Joint Bone Spine xxx (2016) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort

Thomas Krams[a,*], Adeline Ruyssen-Witrand[a,b], Delphine Nigon[a], Yannick Degboe[a], Gabriel Tobon[c], Bruno Fautrel[d,e], Francis Berenbaum[f,g], Alain Cantagrel[a], Arnaud Constantin[a,b]

[a] *Rheumatology, Toulouse University Hospital Purpan, place du Docteur-Joseph-Baylac, 31300 Toulouse, France*
[b] *INSERM/UPS Toulouse III, UMR 1027, 31300 Toulouse, France*
[c] *Brittany University, Hopital Morvan, 29000 Brest, France*
[d] *Rheumatology, Pitié-Salpêtrière Hospital, AP–HP, 75013 Paris, France*
[e] *UPMC, institut Pierre-Louis d'épidémiologie et santé publique, GRC-08, 75013 Paris, France*
[f] *Department of Rheumatology, University Pierre-et-Marie-Curie Paris VI, Saint-Antoine hospital, "Department Hospitalo-Universitaire Inflammation-Immunopathology-Biotherapy" (I2B), AP–HP, 75012 Paris, France*
[g] *INSERM/CDR Saint-Antoine, UMRS 938, 75012 Paris, France*

ARTICLE INFO

Article history:
Accepted 9 September 2015
Available online xxx

Keywords:
Rheumatoid arthritis
Clinical remission
Treatment modalities
Radiography
Radiographic progression
Health Assessment Questionnaire

ABSTRACT

Objectives: To investigate whether age at disease onset determines clinical, radiographic or functional outcomes in a cohort of early RA.
Methods: The ESPOIR cohort is a multicenter cohort of patients with early arthritis. We selected patients fulfilling the 2010 ACR/EULAR criteria for RA during the first 3 years of follow-up. Patients were pooled into 3 groups by age at RA onset: < 45 years (young-onset RA [YORA]), 45 to 60 years (intermediate-onset RA [IORA]) and > 60 years (late-onset RA [LORA]). The following outcomes were compared at baseline and during the first 3 years of follow-up: Simple Disease Activity Index (SDAI) remission rate, one additional erosion, Health Assessment Questionnaire Disability Index (HAQ-DI) < 0.5 and first disease-modifying anti-rheumatic drug (DMARD) continuation rate.
Results: We included 698 patients (median [interquartile range] age 50.3 [39.8–57.2] years), 266 YORA, 314 IORA, and 118 LORA. At 1 year, SDAI remission was greater for YORA than IORA and LORA ($P < 0.0001$). Having at least one additional erosion was greater for LORA and IORA than YORA after 1 year ($P = 0.009$) and 3 years ($P = 0.017$). The proportion of patients with HAQ score < 0.5 was greater for YORA than IORA and LORA at 1 ($P = 0.007$), 2 and 3 years. First DMARD continuation rate was lower for YORA than other groups during the 3 years ($P = 0.005$).
Conclusions: In a cohort of early RA, young age at disease onset is associated with high rate of remission at 1 year, no radiographic progression at 3 years and low functional score during 3-year follow-up.

1. Introduction

Rheumatoid arthritis (RA) onset may vary between childhood and latter decades of life but peaks in the fifth decade [1,2]. Young-onset RA (YORA) usually begins between 30 and 40 years of age, whereas RA developing after 60 to 65 years of age is usually called late-onset RA (LORA) [3,4]. Because the mean age of the population is continually increasing, LORA will probably gain in importance in the future. A better characterization of differences between LORA and YORA prognosis could help rheumatologists with therapeutic decision-making in terms of medicine tailored to the individual patient.

LORA is characterized by a more balanced gender distribution, a higher frequency of acute onset, and more frequent involvement of large joints than YORA [5–8]. Some studies have suggested genetic differences between LORA and YORA, with fewer older patients carrying HLA-DRB1 susceptibility alleles than younger patients [9].

