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SPECIAL ARTICLE

American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis

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Introduction

The majority of patients with a confirmed diagnosis of rheumatoid arthritis (RA) use nonbiologic disease-modifying antirheumatic drugs (DMARDs) and the rate of biologic DMARD use is rising rapidly (1,2). The American College of Rheumatology (ACR) has not updated its recommenda-

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tions for nonbiologic DMARDs since 2002 (3) and has not previously developed recommendations for biologic agents. Although past guidelines have been derived from an informal consensus approach, we used a formal group process to develop recommendations that were as evidence-based as possible.

To develop these new recommendations on behalf of the ACR, following the principles delineated by the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration (4), we first conducted a systematic review of scientific evidence to create an evidence report and draft guidelines. We addressed each of the 5 domains prespecified by the ACR, namely: 1) indications for use; 2) screening for tuberculosis (TB; biologic DMARDs only); 3) monitoring for side effects; 4) assessing the clinical response; and 5) the roles of cost and patient preferences in decision-making (biologic DMARDs only). A Working Group and a Core Expert Panel (CEP) of clinicians and methodologists guided the development of these recommendations. We next convened a Task Force Panel (TFP) of internationally-recognized clinicians, methodologists, and patient representatives with broad expertise in the use of nonbiologic and biologic DMARD therapies, evidence-based medicine, patient preference, and health care economics. They were to critique and rate proposed recommendations using a well-accepted group process, the modified Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method (5) (Figure 1). Although the TFP and CEP considered drug-specific indications from the US Food and Drug Administration (FDA) and other regulatory authorities, in some cases the TFP extrapolated recommendations outside the present bounds of approved labeling. Although terminology used by regulatory agencies varies, in this article we refer to biologic agents as drugs.

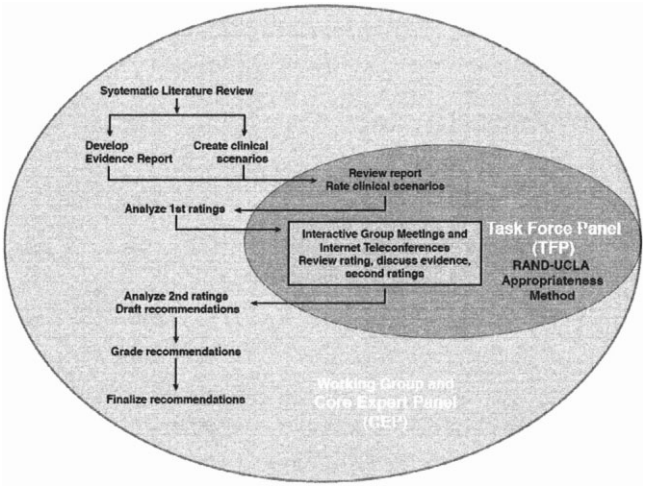

Figure 1. Methodologic process for the American College of Rheumatology recommendations for the use of biologic and nonbiologic disease-modifying antirheumatic drug therapies. RAND/UCLA = Research and Development/University of California at Los Angeles.

Disseminated under the aegis of the ACR, we recognize that recommendations surrounding certain issues (e.g., cost considerations and TB testing approaches) may not be generalizable outside North America; however, we hope that these recommendations will have relevance to arthritis practitioners throughout the world.

To better reflect the underlying purpose of the endeavor, the output from this project is termed recommendations, rather than guidelines. These recommendations were developed for specialist clinicians familiar with assessing RA disease activity and disease severity. Applying

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dividualized patient assessment and clinical decision-making. The recommendations developed are not intended to be used in a "cookbook" or prescriptive manner or to limit a physician's clinical judgment, but rather to provide guidance based on clinical evidence and expert panel input.

Methods for Development of ACR RA Recommendations

Systematic literature review: sources and databases. Literature searches for both nonbiologic and biologic DMARDs relied predominantly on PubMed (from January 1, 1966 through January 31, 2007 and from January 1, 1998 through February 14, 2007, respectively). For biologic DMARDs, systematic searches were also conducted using EMBASE, SCOPUS, Web of Science, and the International Pharmaceutical Abstracts (IPA) computerized bibliographic databases (through June 20, 2006) by applying medical subject headings (MeSH) and relevant keywords (see Appendix A, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). For both nonbiologic and biologic DMARDs, we supplemented searches by checking references cited in published systematic reviews and by reference to the bibliographies of the articles extracted from the literature reviews. To ensure as complete a listing as possible of available important literature, the CEP and TFP identified additional studies.

