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

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Abstract

Objective: To elaborate a clinical practice decision tree for the choice of the first disease-modifying antirheumatic drug (DMARD) for untreated rheumatoid arthritis (RA) of less than 6 months' duration.

Methods: Four steps: 1) review of the literature on DMARD efficacy against RA; 2) inventory of the information available to guide the DMARD choice; 3) selection of the most pertinent information by 12 experts using a Delphi method; 4) choice of DMARDs in 12 clinical situations defined by items selected in step 3 (disease activity score (DAS) 28: ≤3.2; >3.2 and ≤5.1; >5.1), rheumatoid factor status (positive/negative), structural damage (with/without), *i.e.*, 3×2×2). Thus, multiplied by all the possible treatment pairs, 180 scenarios were obtained and presented to 36 experts, who ranked treatment choices according to the Thurstone pairwise method.

Results: Among the 77 items identified, 41 were selected as pertinent to guide the DMARD choice. They were reorganized into 5 domains: RA activity, factors predictive of structural damage; patient characteristics; DMARD characteristics; physician's characteristics. In the majority of situations, the 2 top-ranking DMARD choices were methotrexate and leflunomide. Etanercept was an alternative for these agents when high disease activity was associated with poor structural prognosis and rheumatoid factor positivity.

Conclusions: Starting with simple scenarios and using the pairwise method, we were able to devise a clinical decision tree for the choice of the first DMARD to treat very early RA.

Key Words: Clinical practice, Decision tree, Early rheumatoid arthritis, DMARD, Recommendations

INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatism [1 2]. This disease of unknown autoimmune origin evolves by flares that usually lead to the destruction of joints, functional disability, deterioration of the quality of life and even shortened life expectancy. Because of its frequency, its socioprofessional repercussions and the increasing cost of its management, especially since the advent of biological agents, RA represents a real public health problem.

It has now been well established that early therapy with disease modifying antirheumatic drugs (DMARDs) should be initiated to control the inflammatory activity and slow the structural damage [3]. This treatment, if it is adapted, can have a favorable impact on the evolution of the disease [4 5]. Unfortunately, very little data is available on the efficacy of DMARDs in very early RA. In addition, no guidelines have established the precise information to be taken into account to help orient the clinician's choice of the first DMARD to be prescribed for early RA. Notably, in the rare publications on this topic, disease activity was usually the only information considered [6]. Practical recommendations concerning the type of DMARD to be prescribed in taking these parameters into account in very early RA are also lacking.

On behalf of the French Society of Rheumatology, the Working Group for Therapeutic Strategies for Rheumatoid Arthritis (Stratégies Thérapeutiques de la Polyarthrite Rhumatoïde (STPR)) decided to devise a decision tree in the form of a practical guide to the choice of the first DMARD to be prescribed for RA of less than 6 months' duration.

METHODS

This endeavor was conducted in 4 successive steps: 1) a critical review of the literature on the efficacy of DMARDs against RA activity and structural damage; 2) an inventory as full as possible of all factors that might contribute to the optimal DMARD choice; 3) selection, among the collected items, of the most relevant to orient, in routine practice, this choice; 4) finally, the development of a practical decision tree, taking into account the information selected above.

The STPR Working Group is composed of 13 French Society of Rheumatology members, from 13 different rheumatology units of French university hospitals, who are experts in the management of RA based on their research and clinical experience; 12 of them were recruited for their clinical expertise and the 13th (FG) for his methodological expertise.

We concentrated our efforts exclusively on very early RA, defined as existing for less than 6 months, with a definitive diagnosis and still untreated with DMARD(s) or corticosteroids, but a non-steroidal antiinflammatory drug could have been given.

Step 1, *i.e.*, the literature review, was conducted by the STPR experts according to evidence-based medicine methodology; its detailed methodology [7] and the results obtained have already been published [8]. This literature review focused on recent-onset RA, taking into consideration DMARD efficacy against disease activity and structural damage. In parallel, we took into account the very recent reviews on factors predictive of structural damage [9 10].

