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Original article

Time to initiation of biologic disease-modifying antirheumatic drugs in the French cohort ESPOIR

Joanna Kedra[a,b,*], Benjamin Granger[a,c], Stéphanie Emilie[d], Cécile Gaujoux-Viala[e], Anne-Christine Rat[f], Bernard Combe[g], Bruno Fautrel[a,b]

[a] Sorbonne Université, Institut Pierre Louis d'Épidémiologie et de Santé Publique (iPLESP), UMR S1136, Paris, France
[b] AP–HP, Pitié Salpêtrière hospital, Rheumatology department, Paris, France
[c] AP–HP, Pitié Salpêtrière hospital, Public Health department, Paris, France
[d] Department of internal medicine, Intercommunal Hospital Center of Villeneuve-Saint-Georges, Villeneuve-Saint-Georges, France
[e] IDESP, Montpellier University, and Nîmes University Hospital, Rheumatology Dept, Nimes, France
[f] University of Caen Normandie, UMR-S 1075, Université de Lorraine, EA 4360 and Caen University Hospital, Rheumatology department, Caen, France
[g] Montpellier University, CHU de Montpellier, Rheumatology Dept, Montpellier, France

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ABSTRACT

Objective: To assess the time to initiation of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in ESPOIR, the French cohort of patients with rheumatoid arthritis (RA), and factors associated with the timing of bDMARD initiation.

Methods: In total, 658 patients with early RA satisfying the 2010 ACR/EULAR criteria were included between 2003 and 2005 and followed annually for 10 years (end of follow up: 2013-2015). The timing of bDMARD introduction and predictors of use were analysed by the Kaplan-Meier method based on Cox proportional-hazard models.

Results: Overall, 178 patients (31.0%, 95% confidence interval [27.0–34.7]) initiated a bDMARD during the 10-year follow-up, with a mean delay of 43.6 months. The penetration rate was higher during the first 2 years of follow-up (6% between the first and second year, approximately 3.3% each year between the second and seventh year, and < 2.0% after the eighth year). The first-used bDMARD was etanercept for 72 patients and adalimumab for 71. On multivariate analysis, Disease Activity Score in 28 joints, radiologic progression and positivity for anti-citrullinated protein antibodies were significantly associated with rapid initiation of a bDMARD ($P < 0.0001$), whereas older age at first joint pain was inversely associated ($P < 0.0001$).

Conclusions: Although access to bDMARDs is widespread in France, less than one third of patients with early RA in the ESPOIR cohort initiated a bDMARD over the 10-year follow-up. Poor prognostic factors for RA were associated with more rapid initiation, as expected.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition, involving particularly joints, and resulting in joint pain and deformity that may lead to disability [1]. However, better outcomes in RA have been observed since the use of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) in the early 1990s and biologic therapies in the early 2000s [2,3]. With these treatments, the achievement of sustained remission and minimal or null radiographic progression became more feasible.

Several learned societies aimed to determine the best therapeutic approach in RA. MTX became the anchor drug among DMARDs according to European League Against Rheumatism (EULAR) recommendations in 2006 [4]. In 2009, EULAR developed the first recommendations on the specific use of conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs), and TNF inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab) were recommended if MTX failed to achieve remission and if the patient presented unfavorable prognostic markers (i.e., autoantibodies, high disease activity, early erosions, failure of 2 csDMARDs) [5]. Since EULAR recommendations update in 2013, TNF-inhibitors, abatacept, tocilizumab, and, under certain circum-

* Corresponding author at: Sorbonne Université, Institut Pierre Louis d'Épidémiologie et de Santé Publique (iPLESP), UMR S1136, Paris, France.
E-mail address: jkedra.pro@gmail.com (J. Kedra).

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stances, rituximab, may be prescribed as first-line of bDMARD treatment [6]. In the latest EULAR recommendations update, these major principles have remained intact [7]. These recommendations have led to an update of the therapeutic guidelines formulated by the French Society of Rheumatology (SFR), which are in France the reference for patient care [8].

