Factors determining a DMARD initiation in early inflammatory arthritis patients. The ESPOIR cohort study

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Abstract

Background

To describe the rate and timing of DMARD start in patients with early inflammatory arthritis in France, and to determine the factors leading to this treatment start.

Methods

The ESPOIR cohort study collects data on patients presenting with early arthritis. Baseline characteristics were assessed, and Cox regression analysis was performed to estimate the likelihood of starting DMARD treatment over time, adjusting for patient-, disease- and physician characteristics.

Results

Of the 775 analysed patients, 598 (77.2%) received at least 1 DMARD during the follow-up period, after a median time of 4.0 months. In general, a higher tender joint count, involvement of the hands, involvement of more than 3 joint groups, presence of abnormal CRP-levels or CCP-antibodies significantly increased the likelihood of being treated ($p<0.01$ for all determinants), as well as a positive result on the bilateral foot-squeeze test ($p<0.04$). In addition, a significant heterogeneity in therapeutic strategy across the 14 tested French regions was found: adjusted hazard ratios for DMARD start ranged from 1 to 2.15 ($p<0.01$), depending on the region where a patient was followed. For anti-CCP test and swollen joint count we demonstrated a statistically significant interaction with geographic region, implying that these tests are interpreted differently across regions. The same factors that increased the likelihood to start a DMARD were related to an earlier start.

Conclusion

Rate and timing of treatment start with DMARDs in patients with early inflammatory arthritis in France is determined by well known clinical and biochemical variables. Apart from these variables, however, unknown and intangible factors that seem to cluster geographically are responsible for important variations in practice performance.

Key words

Arthritis, antirheumatic agents/DMARDs, ESPOIR cohort study, physician's practice patterns.

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Introduction

Management of early inflammatory arthritis is not yet clearly standardized, and recommendations regarding its diagnosis and treatment have only recently been developed (1, 2). Although consensus exists on the need for early use of disease-modifying antirheumatic drugs (DMARDs) in patients presenting with inflammatory arthritis that could evolve into persistent and erosive disease (2-5), no general rules have been published on the optimal time to the first introduction and the detailed clinical picture of the characteristic patient requiring DMARDs early (6). Hence, already in patients meeting diagnostic criteria for rheumatoid arthritis (RA), important practice variations with regard to DMARD start are regularly noted between rheumatologists and non-rheumatologist care providers (7, 8) and also across specialists (9). This disparity in care, mainly investigated through surveys, is noteworthy both in patients with undifferentiated early arthritis and in early RA (9-14). The discrepancies could be related to the difficulty in diagnosing RA at an early stage, evaluating its prognosis and excluding a spontaneously resolving disease. Indeed, spontaneous remission is a frequently described outcome in early arthritis (15), and the therapeutic decision shall take it all into account to preserve the risk-to-benefit ratio. Regarding the start of therapy with a DMARD in RA, former studies noted physicians' characteristics (9, 16), the time period of study (17) or disease characteristics as potentially determining factors, but these factors have not yet been examined in a cohort of patients including patients with undifferentiated inflammatory arthritis. We used the data from a French longitudinal prospective cohort study of adult patients with both early undifferentiated inflammatory arthritis and recently developed RA, the ESPOIR cohort study (18, 19), to describe the therapeutic behaviour of French general practitioners (GPs) and rheumatologists between 2002 and 2005 with regard to a decision to the rate and timing of a DMARD start in early inflammatory arthritis, and to determine the factors that contribute to this start of DMARD therapy. In France, GPs should be regarded as front-line physicians with both an early diagnostic and therapeutic role, together with a pivotal referral function to specialists such as rheumatologists. As this is a prospective observational cohort assessing health-care delivery under non-trial conditions, it allowed us to describe and analyse daily practice, which may help in explaining GP and rheumatologist's behaviour.

Patients and methods

The ESPOIR cohort

The ESPOIR cohort (18, 19) is a French prospective observational study of adults over 18 and less than 70 years old recruited from multiple regions across France under auspices of the French Society of Rheumatology. The patients included had to present with inflammatory arthritis lasting for 6 weeks up to 6 months, involving more than 2 joints and diagnosed by the referring physician as RA or suspected to develop into RA. Patients had never undergone treatment with a DMARD or steroids. Patients were excluded if the referring physician had judged they had other clearly defined inflammatory rheumatic diseases or undifferentiated arthritis (UA) which were unlikely to develop into RA.

