The Gap Between Practice and Guidelines in the Choice of First-line Disease Modifying Antirheumatic Drug in Early Rheumatoid Arthritis: Results from the ESPOIR Cohort

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ABSTRACT. ***Objective.*** To compare rheumatologists' prescription for first disease modifying antirheumatic drug (DMARD) in early rheumatoid arthritis (RA) in real-life settings with 2 clinical practice guidelines (CPG), the French Society of Rheumatology/STPR 2004 and EULAR/ESCISIT 2007, and thus assess the gap between practices and guidelines.

Method. ESPOIR was a French multicenter cohort study of 813 patients with early arthritis between 2002 and 2005. "Definite" and "probable" RA were defined according to ACR criteria and the level of diagnostic certainty. The objectives were to assess conformity between the observed first-line DMARD prescribed for those patients and the DMARD recommended in the guidelines; and to conduct a mail survey of patients' usual rheumatologists to investigate the reasons for their nonconformity with guidelines.

Results. In total 627 patients with definite or probable RA were identified. Conformity rates were 58% for STPR guidelines and 54% for EULAR guidelines. At 6 months, 83 (34%) patients with early RA did not receive any DMARD. Main determinants associated with conformity to guidelines were disease activity and presence of severity-predictive factors. The main reason leading to a discrepancy between guidelines and daily practice appeared to be diagnostic uncertainty, i.e., the difficulty to reliably assess RA diagnosis as early as the first visits to the rheumatologist.

Conclusion. There is a substantial gap between CPG and rheumatologists' daily practice concerning the first DMARD to prescribe in early RA. This is explained mainly by diagnostic uncertainty. More attention should be paid in future guidelines to the diagnostic difficulties of early RA. (J Rheumatol First Release March 15 2009; doi:10.3899/jrheum.080762)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EARLY ARTHRITIS CLINICAL PRACTICE GUIDELINE
FIRST-LINE DISEASE MODIFYING ANTIRHEUMATIC DRUG
GUIDELINE ADHERENCE DISEASE MANAGEMENT

Promulgation of clinical practice guidelines (CPG) is intended to synthesize available medical information and improve quality of care[1-7]. Barriers to their application, however, often limit their implementation in daily practice[8,9]. Actual application of CPG depends on a variety of indicators, including confidence in the guideline developer[10,11], accessibility of the guidelines, their ease of use[12], and applicability to specific patients, as well as the strategies used to promote implementation[13,14].

Rheumatoid arthritis (RA) is interesting to consider from this point of view because treatment for it has changed substantially in recent years. Key aspects of these changes include early start of treatment, use of drugs that can prevent joint destruction (that is, proven to prevent or delay

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structural damage) and disease flares, and the importance of regular monitoring of disease activity and structural changes to ensure tight control of the disease[15-20]. For this reason, several expert groups and professional societies have issued guidelines on this topic in recent years[21-24].

Two different groups produced 2 sets of guidelines about prescription of first-line disease modifying antirheumatic drugs (DMARD) in early RA: the French Society of Rheumatologists' STPR working group[21] (French acronym for "Therapeutic Strategies in RA") and a EULAR expert group[22] (European League Against Rheumatism). The STPR guidelines present a decision tree for choosing the first DMARD to be used in early RA (less than 6 months' duration)[21]. The EULAR guidelines identify methotrexate (MTX) as the anchor drug that should be used first in patients at risk of developing persistent disease[22].

To compare these CPG with the usual care provided by rheumatologists, we used the data of a nationwide French cohort, ESPOIR (acronym for "Study and Follow-up of Undifferentiated Early Arthritis"), which included patients between 2002 and 2005[25]. It is important to note the chronology: the ESPOIR inclusion period overlapped with the production and diffusion of both CPG. The STPR results were presented at the American College of Rheumatology (ACR) annual meeting in November 2004 and published in January 2006, while the EULAR results were presented at the EULAR annual scientific meeting in June 2005 and published in January 2007. Our aim therefore was not to assess adherence to guidelines. Instead we sought to investigate the potential gap between daily rheumatologic practice and guidelines for the first DMARD prescription in early RA, before their dissemination, for such gaps are likely to be barriers to implementation.

MATERIALS AND METHODS

Study design. Our primary objective was to assess conformity between the first DMARD prescribed to patients in the ESPOIR cohort and the DMARD recommended by each of the 2 sets of guidelines. At the same time we assessed the determinants of this conformity, the influence of the patient's inclusion date, and the extent of the gap with the STPR guidelines.

Our secondary objective was to determine reasons for any discrepancies we observed between the rheumatologists' decisions and CPG. Accordingly, in cases where the treatment did not match the STPR guidelines, we sent a questionnaire (Appendix 1) to the patients' attending rheumatologists.

