

Favorable Effect of Very Early Disease-Modifying Antirheumatic Drug Treatment on Radiographic Progression in Early Inflammatory Arthritis

Data From the Étude et Suivi des Polyarthrites Indifférenciées Récentes (Study and Followup of Early Undifferentiated Polyarthritis)

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Objective. While there is consensus that treatment with disease-modifying antirheumatic drugs (DMARDs) should be started early in patients with inflammatory arthritis, confirmation that radiographic progression is inhibited with early treatment start is scarce. This study was undertaken to compare radiographic progression in patients treated with a DMARD very early in the course of their disease (within 3 months of diagnosis) and those who began DMARD treatment later.

Methods. Patients included in the French observational ESPOIR (Étude et Suivi des Polyarthrites Indifférenciées Récentes [Study and Followup of Early

Undifferentiated Polyarthritis]) cohort were followed up, and radiographic progression after 12 months was assessed. Propensity scores, reflecting the indication to start a DMARD, were obtained by modeling the start of DMARD therapy by disease-specific and demographic variables obtained at baseline, using logistic regression analysis. The influence of very early versus delayed DMARD start on radiographic progression was evaluated by generalized linear regression, with and without adjustment for propensity scores.

Results. Six hundred sixty-one patients were analyzed. In an unadjusted analysis, patients starting DMARD therapy within 3 months of diagnosis did not show a significant difference in radiographic progression score as compared to those starting DMARD therapy later (1.2 units versus 1.6 units; $P = 0.37$). Adjustment for the propensity score revealed a statistically significant difference in mean progression (0.8 units versus 1.7 units; $P = 0.033$). Analysis by propensity score quintile showed a trend suggesting that early treatment was especially beneficial for patients in the fourth and fifth quintiles (worse prognosis).

Conclusion. Our findings indicate that among patients with inflammatory arthritis in daily clinical practice, early initiation of DMARD therapy reduces 12-month radiographic progression. This strengthens the current recommendations for very early initiation of specific therapy in patients with early arthritis.

A more intensive treatment approach to the management of early inflammatory arthritis has been adopted recently, with the general consensus being that a disease-modifying antirheumatic drug (DMARD) with

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proven structural efficacy should be started as soon as possible in a patient likely to develop persistent and erosive arthritis (1–4). If classic rheumatoid arthritis (RA) with unfavorable prognostic factors is found at presentation, such a recommendation is obvious, but if a patient is referred very early, a diagnosis and prognostic profile often cannot be made. While robust and consistent data have demonstrated both clinical and radiographic superiority of intensive treatment (e.g., combination DMARD therapy), data on impact of the delay between disease onset and DMARD initiation remain inconclusive. Evidence that earlier treatment initiation results in better radiographic outcome in patients with RA is still sparse. Clinical trials have thus far mainly included patients who fulfill criteria for RA, and these studies show that in early RA, intensive therapy is more efficacious than conventional treatment (5–8). Such studies do not, however, prove that an early treatment start is better than a delayed one.

The data suggesting benefit of early treatment initiation often suffer from confounding by indication: physicians base their treatment decisions on the activity and thus severity of the disease. Confounding by indication may lead to a decreased treatment contrast (9,10). In the study by van der Heide et al, for example, earlier treatment of patients with recently diagnosed RA resulted in improved clinical outcomes after 12 months of followup whereas no radiographic benefit could be observed, probably because of the tendency of the investigators to use more intensive additional treatment in patients with more severe or persistently active disease (11). The ideal experiment to investigate whether an early DMARD start is better than a delayed one is a pragmatic randomized controlled trial in which patients are randomized to an arm with an immediate DMARD start versus an arm with a delayed DMARD start. However, such a study seems unethical in light of current treatment algorithms.

Another concern is that no one can precisely define how early is early enough. A current view, also reflected in new treatment recommendations (1), exploits the window-of-opportunity principle for guidance, and many believe that 3 months should be the maximum delay from diagnosis to the initiation of DMARD treatment (12). However, these suggestions are based on expert opinion rather than on scientific data, or were formulated before methotrexate was commonly used as first-line therapy (13).

