

EXTENDED REPORT

Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort

B Combe,¹ I Logeart,² M C Belkacemi,¹ S Dadoun,³ T Schaefferbeke,⁴ J P Daurès,¹ M Dougados⁵

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-2013-204178>).

¹Lapeyronie Hospital, Montpellier I University, Montpellier: UMR 5535, France

²Pfizer, PIO, Paris, France

³Paris-Pitié Salpêtrière University Hospital, Paris, France

⁴Département de Rhumatologie, Hôpital Pellegrin, CHU Bordeaux, Unité sous Contrat, Infections à Mycoplasmes et à Chlamydia chez l'Homme, Université de Bordeaux, Bordeaux, France

⁵Medecine Faculty and Rheumatology B dept, Paris-Descartes University, UPRES-EA 4058; APHP, Cochin Hospital, Paris, France

Correspondence to

Dr Bernard Combe, Département de Rhumatologie, Hôpital Lapeyronie, Montpellier cedex 34295, France; b-combe@chu-montpellier.fr

Received 25 June 2013

Revised 5 December 2013

Accepted 6 December 2013

ABSTRACT

Objective To investigate if patients with early RA with persistent moderate disease activity during the first year after diagnosis have a worse 3–5 year outcome than those who achieve sustained clinical remission within the first year, in a daily life setting.

Methods The ESPOIR cohort included patients with early arthritis of <6 months' duration. Treatment was the standard of care. We had 5-year follow-up data for 573 patients. This study compared patients who had persistent moderate disease activity (Disease Activity Score in 28 joints (DAS28)>3.2 and ≤5.1) at both the 6- and 12-month visits, with those who were in sustained DAS28 remission. The primary outcome was radiographic progression at the 36-month visit. Secondary endpoints were clinical remission (DAS28 score, Simplified Disease Activity Index, ACR/EULAR criteria), Health Assessment Questionnaire-Disability Index (HAQ-DI) and number of missed workdays at months 36 and 60. A Fisher exact test was used to compare categorical variables, and the Kruskal–Wallis test for quantitative variables. Logistic regression analysis was used to determine predictors of outcome.

Results Patients were aged 48.1±12.5 years and their duration of symptoms was 103.2±52.1 days. Mean baseline DAS28 was 5.1±1.3. Persistent moderate disease activity (107 patients) rather than sustained remission (155 patients) during the first year was associated with increased radiographic disease progression at 3 years (OR=1.99 (95% CI 1.01 to 3.79)), increased HAQ-DI at 3 and 5 years (5.23 (2.81 to 9.73) and 4.10 (2.16 to 7.80), respectively), a 7–11 times smaller chance of achieving clinical remission and a five times greater number of missed workdays.

Conclusions Patients with early RA with persistent moderate disease activity during the first year had a worse outcome than patients who achieved sustained clinical remission. Persistent moderate disease activity affects long-term structure, remission rate and functional and work disability. Such patients may benefit from intensive treatment.

RA disease activity, reflected by swollen joints, levels of acute-phase reactants and composite indices such as the Disease Activity Score in 28 joints (DAS28), is associated with further joint damage and physical disability.^{3–8} The ultimate objective in management of RA is to stop or prevent radiographic disease progression, reduce or improve disability and maintain quality of life by early treatment with disease-modifying antirheumatic drugs (DMARDs)⁹ and by achieving sustained clinical remission or, at least, low disease activity.¹⁰ Aiming for clinical remission has been highlighted by the most recent international guidelines for RA management.^{11–13} Despite the current recommendation, mainly based on expert opinion, which proposes remission as the objective at an early stage of the disease and low disease activity at a later stage, there is still a debate about whether the goal of RA treatment should be remission or low disease activity.¹⁰

Patients with moderate disease activity represent a large proportion of the overall RA population.^{14–15} New therapeutic strategies, including early introduction of intensive treatments such as the combination of biological agents and methotrexate, have been essential in achieving the goals of remission or low disease activity.^{16–17} However, in several countries, the use of biological agents is still restricted to patients with high disease activity even though they receive conventional synthetic DMARDs.¹⁸ In addition, patients with moderate disease activity, usually considered more prone to remission than those with high disease activity,^{19–20} show significant progression of joint damage and disability in randomised clinical trials.^{5–21}

The above remarks prompted us to conduct a study aimed at assessing 3–5-year outcomes for patients with persistent moderate disease activity and those who achieved early sustained remission during the first year after enrolment in a cohort of patients with early RA from 'real life', the ESPOIR (Etude et Suivi des POLyarthrites Indifférenciées Récentes) cohort.

