RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/key122

Effect of cumulative exposure to corticosteroid and DMARD on radiographic progression in rheumatoid arthritis: results from the ESPOIR cohort

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Abstract

Objectives. Several authors have tried to predict the risk of radiographic progression in RA according to baseline characteristics, considering exposure to treatment only as a binary variable (Treated: Yes/No). This study aims to model the risk of 5-year radiographic progression taking into account both baseline characteristics and the cumulative time-varying exposure to corticosteroids or DMARDs.

Methods. The study population consisted of 403 patients of the Etude et Suivi des Polyarthrites Indifférenciées Récentes cohort meeting the 1987 ACR or 2010 ACR/EULAR criteria for RA at inclusion and having complete radiographic data at baseline and 5 years. Radiographic progression was defined at 5 years as a significant increase of the Sharp/van der Heidje score (smallest detectable difference $\geqslant 5$). The best logistic regression model was selected from the following: model including only clinico-biological baseline characteristics; model considering baseline characteristics and treatments as binary variables; and model considering baseline characteristics and treatments as weighted cumulative exposure variables.

Results. Radiographic progression occurred in 143 (35.5%) patients. The best model combined anti-citrullinated peptide antibody positivity, ESR, swollen joint count >14 and erosion score at baseline, as well as corticosteroids, MTX/LEF (MTX or LEF) and biologic DMARDs (bDMARDs) as weighted cumulative exposure variables. Recent cumulative exposure to high doses of corticosteroids ($\leqslant$ 3months) was significantly associated with the risk of 5-year radiographic progression and a significant protective association was highlighted for a 36-month exposure to bDMARDs.

Conclusion. Corticosteroids and bDMARDs play an important role in radiographic progression. Accounting for treatment class and intensity of exposure is a major concern in predictive models of radiographic progression in RA patients.

Key words: rheumatoid arthritis, corticosteroids, DMARDs (biologic), DMARDs (synthetic), epidemiology, pharmacology, statistics

CLINICAL SCIENCE

Rheumatology key messages

- Considering cumulative exposure to treatments in predictive models of radiographic progression in RA is a key concern.
- Long-term cumulative exposure to biologic DMARDs is associated with a better 5-year radiographic progression in RA.
- Short-term cumulative exposure to corticosteroids is associated with a worse 5-year radiographic progression in RA.

Introduction

RA is a chronic inflammatory disease responsible for functional disability and severe joint damages. In France, its prevalence is ~0.3% [1].

Medical treatment of RA can be divided into use of two categories of drugs [2–5]: symptomatic medication and DMARDs. Early initiation of DMARDs concomitantly with rapid medical care is highly recommended to prevent serious clinical consequences and to induce remission in some situations [2, 6, 7].

During the past few years, therapeutic management has greatly improved with the development of biological

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Submitted 9 December 2017; revised version accepted 4 April 2018

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DMARDs (bDMARDs) [8–10] providing a noteworthy answer for patients responding insufficiently to conventional synthetic DMARDs (csDMARDs). MTX and LEF are csDMARDs currently used as first line agents, and bDMARDs should be started in combination with MTX in patients showing an insufficient response to csDMARD strategies [2, 7, 11, 12].

The EULAR treat-to-target recommendations have recently been updated, promoting a strategic approach to achieving low-disease activity or remission in routine clinical practice. Maximizing long-term health-related quality of life, controlling structural damage and preventing functional disability are major concerns in the medical strategy for managing RA [2].

Several authors have studied baseline predictive factors potentially associated with various outcomes in RA. Nevertheless, most of them did not take into account therapeutic regimens at all [13, 14] or considered drug exposure as a binary variable (Treated: Yes/No) or as a mean dose [15–20]. If the risk of radiographic progression is related to factors of severity of the disease at diagnosis [2, 7], it is also related to therapeutic management, underlining the need for predictive models integrating treatment variables that reflect the complexity of drug exposure.

Considering drug exposure as a time-dependent factor is a first step but non-immediate effects, extended effects or discontinuation of treatment have also to be taken into account [21–23]. Recently, an analytical method has been developed to model cumulative drug exposure and its influence on the event risk. This method represents the drug intake history as a weighted cumulative exposure (WCE) [21]. Such a variable can be built from available data, without any pharmacokinetic (PK) or pharmacodynamic (PD) *a priori* hypothesis. Intensive simulations have shown its capacity to model drug exposures presenting a complex profile and to assess their effect on an event risk [24]. Dixon *et al.* [25] have used this WCE model to determine the impact of corticosteroids on the risk of serious infections among RA patients. No study has yet used this approach to assess radiographic progression.

From the data of the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) inception cohort, which enrolled patients with early arthritis, we aimed to develop a predictive model of the risk of 5-year radiographic progression. To this end, we compared the performance of three approaches. The first approach considered only baseline clinical and/or biological characteristics, the second considered both baseline characteristics and treatments as binary variables and the third considered both baseline characteristics and treatments as WCE variables. The best predictive model was then used to describe the association between the risk of radiographic progression and variables of interest.

