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ORIGINAL ARTICLE

Choice of Second-Line Disease-Modifying Antirheumatic Drugs After Failure of Methotrexate Therapy for Rheumatoid Arthritis: A Decision Tree for Clinical Practice Based on Rheumatologists' Preferences

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Objective. **To survey rheumatologists' preferences for the choice of a second-line disease-modifying antirheumatic drug (DMARD) after inadequate response with methotrexate (MTX) therapy in rheumatoid arthritis (RA).**

Methods. **Thirty-six rheumatologists stated their preferences for RA treatment after inadequate response with MTX therapy (optimal dose at least 6 months). From the initial scenario, we derived 54 vignettes varying by rheumatoid factor or anti–cyclic citrullinated peptide antibody presence, swollen joint count, Disease Activity Score in 28 joints, and structural damage. Respondents stated their preference among 5 therapeutic options: MTX continuation, switch to another conventional DMARD, addition of another conventional DMARD, addition of anakinra, or addition of a tumor necrosis factor (TNF) blocker. Presentation by pairs yielded 10 combinations of strategies for each variant, totaling 540 vignettes; participants evaluated a random sample of 180 vignettes. Determinants of each top-ranked option were analyzed by logistic regression. The compilation of these data served to define a therapeutic algorithm.**

Results. **The responses of 33 rheumatologists were analyzable. Therapeutic preferences corresponded to the top-ranked options. For patients with mild or moderately active RA, either a switch or step-up strategy to another conventional DMARD was top ranked. TNF blockers were preferred for RA patients with high disease activity or progressive structural damage. On the basis of these preferences, we developed a simple decision tree for use in daily clinical practice.**

Conclusion. **Our simple, easy-to-use decision tree developed from rheumatologists' preferences for therapy after failure of MTX therapy in RA treatment may guide rheumatologists in daily practice to choose a second-line DMARD.**

INTRODUCTION

Rheumatoid arthritis (RA) prognosis is dominated by functional impairment related to joint pain, synovial inflammation, and structural damage (1,2), and by increased cardiovascular morbidity and mortality (3,4). During the past decades, modern conventional and biologic disease-

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modifying antirheumatic drugs (DMARDs) have been effective to various extents in controlling RA-related inflammation, preventing disease flare, the progression of structural damage (5–9), and thus overall improvement in RA prognosis (10). Also related to improved prognosis may be optimization of care through disease management by rheumatology specialists (11) and standardized disease activity monitoring based on RA-specific composite indexes like the Disease Activity Score in 28 joints (DAS28) (12–14). Several randomized controlled trials have shown the introduction or adaptation of such an index in treatment decision making associated with better clinical and radiologic outcomes (15–17).

Recently, initiatives have supported the rapid and wide dissemination of optimal care from clinical research to daily rheumatology practice, and several clinical practice guidelines have been produced at both national and international levels (18,19). In addition to recommendations about overall disease management, specific work has helped physicians in treatment choice. The European League Against Rheumatism has recommended the introduction of methotrexate (MTX) within the first few months following RA onset because it can allow for significant control of RA inflammatory activity and structural damage, and may subsequently be an anchor for adding another DMARD in case of inadequate response (20). Very recently, the American College of Rheumatology (ACR) published recommendations for the use of nonbiologic and biologic DMARDs in RA patients and proposed therapeutic options for patients with both early and established RA (21). However, making decisions about treatment may be complex and challenging. As pointed out in an editorial discussing the 2008 ACR recommendations, guidelines development is hampered by the complexity and the heterogeneity of the clinical reality. On the one hand, the evidence-based approach is limited by the rigidity of both the design and the inclusion/exclusion criteria of randomized controlled trials. On the other hand, the expert opinion approach may fail to reach consensual recommendation in some complex situations, even when adequate methods such as the Delphi method or the RAND Appropriateness Method are used (22).

Within the first years of disease, RA presentation may be incomplete and diagnosis may be difficult (20,23). All RA patients do not experience the same joint inflammation or structural damage, an important point to consider when prescribing a first DMARD in patients with early RA (24,25). Such clinical situations may lead to the consideration of other DMARDs, different in some ways from those recommended by guidelines. Since early treatment plays a key role in RA prognosis (26–29), rheumatologists must choose a molecule or a therapeutic strategy regardless of the difficulties, and decision-making aids may be valuable in this context.

The Stratégies Thérapeutiques dans la Polyarthrite Rhumatoïde (STPR) Group is an expert group working on treatment decision making in RA. Since the scientific literature provides little data to compare the therapeutic options in patients with early- or recent-onset RA and to determine the best option for therapy, the group settled on a preference survey based on RA cases, or vignettes, to develop a therapeutic algorithm for choosing a first DMARD in patients with early RA, presented as a decision tree suitable for daily clinical practice (30). This study constitutes the next step of the STPR program, focusing on clinicians' preferences in choosing a second-line DMARD for RA patients in whom there was an inadequate disease response to a first agent such as MTX. After a preliminary study (31), the group implemented a new survey based on cases of RA patients with progressive loss of efficacy of MTX. MTX was chosen as the leader of conventional DMARDs, proven effective for both disease flare and prevention of structural damage; it is also the DMARD most frequently prescribed worldwide for patients with early- or recent-onset RA (32–34), as well as the recommended anchor drug for early arthritis (20,30).