The prescription of DMARDs has increased during the last decades [9], coinciding with the introduction of bDMARDs on the market. The first available TNF blockers were infliximab and etanercept in 2000, followed by adalimumab in 2003. Certolizumab and golimumab are available since 2009. Intravenous (IV) abatacept and tocilizumab have been marketed since 2007 and 2009 respectively, and these treatments can be taken subcutaneously since 2012 and 2013, respectively. In a study by Harrold et al., the use of traditional DMARDs was about 91% to 93%, and although the initiation of bDMARDs for moderate-to-severe disease activity has increased from 13% to 16% (pre-2008) to 15% to 16% (post-2008), the overall use of bDMARDs is about 20% to 33% [10]. Additional studies concluded that the overall use of biologic DMARDs is suboptimal [11,12]. This underuse can be explained by different factors. First, the possibility to initiate or not a bDMARD depends on factors related to patient and disease characteristics, including comorbidities, or demographic factors such as younger age and female sex [13]. Besides disease characteristics, other factors may have substantial impact on the occurrence and timing of DMARD prescription, such as patient socio-economic status, regional organization of the health care system including physician density or physician prescription habits [14–16]. Moreover, access to bDMARDs can differ depending on the country; indeed, according to a study by Putrik et al., there is great disparity across the European Union in terms of market share, with easier access to biologic agents in Scandinavia but a small proportion of patients receiving such therapies in Eastern Europe [17].

France features only a minor limitation in access to bDMARDs [17], which can be explained by French recommendations (bDMARDs should be initiated as soon as failure to one csDMARD) and by full coverage of these treatments by the French social security system. Thus, when the need for bDMARD occurs in the natural history of early RA could be well assessed in France. Indeed, given that biotherapies are indicated in case of failure of csDMARDs, a better knowledge of the factors leading to the early initiation of biotherapies seems important, because it would allow for identifying the profiles at risk of csDMARD failure and thus avoid wasting time and structural evolution.

In 2002, the French SFR and the Club Rhumatismes et Inflammations (https://www.cri-net.com) initiated a large national multicenter cohort, the Étude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort, for investigating diagnostic and prognostic markers among patients with early undifferentiated, inflammatory arthritis that could later progress to RA [18]. The aim of our study was to determine in the ESPOIR cohort the time to initiation of bDMARDs and the factors associated with rapid initiation.

2. Methods

2.1. Patients

We included patients from 14 French regional centers between December 2002 and March 2005. Inclusion criteria were ages 18 to 70 years; more than two swollen joints for > 6 weeks; < 6 months suspected or confirmed diagnosis of RA; and no intake of DMARDs or glucocorticoids for > 2 weeks [18]. Patients were excluded if the referring physician judged that they had other clearly defined inflammatory rheumatic diseases. In this study, we considered only patients who were fulfilling the 2010 ACR/EULAR criteria for RA at baseline [19]. Each center acted as an observational center and did not interfere with patient treatment, except if managing care of a patient.

Patients were followed up every 6 months during the first 2 years, then every year. At baseline and at each visit, a set of clinical and biological variables were recorded, including the Disease Activity Score in 28 joints (DAS28), physical examination items, treatments, functional capacity using the Health Assessment Questionnaire (HAQ) and quality of life using the Medical Outcomes Study Short Form 36 (SF-36). Therapeutic strategies were not standardized in the cohort and treatment decisions were left to the treating rheumatologist in charge of the patient outside of the cohort. Hand and foot radiographs were assessed at baseline and every year during follow-up and read by 2 experienced readers in known chronological order, with blinding to patient identity, disease characteristics and treatment. The modified Sharp/van der Heijde score was used to quantify structural damage [20].

The protocol of the ESPOIR cohort study was approved by the Ethics Committee of Montpellier, France (No. 020307). All patients gave their signed informed consent before inclusion (ClinicalTrials.gov NCT03666091).

2.2. Outcome

The primary outcome was the time to the initiation (in months) of bDMARDs among tumor necrosis factor blockers, rituximab, tocilizumab and abatacept. The start date was the date of the first stable RA symptom (i.e., the first stable joint swelling according to the patient). The end date was the date of the initiation of the first bDMARD or the date of the last documented follow-up for censured individuals who did not undergo treatment for the duration of their follow-up.

Factors associated with a more rapid initiation of bDMARDs were then assessed, including clinical, biological and radiological features, at baseline and during follow-up in case of repeated measures (i.e., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], DAS28, HAQ, radiographic progression, treatment intake).