Patients. The ESPOIR cohort. ESPOIR was a nationwide prospective cohort study of adults (18 to 70 years old) sponsored by the French Society of Rheumatology[25,26]. Inclusion criteria were inflammatory arthritis for at least 6 weeks but not longer than 6 months, involvement of more than 2 joints, clinical diagnosis of RA as certain or probable or clinical diagnosis of undifferentiated arthritis potentially becoming RA, and no DMARD or steroid treatment since the onset of symptoms. Patients with other definite inflammatory rheumatic diseases or with too much uncertainty of developing RA were excluded.

Recruitment in 14 university hospital rheumatology departments was conducted through several media inviting patients and physicians to participate in each regional area. Each center acted as an observational center and did not interfere with patient treatment, except when in charge of a patient. Patients were routinely treated and followed by private rheumatologists in the local area.

In all, 813 patients were recruited from November 2002 to April 2005 and they have been followed longitudinally since then, seen every 6 months in the 14 hospital centers participating in the project. Baseline data are updated at the 6-month followup.

RA diagnosis. A selection of patients most at risk to become RA patients was conducted in the ESPOIR database, to allow a study of conformity with guidelines in case of less diagnostic uncertainty of RA. Therefore fulfilment of the ACR criteria[27] and the attending rheumatologist's diagnostic certainty at baseline (0 to 100 on a visual analog scale) were considered.

"Definite RA" was defined if patients met at least 4 (of 7) ACR criteria and diagnostic certainty was rated at ≥ 75 (threshold determined by the ESPOIR steering committee). "Probable RA" was defined as meeting at least 3 ACR criteria, even with a diagnostic certainty < 75.

Guidelines. STPR guidelines. The STPR decision tree[21] determines the DMARD to prescribe according to 3 items: level of disease activity based on the Disease Activity Score for 28 joints (DAS28; low ≤ 3.2; moderate 3.2–5.1; high ≥ 5.1), the presence of structural damage, and rheumatoid factor (RF) status. The decision tree leads to 4 possible therapeutic options of increasing severity. Each calls for the choice of one of 2 DMARD: A. hydroxychloroquine or sulfasalazine; B. sulfasalazine or MTX; C. MTX or leflunomide; or D. MTX or tumor necrosis factor (TNF) blocker agents (Appendix 2).

EULAR guidelines. These guidelines[22] recommend MTX as a first treatment for early arthritis at risk to be persistent, since it acts on structural damage and prevents flares and may thus be viewed as an anchor drug for additional DMARD in case of inadequate response.

Conformity with guidelines. We then assessed conformity with the STPR and the EULAR guidelines. To evaluate STPR conformity we needed data about the 3 items of the STPR algorithm, whereas to evaluate EULAR conformity we were able to compare therapeutic decision with the recommended treatment every time.

The possible determinants of conformity studied were as follows: patient's social and demographic characteristics (sex, age, ethnic origin, education, comorbidities), disease characteristics (number of tender joints, number of swollen joints, symptom duration, DAS28 score, Health Assessment Questionnaire score), prognostic factors [presence of RF or anti-cyclic citrullinated peptide antibodies (anti-CCP)], presence of radiographic erosions, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, category of diagnostic certainty (definite vs probable RA), and the geographic area of inclusion.

In view of the length of the ESPOIR inclusion period, we also assessed the influence of the inclusion period, subdivided into 4 quartiles: November 2002 through May 2003, June 2003–December 2003, January 2004–June 2004, and July 2004–April 2005.

When treatment was not the same as the STPR guidelines, the discrepancy could be either important or slight. We therefore pooled the different treatment decisions in 3 broad categories: no DMARD prescription, prescription of DMARD that only prevents flares (hydroxychloroquine, gold salts, tiopronin), and prescription of at least one DMARD that prevents flares and has been proven to inhibit structural damage (MTX, leflunomide, sulfasalazine, and TNF blockers). We then assessed the observed and expected (according to STPR guidelines) DMARD prescriptions according to these 3 categories.

Mail survey. In May 2007, a survey was mailed to the initial attending rheumatologists of all patients whose treatment differed from STPR guidelines. The questionnaire was carefully phrased to not seem judgmental, especially since no aspect of either CPG was mandatory. All therapeutic options were presented at the same level, with no labeling as good or bad, optimal or suboptimal. The questionnaire asked about the reasons for the decision and then about awareness of the STPR and EULAR guidelines. Rheumatologists were also asked about their perception of the guidelines' pertinence and the decision they would make for a similar patient visiting in 2007.

Statistical analysis. Statistical analysis used SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Conformity was scored 1 if the treatment and guidelines matched and 0 if not. Conformity was expressed as a percentage. Categorical variables were compared with Pearson's chi-square test or Fisher's exact test, as appropriate. The statistical significance level was set at $\alpha = 0.05$ in 2-tailed tests.