Among patients with early inflammatory arthritis in the French ESPOIR (Étude et Suivi des Polyarthrites Indifférenciées Récentes [Study and Followup of Early

Undifferentiated Polyarthritis]) cohort, there has been variation in the decision to start DMARD therapy and the amount of time since onset at which rheumatologists have first prescribed DMARD therapy. This may theoretically lead to differences in outcome in these patients, which could be clinically meaningful. In the present study we evaluated the impact of the time lag between arthritis onset (first patient-reported swollen joint) and DMARD initiation on 1-year radiographic progression, adjusting for the spurious effects of confounding by indication.

PATIENTS AND METHODS

The ESPOIR cohort. The ESPOIR cohort (14,15) is a French prospective observational study of adults ages 18–70 years recruited from multiple regions across France under the auspices of the French Society of Rheumatology. To be enrolled in the ESPOIR cohort, patients had to present with inflammatory arthritis lasting 6 weeks to 6 months and involving >2 joints, and the arthritis had to have been diagnosed by the referring physician as RA or RA-like (i.e., a high suspicion of RA). Patients had to have never undergone treatment with a DMARD or steroids before enrollment. Patients were excluded if the referring physician had judged that they had a clearly defined inflammatory rheumatic disease other than RA.

Patients were recruited from general practitioners and rheumatologists in 14 regions across France. Data were collected by the regional university rheumatology department, which was not involved with patient treatment. Patients were routinely treated and followed up by private rheumatologists in the geographic area, and in rare cases by general practitioners with a special interest in rheumatology.

The results of each test performed for study purposes were periodically communicated to the practitioner taking care of the patient. All patients were followed up by the same investigator once every 6 months during the first 2 years and once every year thereafter. Data on medical history, socioeconomic and demographic characteristics, and clinical, biologic, radiographic, and genetic parameters were also collected. One biologic resource center (Paris-Bichat) was responsible for centralizing and managing laboratory data collection.

The first patients were enrolled in the ESPOIR cohort in December 2002, and recruitment concluded in March 2005. A total of 813 patients were included.

Radiographic evaluation. Baseline and 1-year radiographs of the hands, wrists, and feet were read and assessed using the Sharp/van der Heijde score (SHS) (16). The readers were blinded with regard to patient identity and patient characteristics and treatment, but the time order was known, to improve sensitivity to change. In order to evaluate the reproducibility of the radiographic scoring, radiographs from 30 patients representing the entire range of status and change scores observed during the first reading were selected and scored again by the same reader. Intraclass correlation coefficients were calculated for status (baseline and 1 year) as well as for change scores, and the smallest detectable change was computed using standard methodology (17).

Propensity analysis. Principles. It is reasonable to assume that in convenience cohorts without a fixed treatment protocol, such as the ESPOIR cohort, the most important determinant of an immediate DMARD start is the physician's opinion of the severity and activity of the disease as well as the individual prognosis. Severity and activity of the disease may confound the relationship between time to DMARD initiation and radiographic progression (confounding by indication). However, the physician's interpretation of disease severity and activity is by definition unquantifiable, since it encompasses a number of intangible and often unmeasured factors.

The theory underlying propensity modeling assumes that the likelihood of (in this case) a DMARD start, and thus severity of RA in the opinion of the physician, can be approximated by taking into consideration all measured variables at baseline that the physician may or may not implicitly use to base his or her decision to initiate DMARD treatment (18). By adjusting the relationship between the time to DMARD start and radiographic progression for individual propensity scores, one can partially adjust for confounding by indication.

For each patient, propensity to start DMARD treatment within the 6 months after the first reported synovitis was estimated by logistic regression analysis, modeling all available variables at baseline that, in the opinion of the investigators, could have influenced the decision by the treating physician to prescribe the DMARD. DMARD starts taken into account were starts with DMARDs of proven efficacy in radiographic progression, i.e., methotrexate, leflunomide, sulfasalazine, and tumor necrosis factor (TNF) blockers (or combinations of these).