PATIENTS AND METHODS

The ESPOIR cohort is a prospective observational study of patients with early arthritis aged 18–70 years recruited from multiple regions across France under the umbrella of the French Society of

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting 0.3–0.8% of the population. Patients experience substantial disability and handicap after a few years of disease progression.^{1–2}

To cite: Combe B, Logeart I, Belkacemi MC, et al. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2013-204178

Clinical and epidemiological research

Rheumatology. Patients were recruited if they had had inflammatory arthritis in at least two swollen joints lasting for 6 weeks to 6 months, with the potential to develop into RA, and if they had not received DMARDs or steroids. They were followed up every 6 months during the first 2 years, then every year for at least 15 years. The objective, design and patient characteristics of the cohort have been described previously.^{22 23} At baseline and each visit, clinical and biological data relevant to the management of early arthritis were recorded.¹¹ At each visit, patients completed function and quality-of-life self-administered questionnaires, including the Health Assessment Questionnaire–Disability Index (HAQ–DI), a medico-economic questionnaire also asking about number of missed workdays since the last visit. Patients underwent radiography of the hand and wrist (face) and foot (face and oblique) at baseline, then at 1 and 3 years. x-Ray films were scored using the van der Heijde modified total Sharp score (mTSS).⁹

Patients

The ESPOIR cohort included 813 patients. Treatment by the rheumatologists followed the standard of care. Among 573 patients with a 5-year follow-up visit,²³ we selected 532 (93%) who fulfilled the American College of Rheumatology/European League Against Rheumatology (ACR/EULAR) criteria for RA²⁴ for this study. Patients were divided into two groups according to disease activity during the first year: patients with moderate disease activity (DAS28 3.2–5.1) at both 6- and 12-month visits versus those in DAS28 remission (DAS28 <2.6) also at both 6- and 12-month visits. We considered these patients to be the group with persistent moderate disease activity (group 1) and the group with early sustained remission (group 2), respectively, during the remaining part of this report. A third group of patients with low disease activity (LDA) (DAS28 2.6–3.2) at 6 and 12 months was also evaluated as a secondary objective.

Endpoints

This study compared patients who were in persistent moderate disease activity versus those who were in (early) sustained DAS28 remission at 6- and 12-month visits. The primary outcome measure was radiographic evidence of disease progression (change in mTSS) at month 36. Secondary endpoints were clinical remission (DAS28, Simplified Disease Activity Index (SDAI), ACR/EULAR Boolean criteria for RA²⁵), HAQ-DI at months 36 and 60 and number of missed workdays during the first 3 and 5 years of follow-up.

Sample size calculation

At 3 years, the mTSS was 11.2 ± 11.8 for patients with persistent moderate disease activity and 16.1 ± 14.9 for those with early persistent remission. To identify this difference between groups, we needed to include about 120 patients in each group (α risk=5%; β risk=20%). We considered that including available patients from the ESPOIR cohort, with a follow-up at 5 years and persistent moderate disease activity (n=107) or sustained remission (n=155) during year 1 would allow us to answer the questions after adjustment for baseline variables.

Statistical analysis

Data are reported as number (%) or mean \pm SD. A Kruskal–Wallis test was used to compare quantitative variables and a χ^2 test (or Fisher's exact test) for categorical variables (using the median or a predetermined threshold as a cut-off point). Patients with poor prognostic features at baseline had a higher risk of a worse outcome and treatments might influence this

outcome. Therefore, we used multivariate logistic regression to examine predictors of outcome (radiographic progression, DAS remission, HAQ-DI and number of missed workdays at 3 and 5 years of follow-up). To select baseline variables for logistic regression, we used χ^2 analyses to analyse risk factors by outcome variables with level of significance $p=0.20$. The status during the first year (persistent moderate disease activity or early sustained remission) was also included. All the analyses were performed only in the patients from the two selected groups.

A propensity score was used to minimise the patient's selection bias in the two activity groups. This score was built by modelling (logistic regression) inclusion in a specific activity group during the first year with clinical and demographic variables obtained at baseline to make a posteriori those groups of patients comparable while considering potential confounding factors. The propensity score is therefore defined as a patient's probability of being in an activity group, conditional on observed baseline covariates. The covariates statistically retained by the stepwise regression (backward elimination) for estimating the propensity score were age, sex and smoking status. In order to adjust to the potential selection bias the propensity score was then included in the final multivariate logistic regression.