During step 2, the STPR experts were asked to list all the information concerning the patient that might be considered in the choice of a first DMARD. Because it had been established *a priori* that the RA diagnosis was definitive, they were asked not to retain any item having only diagnostic value. Experts were asked to propose only

items available at the time of diagnosis. To constitute a definitive inventory of candidate items, the list was submitted to 132 French community rheumatologists during a continuing education course.

During step 3, only the 12 STPR expert physicians were asked to select from this inventory those items that they consider pertinent in daily practice to guide the choice of the first DMARD for very early RA. This selection was made using the Delphi method [11]. From the onset, the threshold for selection for an item was set at 70% concordant opinions. Then, these experts organized the selected items into 5 domains.

During step 4, the final choice of DMARDs was made among the 6 candidate treatments selected as potentially effective and licensed for use in early RA: gold salts, sulfasalazine, methotrexate, hydroxychloroquine, leflunomide and etanercept (at the time of the study, February 2004, other biologicals had not yet been indicated for first-line therapy). Experts were told that the dosage was given according to the national recommendations with the possibility to increase it up to the maximum permitted and tolerated one. Because all possible combinations could not be tested, we arbitrarily decided to consider only monotherapies. Moreover, the experts were instructed not to consider the cost of DMARDs. A panel of 36 experts from the 12 cities, including the 12 STRP Working Group experts and 24 practicing rheumatologists (see the Appendix), chose treatment options according to the Thurstone pairwise method [12]. Combining the 3 items selected in step 3 (disease activity score (DAS) 28 (≤3.2, >3.2 and ≤5.1 or >5.1), rheumatoid factor (positive/negative) and structural damage (with/without), *i.e.*, 3×2×2) created 12 potential clinical situations, which were then multiplied by the 15 potential treatment pairs, yielding 180 scenarios (collected in a spiral notebook). A well-trained research nurse then presented the scenarios individually to each member of the expert panel, thereby assuring that no question was missed or went unanswered. Each expert then chose the optimal first-line agent out of the pair of DMARDs offered to be prescribed in each scenario presented. This study was done under the sole responsibility of the STPR working group on behalf of the French Society of Rheumatology. A financial support was given by the Club Rhumatismes et Inflammation (CRI), a non profit organization.

Statistical analysis

For each of the 12 clinical situations in step 4, treatment possibilities were ranked by frequency of choice. The 2 top-ranking treatments chosen for each clinical situation were used to construct a decision tree for the selection of the first DMARD to treat early RA. This was conducted by 1) running a hierarchical classification procedure to identify the hierarchy of scenario variables, *i.e.* 3 items selected in step 3, influencing the choice; 2) applying correspondence factor analysis to determine the most frequent associations of alternative DMARDs to treat the clinical scenarios presented. Expert panel characteristics (age, sex, period of training, position, *i.e.* public, private or both) were introduced as supplementary variables into the correspondence factor analysis to search for association with treatment options, and ANOVA was used to search and test for their potential impact on determining choices.

All analyses were conducted using SAS® 8.2 software.

RESULTS

The summary of the literature review on the efficacy of DMARDs against RA activity and structural damage, taking into consideration the duration of the disease and the level of evidence, as recommended by Shekelle *et al* [7], are reported in table 1. The published findings [8] were updated in November 2003 just before starting step 4 (2/2004). No study had demonstrated, with a high level of evidence, the efficacy of any of the molecules tested alone against RA of less than 6 months' duration. Recent reviews devoted to the search for factors predictive of structural damage indicated that the principal items usually identified: the initial presence of structural damage, rheumatoid factor positivity, an elevated erythrocyte sedimentation rate 1st hour (ESR) and/or C-reactive protein (CRP) concentration.

During step 2, the inventory of information that might contribute to guiding the DMARD choice, identified 75 items. The 132 community rheumatologists added 2 and they retained 77 items.