Despite several cross-sectional and a few prospective studies, whether LORA differs from YORA in terms of clinical, radiographic and functional outcomes is not clear [3,4,8,10–16]. Furthermore, whether possible differences between LORA and YORA prognosis result directly from age at onset or indirectly from treatment

* Corresponding author.
E-mail address: Thomaskrams@gmail.com (T. Krams).

http://dx.doi.org/10.1016/j.jbspin.2015.09.010
1297-319X/

modalities is unknown. Indeed, some studies have reported more frequent use of glucocorticoids (GCs) and later initiation of disease-modifying anti-rheumatic drugs (DMARDs) in LORA than YORA patients [8,17,18].

With a cohort of early RA patients, we investigated whether age at disease onset determines clinical, radiographic or functional outcomes, taking into account possible age-related differences in treatment modalities.

2. Methods

2.1. Study population and design

The ESPOIR cohort [19] is a prospective observational study of patients 18 to 70 years old who have early arthritis and were recruited from 14 regional investigation centers across France. Patients had to have inflammatory arthritis in at least 2 swollen joints lasting from 6 weeks to 6 months, with the potential to develop into RA, and had not received DMARDs or GCs. They were followed every 6 months during the first 2 years, then every year. At baseline and each visit, clinical, biological, functional and radiographic data relevant to the management of early arthritis were recorded. Rheumatologist treatment followed the standard of care. The objective, design and characteristics of the cohort have been described previously [19,20].

Among the 813 patients included in the ESPOIR cohort, we selected 698 who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA [21] during the first 3 years of follow-up. Patients were pooled into 3 groups by age at RA onset: YORA, < 45 years; intermediate-onset RA (IORA), 45 to 60 years; and LORA > 60 years [3,4].

2.2. Outcome parameters

The Simplified disease activity index (SDAI) was calculated with tender joint count and swollen joint count on 28 joints, patient and physician global assessment of disease (0- to 10-cm visual analog scale) and C-reactive protein (CRP) level (mg/dl) at baseline and each visit (months 6, 12, 24 and 36). SDAI remission was defined as SDAI $\leq$ 3.3 [22].

Patients underwent radiographs of hands, wrists and feet at baseline, then at 12, 24 and 36 months. Radiographs were scored by a single reader (G Tobon) using the van der Heijde-modified total Sharp score (mTSS), with blinding to patient identity, patient characteristics and treatment but with known time order because of sensitivity to change [23]. The interreader correlation coefficient for mTSS was 0.93; the smallest detectable change was about 1 point [24]. Furthermore, the occurrence of at least one additional erosion was assessed at 12, 24 and 36 months and used as a marker of radiographic disease progression [25].

Patients completed the Health Assessment Questionnaire Disability Index (HAQ-DI) at baseline and at each visit (months 6, 12, 24 and 36) [26]. HAQ remission was defined as HAQ score < 0.5 [27].

The first DMARD survival rate was assessed at each visit (months 6, 12, 24 and 36).

2.3. Statistical analysis

2.3.1. Descriptive statistics

We report the distribution of baseline demographic and disease characteristics in the whole sample and in the 3 groups (YORA, IORA, LORA). The Shapiro-Wilk test was used to verify the normality of continuous data, presented as mean (SD) or median (interquartile range [IQR]), with categorical variables presented as number (percentage). All tests used for comparison were two-tailed, with $P < 0.05$ considered statistically significant.

2.3.2. Clinical outcome

Median SDAI score at 1, 2 and 3 years was compared for the 3 groups by the Kruskall and Wallis test and Cuzick trend test. The proportion of patients in SDAI remission at 1, 2 and 3 years was compared for the 3 groups by Chi^2 test. We performed a test of homogeneity of odds and a test for linear trend of the log odds against the numerical code used for the categories of explanatory variables.

2.3.3. Radiographic outcome

mTSS at baseline, 1, 2 and 3 years as well as mTSS progression over the 3 years were compared for the 3 groups by the Kruskall and Wallis test and Cuzick trend test. The proportion of patients with at least one additional erosion at 1, 2 and 3 years was compared for the 3 groups by Chi^2 test.