Univariate analyses determined the factors associated with conformity. Multivariate logistic regression with generalized estimating equations (mixed model) was used to account for the clusters (14 hospital centers). Variables with a p value < 20% were kept in the final model. The likelihood of dependent variables is presented as odds ratios with their 95% confidence intervals. The responses to the mail survey are expressed as percentages.

The ESPOIR study was approved by the central ethics committee of Montpellier, and written informed consent was obtained from each participant in the cohort. Both the scientific and the steering committee of the ESPOIR cohort approved this study.

RESULTS

Of the 813 cohort members, 627 had definite or probable RA and were included in the extended analysis (Figure 1).

Baseline patient characteristics. Table 1 summarizes the main baseline characteristics of the 627 patients. They were predominantly female (76.6%), with mean age 48.7 years. Almost 30% had at least one comorbid disease at inclusion. They presented with active, very recent-onset disease: mean tender joint count was 9.4 ± 7.1, mean swollen joint count 8.2 ± 5.3, mean DAS28 5.4 ± 1.2, and mean symptom duration (from onset of the first persistently swollen joint) less than 15 weeks.

In all, 505 patients (80.5% of 627 patients) began DMARD treatment within a mean of 17.6 ± 9.1 weeks (median 16.4) from the onset of the first persistently swollen joint. The most frequently prescribed DMARD was MTX, in 340 patients (54.2% of 627). Combination therapies were noted in 41 patients (6.5%) (Table 2).

Conformity with guidelines. Conformity with the STPR guidelines was determined for 581 patients (92.7%; Figure 1) and ranged between centers from 35% to 79%. Overall, 337 DMARD prescriptions (58.0%) matched the STPR guidelines (66% in the definite RA group and 47% in the probable RA group).

Conformity with the EULAR guidelines was determined for all 627 patients and ranged between centers from 22% to 75.4%. In all, 340 DMARD choices (54.2%) matched the EULAR guidelines (61% in the definite RA group and 45% in the probable RA group).