At the end of step 3, the 36 members of the expert panel had retained only 41 (53%) of the 77 items, according to the Delphi method, as being pertinent for the orientation of the DMARD choice. The items were then organized, by consensus, into 5 domains (table 2): RA activity, factors predictive of structural damage, patient characteristics, DMARD characteristics and physician characteristics. In domains I and II, respectively, disease activity is defined by simple items that characterize the actual status of the patient's RA, while the prognostic factors concern data that might be able to predict later structural status. To characterize disease activity, we used the DAS 28 with 4 variables and 3 levels of activity. This composite index takes into account several items selected during step 3: number of painful joints, number of swollen joints and severity, as assessed by ESR and/or CRP. Actual structural damage (yes/no) and rheumatoid factor positivity (yes/no) were retained as factors predictive of structural damage; ESR and/or CRP were not used because they are items included in the DAS 28 [9 10]. DAS 28 and factors predictive of structural damage can thus be used to construct a decision tree. Domains II, IV and V – characteristics of patients, DMARDs and physicians – contain items that constitute the uniqueness of these 3 'actors' in every medical consultation. The items included in these 3 domains vary widely according to the clinical situation and thus cannot be taken into account in the construction of a decision tree to be applied to all patients.

During step 4, the final choice of DMARD(s) was made as described above; the 2 top-ranking choices for the first DMARD are presented in table 3. Pertinently, the percentages of expert preferences were very similar. Finally, the decision tree was developed for the choice of DMARD(S) (fig 1) according to the results of hierarchical classification. Schematically, in the majority of cases, methotrexate and leflunomide were the first-line therapies of choice. Sulfasalazine was prescribed only in the absence of structural damage, when activity was low or moderate, and hydroxychloroquine became the treatment of choice in the less severe context, when activity was low, and structural damage and rheumatoid factor were absent. At the other end of the spectrum, when the clinical picture was severe, associating high disease activity, structural damage and rheumatoid factor positivity, etanercept was the second choice, methotrexate being the first.

According to our multivariate analyses, none of these drug choices were influenced by the characteristics of the expert panel: sex, age, type of practice and period of training.

DISCUSSION

This endeavor enabled us to develop guidelines, in the form of a simple decision tree, to be applied in clinical practice to select the first DMARD for the treatment of very early RA. These recommendations exclusively address untreated, definitively diagnosed RA; they do not concern the relatively frequent situation of an inflammatory rheumatism for which a diagnosis of RA cannot be confirmed. Because no published study demonstrated, with a high level of evidence, the efficacy of any DMARD against the activity or structural damage of RA of less than 6 months' duration [8], the advice of experts is avidly awaited.

We were able to identify 77 items and retained 41 able to orient the choice of a DMARD for definitively diagnosed, untreated, very early RA. To the best of our knowledge, this undertaking has never been attempted before. Notably, no single expert established the entire list of these items alone. This list was then completed and retained by 132 practicing rheumatologists experienced in the management of RA.

These items were easily reorganized into 5 domains. Domain I, disease activity, contains the principal items described in the literature on this subject: the 4 comprising the DAS 28 [13] and the 7 American College of Rheumatology criteria defining RA [14]. Also taken into consideration were items pertinent to the management of RA patients individually: morning stiffness, nighttime awakenings. Domain II, which concerns the prediction of structural damage, contains the 3 elements identified in the greater majority of studies conducted on cohorts of patients with early RA or inflammatory rheumatisms [10 15–18]: initial structural damage, rheumatoid factor status and biological inflammatory syndrome. The presence of anti-cyclic citrulline peptide antibodies was not retained because the results were still contradictory at the time step 4 was completed. The heading 'patient characteristics' covers several expected items, *i.e.*, medical history, age and comorbidity(ies), in addition to others, more recently identified, that are gaining importance in the choice of the DMARD to be prescribed: acceptance of the regimen and its risks, the willingness of the patient to submit to regular monitoring of treatment tolerance… Wolfe *et al* recently underlined this determinant role of the patient's wishes in the United States [19]. Concerning the characteristics of the drugs to be given, the experts did not retain direct and/or indirect costs, as they were instructed not to consider economic factors. Finally, among the characteristics of the treating physician, only experience was retained.

