 months, but aiming for SDAI remission instead of LDA at 1 year was associated with better structural scores at 3 years and should be a preferential goal in early RA.

To date, few studies have examined the long-term evolution of RA in patients in clinical remission and LDA. In the OPTIMA trial,[34] a randomised clinical trial comparing two strategies of treatment in early arthritis, radiographic scores expressed in mTSS at week 26 were better for patients receiving methotrexate plus placebo with SDAI remission rather than DAS28-CRP LDA. This difference was not observed with

Table 4 Three-year HAQ-DI mean (SD) according to remission or LDA in disease activity score at 6 months and 1 and 2 years

	3-year HAQ-DI mean (SD)			
Disease activity measure/status	**No. observed**	**Remission**	**LDA**	**p Value**
Status at 6 months				
SDAI	239	0.26 (0.46)	0.33 (0.41)	**0.0225**
CDAI	238	0.26 (0.46)	0.32 (0.40)	**0.0375**
DAS28	241	0.27 (0.42)	0.42 (0.47)	**0.0021**
Status at 1 year				
SDAI	301	0.23 (0.43)	0.43 (0.52)	**0.0002**
CDAI	294	0.22 (0.39)	0.44 (0.53)	**<0.0001**
DAS28	294	0.31 (1.47)	0.45 (0.53)	**0.0036**
Status at 2 years				
SDAI	330	0.23 (0.41)	0.49 (0.51)	**<0.0001**
CDAI	335	0.24 (0.42)	0.47 (0.51)	**<0.0001**
DAS28	324	0.33 (0.49)	0.41 (0.47)	0.0710

CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Index in 28 Joints; HAQ-DI, Health Assessment Questionnaire Disability Index; LDA, low disease activity; SDAI, simple Disease Activity Index.
p<0.05 values are shown in bold.

Table 5 Multivariate analysis of 3-year progression of log (mTSS) by disease activity and treatment at 1 year

	Pooled estimates after multiple imputation (m=5 / N=496)				
	Univariate analysis		Multivariate analysis		
Fixed effects model	β-Coef. (SD)	t Test p value	β-Coef. (SD)	t Test p value	Global F test p value
Details of continuous variables					
Intercept	–	–	0.858 (0.19)	<0.001	<0.001
Age at baseline (years)	0.145 (0.04)	<0.001	0.090 (0.04)	0.025	**0.005**
Details of categorical variables					
Presence of erosion at baseline					**<0.001**
No	Ref.	–	Ref.	–	
Yes	0.551 (0.10)	<0.001	0.433 (0.10)	<0.001	
SDAI					
At 1 year					**<0.001**
Remission	Ref.	–	Ref.	–	
LDA	0.609 (0.14)	<0.001	0.427 (0.13)	0.002	
MDA or HDA	0.682 (0.13)	<0.001	0.518 (0.15)	<0.001	
At 2 years					0.096
Remission	Ref.	–	Ref.	–	
LDA	0.529 (0.12)	<0.001	0.244 (0.12)	0.046	
MDA or HDA	0.275 (0.12)	0.024	0.055 (0.13)	0.671	
ACPA presence					**<0.001**
Absence	Ref.	–	Ref.	–	
Low titre	0.365 (0.18)	0.042	0.489 (0.17)	0.004	
High titre	0.589 (0.10)	<0.001	0.497 (0.10)	<0.001	
Biological DMARDs at 6 months					**0.010**
Absence	Ref.	–	Ref.	–	
Presence	–0.616 (0.32)	0.055	–1.073 (0.32)	0.001	
Biological DMARDs at 2 years					0.059
Absence	Ref.	–	Ref.	–	
Presence	0.254 (0.15)	0.081	0.338 (0.15)	0.025	
Glucocorticoids at 18 months					**0.009**
Absence	Ref.	–	Ref.	–	
Presence	0.005 (0.10)	0.962	–0.275 (0.10)	0.005	
DMARDs presence					
At baseline					0.124
Absence	Ref.	–	Ref.	–	
Presence	0.250 (0.19)	0.161	0.245 (0.16)	0.132	
At 6 months					0.753
Absence	Ref.	–	Ref.	–	
Presence	0.177 (0.13)	0.181	–0.127 (0.17)	0.465	
At 1 year					0.425
Absence	Ref.	–	Ref.	–	
Presence	0.243 (0.13)	0.062	0.019 (0.21)	0.928	
At 18 months					0.331
Absence	Ref.	–	Ref.	–	
Presence	0.293 (0.14)	0.030	0.145 (0.22)	0.519	
At 2 years					0.834
Absence	Ref.	–	Ref.	–	
Presence	0.312 (0.13)	0.001	–0.033 (0.27)	0.902	
At 36 months					0.686
Absence	Ref.	–	Ref.	–	
Presence	0.371 (0.13)	0.003	0.084 (0.21)	0.685	
Random effects	σ coef.		σ coef.		
Between-centre variability (σ_c)	–		0.173		
Residual variability (σ)	–		0.916		

ACPA, anticitrullinated peptides antibodies; no, low and high titres of ACPA by anti-CCP2 antibodies definition was <50 U/mL, 50–150 U/mL and >150 U/mL, respectively; DMARDs, disease-modifying antirheumatic drugs; HDA, high disease activity; LDA, low disease activity; log (mTSS), log of modified Sharp–van der Heijde total score; MDA, moderate disease activity; SDAI, Simple Disease Activity Index.
p<0.05 values are shown in bold.

methotrexate plus adalimumab. Furthermore, patients in SDAI remission in both arms had better HAQ-DI scores at week 26 than patients who achieved only DAS28-CRP LDA. In another study of an inception cohort of RA patients included between 1985 and 2002,[35] structural scores at 3 years were better for patients in DAS28 remission than LDA for only ACPA-positive patients. Because long-term structural outcomes did not differ by DAS status in ACPA-negative patients, the authors suggested that DAS28 LDA could be a target for ACPA-negative patients.