2.3.4. Functional outcome

The proportion of patients with HAQ score < 0.5 at 1, 2 and 3 years was compared for the 3 groups by Chi^2 test.

2.3.5. First DMARD survival analysis

The 3 groups were compared for delay in introduction of first DMARD and maintenance of the first DMARD at 1 and 3 years by chi-square test. Drug survival was compared for the 3 groups and represented in a graph by the Kaplan-Meier method, with analysis by log-rank test. The reasons for drug discontinuation (lack of efficacy or toxicity) were available only at 1 year and were compared for the 3 groups.

2.3.6. Multivariate analysis

To identify the possible independent effect of age at RA onset on SDAI remission, radiographic score or HAQ score, we built a logistic regression model including baseline characteristics with $P < 0.20$ found on univariate analysis; variables considered were sex, disease duration, smoking history, body mass index (BMI), baseline erosion, rheumatoid factor (RF), anti-CCP antibodies and presence of at least one HLA-DRB1 allele encoding the shared epitope, mean GC dose during the first year, with adjustment for delay to the first DMARD. The investigation center was used as a random effect. Variables with $P < 0.05$ were entered in descending stepwise order in the model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. To assess the independent association of age and first DMARD survival, we build a Cox model by the same method, with hazard ratios (HRs) and 95% CIs calculated.

Statistical analysis involved use of Stata IC v12.1 (StataCorp, College Station, TX).

3. Results

3.1. Baseline demographic and disease characteristics

The main baseline demographic and disease characteristics of the whole sample of early RA patients ($n = 698$) and the 3 age groups – YORA ($n = 266$), IORA ($n = 314$) and LORA ($n = 118$) – stratified by age at disease onset are in Table 1. The prevalence of RF was greater for YORA than IORA and LORA patients (59% vs 50% and 47%, $P = 0.04$) as was the prevalence of anti-citrullinated protein antibodies (ACPAs) (52% vs 44% and 34%, $P = 0.004$).

3.2. Clinical outcome

At baseline, the prevalence of SDAI remission was 0% in the 3 age groups. At 1 year, the prevalence was higher for YORA than

Please cite this article in press as: Krams T, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort. Joint Bone Spine (2016), http://dx.doi.org/10.1016/j.jbspin.2015.09.010

Table 1
Baseline demographic and disease characteristics.

	Whole sample ($n=698$)	YORA, < 45 years ($n=266$)	IORA, 45–60 years ($n=314$)	LORA, > 60 years ($n=118$)	*P*-value[a]
Age (year), median (IQR)	50.3 (39.8–57.2)	36.6 (30.0–41.7)	53.7 (50.1–56.6)	64.6 (62.7–66.4)	–
Female, *n* (%)	546 (73)	215 (81)	248 (79)	83 (70)	0.07
Disease duration (month), median (IQR)	4.9 (3.0–7.3)	5.3 (3.1–7.7)	4.6 (2.8–7.3)	4.9 (3.1–6.4)	0.2
Rheumatoid factor positivity, *n* (%)	372 (53)	158 (59)	158 (50)	56 (47)	0.04
ACPA positivity, *n* (%)	315 (45)	138 (52)	137 (44)	40 (34)	0.004
Tender joint count, median (IQR)	7 (4–14)	7 (4–12)	8.5 (4–15)	8 (5–14)	0.07
Swollen joint count, median (IQR)	6 (4–11)	6 (3–10)	7 (4–11)	6.5 (4–12)	0.02
ESR, median (IQR)	22.5 (12–38)	21 (12–34)	22 (12–38)	25 (14–52)	0.02
CRP, median (IQR)	9 (0–24)	9.5 (3–24)	8 (0–20)	13 (0–38)	0.07
SDAI, median (IQR)	28.5 (20.6–38.6)	26.3 (20.6–35.8)	29.4 (20.5–39.5)	32.15 (22.3–40)	0.04
mTSS, median (IQR)	3 (0–7)	1 (0–4)	4 (1–8)	6 (2–11)	0.0001
HAQ-DI, median (IQR)	1 (0.5–1.5)	0.875 (0.38–1.38)	1 (0.50–1.50)	1.0625 (0.50–1.625)	0.09

YORA: young-onset RA; IORA: intermediate-onset RA; LORA: late-onset RA; IQR: interquartile range; ACPA: anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; mTSS: van der Heijde-modified total Sharp score; HAQ-DI: Health Assessment Questionnaire Disability Index.