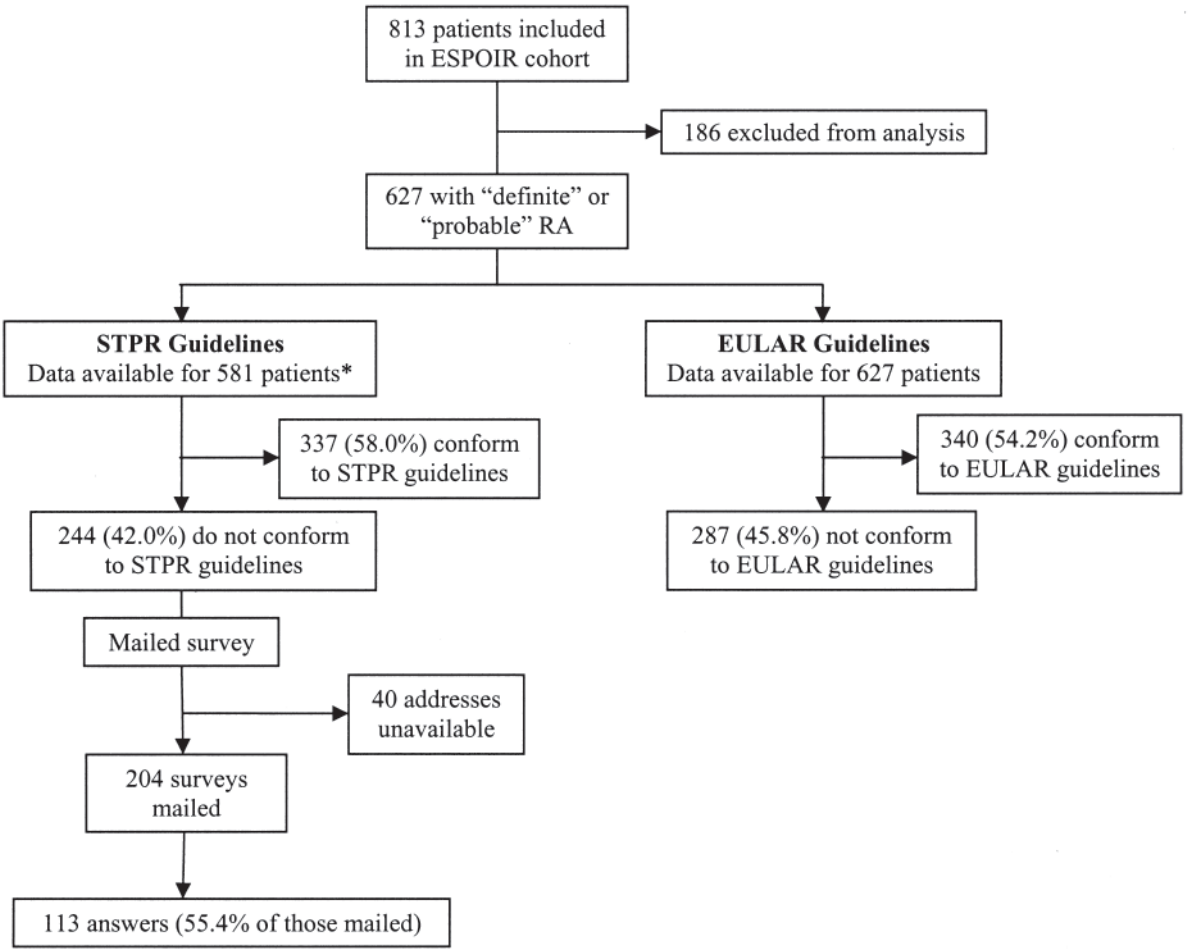

Figure 1. The design of the study. *581 (92.7%) patients had complete data sets (DAS28 score, structural status, RF status).

Table 1. Baseline characteristics of ESPOIR cohort patients.

Characteristics	Definite and Probable RA, n = 627
Social and demographic	
Women, n (%)	480 (76.6)
Age, yrs, mean ± SD (median)	48.7 ± 12.4 (51.1)
Caucasian, n (%)	582 (92.8)
Postsecondary education, n (%)	96 (15.3)
History/comorbidities	
Personal or family history of psoriasis, n (%)	103 (16.4)
At least 1 comorbid factor*, n (%)	178 (28.7)
BMI, kg/m^2, mean ± SD (median)	25.2 ± 4.6 (24.5)
Disease characteristics	
Tender joints **, mean ± SD (median)	9.4 ± 7.1 (8.0)
Swollen joints**, mean ± SD (median)	8.2 ± 5.3 (7.0)
Symptom duration, wks, mean ± SD (median)	14.7 ± 7.5 (13.4)
DAS28 value, mean ± SD (median)	5.4 ± 1.2 (5.3)
HAQ, mean ± SD (median)	1.0 ± 0.7 (1.0)
Prognostic factors	
Positive for RF, n (%)	343 (54.7)
Positive for anti-CCP, n (%)	278 (44.8)
Presence of bone erosion on radiograph, n (%)	146 (26.0)
ESR, mm/h, mean ± SD (median)	30.4 ± 24.4 (24.0)
CRP, mg/l, mean ± SD (median)	23.4 ± 34.3 (10.0)
RA diagnosis	
Fulfilled 4 ACR criteria, n (%)	539 (86.0)
RA diagnostic certainty on 0–100 VAS, mean ± SD (median)	78 ± 18 (80)
Patients with	
Definite RA, n (%)	359 (57.3)
Probable RA, n (%)	268 (42.7)

* Presence of at least 1 comorbid factor: ischemic heart disease, diabetes mellitus, hypertension, renal disease (clearance < 60 ml/min or proteinuria or hematuria), current cancer, or chronic viral infection (HIV, HBV, HCV). ** Number of tender and swollen joints on a 28-joint count. BMI: Body mass index; DAS28: Disease Activity Score on 28 joints; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; CCP: anti-CCP antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ACR: American College of Rheumatology.

Table 2. Details of therapeutic decisions.

Type of DMARD Prescribed	Definite and Probable RA, n = 627 (%)
No DMARD	122/627 (19.5)
1 DMARD	464/627 (74.0)
MTX	300/464 (64.7)
Sulfasalazine	59/464 (12.7)
Hydroxychloroquine	58/464 (12.5)
Leflunomide	31/464 (6.7)
Others	14/464 (3.0)
TNF blocker agents (etanercept, adalimumab)	2/464 (0.4)
2 DMARD	32/627 (5.1)
MTX + hydroxychloroquine	18/32 (56)
MTX + TNF blocker agents (etanercept, adalimumab)	8/32 (25)
MTX + others	3/32 (10)
MTX + sulfasalazine	2/32 (6)
Hydroxychloroquine + sulfasalazine	1/32 (3)
3 DMARD	9/627 (1.4)
MTX + hydroxychloroquine + gold salts	9/9 (100)

DMARD: disease modifying antirheumatic drug; MTX: methotrexate; TNF: tumor necrosis factor.

Determinants associated with conformity to STPR guidelines. Results of the univariate analysis are presented in Table 3. The final multivariate analysis, adjusted for center, found 3 variables to be significantly associated with conformity: presence of RF or anti-CCP antibodies and a "definite" diagnosis of RA were associated with better conformity (odds ratios > 1), while poorer conformity was found for women patients (odds ratios < 1) (Table 4).

EULAR guidelines. The data from the univariate analysis are not shown. The multivariate analysis, adjusted for center, found the following significant determinants associated with better conformity: moderate and high DAS28 scores, radiographic bone erosions, and the presence of RF or anti-CCP antibodies (odds ratios > 1) (Table 4).