This logistic regression analysis resulted in a propensity score for each patient for starting treatment within 6 months, which was the time frame within which most patients prescribed treatment had actually started this treatment. According to propensity modeling theory, in patients with similar propensities (e.g., in the same quintile), the treatment decision actually observed at the individual level can be regarded as independent of disease severity, apart from residual confounding.

Propensity score. The logistic model used the following variables to estimate the probability of being treated with methotrexate, leflunomide, sulfasalazine, and/or anti-TNF within 6 months after first reported synovitis: center, age, 28-joint Disease Activity Score (DAS28) (19), sex, C-reactive protein (CRP) level, erosions present (yes/no), comorbidity present (yes/no), rheumatoid factor (RF) present (yes/no), anti-cyclic citrullinated peptide 2 (anti-CCP-2) antibodies present (yes/no), time to first visit to a rheumatologist (<12 weeks versus >12 weeks), symmetric arthritis present (yes/no), involvement of hand joints (yes/no), and involvement of >3 joint groups (yes/no). Contributory variables were selected by stepwise forward selection, with $P = 0.3$ as a limit for including a potential variable. Baseline was defined as the time point of first reported synovitis. To ascertain this, patients were asked when they had first noticed any swelling in a joint that was (according to the rheumatologist) currently swollen.

Hypotheses. The following hypotheses were tested: 1) an earlier DMARD start—defined as <3 months from the time of arthritis onset (i.e., first swollen joint)—would lead to less radiographic progression than a later DMARD start after

adjustment for propensity scores; and 2) this gain would be greatest in patients with more severe disease (quintiles with highest propensity scores).

Statistical analysis. Radiographic progression in patients who were versus those who were not treated within the first 3 months was compared by Mann-Whitney U test. The effect of an early DMARD start on radiographic progression was evaluated using a generalized linear model in which change in 1-year SHS was modeled by treatment start (early versus late) as well as propensity score.

Patients were divided into propensity quintiles based on their individual propensity scores. By definition, the proportion of patients starting DMARD treatment early should increase per quintile because of the physician's perception of increasing prognostic severity and disease activity. Subsequently, in an exploratory analysis, radiographic progression was analyzed by quintile according to early DMARD start (yes versus no). Because the limited number of patients per propensity quintile likely precludes meaningful statistical comparison, we refrained from statistically comparing within subgroups and report the results as a trend.

RESULTS

Patient characteristics. Of the 813 patients in the ESPOIR cohort, 661 had complete data and were included in the present analyses and the remaining 152 could not be analyzed. The main reason for exclusion of patients from analysis was missing radiographs at baseline ($n = 82$) and/or at 1 year ($n = 141$). Baseline characteristics in the group of 661 patients who were

Table 1. Baseline characteristics of the ESPOIR cohort patients included in the present analysis and those not included in the present analysis*

Characteristic	Included (n = 661)	Not included (n = 152)
Age, mean \pm SD years	48.6 \pm 12.1	45.7 \pm 14.2
Female sex, no. (%)	510 (77.2)	114 (75.0)
DAS28, mean \pm SD	5.1 \pm 1.3	5.2 \pm 1.4
SHS, mean \pm SD	5.8 \pm 7.8	NA
CRP, mean \pm SD mg/liter	9 \pm 33.5	19.4 \pm 27.3
Hand involvement, no. (%)	624 (94.4)	132 (86.8)
RF positive, no (%)	294 (44.5)	48 (31.6)
Anti-CCP-2 positive, no. (%)	271 (41)	57 (37.5)
Fulfilled 2010 ACR/EULAR criteria for RA, no. (%)†	525 (79.4)	116 (76.3)
Fulfilled 1987 ACR criteria for RA, no. (%)‡	483 (73.1)	94 (61.8)

* ESPOIR = Étude et Suivi des Polyarthrites Indifférenciées Récentes (Study and Followup of Early Undifferentiated Polyarthritis); DAS28 = 28-joint Disease Activity Score; SHS = Sharp/van der Heijde score; NA = not available; CRP = C-reactive protein; RF = rheumatoid factor; anti-CCP-2 = anti-cyclic citrullinated peptide 2; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis.