2.3. Statistical analysis

A survival analysis was run to assess time to bDMARD initiation. The variable was considered right-censored data. Kaplan–Meier curves were used to measure the time to bDMARDs initiation.

We analysed which factors affected the delay before use of the first biologic agent by a Cox proportional-hazards model with time dependent covariates, first on univariate analysis, then including factors significant on univariate analysis in a multivariable model, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). To control for type I errors during univariate selection, the Benjamini and Hochberg procedure was used to assess adjusted p-values [21]. The threshold of significance was set at 0.05. Predictor colinearity was then assessed by adapted tests. Proportional hazards, log linearity hypothesis, and influential observations were checked. All statistical analyses involved using R v3.5.1.

3. Results

3.1. Population

Among the 813 patients of the ESPOIR cohort, 658 fulfilled 2010 ACR/EULAR criteria for RA and were considered in the present study. Overall, 506 (76.9%) patients were women, 317 (48.2%) were smokers, 306 (46.5%) were positive for RF, 265 (40.7%) were positive for anti-citrullinated protein antibodies (ACPA), and 359 (54.6%) had polyarticular presentation at baseline. More details regard-

Table 1
Baseline characteristics of the ESPOIR cohort patients fulfilling ACR/EULAR 2010 criteria for rheumatoid arthritis.

Variables	Fulfilling ACR/EULAR 2010 criteria $n = 658$	Ever received a bDMARD during 10-year follow-up $n = 178$	Never received a bDMARD during 10-year follow-up $n = 480$
Patient characteristics			
Age of first pain, years	48 ± 12.3 (49.9)	45.0 ± 12.5 (47.1)	49.1 ± 12.0 (51.4)
Age of first swelling, years	48.2 ± 12.2 (50.1)	45.2 ± 12.4 (47.1)	49.3 ± 12.0 (51.8)
Age of first fixed swelling, years	48.3 ± 12.2 (50.4)	45.4 ± 12.4 (47.3)	49.4 ± 12.0 (51.8)
Female sex	506 (76.9)	131 (73.6)	375 (78.1)
Paid work	630 (95.7)	167 (93.8)	463 (96.5)
Living in a couple relationship	482 (3.2)	125 (70.2)	357 (74.4)[d]
Cardiovascular comorbidity[a]	10 (1.52)	1 (0.6)	9 (1.9)
Tuberculosis history	28 (4.26)	7 (3.9)	21 (4.4)
Lymphoma history	5 (0.76)	0 (0)	5 (1.0)
Neoplasia	24 (3.65)	6 (3.4)	18 (3.8)
Smokers	317 (48.2)	83 (46.6)	234 (48.8)
Disease characteristics			
Joint involvement at baseline			
Monoarticular	120 (18.2)	36 (20.2)	84 (17.5)
Oligoarticular	179 (27.2)	50 (28.1)	129 (26.9)
Polyarticular	359 (54.6)	92 (51.7)	267 (55.6)
DAS28 at baseline	5.2 ± 1.24 (5.1)[b]	5.4 ± 1.3 (5.3)[c]	5.1 ± 1.2 (5.1)[d]
HAQ score at baseline	1.0 ± 0.68	1.1 ± 0.7 (1.1)	1.0 ± 0.7 (0.9)
RF positive	306 (46.5)	122 (68.5)	184 (38.3)
ACPA positive	283 (43.0)	125 (70.2)	158 (32.9)
ESR at inclusion, mm 1st hour	29 ± 24.13 (22)[b]	36.6 ± 25.5 (26.0)	27.8 ± 23.5 (20.0)[d]
CRP level at inclusion, mg/L	22.2 ± 34.3 (9)[b]	26.5 ± 37.0 (12.0)[c]	20.7 ± 33.2 (8.0)[d]
X-ray erosion at baseline	93 (14.1)	35 (19.7)	58 (12.1)
Health-care system characteristics			
Time to access rheumatologist, days	74.1 ± 75.8 (60)	82.2 ± 93.2 (60.0)[c]	71.0 ± 68.0 (59.0)[d]

Data are mean ± SD (median) or *n* (%). bDMARD: biologic disease modifying anti-rheumatic drug; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; ESR: erythrocyte sedimentary rate; CRP: C-reactive protein; SD: standard deviation.