Data from the FDA Adverse Event Reporting System and unpublished data from product manufacturers or investigators were not solicited or included in the systematic review unless they were identified by the literature search and met the inclusion criteria.

Literature search domains. Literature on the following nonbiologic DMARDs was examined: azathioprine, hydroxychloroquine, leflunomide, methotrexate, minocycline, organic gold compounds, sulfasalazine, and, when appropriate, combination therapy with methotrexate plus cyclosporine, methotrexate plus hydroxychloroquine, methotrexate plus leflunomide, methotrexate plus sulfasalazine, sulfasalazine plus hydroxychloroquine, and methotrexate plus hydroxychloroquine plus sulfasalazine. Additionally, the medical literature was examined for 6 biologic agents: etanercept, infliximab, adalimumab, anakinra, abatacept, and rituximab.

The 2 principles of our maximally inclusive search approach were to address indications and therapeutic response to nonbiologic DMARDs and biologic agents for RA, and to address the potential adverse events of nonbiologic and biologic DMARDs including TB for biologic DMARDs. Cost and patient preference were addressed for biologic DMARDs but not nonbiologic DMARDs, based on the specific ACR mandate for cost recommendations.

Subheadings, MeSH terms, and synonyms for the 6 biologic DMARDs and the 6 nonbiologic DMARDs (plus 5 nonbiologic DMARD combinations) were imputed as "substance names" and as "text words" that were applied to the medical databases. Details of the search strategy are listed in an online appendix (available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html).

Literature search limits and article selection criteria. Appropriate studies addressing the use of nonbiologic DMARDs and biologic agents were identified within each of the 5 domains that were specified by the ACR. Our literature search was limited to original research involving human subjects, published in English, and having abstracts. The search identified 3,878 citations for nonbiologic DMARDs and 6,818 citations of potential interest for biologic therapies (see Appendix B, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). Seven reviewers (3 for biologics, 4 for nonbiologics) screened each title and abstract for relevance to the domains.

Reviewers excluded articles based on abstract review if: 1) the report was a meeting abstract, case series, or case report with <30 patients or the study duration was <6 months; 2) nonbiologic DMARDs were used for non-RA conditions (e.g., psoriatic arthritis, systemic lupus erythematosus); 3) biologic DMARDs were used in health conditions not included in the FDA label (e.g., Wegener's granulomatosis); or 4) biologic DMARDs were used in conditions not relevant to the ACR domains of interest (e.g., the use of rituximab in the treatment of lymphoma). Review articles and meta-analyses were excluded from our systematic reviews. However, meta-analyses were examined later to find other references, and they were referenced in supplementary qualitative reviews on selected adverse event domains (e.g., perioperative, vaccinations, pregnancy).

After exclusions based on abstract review, 801 full-text articles were retrieved and considered further for full review. This number included 515 articles that focused on nonbiologic DMARDs, 226 that focused on biologic DMARDs, and 60 that focused on cost. For nonbiologic DMARDs, a consensus of 2 reviewers determined articles not appropriate for full review. For biologic agents, the full text of all articles was reviewed by 2 independent reviewers by applying the same criteria as for nonbiologic DMARDs. If there was discordance on whether to include a study, it was resolved by a third reviewer. After additional exclusion of reviews, non–English language articles, nondomain topics, unapproved disease indications, lack of clinical outcomes of interest, non–FDA-approved regimens, study duration <6 months, and case series (n <30), the final number of included articles for biologic agents was 125 (see Appendices B and C, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). Twenty-eight articles that also addressed cost factors associated with biologic agents were included. For nonbiologic DMARDs, the number of included articles was 142 (see Appendix B, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html).

Each article about nonbiologic DMARDs was reviewed and key article elements entered into a database by 1 of

Table 1. Instruments used to measure rheumatoid arthritis disease activity*

Instrument (ref.)	Score range	Thresholds of disease activity		
		Low	Moderate	High
Disease Activity Score in 28 joints (253)	0–9.4	≤3.2	>3.2 and ≤5.1	>5.1
Simplified Disease Activity Index (103)	0.1–86.0	≤11	>11 and ≤26	>26
Clinical Disease Activity Index (103)	0–76.0	≤10	>10 and ≤22	>22
Rheumatoid Arthritis Disease Activity Index (254)	0–10	<2.2	≥2.2 and ≤4.9	>4.9†
PAS or PASII (14)	0–10	<1.9	≥1.9 and ≤5.3	>5.3
Routine Assessment Patient Index Data (255)	0–30	<6	≥6 and ≤12	>12