† Ref. 23.

‡ Ref. 24.

analyzed and the group of 152 patients who were excluded were similar (Table 1).

Overall, 527 (79.7%) of the 661 analyzed patients were started on DMARD therapy within 1 year following symptom onset. Methotrexate was the most commonly prescribed first DMARD (336 of 527 [64%]), either as monotherapy (307 of 527 [58%]) or in combination with other DMARDs (hydroxychloroquine, sulfasalazine, leflunomide, or TNF-blocking drugs) (29 of 527 [5.5%]). Sulfasalazine was chosen in 66 patients (13%), and leflunomide in 31 patients (6%). DMARDs not taken into account in our analysis (mainly hydroxychloroquine monotherapy) were prescribed in 90 patients.

Time to DMARD initiation was very heterogeneous, as shown in Figure 1. The proportion of patients starting DMARD therapy increased rapidly over the first 6 months and leveled off thereafter. Of the 437 patients who started a DMARD of interest for the present study, 140 (32%) did so within the first 3 months after symptom onset, and 205 (47%) within 6 months. Baseline characteristics of the patients who began treatment within 3 months and those who did not begin treatment within 3 months are reported in Table 2. An imbalance in the type of DMARD treatment used may theoretically have had an impact on radiographic progression. However, we did not identify such an imbalance. The somewhat higher frequency of TNF blockade

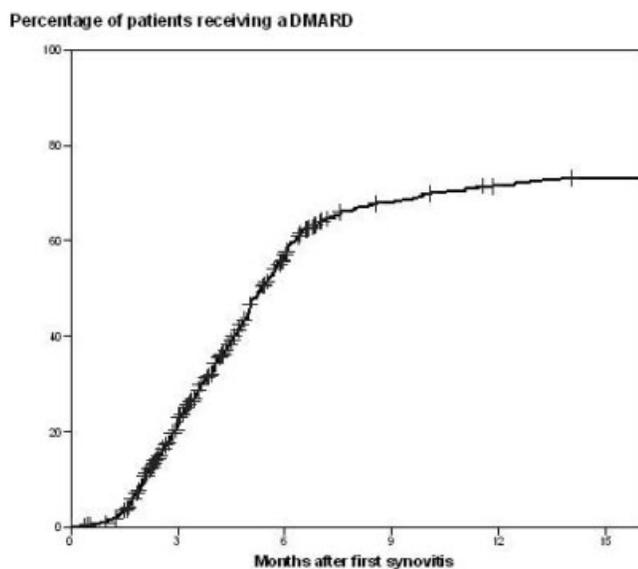


Figure 1. Percentage of patients starting disease-modifying antirheumatic drug (DMARD) treatment, by amount of time since the onset of synovitis.

Table 2. Baseline characteristics of the patients who were and those who were not treated with disease-modifying antirheumatic drugs within 3 months after the onset of synovitis*

Characteristic	Treated within 3 months (n = 140)	Not treated within 3 months (n = 521)
Age, mean ± SD years	46.7 (±12.6)	49.2 (±11.9)
DAS28, mean ± SD	5.61 (±1.18)	4.96 (±1.30)
SHS, mean ± SD	4.7 (±5.9)	6.1 (±8.2)
CRP, mean ± SD mg/liter	26.9 (±42)	18.8 (±30.6)
RF positive, no. (%)	73 (52.1)	221 (42.4)
Anti-CCP-2 positive, no. (%)	77 (55)	194 (37.2)
Fulfilled 2010 ACR/EULAR criteria for RA, no. (%)†	126 (90)	399 (76.6)

* See Table 1 for definitions.