In addition to this score and the status during the first year (persistent moderate disease activity or early sustained remission), the following baseline variables were included in the final multivariate stepwise regression model: age, sex, disease activity, symptom duration, smoking, acute-phase reactants, rheumatoid factor, anti-cyclic citrullinated peptide 2 (anti-CCP2) antibodies and radiographic score as well as concurrent treatments with methotrexate (MTX), or biological DMARDs. A value of $p<0.05$ was considered statistically significant. Data were analysed using SAS V.9.2 (SAS Inst, Cary, North Carolina).

RESULTS

Patients' characteristics and treatment

Baseline characteristics of the whole cohort of patients with 5-year follow-up data (n=573) and of patients with persistent moderate disease activity (n=107) and early sustained remission (n=155) within the first year after inclusion are shown in table 1 and online supplementary appendix table S1. Disease activity was higher in the 'moderate' group but anti-CCP, rheumatoid factor status, mTSS and rate of employed workers were similar between the two groups. Only 28 patients were in persistent LDA during the first year. During this follow-up most patients (90.4%) from the whole cohort with 5-year follow-up data had received at least one synthetic DMARD, 21.8% a biological DMARD and 38.5% daily prednisone for more than 1 year. In all, 72 patients (67.3%) with moderate disease activity received MTX and 31 (29.0%) biological agents for at least 3 months versus 101 (65.2%) and 11 (7.1%), respectively, of patients with early sustained remission. Four patients in each group received a tumour necrosis factor blocker during the first year. Most patients of the two groups received synthetic DMARDs during the first 6 months (86.5% in group 1 and 81.6% in group 2).

The mean MTX dose was similar in both groups at 6 months (10.6 ± 4.9 in group 1 and 11.2 ± 4.9 in group 2) and 12 months (11.9 ± 5.6 in both groups 1 and 2). But at 3 and 5 years the MTX dose was significantly higher in group 1 than in group 2: at 3 years, 14.7 ± 4.2 mg/week vs 10.5 ± 4.2 , ($p<0.0001$); at 5 years, 13.6 ± 3.5 vs 9.8 ± 4.9 , respectively ($p=0.017$). Patients with moderate disease activity received more synthetic DMARDs courses during the 5-year follow-up period than the patients with early sustained DAS28 remission

Table 1 Outcome of main variables for patients with persistent moderate disease activity (group 1) or sustained DAS28 remission (group 2) during the 5 years of follow-up

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Group 1						
DAS28	5.3±1.1	4.0±0.5	3.7±1.3	3.5±1.3	3.2±1.2	3.0±1.2
SDAI	30.2±12.7	16.5±6.1	14.9±12.9	13.7±11.9	11.6±10.2	10.4±9.6
SJC	7.2±4.6	2.9±3.1	2.3±3.8	2.0±2.8	1.9±3.3	1.5±2.4
TJC	9.8±6.4	5.5±4.1	5.3±6.6	5.2±7.0	3.6±4.8	3.3±4.9
HAQ-DI	1.1±0.7	0.8±0.6	0.7±0.6	0.7±0.6	0.6±0.6	0.6±0.6
ESR (mm/h)	30.2±29.4	18.0±13.3	17.2±14.0	17.3±15.4	16.0±12.9	16.1±13.4
CRP (mg/L)	19.4±32.6	8.0±8.2	7.9±16.4	7.6±12.1	10.0±21.2	7.7±12.0
mTSS	5.5±7.4	9.8±9.5	13.6±13.2	16.1±14.9	/	/
Group 2						
DAS28	4.5±1.3	1.7±0.6	2.0±1.1	1.9±1.0	2.0±1.1	1.9±0.9
SDAI	23.1±13.9	3.0±2.9	5.0±6.9	4.4±5.1	5.4±8.5	4.3±5.4
SJC	6.2±5.3	0.4±1.1	0.4±0.9	0.5±1.2	1.0±3.6	0.4±0.9
TJC	5.6±5.7	0.2±0.8	0.8±2.2	0.8±1.7	1.2±3.7	0.8±2.2
HAQ-DI	0.8±0.7	0.2±0.3	0.2±0.4	0.2±0.3	0.2±0.4	0.2±0.4
ESR (mm/h)	25.8±22.4	8.9±6.1	10.8±9.1	10.6±10.2	10.6±11.1	10.6±10.3
CRP (mg/L)	21.0±42.9	4.1±4.7	6.1±13.1	4.6±7.0	4.6±6.5	5.3±8.0
mTSS	4.5±6.9	6.3±6.9*	8.2±9.5**	11.2±11.8***	/	/

*p=0.001 versus group 1; **p=0.0005 versus group 1; ***p=0.019 versus group 1.

CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified total Sharp score; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

(1.42±0.73 vs 1.25±0.66; p=0.031) and in addition received a higher dose of glucocorticoids at 12 months (6.5±4.9 vs 4.2±2.6 mg/day; p=0.020), but the difference was not significant at 6 months and at the other yearly visits (data not shown).

The outcome of the main core set variables is presented in table 1.

Structural outcome

Three-year mTSS (online supplementary appendix figure S1) and change in radiographic score were greater for patients with persistent moderate disease activity than for those in early sustained

DAS28 remission during the first year (16.1±14.9 vs 5.5±7.4 and 11.2±11.8 vs 4.5±6.9, respectively) (tables 1 and 2). Multivariate logistic regression identified anti-CCP2 antibodies, baseline erythrocyte sedimentation rate, age and moderate disease activity during the first year as significant independent risk factors of 3-year radiographic progression (table 3).

Clinical remission

Whatever the criteria for remission (DAS28, SDAI, ACR/EULAR Boolean definition), fewer patients with persistent moderate disease activity (group 1) than early sustained remission (group 2) were considered to be in remission at 3 and 5 years (tables 2 and 4). Most of the patients in group 2 were in DAS28 remission over time; during the 5 years of follow-up the rate of DAS28 remission varied from 77.8% to 81.0% at the different yearly visits and only four out of 155 patients were once in high disease activity. By contrast only 20.0–39.2% of patients in group 1 achieved the DAS28 remission state; 7.7–11.0% of patients in this group were in high disease activity at different visits.

By logistic regression, persistent moderate disease activity during the first year was identified as the most significant risk factor for not achieving clinical remission at 3 years (table 5)

Table 2 Three-year outcome for patients with rheumatoid arthritis with persistent moderate disease activity (group 1) and sustained DAS28 remission (group 2) during the first year of follow-up

Outcome variable	Group 1 (n=107)	Group 2 (n=155)	p Value
mTSS	16.1±14.9	11.2±11.8	0.019
ΔmTSS from day 0*	10.8±6.5	6.5±8.9	0.006
ΔmTSS≥5†(%)	56.0	39.2	0.021
DAS28 remission (%)	27.4	81.0	<0.0001
SDAI remission (%)	13.8	56.0	<0.0001
ACR/EULAR remission‡ (%)	10.3	50.4	<0.0001
HAQ-DI	0.68±0.61	0.21±0.38	<0.0001
HAQ-DI <0.5 (%)	43.7%	80.6	<0.0001
Missed workdays§	157.3±226.2	30.9±75.9	0.001
Missed workdays=0¶ (%)	51.4	67.7	0.007

Data are mean±SD unless indicated.

*Change in mTSS from day 0; †change in mTSS≥5 from day 0; ‡Boolean definition; §mean missed workdays since baseline; ¶percentage of patients without any missed workdays during follow-up.

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified total Sharp score; SDAI, Simplified Disease Activity Index.

Table 3 Multivariate logistic regression analysis of factors predicting 3-year radiographic progression*

	OR	95% CI
Anti-CCP2 antibodies	3.65	1.91 to 6.96
Baseline ESR (mm/h)	2.59	1.30 to 5.15
Group 1 versus group 2	1.95	1.01 to 3.79
Age (years)	1.94	1.03 to 3.68

*Change from baseline.

CCP2, cyclic citrullinated peptide 2; ESR, erythrocyte sedimentation rate.