Patients were recruited from general practitioners and rheumatologists from 14 regions across France, and data were collected by the regional university rheumatology department. Each regional center collected data but did not interfere with patients' treatment. Patients were routinely treated and followed up by private rheumatologists in the geographical area, but in exceptional cases by GPs with a special interest in rheumatology. It may have happened that the investigator was also the patient's physician. The results of each test carried out within the framework of the study were periodically communicated to the practitioner taking care of the patient. All patients were followed up by the same investigator every 6 months during the first 2 years and every year thereafter. Data concerning medical history, socioeconomic and demographic characteristics, clinical,

biological, radiographic and genetic parameters, were also collected. One biological resources center (Paris-Bichat, Joelle Benessiano) was in charge of centralising and managing biological data collection.

The first inclusions began in December 2002, and 813 patients were included by March 2005 when the database was locked for the present analysis.

Study objectives

The primary objective of this study was to describe the rate and timing of DMARD use (excluding corticosteroids), and to determine factors leading to the start of a drug in a cohort of patients with early inflammatory arthritis treated by rheumatologists in France.

Explanatory variables

The following clinical, biological and sociodemographic characteristics, possibly influencing the decision to begin DMARD treatment, were assessed:

1. Sociodemographic variables: sex, age (tertiles), educational level (at least high school).
2. Baseline clinical disease characteristics: type of disease onset [acute (symptoms appearing in less than 1 week), insidious or intermittent]; number of tender joints (28-joint count) (tertiles); number of swollen joints (28-joint count) (tertiles); symmetrical onset of disease; clinical involvement of the hands; presence of rheumatoid nodules; involvement of more than 3 joint groups; morning stiffness lasting for more than 60 minutes; induced pain by the foot-squeeze test; the latter 6 treated as binary variables.
3. Prognostic characteristics at baseline: presence of typical erosions as seen on hand or feet x-rays; positivity for rheumatoid factor (RF); positivity for anti-citrullinated peptide antibodies (CCP-Abs); elevated level of C reactive protein (CRP >10 mg/l) and impaired functional status (Health Assessment Questionnaire [HAQ] ≥1).
4. Comorbidity (binary): presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or hematuria) or current cancer.
5. Time from symptom onset to first visit to a physician (GP or rheumatologist) (tertiles).
6. Observational center of the patient (among the 14 French centers).

Statistical analysis

Outcome assessment. Time to actual start of first DMARD was calculated based on the date of first prescription of a DMARD (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, sodium aurothiopropanol sulfonate, thiopronine, biologics or combination therapy). If patients did not start a DMARD at the last available follow-up visit, outcome was censored (minimum follow-up time was 12 months after inclusion visit). Survival analysis was calculated as the time from the first visit to a physician (either GP or rheumatologist) for arthritis symptoms, to the time of first DMARD prescription.

Analyses. Multivariate Cox proportional hazard analysis was used to evaluate the independent contribution of baseline features on a decision to start a DMARD. A forward stepwise procedure was used to select variables in the model. The inclusion significance level was 0.05 and the exclusion significance level 0.20. Heterogeneity across observational centers was further investigated by testing interactions between center and each of the baseline characteristics of the patients, in a Cox-model including the interaction term, and the center and the variable of interest (main effects). Concerning the timing of DMARD start, median time per category of baseline characteristics was estimated by Kaplan-Meier analysis and Log-rank test was used to test the difference between categories. All statistical analyses were performed with SPSS 13 for Windows.

The study was approved by a central ethics committee, and written informed consent was obtained from each participant.

Results

Baseline characteristics

The main baseline characteristics of the 813 patients are shown in Table I. They presented with active, recent-onset disease: mean DAS28 of 5.1, mean disease duration less than 15 weeks (from first symptoms, ie any first persistently swollen joint, to first ESPOIR follow-up visit). The biological patterns were similar to those of other published data on early inflammatory arthritis, with 42.2% of the patients having a positive test result for RF at baseline, 39.5% for anti-CCP ab, and elevated blood inflammatory criteria (mean CRP 22.2 mg/l; mean erythrocyte sedimentation rate (ESR) 29.4 mm). ACR criteria for RA (20) were met by 71% of the patients at the time of inclusion in ESPOIR.