Among these 5 domains, we found only domains I and II – disease activity and prediction of structural damage – to be pertinent for the development of guidelines in the form of a decision tree. Indeed, the 3 others vary in each clinical situation and thus cannot be applied. For activity, the DAS 28 with 4 variables was chosen because of its properties (facility of assessing these traits) and the ability to distinguish 3 levels of activity [13]. As regards the prognosis, the choice was much more difficult because no publications are available on community-recruited patients with RA of less than 6 months' duration, untreated and followed for sufficiently long times to advance a prediction of structural damage for each patient. Analysis of the rare cohorts satisfying these conditions showed that, in the best of cases, only 80% of the patients were correctly classified [10 15–18]. Despite these difficulties, we thought it imperative to consider factors predictive of structural damage because, henceforth, agents acting on this manifestation, notably biologicals, will be available [8]. The results of studies on very recent-onset RA allow us to hope that new

prognostic markers, applicable individually to each patient, will be identified [20–22]. After considering the published data, we retained the factors predictive of structural damage most frequently cited in the literature: initial presence of structural damage and rheumatoid factor status. The presence of a biological inflammatory syndrome was not retained because it is 1 of the DAS 28 variables chosen to define activity and it was inconsistently identified as a prognostic factor when the judgment criterion was structural damage [9 10].

Short clinical scenarios describing disease activity and structural prognosis were presented individually to the members of the expert panel. Each scenario was intentionally not detailed, so as to correspond to a wide variety of real clinical situations. For each scenario, the expert was asked to choose between 2 treatments. Experts were sometimes reluctant to opt for 1 or the other when they felt that the treatments proposed were not consistent with regard to the clinical scenario. The visiting nurse explicitly requested that they exclude the worst option, and thereby provide an answer and avoid missing data. Because experts found themselves confronted with this inconsistent treatment priority for only a limited number of scenarios, these choices were indeed counted but they ranked low among the various options and had no chance of being retained in the final decision tree.

The decision tree proposed is easy to use. It takes into consideration basic items: DAS 28, initial structural damage and rheumatoid factor status. The therapeutic options proposed are user-friendly: for most 'cases', methotrexate was the first choice, followed closely by leflunomide, especially when structural damage was already present initially. It should be kept in mind that we considered only DMARD monotherapies. Furthermore, to the best of our knowledge, DMARD combinations have never been tested to treat RA of less than 6 months' duration.

When activity was low without structural damage or rheumatoid factor, hydroxychloroquine was the first-line therapy of choice; however, it is true that, in this scenario, the diagnosis of RA is rarely certain. So, in the real life the choice can be difficult. On the other hand, when all the indicators were pejorative, a biological, etanercept, was recommended as second choice. When this decision tree was developed, that molecule was the only biological agent authorized without prior methotrexate treatment, in France. To the best of our knowledge, this is the first time that recommendations for DMARD use in very early RA have been presented as an easy-to-apply decision tree. The only recommendations that have been published are those of the American College of Rheumatology that were last updated in 2002 [6]. The latter comprise a complete review of the objectives and means available to control RA, but they do not attribute the respective place of each of the DMARD as a function of activity and prediction of structural damage. The guidelines of the Scottish Society of Rheumatology, available on the Internet, are not presented as a decision tree [23]. Smolen *et al* recently devised an algorithm intended to control RA as much as possible, especially at its onset [24]. Methotrexate was systematically recommended at rapidly increasing doses, regardless of the disease activity or prediction of structural damage. We plan to reevaluate these guidelines, as a function of the progress made concerning DMARDs, and better understanding of prognostic factors and even better definition of RA activity. In that way, we will consider anti-cyclic citrulline peptide antibodies as a variable. Considering the recent evidence of inducing remission [25] especially in early disease, we will modify the wording of the questions asked to the experts when we will update these recommendations. Finally, we will continue to develop this decision tree for RA of longer duration.