Clinical and epidemiological research

Table 4 Five-year outcome for patients with rheumatoid arthritis with persistent moderate disease activity (group 1) and sustained DAS28 remission (group 2) during the first year of follow-up

Outcome variable	Group 1 (n=107)	Group 2 (n=155)	p Value
DAS28 remission (%)	39.2	80.7	<0.0001
SDAI remission (%)	24.0	59.6	<0.0001
ACR/EULAR remission* (%)	21.5	47.4	0.0003
HAQ-DI	0.58±0.59	0.21±0.38	<0.0001
HAQ-DI <0.5 (%)	51.6	80.7	<0.0001
Missed workdays†	272.2±338.9	45.2±90.2	0.0006
No missed workdays=0‡ (%)	46.7	62.6	0.011

Data are mean±SD unless indicated.

*Boolean definition; †mean missed workdays since baseline; ‡percentage of patients without any missed workdays during follow-up.

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-Disability Index; SDAI, Simplified Disease Activity Index.

and at 5 years (DAS28 remission (OR=5.79 (95% CI 2.95 to 11.36)), SDAI remission (4.42 (2.30 to 8.53)) and ACR/EULAR remission (3.23 (1.68 to 6.22)).

HAQ disability and work productivity

HAQ-DI was higher at 3 and 5 years and more workdays were missed by patients with persistent moderate disease activity than by those with early sustained remission during the first year (tables 2 and 4). In addition, patients with early sustained remission more frequently showed normal HAQ-DI (HAQ-DI <0.5) and fewer did not miss any workdays during the 3- or 5-year follow-up as compared with patients with persistent moderate disease activity (tables 2 and 4).

On logistic regression analysis, 'persistent moderate disease activity' was identified as a significant risk factor for worse 3- and 5-year HAQ-DI (OR=5.23 (2.81 to 9.73) and 4.10 (2.16 to 7.80), respectively) as well as 3-year work disability (1.88 (1.08 to 3.30)) (table 6). At 5 years, only use of biological therapy was an independent predictor of work disability (5.39 (2.51 to 11.55)).

Patients with persistent LDA

Owing to the small sample size (n=28), comparisons with the group with persistent LDA should be analysed with caution.

Table 5 Multivariate logistic regression analysis of factors predicting 3-year clinical remission

	OR	95% CI
DAS28 remission		
Group 2 versus group 1*	11.35	5.82 to 22.14
SDAI remission		
Group 2 versus group 1*	7.52	3.71 to 15.25
Baseline ESR (mm/h)	2.17	1.01 to 4.67
ACR/EULAR remission		
Group 2 versus group 1*	9.17	4.15 to 20.97
Baseline ESR (mm/h)	1.96	1.03 to 3.74

*Group 1, patients with persistent moderate disease activity at 6- and 12-month visits; group 2, patients with sustained DAS28 remission at 6- and 12-month visits. ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; SDAI, Simplified Disease Activity Index.

Table 6 Multivariate logistic regression analysis of factors predicting 3-year disability

	OR	95% CI
HAQ-DI		
Group 1 versus group 2*	5.23	2.81 to 9.73
Work disability		
Use of biological agents	3.83	1.56 to 9.42
Age (years)	2.13	1.24 to 3.68
Group 1 versus group 2*	1.88	1.08 to 3.30

* Group 1, patients with persistent moderate disease activity at 6- and 12-month visits; group 2, patients with sustained DAS28 remission at 6- and 12-month visits. DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-Disability Index.

These patients seem to have a similar radiographic progression to those with persistent DAS28 remission (mTSS=3.5±4.9 at baseline and 10.9 at 3 years). However, the difference was not statistically different compared with group 1, probably owing to the small number of patients in the group with LDA. Clinical outcome values were between those of the two other groups. As an example, the rate of DAS28 remission was 47.8% at 3 years and 50.0% at 5 years (p=0.062 and 0.36 vs group 1, respectively) and the mean HAQ-DI was 0.38±0.44 and 0.24±0.38, which was significantly lower than for patients with persistent moderate disease activity (p=0.030 and 0.0051, respectively).

DISCUSSION

In a cohort of patients with very early RA from real life, we investigated the effect of persistent moderate disease activity as compared with early sustained remission during the first year after diagnosis on the 3-year outcome. This study demonstrated a worse outcome for patients with persistent moderate disease activity than for those who achieved early sustained remission during the first year. Patients with persistent moderate disease activity had greater radiographic progression, HAQ disability and number of missed workdays and a lower rate of long-term remission than those with early sustained remission.

The patients with most active disease (group 1) received more treatments over time (eg, number of biological agents, number of DMARDs courses, MTX doses); however, the treatment regimens were similar between the two groups during the first year, since the only significant difference was the mean corticosteroid dose at month 12.