The aim of this study was to establish physician preferences for the choice of a second-line DMARD after loss of efficacy of a first-line conventional DMARD in patients with RA by assessing the preferences of a sample of practicing rheumatologists experienced in the care of RA.

MATERIALS AND METHODS

Study design. The survey was based on individual interviews held in January and February 2006, during which rheumatologists were presented with standardized clinical vignettes and were asked to choose between 2 therapeutic options for each vignette (Figure 1). The interviews were directed by a research nurse who was responsible for checking the time schedule and the exhaustiveness of responses.

Participating rheumatologists. In addition to a methodologist (FG), the STPR Working Group consists of 12 teaching rheumatologists with substantial expertise in the treatment of RA, practicing exclusively in university rheumatology departments throughout France. In each center, rheumatologists selected 2 nonteaching collabora-

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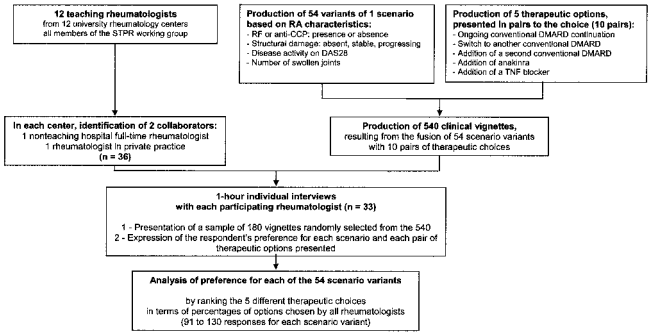

Figure 1. Flow chart of the study. STPR = Stratégies Thérapeutiques dans la Polyarthrite Rhumatoïde; RA = rheumatoid arthritis; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide antibodies; DAS28 = Disease Activity Score in 28 joints; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

tors, one practicing exclusively in a hospital department and the other working predominantly in a private setting. The survey was then proposed to a sample of 36 rheumatologists, 3 per center, whose selection was detailed previously (30). Each interview was performed individually. The respondents were unaware of the vignettes before the study. They were also blind to their colleagues' responses in order to elicit their own individual preferences.

Base-case scenario and 54 variants. The base-case scenario was derived from the first STPR study assessing rheumatologists' preferences for the first DMARD in patients with early RA (30). As a reminder, the disease characteristics included in the vignette were selected by a Delphi method among the STPR Group members, exploring the relevant variables to take into account to make a decision about RA treatment (30). For the present study, the base-case description included the following characteristics: RA diagnosis made at least 12 months prior, MTX as the first DMARD prescribed for >6 months at the maximum tolerated dosage (e.g., 20 mg/week) associated with low-dose prednisone (e.g., 3 mg/day), and initial response to MTX but subsequent loss of efficacy of the drug for a few weeks.

A total of 54 variants were derived, differing by 4 RA severity markers (24,35): presence or absence of rheumatoid factor (RF) or anti–cyclic citrullinated protein (anti-CCP) antibodies as a predictor of severity; presence or absence of structural damage and stable or progressing since last radiologic evaluation; disease activity on the DAS28 (13), categorized as mild (DAS28 ≤3.2), moderate (DAS28 3.3–5.1), or high (DAS28 >5.1); and number of swollen joints 2, 6, or 10 (not limited to the DAS28 localizations).

Therapeutic options to choose. Five potential strategies for therapy were identified: 1) continuation of the ongoing conventional DMARD (i.e., MTX at the maximum tolerated dose, associated with steroid joint injection if needed), 2) MTX replaced by a second conventional DMARD able to control both inflammation and structural damage, 3) addition of a second conventional DMARD to MTX (or even 3 if the addition of both sulfasalazine and hydroxychloroquine was considered), 4) addition of anakinra, an interleukin-1 (IL-1) inhibitor, or 5) addition of a tumor necrosis factor (TNF) blocker. Of note, at the time of the study, IL-1 receptor antagonists and TNF blockers were the only biologics licensed in France for cases of inadequate response to MTX therapy. Moreover, replacing the ongoing conventional DMARD with a TNF blocker was not proposed because the French clinical practice guideline on the use of TNF blockers in patients with RA expressly recommends using biologics associated with MTX.

Assessment of preference for therapy. To assess respondents' preferences for therapy, therapeutic options were presented in pairs according to the Thurstone pairwise method (36). This method has been developed to facilitate preference elicitation in difficult decision-making processes by disentangling a complex situation with a series of simplified scenarios in which choice options can be presented against one another, i.e., by pairs. In comparison to other expert opinion approaches such as the RAND Appropriateness Method used in the 2008 ACR recommendations, in which respondents were asked to rate the appropriateness of a specific option (21,37), the pairwise method does not require any direct or absolute rating (or ranking) of the proposed options, but simply asks respondents to choose between 2 possibilities for each vignette. Response compilation enables the ranking of the different choice options, which expresses respondents' overall preferences for each clinical situation (38).