[a] *P* global comparison for the 3 groups by Kruskal-Wallis test.

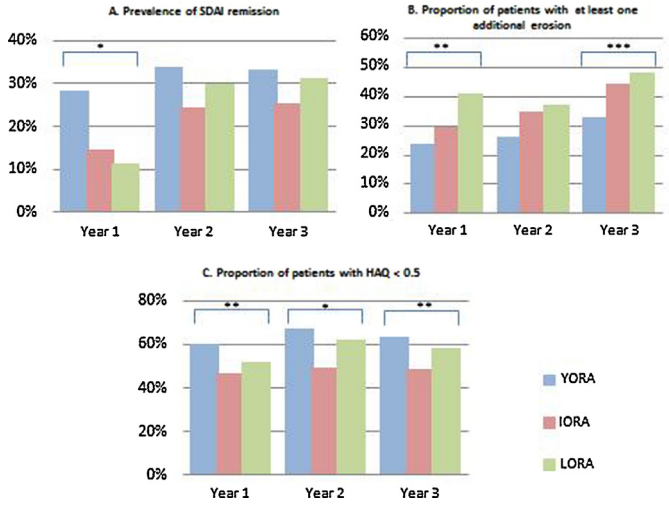

Fig. 1. Prevalence of SDAI remission (A), proportion of patients with at least one additional erosion (B) and proportion of patients with Health Assessment Questionnaire score < 0.5 (C) in young-onset rheumatoid arthritis (YORA), intermediate-onset RA (IORA), late-onset RA (LORA) during 3 years of follow-up. $^{*}P<0.0001$, $^{**}P<0.01$, $^{***}P<0.05$

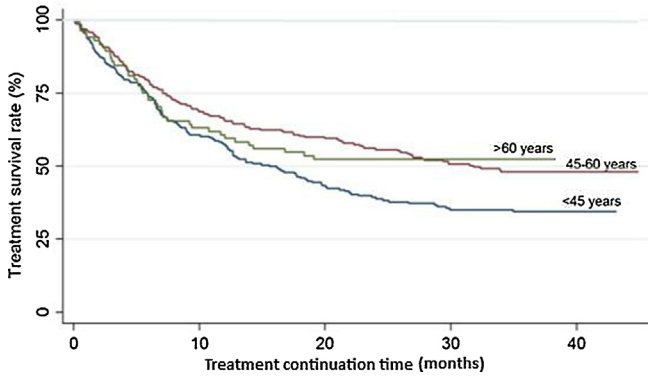

Figure 2. First DMARD survival rate during 3 years of follow-up by age at RA onset. Differences between YORA and IORA patients ($P=0.002$) and between YORA and LORA patients ($P=0.03$) but not IORA and LORA patients ($P=0.9$)

IORA and LORA patients (Fig. 1A). This difference did not remain significant at 2 and 3 years.

3.3. Radiographic outcome

The median (IQR) mTSS was higher for LORA and IORA than YORA patients at baseline. This difference remained significant at 1, 2 and 3 years.

The proportion of patients with at least one additional erosion was significantly higher for LORA and IORA than YORA after 1 year and 3 years but not 2 years (Fig. 1B).

3.4. Functional outcome

HAQ score did not differ at baseline for YORA, IORA and LORA patients. The proportion of patients with HAQ score < 0.5 was greater for YORA than IORA and LORA at 1, 2 and 3 years (Fig. 1C).