Structural progression

Among these patients with early RA, persistent moderate disease activity (group 1) during the first year was significantly associated with both 3-year radiographic evidence of damage and progression as compared with early sustained DAS28 remission (group 2), even though some other features such as anti-CCP2 antibodies or baseline erythrocyte sedimentation rate were better predictors of structural outcome. However, treatment was mostly MTX or other synthetic DMARDs with or without glucocorticoids but not biological agents during the first year. This finding is consistent with previous reports showing that disease activity is associated with radiographic evidence of progression of joint damage.^{5 6 25} A systematic literature review highlighted the fact that patients who achieved a state of clinical remission were less likely to show deterioration of long-term structural damage than patients who did not reach a state of remission.²⁶ In a clinical trial, patients receiving MTX who achieved only

moderate disease activity by week 14 showed greater radiographic disease progression at week 54 than those who were in remission at week 14 as assessed by the SDAI.⁵ In addition, in a recent report²⁷ we have shown in ESPOIR that patients who adhered to the EULAR guidelines for early arthritis,¹¹ including aiming for remission, had a better 1-year structural and functional outcome than those who did not. All these data support the strategy of reducing, as much as possible, the inflammatory process and disease activity to achieve remission in patients with RA and prevent further disease progression.^{10–13}

Long-term remission

The chance of achieving long-term remission was about seven times greater for patients who achieved early sustained remission than for those with moderate disease activity during the first year after diagnosis regardless of the endpoint definition of clinical remission, DAS28, SDAI or ACR/EULAR criteria. Substantial reduction of disease activity in the early stage of the disease process has been shown to increase the chance of further clinical remission.⁸ In addition, initial lower disease activity was found an independent predictor of RA remission.^{19 28 29} Finally, in an observational cohort of patients with newly diagnosed RA (n=418), 74% with low disease activity at year 1 (DAS28 \leq 3.2) achieved a DAS28 score \leq 3.2 at year 2 versus only 27% of patients with moderate disease activity (DAS28 3.2–5.1).³⁰ The authors concluded a very low likelihood of achieving a target DAS28 $<$ 2.6 or 3.2 at years 2 or 3 with conventional DMARDs in patients with early RA who had not already achieved the target by year 1. Strategic trials have also shown an association between aiming for clinical remission or low disease activity by tightly controlling and adjusting treatment every 1–3 months and better clinical outcome.^{31–33}

Functional disability

Patients with persistent moderate activity (group 1) during the first year also had worse 3- and 5-year HAQ disability than those who achieved early sustained remission (group 2). They also had a 7- to 11-fold smaller chance of achieving a HAQ-DI $<$ 0.5, usually considered as absence of functional disability.³⁴ The importance of early remission in reducing long-term disability has been suggested by some other studies.^{29 35 36} In an important cohort of patients with early arthritis, achievement of remission within the first 3 years of follow-up was associated with a decrease of about 70% in the risk of moderate disability after 5 years.³⁵ In a cohort of patients with early RA (n=194), a persistently moderate increase in DAS28 score (DAS28 3.2–5.1) during the first 12 months was associated with increased functional deterioration³⁶; 21.4% of these patients showed HAQ scores which had worsened as compared with only 10.9% of patients with persistently low DAS28 (\leq 3.2).

Work disability

Rates of work disability are higher in people with RA than in the general population after adjusting for age and gender.³⁷ Being employed may have positive effects on a person's quality of life. In our study, the mean number of missed workdays was more than five times higher at 3 and 5 years for patients with persistent moderate disease activity than for those with early sustained remission. People with RA who are work disabled usually have more radiographic damage, disease activity and physical disability. Other factors such as age, sex, occupation, level of education and societal settings may influence employment status.³⁷ We have only limited data on the relationship between disease activity and work ability. Some clinical trials

have shown that early intensive treatments lead to significantly less absenteeism and more presenteeism than for patients with MTX monotherapy and suggested that these differences may be linked to more pronounced reduction in disease activity for patients who received the intensive strategy.^{38 39} However, reducing disease activity alone does not bring the patients with RA back to work, which may suggest that temporary work disability should be prevented in patients with early RA.