Methods

Study population

The ESPOIR cohort is a French multicentre cohort composed of 813 patients included between December 2002 and March 2005 with RA or undifferentiated arthritis susceptible to evolving as RA [26]. Inclusion criteria were age 18–70 years, two or more swollen joints for >6 weeks and evolving for <6 months, suspected or confirmed diagnosis of RA and no DMARDs or corticosteroids intake for >2 weeks before enrolment.

The ESPOIR cohort study was approved by the ethics committee of Montpellier University Hospital, France in July 2002. Our study was approved by the scientific committee of the ESPOIR cohort, and additional ethical approval was not required. All included patients gave their signed informed consent.

The study sample consisted of patients included in the ESPOIR cohort classified as RA at the inclusion visit according to the 1987 ACR and 2010 ACR/EULAR criteria and who had radiographic data both at inclusion visit and at 5 years of follow-up.

Data collection

Clinical, biological and radiological data

Patients were followed by a rheumatologist every 6 months during the first 2 years and every 12 months during the eight remaining years (total follow-up: 10 years). Clinical data were assessed at each visit. Biological and radiological data were collected concomitantly.

Treatment data

Therapeutic strategy information was collected at each visit. Initiation and discontinuation (if applicable) dates, posology and route of administration were detailed for oral corticosteroids and all DMARD prescriptions including csDMARDs (MTX either injectable or *per os*, LEF, SSZ and HCQ) and bDMARDs (adalimumab, etanercept, infliximab, rituximab, tocilizumab and abatacept). Treatment decisions were not protocol-based in the ESPOIR cohort and patients received usual care from their rheumatologist.

Oral corticosteroid data were converted to daily prednisone equivalent dosage (PEQ).

DMARD doses were quantified consistently with Defined Daily Doses [27]. Each observed posology was expressed as a common dose quotient (DoseQ, i.e. the ratio between the received dose and the recommended dose of each drug) unit (see supplementary Table S1, available at *Rheumatology* online), in order to standardize the exposure to different drugs.

In addition, all bDMARDs (adalimumab, etanercept, infliximab, rituximab, tocilizumab and abatacept) were considered as unique exposure bDMARDs. Similarly, MTX and LEF were gathered together as MTX/LEF due to their equivalent symptomatic and structural efficacy [28]. Other csDMARDs (SSZ and HCQ) were considered separately.

Outcome definition

Radiographic data were collected in the radiography coordinating centre and were evaluated in chronological order following a multireader assessment blinded to clinical parameters and treatments received [29]. Radiographic progression was assessed and quantified according to the

Sharp/van der Heidje score (SHS) based on the observation of typical RA erosion on 22 joints (erosion score) and of joint space narrowing on 21 joints [30–32].

According to the smallest detectable difference, significant radiographic progression was defined at 5 years as a change in SHS (ΔSHS) $\geqslant 5$ [33, 34].

Statistical analysis

Patient and baseline characteristics were described in terms of mean (S.D.) for quantitative variables and in terms of number (%) for qualitative variables.

Drug exposure modelling

Two different approaches were considered to represent drug exposures. First, drug exposures (corticosteroids, MTX/LEF, bDMARDs, etc.) were represented as binary indicator variables (Treated: Yes/No at any time during the follow-up) as in the previously published articles (the classical approach). Second, drug exposures were represented as the weighted sum of past doses with WCE variables:

$$\mathrm{WCE}(u) = \sum_{t=u-a}^{u} w(u-t)X(t)$$

where u is the current time (when the risk of event is assessed); $X(t)$ is the dose taken at time t, $w(u-t)$ is the function weighting the importance of this dose as a function of time elapsed between t and u and a is the time window during which the treatment can have a non-null effect (outside this time window, $w = 0$).

As PK and PD characteristics of treatments are rarely known in the study population, Abrahamowicz and colleagues [21] have developed a flexible WCE model approach in which the weight function w and the time window a are set with the available data. Cubic splines were used to estimate the weight function, as they allow representation of a variety of clinically plausible shapes [21]. Contrary to the classical approach, this approach is able to represent a cumulative exposure to treatment with full consideration of kinetic parameters. The number of knots of the cubic splines equation was chosen using the Akaike information criterion (AIC). The AIC was also used to select the best time windows among various possibilities ($a \in$ 12, 18, 36 or 60 months). Simulation studies have demonstrated that this method is flexible enough to model various shapes, and that the AIC has correct performance in selecting the model parameters [24].

Predictive model development

Logistic regression was used to develop the predictive model of 5-year radiographic progression.

Three multivariate models were successively built.

Firstly, a baseline clinical model was built including only clinical and/or biological baseline characteristics. Univariate analysis was realized by means of the Mann–Whitney test (quantitative variables) and Fisher's exact test (qualitative variables). The assumption of linearity of quantitative variables was tested and a categorization was performed if needed according to clinical and statistical relevance. All baseline variables with $P \leqslant 0.25$ were considered candidates for inclusion into the multivariate model. A conventional forward stepwise procedure was performed to choose the variables included in the model, based on the minimization of the AIC.

Secondly, a classical combined model was built including previously selected baseline characteristics and the same treatment variables as in the WCE combined model (see above), but considered as simple binary variables (Treated: Yes/No at any time during the follow-up).