Influence of inclusion period. We observed a trend towards better conformity with the STPR guidelines over time during the ESPOIR inclusion period. During the last period (July 2004 through April 2005), conformity with STPR reached 67.4%, compared with 56.5% for the previous

Table 3. Conformity with STPR guidelines and univariate analysis of determinants.

Determinants	N = 581	% of Conformity	p
Sex			
Male	141	65.3	0.04
Female	440	55.7	
Postsecondary education			
No	493	60.0	0.02
Yes	88	46.6	
Personal or family history of psoriasis			
No	484	60.3	0.01
Yes	97	46.4	
No. swollen joints (28–joint count)			
0-3	105	49.5	0.04
4–8	238	55.9	
9-28	238	63.9	
DAS28 value			
0–3.2	29	37.9	0.03
3.2–5.1	232	56.0	
> 5.1	318	61.6	
Elevated level of ESR			
No	305	53.8	0.02
Yes	274	63.1	
Positive for RF and/or anti-CCP			
No	237	45.6	< 0.001
Yes	344	66.6	
Definite RA			
No	249	47.0	< 0.001
Yes	332	66.3	
Fulfilled 4 ACR criteria for diagnosis of RA			
No	80	42.5	0.003
Yes	501	60.5	
Observational center (14 centers)	19 to 62	Range 35.0% to 79.0%	—

DAS28: Disease Activity Score 28 joints; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; anti-CCP: anti-CCP antibodies; ACR: American College of Rheumatology.

Table 4. Multivariate analysis of determinants of conformity with guidelines.

Variables	Odds Ratio	95% CI	p
Conformity with STPR guidelines			
Women	0.70	0.50–0.98	0.04
Positive for RF and/or anti-CCP	1.96	1.34–2.87	< 0.001
Definite RA	1.77	1.29–2.44	< 0.001
Conformity with EULAR guidelines			
DAS28 value			
3.2–5.1 vs 0–3.2	3.03	1.28–7.18	0.01
> 5.1 vs 0–3.2	4.18	1.57–11.1	0.004
Positive for RF and/or anti-CCP	2.28	1.71–3.02	< 0.001
Bone erosion on radiograph	1.45	1.01–2.08	< 0.05

DAS28: Disease Activity Score 28 joints; RF: rheumatoid factor; anti-CCP: anti-CCP antibodies.

periods. This difference was not statistically significant, however (chi-square = 6.9, DF = 3, p = 0.07).

Extent of the divergence in cases of nonconformity with the STPR guidelines. Overall, 433 patients (69.1%) received at least one DMARD proven to inhibit structural damage, 72 (11.5%) a DMARD that did not, and 122 (19.5%) received no DMARD until the 6-month followup visit.

We then focused on the 244 patients treated differently than the STPR guidelines recommend (Table 5): 116 (47.5%) patients had mild to moderate disease (no structural damage and low or moderate DAS28 scores). In this group, 62 patients (25.4%) had no DMARD prescribed, 31 (12.7%) only a flare-preventing DMARD, and 23 (9.4%) at least one flare-preventing DMARD also proven to inhibit

Table 5. Comparison of the observed prescribed DMARD classified in 3 categories with 4 STPR-recommended therapeutic options (Appendix 2) in the 244 patients treated differently from STPR guidelines. A: hydroxychloroquine or sulfasalazine; B: sulfasalazine or methotrexate; C: methotrexate or leflunomide; D: methotrexate or TNF blocker agents.

	STPR-recommended Therapeutic Options				
	A, n = 35	B, n = 81	C, n = 120	D, n = 8	Total, n = 244 (%)
Observed prescribed DMARD					
No DMARD prescribed	32	30	20	1	83 (34.0)
Only flare-preventing DMARD	0	31	38	1	70 (28.7)
At least 1 DMARD with proven structural effect	3	20	62	6	91 (37.3)

structural damage. Of the 128 (52.5%) patients with severe disease (either structural damage or high DAS28 score), 21 (8.6%) had no DMARD prescribed, 39 (16.0%) only a flare-preventing DMARD, and 68 (27.9%) at least one DMARD that inhibited structural damage and prevented flares.

Mail survey. The mail questionnaire was sent out in May 2007 and the analysis was performed in August 2007: 204 separate surveys were sent to 124 rheumatologists. We received 113 answers (55.4% of 204) from 73 rheumatologists (58.9% of 124) (Figure 1). They responded that their treatment decision was based, in decreasing order, on diagnostic uncertainty (36.1%), presumed best benefit/risk ratio (25.0%), hospital decision (13.9%), usual practice (7.4%), patient decision (5.6%), "don't remember" (4.6%), inclusion in a clinical trial (3.7%), and patient comorbidities (3.7%). The percentages reported by respondents who decided not to use any DMARD differed slightly, with diagnostic uncertainty accounting for 47.4% of the reasons; the order thereafter did not differ.