In the present study, the 5 different strategies presented by pairs resulted in 10 combinations for each of the 54 scenario variants, i.e., 540 vignettes. Each participant evaluated a random sample of 180 vignettes in a 1-hour interview conducted by a research nurse, unaware of RA care and specially trained to respect and not influence panelist responses in any way. Each participant stated his therapeutic preference between the 2 therapeutic options presented for a given scenario variant.

Data management and statistical analysis. The compilation of answers enabled the ranking of the 5 therapeutic options for each of the 54 variants on the basis of the number of times an option was chosen, shown as the percentage of all responses expressed for a given variant. The respondents' preferred options corresponded to the top-ranked option or to the top 2 ranked options if the frequencies of selection were close.

The determinants associated with the 5 therapeutic options were analyzed by logistic regression. The dependant variable was the considered option, valued as 1 if the option was top ranked and 0 if not. The explanatory variables were the variant characteristics. The potential impact of respondents' characteristics, including age, sex, year of final graduation, and setting of rheumatology practice, was studied by generalized linear modeling. All statistical analyses involved use of Microsoft Excel (Microsoft, Redmond, WA) or SAS, version 8.2 (SAS Institute, Cary, NC).

Table 1. Rheumatologists' preferences for second-line therapy after failure of MTX therapy in RA patients without structural damage*

DAS28	Swollen joint count	Therapeutic option preferences			
		RF and anti-CCP negative	%	RF or anti-CCP positive	%
Low	2	Continuation of ongoing treatment	36.7	Continuation of ongoing treatment	36.3
		Switch to another conventional DMARD	34.4	Switch to another conventional DMARD	31.0
		Add another conventional DMARD	17.8	Add another conventional DMARD	23.0
Low	6	Continuation of ongoing treatment	33.0	Switch to another conventional DMARD	33.3
		Add another conventional DMARD	27.4	Add another conventional DMARD	26.7
		Switch to another conventional DMARD	26.4	Continuation of ongoing treatment	22.9
Low	10	Switch to another conventional DMARD	31.6	Switch to another conventional DMARD	32.3
		Add another conventional DMARD	24.2	Add another conventional DMARD	26.2
		Continuation of ongoing treatment	21.1	Continuation of ongoing treatment	20.8
Moderate	2	Switch to another conventional DMARD	37.3	Continuation of ongoing treatment	37.6
		Continuation of ongoing treatment	30.0	Switch to another conventional DMARD	22.0
		Add another conventional DMARD	19.1	Add another conventional DMARD	22.0
Moderate	6	Switch to another conventional DMARD	30.6	Switch to another conventional DMARD	33.6
		Add another conventional DMARD	27.6	Add another conventional DMARD	31.2
		Continuation of ongoing treatment	23.5	Continuation of ongoing treatment	18.4
Moderate	10	Switch to another conventional DMARD	32.1	Switch to another conventional DMARD	31.3
		Add another conventional DMARD	25.0	Add another conventional DMARD	21.2
		Continuation of ongoing treatment	17.0	Addition of TNF blocker	21.2
High	2	Switch to another conventional DMARD	34.9	Add another conventional DMARD	31.1
		Add another conventional DMARD	25.7	Continuation of ongoing treatment	24.5
		Continuation of ongoing treatment	18.3	Switch to another conventional DMARD	23.6
High	6	Switch to another conventional DMARD	37.1	Add another conventional DMARD	32.7
		Add another conventional DMARD	26.7	Switch to another conventional DMARD	24.8
		Continuation of ongoing treatment	17.1	Addition of TNF blocker	22.8
High	10	Switch to another conventional DMARD	35.7	Addition of TNF blocker	32.1
		Add another conventional DMARD	32.7	Switch to another conventional DMARD	29.2
		Addition of TNF blocker	13.3	Add another conventional DMARD	26.4

* No structural damage seen on radiographs. MTX = methotrexate; RA = rheumatoid arthritis; DAS28 = Disease Activity Score in 28 joints; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide antibodies; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

Decision tree construction. From these data on the preferences of rheumatologists, the STPR Group built a comprehensive algorithm. In a second step, the 12 STPR faculty members converted the algorithm into a simple decision tree for clinical practice by introducing, in addition to statistical rules, specific considerations based on this subgroup's clinical experience.

RESULTS

Of the 36 panelists contacted, 33 participated in the survey. One university rheumatologist, 1 hospital-based practitioner, and 1 private office-based practitioner declined the invitation.

Preferences for therapy. Rheumatologists' preferences were expressed as the percentage of times each therapeutic option was chosen. For RA without radiographic evidence of structural damage (Table 1), continuation of the ongoing treatment was the preferred option for patients with low disease activity and swollen joint count (SJC) limited to 2 (or possibly 6 in the absence of RF and anti-CCP antibodies), but not for moderate or high disease activity and an SJC of 10. A zone of uncertainty was noted for patients with RA with moderate disease activity but no objective sign of inflammation (with SJC $\leq$2). A switch to another conventional DMARD was generally preferred for patients with RA with moderate disease activity. The addition of another conventional DMARD to MTX therapy appeared to be reserved for patients with more severe disease (i.e., RF and/or anti-CCP antibody positivity or both high disease activity and high SJC). Finally, therapy with TNF blockers was the preferred option only for patients with the most severe presentation of RA (i.e., concomitant positivity for RF or anti-CCP antibodies, 10 swollen joints, and high DAS28).