Thirdly, a WCE combined model was built including previously selected baseline characteristics and drug exposure defined in the section 'Treatment data' as WCE variables.

Final baseline characteristics selected in the baseline clinical model were forced into the classical combined model and the WCE combined model. Then, all treatments previously described were considered candidates for inclusion in the multivariate model. Drug exposure predictors were selected with a conventional forward stepwise procedure, based on the minimization of the AIC.

Performance of the baseline clinical, classical combined and WCE combined models was evaluated and compared with the receiver operating characteristic curve and calculation of the area under the curve (AUC) and its 95% CI.

Calibration of all models was assessed by the Hosmer–Lemeshow test comparing expected and observed event rates in subgroups. A model is considered well calibrated in the case of no significant difference. All statistical analyses were performed with R 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Significance was defined as $P \leqslant 0.05$.

Results

Descriptive analysis

From the 813 patients included in the ESPOIR cohort, 697 (85.7%) met the 1987 ACR or 2010 ACR/EULAR criteria at inclusion visit. These 697 patients were comparable to the rest of the cohort in terms of age, sex, ethnical origin, time elapsed since first joint pain, disease emerging type, biological inflammation, haemoglobinaemia, functional disability and disease activity. However, mean DAS28 score, tender joint count and swollen joint count were higher and anti-citrullinated peptide antibodies (ACPA) and RF positivity were more frequent (supplementary Table S2, available at *Rheumatology* online).

Four hundred and three (57.8%) patients who met the 1987 ACR or 2010 ACR/EULAR criteria at inclusion visit had radiographic data both at inclusion visit and at 5 years of follow-up. Baseline characteristics and number of patients exposed to corticosteroids and DMARDs among these 403 patients are presented in Table 1. Mean baseline SHS was 3.3 (5.2) (median 2.0) and mean structural progression assessed by SHS was 6.04 (9.96) (median 2.5). Radiographic progression (ΔSHS $\geqslant 5$) occurred in 143 (35.5%) patients with a mean SHS progression of 15.0 (12.2) (median 10.5). In the 260 (64.5%)

Table 1 Baseline characteristics of study population

Characteristic	Patients who met the 1987 ACR or 2010 ACR/EULAR criteria at inclusion with available radiographic data (*n* = 403)
Age, mean (S.D.), years	48.9 (11.2)
Female sex, *n* (%)	318 (78.9)
Caucasian origin, *n* (%)	385 (95.5)
Disease emerging type, *n* (%)	
Explosive	98 (24.3)
Subacute	107 (26.6)
Insidious	162 (40.2)
Paroxystic	36 (8.9)
Tender joint count in 28 joints, median (IQR)	7 (4–13)
Swollen joint count in 28 joints, median (IQR)	7 (4–11)
Time elapsed since first joint pain, mean (S.D.), days	241.5 (283.6)
Haemoglobinaemia, mean (S.D.), g/dl	12.9 (1.3)
CRP, mean (S.D.), mg/l	21.9 (35.9)
ESR, mean (S.D.), mm/h	29.7 (24.3)
DAS28 score, mean (S.D.)	5.3 (1.3)
IgM RF positivity, *n* (%)	221 (54.8)
IgA RF positivity, *n* (%)	213 (52.9)
ACPA positivity, *n* (%)	201 (49.9)
HAQ score, mean (S.D.)	1.0 (0.7)
Erosion score, mean (S.D.)	2.4 (3.6)
SHS, mean (S.D.)	3.3 (5.2)
Treatment received during the follow-up, *n* (%)	
Corticosteroids	279 (69.2)
MTX	317 (78.7)
LEF	88 (21.8)
SSZ	82 (20.3)
HCQ	86 (21.3)
Adalimumab	66 (16.4)
Etanercept	69 (17.1)
Infliximab	11 (2.7)
Rituximab	23 (5.7)
Abatacept	7 (1.7)
Tocilizumab	7 (1.7)

Baseline CRP level (normal <10 mg/l), IgM and IgA RF (positive >9 UI/ml) and ACPA (positive >50 UI/ml) were detected in the same laboratory (Bichat Hospital, Paris). Treatments received refer to the number of patients with at least one intake history of the designated molecule. SHS: Sharp/van der Heidje score.

patients with no radiographic progression, mean SHS progression was 1.1 (2.0) (median 1.0).

These 403 patients comprising our study sample were more likely to be Caucasian, ACPA positive and have a higher time elapsed since first joint pain compared with the patients who met the 1987 ACR or 2010 ACR/EULAR criteria with no available radiographic data (supplementary Table S2, available at *Rheumatology* online). No significant differences were found for others listed variables.

Baseline predictors of baseline clinical model

Results of univariate analysis are presented in Table 2. Univariate analysis of baseline characteristics led to 11 candidate variables for inclusion in the multivariate model. DAS28 showed no significance in univariate analysis neither as a four-levels variables ($P = 0.49$) nor as a binary variables ($P = 0.23$). The multivariate baseline clinical model included 4 variables: ACPA status, ESR, swollen joint count (as categorical variable) and erosion score. Adjusted odds ratio (OR) and 95% CI for baseline characteristics are presented in Table 2. Receiver operating characteristic curve analysis showed a moderate discriminative ability of the model with an AUC (95% CI) of 0.702 (0.647, 0.756) (Fig. 1). The hypothesis of correct calibration of the model was not rejected by the Hosmer–Lemeshow test ($P = 0.28$).