3.5. First DMARD survival analysis

The delay of first DMARD initiation did not differ for YORA, IORA and LORA patients (median [IQR] = 5.9 [4.0–10.0], 5.9 [3.9–8.8] and 6.0 [4.0–8.0] months, respectively, $P=0.82$). The nature of the first DMARD was conventional synthetic DMARD (csDMARD) monotherapy for 92.8% (205/221), 91.9% (238/259) and 97.9% (95/97), respectively; biologic DMARD (bDMARD) monotherapy for 0.4% (1/221), 0.4% (1/259) and 0.0% (0/97), respectively; combined csDMARDs for 6.3% (14/221), 5.4% (14/259) and 2.1% (2/97), respectively, and combined csDMARDs and bDMARDs for 0.4% (1/221), 2.3% (6/259), and 0.0% (0/97), respectively. The proportion of patients receiving corticosteroids was 32.3% (86/266), 40.1% (126/314), and 36.4% (43/118), respectively, at 1 year; 27.8% (74/266) 33.1% (104/314), and 26.3% (31/118) at 2 years; and 24.0% (64/266), 30.3% (95/314) and 22.0% (26/118) at 3 years.

The first DMARD survival rate was lower for YORA than IORA and LORA patients during the 3 years ($P=0.005$) (Fig. 2). The first DMARD survival did not differ among groups at 1 year (proportion of first DMARD survival: 63.6%, 68.3% and 64.5% for YORA, IORA and LORA patients, respectively; $P=0.5$) but did differ at 3 years (34.9%, 47.6% and 51.1%, respectively; $P=0.006$). The treatment survival rate by reason for interruption (lack of efficacy or adverse events) was the same for the 3 groups at 1 year (data not shown).

3.6. Multivariate analysis

3.6.1. Clinical outcome

Age at RA onset was independently associated with SDAI remission at 1 and 2 years (Table 2) but not at 3 years. In addition, mean daily dose of steroids (total dose of steroids over the first year divided by 365) was independently associated with SDAI remission at 1 year (OR = 0.87 [0.80–0.94], $P<0.001$, per additional mg/day of steroids) (data not shown).

Please cite this article in press as: Krams T, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort. Joint Bone Spine (2016), http://dx.doi.org/10.1016/j.jbspin.2015.09.010

Table 2
Adjusted odds ratios (aORs) for SDAI remission, additional erosion and HAQ score < 0.5 at 1-, 2- and 3-year follow-up.

Outcome	Follow-up, years	Age at RA onset				
		YORA	IORA		LORA	
			aOR [95% CI]	*P*-value vs YORA*	aOR [95% CI]	*P*-value vs YORA*
SDAI remission	1	1 (referent)	0.41 [0.25–0.69]	0.001	0.33 [0.16–0.71]	0.005
	2	1 (referent)	0.63 [0.41–0.97]	0.038	1.01 [0.57–1.77]	0.972
	3	1 (referent)	0.68 [0.45–1.02]	0.061	0.90 [0.53–1.54]	0.707
Additional erosion	1	1 (referent)	1.28 [0.79–2.07]	0.314	1.68 [0.89–3.18]	0.111
	2	1 (referent)	1.46 [0.90–2.36]	0.125	1.30 [0.67–2.50]	0.438
	3	1 (referent)	1.86 [1.15–3.00]	0.011	1.45 [0.76–2.76]	0.257
HAQ score < 0.5	1	1 (referent)	0.57 [0.38–0.86]	0.007	0.88 [0.50–1.54]	0.649
	2	1 (referent)	0.50 [0.33–0.75]	0.001	1.09 [0.61–1.94]	0.767
	3	1 (referent)	0.56 [0.36–0.86]	0.008	1.05 [0.57–1.91]	0.883

Adjusted OR (aOR): odds ratio adjusted for confounding factors including the baseline characteristics found to with $P < 0.20$ on univariate analysis among sex, disease duration, smoking history, body mass index, baseline erosion, RF, anti-CCP and presence of at least one HLA-DRB1 allele encoding the shared epitope, mean glucocorticoids dose after the first year. Multivariate analysis was performed with adjustment for delay before the first disease-modifying anti-rheumatic drug intake.
* Chi^2 test.