[a] Cardiovascular comorbidity: myocardial ischemia or cerebrovascular accident.

[b] Because of missing data, results are shown for 645 patients for DAS28 at inclusion, 648 for ESR at inclusion, and 647 for CRP level at inclusion.

[c] Because of missing data, results are shown for 175 patients for DAS28 at inclusion, 176 for CRP level and ESR at inclusion, and 177 for time to first rheumatologist consultation.

[d] Because of missing data, results are shown for 470 patients for DAS28 at inclusion, 471 for CRP level at inclusion, 472 for ESR at inclusion, and 470 for time to first rheumatologist consultation.

ing baseline characteristics are provided in Table 1. The median follow-up was 120 months (interquartile range 107–120).

3.2. Time to initiation of the first bDMARD

Overall, 178 patients (31%) initiated a bDMARD during the 10-year follow-up (Fig. 1). On these 178 patients, the mean delay for bDMARD initiation was 43.6 months (SD 30.1); according Kaplan Meier estimator the median onset was unavailable because less than half of the sample received bDMARDs (1st quartile onset was around 60 months). The biologic penetration rate appeared to be greater during the 2 first years of follow-up: 6% of new patients received bDMARDs during the first and second years of follow-up, 3.3% for each additional year between the second and seventh years, with a plateau < 2.0% after the eighth year.

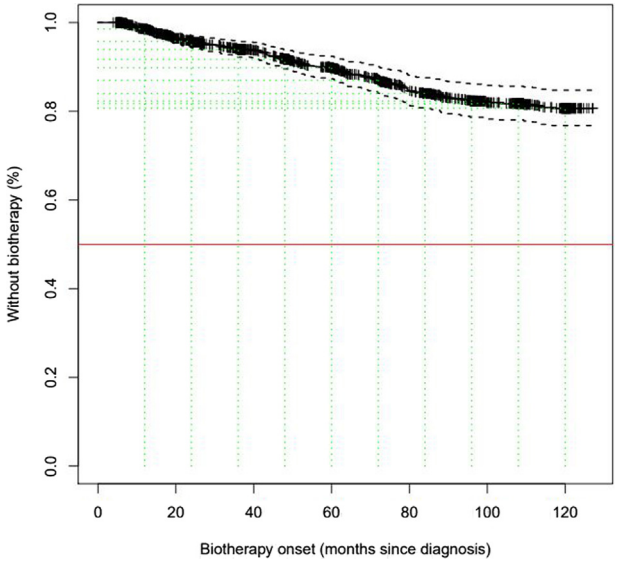

Fig. 1. Survival with rheumatoid arthritis without any biologic agent. The Kaplan–Meier curve is provided with 95% confidence intervals.

The first used bDMARD was etanercept in 72 patients and adalimumab in 71. Infliximab was initiated in 16 patients, certolizumab in 3, rituximab in 10, and abatacept, tocilizumab and anakinra in 2 each.

3.3. Factors affecting the initiation of the first bDMARD in early RA

The factors affecting the delay in introducing a biologic agent according to Cox modelling are in Tables 2 and 3 for univariate and multivariable analysis, respectively.

On univariate analysis, the delay in introducing the first biologic agent was associated with disease severity markers such as ACPA positivity (HR 3.36; 95% CI: 2.47–4.57), DAS28 (HR 2.08; 95% CI: 1.87–2.31) or structural damage progression (HR 3.26; 95% CI: 2.41-4.43). Older age at the first joint pain was associated with less rapid biologic prescription: HR 0.98 (95% CI: 0.97–0.99). Kaplan-Meier curves according to the latter variables are provided in Fig. 2. On multivariate analysis, ACPA positivity, time dependent DAS28, structural damage progression and younger age at RA onset remained significantly associated with more rapid bDMARD initiation.