Baseline and drug exposure predictors of classical combined model and WCE combined model

The results for the development and selection of WCE variables are detailed in supplementary data, section

TABLE 2 Association between baseline characteristics of patients and 5-year radiographic progression

Variables	With radiographic progression ($n = 143$)	Without radiographic progression ($n = 260$)	OR (95% CI), univariate analysis	*P*-value (Wald test)	Adjusted OR (95% CI), multivariate analysis	*P*-value
Age >40 years	118 (82.5)	199 (76.5)	1.45 (0.87, 2.46)	**0.16**		
Male sex	31 (21.7)	54 (20.8)	1.06 (0.64, 1.73)	0.83		
Caucasian origin	139 (97.2)	246 (94.6)	1.98 (0.69, 7.08)	**0.24**		
Disease emerging type						
Explosive	31 (21.7)	67 (25.8)	Reference	0.73		
Subacute	42 (29.4)	65 (25.0)	1.40 (0.79, 2.50)			
Insidious	57 (39.9)	105 (40.4)	1.17 (0.69, 2.01)			
Paroxystic	13 (9.1)	23 (8.9)	1.22 (0.54, 2.70)			
Swollen joint count in 28 joints >14	26 (18.2)	28 (10.8)	1.84 (1.03, 3.29)	**0.04**	2.06 (1.09, 3.86)	**0.02**
Tender joint count in 28 joints, mean (S.D.)	9.2 (7.4)	9.1 (7.0)	1.00 (0.97, 1.03)	0.91		
Time elapsed since first joint pain ⩾150 days	81 (56.6)	135 (51.9)	1.21 (0.80, 1.83)	0.36		
Anaemia	43 (30.1)	53 (20.5)	1.67 (1.04, 2.67)	**0.03**		
CRP ⩾10 mg/l	80 (55.9)	111 (42.7)	1.79 (1.19, 2.72)	**0.006**		
ESR, mean (S.D.), mm/h	34.7 (26.3)	26.9 (22.6)	1.01 (1.00, 1.02)	**0.003**	1.01 (1.00, 1.02)	**0.04**
IgM RF positivity	97 (67.8)	124 (47.7)	2.31 (1.52, 3.57)	<**0.001**		
IgA RF positivity	92 (64.3)	121 (46.5)	2.07 (1.37, 3.17)	<**0.001**		
ACPA positivity	94 (65.7)	107 (41.2)	2.74 (1.80, 4.22)	<**0.001**	2.86 (1.83, 4.53)	<**0.001**
DAS28 score						
<2.6	1 (0.7)	5 (2.0)	Reference	0.49*		
2.6–3.2	5 (3.6)	8 (3.1)	3.13 (0.35, 69.50)			
3.2–5.1	52 (36.9)	108 (42.4)	2.41 (0.38, 46.75)			
>5.1	83 (58.9)	134 (52.6)	3.10 (0.49, 59.89)			
HAQ score ⩾1	79 (55.2)	119 (45.8)	1.46 (0.97, 2.21)	**0.07**		
Erosion score, mean (S.D.)	3.5 (4.7)	1.8 (2.7)	1.15 (1.08, 1.23)	<**0.001**	1.15 (1.08, 1.24)	<**0.001**
SHS, mean (S.D.)	4.8 (6.8)	2.5 (3.9)	1.10 (1.05, 1.15)	<**0.001**		

Data are *n* (%) unless otherwise stated. Baseline CRP level (normal <10 mg/l), IgM and IgA RF (positive >9 UI/ml) and ACPA (positive >50 UI/ml) were detected in the same laboratory (Bichat Hospital, Paris). Bold *P*-values indicate candidate variables for multivariate analysis ($P \leqslant 0.25$). *P-values for DAS 28 score as binary variable (>5.1 *vs* ⩽5.1) was 0.23. SHS: Sharp/van der Heidje score.

'Drug exposure predictors selection', available at *Rheumatology* online.

The drug exposure predictors finally included in the classical combined model and the WCE combined model were corticosteroids, MTX/LEF and bDMARDs. Baseline predictors of radiographic progression (ACPA status, ESR, swollen joint count and erosion score) were also included in these models. The hypothesis of correct calibration was not rejected by the Hosmer–Lemeshow test ($P = 0.32$). Despite the overlap of AUC 95% CIs, the WCE combined model [AUC (95% CI): 0.757 (0.705, 0.808)] showed a better discriminative ability than the baseline clinical model [AUC (95% CI): 0.702 (0.647, 0.756)] and the classical combined model [AUC (95% CI): 0.721 (0.668, 0.774)] (Fig. 1).