3.6.2. Radiographic outcome

Age at RA onset was independently associated with at least one additional erosion at 3 years (Table 2). Age at RA onset was not independently associated with at least one additional erosion at 1 or 2 years. Other baseline characteristics independently associated with at least one additional erosion at 3 years were RF status (OR = 2.86 [1.83–4.46], $P = 0.03$), erosive status (OR = 3.10 [1.98–4.85], $P < 0.001$) and carriage of shared epitope (OR = 1.69 [1.09–2.63], $P = 0.019$).

3.6.3. Functional outcome

Age at RA onset was independently associated with HAQ remission (HAQ score < 0.5) at 1 year (Table 2). Other baseline characteristics independently associated with HAQ remission at 1 year were female sex (OR = 0.40 [0.25–0.64], $P < 0.001$), mean daily dose of steroids (OR = 0.89 [0.85–0.94], $P < 0.001$), BMI (for BMI > 30 kg/m^2 versus < 25 kg/m^2 with OR = 0.49 [0.28–0.86], $P = 0.014$ but not for BMI = 25–30 kg/m^2 versus < 25 kg/m^2 and with OR = 0.69 [0.45–1.06], $P = 0.09$) and RF positivity (OR = 1.67 [1.15–2.43], $P = 0.007$).

3.6.4. First DMARD survival

Young age at RA onset was independently associated with a low first DMARD survival over 3 years for YORA versus IORA (HR = 0.71 [0.55–0.92], $P = 0.009$) but not significantly for YORA versus LORA patients (HR = 0.75, [0.52–1.09], $P = 0.13$). Other baseline characteristics independently associated with first DMARD survival at 3 years were mean daily dose of steroids (HR = 1.05 [1.02–1.08], $P = 0.002$) and carriage of shared epitope (HR = 0.78 [0.61–0.99], $P = 0.041$).

4. Discussion

In our study, we investigated the effect of age at disease onset on clinical, radiographic and functional outcomes in a prospective cohort of early RA patients. We found greater SDAI remission at 1 year; lower radiographic damage and lower rate of at least one additional erosion at 3 years; higher proportion of HAQ remission at 1, 2 and 3 years; and lower first DMARD survival rate over 3 years for YORA than IORA and LORA patients.

We lack a single definition for "older adults" that could be applied in a consistent manner or would be useful in all contexts for RA research. Some authors define LORA as > 65 years [3,14,27,28] and others > 60 years [7,29]. We divided patients into 3 classes, with cut-offs of 45 and 60 years because we considered that we might obtain more information between younger and older groups than with 2 groups. In addition, the ESPOIR cohort patients are aged 18 to 70 years, for few patients older than 65 years, so we chose a cut-off of 60 years. This division allowed for 3 balanced groups. However, this population did not allow for studying outcomes in very old patients, which is a limitation of our study.

Concerning the clinical outcome, we found a higher proportion of SDAI remission at 1 year for YORA than IORA and LORA. This difference disappeared at years 2 and 3. Pease et al. [3] analyzed the influence of age on clinical outcome and showed that the proportion of remission was higher in the oldest than the youngest patients (45.8% of late-onset RA vs 20.4% of young-onset RA patients had clinically inactive disease at final follow-up [$P < 0.01$] [median follow-up, 3.6 years (range 1–7 years)]). Mueller et al. [17] did not show any difference in clinical outcome by RA onset in patients younger and older than 65 years. These apparently conflicting results could arise from differences in age cut-offs between studies, while the main clinical outcome differences in our study were observed between younger patients (< 45 years) and the others and not between middle-aged (45–60 years) and older patients (> 60 years), whereas Pease et al. and Mueller et al compared only 2 groups with a cut-off at 65 years old. In a recent study, Innala et al. [18] evaluated the impact of age at disease onset on prognostic risk factors, disease progression and pharmacological treatment in a large inception cohort of patients with RA from northern Sweden. Disease activity, measured by a combination of ESR, CRP level, and accumulated disease activity score was higher for LORA than those with disease onset at a younger age (LORA and YORA were defined as RA onset after and before 58 years old, respectively).