APPENDIX
The 24 other members of the expert panel: Allain J, Auge B, Collanges C, Constantin A, Daragon A, De Person JF, Debrock J, Desmas V, Dieudé P, Jousse S, Lecrosnier M A, Legouffe M C, Lhose A, Loeuille D, Malaizier D, Maugars Y, Mistrih R, Morel J, Palazzo E, Piroth C, Pouyol F, Rozenberg S, Solau Gervais E and Vittecoq O.

REFERENCES

1 **Guillemin F**, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, *et al*. Prevalence of rheumatoid arthritis in France – 2001. *Ann Rheum Dis* 2004; in press.

2 **Gabriel SE**. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;**27**:269–81.

3 **Möttönen T**, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, *et al*. Delay of 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.

4 **Albers JM**, Paimela L, Kurki P, Eberhardt KB, Emery P, van't Hof MA, *et al*. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. *Ann Rheum Dis* 2001;**60**:453–8.

5 **Lard LR**, Boers M, Verhoeven A, Vos K, Visser H, Hazes JMW, *et al*. Early and aggressive treatment of rheumatoid arthritis patients affects the association of HLA class II antigens with progression of joint damage. *Arthritis Rheum* 2002;**46**:899–905.

6 **American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines**. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;**46**:328–46.

7 **Shekelle PG**, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;**318**:593–6.

8 **Stratégies thérapeutiques de la polyarthrite rhumatoïde**. Étude critique de la littérature consacrée aux traitements de fond de la polyarthrite rhumatoïde. *Rev Rhum* [Ed Fr] 2002;**69**(suppl 2):21–100.

9 **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.

10 **Le Loët X**. Utility of early prognosis in rheumatoid arthritis. *Rev Rhum* 2004;**71**:28s–33s.

11 **Dalkey N**, Helmer O. An experimental application of the Delphi method to the use of experts. *Management Science* 1963;**9**:458–67.

12 **Thurstone LL**. A law of comparative judgement. *Psychol Rev*. 1927;**34**:273–86.

13 **Prevoo MLL**, 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. *Arthritis Rheum* 1995;**38**:44–8.

14 **Felson DT**, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, *et al*. The American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.

15 **Scott DL**. The diagnosis and prognosis of early arthritis: rationale for new prognostic criteria. *Arthritis Rheum* 2002;**46**:286–90.

16 **van der Heijde DMFM**, van Riel PLCM, van Leewen MA, van Thof MA, van Rijjwijk MH, van de Putte LBAI. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up of 147 patients. *Br J Rheumatol* 1992;**31**:519–25.

17 **van der Heide A**, Remme CA, Hofman DM, Jacobs JWG, Bijcsma JWJ. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:1466–74.

18 **Van Leuwen MA**, Wiestra J, van Riel PLCM. IgM, IgA and IgG rheumatoid factors in early rheumatoid arthritis are predictive of radiological progression. *Scand J Rheumatol* 1995;**24**:146–53.

19 **Wolfe F**, Rehman Q, Lane NE, Kremer J. Starting a disease modifying antirheumatic drug or a biologic agent in rheumatoid arthritis: standards of practice for RA treatment. *J Rheumatol* 2001;**28**:1704–11.

20 **Garnero P**, Landewe R, Boers M, Verhoeven A, van der Linden S, Christgau S, *et al*. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. *Arthritis Rheum* 2002;**46**:2847–56.

21 **Drossaers-Bakker KW**, Zwinderman AH, Vlieland TP, van Zeben D, Vos K, Breedveld FC, *et al*. Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year follow up. *Arthritis Rheum* 2002;**47**:383–90.

22 **Visser H**, Le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: model for persistent (erosive) arthritis. *Arthritis Rheum* 2002;**46**:357–65.

23 **Scottish Intercollegiate Guidelines Network**. Management of early rheumatoid arthritis. Edinburgh: SIGN 2000 (SIGN Publication no. 8). http://www.sign.ac.uk

24 **Smolen JS**, Sokka T, Pincus T, Breedveld FC. A proposed treatment algorithm for rheumatoid arthritis: aggressive therapy, methotrexate, and quantitative measures. *Clin Exp Rheumatol* 2004;**21**(suppl 31):S209–10.