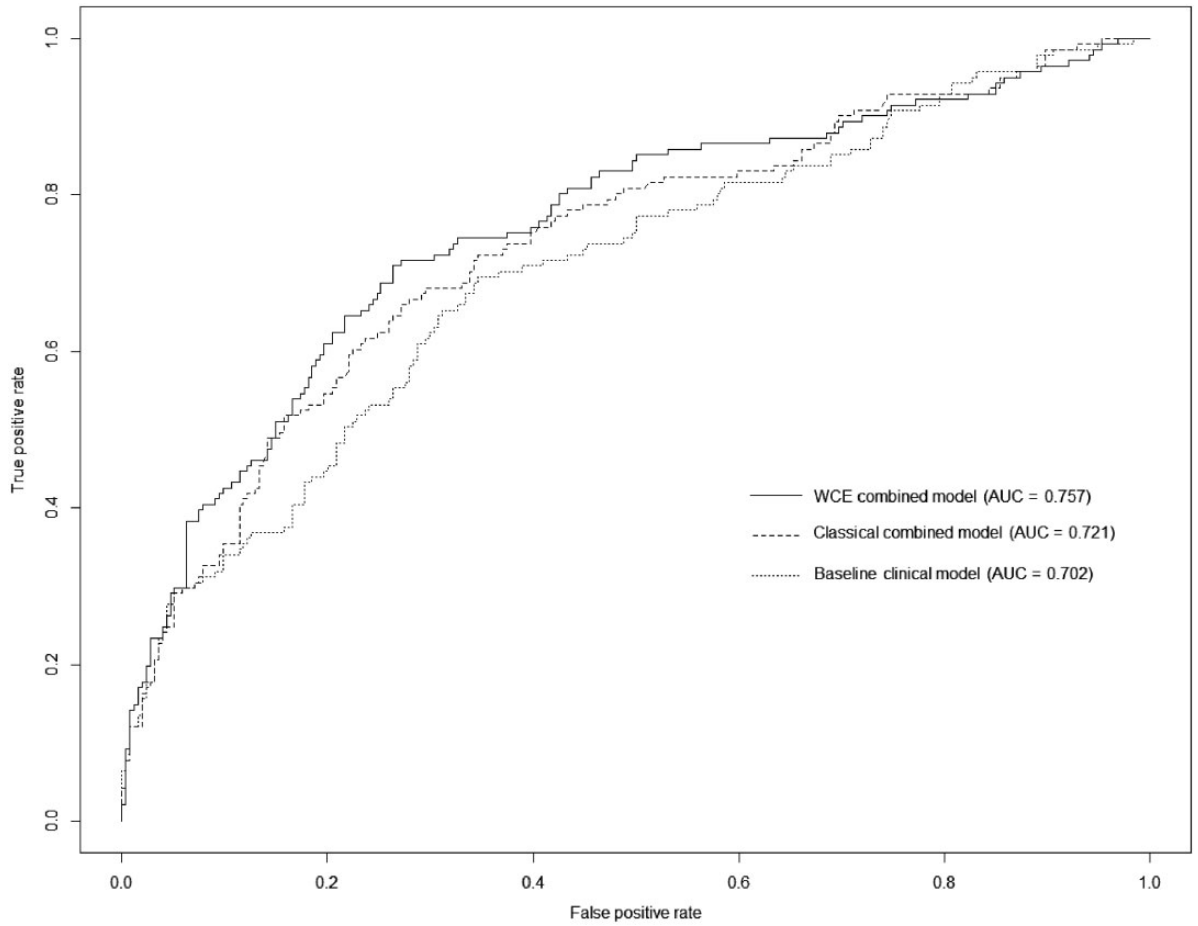
Odds ratios for the association between predictor variables and radiographic progression from the classical combined model and WCE combined model are presented in Table 3. From the WCE combined model, recent doses (⩽3 months) of corticosteroids were significantly associated with a higher risk of radiographic progression, with the risk increasing with the doses (Fig. 2). For instance, OR for 5 mg PEQ daily intake during the previous month was thus lower than OR for 20 mg PEQ daily intake during the previous 3 months [OR (95% CI): 1.05 (1.01, 1.10) *vs* 3.87 (1.04, 14.40)]. MTX/LEF intake was not significantly associated with the risk of radiographic progression.

Finally, an overall protective association of bDMARDs on 5-year radiographic progression, which was only statistically significant for 36 months' use of bDMARDs [OR (95% CI): 0.15 (0.03, 0.69)], was observed.

Discussion

In this article, we have developed a predictive model assessing the risk of 5-year radiographic progression in RA patients, including both baseline characteristics and

Fig. 1 Receiver operating characteristic curves associated with the three developed models



Receiver operating characteristic curves assessing the performance of baseline clinical model, classical combined model and WCE combined model for 5-year radiographic progression. AUC: area under curve; WCE, weighted cumulative exposure.

cumulative drug exposure to corticosteroids and DMARDs. This model had the best performance compared with a model taking into account baseline characteristics only, or a model taking into account drug exposures as simple binary covariates.