Concerning radiographic outcome, we found a lower radiographic damage score and a lower proportion of patients with at least one additional erosion at 3 years for YORA than IORA and LORA. The lower radiographic damage score at baseline in YORA agrees with some previous studies [15,17]. This difference at baseline cannot be explained by only a higher prevalence of osteoarthritis in older adults but does concern both the erosion and the narrowing components of the mTSS (data not shown). The low proportion of YORA with one additional erosion at 3 years also agrees with previous studies. In a recent study, Mueller et al. [17] showed a similar radiographic progression in young and late-onset RA (RA onset < 65 and > 65 years, respectively). However, in this study, the proportion of patients with a Ratingen score > 24 (considered high radiographic progression) was higher for LORA than YORA patients after 5 years of follow-up. Innala et al. [18] showed LORA status significantly more often associated with presence of erosions and high Larsen score at both 0 and 24 months, with no significant difference between YORA and LORA in progression of Larsen score or presence of erosions.

Please cite this article in press as: Krams T, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort. Joint Bone Spine (2016), http://dx.doi.org/10.1016/j.jbspin.2015.09.010

Concerning functional outcome, we found a higher proportion of HAQ remission at 1, 2 and 3 years for YORA than IORA and LORA. These results agree with a previous study by Camacho et al, who showed older age of first symptom onset associated with increasingly steep disability progression. Innala et al. [18] showed that LORA had reduced physical function as measured by HAQ at baseline.

Concerning treatment modalities, we found a lower first DMARD survival rate over 3 years for YORA than IORA and LORA patients, suggesting that rheumatologists are quicker to adapt treatment in YORA patients than in IORA and LORA patients. This results are concordant with previous studies which suggested that LORA patients had less aggressive treatment than YORA patients, despite identical disease duration and comparable disease severity and activity [5] and that LORA patients received more frequently corticosteroids and less frequently csDMARDs or bDMARDs than younger patients [17,30].

In conclusion, in a cohort of early RA, younger age at disease onset was associated with higher rate of SDAI remission at 1 year, lower radiographic disease progression and lower functional score during 3-year follow-up than older age at disease onset. Moreover, young age at disease onset was associated with low first DMARD survival during 3 years, which suggests that late-onset RA patients may receive a less aggressive treatment strategy than younger patients.

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. The pharmaceutical companies were not involved in the study design, data collection data analysis, manuscript preparation or decision to publish.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

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 centralizing 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; P. Goupille, Tours; F. Liote, Paris-Lariboisière; X. Le Loet and O. Vittecoq, Rouen; X. Mariette, Paris Bicêtre; O. Meyer, Paris-Bichat; A. Saraux, Brest; T. Schaeverbeke, Bordeaux; J. Sibilia, Strasbourg).

The authors thank Mogens Thomsen and Jane Miller for critical reading of the manuscript.