Treatment patterns

Because one or more data required for this analysis were missing, 38 out of the 813 patients could not be included in the analysis. Of the 775 analysed, a total of 598 patients (77.2%) received at least 1 DMARD during the follow-up period (Fig. 1). The median time to first DMARD introduction was 4.0 months [95% confidence interval ($CI_{95\%}$) 3.7; 4.3]. Of the 598 treated patients, 281 (47%) started their first DMARD within 3 months after the first visit to a physician, and 522 (87%) within 6 months.

The most frequently first-prescribed DMARD was methotrexate (57.7%), followed by hydroxychloroquine (14.5%), sulfasalazine (12.3%), leflunomide (6.3%), sodium aurothiopropanol sulfonate (2.1%), and thiopronine (0.3%). Combination therapies as first-prescribed DMARD (methotrexate associated with hydroxychloroquine, and/or sodium aurothiopropanol sulfonate, leflunomide, sulfasalazine, etanercept, adalimumab) were used in 36 patients (6.0%) only.

Adjusted hazards ratios for DMARD start decision

Table II displays the adjusted Hazards ratios (HR) for DMARD therapy start from the Cox regression analysis, which accounts for all baseline data that might influence a physician's decision to start therapy. Baseline tender joint count was closely related to DMARD treatment (p=0.001): the adjusted HR was 1.25 ($CI_{95\%}$ 1.01-1.55) for a DMARD start of an "active disease" (tender joint count ranging from 5 to

Table I. Baseline characteristics of the ESPOIR patients (n=813).

Variable	n (%)	Mean (SD)
Sex, female, n (%)	624 (76.8%)	–
Age, years	–	48.1 (12.5)
Disease duration, months	–	3.39 (1.73)
Number of tender joints (28 joint count)	–	8.43 (7.01)
Number of swollen joints (28 joint count)	–	7.19 (5.37)
Rheumatoid Factor positivity, n (%)	343 (42.2%)	–
Anti-CCP antibodies positivity, n (%)	321 (39.5%)	–
Time to first general practitioner visit, days	–	26.4 (41.1)
Time to first rheumatologist visit, days	–	74.9 (76.6)
ESR (mm)	–	29.4 (24.5)
ESR≥28 mm	318 (40.9%)	–
CRP (mg/l)	–	22.2 (34.0)
CRP≥10mg/l	387 (50.0%)	–
HAQ	–	0.98 (0.68)
Disease Activity (Patient self-assessment, Visual Analogic Scale 0-100mm)	–	59.9 (25.6)
Joint Pain at rest (Visual Analogic Scale 0-100mm)	–	37.2 (27.7)
DAS28 value	–	5.11 (1.31)
DAS28 <2.6, n (%)	21 (2.60%)	–
DAS28 2.6-5.1, n (%)	385 (47.4%)	–
DAS28 >5.1, n (%)	393 (48.3%)	–
At least one co-morbid factor, n (%)*	187 (23.0%)	–

*presence of at least 1 comorbid factor: ischemic heart disease, hypertension, diabetes mellitus, renal disease (proteinuria or hematuria) or current cancer.
DAS28: disease activity score 28; ESR: erythrocyte sedimentation rate; CCP: citrullinated peptide antibodies; CRP: C-reactive protein.

9) versus a "mild disease" (tender joint count below 5), and 1.57 ($CI_{95\%}$ 1.25-1.97) for a DMARD start of a "very active disease" (*i.e.* with baseline tender joint count >9) versus a "mild disease". The swollen joint count was not an independent predictor when tender joint count was in the model, probably due to the high correlation between the two. In a model without tender joint count however, swollen joint count became an independent predictor. The following disease variables were independent contributors to DMARD start: involvement of at least 3 distinct joint groups, or arthritis in the hands (HRs 1.49 and 1.79 respectively), and a positive bilateral foot-squeeze test with an HR of 1.22 (p=0.004).