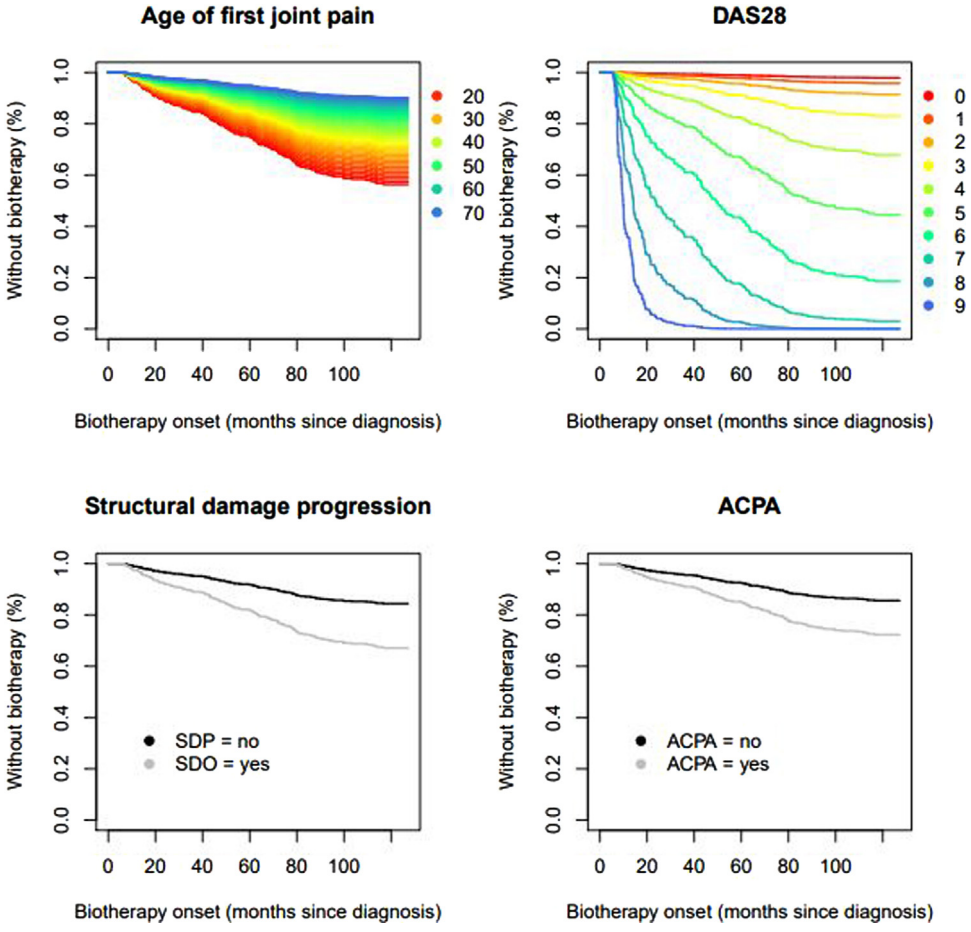

Fig. 2. Survival without any biologic agent according to different variables. (ACPA: anti-citrullinated peptide antibodies; DAS28: disease activity score 28 during the follow-up). Structural damage progression was assessed according to Sharp modified by van der Heijde method.

Glucocorticoids and non-steroidal anti-inflammatory drug (NSAID) intake during follow-up were significantly associated with more rapid bDMARD initiation: HR 3.31 (95% CI: 2.40–4.56) and HR 2.03 (95% CI: 1.46–2.82), respectively.

A medical history of cardiovascular, neoplasic diseases or tuberculosis was not associated with delayed introduction of the first bDMARD, nor was the number of comorbidities.

An exploratory analysis was performed to assess the association between rapid radiographic progression (RRP, defined as an increase in the Sharp/van der Heijde score of at least 5 points per year) and bDMARD initiation. RRP was significantly associated with earlier bDMARD initiation: HR 2.88 (95%CI: 1.97-4.21).

4. Discussion

This study reveals that less than one third of patients presenting an early RA between 2003 and 2005 initiated a bDMARD at the end of the 10-year follow-up, with a mean delay of initiation of 43.6 months.