† Ref. 23.

treatment among patients starting DMARDs later may have worked against such a bias. Combination therapy was rarely chosen, which makes it unlikely that differences in the usage of combination therapy had an effect.

Radiographic progression. The mean ± SD total SHS at baseline was 5.8 ± 7.8 (range 0–56), with a median score of 3 and an interquartile range (IQR) of 1–7.5. The rather high baseline values in some patients appear surprising, but they are seen more frequently in cohorts of patients with short symptom duration. There may be several reasons for this: early subclinical joint inflammation that is not recognized by the patient, inaccurate symptom recall, and associated osteoarthritis that may cause damage resembling erosions and joint space narrowing in RA. The median radiographic progression at 1 year was 0 (IQR 0–1) and the mean ± SD change was 1.5 ± 4.3 units (range 0–36). Most patients (72%) did not show any radiographic progression over 1 year, but 8% had severe progression (≥5 units). The erosion score at baseline was 2.8 ± 4.7 (range 0–40). Change in the erosion score at 1 year was observed in 179 patients (27.1%). The mean change in the erosion score was 1.2 ± 3.5 units (range 0–37). When patients were grouped according to whether they did or did not begin DMARD treatment within 3 months of symptom onset, the difference in crude mean radiographic progression was not significant (1.2 ± 3.4 units [range 0–19] in patients starting DMARDs within 3 months and 1.6 ± 4.5 units [range 0–37] in patients starting DMARDs later [P = 0.37]).

Intraclass correlation coefficients were >0.99 for both radiographic status scores and radiographic change scores. The smallest detectable change was calculated at 1.0 SHS unit.

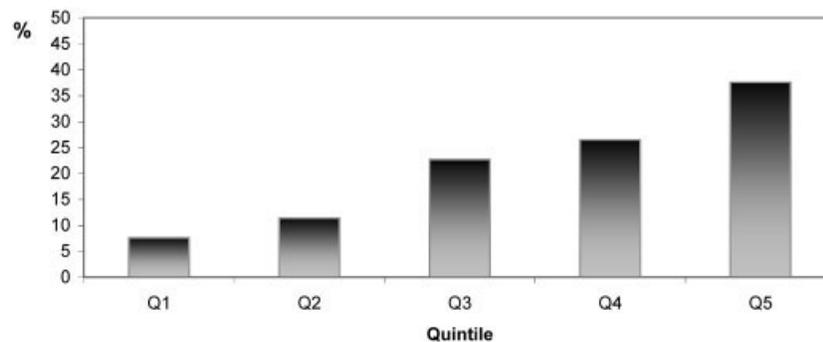


Figure 2. Percentage of patients starting disease-modifying antirheumatic drug treatment within 3 months of synovitis onset, by propensity score quintile (Q) (higher quintiles reflect greater disease severity).

Findings of the propensity analysis. In the final logistic model, the investigation center, DAS28 score, time to first rheumatologist visit, RF positivity, involvement of >3 joint groups, CRP level, and anti-CCP antibody positivity remained as contributory factors (listed in decreasing order of contribution). Age, sex, presence of erosions, comorbidity, symmetric arthritis, and involvement of hand joints were not contributory in the model. Subsequently, in order to investigate whether the perceived disease activity and severity were influencing the crude differences in radiographic progression rate, the propensity score was included as a covariate in the linear regression analysis. The estimated marginal means were 0.8 units (SEM 0.37) in patients starting DMARDs within 3 months and 1.7 units (SEM 0.19) in patients starting DMARDs later ($P = 0.033$), thus confirming the difference found in the crude analysis. (SEM is reported here because it is the estimation provided in a generalized linear model.) Subsequently, patients were divided into propensity quintiles (Figure 2). As expected, the proportion of patients starting DMARDs early increased by increasing quintile (increasing prognostic severity), although only 37.6% of patients in the highest quintile (worst prognosis) started DMARD treatment within 3 months of the onset of synovitis.