Anti-CCPab positivity independently increased the likelihood of a DMARD start, (HR: 1.71 ($CI_{95\%}$ 1.44-2.03)). In a separate model with only RF and not anti-CCPab included, the HR of RF was 1.60 (p<0.001) (with a better fit of the model including anti-CCP). Elevated CRP resulted also in a significantly more frequent DMARD start (HR 1.28, p=0.003), while a model without CRP resulted in a HR of 1.19 (p=0.05) for having an elevated ESR. Finally, we observed a marked regional diversity in second-line therapy use (HRs from each of the 14 observational centers ranging from 1.02 to 2.15, p=0.006 for comparison test), after adjustment for patient and disease characteristics at baseline. When further investigating this heterogeneity across observational centers, we identified a few characteristics that contributed to explain regional variations in DMARD start: The interactions between observational center and number of swollen joints (p=0.008), and between observational center and presence of anti-CCPab (p=0.045) were statistically significant. The implications of these interactions are illustrated by an example: while in first center (Fig. 2 lower graph) there was an important difference between anti-CCP positive (100% DMARD start) and anti-CCP negative patients (40% DMARD start), almost no difference between DMARD start in anti-CCP positive and negative patients could be found in the other center (Fig. 2 upper graph).

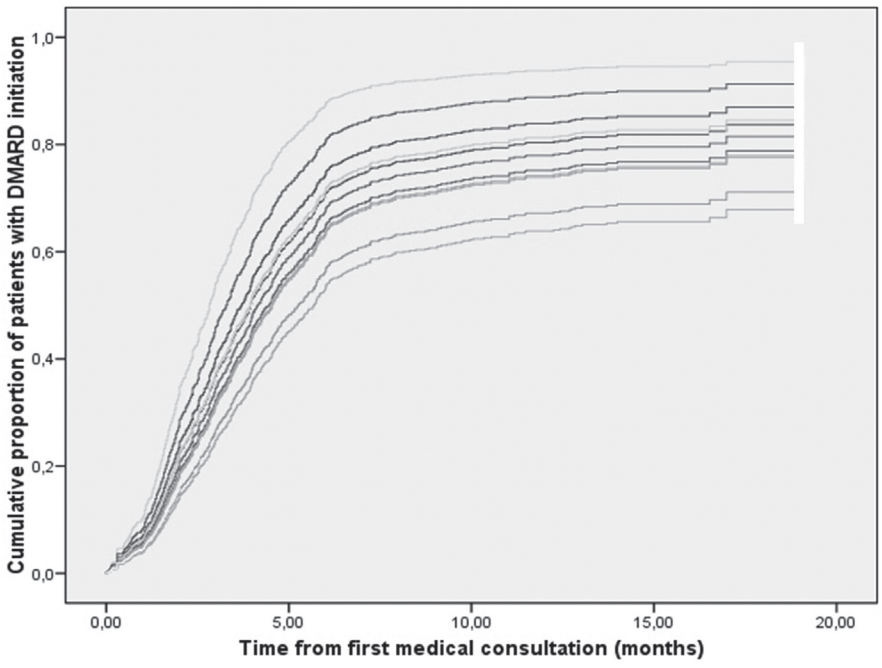

Fig. 1. Cumulative proportion of treated patients over time, in each of the 14 observational center.

Baseline characteristics linked to earlier DMARD start

Table III shows the univariate relationships between baseline variables and time to DMARD start. Sociodemographic variables had no relevant impact on the time to first DMARD: gender was not found to play any role (p=0.46), nor was the age of the patient (p=0.29) or the educational level (p=0.65). Baseline clinical findings, on the other hand, were determinants

Table II. Adjusted hazard ratio for starting a DMARD after first medical visit.

	HR	[95% CI]	*p*
Anti-CCP test (positive *vs*. negative)	1.71	[1.44-2.03]	<0.001
Observational center (range of HR)	range of HRs:		0.006
(reference = center with lowest HR)	1.02 – 2.15		
Number of tender joints			0.001
Second tertile (5-9) *vs*. first tertile (≤4)	1.25	[1.01-1.55]	0.042
Third tertile (>9) *vs*. first tertile (≤4)	1.57	[1.25-1.97]	<0.001
Involvement of at least 3 joint groups	1.49	[1.15-1.93]	0.003
CRP (>10 mg/l *vs*. <10mg/l)	1.28	[1.09-1.52]	0.003
Initial hand involvement (yes *vs*. no)	1.79	[1.16-2.76]	0.009
Foot-squeeze test (positive *vs*. negative)	1.22	[1.01-1.46]	0.035