CONCLUSION

We may argue that this prospective study has some limitations, including the relatively small number of patients with persistent moderate disease activity and that only two measurements of disease activity during the first year of follow-up were performed (months 6 and 12); therefore we cannot be completely sure, that these patients were really in sustained remission or moderate disease activity throughout this period. However, the study also has important strengths, including the prospective independent collection of the data, the quality of the collected data with low rate of missing data²³ and low rate of loss of follow-up patients, the strict data management and the daily practice setting.²³ In addition, the data are highly significant and confirm that persistent moderate disease activity, despite treatment with synthetic DMARDs, is not a benign state in patients with early RA since they are at high risk of further functional impairment, work disability, structural progression of disease and absence of clinical remission. The data strongly support the recommendations emphasising that achieving clinical remission must be the primary therapeutic aim in early RA and that persistent residual clinical inflammation should result in treatment adjustments in every patient.^{10–13}

Acknowledgements We thank N Rincheval for data management and expert monitoring, G Tobon for expert X-ray reading and S Martin for centralised analysis of the C-reactive protein level, rheumatoid factor and anti-cyclic citrullinated peptide antibodies. We also thank the French rheumatologists who referred their patients to the ESPOIR cohort in the following rheumatology departments: Amiens (P Boumier), Bobigny (G Falgaronne), Bordeaux (T Schaefferbecke), Brest (A Saroux), Lille (RM Flipo), Montpellier (B Combe), Paris-Bicêtre (X Mariette), Paris-Bichat (O Meyer), Paris-Cochin (M Dougados), Paris-Lariboisière (F Lioté), Paris-La Pitié (B Fautrel), Paris-St Antoine (F Berenbaum), Rouen (O Vittecoq), Strasbourg (J Sibilia), Toulouse (A Cantagrel) and Tours (P Goupille).

Contributors BC, IL and MD participated in the conception and design of the study. All authors contributed to the acquisition of data, participated in the analysis and interpretation of data, read, revised and approved the final manuscript.

Funding An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years of the ESPOIR study. Two additional grants from INSERM supported part of the biological database. The French Society of Rheumatology, Pfizer, Abbott and Roche-Chugai also supported the ESPOIR cohort. An unrestricted grant from Pfizer was provided to perform the statistical analysis of this study.

Competing interests IL is currently a Pfizer employee. All other authors declare that they have no competing interests.

Ethics approval EC Montpellier University Hospital, France.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Pincus T, Callahan LF, Sale WG, *et al*. Severe functional declines, work disability and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984;27:864–72.
- 2 Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. *J Rheumatol* 1998;25:2108–17.
- 3 van der Heijde DM, van Riel PL, van Leeuwen MA, *et al*. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992;31:519–25.
- 4 Combe B, Dougados M, Goupille P, *et al*. Prognostic factors for radiographic damage in early rheumatoid arthritis. A multiparameter prospective study. *Arthritis Rheum* 2001;44:1736–43.