The ESPOIR cohort was an appropriate database with which to perform such a study because of its community-based nature. Thus, it provided medical data more representative of daily medical practice than randomized clinical trials. Characteristics of the subjects are consistent with previous studies [1, 35]. The principal interest of the ESPOIR cohort was that therapeutic regimens were not protocol-based and patients received treatment with respect to usual care and current recommendations. Moreover, exhaustive registration of treatments prescribed during the follow-up provided a considerable asset for studying drug exposure.

We decided to focus on patients presenting the 1987 ACR or 2010 ACR/EULAR criteria from the inclusion visit. As the ESPOIR cohort included patients with RA or undifferentiated arthritis susceptible to evolve as RA, the aim was to select a homogeneous population to limit the indication bias. Treatment with DMARDs in patients with early undifferentiated arthritis is indeed very likely to be influenced by unidentified factors [36].

To our knowledge, this is the first study to present a predictive model in RA combining baseline variables and treatment exposure during the follow-up described as WCE variables. This innovative method allowed the expression of therapeutic regimens as time-dependent variables. The predictive models developed so far have only considered therapeutic regimens as binary variables or as treatment strategies [15, 16, 18–20], resulting in a considerable loss of information and exposure misclassification.

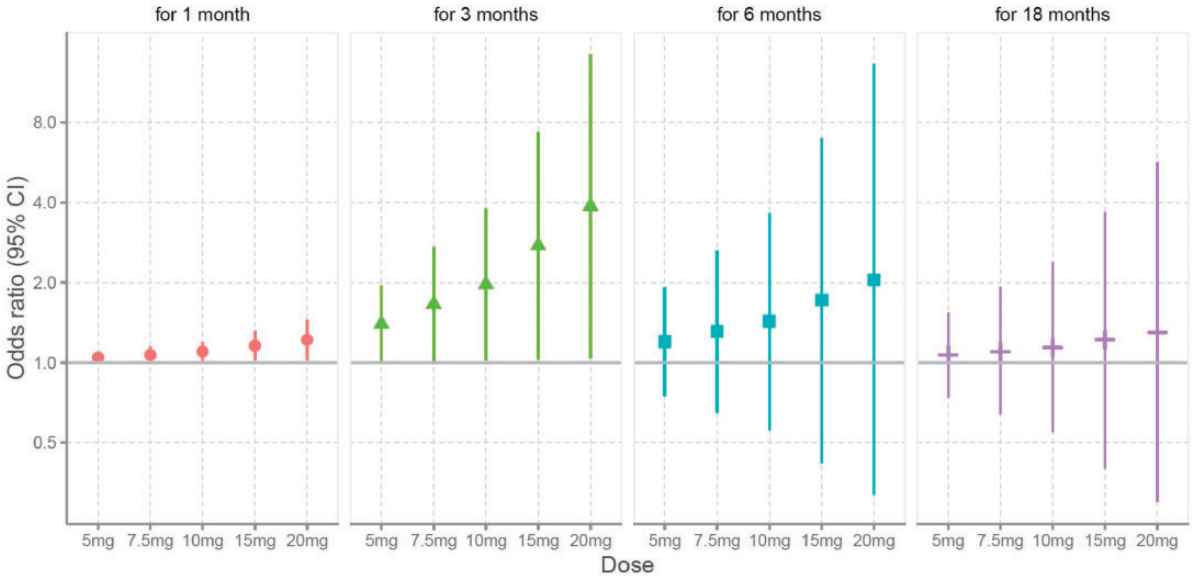
Using the Orencia and Rheumatoid Arthritis register, Salmon *et al.* [15] have tried to determine predictive factors of serious infection among RA patients treated with abatacept. The Cox model did not take into account the presence of concomitant treatment such as corticosteroids. Their influence has been secondarily studied with a univariate analysis on mean doses. Yet, a mean dose does not reflect adequately the effect of a

Table 3 Odds ratio for the association of baseline variables and patterns of drug regimen with 5-year radiographic progression