25 **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 randomized controlled trial. *Lancet* 2004;**364**:263-9.

Table 1 DMARD efficacy against rheumatoid arthritis (RA) activity and structural involvement as a function of RA duration, as assessed in November 2003

DMARD	Efficacy against inflammation*					Efficacy against structural involvement*				
	< 6 mo	< 1 yr	< 2 yr	< 5 yr	Any duration	< 6 mo	< 1 yr	< 2 yr	< 5 yr	Any duration
Hydroxychloroquine			A	A	A					
Gold salts			A	A	A			A	A	A
Auranofin			A		A			A		
D-Penicillamine			A		A					A
Tiopronin					B					
Minocycline		A			A					
Sulfasalazine			A		A			A		A
Azathioprine					A					C
Cyclosporine	C	C	C	C	A	C	C	C		A
Methotrexate					A				A	A
Leflunomide			B		A			D		A
Etanercept			A		A			A		A
Infliximab		D		D	A	D			D	A
Adalimumab			D		A			D		A
Anakinra					A					A
Corticosteroids			A	A	A			A	A	A

*Level of evidence as defined by Shekelle *et al* [7]. **A**: based on evidence from at least 1 randomized controlled trial

(RCT) or meta-analyses of RTC. **B**: based on evidence from at least 1 controlled but not randomized trial, another type of experimental study or extrapolated recommendations from RCT or meta-analyses. **C**: based on non-experimental descriptive studies, *e.g.* comparative, correlational and case–control studies, which are extrapolated from RCT, non-RTC or other experimental studies. **D**: based on expert committee reports or clinical experience of respected authorities or both, or those in levels B and C.

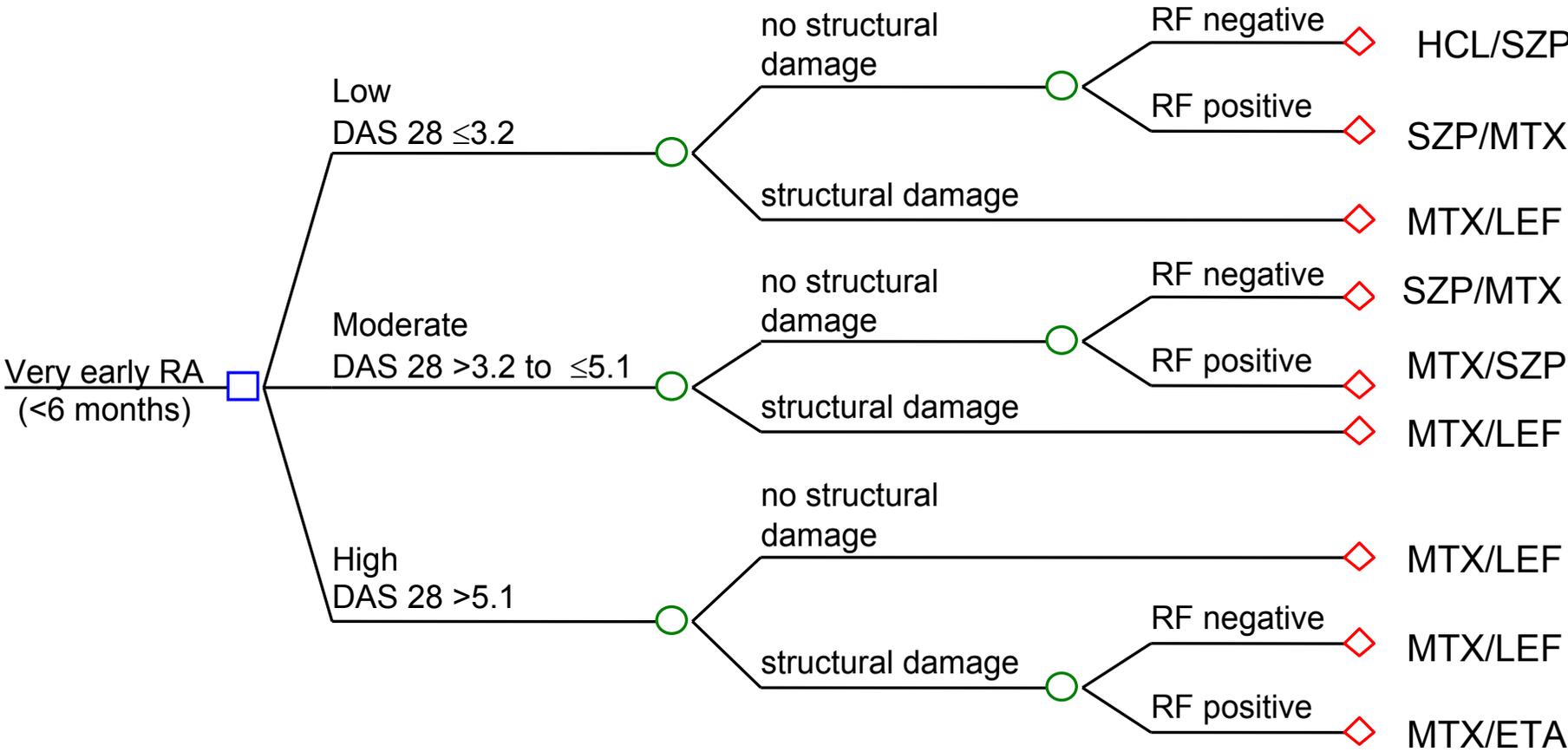**Table 2** Reorganization of the items selected by the 12 experts into 5 domains