* Methods for calculating various instrument scores are shown in Appendix E (available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). PAS = Patient Activity Scale.
† Median.

by one reviewer; concordance on this re-review was >80%. For biologic agents, the article review was performed by 1 reviewer and checked by a second reviewer. Discordance on the database entries was resolved by consensus between the 2 reviewers, and in the event of continuing disagreement, the opinion of a third reviewer was considered final. For each included article, study characteristics were summarized in tabular and graphic format, and a synthesis of the systematic literature review was developed into a comprehensive evidence report and used to craft clinical scenarios (described below and in Appendix D, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html).

Quality assessment of articles included in the literature review. The quality of randomized controlled trials (RCTs) was assessed by 2 reviewers using the Jadad instrument (6). Higher scores on this 5-point scale indicate higher quality. Articles related to nonbiologic DMARDs had a median Jadad score of 3 (interquartile range [IQR] 2–4). For biologic DMARDs, articles reviewed for these recommendations had a median Jadad score of 5 (IQR 3–5), reflecting the more modern study designs for the biologic DMARDs.

For observational studies (case–control and cohort), we used the Newcastle-Ottawa Scale (NOS) (range 0–9) (7). Higher scores on this scale indicate higher quality. For nonbiologic DMARD articles reviewed, the median NOS score was 3 (IQR 2.25–3.75), while the median NOS score for the biologic DMARDs was 7 (IQR 5–8), reflecting the newer literature and study designs for the biologic DMARDs.

Defining important clinical factors necessary for therapeutic decision-making. *Modified Delphi process by the CEP to establish key parameters for decision scenarios.* After establishing a diagnosis of RA, risk assessment is crucial for guiding optimal treatment. We used a modified Delphi process (8) to reach consensus and enrich response categories on questions related to key clinical thresholds and decision branch points of RA treatment strategies. This included definitions of what constituted DMARD failure, definitions of poor prognosis, categories of potential contraindications to DMARD use, and reasons for discon-

To apply results from research studies to clinical practice, the CEP recommended that RA disease duration, disease activity, and factors related to a poor prognosis in RA be explicitly defined and used to help formulate practical recommendations (see below).

RA disease duration. Based on RA disease duration intervals commonly used in published RA clinical trials, disease duration thresholds were chosen to help with clinical decision-making. There were 3 categories of disease duration: <6 months (considered to be equivalent to early disease), 6–24 months (considered to be equivalent to intermediate disease duration), and >24 months (considered to be long or longer disease duration). For biologic therapies, early disease was further subdivided by disease duration of ≤3 months or 3–6 months, when disease activity was high.

RA disease activity assessment. Several indices to measure RA disease activity have been developed, each of which has advantages and disadvantages (9–15). Recent composite and patient-reported disease activity measures, many of which do not require laboratory testing, are summarized in Table 1 and Appendix E (available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). Evidence-based guidelines require clear definitions of disease activity to make rational therapeutic choices, but it is not possible or appropriate to mandate use of a single disease activity score for the individual physician, and different studies have used different definitions. Therefore, the TFP was asked to consider a combined estimation of disease activity, which allowed reference to many past definitions. With the instruments in Table 1 as a guide, we rated RA disease activity in an ordinal manner as low, moderate, or high, as previously requested by the CEP (Table 1). The TFP was then asked to make judgments based on these cut points.

Prognostic factors for RA. RA patients with features of a poor prognosis have active disease with high tender and swollen joint counts, often have evidence of radiographic erosions, elevated levels of rheumatoid factor (RF) and/or anti–cyclic citrullinated peptide (anti-CCP) antibodies (16–20), an elevated erythrocyte sedimentation rate, and/or an elevated C-reactive protein level (21,22). Older age, female sex, genotype (HLA–DRB1 shared epitope),

ment Questionnaire (HAQ) score, and cigarette smoking are also important predictors for a worse RA outcome, radiographic progression, early disability, and morbidity (such as increased risk of the need for joint replacement) (23–31). Through a modified Delphi process, the CEP selected the following as the most clinically important markers of poor prognosis: functional limitation (e.g., HAQ Disability Index), extraarticular disease (e.g., vasculitis, Sjögren's syndrome, RA lung disease, etc.), RF positivity and/or positive anti-CCP antibodies (both characterized dichotomously, per CEP recommendation), and/or bony erosions by radiography. For the purposes of selecting therapies, physicians should consider the presence of these prognostic factors at the time of the treatment decision. Although these prognostic factors are not exclusive, they are commonly used and have good face validity. Including combinations of these factors to guide decision-making would have added untenable complexity to a process that involved deliberate consideration of every permutation in a separate clinical scenario.