HR: Hazards ratio; DMARD: disease-modifying antirheumatic drug, CI: confidence interval.

in the decision of starting a DMARD earlier: initial hand involvement led to earlier treatment start ($p<0.0001$), as did a positive bilateral foot-squeeze test result ($p<0.0001$). Baseline disease activity, reflected by the counts of tender or swollen joints (tertiles), was also a strong determinant of earlier DMARD start: Patients with lowest number of tender joints (less than 5) received a second-line therapy later than those from the remaining categories (*i.e*. with 5 to 9, and more than 9 tender joints, $p\leq0.02$ for all pairwise comparisons). Similar results were obtained when comparing timing of treatment start in patients with low (less than 4), intermediate (4 to 8), or high (more than 8) number of swollen joints ($p<0.003$ for all pairwise comparisons).

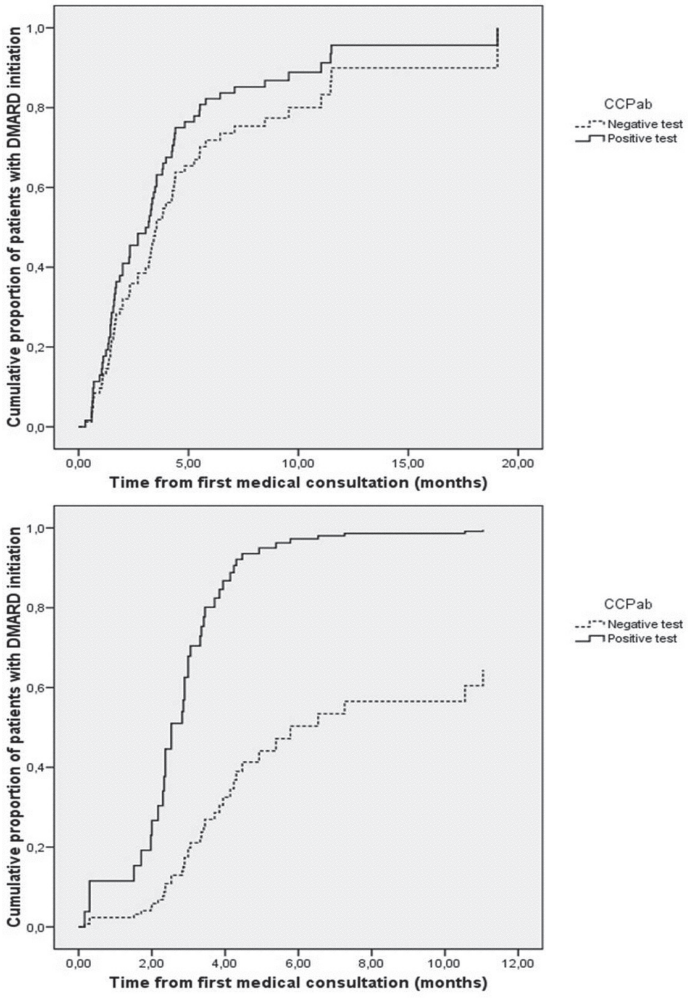

Fig. 2. Cumulative proportion of treated patients over time following first medical consultation, in 2 independent observational centers (lower and upper graphs), depending on results of the anti-CCP test (positive: continued curves, negative: dotted curves).

A symmetrical arthritis also led to an earlier start of treatment ($p=0.0001$), as did an involvement of more than 3 joint groups ($p<0.0001$) or a duration of morning stiffness exceeding 60 minutes ($p=0.009$).

Among characteristics considered to have prognostic value, a high acute phase response led to earlier DMARD treatment ($p<0.001$ for patients with high, *i.e*. over 10 mg/l, *vs*. normal level of CRP). The treatment start was also significantly earlier in patients having a positive RF- and anti-CCPab-test result as compared to those with negative tests ($p<0.0001$ for both comparisons). An early erosive disease (erosions seen on first evaluation-radiographs) was also related to an earlier start of treatment, but the statistical significance was weak ($p<0.04$), probably due to the small number of patients showing structural abnormalities at inclusion according to the referring doctor (less than 15%). A marked functional impairment, as reflected by a HAQ≥1 at the time of the first medical evaluation of the patient, was also related to an earlier DMARD initiation ($p<0.001$).