In this study, we found no difference in 3-year structural scores between patients in DAS28 remission and LDA at 6 months or 1 or 2 years. Therefore, the SDAI remission criterion may be more stringent and lead to better structural outcomes, whereas DAS28 remission may be no better than LDA in preventing long-term structural damage. In this study, we focused on SDAI criterion to follow EULAR's recommendations for the definition of remission. However, use of the CDAI led to similar results, and this index may be helpful in clinical practice because no biological test is needed to calculate the score.

Several studies have shown that the goal of remission is difficult to obtain in clinical practice[18–20 36 37] and that LDA is more feasible. Furthermore, the proportion of patients who maintain remission during follow-up is low.[37] One difficulty in classifying patients in remission according to the new ACR/EULAR criteria is obtaining patient global assessment ≤1, because most patients report higher global assessment scores, which can be influenced by non-inflammatory conditions.[10 38–40] In this study, structural outcomes were better with the target of SDAI remission at 1 year in patients treated in clinical practice and may be preferred to LDA status.

We found a difference in 3-year structural outcomes between patients in SDAI remission and LDA at 1 and 2 years but not 6 months. Thus, as the EULAR recommended, SDAI remission or LDA is an appropriate target in early RA at 6 months, but SDAI remission at 1 and 2 years should be preferred to prevent long-term structural damage.

In this study, as was previously shown, the strongest predictors of structural damage in the multivariate analysis were the baseline mTSS and ACPA presence. Biological DMARDs or glucocorticoids intake also had a significant effect on structural outcome. These results must be interpreted with caution because they are from an observational study and not a randomised trial and we did not use a propensity score in this model since the main objective was to study the relationship between SDAI status and 3-year outcomes and not the impact of biological DMARDs on structural progression.

This study has several limitations. The ESPOIR cohort was an inception cohort study of early RA with no treatment strategy recommended to physicians. Thus, various DMARDs could be initiated, including biologics therapy, and several regimens of glucocorticoids were given within the first 3 years of follow-up. This treatment might introduce potential bias in interpreting the results. However, we included DMARDs, cumulative glucocorticoids and biologics use in the multivariate analysis to adjust for these confounding factors. Furthermore, patients in the ESPOIR cohort were monitored every 6 months the first 2 years, then yearly. Our multivariate analysis involved a linear mixed model and included disease activity scores at each assessment to control for disease activity during the whole follow-up. However, potential flares of the disease could occur between two assessments and were not captured in the database of the ESPOIR cohort. In this study, the assessment of disease activity at 1 year did not imply that patients had started a DMARD for 1 year. To be included in ESPOIR cohort, patients had to be DMARD-naive, and most patients began their treatment just after inclusion in the cohort (mean delay before first DMARD intake about 1 month). Thus, the visit at 1 year after inclusion in the ESPOIR cohort might be a good approximation of disease assessment 1 year after beginning the DMARD (mean DMARDs exposure at 1 year: 11.1 months, SD 2.0).

Despite these methodological limitations, this study identified a significant difference in 3-year radiographic disease scores between patients in SDAI remission and LDA 1 year after the diagnosis of RA in patients treated in routine practice. The EULAR recommends aiming for remission or at least LDA within 3–6 months after beginning a DMARD;[41] our data suggest that aiming for SDAI remission at least within the first year after the first DMARD initiation is the best target for early RA treated in clinical practice.

Acknowledgements The authors thank Nathalie Rincheval for expert monitoring and data management; S Martin for measuring the central doses of CRP level, IgA and IgM rheumatoid factor and anti-CCP antibodies; the Biological Resources Centre (Paris-Bichat, J Benessiano), which was in charge of centralising and managing biological data collection; and all the investigators who recruited and followed patients (F Berenbaum, Paris-Saint Antoine; M C Boissier, Paris-Bobigny; B Combe, Montpellier; M Dougados, Paris-Cochin; P Fardelonne and P Boumier, Amiens; B Fautrel and P Bourgeois, Paris-La Pitié; R M Flipo, Lille; Ph Goupille, Tours; F Liote, Paris-Lariboisière; X Le Loet and O Vittecoq, Rouen; X Mariette, Paris Bicêtre; O Meyer, Paris Bichat; A Saraux, Brest; ThSchaeverbeke, Bordeaux; J Sibilia, Strasbourg). The authors thank Mogens Thomsen and Jane Miller for critical reading of the manuscript.

Contributors All the authors contributed to the conception of the study and manuscript final approval. ARW, GG and DN were involved in data analysis. ARW and AC were involved in data interpretation and manuscript writing.

Funding An unrestricted grant from Merck, Sharp and Dohme (MSD) was allocated for the first 5 years of the ESPOIR cohort. Two additional grants from INSERM were obtained to support establishing part of the biological database. The French Society of Rheumatology, Abbott and Wyeth also supported the ESPOIR cohort study but the industrial firms were not involved in study design, data collection, data analysis, manuscript preparation and decision to publish this article.

Competing interests None.

Patient consent Obtained.

Ethics approval Montpellier ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes

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Ann Rheum Dis published online May 2, 2014
doi: 10.1136/annrheumdis-2013-204906

Notes