This result can be interpreted in several ways. On the one hand, it is to be remembered that only three bDMARDs were available in France at the time of patients' inclusion in the ESPOIR cohort, whereas at the end of the follow-up, eight bDMARDs were available. Additionally, the place of bDMARDs in RA treatment management was not clearly defined before 2009, and TNF inhibitors were considered the only first line biologics until 2013 (a chronological frieze is provided in Doc S1 [See the supplementary material associated with this article online]) [5]. However, we did not find an increase in bDMARDs prescription after 2010 (corresponding to 60 to 80 months of follow-up approximately), suggesting a stable trend for bDMARD initiation during the follow-up. On the other hand, because bDMARDs are second-line treatments, these results suggest that about 70% of the patients in the French cohort ESPOIR show good response to csDMARDS. In fact, as mentioned earlier, biologic agents are prescribed in France after the failure of one csDMARD. Moreover, these treatments are integrally reimbursed by the social security system in France and therefore do not represent a financial burden for patients in terms of limiting their prescription in populations with lower incomes. Additionally, even if these treatments still represent an important cost on the country scale, with an average annual cost per patient of more than 10,000€, France is one of the countries with lower prices for DMARDs; indeed, according to the results from the METEOR registry, France was in third position in terms of lower cost for csDMARDs and in first position for lower cost of bDMARDs [22]. In comparison, average annual prices were 5.9 times higher in the United States. Moreover, low socioeconomic status of a country and stricter rules for reimbursement of bDMARDs were found associated with reduced bDMARD usage, which is negatively associated with disease activity [22]. Thus, even if the Putrik et al. study stated that France had only a mild access to biologic agents [17], the French population (and thus patients in the ESPOIR cohort) seems in a globally favorable condition to follow recommendations for RA treatment and therefore achieve remission.

Factors associated with a more rapid initiation were also predictors of poor RA outcomes, such as immunopositivity, structural damage progression or elevated DAS28. These factors have been identified in previous studies [23,24]. The association can be

Table 2
Results of the univariate analysis of the factors influencing a more rapid bDMARD initiation (Cox proportional-hazard models, performed on the 658 patients of the study).

Variables	HR	95% CI
Male sex	1.18	0.86–1.63
Age	0.98	0.97–0.99*
Age of first joint pain[a]	0.98	0.97–0.99*
Living in a couple relationship	0.64	0.44–0.93
At baseline		
DAS28	1.22	1.09–1.44*
RF	2.68	1.98–3.63**
ACPA[a]	3.36	2.47–4.57**
Joint pain at rest	1.00	0.99–1.01
Joint pain on mobilisation	1.01	1.00–1.01***
HAQ score	1.41	1.16–1.72*
Erosion score	1.59	1.12–2.25
ESR	1.01	1.00–1.02***
CRP level	1.46	1.10–1.95
Time to first rheumatologist visit	1.002	1.000–1.004
During follow-up		
HAQ score	2.46	2.01–2.31**
DAS28[a]	2.08	1.87–2.31**
Radiographic structural damage progression[a]	3.26	2.41–4.43**
ESR	1.03	1.02–1.04**
CRP level	1.01	1.00–1.01**
NSAIDs intake	2.03	1.46–2.82**
GC intake	3.31	2.40–4.56**
Analgesics intake	1.20	0.90–1.62
Grade 2 analgesics intake	1.41	1.03–1.92
Grade 3 analgesics intake	2.39	1.20–4.78***

bDMARD: biologic disease modifying anti-rheumatic drugs; DAS28: Disease Activity Score in 28 joints; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentary rate; CRP: C-reactive protein; NSAID: non-steroidal anti-inflammatory drug; GC: glucocorticoids; HR: hazard ratio; 95% CI: 95% confidence interval.

[a] Variables included in the multivariate analysis.

* $P < 0.01$.

** $P < 0.001$.

*** $P < 0.05$.

Table 3
Results of the multivariate analysis of the factors influencing a more rapid bDMARD initiation (Cox proportional-hazard models, performed on the 658 patients of the study).

Variable	HR	95% CI
Patient characteristics		
Age of first joint pain	0.97	0.96–0.98*
Disease characteristics		
Structural damage progression	2.35	1.68-3.29*
ACPA+	2.09	1.45-3.00*
DAS28	2.08	1.88-2.30*

bDMARD: biologic disease modifying anti-rheumatic drugs; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28: Disease Activity Score in 28 joints; HR: hazard ratio; 95%CI: 95% confidence interval.