Preference patterns were slightly different for erosive but structurally stable RA (Table 2). Continuation of ongoing treatment was mainly considered for patients with RA with 2 swollen joints and low or moderate disease activity. The addition of a second conventional DMARD was more likely chosen for RA patients with both RF positivity and/or anti-CCP antibodies and an SJC of 6; it was also chosen in RF/anti-CCP antibody–negative RA patients with both high disease activity and 6 or 10 swollen joints. Therapy with TNF blockers was top ranked for RA patients with RF or anti-CPP positivity, high disease activity, and an SJC of 6 or 10. The addition of TNF blockers was also considered for RA patients with moderate disease activity but with 10 swollen joints and detectable autoantibodies.

Table 2. Rheumatologists' preferences for second-line therapy after failure of MTX therapy in RA patients with stable structural damage*

DAS28	Swollen joint count	Therapeutic option preferences			
		RF and anti-CCP negative	%	RF or anti-CCP positive	%
Low	2	Continue ongoing treatment	41.2	Continue ongoing treatment	40.7
		Add another conventional DMARD	26.5	Switch to another conventional DMARD	23.1
		Switch to another conventional DMARD	19.6	Add another conventional DMARD	19.8
Low	6	Switch to another conventional DMARD	32.5	Add another conventional DMARD	35.2
		Continue ongoing treatment	30.9	Switch to another conventional DMARD	26.4
		Add another conventional DMARD	24.4	Continue ongoing treatment	24.2
Low	10	Add another conventional DMARD	31.0	Switch to another conventional DMARD	28.6
		Switch to another conventional DMARD	23.9	Add another conventional DMARD	26.7
		Continue ongoing treatment	20.4	Addition of TNF blocker	19.0
Moderate	2	Continue ongoing treatment	29.6	Continue ongoing treatment	33.9
		Switch to another conventional DMARD	27.8	Switch to another conventional DMARD	25.2
		Add another conventional DMARD	24.1	Add another conventional DMARD	25.2
Moderate	6	Switch to another conventional DMARD	28.9	Add another conventional DMARD	30.4
		Add another conventional DMARD	25.8	Switch to another conventional DMARD	25.9
		Continue ongoing treatment	18.6	Continue ongoing treatment	19.6
Moderate	10	Switch to another conventional DMARD	28.1	Switch to another conventional DMARD	29.7
		Add another conventional DMARD	27.3	Addition of TNF blocker	23.1
		Addition of TNF blocker	14.9	Add another conventional DMARD	22.0
High	2	Switch to another conventional DMARD	40.0	Switch to another conventional DMARD	29.3
		Add another conventional DMARD	26.3	Add another conventional DMARD	23.3
		Continue ongoing treatment	13.7	Addition of TNF blocker	23.3
High	6	Add another conventional DMARD	32.3	Addition of TNF blocker	28.9
		Switch to another conventional DMARD	27.1	Add another conventional DMARD	25.6
		Addition of TNF blocker	21.9	Switch to another conventional DMARD	22.3
High	10	Add another conventional DMARD	31.0	Addition of TNF blocker	38.1
		Addition of TNF blocker	26.5	Add another conventional DMARD	28.9
		Switch to another conventional DMARD	19.5	Switch to another conventional DMARD	16.5

* Stable structural damage seen on radiographs. See Table 1 for abbreviations.

Finally, in the most severe situation, the preferred option for RA patients with progressing structural damage (Table 3) was consistently the addition of a TNF blocker to an ongoing conventional DMARD, regardless of the other characteristics. The biologic agent that targets the IL-1 pathway was often mentioned in the top 3 options but was never top ranked.

Determinants of the therapeutic choices. The results of the logistic regression exploring the influence of disease characteristics on therapeutic choices are shown in Table 4. Continuation of ongoing treatment mainly depended on overall disease activity and structural damage; such an option was considered only for RA patients with low disease activity and no progressing structural damage. No strong positive determinants were observed for the choice of either the switch to or the addition of another conventional DMARD; however, progressing structural damage was significantly associated with the rejection or nonselection of such options. In contrast, the presence or progression of structural damage was significantly and positively associated with the decision to add a TNF blocker to MTX. The determinants associated with the introduction of TNF blockers were high SJC, presence and progression of structural damage, positivity for RF or anti-CCP antibodies, and high disease activity.

The participants' characteristics seem to have no impact on therapeutic choices. Neither age, sex, year of graduation, nor settings of medical practice significantly changed the distribution of the preferences expressed by the panelists on the different scenarios.

Derivation of the decision tree. From the previous results, a comprehensive algorithm was developed to gather, in a decision tree, the preferences for therapy from all variants. For convenience in daily clinical practice, some of the branches were reduced (Figure 2). The final tree displays graded therapeutic adaptations based on the main disease characteristics and the presence or absence of the 4 severity markers selected for the construction of the vignettes.