Clinical and epidemiological research

- 5 Smolen JS, Han C, Van der Heijde DM, *et al.* Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and TNF-blockade. *Ann Rheum Dis* 2009;68:823–7.
- 6 Welsing PM, Landewe RB, van Riel PL, *et al.* The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004;50:2082–93.
- 7 Drossaers-Bakker KW, de Buck M, van Zeben D, *et al.* Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999;42:1854–60.
- 8 Aletaha D, Funovits J, Keystone EC, *et al.* Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. *Arthritis Rheum* 2007;56:3226–35.
- 9 Lukas C, Combe B, Ravaud PH, *et al.* Very early DMARD initiation in inflammatory arthritis is effective in inhibition of radiographic progression. *Arthritis Rheum* 2011;63:1804–11.
- 10 Smolen JS, Aletaha D, Bijlsma JW, *et al.* T2 T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
- 11 Combe B, Landewe R, Lukas C, *et al.* EULAR recommendations for the management of early arthritis. Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2007;66:34–45.
- 12 Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75. Erratum in: *Ann Rheum Dis* 2011;70:1519.
- 13 Singh JA, Furst DE, Bharat A, *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
- 14 Montag K, Gingold M, Boers A, *et al.* Disease-modifying anti-rheumatic drug usage, prescribing patterns and disease activity in rheumatoid arthritis patients in community-based practice. *Intern Med J* 2011;41:450–5.
- 15 Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003;30:1138–46.
- 16 Kuriya B, Arkema EV, Bykerk VP, *et al.* Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. *Ann Rheum Dis* 2010;69:1298–304.
- 17 Emery P, Breedveld FC, Hall S, *et al.* Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372:375–82.
- 18 Emery P, van Vollenhoven R, Ostergaard M, *et al.* Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. *Ann Rheum Dis* 2009;68:456–9.
- 19 Listing J, Strangfeld A, Rau R, *et al.* Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the German biologics register. *Arthritis Res Ther* 2006;8:R66.
- 20 Smolen JS, Nash P, Durez P, *et al.* Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918–29.
- 21 van der Heijde D, Landewe R, van Vollenhoven R, *et al.* Level of radiographic damage and radiographic progression are determinants of physical function: A longitudinal analysis of the TEMPO trial. *Ann Rheum Dis* 2008;67:267–70.
- 22 Combe B, Benessiano J, Berenbaum F, *et al.* The 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.
- 23 Combe B, Rincheval N, Benessiano J, *et al.* Five-year favourable outcome of patients with early rheumatoid arthritis in the 2000s: data from the ESPOIR cohort. *J Rheumatol* 2013;40:1650–7.
- 24 Aletaha D, Neogi T, Silman AJ, *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8. and *Arthritis Rheum*. 2010;62:2582–91.
- 25 Felson DT, Smolen JS, Wells G, *et al.* Provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;63:573–86.
- 26 van Tuyl LH, Felson DT, Wells G, *et al.* Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. *Arthritis Care Res* 2010;62:108–17.
- 27 Escalas C, Dalichamp M, Combe B, *et al.* Effect of adherence to European treatment guidelines on early arthritis outcome. *Ann Rheum Dis* 2012;71:1803–8.
- 28 Katchamart W, Johnson S, Lin HJL, *et al.* Predictors for remission in rheumatoid arthritis patients: a systematic review. *Arthritis Care Res* 2010;62:1128–43.
- 29 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.
- 30 Kiely P, Walsh D, Williams R, *et al.* Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity: the Early RA Network (ERAN). *Rheumatology (Oxford)* 2011;50:926–31.
- 31 Grigor C, Capell H, Stirling A, *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263–9.
- 32 Verstappen SSM, Jacobs JWG, van der Veen MJ, *et al.* Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443–9.
- 33 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.
- 34 Bruce B, Fries JF, The Stanford Health Assessment Questionnaire (HAQ): a review of its history, issues, progress and documentation. *J Rheumatol*. 2003;30:167–78.
- 35 Scirè CA, Verstappen SM, Mirjafari H, *et al.* Reduction of long-term disability in inflammatory polyarthritis by early and persistent suppression of joint inflammation: results from the Norfolk Arthritis Register. *Arthritis Care Res (Hoboken)* 2011;63:945–52.
- 36 Conaghan PG, Hensor EM, Keenan AM, *et al.* Persistently moderate DAS-28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy. *Rheumatology (Oxford)* 2010;49:1894–9.
- 37 Sokka T, Kautiainen H, Pincus T, *et al.* Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res Ther* 2010;12:R42.
- 38 van Vollenhoven RF, Cifaldi MA, Ray S, *et al.* Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. *Arthritis Care Res (Hoboken)* 2010;62:226–34.
- 39 Anis A, Zhang W, Emery P, *et al.* The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. *Rheumatology (Oxford)* 2009;48:1283–9.



Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort

B Combe, I Logeart, M C Belkacemi, et al.

Ann Rheum Dis published online January 7, 2014
doi: 10.1136/annrheumdis-2013-204178

Updated information and services can be found at:
<http://ard.bmj.com/content/early/2014/01/07/annrheumdis-2013-204178.full.html>

These include:

- | | |
|-------------------------------|---|
| Data Supplement | "Supplementary Data"
http://ard.bmj.com/content/suppl/2014/01/07/annrheumdis-2013-204178.DC1.html |
| References | This article cites 39 articles, 18 of which can be accessed free at:
http://ard.bmj.com/content/early/2014/01/07/annrheumdis-2013-204178.full.html#ref-list-1 |
| P<P | Published online January 7, 2014 in advance of the print journal. |
| Email alerting service | Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article. |

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>

Topic Collections

Articles on similar topics can be found in the following collections

[Connective tissue disease](#) (3324 articles)
[Degenerative joint disease](#) (3611 articles)
[Immunology \(including allergy\)](#) (3928 articles)
[Musculoskeletal syndromes](#) (3869 articles)
[Rheumatoid arthritis](#) (2522 articles)

Notes

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>