At the time of the survey, 56 rheumatologists (76.7%) were aware of the STPR guidelines and 59 (80.8%) were aware of the EULAR guidelines.

In 66 cases (58.4% of 113), the rheumatologist reported they would choose a different treatment now, and 57 (50.4%) would choose the treatment recommended by STPR. The main reason for continued disagreement with STPR guidelines remained diagnostic uncertainty.

DISCUSSION

Our study demonstrates a rather substantial discrepancy between the recently published guidelines for the first-line DMARD to be prescribed for patients with early RA and daily French practice between 2002 and 2005.

We have found no similar data in the literature with which we can compare our results. Although some studies that retrospectively assessed the application of CPG for therapeutic decisions report conformity rates ranging from 40% to 60%, study designs and methods vary greatly[6,28-30]. For example, in the field of rheumatology, Denoeud, *et al* showed that the French general practitioners treating osteoarthritis of the knee conform with the EULAR guidelines in 54% of cases[28]. The conformity rates in our study, even before implementation of the CPG, are rather encouraging and suggest that rheumatologists will find them acceptable.

The conformity with guidelines improved during the study period, with a rate of 67% for the STPR guidelines during the last period of the ESPOIR studies. There were connections between the members of the STPR group and the ESPOIR steering committee as a few people participated in both groups. This could have led to better dissemination of the STPR guidelines in the ESPOIR study centers, even if patients were followed by their usual rheumatologist. Moreover, some discrepancies have been observed in the different centers, which might be due to local prescription habits or the influence of local opinion leaders. Some of the ESPOIR centers are also important recruitment centers for clinical trials, leading to DMARD prescriptions that are different from the guidelines. However, treatment decisions were made by the usual practising rheumatologist and not directly by the people involved in the recruitment and followup of the ESPOIR patients.

Our study found quite similar rates of conformity for both sets of guidelines, which recommend MTX as the principal treatment in early RA. Of the 505 (67%) patients who received a DMARD in this study, 340 were prescribed MTX. These results are similar to those in other studies. MTX is the leading DMARD prescribed for RA in Europe, the United States, and Australia; it accounts for 46% to 83% of all DMARD prescribed, according to country[31-36].

We also wondered if the results of conformity with EULAR guidelines would be different by assuming that using leflunomide as a first DMARD was equivalent to use of MTX. The rate of conformity was then 59.2% instead of 54.2%.

A key point in the recent therapeutic advances in the management of RA is the need to start treatment early with a DMARD that reduces joint damage (radiographic progression)[16,18,20]. Delaying its initiation in patients with early RA is thus very clearly suboptimal treatment.

The STPR and EULAR guidelines differ in that STPR grades the prescription according to disease activity and factors that are predictive of severity (structural damage, RF status). In particular, the STPR group does not recommend MTX for RA patients who have a low DAS28 and no structural damage and are negative for RF, that is, for mild or perhaps doubtful RA. The randomized controlled PROMPT study points in the same direction[37]. In a subgroup of patients with early arthritis who were negative for RF and anti-CCP antibodies and thus might not develop RA, it showed that MTX did not improve patient outcomes at 3 years[37]. The STPR guidelines rely on this concept and introduce treatment that is graded according to the potential benefit/risk ratio of MTX, compared with other conventional DMARD such as hydroxychloroquine.

It was also interesting to determine whether the patients treated differently than the STPR guidelines recommend had received a DMARD that stops joint damage. Although only 23 of the 116 patients with mild or moderate disease (20%) had been treated with such a drug, negative consequences for this lack of treatment were least likely in this group[37]. On the other hand, 60 of the 128 patients with severe disease (47%) had still not received a DMARD effective against structural involvement 6 months after inclusion in the study, and their treatment can be considered suboptimal, as several authors have shown[18,38,39].

An important reason for nonconformity with guidelines and, by extension, for suboptimal care is diagnostic uncertainty, a well known difficulty in the management of early RA. Classification criteria and clinical standards for diagnosis are useful after one or 2 years of disease, but not necessarily at the first consultation. In practice, early arthritis is frequently undifferentiated[40]. An RA diagnosis is thus generally based upon the rheumatologist's opinion, perhaps after consideration of the ACR classification criteria[27], as here. However, these criteria do not perform as well in early arthritis as they do in established RA[41]. Other criteria, such as those from the Leiden clinic[42], have been developed to address early RA diagnosis more specifically.

Some limitations in our study must be noted. Although the cohort was observational and intended for the study of routine practice, it is not certain that mere participation did not influence rheumatologists' treatment decisions and thereby introduce possible bias. Further, compliance bias undoubtedly plays a role in physicians' answers to questions about their practices, because it is well known that even the experts' answers about their prescription habits are sometimes rather far from their real practice, as Headrick, *et al* showed[43].