DISCUSSION

The present survey enabled the extraction of panelists' preferences in choosing a second-line DMARD after failure of MTX therapy or equivalent first-line DMARD in patients with RA, and the development of an algorithm (in a decision tree format) to help rheumatologists choose the optimal treatment in daily practice. Panelists choosing between pairs of options for therapy allowed for gathering information on preferences simply by ranking the

Table 3. Rheumatologists' preferences for second-line therapy after failure of MTX therapy in RA patients with progressing structural damage*

DAS28	Swollen joint count	Therapeutic option preferences			
		RF and anti-CCP negative	%	RF or anti-CCP positive	%
Low	2	Addition of TNF blocker	32.0	Addition of TNF blocker	27.9
		Switch to another conventional DMARD	26.8	Switch to another conventional DMARD	24.3
		Addition of IL-1 inhibitor	17.5	Add another conventional DMARD	23.4
Low	6	Addition of TNF blocker	32.7	Addition of TNF blocker	33.3
		Switch to another conventional DMARD	22.7	Addition of IL-1 inhibitor	23.8
		Addition of IL-1 inhibitor	20.9	Add another conventional DMARD	20.0
Low	10	Addition of TNF blocker	34.9	Addition of TNF blocker	32.7
		Add another conventional DMARD	23.6	Add another conventional DMARD	23.1
		Addition of IL-1 inhibitor	23.6	Addition of IL-1 inhibitor	21.2
Moderate	2	Addition of TNF blocker	26.5	Addition of TNF blocker	32.7
		Addition of IL-1 inhibitor	21.2	Add another conventional DMARD	22.1
		Add another conventional DMARD	20.4	Switch to another conventional DMARD	22.1
Moderate	6	Addition of TNF blocker	34.9	Addition of TNF blocker	31.5
		Switch to another conventional DMARD	25.7	Addition of IL-1 inhibitor	24.1
		Addition of IL-1 inhibitor	18.3	Switch to another conventional DMARD	23.1
Moderate	10	Addition of TNF blocker	41.1	Addition of TNF blocker	35.1
		Add another conventional DMARD	21.4	Switch to another conventional DMARD	22.5
		Addition of IL-1 inhibitor	19.6	Addition of IL-1 inhibitor	22.5
High	2	Addition of TNF blocker	31.7	Addition of TNF blocker	42.2
		Add another conventional DMARD	25.0	Addition of IL-1 inhibitor	19.6
		Switch to another conventional DMARD	21.2	Switch to another conventional DMARD	16.7
High	6	Addition of TNF blocker	39.6	Addition of TNF blocker	31.4
		Add another conventional DMARD	20.8	Addition of IL-1 inhibitor	27.5
		Switch to another conventional DMARD	20.8	Add another conventional DMARD	20.6
High	10	Addition of TNF blocker	42.3	Addition of TNF blocker	40.9
		Addition of IL-1 inhibitor	20.6	Addition of IL-1 inhibitor	25.5
		Switch to another conventional DMARD	18.6	Add another conventional DMARD	20.0

* Progressing structural damage seen on radiographs. IL-1 = interleukin-1; see Table 1 for additional definitions.

weighted decisions. The strength of such a methodology relies on its capacity to discern trends and draw conclusions in situations of insufficient or no scientific evidence. At the beginning of the STPR research program, literature review and discussions within the group led to inconclusive information, and no consensus could be reached.

Table 4. Determinants of preference for each therapeutic option*

	Continuation of ongoing treatment	Switch to another conventional DMARD	Addition of a second conventional DMARD	Addition of IL-1 inhibitor	Addition of TNF blocker
Structural damage					
None (reference)	1	1	1	1	1
Stable	0.86 (0.73–1.00)	0.79 (0.69–0.91)	1.05 (0.92–1.21)	1.30 (1.06–1.60)	1.40 (1.17–1.68)
Progressing	0.17 (0.14–0.22)	0.58 (0.50–0.67)	0.70 (0.61–0.81)	2.75 (2.28–3.32)	3.71 (3.15–4.37)
Swollen joint count					
2 (reference)	1	1	1	1	1
6	0.56 (0.47–0.66)	1.00 (0.88–1.16)	1.16 (1.01–1.34)	1.17 (0.98–1.42)	1.27 (1.08–1.50)
10	0.35 (0.29–0.42)	0.90 (0.78–1.03)	1.13 (0.98–1.31)	1.38 (1.14–1.65)	1.76 (1.50–2.06)
DAS28					
Low (reference)	1	1	1	1	1
Moderate	0.76 (0.65–0.90)	1.02 (0.88–1.17)	0.96 (0.83–1.11)	1.16 (0.97–1.40)	1.17 (0.99–1.38)
High	0.32 (0.26–0.39)	0.91 (0.79–1.05)	1.04 (0.90–1.20)	1.19 (0.99–1.43)	1.85 (1.58–2.17)
Biologic markers					
RF and anti-CCP negative (reference)	1	1	1	1	1
RF or anti-CCP positive	0.90 (0.78–1.05)	0.89 (0.80–1.00)	1.01 (0.90–1.13)	1.04 (0.90–1.21)	1.20 (1.05–1.36)

* Values are the odds ratio (95% confidence interval). DMARD = disease-modifying antirheumatic drug; IL-1 = interleukin-1; TNF = tumor necrosis factor; DAS28 = Disease Activity Score in 28 joints; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide antibodies.