References

[1] Carbonell J, Cobo T, Balsa A, et al. The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry. Rheumatology (Oxford) 2008;47:1088–92.
[2] Symmons DP, Barrett EM, Bankhead CR, et al. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 1994;33:735–9.
[3] Pease CT, Bhakta BB, Devlin J, et al. Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors. Rheumatology (Oxford) 1999;38:228–34.
[4] van der Heijde DM, van Riel PL, van Leeuwen MA, et al. Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective follow-up study of early rheumatoid arthritis. J Rheumatol 1991;18:1285–9.
[5] Tutuncu Z, Reed G, Kremer J, et al. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis 2006;65:1226–9.
[6] van Schaardenburg D, Breedveld FC. Elderly-onset rheumatoid arthritis. Semin Arthritis Rheum 1994;23:367–78.
[7] Mavragani CP, Moutsopoulos HM. Rheumatoid arthritis in the elderly. Exp Gerontol 1999;34:463–71.
[8] Villa-Blanco JI, Calvo-Alén J. Elderly onset rheumatoid arthritis: differential diagnosis and choice of first-line and subsequent therapy. Drugs Aging 2009;26:739–50.
[9] Wu H, Khanna D, Park G, et al. Interaction between RANKL and HLA-DRB1 genotypes may contribute to younger age at onset of seropositive rheumatoid arthritis in an inception cohort. Arthritis Rheum 2004;50:3093–103.
[10] Hellier JP, Eliaou JF, Daurès JP, et al. HLA-DRB1 genes and patients with late onset rheumatoid arthritis. Ann Rheum Dis 2001;60:531–3.
[11] Kaarela K. Prognostic factors and diagnostic criteria in early rheumatoid arthritis. Scand J Rheumatol Suppl 1985;57:1–54.
[12] Luukkainen R, Kaarela K, Isomäki H, et al. The prediction of radiological destruction during the early stage of rheumatoid arthritis. Clin Exp Rheumatol 1983;1:295–8.
[13] Mikuls T, Saag K, Criswell L, et al. Health related quality of life in women with elderly onset rheumatoid arthritis. J Rheumatol 2003;30:952–7.
[14] Ferraccioli GF, Cavalieri F, Mercadanti M, et al. Clinical features, scintiscan characteristics and X-ray progression of late onset rheumatoid arthritis. Clin Exp Rheumatol 1984;2:157–61.
[15] Bukhari M, Lunt M, Barton A, et al. Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis. Ann Rheum Dis 2007;66:389–93.
[16] Naz SM, Farragher TM, Bunn DK, et al. The influence of age at symptom onset and length of follow-up on mortality in patients with recent-onset inflammatory polyarthritis. Arthritis Rheum 2008;58:985–9.
[17] Mueller RB, Kaegi T, Finckh A, et al. Is radiographic progression of late-onset rheumatoid arthritis different from young-onset rheumatoid arthritis? Results from the Swiss prospective observational cohort. Rheumatology (Oxford) 2014;53:671–7.
[18] Innala L, Berglin E, Möller B, et al. Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2014;16:R94.
[19] Combe B, Rincheval N. Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR. Joint Bone Spine 2015;82:13–7.
[20] Combe B, Logeart I, Belkacemi MC, et al. 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. Ann Rheum Dis 2015;74:724–9.
[21] 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.
[22] Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 2007;21:663–75.
[23] 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.
[24] Tobón G, Saraux A, Lukas C, et al. First-year radiographic progression as a predictor of further progression in early arthritis: results of a large national French cohort. Arthritis Care Res (Hoboken) 2013;65:1907–15.
[25] Escalas C, Dalichampt M, Combe B, et al. Effect of adherence to European treatment recommendations on early arthritis outcome: data from the ESPOIR cohort. Ann Rheum Dis 2012;71:1803–8.
[26] Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003;30:167–78.
[27] Aletaha D, Machold KP, Nell VPK, et al. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology (Oxford) 2006;45:1133–9.
[28] Calvo-Alén J, Corrales A, Sánchez-Andrada S, et al. Outcome of late-onset rheumatoid arthritis. Clin Rheumatol 2005;24:485–9.
[29] Spinel-Bejarano N, Quintana G, Heredia R, et al. Comparative study of elderly-onset rheumatoid arthritis and young-onset rheumatoid arthritis in a Colombian population: clinical, laboratory and HLA-DRB1 findings. Clin Exp Rheumatol 2013;31:40–6.
[30] Lahaye C, Tatar Z, Dubost JJ, et al. Overview of biologic treatments in the elderly. Joint Bone Spine 2015;82:154–60.

Please cite this article in press as: Krams T, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort. Joint Bone Spine (2016), http://dx.doi.org/10.1016/j.jbspin.2015.09.010