Presence of at least one comorbid factor was not found to influence the timing of treatment ($p=0.87$), and the lag time between symptom onset and the first visit to a doctor (general practitioner or rheumatologist) also did not have an impact ($p=0.36$).

The time to DMARD start was also found to be substantially heterogeneous across the 14 observational centers ($p<0.001$).

Discussion

This is the first report of French rheumatologists' performance concerning DMARD therapy initiation in early inflammatory arthritis in daily practice, both for outpatients of university centers and private care practice. An important observation is the heterogeneity we found across regions within a single European country with regard to the decision of starting a specific therapy, even after controlling for activity- or severity-related (prognostic) factors which are expected to guide such a decision. Theoretically, the adjustment for these factors such as the level

Table III. Median time (months) to first DMARD as per baseline characteristics of the patients, and results of the Log-Rank test for the respective comparison.

	Compared categories		Median time (months)	$p^{\dagger}$
Sociodemographics	Sex	Female	4.04 [3.69-4.39]	0.455
		Male	3.94 [3.43-4.45]	
	Age‡	<43 years	4.11 [3.59-4.62]	0.134*
		43-55 years	3.84 [3.38-4.31]	
		>55 years	4.11 [3.69-4.52]	
	Education	< high school	4.24 [3.89-4.58]	0.654
		≥ high school	3.94 [3.58-4.30]	
Clinical disease characteristics	Initial hand involvement	Yes	3.84 [3.38-4.31]	<0.001
		No	14¶	
	Type of onset	Symmetrical	3.81 [3.54-4.09]	<0.001
		Asymmetrical	5.22 [4.37-6.08]	
	Rheumatoid nodules	Present	4.37 [1.43-7.32]	0.853
		Absent	4.01 [3.69-4.33]	
	Type of onset	Acute	3.98 [3.25-4.70]	>0.886*
		Progressive	4.01[3.51-4.51]	
		Intermittent	4.04 [3.68-4.40]	
	Tender joint count‡	≤4 tender joints	4.96 [4.30-5.62]	<0.015*
		5-9 tender joints	4.24 [3.78-4.70]	
		>9 tender joints	3.32 [2.84-3.79]	
	Swollen joint count‡	≤3 swollen joints	5.45 [4.42-6.49]	<0.003*
		4-8 swollen joints	4.11 [3.69-4.52]	
		>8 swollen joints	3.25 [2.86-3.65]	
	Foot-squeeze test	Positive	3.58 [3.26-3.90]	<0.001
		Negative	4.96 [4.30-5.62]	
	Involvement of at least 3 joint groups	Yes	3.78 [3.51-4.04]	<0.001
		No	6.90 [4.15-9.65]	
	Duration of morning stiffness	> 60 minutes	3.94 [3.65-4.24]	<0.01
		< 60 minutes	5.06 [3.98-6.14]	
Prognosis-related factors	Radiographic erosions	Present	3.98 [3.35-4.60]	<0.04
		Absent	4.04 [3.71-4.37]	
	CRP	≥10 mg/l	3.42 [2.97-3.87]	<0.001
		<10 mg/l	4.57 [4.02-5.12]	
	Anti-CCP antibody test	Positive	3.29 [2.93-3.64]	<0.001
		Negative	4.73 [4.18-5.29]	
	Rheumatoid Factor test	Positive	3.42 [3.07-3.77]	<0.001
		Negative	4.80 [4.24-5.35]	
	HAQ	≥1	3.42 [3.03-3.81]	<0.001
		<1	4.70 [4.22-5.18]	
Referral	Lagtime from symptom onset to first physician‡	<1 week	4.14 [3.54-4.74]	>0.213*
		2-4 weeks	4.21 [3.87-4.54]	
		>4 weeks	3.68 [3.21-4.15]	
Observational center	Observational center (14 centers)	Range : 3.19 – 5.68		<0.001
Comorbidity	At least one comorbidity	Yes	3.91 [3.34-4.48]	0.650
		No	4.04 [3.71-4.37]	