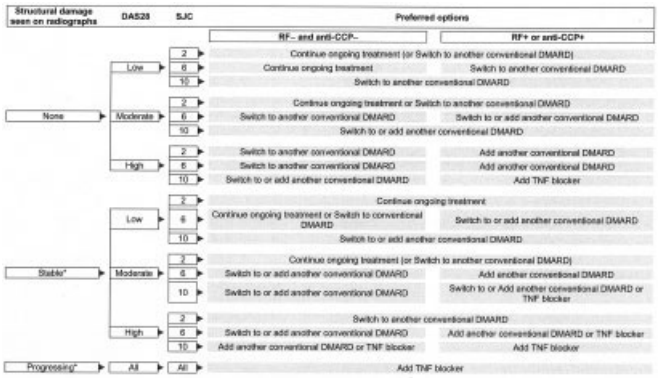

Figure 2. Simplified decision tree presenting rheumatologists' therapeutic choices for 12-month rheumatoid arthritis with loss of response to methotrexate at the maximum tolerated dosage. * Stable or progressing since the last radiograph evaluation. DAS28 = Disease Activity Score in 28 joints; SJC = swollen joint count; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide antibodies; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

The use of vignettes to study medical behaviors has been validated in a randomized controlled study investigating methods of assessing quality of care (39). In this study, information about physicians' practices extracted through clinical vignettes was consistent with information collected through consultations with simulated patients, i.e., trained actors presenting unannounced to a clinic. This consistency led to use of such paper cases for the present survey, in which respondents' preferences were expected to be based on their usual practice. The use of vignettes and the paired-choice framework made the disentanglement of a complex problem into a series of clinical situations familiar to clinicians possible. Although the succession of the 180 questions was perceived as repetitive, the survey was fairly well accepted by respondents, who were able to provide quick answers to most of the vignettes. Only a small subset of questions seemed difficult to address and needed more reflection; the role of the research nurse in such cases was important to avoid lack of choice for a specific question (i.e., missing data).

The selection of the determinants to be varied in the vignettes was based on the first step of the STPR research, when the most meaningful parameters were identified (30). The determinants also corresponded to main RA prognostic factors found in the literature (24,25). Structural damage progression strongly predicted the addition of a TNF blocker, which was highly consistent with national and international recommendations for the use of TNF blockers in patients with RA (40,41). Although no specific definition of structural damage progression was given to the respondents, there is somewhat of a consensus in the country to define such a progression as any definite new erosion or joint space narrowing on joint radiographs as assessed by rheumatologists in daily practice (42). SJC seemed to be more predictive of DMARD escalation than the DAS28. At the conception of the study, in addition to DAS28 in the variants, which is partly redundant, SJC was provided to give a more meaningful description of the clinical situation to the respondents. Our results seem to indicate that physicians gave more weight to or felt more comfortable with such objective information than with the composite index itself. Our data also indicate that RF and anti-CCP antibodies influenced panelists' preferences. However, their impact seemed rather weak, although several studies have shown that both markers are predictive of more aggressive RA (43–45). In addition to disease features, parameters such as patient characteristics (e.g., comorbidities that could contraindicate certain DMARDs) could have been used to explore the therapeutic decision-making process. However, regulatory documents provide substantial and rather consensual information in this area, and the inclusion of these parameters would have increased the number of vignettes. No modern imaging technique parameters were introduced in the vignettes. Recent studies have shown the capacity of ultrasonography (US) and magnetic resonance imaging (MRI) to detect early structural damage with higher sensitivity than radiography (46,47). Moreover, some features may be predictive of rapid progression of structural damage, such as positive power Doppler signal on US or bone edema on MRI (48,49). However, the rheumatologists did not regularly use US and MRI in everyday practice at the time of the survey, and their introduction in the vignettes might have hampered the extrapolation of our results to other contexts.

From its conception, the present study aimed to assess physicians' preferences for therapy and derive an algorithm to help rheumatologists with therapeutic decision making, choosing the best DMARD option for a specific RA patient. Such choices in daily clinical practice may be challenging because of the complexity of some clinical situations and the limited duration of the consultation. In practice, choices are often implicitly made on the basis of clinicians' experiences. The present study gave the opportunity to reveal more explicit choices. Although we included in our respondent sample both teaching and nonteaching rheumatologists working either in public settings or in private practice, no difference was observed in the distribution of their responses. This may partially be explained by the substantial effort of information and education of health professionals about RA over the last decade, due to the launch of biologic agents. The decision tree seemed to be the most appropriate format in this context because it provides physicians with a short but comprehensive overview of the different therapeutic options and allows for quick progression through the branches to the therapeutic decision. Such tools are favored by physicians and other health care professionals, which is the key of successful implementation in usual care (50). In addition to having decision aid aspects, such tools may be used for Continuing Medical Education programs or even evaluation of medical practice, activities that are highly encouraged by health authorities. In such situations, STPR decision trees might be used not for making the right choice, but for providing participants with a landmark or a reference point to organize thinking. The format of such Continuing Medical Education programs is often highly appreciated by participating physicians; however, their efficacy in terms of knowledge improvement has not been evaluated.