RAND/UCLA appropriateness method using the TFP. The RAND/UCLA appropriateness process (32–34), which incorporates elements of the nominal and Delphi methods, was used to craft the final recommendations from clinical scenarios. These clinical scenarios, which described the potential key permutations of particular therapeutic considerations, were drafted by the investigators and CEP, based on the evidence report (Figure 1 and Appendix D, available at the *Arthritis Care & Research* Web site at http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html). Via e-mail, the TFP received these clinical scenarios, instructions for grading scenarios, and definitions of all variables. Using a 9-point Likert scale, panelists were asked to use the evidence report and their clinical judgment to rate the appropriateness of various clinical scenarios pertaining to key clinical parameters (e.g., "In a patient who has had an inadequate response to a nonbiologic DMARD, has RA of 6 months duration, poor RA prognostic features, and moderate RA disease activity, would it be appropriate to add or switch to an anti–tumor necrosis factor α [anti-TNFα] agent?"). An initial set of scenario ratings occurred before each TFP meeting, and a second set of ratings occurred after discussion of the evidence at each TFP meeting. Disagreement regarding a specific scenario (e.g., disagreement with the initiation of combination therapy with methotrexate and hydroxychloroquine in mild early RA) was defined when one-third or more of the panelists rated a scenario in the lowest 3 points of the appropriateness scale (ordinal scores 1, 2, or 3) and one-third or more of the panelists rated the same scenario in the highest 3 points (ordinal scores 7, 8, or 9). In the absence of disagreement, a median rating in the lowest 3 points classified a scenario permutation as "inappropriate," and a median rating in the upper 3 points classified a scenario as "appropriate." Those scenario permutations rating in the 4–6 range together with those with disagreement were classified as "uncertain."

The dispersion of the scores and ranges plus each in-

median score provided the degree of agreement. In most circumstances, the recommendations for indications, contraindications, and safety monitoring for use of therapeutic agents include only positive statements. For example, it was agreed that methotrexate should be used in the setting of early RA without features of a poor prognosis. In contrast, there was no agreement regarding the use of rituximab in that circumstance, so no statement or recommendation was made. As another example, the TFP believed that hydroxychloroquine was not contraindicated for patients with acute serious bacterial infection. Since this was a negative statement (no contraindication), no recommendation was provided. For some particularly contentious areas (e.g., the use of biologic agents during pregnancy or the use of nonbiologic agents during the perioperative period), an absence of consensus is documented, and we directly state that no recommendation is provided. An absence of consensus and consequent lack of a positive statement should not be construed to indicate that the TFP did not consider these issues important, only that consensus was not reached, often due to absent or conflicting evidence. In these areas, therapeutic decisions are left to the careful consideration of risks/benefits by the patient and physician.

The anonymous ratings of the first round of ordinal voting were reviewed with the panelists at each meeting. The CEP were invited to participate during all the discussions with the TFP but were nonvoting participants. Through these discussions, the reasons for any uncertainty were identified, and resolution of discordance was attempted by modification of the clinical scenarios, clarification of definitions, or acknowledgment of discordance between clinical experience and the medical literature. In addition, the TFP identified important clinical situations that were not discussed during the face-to-face meeting or during the 4 subsequent Internet teleconferences. When identified and necessary, additional clinical questions were recommended by the panelists, formulated into decision scenarios, and evaluated using the same process. All clinical scenarios were subjected to at least 2 rounds of voting.

Conversion of clinical scenarios to ACR RA treatment recommendations. Following the second round of voting, recommendation statements were developed from a direct distillation of the scenario votes, and these statements were reviewed by the CEP. Although more than 2,000 clinical scenarios were graded by the TFP, there were very few areas of inconsistency or illogical results. When inconsistent or illogical findings were identified, the TFP was asked to reconsider and in some cases revote on these scenarios, using a new Delphi process.

Rating the strength of evidence for recommendations. For each final recommendation, the strength of evidence was assigned using the methods of the American College of Cardiology (35) as follows: 1) for level of evidence A, data were derived from multiple RCTs or meta-analyses;

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