* $P < 0.001$

explained by the fact that those factors are also associated with failure of csDMARDs (and in particular MTX) and that according to the last recommendations for management of early RA, the initiation of a biologic agent should be considered as early as possible with poor prognosis and csDMARD failure [7]. However, it is also to be recalled that, in the overall population of the study, the rate of positive RF or ACPA was relatively low compared to more recent RA cohorts, in which this rate is about 60-70% [25]. Therefore, it cannot be formally excluded that some seronegative patients included in this study, although meeting the ACR EULAR 2010 criteria, may in fact have other inflammatory rheumatic conditions.

In the present study, glucocorticoids and NSAID intake was associated with more rapid initiation of a biologic agent, which was consistent with previous findings [26]. Indeed, the prolonged use of anti-inflammatory treatments could reflect a more active and therefore more severe disease, requiring a more rapid bDMARD initiation to prevent RA progression.

We did not find any association between delayed initiation of bDMARDs and comorbidities, in particular cardiovascular or infectious comorbidities. This finding may be explained by the fact that patients included had low comorbidity rates: for example, diabetes frequency was 3.8% but is 6.0% in the French population [27,28]. It could also be explained by the adequate management of comorbidities in French settings, rendering them easily manageable even in candidates for bDMARDs.

Older age at the first symptom onset was the only negative protective factor identified in the present study, which can be explained by prescribers' reluctance to initiate bDMARDs in older patients. This finding is consistent with results of previous studies; indeed, in a German cohort study, patients < 35 years old had almost tenfold higher probability of receiving a bDMARD than those ≥ 65 years old (odds ratio 9.5, 95% CI: 8.0–11.3) [29]. In the same way, an American cohort study based on Truven's MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits found TNF inhibitor initiation associated with a predisposing factor of age, with an odds ratio of 0.98 (95% CI: 0.97–0.98) for each year increase [26]. However, unlike our study, these 2 studies were retrospective and with a shorter follow-up.

In this study, etanercept and adalimumab were the first prescribed biologic agents. These findings are consistent with bDMARD commercialization and French recommendations at the time of inclusion in the ESPOIR cohort [30]. However, similar results have been found in more recent studies, such as the retrospective cohort study performed by Steffen et al. in 2018, in which adalimumab and etanercept were the 2 most prescribed bDMARDs [29]. Thus, bDMARD preferences do not seem greatly changed during the last decade and are comparable between countries. This finding shows the persistence of rheumatologists' confidence in the efficacy and safety of these treatments [31,32].

This work has several strengths. The first is the large number of patients from 14 French regional centers with a long prospective follow-up representing the real-life management of early RA patients in France. Additionally, the possibility of unobserved confounding covariates was reduced, given the large number of baseline variables available in the ESPOIR cohort. Furthermore, to our knowledge, we lacked previous data describing the delay before introduction of the first biologic agent, in particular during a 10-year follow-up. The only comparable works were studies based on the British Society for Rheumatology Biologics Register database and the CORRONA registry in the United States [33,34], but the duration of follow-up was shorter than in the present study.

The main limitation of this work is that patients were included in ESPOIR cohort between 2002 and 2005 and that prescription patterns might have been influenced by the standards of care at that time. However, as seen previously, these patterns do not seem to have greatly changed during the last decade.

In conclusion, this study found that less than one third of patients with early RA initiated a bDMARD during a 10-year follow-up and that the delay from the first symptoms to the first biologic agent intake was affected by factors associated with poor outcomes in RA. These findings are consistent with the latest recommendations for RA management, because the same profiles are the most at risk of csDMARD failure. An evaluation of the impact of early bDMARD initiation on structural damage progression is needed in real-life studies.

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None to declare.

Contributions of authors

The authors participated as follows in the study:
Design of the study: B.F., BC., C.G.V., A.C.R.
Statistical analysis: B.G., S.E., J.K.
Redaction of the manuscript: J.K., S.E., B.G., B.F.
Critical review of the manuscript: B.C., C.G.V., A.C.R.

Disclosure of interest

J.K., B.G., S.E. declare that they have no competing interest.

CGV: has received honoraria from Abbvie, Amgen, BMS, Celgene, Gilead, Janssen, Lilly, Medac, MSD, Mylan, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi, UCB.

BC: has received consulting fees from AbbVie, BMS, Eli-Lilly, Gilead, Janssen, Merck, Novartis, Pfizer, Roche-Chugai, Sanofi, UCB.

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Appendix A. Supplementary data

Supplementary data (Doc S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2020.07.009.

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