Figure 3 shows probability plots of individual radiographic progression scores by DMARD treatment start (early versus delayed) in the individual quintiles. In the first 3 quintiles (better prognosis) there were no important differences in radiographic progression between those who started DMARDs within 3 months and those who started DMARDs beyond 3 months. A trend suggesting benefit of early treatment, especially in patients in the fourth and fifth quintiles (worse prognosis), was observed.

Findings of sensitivity analysis. Additional analyses, conducted in order to test the robustness and validity of the approach, yielded similar conclusions. The conclusions were unchanged when corticosteroid use was one of the factors included in the propensity model or when only specific DMARDs were used to define early treatment start. Taking as a minimum the use of at least 7.5 mg/day prednisone equivalent for >3 months in the first year of disease, the estimated marginal means for the change in radiographic progression score were similar to those obtained in the original propensity analysis (0.6 SHS units versus 1.8 SHS units in patients who did versus those who did not start DMARD treatment within 3 months; $P = 0.008$). When the propensity score was based on the start of only methotrexate and/or anti-TNF, and not the other DMARDs of interest, within 6 months, radiographic progression was also lower in patients who had started treatment within 3 months versus those who had started later (0.9 SHS units versus 1.6 SHS units), although the difference was not statistically significant ($P = 0.11$). Other approaches to determining the propensity score (such as the inclusion of the baseline SHS score instead of the presence or absence of erosions) also resulted in similar conclusions.

DISCUSSION

The results of this study add to the sparse evidence that starting DMARD treatment very early in patients with inflammatory arthritis is favorable with regard to radiographic progression. A trend appears to suggest that especially patients with a relatively unfavorable prognosis benefit from early initiation of treatment. This observation must be interpreted with caution in view of the limited sample size and short followup period in the present study. However, it is in accordance