Domain I Rheumatoid arthritis activity	Domain II Factors predictive of structural damage	Domain III Patient characteristics	Domain IV DMARD characteristics	Domain V Physician's characteristics
Number of painful joints	CRP and/or ESR 1st h	Age	Rapidity of treatment action	Personal experience
Number of swollen joints	Structural damage present	Desire to conceive within the year	Efficacy against inflammation	
Overall severity	Rheumatoid factor	Menopause/contraception	Efficacy against structural damage	
Patient's assessment		Personal medical history, general	Interaction with comedications	
Doctor's assessment		Drug intolerance	Constraints of monitoring	
Overall intensity of pain		Comorbidities		
Morning stiffness		Hypertension		
Nighttime awakenings		Liver (AST, ALT, hepatitis B/C serology)		
Functional disability		Kidney (creatinine, urine dipstick)		
ESR 1st h/CRP		Lung (chest X-ray)		
		Alcohol abuse		
		Hematological anomalies		
		Patient's acceptance of treatment		
		Patient's acceptance of therapeutic risk		
		Patient's willingness to submit to rigorous follow-up		

Table 3 The 2 top-ranking choices, expressed as percentages, of the first DMARD selected by the 36 members of the expert panel for very early rheumatoid arthritis

DAS 28	No structural damage		With structural damage	
	RF negative	**RF positive**	**RF negative**	**RF positive**
Low 28 ≤ 3.2	HCL: 27.0	SZP: 24.4	MTX: 29.1	MTX: 30.2
	SZP: 25.2	MTX: 22.0	LEF: 23	LEF: 23.7
Moderate > 3.2 to ≤ 5.1	SZP: 25.7	MTX: 29.3	MTX: 29.6	MTX: 30.2
	MTX: 23.5	SZP: 22.8	LEF: 24.3	LEF: 24.6
High > 5.1	MTX: 25.7	MTX: 29.3	MTX: 29.6	MTX: 30.2
	LEF: 23.5	LEF: 22.8	LEF: 24.3	ETA: 24.6

ETA: etanercept; HCL: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; RF: rheumatoid factor; SZP: sulfasalazine.

Figure 1. Decision tree for the choice of the first DMARD for very early rheumatoid arthritis based on the expert panel's 2 top-ranking choices.

ETA: etanercept; HCL: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; RF: rheumatoid factor; SZP: sulfasalazine.