To conclude, we found a gap between recent guidelines for treatment of early RA and daily practice by specialists during the period the guidelines were under development. In some cases, especially when the RA diagnosis is uncertain or predictive factors of severity are absent, these differences

APPENDIX 1. Questionnaire mailed to patients' attending rheumatologists.

You participated in the ESPOIR cohort between 2002 and 2005, by including a patient on (date).
Your patient, Mr/Mrs xxx, ___ years old, presented with:

- ___ tender joints, ___ swollen joints
- erythrocyte sedimentation rate was ___ mm at 1st hour, C-reactive protein was ___ mg/L, rheumatoid factor was positive/negative
- DAS 28 was ___
- Radiography showed some (did not show any) structural damage typical of rheumatoid arthritis (RA)

The therapeutic decision was to: start (not start) a DMARD.

I. Can you explain the reasons leading to this therapeutic decision, reviewing your file if necessary? *(Please circle the answer you prefer)*

1. This was my usual practice
2. This option had the best benefit/risk ratio
3. This was the best option because of patient comorbidities
4. The RA diagnosis was uncertain
5. Therapeutic decision was due to hospital colleagues
6. The patient refused another proposal
7. The patient was included in a clinical trial
8. I don't remember

II. Various guidelines have been published for choosing the first DMARD for patients presenting with early RA. Are you aware of the following guidelines? *(Please fill in one circle per item)*

1. STPR, in 2006 (Le Loët X, et al, ARD 2006;65:45-50).
   ○ Yes ○ No
2. EULAR, in 2007 (Combe B, et al, ARD 2007;66:34-45).
   ○ Yes ○ No

III. Considering these guidelines and their impact in your practice, how would you treat a similar case today? *(Please circle the answer you prefer)*

1. Would not start a DMARD
2. Introduction of:
   - Hydroxychloroquine
   - Sulfasalazine
   - Gold salts
   - Methotrexate
   - Leflunomide
   - Combined therapy:
   - Hydroxychloroquine + sulfasalazine
   - Methotrexate + hydroxychloroquine
   - Methotrexate + sulfasalazine
   - Methotrexate + leflunomide
   - Methotrexate + gold salts
   - Methotrexate + hydroxychloroquine + gold salts
   - TNF blocker agent alone or with another DMARD
   - Others: ___

IV. In a similar case, the STPR work group (Stratégies Thérapeutiques dans la Polyarthrite Rhumatoïde) would have recommended:
Either ___ or ___ as a single treatment. Do you agree with this guideline in this patient's case? *(Please circle the answer you prefer)*
○ Yes ○ No

If you answered "No", please circle the reason why or describe why under "other":

- This is not my usual practice
- This option does not have the best benefit/risk ratio
- This is not the best option because of patient comorbidities
- The diagnosis of RA is uncertain
- I think that a combination of DMARD is needed, including one of the drugs recommended
- I think that a combination of DMARD is needed, not including either of the two recommended drugs
- Other: ___

APPENDIX 2. Therapeutic options recommended by STPR for prescription of first DMARD in early RA, derived from the STPR guidelines[21]: A: hydroxychloroquine or sulfasalazine; B: sulfasalazine or methotrexate; C: methotrexate or leflunomide; D: methotrexate or TNF blocker agents.

	Patients			
	No Structural Damage		With Structural Damage	
DAS28	RF–	RF +	RF–	RF+
Low: 0–3.2	A	B	C	C
Moderate: 3.2–5.1	B	B	C	C
High: > 5.1	C	C	C	D

DAS28: Disease Activity Score 28 joints; RF: rheumatoid factor.

are unlikely to be harmful. In other cases, however, care appeared to be suboptimal. Future efforts will concern the establishment of reliable criteria for diagnosis of early RA, necessary to improve the implementation of the treatment guidelines.