The acceptance of clinical guidelines by health profes-

sionals is critical. Some physicians consider such clinical practice guidelines and related algorithms to be an attempt to reduce medicine to simple equations for solving medical problems. This perception is even more confirmed when guidelines are used by regulatory authorities to impose mandatory practice (51). Several guidelines have already been published at the national and international levels. The most recent ones, those published by the ACR in 2008 (21), attempted to cover many different clinical situations depending on RA duration, disease activity level, presence of features of poor prognosis, or previous failure of MTX therapy. Although these recommendations were based on a different methodology, the RAND Appropriateness Method (37), there was no substantial discrepancy between their main conclusions and the preferences expressed by the participants in our study. However, 2 main differences have to be mentioned. First, the ACR recommendations introduced costs or insurance coverage limitations, which were not included in our algorithm since universal public insurance coverage is offered to the entire population of France and therefore does not extensively influence physicians' therapeutic choices at the patient level. Second, although the ACR guidelines mainly concentrated on nonbiologic versus biologic DMARDs, the pairwise method we used enabled us to propose more detailed options in the final algorithm, i.e., switch from one conventional DMARD to another, addition of a second conventional DMARD, addition of anakinra, or addition of a TNF blocker. This was also possible since our study did not aim to produce professional recommendations, but simply to be an aid for routine clinical practice based on physicians' preferences.

The STPR Group was developed within the French Society of Rheumatology, whose efforts are mainly dedicated to rheumatologists and other health care professionals working in the rheumatology area. Therefore, the STPR research has focused mainly on physicians' preferences and does not include patients' opinions. Several studies of RA as well as other chronic diseases have shown that involvement of patients in the care of and sharing of disease management between physicians and patients is associated with patients better accepting their treatment (52–54). Far from neglecting patients' input, STPR decision trees may also serve as a basis for discussion and interaction between physicians and patients, and thus include patients' involvement in the therapeutic decision-making process. Of note, several preference studies of RA patients have already been conducted (55,56). Interestingly, in addition to efficacy, which may be difficult for patients to capture, 2 major parameters significantly influenced treatment preferences: risk aversion, because many patients were anxious about potential side effects, and medication costs when a substantial copayment was required.

When scientific evidence is missing or insufficient, vignette-based pairwise preference surveys might be an interesting way to disentangle complex problems for more explicit decision making in clinical practice. Such surveys and their resulting decision trees may lead to better quality and homogeneity of health care. In the present study, TNF blocker introduction is preferred by rheumatologists when structural damage is progressing, no matter what the value of DAS28, SJC, or RF and anti-CCP antibodies is.

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AUTHOR CONTRIBUTIONS

Dr. Fautrel 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 design. Fautrel, Guillemin, Meyer, De Bandt, Berthelot, Flipo, Lioté, Maillefert, Wendling, Saraux, Combe, Le Loët.

Acquisition of data. Fautrel, Meyer, De Bandt, Berthelot, Flipo, Lioté, Maillefert, Wendling, Saraux, Combe, Le Loët.

Analysis and interpretation of data. Fautrel, Guillemin, Meyer, De Bandt, Berthelot, Flipo, Lioté, Maillefert, Wendling, Saraux, Combe, Le Loët.

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Statistical analysis. Fautrel, Guillemin.

ROLE OF THE STUDY SPONSOR

Sanofi-Aventis France did not have access to the data and was not involved in the research design and realization or data analysis. The authors have worked independently of the funding source and have no competing interest to declare.

REFERENCES

1. Callahan LF, Pincus T, Huston JW 3rd, Brooks RH, Nance EP Jr, Kaye JJ. Measures of activity and damage in rheumatoid arthritis: depiction of changes and prediction of mortality over five years. Arthritis Care Res 1997;10:381–94.
2. Uhlig T, Smedstad LM, Vaglum P, Moum T, Gerard N, Kvien TK. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. Rheumatology (Oxford) 2000;39:732–41.
3. Del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737–45.
4. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722–32.
5. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet 2001; 358:903–11.
6. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Emery P, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2006. Ann Rheum Dis 2006;65 Suppl 3:iii2–15.
7. Pincus T, Ferraccioli G, Sokka T, Larsen A, Rau R, Kushner I, et al. Evidence from clinical trials and long-term observa-