Variables	Pattern use		Reference	Adjusted OR (95% CI)
WCE combined model				
Baseline variables				
ACPA positivity	—		—	2.72 (1.63, 4.60)
ESR, mm/h	—		—	1.01 (1.00, 1.02)
Swollen joint count >14	—		—	2.14 (1.09, 4.22)
Erosion score	—		—	1.16 (1.08, 1.25)
Treatment variables				
MTX/LEF	Current user	1 DoseQ, for past month	Non-user	0.99 (0.98, 1.00)
		1 DoseQ, for past 3 months		0.89 (0.77, 1.02)
		1 DoseQ, for past 12 months		0.54 (0.21; 1.41)
		1 DoseQ, for past 24 months		1.98 (0.72, 5.43)
		1 DoseQ, for past 36 months		2.07 (0.71, 6.05)
		1 DoseQ, for past 60 months		0.90 (0.38, 2.18)
bDMARDs	Current user	1 DoseQ, for past month	Non-user	0.99 (0.98, 1.00)
		1 DoseQ, for past 3 months		0.93 (0.82, 1.05)
		1 DoseQ, for past 12 months		0.44 (0.13, 1.48)
		1 DoseQ, for past 24 months		0.17 (0.03, 1.09)
		1 DoseQ, for past 36 months		**0.15 (0.03, 0.69)**
		1 DoseQ, for past 60 months		0.59 (0.14, 2.38)
Corticosteroids	Current user	5 mg, for past month	Non-user	**1.05 (1.01, 1.10)**
		7.5 mg, for past month		**1.07 (1.01, 1.15)**
		10 mg, for past month		**1.10 (1.01, 1.20)**
		15 mg, for past month		**1.16 (1.02, 1.32)**
		20 mg, for past month		**1.22 (1.02, 1.45)**
		5 mg, for past 3 months		**1.40 (1.01, 1.95)**
		7.5 mg, for past 3 months		**1.66 (1.01, 2.72)**
		10 mg, for past 3 months		**1.97 (1.02, 3.79)**
		15 mg, for past 3 months		**2.76 (1.03, 7.39)**
		20 mg, for past 3 months		**3.87 (1.04, 14.40)**
		5 mg, for past 6 months		1.20 (0.75, 1.91)
		7.5 mg, for past 6 months		1.31 (0.65, 2.64)
		10 mg, for past 6 months		1.43 (0.56, 3.64)
		15 mg, for past 6 months		1.72 (0.42, 6.96)
		20 mg, for past 6 months		2.05 (0.32, 13.28)
		5 mg, for past 18 months		1.07 (0.74, 1.54)
		7.5 mg, for past 18 months		1.10 (0.64, 1.92)
		10 mg, for past 18 months		1.14 (0.55, 2.38)
		15 mg, for past 18 months		1.22 (0.40, 3.68)
		20 mg, for past 18 months		1.30 (0.30, 5.67)
Classical combined model				
Baseline variables				
ACPA positivity	—		—	2.00 (1.22, 3.27)
ESR, mm/h	—		—	1.01 (1.00, 1.02)
Swollen joint count >14	—		—	1.93 (1.01, 3.69)
Erosion score	—		—	1.17 (1.09, 1.26)
Treatment variables				
MTX/LEF	Treated at any time		Non-user	1.97 (0.89, 4.36)
bDMARDs	Treated at any time		Non-user	**1.98 (1.20, 3.28)**
Corticosteroids	Treated at any time		Non-user	1.34 (0.79, 2.26)

For WCE variables, we assessed the adjusted OR associated with different patterns of cumulative drug exposure during different time windows. The first column identifies the drug, the second describes a clinically coherent pattern of drug use in RA, the third describes the comparator pattern of drug exposure and the fourth presents the adjusted OR and 95% CI. DoseQ (dose quotient) is the ratio between the received dose and the recommended dose of each drug. For example, 1 DoseQ for past month means that the patient has used the full recommended dose for the entire last month before radiographic progression. Bold OR indicates a significant association of drug exposure with 5-year radiographic progression. bDMARDs: biological DMARDs; DoseQ: dose quotient; OR: odds ratio; WCE, weighted cumulative exposure.

Fig. 2 Adjusted odds ratio associated with different patterns of cumulative corticosteroid exposure



Adjusted odds ratio (OR) and 95% CI for different patterns of cumulative corticosteroid exposure on the risk of 5-year radiographic progression (multivariate analysis, weighted cumulative exposure combined model). High and recent doses of corticosteroids are significantly associated with a higher risk of radiographic progression.

corticosteroid treatment: high doses of corticosteroids on a short time scale don't affect the infection risk in the same way as low doses on a much longer time scale.

Fautrel *et al.* [18] have built a rapid radiographic progression (defined as a radiographic progression at 1 year from the diagnosis) predictive matrix on MTX- or leflunomide-treated patients using a multivariate logistic regression. The influence of concomitant treatments on the prognosis has not been studied. In a *post hoc* analysis of the BeSt study, Visser *et al.* [16] have built a rapid radiographic progression predictive model. Treatments have only been taken into account in terms of initial therapeutic strategy adopted. The performance of these two previous models has been discussed and a poor discriminatory capacity has been highlighted [37]. Finally, Combe *et al.* [19] and Gaujoux-Viala *et al.* [20] have studied the disease progression in the ESPOIR cohort but treatments have been analysed as Boolean variables at baseline only.

Regarding performance assessment, including baseline and WCE variables provided the best performances. Although AUCs were not substantially different, these results confirm the interest of WCE models for pharmacoepidemiological studies [23, 25]. Classical modeling of exposure (mean doses, Treated: Yes/No, etc.) may lead to inappropriate conclusions regarding the association between drug exposure and the outcome [24, 36]. Flexible WCE models bring more clinically plausible conclusions and represent an important step in better understanding of the relationship between treatments (DMARDs and corticosteroids) and radiographic progression in real life studies. Indeed, this methodology allows the consideration of a time-dependent exposure and the evaluation of risk associated with a vast number of patterns of drug exposure. Moreover, it permits the comparison of same dose intakes but taken for different duration or at different times with respect to the event of interest. Recently, Robinson *et al.* [38] have highlighted the assets of these WCE models in defining glucocorticoid exposure when investigating the risk of fracture in RA patients.