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REFERENCES

1. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22.
2. Kulkarni K, Castle G, Gregory R, et al. Nutrition practice guidelines for type 1 diabetes mellitus positively affect dietitian practices and patient outcomes. The Diabetes Care and Education Dietetic Practice Group. J Am Dietetic Assoc 1998;98:62-70.
3. Debnath D, Dielehner N, Gunning KA. Guidelines, compliance, and effectiveness: a 12 months' audit in an acute district general healthcare trust on the two week rule for suspected colorectal cancer. Postgrad Med J 2002;78:748-51.
4. Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol 2004;22:3685-93.
5. Vikman S, Airaksinen KE, Tierala I, et al. Improved adherence to practice guidelines yields better outcome in high-risk patients with acute coronary syndrome without ST elevation: findings from nationwide FINACS studies. J Intern Med 2004;256:316-23.
6. Nieuwlaat R, Olsson SB, Lip GY, et al. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J 2007;153:1006-12.
7. Rogers AM, Ramanath VS, Grzybowski M, et al. The association between guideline-based treatment instructions at the point of discharge and lower 1-year mortality in Medicare patients after acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) initiative in Michigan. Am Heart J 2007;154:461-9.
8. Kosecoff J, Kanouse DE, Rogers WH, McCloskey L, Winslow CM, Brook RH. Effects of the National Institutes of Health Consensus Development Program on physician practice. JAMA 1987;258:2708-13.
9. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458-65.
10. Tunis SR, Hayward RS, Wilson MC, et al. Internists' attitudes about clinical practice guidelines. Ann Intern Med 1994;120:956-63.
11. Stange KC, Kelly R, Chao J, et al. Physician agreement with US Preventive Services Task Force recommendations. J Fam Pract 1992;34:409-16.
12. Grilli R, Lomas J. Evaluating the message: the relationship between compliance rate and the subject of a practice guideline. Med Care 1994;32:202-13.
13. Durieux P, Ravaud P, Dosquet P, Durocher A. Effectiveness of clinical guideline implementation strategies: systematic review of systematic reviews. [French] Gastroenterol Clin Biol 2000; 24:1018-25.
14. Saillour-Glenisson F, Michel P. Individual and collective facilitators of and barriers to the use of clinical practice guidelines by physicians: a literature review. Rev Epidemiol Sante Publique 2003;51:65-80.
15. O'Dell JR. How is it best to treat early rheumatoid arthritis patients? Best Pract Res 2001;15:125-37.
16. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology Oxford 2001;40:1211-20.
17. Verstappen SM, Jacobs JW, Bijlsma JW, et al. Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. Arthritis Rheum 2003;48:1797-807.
18. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology Oxford 2004;43:906-14.
19. Keen HI, Emery P. How should we manage early rheumatoid arthritis? From imaging to intervention. Current Opin Rheumatol 2005;17:280-5.
20. Weinblatt ME. Rheumatoid arthritis: treat now, not later! Ann Intern Med 1996;124:773-4.
21. Le Loet X, Berthelot JM, Cantagrel A, et al. Clinical practice decision tree for the choice of the first disease modifying antirheumatic drug for very early rheumatoid arthritis: a 2004 proposal of the French Society of Rheumatology. Ann Rheum Dis 2006;65:45-50.
22. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
23. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis 2002;61:290-7.
24. Kennedy T, McCabe C, Struthers G, et al. BSR guidelines on standards of care for persons with rheumatoid arthritis. Rheumatology Oxford 2005;44:553-6.
25. Combe B. The French early arthritis registry. Clin Exp Rheumatol 2003;21:S123-8.
26. Combe B, Benessiano J, Berenbaum F, et al. The ESPOIR cohort: A ten-year follow-up of early arthritis in France. Methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74:440-5.
27. Arnett FC, Edworthy SM, Bloch DA, et al. The American

Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
28. Denoeud L, Mazieres B, Payen-Champenois C, Ravaud P. First line treatment of knee osteoarthritis in outpatients in France: adherence to the EULAR 2000 recommendations and factors influencing adherence. Ann Rheum Dis 2005;64:70-4.
29. Irwin ME, Bainey KR, Senaratne MP. Evaluation of the appropriateness of pacemaker mode selection in bradycardia pacing: how closely are the ACC/AHA guidelines followed? Pacing Clin Electrophysiol 2003;26:2301-7.
30. Perlis RH. Use of treatment guidelines in clinical decision making in bipolar disorder: a pilot survey of clinicians. Current Med Res Opin 2007;23:467-75.
31. Kvien TK, Heiberg, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23:S188-94.
32. Maravic M, Berge C, Daures JP, Boissier MC. Survey of practices regarding management of early rheumatoid arthritis by rheumatologists in France. Clin Exp Rheumatol 2004;22:319-27.
33. Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. Rheumatology Oxford 2002;41:1367-74.
34. Jobanputra P, Wilson J, Douglas K, Burls A. A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. Rheumatology Oxford 2004;43:206-10.
35. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol 2002;29:2521-4.
36. Chan V, Tett SE. Changes in use of disease-modifying anti-rheumatic drugs in Australia over the period 1992-2004. Pharmacoepidemiol Drug Safety 2006;15:462-8.
37. van Dongen H, van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56:1424-32.
38. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-51.
39. van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004;63:274-9.
40. Dixon WG, Symmons DP. Does early rheumatoid arthritis exist? Best Pract Res 2005;19:37-53.
41. Saraux A, Berthelot JM, Chales G, et al. Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. Arthritis Rheum 2001;44:2485-91.
42. Huizinga TW, Machold KP, Breedveld FC, Lipsky PE, Smolen JS. Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis. Arthritis Rheum 2002;46:1155-9.
43. Headrick LA, Speroff T, Pelecanos HI, Cebul RD. Efforts to improve compliance with the National Cholesterol Education Program guidelines. Results of a randomized controlled trial. Arch Intern Med 1992;152:2490-6.