† Log-Rank test; ‡ Tertiles; ¶ Confidence interval not computable; DMARD: disease-modifying antirheumatic drug; CRP: C-reactive protein; CCP: citrullinated peptide antibodies. * For all pairwise comparisons.

of disease activity and the presence or absence of anti-CCP/RF should result in a very consistent pattern in treatment strategies, not only with regard to the lag-time between symptom onset and treatment start, but also with regard to the proportion of patients with early arthritis in which DMARDs are actually started. However, the remaining discrepancies across French regions demonstrate that similar results of diagnostic and prognostic procedures may result in different consequences with regard to DMARD start, which probably depends on differences in opinions, beliefs and interpretations of the treating physician. A prerequisite is that the greater part of the relevant patient's disease characteristics can be captured and summarized (21). It is rational to assume that several determinants of the therapeutic decision to start DMARDs can not be assessed, but we still believe that the most important diagnostic and prognostic factors in early inflammatory arthritis, about which broad consensus exists in the rheumatological community, were used in the present analysis.

The independent significant variation in medical practice across observational centers revealed a geographical heterogeneity in practice performance among French rheumatologists. The ESPOIR

patients are most often treated and followed up by private rheumatologists, but these rheumatologists generally collaborate with the observational center in their region, which is also the center in which they usually were trained, and with which they tune their performance in clinical practice, thus explaining the geographical rather than individual variation. This formerly reported source of variation (16, 17) should strongly encourage initiatives for improving the management of early inflammatory arthritis. In particular, development and implementation of guidelines (like the recently formulated recommendations for the management of patients with early arthritis (1) could help practitioners propose the most appropriate strategy in individual patients.

Expectedly, clinical and biochemical features, particularly those indicating a possible early RA, such as involvement of more than 3 joint groups of the hands, and the presence of anti-CCP antibodies, were most relevant in the final therapeutic decision to start DMARDs. Apart from these factors typical of the classical RA presentation (22), and after adjustment for them in a multivariate model, we still found other independent determinants of the start of antirheumatic therapy. Baseline disease activity, reflected by the tender joint count in our study, is known as a prognostic tool in early RA (23-27) and as a predictor of disease persistence in UA (25, 28-30) and was thus expected to be closely related to DMARD treatment start in early inflammatory arthritis. This hypothesis was clearly confirmed by our results showing an independent and significant link between illness activity and a prompt treatment start. Another determinant of an early DMARD start was the bilateral foot-squeeze test. This simple clinical test, implying a transversal compression of the metatarsophalangeal joints that may cause pain (a positive test), was previously suggested to be a predictor of disease persistence (22, 31). This test was independently contributory to a DMARD start, and a positive test apparently reflects the perception of the physician that this patient will run a chronic and destructive disease course (see Table II). Its assessment in early arthritis is thus recommended (1, 31), especially when formal clinical evaluation of RA (by 28-joint counts) does not take into account the patients' feet.

A positive test result for anti-CCP antibodies at disease onset independently contributed to starting DMARD therapy. This observation is understandable, and in accordance with results of other studies showing that a positive anti-CCP antibody test is an independent predictor of disease persistence and radiographic evolution (22, 24, 32-35). Far less understandable from an evidence-based point of view, however, is the geographical heterogeneity in performance that we demonstrated with regard to the consequences of a positive anti-CCP test: in some geographical areas, a positive test dominated the decision to start DMARDs in a patient, while in other geographical areas such a decision was completely independent of the test result. A similar kind of geographical heterogeneity could be demonstrated for the swollen joint count. These examples illustrate that care providers handle and interpret the available prognostic information differently in their practice with individual patients, and as such contribute to important differences in practice performance across regions. Ideally, practice variation should be largely explained by true differences in individual prognosis rather than by differences in the interpretation of prognostic literature or lack of knowledge of these.

We have here described the French practice of DMARD therapy in early inflammatory arthritis within the context of the concept of a "window of opportunity," that is supported by the results of several trials and meta-analyses (6, 36-49), and underscores an early treatment start in recent-onset RA. Prospectively following up patients in the ESPOIR cohort will enable us to establish whether such a strategy – with inherent geographical variation – will have an impact on long-term clinical, radiological, functional and social outcomes.

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