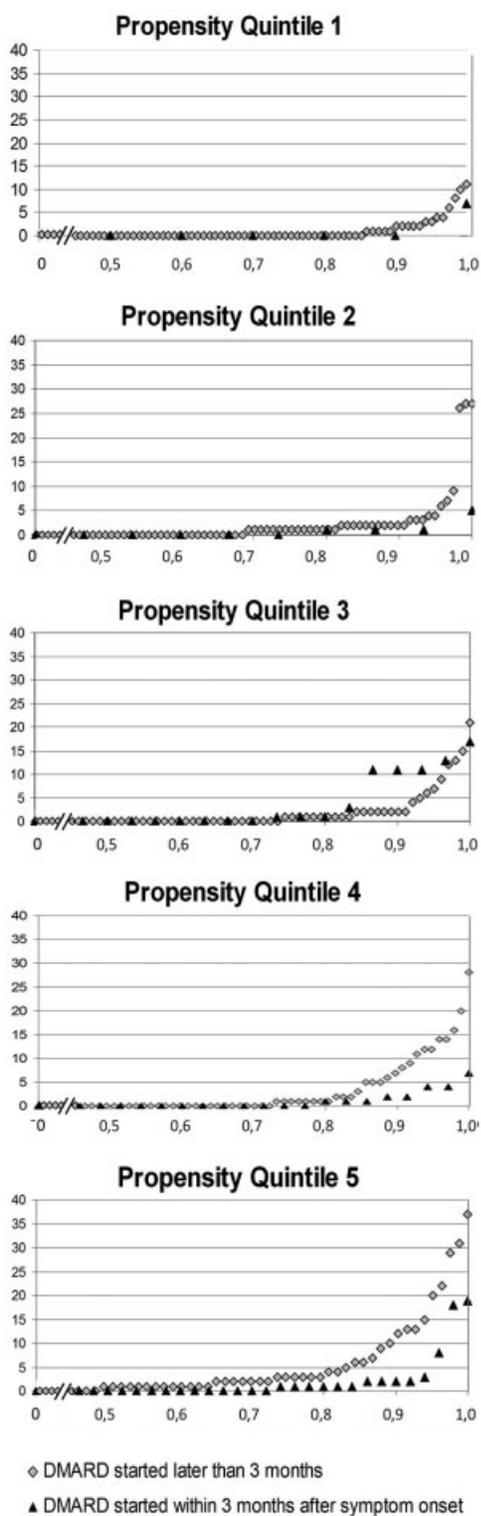


Figure 3. Probability plots of individual radiographic progression scores, by treatment category (disease-modifying antirheumatic drug [DMARD] treatment started within 3 months of synovitis onset [triangles] or not started within 3 months of synovitis onset [diamonds]) and by propensity score quintile.

with observations stemming from post hoc analyses from clinical trials comparing intensive and less intensive treatment, which have shown that patients with the worst prognostic profile especially benefit from intensive treatment, while those with relatively mild disease do well with less intensive therapy (20,21). Our observations could be interpreted to suggest that the prognostic profile is important not only in the choice between intensive and less intensive treatment strategies, but also in the choice between a very early start and a delayed one. Unfortunately, the propensity score cannot be translated directly into prognostic variables.

Previous studies have also investigated the impact of early versus delayed treatment start in patients with early inflammatory arthritis. Lard et al prospectively followed up patients referred to an early arthritis clinic who first received symptomatic treatment and subsequently received sulfasalazine or hydroxychloroquine (13). They compared radiographic progression in these patients versus radiographic progression in patients starting DMARD therapy within 15 days after referral, and found that progression was significantly lower in the group that received early DMARD treatment. Such studies have led to a paradigm shift in the treatment strategy for RA, resulting in a recommendation of early aggressive treatment rather than a pyramid-like approach in which the initiation of effective DMARDs is postponed. Important limitations of such studies are that the drugs investigated did not include methotrexate (the current anchor drug in early RA), in the majority of patients the lag time between symptom onset and treatment initiation was beyond current recommendations, and different periods in history—covering different treatment paradigms—were compared.

Bukhari et al were the first to report on radiographic progression in an early arthritis cohort in which there was no formal treatment protocol (22). Using propensity modeling, they convincingly argued that radiographic progression at 5 years remained worse in patients for whom treatment had been delayed by >6 months. In their work, however, the propensity model was based on the start of any DMARD, including corticosteroids, over the entire 5-year followup period and the probability of receiving treatment was evaluated based on data collected at baseline only, while clinical status does not necessarily remain stable over such a long period of time.

The strength of our approach is mainly that the propensity score we have designed includes a prognostic profile that is based both on data at first evaluation and on data during the first 6 months of followup. Of note, the patients were closely monitored since they were

included in the ESPOIR cohort, but treatment decisions were left entirely to the discretion of the local physician(s), and can thus be regarded as a reflection of current daily clinical practice.

One may expect that the observed differences in prognostic factors at first evaluation are an appropriate reflection of the heterogeneity rheumatologists encounter among patients referred with early inflammatory arthritis. The methodologic approach we have used enables comparisons of therapeutic interventions that could not be made under conditions of a clinical trial that does not incorporate judgments of severity but rather allocates patients irrespective of prognostic profile.

However, the propensity model also has limitations. There are several potentially important variables that were not assessed but might be taken into account by the rheumatologist during the clinical evaluation (intangible factors). Obviously, it is impossible to adjust for such unmeasured characteristics, and the possibility of residual and/or unmeasured confounding remains.

In conclusion, our study showed that patients with early inflammatory arthritis who began DMARD treatment early had improved radiographic outcome after adjustment for propensity score. These findings corroborate the recommendation of very early treatment initiation in patients with early inflammatory arthritis, in order to improve long-term prognosis.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lukas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lukas, Combe, Ravaud, Sibilia, Landewé, van der Heijde.

Acquisition of data. Combe, Ravaud, Sibilia.

Analysis and interpretation of data. Lukas, Combe, Ravaud, Sibilia, Landewé, van der Heijde.

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