tional studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford) 2002;41:1346–56.
8. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173–7.
9. Michaud K, Wolfe F. Reduced mortality among RA patients treated with anti-TNF therapy and methotrexate [abstract]. Arthritis Rheum 2005;52 Suppl:S145.
10. Sokka T, Kautiainen H, Hakkinen A, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis: results of 3 cohorts over 5 years. J Rheumatol 2004;31:1073–82.
11. Ward MM, Leigh JP, Fries JF. Progression of functional disability in patients with rheumatoid arthritis: associations with rheumatology subspecialty care. Arch Intern Med 1993; 153:2229–37.
12. Prevoo ML, van Riel PL, van 't Hof MA, van Rijswijk MH, van Leeuwen MA, Kuper HH, et al. Validity and reliability of joint indices: a longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol 1993;32:589–94.
13. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
14. Van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
15. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
16. Fransen J, Moens HB, Speyer I, van Riel PL. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis 2005;64:1294–8.
17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
18. 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.
19. Pham T, Gossec L, Fautrel B, Combe B, Flipo RM, Goupille P, et al. Physical examination and laboratory tests in the management of patients with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005;72: 222–8.
20. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, 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.
21. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762–84.
22. Bathon JM, Cohen SB. The 2008 American College of Rheumatology recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis: where the rubber meets the road [editorial]. Arthritis Rheum 2008;59:757–9.
23. Saraux A, Berthelot JM, Chales G, Le Henaff C, Thorel JB, Hoang S, 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.
24. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46:357–65.
25. Morel J, Combe B. How to predict prognosis in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:137–46.
26. Hochberg MC. Early aggressive DMARD therapy: the key to slowing disease progression in rheumatoid arthritis. Scand J Rheumatol Suppl 1999;112:3–7.
27. Lard LR, Visser H, Speyer I, van der Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, 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.
28. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination–disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46:894–8.
29. Emery P. Evidence supporting the benefit of early intervention in rheumatoid arthritis. J Rheumatol Suppl 2002;66:3–8.
30. Le Loet X, Berthelot JM, Cantagrel A, Combe B, de Bandt M, Fautrel B, 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.
31. Meyer O, de Bandt M, Berthelot JM, Cantagrel A, Combe B, Fautrel B, et al. Clinical practice format for choosing a second-line disease modifying anti-rheumatic drug in early rheumatoid arthritis after failure of 6 months' first-line DMARD therapy. Joint Bone Spine 2007;74:73–8.
32. Aletaha D, Smolen JS. DMARD use in early rheumatoid arthritis: lessons from observations in patients with established disease. Clin Exp Rheumatol 2003;21(5 Suppl 31): S169–73.
33. 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.
34. Kvien TK, Heiberg, Lie E, Kaufmann C, Mikkelsen K, Nordvag BY, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23(5 Suppl 39): S188–94.
35. Dixey J, Solymossy C, Young A. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol Suppl 2004;69: 48–54.
36. Thurstone LL. A law of comparative judgment. Psychol Rev 1927;34:273–86.
37. Shekelle P. The appropriateness method. Med Decis Making 2004;24:228–31.
38. Prieto L, Alonso J. Exploring health preferences in sociodemographic and health related groups through the paired comparison of the items of the Nottingham health profile. J Epidemiol Community Health 2000;54:537–43.
39. Peabody JW, Luck J, Glassman P, Dresselhaus TR, Lee M. Comparison of vignettes, standardized patients, and chart abstraction: a prospective validation study of 3 methods for measuring quality. JAMA 2000;283:1715–22.
40. Fautrel B, Pham T, Mouterde G, Le Loet X, Goupille P, Guillemin F, et al. Recommendations of the French Society for Rheumatology regarding TNFα antagonist therapy in patients with rheumatoid arthritis. Joint Bone Spine 2007;74:627–37.
41. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis 2007;66 Suppl 3:iii2–22.
42. Gossec L, Fautrel B, Pham T, Combe B, Flipo RM, Goupille P, et al. Structural evaluation in the management of patients

with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005;72:229–34.
43. Meyer O, Labarre C, Dougados M, Goupille P, Cantagrel A, Dubois A, et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Ann Rheum Dis 2003;62:120–6.
44. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090–5.
45. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196–201.
46. Backhaus M, Burmester GR, Sandrock D, Loreck D, Hess D, Scholz A, et al. Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Ann Rheum Dis 2002;61: 895–904.
47. Ostergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkudlarek M, Pedersen-Zbinden B, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. Arthritis Rheum 2003;48:2128–31.
48. Bajaj S, Lopez-Ben R, Oster R, Alarcon GS. Ultrasound detects rapid progression of erosive disease in early rheumatoid arthritis: a prospective longitudinal study. Skeletal Radiol 2007;36:123–8.
49. McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. Ann Rheum Dis 1999;58: 156–63.
50. Durieux P, Ravaud P, Dosquet P, Durocher A. Effectiveness of clinical guideline implementation strategies: systematic review of systematic reviews. Gastroenterol Clin Biol 2000;24: 1018–25.
51. Durieux P, Chaix-Couturier C, Durand-Zaleski I, Ravaud P. From clinical recommendations to mandatory practice: the introduction of regulatory practice guidelines in the French healthcare system. Int J Technol Assess Health Care 2000;16: 969–75.
52. Edworthy SM. How important is patient self-management? Baillieres Best Pract Res Clin Rheumatol 2000;14:705–14.
53. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. Br Med J 2003;326:1308–9.
54. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 2004;363:1589–97.
55. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146:406–15.
56. Fraenkel L, Bogardus ST, Concato J, Felson DT, Wittink DR. Patient preferences for treatment of rheumatoid arthritis. Ann Rheum Dis 2004;63:1372–8.