Baseline characteristic variables associated with radiographic progression in our final multivariate model are consistent with previous studies [14, 16, 18]. The effects of bDMARDs in preventing structural damage progression in RA patients were also consistent with the literature [28, 39–42].

If the protective association, observed in clinical trials, of bDMARDs with radiographic progression has been confirmed with the WCE combined model, the beneficial effect of low-dose corticotherapy in preventing radiographic progression demonstrated in clinical trials in RA patients [43–46] has not been observed in our study. On the contrary, a significant deleterious association was found between recent ($\leqslant$3 months) cumulative exposure to corticosteroids and risk of 5-year radiographic progression. This association increases concomitantly with higher doses of corticosteroids. Our results can be explained by the gap between clinical trials and daily life clinical practices in which corticosteroids are more likely to be prescribed in elderly patients with comorbidities and more severe RA disease activity. Indeed, this particular population is more likely to present contraindications to DMARDs, resulting in a corticotherapy prescription by default and inducing thereby an indication bias. This deleterious association of recent doses of corticosteroids may also be the expression of a recent initiation of a

treatment consequent to a disease progression. This leads to a phenomenon of confounding by indication, and interpretations must be made with caution. Nevertheless, the beneficial role of glucocorticoids in RA is subject to rheumatology expert review reservations [2, 47, 48].

Our observational study has some limitations. The ESPOIR cohort provides data on prescribed drugs but the real compliance could not be assessed. Consequently, true effects of drug exposures may have been underestimated.

Regarding treatments analyses, additional symptomatic treatments and especially NSAID self-medication, were not collected with enough precision in the ESPOIR cohort to allow adjustment on these treatments. Moreover, some drugs with a close mechanism of action were gathered together and considered as a unique variable. The separate study of each molecule would be interesting, but would require a much larger sample size to correctly model each exposure.

Even if our final models took into account determinants and well-known baseline characteristics, time-varying confounding is an important point that must be taken into consideration. Thus, OR associated with WCE variables must be interpreted carefully as unobserved time-varying confounding factors such as disease activity, erosion score or ESR during the follow-up were not accounted for in our analysis of the ESPOIR cohort. Such an analysis would require a more regular and exhaustive clinical data collection during follow-up and a larger sample size.

Conclusion

Our study has highlighted the importance of accounting for treatments in predictive models of radiographic progression in RA patients and the advantage of WCE modelling, which leads to slightly better risk prediction and better describes the effect of different profiles of cumulative exposure to treatment. Using this method, an overall protective association of bDMARDS and a deleterious association of corticosteroids with radiographic progression was described using a database representative of daily medical practice. Nevertheless, these results have to be considered with moderation due to limitations of the analysis (confounding by indication resulting from corticosteroid prescription in flaring patients or when the disease is uncontrolled) and further studies are needed to confirm these observations.

Acknowledgements

We wish to thank Nathalie Rincheval (Centre Hospitalo-Universitaire Montpellier and Equipe d'accueil 2415), who performed expert monitoring and data management of the ESPOIR cohort, and all the investigators who recruited and followed the patients (F. Berenbaum, Paris-Saint Antoine, M. C. Boissier, Paris-Bobigny, A. Cantagrel, Toulouse, B. Combe, Montpellier, M. Dougados, Paris-Cochin, P. Fardelone and P. Boumier, Amiens, B. Fautrel, Paris-La Pitié, R. M. Flipo, Lille, Ph. Goupille, Tours, F. Liote, Paris-Lariboisière, O. Vittecoq, Rouen, X. Mariette, Paris Bicetre, O. Meyer and Ph. Dieude, Paris Bichat, A. Saraux, Brest, Th. Schaeverbeke, Bordeaux, J. Sibilia, Strasbourg). We also wish to thank A. Fradin, Poitiers, M. Afshar, Bondy, M. Couderc, Clermont-Ferrand, L. Biale, Saint Mande, J. D. Albert, Rennes, E. Constant, Saint Etienne, D. Denarie, Saint-Etienne, V. Martaille, Orleans, A. Pierreisnard, Paris-La Pitié, N. Poursac, Bordeaux, for expert X-ray reading.

Funding: This work was supported by the Interdisciplinary research programme on health crisis and health protection (PRINCEPS) of Sorbonne Paris Cité University, within the programme 'Investissements d'Avenir' launched by the French State.

The ESPOIR cohort was supported by an unrestricted grant from Merck Sharp and Dohme (MSD) for the first 5 years of the ESPOIR cohort study. Support was also provided by the French Society of Rheumatology, Pfizer, Abbvie and Roche-Chugai. Two additional grants from INSERM were obtained to support part of the biological database of this cohort.

Disclosure statement: B.F. has declared consulting fees from AbbVie, Biogen, Bristol Myers Squibb, Celgène, Hospira, Janssen, Lilly, Medac, MSD, NORDIC Pharma, Pfizer, Roche, SOBI, Union Pharmaceutique Belge and research grants from AbbVie, MSD, Pfizer. F.G. has declared research grants from Abbvie, Expansciences, Sanofi. A.S. has declared research grants from Abbvie, Bristol Myers Squibb, Lilly, MSD, Novartis, Pfizer, Roche-Chugai, UCB. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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